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Ravulizumab for paroxysmal nocturnal haemoglobinuria

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Remziye Zaim, Irene Santi, Matthijs Versteegh, Charlotte Ahmadu and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Marie Westwood and Annette Chalker acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Shelley de Kock critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ADAs	Antidrug antibodies
AE	Adverse events
AIC	Akaike Information Criterion
ASH	American Society of Hematology
BI	Budget impact
BIC	Bayesian information criterion
BSH	British Society for Haematology
BTH	Breakthrough haemolysis
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
cRBC	Chicken red blood cell
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
CV	Cardiovascular
DC	Discontinuation
DCE	Discrete choice experiment
DSU	Decision Support Unit
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
EUR	Erasmus University Rotterdam
FACIT	Functional Assessment of Chronic Illness Therapy
FAD	Final appraisal document
FAS	Full analysis set
FDA	Food and Drug Administration
GHS	Global health score
GPI	Glycophosphatidylinositol
Hb	Haemoglobin
HGB-S	Haemoglobin stabilisation
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IC	Indirect comparison
ICER	Incremental cost effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
IVRS	Interactive voice response system
KSR	Kleijnen Systematic Reviews
LDH	Lactate dehydrogenase
LDH-N	Normalisation of lactate dehydrogenase levels
LDH-PCHG	Lactate dehydrogenase-percent change
LSM	Least squares mean
LYs	Life years
LYG	Life years gained

MAVE	Major adverse vascular event
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIM	Non-inferiority margin
NMA	Network meta-analysis
NO	Nitric oxide
NR	Not reported
OS	Overall survival
PAS	Patient access scheme
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal haemoglobinuria
PP	Per protocol
pRBC	Packed red blood cells
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
q8w	Every eight weeks
RBC	Red blood cell
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Relative risk; Risk ratio
SAE	Serious adverse events
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
STA	Single technology appraisal
TA	Transfusion avoidance
TEAE	Treatment emergent adverse events
TTO	Time trade-off
UK	United Kingdom
ULN	Upper limit of normal
UMC	University Medical Centre
URTI	Upper respiratory tract infection
WBC	White blood cell
WHO	World Health Organization
WRS	Web response system
WTP	Willingness-to-pay

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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. Where possible, it also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 discusses the decision problem, Section 1.3 issues related to clinical effectiveness, and Section 1.4 issues related to cost effectiveness. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report, see Sections 2 (background), 3 (decision problem), 4 (clinical effectiveness) and 5 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report sections
1	Generalisability of the trial populations to UK patients	Section 4.2.3
2	Dosing of eculizumab	Sections 3.3 and 4.2.2
3	Short follow-up in the trials	Section 4.2.5
4	Appropriateness of the company's base-case analysis	Section 5.2.3, 6.1 and 6.3
5	Appropriateness of the company's "equal effectiveness" scenario	Section 5.2.3
6	Generalisability of the ERG base-case to UK clinical practice	Section 5.2.2 and 5.2.3
7	Health-related quality of life	Section 5.2.8
8	Ravulizumab treatment effect duration	Section 5.2.6
9	Treating undetermined and CAC-related BTH events	Section 5.2.2

The most important deviation from the company's base-case was to assume no eculizumab up-dose to align the cost effectiveness analyses with the clinical trials. As explained below, the ERG acknowledged that this assumption is not completely representative of UK clinical practice. However, as the company stated in the company submission (CS), the majority (about [redacted]%) of PNH patients in UK clinical practice are managed at the standard eculizumab dose for whom an additional eculizumab up-dose is not needed. Additionally, the ERG proposed a different approach to utilities under the assumption that the ravulizumab quality of life benefit due to reduced treatment frequency might be captured by the treatment effect coefficient included in the mixed-effects regression equations used by the company to estimate utilities. This also implied that the additional ravulizumab utility for reducing treatment frequency, which was estimated from an external discrete choice experiment (DCE) and included in the company's base-case, was not used (set equal to 0) in the ERG preferred base-case. Finally, for the cost calculations, the ERG assumed the currently licensed 10mg/ml ravulizumab formulation, as opposed to 100mg/ml assumed by the company.

1.2 Overview of key model outcomes

The company's base-case results indicated that ravulizumab accrued [redacted] incremental quality adjusted life years (QALYs) and was cost saving compared to eculizumab. The largest differences in costs

across treatment arms were due to acquisition costs in the "No BTH" health state, which resulted in [redacted] difference for ravulizumab compared to eculizumab. However, these costs were outweighed by eculizumab due to patients requiring eculizumab up-dose. Thus, in the health state "continuous up-dose with history of incomplete C5 inhibition-related BTH event", the costs for eculizumab are [redacted], while there are no costs for ravulizumab in this health state (no incomplete C5 inhibition-related BTH events and no up-dose in the ravulizumab arm). However, the proportion of time spent in the continuous up-dose health states across the complete model time horizon was [redacted]%, which is approximately twice as much as the [redacted]% reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice. Consequently, the company's base-case results might be biased against eculizumab.

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is uncertainty about the trial population being representative for UK patients (Table 1.2) as well as the dosing of the comparator: eculizumab (Table 1.3).

Table 1.2: Key issue 1: Generalisability of the trial populations to UK patients

Report section	**Section 4.2.3 and 5.2.3**
Description of issue and why the ERG has identified it as important	Both trials were international trials with most patients included from countries other than the UK. Therefore, there is a question about the generalisability of the trial populations to UK clinical practice. In the ALXN1210-PNH-301 trial, 246 patients were included with [redacted] patients treated in England. In the ALXN1210-PNH-302 trial, 195 patients were included with [redacted] patients treated in England and [redacted] patients treated in Scotland. It is possible that patients included in the two trials have less severe disease than UK patients.
What alternative approach has the ERG suggested?	It is unclear how this difference in population characteristics influences results. Therefore, the ERG has no alternative approach.
What is the expected effect on the cost effectiveness estimates?	The expected change to the ICER is unclear.
What additional evidence or analyses might help to resolve this key issue?	The ERG is unclear how this issue can be resolved without new evidence.

Table 1.3: Key issue 2: Dosing of eculizumab

Report section	**Section 3.3, 4.2.2 and 5.2.3**
Description of issue and why the ERG has identified it as important	In UK clinical practice, an increased dose of eculizumab is used to manage breakthrough haemolysis (BTH) due to incomplete C5 inhibition. Data from the Paroxysmal nocturnal haemoglobinuria (PNH) national service indicate this is necessary for [redacted]% of the population (see CS, Section B.3.2.1), with the majority of patients remaining stable on the licensed eculizumab dose (900 mg). However, in the two ravulizumab trials included in the company submission, dose-escalation/up-dosing of eculizumab was not permitted (CS, page 89). This may have resulted in worse clinical outcomes for patients in the eculizumab arms of the two trials. Therefore, the

	effectiveness of ravulizumab may have been overestimated.
What alternative approach has the ERG suggested?	The size of this overestimation is not clear. Therefore, the ERG has no alternative approach.
What is the expected effect on the cost effectiveness estimates?	In the cost effectiveness analysis the company made assumptions regarding up-dosing of eculizumab and assumed equal effectiveness in a scenario analysis, which resulted in a very small increase in the number of QALYs with eculizumab, although ravulizumab was still dominant. However, as discussed more fully below, the ERG has concerns about the assumptions regarding up-dosing, which might have led to the effectiveness of eculizumab still being underestimated and the cost overestimated.
What additional evidence or analyses might help to resolve this key issue?	The company could not present evidence of the effectiveness of eculizumab at a dose at or closer to one that would be observed in UK clinical practice. Therefore, the ERG is unclear how this issue can be resolved without new evidence.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG identified one major concern with the evidence presented on the clinical effectiveness, namely the short follow-up of the included randomised controlled trials (RCTs; see Table 1.4).

Table 1.4: Key issue 3: Short follow-up in the trials

Report section	**Section 4.2.5**
Description of issue and why the ERG has identified it as important	Data are relatively immature in that they currently provide data for up to 52 weeks for a chronic condition requiring lifelong treatment. There is uncertainty about the long-term effectiveness of ravulizumab.
What alternative approach has the ERG suggested?	It is unclear how this will affect results. Therefore, the ERG has no alternative approach.
What is the expected effect on the cost effectiveness estimates?	The expected change to the ICER is unclear
What additional evidence or analyses might help to resolve this key issue?	The ERG is unclear how this issue can be resolved without new evidence.

1.5 The cost effectiveness evidence: summary of the ERG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 7.4 of this report. The company's cost effectiveness results are presented in Section 6, the ERG's summary and detailed critique in Section 5, and the ERG's amendments to the company's model and results are presented in Section 7. The key issues in the cost effectiveness evidence are discussed in Tables 1.5 to 1.10.

Table 1.5: Key issue 4: Appropriateness of the company's base-case analysis

Report section	5.2.3 Population, 6.1 Company's cost effectiveness results and 6.3 Model validation and face validity check
Description of issue and why the ERG has identified it as important	The proportion of time spent in the continuous up-dose health states of the model, across the complete model time horizon, was [redacted]% in the company's base-case analysis. This is approximately twice as much as the [redacted]% reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice. The ERG is concerned that the company's base-case analysis might overestimate the proportion of time spent in the continuous up-dose health states and consequently the results might be biased against eculizumab.
What alternative approach has the ERG suggested?	In the company's "equal effectiveness" scenario, the proportion of time spent in the continuous up-dose health states *across the complete model time horizon* was assumed to be exactly [redacted]%, matching the PNH National Service estimate of the proportion of patients expected to receive an increased dose of eculizumab in UK clinical practice. This is the main reason why the ERG considers that the "equal effectiveness" scenario may provide a better representation of UK clinical practice than the company's base-case scenario.
What is the expected effect on the cost effectiveness estimates?	Ravulizumab is more effective and cost saving compared to eculizumab, as in the company's base-case. Incremental costs in the "equal effectiveness" scenario are lower than in the company's base-case (i.e. ravulizumab "less" cost saving).
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion should help assessing the plausibility of the company's base-case scenario.

Table 1.6: Key issue 5: Appropriateness of the company's "equal effectiveness" scenario

Report section	5.2.3 Population
Description of issue and why the ERG has identified it as important	The ERG is concerned that the sub-population of patients who would require an eculizumab up-dose might be underestimated in the trials. The company explained that approximately 5% of patients in the trial population would need an eculizumab up-dose, which is approximately [redacted] lower than the [redacted]% estimate from the PNH National Service. The ERG wonders whether the conclusions from the trials, in which only 5% of patients would be "eligible" for an eculizumab up-dose, would be the same if there were approximately [redacted]% of patients who would need such an up-dose (as in UK clinical practice).
What alternative approach has the ERG suggested?	The ERG prefers a base-case scenario based completely on the clinical trials, thus, with no eculizumab up-dose included in the model.
What is the expected effect on the cost effectiveness estimates?	Could potentially have a substantial impact on the cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Additional data may help reducing the uncertainty regarding this aspect of the analysis.

Table 1.7: Key issue 6: Generalisability of the ERG base-case to UK clinical practice

Report section	5.2.2 Model structure and 5.2.3 Population
Description of issue and why the ERG has identified it as important	The ERG prefers a base-case scenario based on the clinical trials. Thus, with no eculizumab up-dose included in the model. The majority (about [redacted]%) of PNH patients in UK clinical practice are managed at the standard eculizumab dose for whom an additional eculizumab up-dose is not needed. Therefore, the ERG base-case is not completely representative of UK clinical practice.
What alternative approach has the ERG suggested?	No alternative suggested. The ERG considers that, with the current evidence, neither the company base-case nor the equal effectiveness scenario would provide a better representation of UK clinical practice.
What is the expected effect on the cost effectiveness estimates?	Could potentially have a substantial impact on the cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Additional data may help reducing the uncertainty regarding this aspect of the analysis.

Table 1.8: Key issue 7: Health-related quality of life

Report section	5.2.8 Health-related quality of life
Description of issue and why the ERG has identified it as important	The ERG disagrees that health-related quality of life (HRQoL) could not be assessed in the trial, as the administration frequency for ravulizumab was lower in the trial and substantial benefits, other than time of the patient, ought to be captured in the trial. Furthermore, the ERG argues that the methodological challenges of the discrete choice experiment outweigh its benefit as an external source for utility values.
What alternative approach has the ERG suggested?	The ERG prefers a non-significant utility benefit of 0.0103 and 0.0197 for ravulizumab, derived from a mixed-effects regression model, as the source of HRQoL benefit in the cost effectiveness model and prefers not to use the utility benefit for treatment frequency of 0.057 as derived from the discrete choice experiment.
What is the expected effect on the cost effectiveness estimates?	Substantial impact on the cost effectiveness under the ERG base-case settings (no eculizumab up-dose).
What additional evidence or analyses might help to resolve this key issue?	The ERG would recommend collecting EQ-5D data in the patient population rather than the cancer oriented QLQ-C30. The ERG would also recommended that the HRQoL benefit, including that related to frequency of administration, is measured in patients with a generic preference-based measure rather than externally through a DCE.

Table 1.9: Key issue 8: Ravulizumab treatment effect duration

Report section	5.2.6 Treatment effectiveness and extrapolation
Description of issue and why the ERG has identified it as important	The ERG is concerned about the company's assumption of a constant lifelong ravulizumab treatment effect. In response to clarification question B13, the company refused to model a decline in treatment effect over time as this was not considered clinical plausible. However, it can be argued that data from over 10 years are available only for eculizumab and the long-term effects of ravulizumab are unknown.
What alternative approach has the ERG suggested?	Given the time constraints associated to this project, the ERG was unable to run a scenario where a decline in treatment effect over time was included in the model.
What is the expected effect on the cost effectiveness estimates?	Could potentially have a substantial impact on the cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Additional data may help reducing the uncertainty regarding this aspect of the analysis. Additional scenario analyses may provide an estimation of the impact of this uncertainty on the cost effectiveness results.

Table 1.10: Key issue 9: Treating undetermined and CAC-related BTH events

Report section	5.2.2 Model structure
Description of issue and why the ERG has identified it as important	The ERG is unclear how patients with undetermined BTH events were treated in the clinical trials. Therefore, the ERG was unable to judge the appropriateness of modelling undetermined BTH events as complement-amplifying condition (CAC)-related BTH events. Also, the ERG feels that the rationale to assume to treat all CAC-related events with one single up-dose of eculizumab should have been better justified.
What alternative approach has the ERG suggested?	With the evidence presented in the CS and the response to the clarification letter, the ERG preferred to assume that CAC-related BTH events would not be treated with an eculizumab up-dose, in line with what was observed in the clinical trials in which up-dose was not allowed.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion may help reducing the uncertainty regarding this aspect of the analysis.

1.6 Other key issues: summary of the ERG's view

No other key issues were identified by the ERG.

1.7 Summary of the ERG's view

1.7.1 ERG preferred base-case

Fixing errors

1. Error in the model "Output" sheet in the ca1culation of the proportion of time spent in the model health states. This has no impact on the model cost effectiveness results, but it is important for clinical validation.

Fixing violations

2. No violations to the NICE reference case, scope or best practice were identified by the ERG.

Matters of judgement

3. Eculizumab up-dose: based completely on the clinical trials ALXN1210-PNH-301 and ALXN1210-PNH-302. Thus, without modelling eculizumab up-dose.
4. Utilities: ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate.
5. Utilities: additional utility benefit for treatment frequency set to 0 (instead of 0.057, as derived from the DCE).
6. Ravulizumab currently licensed 10mg/ml formulation (instead of 100mg/ml).

1.7.2 ERG scenarios

1. Cohort 3 is assumed to reflect UK clinical practice, where a continuous increased dose of eculizumab is used to manage BTH events. The reported range of PNH patients requiring this up-dose is between 5% and 29%, with an estimated mean value of [redacted]%. In this scenario, the impact of assuming a smaller population (5%) in Cohort 3 was explored by the ERG.
2. In this scenario, the ERG assumed [redacted]% of patients in Cohort 3, the ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate, the additional utility benefit for treatment frequency set to 0 and the ravulizumab formulation of 10mg/ml.
3. In this scenario, the ERG assumed eculizumab up-dose as in the company's base-case (continuous after second incomplete C5 inhibition-related BTH event), the ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate, the additional utility benefit for treatment frequency set to 0 and the ravulizumab formulation of 10mg/ml.
4. The ERG explored the impact of assuming the utility decrement of 0.057 (instead of 0) as in the company base-case, and half of this value (0.029). The remaining ERG preferred assumptions were as in the ERG base-case (no eculizumab up-dose and the ravulizumab formulation of 10mg/ml).
5. In this scenario, the ERG base-case was run with the assumption of BTH excess mortality as reported by Jang et al. (2016). A standard mortality ratio of 4.81 was applied.

1.7.3 Conclusion

The changes made by the ERG led to a situation where ravulizumab was not cost saving compared to eculizumab, unlike the company's base-case. The ICER from the ERG base-case was £38,290, obtained from the estimated [redacted] incremental QALYs gained by ravulizumab at an incremental cost of [redacted] compared to eculizumab. The differences with respect to the company's base-case were mostly explained by the assumption of no eculizumab up-dose. The ERG also conducted a

probabilistic sensitivity analysis (PSA) based on its preferred assumptions. The probabilistic ICER was £46,976 per QALY gained (incremental costs were [redacted] and incremental QALYs were [redacted]), thus, £8,686 larger than the ERG deterministic ICER. The ERG considers that this relatively large difference might be explained because the ERG PSA allows a (small) proportion of patients in the ravulizumab arm to transition to the incomplete C5 inhibition-related BTH events related health states. The cost effectiveness (CE)-plane showed approximately [redacted]% of the simulations in the south eastern quadrant, in which ravulizumab is dominant. The remaining simulations were in the north eastern quadrant. The cost effectiveness acceptability curve (CEAC) showed that the probability of ravulizumab being cost effective was [redacted]% (as opposed to [redacted]% in the company's PSA) at a threshold ICER of £30,000 per QALY gained. The ERG also conducted additional scenario analyses to explore important areas of uncertainty in the model. These key uncertainties were related to the so-called "equal effectiveness" scenario, utilities and BTH mortality. Other sources of uncertainty were deemed less important and were not explored in this section.

The results of these analyses showed that when eculizumab up-dose was included in the analysis, ravulizumab becomes a cost saving (and more effective) option compared to eculizumab. These analyses highlight the large impact that the proportion of patients treated with eculizumab up-dose has on the overall cost effectiveness results, even though this sub-population represents a minority (approximately [redacted]%) of the total PNH patients. The other assumptions tested by the ERG had an impact on the model results only when up-dose was not included in the analyses, thus under the ERG preferred assumption. The choice of non-zero values for the additional ravulizumab utility for reducing treatment frequency, had a relatively large impact on the ERG preferred base-case ICER. When the value estimated from the DCE and used by the company in their base-case, was used (0.057), the ICER decreased to £11,790 and when this utility value was halved (0.029) the ICER was £17,688. Thus, in both cases below the £30,000 threshold ICER. Finally, when excess mortality risk of BTH events was added to the ERG preferred analysis, by applying a hazard ratio of 4.81 to patients experiencing BTH events, sourced from the Korean PNH registry by Jang et al. 2016, the ICER increased to £124,433. This scenario highlights the impact of BTH excess mortality on the ERG base-case results. Additional data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trial Extension Phases reporting clinical outcomes up to 104 weeks are expected to be available in [redacted]. When the new data become available, the company will conduct an analysis of overall survival, which might be useful in reducing the uncertainty regarding BTH excess mortality.

It should be emphasised that throughout the CS and the responses to the clarification letter, the company have made it clear that eculizumab 'up-dosing' is only necessary in approximately [redacted]% of the PNH population and that most patients would achieve an adequate terminal complement inhibition on the licensed eculizumab dose. However, despite being a minority, the assumptions about patients who would require an eculizumab up-dose are the main driver of the cost effectiveness results. A summary of the ERG's base-case results is presented in Table 1.11.

Table 1.11: Summary of ERG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER
Company base-case (after clarification)	[redacted]	[redacted]	Ravulizumab dominates
ERG change 1: no eculizumab up-dose (key issue 6)	[redacted]	[redacted]	£14,798
ERG change 2: utilities treatment arm as	[redacted]	[redacted]	£11,538

Scenario	Incremental cost	Incremental QALYs	ICER
covariate (key issue 7)			
ERG change 3: utilities no additional utility benefit for treatment frequency (key issue 7)	[redacted]	[redacted]	£37,474
ERG's preferred base-case (ravulizumab formulation 10mg/ml)	[redacted]	[redacted]	£38,290

Based on the CS and the electronic model of the CS.
Abbreviations: CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year

2. BACKGROUND

2.1 Introduction

In this report, the Evidence Review Group (ERG) provides a review of the evidence submitted by Alexion Pharmaceuticals in support of ravulizumab, trade name Ultomiris®, for patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolysis with clinical symptoms indicative of high disease activity, or whose disease is clinically stable after receiving eculizumab treatment for a minimum of six months. In this section, the ERG summarises and critiques the company's description of the underlying health problem and the company's overview of the current service provision. The information for this critique is taken from Document B of the company submission (CS).[1]

2.2 Critique of company's description of the underlying health problem

PNH is caused by an acquired mutation in the *PIG-A* gene in haematopoietic stem cells,[1, 2, 3] that results in a partial or absolute deficiency in proteins linked to the cell membrane by a glycosylphosphatidylinositol (GPI) anchor. PNH is a rare condition, with an estimated 725 diagnosed cases in the UK (2018 figures).[4]

PNH is a progressive, life-threatening haematological disorder that is characterised by uncontrolled activation of the terminal complement pathway, which can lead to intravascular haemolysis, anaphylaxis, inflammation and thrombosis.[1] The CS states that, *'without complement-inhibitor treatment, the majority of patients (up to 75%) die within 20 years of diagnosis, and the median survival time is estimated at approximately 10 years (from diagnosis).'*[1, 5]

ERG comment: The ERG notes that reference cited, in support of the statements about the life expectancy of patients with PNH who are not treated with complement-inhibitors, refers to a study of patients wo were referred to Hammersmith Hospital, London between 1940 and 1970. It is not clear that whether the life expectancy of patients with PNH had improved, over time, prior to the introduction of compliment-inhibitors.

The clinical course of PNH varies, with some patients experiencing sudden symptom onset with rapid progression to death and others experiencing chronic illness with limited life-threatening complications.[1, 6] Chronic haemolysis is considered to be the underlying cause of morbidity and premature mortality in patients with PNH,[1] and can result in a variety of symptoms and adverse outcomes, including anaemia, fatigue, dyspnoea, haemoglobinuria, pulmonary hypertension, thrombosis.[1] The symptoms of PNH can have a substantial impact on patients' quality of life and functioning. A 2007 multi-national survey of 29 patients with PNH found that 76% were forced to modify their daily activities in order to manage their disease and 17% were unemployed due to PNH; nearly all (96%) patients in the study reported experiencing fatigue and more than half reported abdominal pain, headache and shortness of breath.[7] However, 31% of patients surveyed also reported not receiving any medication for their PNH.[7]

2.3 Critique of company's overview of current service provision

Current service provision for patients with PNH, in NHS England, is managed through a PNH National Service that was initiated in April 2009.[1, 4] This service is provided through two main centres, one at St James' University Hospital in Leeds, and the second at King's College Hospital in London, and a further eight outreach clinics around the UK (Birmingham, Bristol, Lanarkshire, Liverpool, Manchester, Oxford, Peterborough and Southampton).[1] Referrals for suspected PNH are

usually made by haematologists and, on confirmed diagnosis, patients are managed on a shared care basis between the PNH National Service and referring haematologists.[1]

Adult patients with PNH and haemolysis with clinical symptom(s) indicative of high disease activity in the UK are currently treated with eculizumab.[1, 8] In the treatment initiation phase, patients receive eculizumab 600mg via 25 to 45 minute intravenous infusion every week for the first four weeks.[1, 9] In the treatment maintenance phase, patients receive eculizumab 900mg via 25 to 45 minute intravenous infusion every 14 ± 2 days. For patients in England, initial dose(s) are administered at one of the PNH National Service centres, after which most patients choose to have treatment administered at their home through a homecare service.[1, 10, 11]

The criteria used, by the PNH National Service, to determine treatment eligibility are[1]:

- Thrombosis related to PNH
- Complications associated with haemolysis:
    - Renal failure
    - Pulmonary hypertension
- Pregnancy (and for at least three months post-partum)
- Haemolytic (lactate dehydrogenase [LDH] levels > 1.5 times the upper limit of normal [ULN]) PNH with either of the following:
- With anaemia (Hb < 9 g/L) or
- With agreement with Joint Service colleagues at multidisciplinary team (MDT)
- Exceptional cases (not fulfilling the above criteria) with approval across PNH National Service centres and the National Commissioners

With respect to remaining unmet need, the CS notes that approximately 20% of patients experience breakthrough haemolysis while receiving recommended dose of eculizumab (900mg) treatment (reported range: 5–29%),[1, 12-15] and states that experiencing breakthrough haemolysis have an increased risk of potentially fatal thromboembolic events and other debilitating PNH-related symptoms.[1]

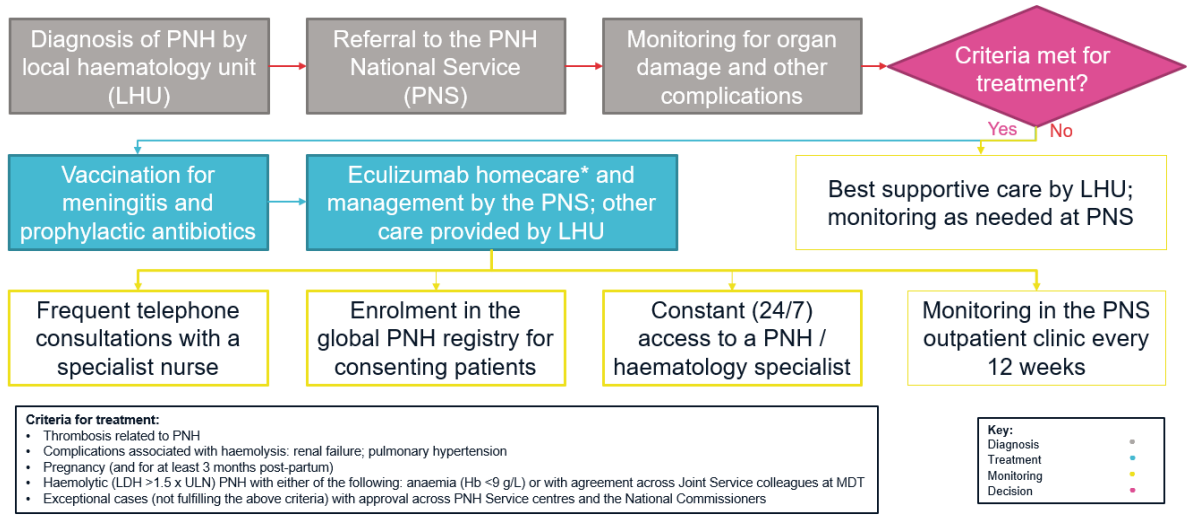
Breakthrough haemolysis can occur when the blood concentration of complement inhibitor is insufficient to provide complete C5 inhibition, or as a result of a concomitant complement-amplifying condition (CAC) such as pregnancy or infection.[1, 14, 16] Treatment with complement-inhibitors cannot prevent breakthrough haemolysis due to a CAC, it should prevent breakthrough haemolysis due to incomplete C5 inhibition. In confirmed cases of incomplete terminal complement inhibition, the PNH National Service recommend permanently increasing the dose of eculizumab to 1,200mg or higher if needed.[1, 17] According to UK data from the International PNH Registry (2 October 2018) and PNH National Service data (March 2019), approximately [redacted]% of patients treated in current practice are receiving a dose of eculizumab that is higher than the recommended 900mg.[1]

ERG comment: The extent to which breakthrough haemolysis occurs on higher doses of eculizumab and the clinical consequences of breakthrough haemolysis (e.g. incidence of thrombosis) remain unclear.

The CS also notes that eculizumab is associated with a high administration burden due to its relatively short half-life, with patients requiring bi-weekly infusions to maintain C5 inhibition.[1]

The proposed position of ravulizumab is as an alternative to eculizumab to address the remaining areas of unmet need described above.[1] Figure 2.1 shows the proposed treatment pathway for adult patients with PNH.[1]

Figure 2.1: The clinical pathway for adult patients with PNH



Source: Figure 1 of Document A

LDH = lactate dehydrogenase; LHU = local haematology unit; PNS = PNH National Service; PNH = paroxysmal nocturnal haemoglobinuria

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	Adults with paroxysmal nocturnal haemoglobinuria: • who have haemolysis with clinical symptom(s) indicative of high disease activity or • whose disease is clinically stable after having eculizumab for at least 6 months	Adults with paroxysmal nocturnal haemoglobinuria: • who have haemolysis with clinical symptom(s) indicative of high disease activity or • whose disease is clinically stable after having been treated with eculizumab for at least 6 months	Not applicable	The population is in line with the NICE scope
Intervention	Ravulizumab	Ravulizumab	Not applicable	The intervention is in line with the NICE scope
Comparator(s)	Eculizumab	Eculizumab	Not applicable	The comparators are in line with the NICE scope.
Outcomes	The outcome measures to be considered include: • overall survival • haemolysis (measured by lactate • dehydrogenase [LDH] level) • breakthrough haemolysis • transfusion avoidance • stabilised haemoglobin • thrombotic events • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • haemolysis (measured by lactate • dehydrogenase [LDH] level) • breakthrough haemolysis • transfusion avoidance • stabilised haemoglobin • thrombotic events • adverse effects of treatment • health-related quality of life	Overall survival was not a pre-specified endpoint in the ravulizumab trial programme, although deaths were captured as a safety outcome. Eculizumab has aligned the life expectancy of paroxysmal nocturnal haemoglobinuria patients to the general population such that the economic model uses standard mortality estimates. Health-related quality of life data collection was limited to patients in the ravulizumab trial programme. Thus,	The outcomes reported are in line with the NICE scope

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	(for patients and carers)	(for patients and carers)	health-related quality of life for carers is only considered in a qualitative sense and not captured in the economic model.	
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per QALY	Cost effectiveness is expressed in terms of incremental cost per QALY	Not applicable	The cost effectiveness analyses were conducted according to the NICE reference case.
Time horizon	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	A lifetime horizon (100 − mean age at baseline) was adopted to capture costs over a sufficient length of time and consistent with previous analyses in PNH	Not applicable	The time horizon selected by the company is appropriate.
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	Health effects, expressed in QALYs, based on EORTC QLQ-C30 data, mapped to EQ-5D-3L	Not applicable	Health effects are expressed in line with the NICE scope and according to the NICE reference case.

Source: CS, Table 1, page 7 (Document B0 and Table 3, pages 10-12 (Document A).

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-3L, three-level EQ-5D; HRQL, health-related quality of life; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; PSS, personal social services; QALY, quality-adjusted life years.

3.1 Population

The population defined in the scope is: Adults with paroxysmal nocturnal haemoglobinuria who have haemolysis with clinical symptom(s) indicative of high disease activity or whose disease is clinically stable after having eculizumab for at least six months.[18] This population is in line with the population in the CS, and with the license indication for ravulizumab (Ultomiris®) (CS, Table 2, page 10).[1]

See also Sections 4.2.2, 4.2.3 and 5.2.3 for the generalisability of the trial populations to UK patients.

3.2 Intervention

The intervention (ravulizumab) is in line with the scope.

Ravulizumab is administered by intravenous infusion. The dosing schedule consists of an initial loading dose, followed by maintenance dosing, starting two weeks after the loading dose. Dosage is determined by weight with a loading dose of 2400mg to 3000mg, and maintenance dose of 3000mg to 3600mg every eight weeks. Treatment is recommended to continue for the patient's lifetime, unless discontinuation is clinically indicated, for example, in the rare circumstance of spontaneous remission or recovery due to bone marrow transplant for underlying bone marrow failure. In trials ALXN1210-PNH-301 and ALXN1210-PNH-302 a loading dose of ravulizumab was given on Day 1 with maintenance doses on Days 15, 71 and 127.

According to the company, no additional tests are required prior to the administration of ravulizumab (CS, page 10).[1]

3.3 Comparators

Eculizumab is the only comparator specified in the NICE scope.[18]

In the treatment initiation phase, patients receive eculizumab 600mg via 25–45 minute intravenous infusion every week for the first four weeks.[9] In the treatment maintenance phase, patients receive eculizumab 900mg via 25–45 minute intravenous infusion every 14 ± 2 days. For patients in England, up to the first five eculizumab doses (often only the first dose) are administered at one of the PNH National Service centres, after which most patients choose to have treatment administered at their home through a homecare service.[10, 11] (CS, page 13-14).[1]

In UK clinical practice, an increased dose of eculizumab is used to manage BTH due to incomplete C5 inhibition. Data from the PNH national service indicate this is necessary for [redacted]% of the population (see CS, Section B.3.2.1), with most patients remaining stable on the licensed eculizumab dose (900mg). However, in the two ravulizumab trials included in the company submission, dose-escalation/up-dosing of eculizumab was not permitted (CS, page 89). According to the company: "[redacted]" (CS, page 145), and "*The lack of 'up-dosing' in the pivotal clinical trial programme compared with clinical practice may also result in slightly worse clinical outcomes for patients in the eculizumab arm of ALXN1210-PNH-301 and ALXN1210-PNH-302"* (CS, page 68).[1]

ERG comment: As the company states the lack of 'up-dosing' in the two trials compared with UK clinical practice may result in worse clinical outcomes for patients in the eculizumab arms. It is not clear how much effect the difference in dosing of eculizumab has. In theory it is possible that eculizumab administered at a dose that would be observed in UK clinical practice might even be more effective than ravulizumab. When asked about this in the clarification letter (Question A5), the company responded: "*UK clinical practice demonstrates that the majority of PNH patients (~ [redacted])*

are managed at the standard dose of eculizumab as per the marketing authorisation, i.e. 900mg every 2 weeks. This is also the dosing schedule that was applied in the pivotal clinical trial programme comparing ravulizumab with eculizumab. However, approximately [redacted]% of UK PNH patients require an eculizumab dosing adjustment to achieve complete terminal complement inhibition and prevent the symptoms of their PNH and accompanying haemolysis to recur….. Therefore, eculizumab administered at higher doses than the standard dose would not be more effective than ravulizumab, but would likely prevent the breakthrough haemolysis due to incomplete C5 inhibition events observed in the eculizumab arm of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials".[19]

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- Overall survival
- Haemolysis (measured by lactate dehydrogenase [LDH] level)
- Breakthrough haemolysis
- Transfusion avoidance
- Stabilised haemoglobin
- Thrombotic events
- Adverse effects of treatment
- Health-related quality of life (for patients and carers)

These were all assessed in the two included ravulizumab trials ALXN1210-PNH-301 and ALXN1210-PNH-302. Although, health-related quality of life data collection was limited to patients in the ravulizumab trial programme. Thus, health-related quality of life for carers is only considered in a qualitative sense and not captured in the economic model.

3.5 Other relevant factors

Ravulizumab was derived from eculizumab and the technologies share over 99% homology, in that sense ravulizumab is not an innovative technology. Nevertheless, the company states that "*the small differences in their design and administration have a substantial impact: alleviating the risk of breakthrough haemolysis associated with incomplete C5 inhibition, and reducing the frequency of regular infusions to 6–7 per year in the treatment maintenance phase (from 26 per year)*" (CS, Section B.12).[1] In addition, the company claims that health-related benefits are likely to exist outside of the formal QALY calculations, especially for carers.

A Patient Access Scheme (PAS) is in place between the Department of Health and the company (Alexion) for ravulizumab.

[redacted] (representing a discount of [redacted]% on the list price).

This appraisal does not fulfil the End-of-Life criteria as specified by NICE because the life expectancy of patients eligible for ravulizumab is well beyond 24 months. Therefore, treatment is not indicated for patients with a short life expectancy (normally less than 24 months). As stated by the company, "*Eculizumab has transformed the prognosis of patients with haemolytic PNH, significantly reducing progressive morbidity and aligning the life expectancy of patients to that of the general population*" (CS, page 14).[1]

According to the company, no equality issues are anticipated for the appraisal of ravulizumab (CS, Section B.1.4).

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D of Document B of the CS details a systematic literature review (SLR) conducted to identify the available clinical evidence for the current treatment options for adult patients with PNH. Searches were conducted on 31 January 2020, with a subsequent update on 2 July 2020. Searches were designed to only include terms relating to the population, study designs and adverse events. No language or publication date limits were reported. Databases were searched from date of inception. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the clinical effectiveness systematic review (as reported in CS and response to clarification)

	Resource	Host/source	Date ranges	Dates searched
Electronic databases	MEDLINE and Epub Ahead of Print, In-Process and Daily Versions	Ovid	1946-2020	(i) 31.1.20 (ii)2.7.20
	Embase	Ovid	1974-2020	(i) 31.1.20 (ii)2.7.20
	Cochrane CDSR	Ovid	2005-2020	(i) 31.1.20 (ii)2.7.20
	Cochrane CENTRAL	Ovid	2005-2020	(i) 31.1.20 (ii)2.7.20
	DARE	Ovid	Not provided	(i) 31.1.20 (ii)2.7.20
Conference proceedings	American Society of Hematology Annual Meeting	https://ashpublications.org/blood/issue/134/Supplement_1	2019	
		https://ashpublications.org/blood/issue/132/Supplement%201	2018	
		https://ashpublications.org/blood/issue/130/Supplement%201	2017	
	European Haematology Association Annual Meeting	https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=19379	2019	
		https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=18567	2018	
		https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=15847	2017	

ERG comments:

- Searches were undertaken to identify clinical effectiveness data. The CS provided sufficient details for the ERG to appraise the literature searches. A range of database and conference

proceedings were searched. Both the original and the update searches were overall well conducted and documented, making them transparent and reproducible. In response to clarification, it was confirmed that all databases were searched from inception.

- No date or language limits were unnecessarily applied to the database searches.
- Study design filters were applied but not appropriately referenced. In response to clarification, a link was provided to the ISSG search filters website but it was not clear which filters were used.
- Terms to identify adverse events were included and combined with the population which seemed appropriate.
- Only the population was searched for which seemed appropriate considering the sparsity of literature.
- Although thesaurus terms for the population were searched for, free text terms for the population were limited and it is possible that use of more synonyms, truncation and adjacency may have increased the retrieval of potentially relevant records.
- It was not reported if reference checking had been undertaken. Best practice outlined in the Cochrane Handbook states that, "Checking reference lists within eligible studies supplements other searching approaches and may reveal new studies, or confirm that the topic has been thoroughly searched."[20]

4.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for randomised controlled trials (RCTs) and non-RCTs is presented in Table 4.2.

Table 4.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult patients Diagnosis of PNH	Paediatric patients No diagnosis of PNH
Intervention	Ravulizumab Eculizumab Allogenic stem cell transplant Blood or erythrocyte transfusion Iron supplementation Folic acid supplementation Vitamin B12 supplementation Steroid or androgen therapy Anticoagulation Immunosuppressive treatment	Any intervention not listed for inclusion
Comparators	Any comparator	–
Outcomes	Any efficacy outcome Any safety outcome	No efficacy or safety outcomes reported
Study design	Randomised controlled trial Non-randomised controlled trial Single-arm trial Prospective observational study Retrospective observational study	Preclinical studies Case reports/series Editorials Commentaries and letters
Language restrictions	English	Non-English

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Source: CS, Appendix D, Table 2. PNH = paroxysmal nocturnal haemoglobinuria.		

ERG comment: The inclusion criteria are wider than the scope and cover a number of comparators not mentioned in the NICE scope. Therefore, the inclusion criteria are more than appropriate for this appraisal. However, only English language papers were included. This seems adequate for NICE appraisals but is not in line with best practice.

4.1.3 Critique of data extraction

Double data extraction was completed on the eligible studies and clinical study reports. Discrepancies were resolved through discussion until consensus was reached.[21] The extracted data included the study author and year of publication, study design and population, geographic location, baseline demographic characteristics, baseline clinical characteristics, sample size, intervention and comparator information, clinical outcomes, adverse events (AEs), serious adverse events (SAEs), and treatment-related adverse events (TRAEs). Of the clinical characteristics, the extracted information included breakthrough haemolysis, transfusion dependence, lactate dehydrogenase levels, haemoglobin levels, thrombotic events, and renal function.[21]

ERG comment: The ERG has no further comment on this matter.

4.1.4 Quality assessment

According to D.1.3 of the appendices of CS, the Cochrane Risk of Bias assessment tool for randomised trials or Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement for observational studies were utilised.

ERG comment: STROBE is not a risk of bias tool; it is a reporting guideline. Therefore, it would not be appropriate. However, as no non-RCTs were included this is not an issue.

4.1.5 Evidence synthesis

An evidence synthesis of ravulizumab studies was not appropriate according to the company, because the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials provide data for distinct populations: complement-inhibitor naïve and eculizumab exposed patients, respectively.

ERG comment: The ERG agrees that it is not appropriate to pool results from the two ravulizumab studies.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Included studies

The company identified two trials providing evidence of the clinical benefits of ravulizumab for the treatment of adult patients with PNH: ALXN1210-PNH-301 and ALXN1210-PNH-302, as summarised in Table 4.3. Both are non-inferiority, randomised controlled trials (RCTs) which were designed to show that ravulizumab was non-inferior to eculizumab. Both trials report outcomes of relevance to the decision problem and are used to populate the subsequent economic modelling.

Table 4.3: Clinical effectiveness evidence

	ALXN1210-PNH-301 NCT02946463	**ALXN1210-PNH-302 NCT03056040**
Study design	Phase III Open-label; parallel assignment. Non-inferiority	Phase III Open-label; parallel assignment. Non-inferiority
Population	Adult patients with PNH who are complement-inhibitor naïve	Adult patients with PNH who are clinically stable following ≥ 6 months treatment with eculizumab
Intervention(s)	Ravulizumab	Ravulizumab
Comparator(s)	Eculizumab	Eculizumab
Reported outcomes specified in the decision problem	Haemolysis (measured by LDH levels) **Breakthrough haemolysis** Transfusion avoidance Stabilised haemoglobin Thrombotic events **Adverse effects of treatment** **HRQL (for patients)**	Haemolysis (measured by LDH levels) **Breakthrough haemolysis** Transfusion avoidance Stabilised haemoglobin Thrombotic events **Adverse effects of treatment** **HRQL (for patients)**
All other reported outcomes	**Transfusion units** PK and PD endpoints	**Transfusion units** PK and PD endpoints
Complete published reports	Lee et al. 2019[22] Brodsky et al. 2020[23]	Kulasekararaj et al. 2019[24] Brodsky et al. 2020[23]
Regulatory materials	European Public Assessment Report[25] Summary of Product Characteristics[26]	European Public Assessment Report[25] Summary of Product Characteristics[26]
Clinical study reports	Clinical study report[27] 52-week data addendum[28]	Clinical study report[29] 52-week data addendum[30]

Source: CS, Table 4, pages 17-18.
HRQL = health-related quality of life; LDH = lactate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal haemoglobinuria;.
Notes: Outcomes in bold are those directly used in the economic modelling.

In addition, the company identified two earlier phase ravulizumab trials providing additional safety data on patients with PNH treated with ravulizumab, which are detailed in Section 4.2.6 of this report (see also (Appendix F of the CS).

4.2.2 Methodology of included studies

4.2.2.1 ALXN1210-PNH-301and ALXN1210-PNH-302

ALXN1210-PNH-301 and ALXN1210-PNH-302 were both open-label, multicentre, randomised active-controlled, non-inferiority studies. The populations differed between the two trials in that the ALXN1210-PNH 302 patients had to have been treated with eculizumab for PNH for at least six months, whereas patients in the ALXN1210-PNH-301 trial were complement-inhibitor naïve.

Both trials received the same loading doses of ravulizumab according to body weight. The trials differed in terms of comparator doses of eculizumab, due to the different populations enrolled. ALXN1210-PNH-301 utilised 600mg induction doses on Days 1, 8, 15, and 22 and then increased to 900mg maintenance doses afterwards, while the ALXN1210-PNH-302 trial delivered 900mg of eculizumab all throughout (as patients had received induction doses at least 6 months prior to enrolment). However, the utilised doses of eculizumab in both trials was stated not to fully reflect UK

clinical practice, which according to the CS, recommends a permanent escalation to at least 1200mg for maintenance dosing in the minority of patients for whom the licensed 900mg maintenance dosing does not provide complete complement inhibition. The ERG requested justification of why eculizumab administered at a dose that would be observed in UK clinical practice (i.e. allowing 'up-dosing' in patients with incomplete complement inhibition) might not be more effective than ravulizumab.

The company stated that the majority (about [redacted]%) of PNH patients in UK clinical practice managed at the standard eculizumab dose of 900mg every two weeks. The company noted in their response to clarification that up-dosing was not permitted in either trial. Further noting that patients in the ALXN1210-PNH-302 trial had been clinically stable for more than six months on eculizumab, which then identified the optimised dose for these patients at the study entry. The ERG also requested the company provide additional evidence regarding the effectiveness of eculizumab at a dose at or closer to one observed in UK clinical practice. The company stated that there was no published data available that could provide an overview of the effectiveness of the up-dosing eculizumab observed in the UK.

Details of the trial design, key inclusion criteria and outcomes for both trials are provided in Table 4.4.

The randomised period for both trials was 26 weeks, while the extension period was two years during which all patients were treated with ravulizumab. Both trials received a ravulizumab loading dose that was given on Day 1 (ranging from 2400- 3000mg based on patient body weight) with maintenance doses (ranging from 3000- 3600mg based on patient body weight) on Days 15, 71, and 127. In the ALXN1210-PNH-301 trial, eculizumab was administered as a 600mg induction dose on Days 1, 8, 15, and 22, followed by maintenance doses of 900mg on Days 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169. Whereas the ALXN1210-PNH-302 trial received 900mg doses of eculizumab on Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169. Use of complement inhibitors other than the randomised treatment was prohibited.

The co-primary efficacy endpoints of the ALXN1210-PNH-301 trial were transfusion avoidance (the proportion of patients who remained transfusion-free and did not require a transfusion per protocol-specified guidelines to Week 26) and haemolysis, measured by LDH-N (≤ 1 x ULN, from Day 29 to Day 183 (Week 26)). Details of other outcomes measured at Week 26 are shown in Table 4.4.

The primary efficacy endpoint for the ALXN1210-PNH-302 was percent change in LDH from baseline to Week 26. Details of other outcomes measured at Week 26 are shown in Table 4.4.

ERG comment: Multiple clarifications regarding the use of eculizumab as a comparator in either trial against UK clinical practice were required. According to the company the use of eculizumab up-dosing was not permitted in the trials. The company could not present evidence of the effectiveness of eculizumab at a dose at or closer to one that would be observed in UK clinical practice.

Table 4.4: Trial methods

	ALXN1210-PNH-301 **NCT02946463**	**ALXN1210-PNH-302** **NCT03056040**
Centres and randomisation	123 sites across 25 countries including the UK (N=246; [redacted] patients from England). Randomisation was 1:1 using computer-generated sequence (IVRS/IWRS), stratified into six groups based on patient's transfusion history (0, 1 to 14, or > 14 units of pRBCs in year prior to first dose of study drug) and screening LDH levels (1.5 to < 3 or ≥ 3 x ULN).	52 sites across 12 countries including the UK (N=195; [redacted] patients from England; [redacted] patients from Scotland). Randomisation was 1:1 using computer-generated sequence (IVRS/IWRS), stratified into two groups based on patient's transfusion history (received a transfusion of pRBCs in year prior to first dose of study drug, yes or no).
Trial periods	Screening Period: 4 weeks Randomised Period: 26 weeks Extension Period: up to 2 years Primary Evaluation Period includes Screening and Randomised. Extension Period, all patients received ravulizumab.	Screening Period: 4 weeks Randomised Period: 26 weeks Extension Period: up to 2 years Primary Evaluation Period includes Screening and Randomised. Extension Period, all patients received ravulizumab.
Inclusion criteria	1. Male or female, 18 years of age or older 2. Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation or RBCs and WBCs with granulocyte or monocyte clone size of ≥ 5% 3. Presence of one or more of the following PNH-related signs or symptoms within 3 months of screening: • Fatigue • Haemoglobinuria • Abdominal pain • Shortness of breath (dyspnoea) • Anaemia (haemoglobin < 10 g/dL) • History of major adverse vascular event, including thrombosis • Dysphagia • Erectile dysfunction	1. Male or female, 18 years of age or older 2. Treated with eculizumab according to the labelled dosing recommendation for PNH for at least six months prior to Day 1 3. LDH ≤ 1.5 x ULN at screening 4. Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation or RBCs and WBCs with granulocyte or monocyte clone size of ≥ 5% 5. Vaccinated against meningococcal infections within three years prior to, or at the time of, initiating study drug. Patients who initiated study drug treatment less than two weeks after receiving a meningococcal vaccine were required to have received treatment with appropriate prophylactic antibiotics until two weeks after vaccination 6. Female patients of childbearing potential and male patients with female partners of childbearing potential must have followed protocol-specified guidance for avoiding pregnancy

	ALXN1210-PNH-301 **NCT02946463**	**ALXN1210-PNH-302** **NCT03056040**
	• History of pRBC transfusion due to PNH 4. LDH ≥ 1.5 x ULN at screening 5. Vaccinated against meningococcal infections within three years prior to, or at the time of, initiating study drug. Patients who initiated study drug treatment less than two weeks after receiving a meningococcal vaccine were required to have received treatment with appropriate prophylactic antibiotics until two weeks after vaccination 6. Female patients of childbearing potential and male patients with female partners of childbearing potential must have followed protocol-specified guidance for avoiding pregnancy while on treatment	while on treatment
Main exclusion criteria	1. Current or previous treatment with a complement inhibitor 2. Platelet count < 30,000/mm^3 at screening 3. Absolute neutrophil count < 500/µl at screening 4. History of bone marrow transplantation 5. Body weight < 40kg at screening 6. History of *N. meningitidis* infection 7. History of unexplained, recurrent infection 8. Active systemic bacterial, viral or fungal infection within 14 days prior to study drug administration on Day 1	1. LDH value > 2 x ULN in the six months prior to Day 1 2. Major adverse vascular event in the six months prior to Day 1 3. Platelet count < 30,000/mm^3 at screening 4. Absolute neutrophil count < 500/µl at screening 5. History of bone marrow transplantation 6. Body weight < 40kg at screening 7. History of *N. meningitidis* infection 8. History of unexplained, recurrent infection 9. Active systemic bacterial, viral or fungal infection within 14 days prior to study drug administration on Day 1.
Primary outcomes	Co-primary efficacy endpoints: 1. Transfusion avoidance, defined as the proportion of patients who remained transfusion-free and did not require a transfusion per protocol-specified guidelines to Day 183 (Week 26) 2. Haemolysis as measured by LDH-N, defined as LDH levels ≤ 1 x ULN, from Days 29 to 183 (Week 26)	Primary efficacy endpoint: Percent change in LDH, from baseline to Day 183 (Week 26)
Secondary outcomes	Key secondary efficacy endpoints tested in a hierarchical manner:	Key secondary efficacy endpoints tested in a hierarchical

	ALXN1210-PNH-301 **NCT02946463**	**ALXN1210-PNH-302** **NCT03056040**
	1. Percentage change in LDH from baseline to Day 183 (Week 26) 2. Change in QoL assessed via the FACTIT-Fatigue Scale from baseline to Day 183 (Week 26) 3. Proportion of patients with BTH, defined as at least one new or worsening symptom or sign of intravascular haemolysis (including fatigue, haemoglobinuria, abdominal pain, shortness of breath, anaemia [Hb < 10 g/dL], major adverse vascular events, dysphagia or rectile dysfunction) in the presence of elevated LDH (defined as ≥ twice the ULN) 4. Proportion of patients with stabilised Hb, defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26) Safety including AEs, SAEs and ADAs	manner: 1. Proportion of patients with BTH, defined as at least one new or worsening symptom or sign of intravascular haemolysis (including fatigue, haemoglobinuria, abdominal pain, shortness of breath, anaemia [Hb < 10 g/dL], major adverse vascular events, dysphagia or erectile dysfunction) in the presence of elevated LDH (defined as ≥ twice the ULN) 2. Change in QoL assessed via the FACIT-Fatigue Scale from baseline to Day 183 (Week 26) 3. Transfusion avoidance, defined as the proportion of patients who remained transfusion-free and did not require a transfusion as per protocol-specified guidelines from baseline through Day 183 (Week 26) 4. Proportion of patients with stabilised Hb, defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26) Safety including AEs, SAEs and ADAs

Source: CS, Table 5.
ADA = antidrug antibodies, AE = adverse events, BTH = breakthrough haemolysis; Hb = haemoglobin; IVRS = interactive voice response system; IWRS = interactive web response system; LDH = lactate dehydrogenase; PNH = paroxysmal nocturnal haemoglobinuria; ULN = upper limit of normal.

4.2.3 Baseline characteristics

The baseline characteristics of the two included studies are presented in Table 4.5.

Table 4.5: Baseline patient characteristics

	ALXN1210-PNH-301		ALXN1210-PNH-302	
	Ravulizumab (n=125)	**Eculizumab (n=121)**	**Ravulizumab (n=97)**	**Eculizumab (n=98)**
Male, n (%)	65 (52.0)	69 (57.0)	50 (51.5)	48 (49.0)
Race, n (%)				
Asian	72 (57.6)	57 (47.1)	23 (23.7)	19 (19.4)
White/Caucasian	43 (34.4)	51 (42.1)	50 (51.5)	61 (62.2)
Black/African	2 (1.6)	4 (3.3)	5 (5.2)	3 (3.1)
American Indian/Alaska	1 (0.8)	1 (0.8)	–	–
Other/Unknown	7 (5.6)	8 (6.6)	19 (19.6)	15 (15.3)
Age at diagnosis				
Mean years (SD)	37.9 (14.9)	39.6 (16.7)	34.1 (14.4)	36.8 (14.1)
Age at first infusion				
Mean years (SD)	44.8 (15.2)	46.2 (16.2)	46.6 (14.4)	48.8 (14.0)
Years on eculizumab before study infusion, mean (SD)	NA	NA	6.0 (3.5)	5.6 (3.5)
Weight, mean kg (SD)	68.2 (15.6)	69.2 (14.9)	72.4 (16.8)	73.4 (14.6)
Weight at first infusion, % < 40 kg 40 to < 60 kg 60 to < 100 kg ≥ 100 kg Unknown	[redacted]	[redacted]	[redacted]	[redacted]
LDH, mean U/L (SD)[a]	1633.5 (778.8)	1578.3 (727.1)	228.0 (48.7)	235.2 (49.7)
LDH ratio, n (%) 1.5 to < 3 x ULN[a] ≥ 3 ULN	 18 (14.4) 107 (85.6)	 16 (13.2) 105 (86.6)	NA[b]	NA[b]
pRBC units received within 1 year prior to first dose, n (%)[c]				
0	23 (18.4)	21 (17.4)	84 (86.6)	86 (87.8)
1-14 units	102 (81.6)	100 (82.6)	13 (13.4)	12 (12.2)
>14 units	23 (18.4)	22 (18.2)	–	–
PNH clone size, mean % (SD)				
Type II RBCs[d]	12.4 (20.5)	13.7 (17.7)	14.9 (19.6)	16.3 (23.6)
Type III RBCs[d]	26.3 (17.2)	25.2 (16.9)	44.6 (30.5)	43.5 (29.7)
Total RBCs	38.4 (23.7)	38.7 (23.2)	60.6 (32.5)	59.5 (31.4)
Granulocytes	84.2 (21.0)	85.3 (19.0)	82.6 (23.6)	84.0 (21.4)
Monocytes	86.9 (18.1)	89.2 (15.2)	85.6 (20.5)	86.1 (19.7)
Haemoglobin, mean g/L (SD)[e]	[redacted]	[redacted]	[redacted]	[redacted]

	ALXN1210-PNH-301		ALXN1210-PNH-302	
	Ravulizumab (n=125)	Eculizumab (n=121)	Ravulizumab (n=97)	Eculizumab (n=98)
Haptoglobin, g/L (SD)[f]	[redacted]	[redacted]	[redacted]	[redacted]
History of MAVE, n (%)	17 (13.6)	25 (20.7)	28 (28.9)	22 (22.4)
History of aplastic anaemia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 6 of the CS
NA = not applicable; GPI = glycophosphatidylinositol; MAVE = major adverse vascular event; PNH = paroxysmal nocturnal haemoglobinuria; SD = standard deviation.
Notes: a) Normal range defined as 120–246 U/L, ULN defined as 246 U/L; b) patients enrolled to Study 302 had stable disease and thus LDH within normal range; c) randomisation strata; d) n = 124 for ravulizumab arm and n = 120 for eculizumab arm of Study 301; e) normal range defined as 11.5–16.0 g/dL for women and 13.0–17.5 g/dL for men; f) normal range defined as 0.4–2.4 g/dL.

Both trials were international trials with the majority of patients included from countries other than the UK. Therefore, there is a question about the generalisability of the trial populations to UK practice. In the ALXN1210-PNH-301 trial, 246 patients were included with [redacted] patients treated in England. In the ALXN1210-PNH-302 trial, 195 patients were included with [redacted] patients treated in England and [redacted] patients treated in Scotland.

To show that the clinical characteristics of patients enrolled in the two trials are generally comparable with those of UK patients, the company provided a comparison with characteristics of UK patients 'ever treated' according to International PNH Registry data. In the response to clarification (Question A16), the company provided the most up-to-date results from the International PNH Registry (June 2020 data (n=[redacted])).[19] However, these data were less complete than the 2019 data, provided in the CS and reproduced in the Table below (Table 4.6).

Table 4.6: Characteristics of patients enrolled in ravulizumab trials versus UK patients 'ever treated' in the International PNH Registry (up to 08 July 2019)

	ALXN1210-PNH-301 (n=246)	ALXN1210-PNH-302 (n=195)	UK patients ever treated (n=[redacted])
Male, n (%)	134 (54.4)	98 (50.3)	[redacted]
Race, n (%) Asian White/Caucasian Black/African American American Indian/Alaska Other/Unknown	 129 (52.4) 94 (38.2) 6 (2.4) 2 (0.8) 15 (6.1)	 42 (21.5) 111 (56.9) 8 (4.1) – 34 (17.4)	[redacted]
Age at diagnosis Mean	n=241 38.7 (15.8)	35.5 (14.3)	[redacted]

	ALXN1210-PNH-301 (n=246)	ALXN1210-PNH-302 (n=195)	UK patients ever treated (n=[redacted])
years (SD)			
Age at first infusion. Mean years (SD)	45.5 (15.7)	47.7 (14.2)	[redacted]
Weight, Mean kg (SD)	68.7 (15.2)	72.9 (15.7)	[redacted]
Weight at first infusion, % 40 to < 60 kg 60 to < 100 kg ≥ 100 kg	[redacted]	[redacted]	[redacted]
LDH Mean U/L (SD)[a]	1606.4 (752.7)	231.6 (49.2)	[redacted]
LDH ratio, n (%)[a] < 1.5 ≥ 1.5 x ULN	0 246 (100)	NA[b]	[redacted]
pRBC units received within 1 year of study entry or RBC transfusions, n (%)[c] 0 ≥ 1	44 (17.9) 202 (82.1)	170 (87.2) 25 (12.8)	[redacted]
History of major adverse vascular event, n (%)	42 (17.1)	50 (25.6)	[redacted]
History of aplastic anaemia (or	[redacted]	[redacted]	[redacted]

	ALXN1210-PNH-301 (n=246)	ALXN1210-PNH-302 (n=195)	UK patients ever treated (n=[redacted])
hypoplastic anaemia in registry), n (%)			

Sources: CS, Table 16, pages 66-67 and Response to Clarification, Question A16.
GPI = glycophosphatidylinositol; LDH = lactate dehydrogenase; PNH = paroxysmal nocturnal haemoglobinuria; pRBC = packed red blood cell; RBC = red blood cell; SD = standard deviation.
Notes: [a]) Normal range defined as 120–246 U/L = ULN defined as 246 U/L; [b]) patients enrolled to Study 302 had stable disease and thus LDH within normal range; [c]) randomisation strata for Study 301 and Study 302 and RBC transfusions ever received for registry data.

As can be seen from Table 4.6, there are some differences in baseline LDH levels, transfusion history and a history of MAVE or aplastic anaemia (all generally higher in the UK population). However, according to the company, "*these are likely due to differences in the management pathway at the time of study initiation/registry enrolment. There are no clear clinical indications that the clinical characteristics of patients enrolled in ALXN1210-PNH-301 and ALXN1210-PNH-302 are not generalizable to UK patients".*[1] Nevertheless, it is possible that patients included in the two trials have less severe disease than UK patients.

4.2.4 Statistical analyses

Details of the statistical analysis methods of ALXN1210-PNH-301 and 302 are provided in Table 4.7. Both trials were non-inferiority trials designed to show that ravulizumab was non-inferior (no worse than) eculizumab. ALXN1210-PNH-301 had two co-primary endpoints and both were required to show non-inferiority where the lower limit of the 95% confidence interval (CI) for the difference between ravulizumab and eculizumab lies above a predefined non-inferiority margin (NIM). ALXN1210-PNH-302 had just the one primary endpoint which was also used to demonstrate non-inferiority. The primary population for the efficacy analyses were the full analysis sets (FAS) defined as all randomised patients who received at least one dose of drug and had at least one efficacy assessment. Although this is not the full intention-to-treat (ITT) population, this is a standard dataset commonly used in trials.

Table 4.7: Statistical analysis methods

	ALXN1210-PNH-301 NCT02946463	**ALXN1210-PNH-302 NCT03056040**
Primary objective	To assess the non-inferiority of ravulizumab compared with eculizumab in adult patients with PNH who are complement-inhibitor naïve.	To assess the non-inferiority of ravulizumab compared with eculizumab in adult patients with PNH who are clinically stable following ≥6 months treatment with eculizumab.
Statistical testing	Non-inferiority was tested for co-primary efficacy endpoints, with a two-sided 95% CI calculated. Ravulizumab was concluded to be non-inferior to eculizumab if (i) the lower bound of the 95% CI for the difference in transfusion avoidance rate (ravulizumab–eculizumab) was greater than the NIM of -20% and (ii) the lower bound of the 95% CI for the odds ratio for LDH-N (ravulizumab vs eculizumab) was greater than 0.39. LDH-N analyses used a GEE model for repeated measures, adjusted for treatment, transfusion history and baseline LDH If non-inferiority was met for both co-primary endpoints, key secondary endpoints were tested using a closed-testing procedure in order of presentation of key secondary endpoints. Point estimates and two-sided 95% CIs were computed.	Non-inferiority was tested for the primary efficacy endpoint, with a two-sided 95% CI calculated. Ravulizumab was concluded to be non-inferior to eculizumab if the lower bound of the 95% CI for the difference (ravulizumab–eculizumab) was greater than the NIM of -15%. Analyses used a mixed-effect repeated measures model, adjusted for treatment, visit, treatment by visit interaction, transfusion history and baseline LDH. If non-inferiority was met for the primary endpoint, key secondary endpoints were tested using a closed-testing procedure in order of presentation of key secondary endpoints. Point estimates and two-sided 95% CIs were computed.
Power calculation	Approximately 214 patients were planned to be randomly assigned to ensure at least 193 evaluable patients (assumes ≤10% dropout). Using a NIM of 0.39 for the co-primary endpoint of LDH-N and a Type I error of 1-sided 2.5%, a minimum of 142 patients would be expected to provide 80% power to demonstrate non-inferiority of ravulizumab to eculizumab. Using a NIM of 20% for the co-primary endpoint of transfusion avoidance, a minimum of 193 patients would be expected to provide 80% power to demonstrate non-inferiority of ravulizumab to eculizumab. The NIMs were based on the TRIUMPH trial	Approximately 192 patients were planned to be randomly assigned to ensure at least 172 evaluable patients (assumes ≤10% dropout). Using a NIM of 15% for the primary endpoint, a Type I error of 1-sided 2.5% and SD of 30%, a minimum of 172 patients would be expected to provide 90% power to demonstrate non-inferiority of ravulizumab to eculizumab. The NIM was based on data from the company's PNH registry.
Analysis sets	**FAS:** all patients who received at least one dose of randomised treatment and had at least one efficacy assessment. **PP:** sensitivity population included patients who:	**FAS:** all patients who received at least one dose of randomised treatment and had at least one efficacy assessment. **PP:** sensitivity population included patients who:

	ALXN1210-PNH-301 NCT02946463	ALXN1210-PNH-302 NCT03056040
	• Missed no doses of ravulizumab or no more than one dose of eculizumab • Met inclusion criteria #2, 3 and 4 • Did not meet exclusion criteria #1, 2, 3 or 4 • Never received the wrong randomised treatment • Followed the protocol-specified transfusion guidelines. **Safety:** patients who received at least one dose of randomised treatment.	• Missed no doses of ravulizumab or no more than one dose of eculizumab • Met inclusion criteria #2, 3 and 4 • Did not meet exclusion criteria #1, 2, 3 or 4 • Never received the wrong randomised treatment • Followed the protocol-specified transfusion guidelines. **Safety:** patients who received at least one dose of randomised treatment.
Missing data	Missing data were not imputed for LDH-N. For transfusion avoidance, patients withdrawing due to lack of efficacy were considered non-responders and counted as requiring transfusion	Missing data were not imputed for percent change in LDH

Source: Table 7 of the CS.
BTH = breakthrough haemolysis; CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy; FAS = full analysis set; GEE = generalised estimating equation; Hb = haemoglobin; LDH-N = normalisation of lactate dehydrogenase levels; NIM = non-inferiority margin; PNH = paroxysmal nocturnal haemoglobinuria; PP = per protocol.

ERG comment: Both trials were designed as non-inferiority trials to show that ravulizumab was non-inferior to eculizumab at the end of the 26-week randomised trial period. They were not designed to show that ravulizumab was superior to eculizumab. The primary analyses of both were based on the effect size and 95% CI for the treatment difference or ratio of ravulizumab compared with eculizumab. If the lower limit of the 95% CI lay above the predefined non-inferiority margin, then it was concluded that ravulizumab was non-inferior to eculizumab. if noninferiority was established for all key secondary endpoints, then superiority was assessed using a closed-testing procedure using a 2-sided 0.05 test of significance for each parameter.

4.2.5 Results

The CS reported the summary of efficacy results from the randomised period for each trial in Table 8 of the CS, see Table 4.8 and Table 4.9 below. The submission also reported summary tables of efficacy results for each trial during the extension periods, which are provided in Table 4.10 and Table 4.11.

Table 4.8: Summary of efficacy results from ALXN1210-PNH-301: randomised period

	ALXN1210-PNH-301		
	Ravulizumab (n=125)	**Eculizumab (n=121)**	**Treatment effect (95% CI)**
Transfusion avoidance rate, % (95% CI)	73.6 (65.87, 81.33)	66.1 (57.68, 74.55)	6.8 (-4.66, 18.14)
LDH-normalisation rate, % (95% CI)	53.6 (45.9, 61.2)	49.4 (41.7, 57.0)	1.19 (0.80, 1.77)
Percent change in LDH, LSM (95% CI)	-76.84 (-79.96, -73.73)	-76.02 (-79.20, -72.83)	0.83 (-3.56, 5.21)
Change in FACIT-Fatigue score, LSM (95% CI)	7.07 (5.55, 8.60)	6.40 (4.85, 7.96)	0.67 (-1.21, 2.55)
≥ 3-point improvement in FACIT-Fatigue score, n (%)	77 (61.6)	71 (58.7)	2.2 (-9.9, 14.3)
Breakthrough haemolysis rate, % (95% CI)	4.0 (0.56, 7.44)	10.7 (5.23, 16.26)	6.7 (-0.18, 14.21)
Haemoglobin stabilisation rate, % (95% CI)	68.0 (59.82, 76.18)	64.5 (55.93, 72.99)	2.9 (-8.80, 14.64)
EORTC QLQ-C30 GHS/QOL Absolute change, mean (SD) ≥ 10-point improvement, n (%)	13.2 (21.4) n = 124 64 (51.2)	12.9 (21.8) n = 118 55 (45.5)	4.8 (-7.7, 17.1)
EORTC QLQ-C30 PF Absolute change, mean (SD) ≥ 10-point improvement, n (%)	13.2 (15.7) 60 (48.0)	11.5 (17.6) n=119 53 (43.8)	3.7 (-8.7, 16.0)
EORTC QLQ-C30 Fatigue Absolute change, mean (SD) ≥ 10-point improvement, n (%)	-20.2 (24.5) 92 (73.6)	-18.6 (24.5) n=119 77 (63.6)	9.1 (-2.5, 20.5)
Number (%) of patients who received any pRBC transfusions	32 (25.6)	40 (33.1)	–

	ALXN1210-PNH-301				
	Ravulizumab (n=125)		**Eculizumab (n=121)**		**Treatment effect (95% CI)**
Number of transfusions per patient, mean (SD)	3.3 (4.2)		3.6 (3.1)		–
Total number of pRBC units transfused per transfusion, mean (SD)	4.8 (5.1)		5.6 (5.9)		–
Patients with MAVE, n (%)	2 (1.6)		1 (0.8)		–
Clinical manifestations of PNH, %	BL	D183	BL n=119	D183 n=119	
Fatigue	64.0	28.8	63.9	30.3	–
Abdominal pain	13.6	4.8	12.6	5.0	
Dyspnoea	33.6	14.4	31.9	14.3	
Dysphagia	10.4	2.4	13.4	0.8	
Chest pain	4.0	2.4	14.3	5.9	
Haemoglobinuria	56.8	10.4	47.5	9.3	
Erectile dysfunction	12.8	8.0	17.6	4.2	

Source: Based on Table 8 of the CS.
BL= baseline; CI = confidence interval; D183 = Day 183; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT = Functional Assessment of Chronic Illness Therapy; FAS = full analysis set; GHS = global health score; LDH = lactate dehydrogenase; LSM = least squares mean; MAVE = major adverse vascular event; PF = physical function; PNH = paroxysmal nocturnal haemoglobinuria; pRBC = packed red blood cells; SD = standard deviation; QOL = quality of life.

Table 4.9: Summary of efficacy results from ALXN1210-PNH-302: randomised period

	ALXN1210-PNH-302		
	Ravulizumab (n=97)	**Eculizumab (n=98)**	**Treatment effect (95% CI)**
Transfusion avoidance rate, % (95% CI)	87.6 (81.1, 94.2)	82.7 (75.2, 90.2)	5.5 (-4.3, 15.7)
LDH-normalisation rate, % (95% CI)	66.0[b]	59.2[b]	–
Percent change in LDH, LSM (95% CI)	-0.82 (-7.8, 6.1)	8.4 (1.5, 15.3)	9.21 (-0.42, 18.8)
Change in FACIT-Fatigue score, LSM (95% CI)	2.0 (0.6, 3.4)	0.54 (-0.8, 1.9)	1.5 (-0.2, 3.2)
≥ 3-point improvement in FACIT-Fatigue score, n (%)	36 (37.1)	33 (33.7)	–
Breakthrough haemolysis rate, % (95% CI)	0 (0, 3.7)	5.1 (1.7, 11.5)	5.1 (-8.9, 19.0)
Haemoglobin stabilisation rate, % (95% CI)	76.3 (67.8, 84.8)	75.5 (67.0, 84.0)	1.4 (-10.4, 13.3)
EORTC QLQ-C30 GHS/QOL Absolute change, mean (SD) ≥ 10-point improvement, n (%)	1.15 (16.51) 18 (18.6)	-1.93 (15.34) 14 (14.3)	4.2 (-6.6, 15.0)
EORTC QLQ-C30 PF Absolute change, mean (SD) ≥ 10-point improvement, n (%)	3.26 (8.71) 21 (21.6)	1.20 (8.89) 12 (12.2)	9.1 (-1.9, 19.7)
EORTC QLQ-C30 Fatigue Absolute change, mean (SD) ≥ 10-point improvement, n (%)	 -4.97 (17.26) 41 (42.3)	 -0.71 (15.27) 31 (31.6)	 9.6 (-4.1, 22.9)
Number (%) of patients who received any pRBC transfusions	10 (10.3)	14 (14.3)	–

	ALXN1210-PNH-302				
	Ravulizumab (n=97)		**Eculizumab (n=98)**		**Treatment effect (95% CI)**
Number of transfusions per patient, mean (SD)	2.7 (2.8)		2.0 (1.3)		–
Total number of pRBC units transfused per transfusion, mean (SD)	4.3 (4.8)		3.4 (3.0)		–
Patients with MAVE, n (%)	0		0		–
Clinical manifestations of PNH, %	BL n=96	D183 n=96	BL n=95	D183 n=95	
Fatigue	30.2	43.8	40.0	37.9	–
Abdominal pain	5.2	5.2	6.3	12.6	
Dyspnoea	6.3	6.3	10.5	17.9	
Dysphagia	2.1	5.2	2.1	5.2	
Chest pain	0	2.1	1.1	5.2	
Haemoglobinuria	4.2	8.3	7.4	9.5	
Erectile dysfunction	10.0	12.0	14.6	12.5	

Source: Based on Table 8 of the CS.
BL = baseline; CI = confidence interval; D183 = Day 183; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT = Functional Assessment of Chronic Illness Therapy; FAS = full analysis set; GHS = global health score; LDH = lactate dehydrogenase; LSM = least squares mean; MAVE = major adverse vascular event; PF = physical function; PNH = paroxysmal nocturnal haemoglobinuria; pRBC = packed red blood cells; SD = standard deviation; QOL = quality of life.

Table 4.10: Summary table of efficacy results from ALXN1210-PNH-301: extension period up to 52 weeks

	ALXN1210-PNH-301			
	Ravulizumab to ravulizumab (n=124)		Eculizumab to ravulizumab (n=119)	
	0–26 weeks	27–52 weeks	0–26 weeks	27–52 weeks
Transfusion avoidance, n (%)	92 (73.6)	95 (76.6)	79 (66.4)	80 (67.2)
LDH-normalisation, n (%)	60 (48.4)	54 (43.6)	50 (42.1)	48 (40.4)
Percent change in LDH, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change in FACIT-Fatigue score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Breakthrough haemolysis, n (%)	5 (4.0)	4 (3.2)	13 (10.7)	2 (1.7)
Haemoglobin stabilisation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase.

Table 4.11: Summary table of efficacy results from ALXN1210-PNH-302: extension period up to 52 weeks

	ALXN1210-PNH-302			
	Ravulizumab to ravulizumab		Eculizumab to ravulizumab	
	0–26 weeks (n=97)	27–52 weeks (n=96)	0–26 weeks (n=98)	27–52 weeks (n=95)
Transfusion avoidance, n (%)	85 (87.6)	83 (86.5)	81 (82.7)	79 (83.2)
LDH-normalisation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Percent change in LDH, Mean (SD)	2.9 (26)	8.8 (29)	6.5 (31)	5.8 (27)
Change in FACIT-Fatigue score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Breakthrough haemolysis, n (%)	0	3 (3.1)	5 (5.1)	1 (1.1)
Haemoglobin stabilisation, n (%)	74 (76.3)	78 (81.2)	74 (75.5)	77 (81.1)

FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase.

ERG comment: Both trials met their primary objective and demonstrated that ravulizumab was non-inferior to eculizumab in terms of transfusion avoidance rate and LDH-N (ALXN1210-PNH-301) and percentage change in LDH (ALXN1210-PNH-302). Although the point estimates for the primary and secondary outcomes were in favour of ravulizumab none of the results were statistically significant. However, data are relatively immature in that they currently provide randomised data for up to 26 weeks for a chronic condition requiring lifelong treatment. In addition, the lack of 'up-dosing' in the two trials compared with UK clinical practice may result in worse clinical outcomes for patients in the eculizumab arms; the effect of this is unclear.

4.2.6 Adverse events

Both trials reported low infusion interruptions during the randomised period. In the ALXN1210-PNH-301 trial of the 125 ravulizumab patients, 110 experienced an adverse event, whereas of the 121 eculizumab patients, 105 experienced an adverse event. In the ALXN1210-PNH-302 trial, 85 of the 97 ravulizumab patients experienced an adverse event, while 86 of the 98 eculizumab patients experienced an adverse event. The most common reported adverse events for both trials included headache, nasopharyngitis, nausea, upper respiratory tract infection (URTI), and pyrexia. In the ALXN1210-PNH-301 trial, an SAE was experienced by 11 of the ravulizumab patients and nine of the eculizumab patients, whereas in the ALXN1210-PNH-302 trial an SAE was experienced by four of the ravulizumab patients and eight of the eculizumab patients.

In the extension period of the ALXN1210-PNH-301 trial the number of participants in the ravulizumab group who experienced an AE was 79. The number of participants who had experienced an AE who had switched from eculizumab to ravulizumab during the extension period was 89. The most experienced AEs included headache, URTI, pyrexia, and nasopharyngitis. The CS states ravulizumab to be well tolerated among complement-inhibitor naïve patients. In the ALXN1210-PNH-302 trial, 76 patients from the ravulizumab group were noted to have experienced an AE, whereas in the group of patients who switched from eculizumab to ravulizumab 71 patients experienced an AE. In this trial the most commonly experienced AEs during the extension period included headache, URTI, pyrexia, nasopharyngitis, and fatigue. There was one reported death among both trials, which was deemed to be unrelated to treatment. The company emphasised that ravulizumab appeared similar to eculizumab in terms of safety.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

An indirect treatment comparison was not required as the two included trials provide head-to-head data regarding ravulizumab and eculizumab.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

An indirect treatment comparison was not required as the two included trials provide head-to-head data regarding ravulizumab and eculizumab.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The considered population of adults with paroxysmal nocturnal haemoglobinuria who have haemolysis with clinical symptoms indicative of high disease activity or whose disease is clinically stable after having eculizumab for at least six months is in line with the scope. The intervention, and

listed outcomes are also in line with the scope. There is, however, a discrepancy between the comparator in the scope and the comparator as delivered in the ravulizumab trials. This is that in the scope eculizumab is as would be delivered in UK clinical practice, which permits up-dosing to manage BTH due to incomplete C5 inhibition, whereas in the trials up-dosing was not permitted. It is unclear what the impact of this would be on the relative effectiveness of ravulizumab versus eculizumab.

The company identified two randomised trials. The ALXN1210-PNH-301 trial was designed to assess the non-inferiority of ravulizumab compared with eculizumab in adult patients with PNH who are complement-inhibitor naïve. The ALXN1210-PNH-302 trial was designed to assess the non-inferiority of ravulizumab compared with eculizumab in adult patients with PNH who are clinically stable following six or more months of treatment with eculizumab.

- ALXN1210-PNH-301: An open-label, randomised, active-controlled, multicentre study, which compared ravulizumab to eculizumab during a 26-week randomisation period followed by an extension period which lasted up to two years. The study was conducted in Argentina, Australia, Austria, Belgium, Brazil, Canada, Czechia, Estonia, France, Germany, Italy, Japan, Korea, Malaysia, Mexico, Poland, Russia, Singapore, Spain, Sweden, Taiwan, Thailand, Turkey, UK, and USA.
- ALXN1210-PNH-302: An open-label, randomised, active-controlled, multicentre study, which compared ravulizumab to eculizumab during a 26-week randomisation period followed by an extension period which lasted up to two years. The study was conducted in Australia, Canada, France, Germany, Italy, Japan, Korea, Netherlands, Spain, UK, and USA.

The ERG notes that the populations of the two trials had distinct differences. The ALXN1210-PNH-301 trial included a population comprised of adult patients with PNH who are complement-inhibitor naïve, whereas the patients in the ALXN1210-PNH-302 trial had PNH who were clinically stable following six or more months of treatment with eculizumab. Due to this, a meta-analysis was not appropriate.

Ravulizumab was found to be non-inferior to eculizumab for the primary outcomes of both the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials. Although the point estimates for the primary and secondary outcomes were in favour of ravulizumab none of the results were statistically significant. However, data are relatively immature in that they currently provide data for up to 26 weeks for a chronic condition requiring lifelong treatment. In addition, the lack of ‘up-dosing’ in the two trials compared with UK clinical practice may result in worse clinical outcomes for patients in the eculizumab arms; the effect of this is unclear. Ravulizumab appeared similar to eculizumab in terms of safety.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

Appendix G of Document B detail an SLR conducted to identify all economic, HRQoL and resource use outcomes literature on patients with PNH.[21] Searches were run on 3 February 2020 and updated on 2 July 2020. No language or publication date limits were reported. In response to clarification, it was confirmed that all databases were searched from inception to time of search.[19] A summary of the sources searched is provided in Table 5.1.

Table 5.1: Data sources for the cost effectiveness systematic review (as reported in CS and response to clarification)

	Resource	Host/source	Date range	Date searched
Electronic databases	MEDLINE and Epub Ahead of Print, In-Process and Daily Versions	Ovid	1946-2020	(i)3.2.20 (ii)2.7.20
	Embase	1974-2020	1974-2020	(i)3.2.20 (ii)2.7.20
	Health Technology Assessment Database	Ovid	Not provided	(i)3.2.20 (ii)2.7.20
	NHS EED	Ovid	Not provided	(i)3.2.20 (ii)2.7.20
	EconLit	EBSCO	1969-2020	(i)3.2.20 (ii)2.7.20
	Cochrane Central Register of Controlled Trials	Ovid	2005-2020	(i)3.2.20 (ii)2.7.20
	Cochrane Database of Systematic Reviews	Ovid	2005-2020	(i)3.2.20 (ii)2.7.20
	Database of Abstracts of Reviews of Effects	Ovid	2005-2020	(i)3.2.20 (ii)2.7.20
Conference proceedings	American Society of Hematology Annual Meeting	https://ashpublications.org/blood/issue/134/Supplement_1	2019	
		https://ashpublications.org/blood/issue/132/Supplement%201	2018	
		https://ashpublications.org/blood/iss	2017	

	Resource	Host/source	Date range	Date searched
		ue/130/Supplement%201		
	European Haematology Association Annual Meeting	https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=19379	2019	
		https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=18567	2018	
		https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=15847	2017	
Additional resources	Scottish Medicines Consortium			

ERG comments:

- Individual searches were undertaken for an SLR to identify all cost effectiveness, HRQoL and cost and resource use studies. The CS provided sufficient details for the ERG to appraise the literature searches. A range of databases and conference proceedings were searched and the Scottish Medicines Consortium. The original and the update searches were overall well conducted and were transparent and reproducible.
- No date or language limits were unnecessarily applied to the database searches.
- Study design filters were applied but not appropriately referenced. In response to clarification, a link was provided to the ISSG search filters website but it was not clear which filters were used.[19]
- As with clinical effectiveness searches, more synonyms and use of truncation and adjacency for the population terms may have increased the yield.

5.1.2 Inclusion/exclusion criteria used in the study selection

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 5.2.

Table 5.2: Eligibility criteria used for the systematic literature review

PICOS	Inclusion criteria	Exclusion criteria
Patient population	Individuals with paroxysmal nocturnal haemoglobinuria	Children
Interventions	Eculizumab	Non-interventional
	Ravulizumab	
	Allogeneic stem cell transplantation	
	Blood or erythrocyte transfusion	
	Iron supplementation	
	Folic acid supplementation	
	Vitamin B12 supplementation	
	Steroid or androgen therapy	
	Anticoagulation	

PICOS	Inclusion criteria	Exclusion criteria
	Immunosuppressive treatment	
Comparators	Costs	Clinical outcomes
	Resource use	
	Utilities or HRQoL	
	Cost effectiveness	
Study Design	Economic studies	Animal studies
	Randomised controlled trials	Individual case reports
	Prospective or retrospective observational studies	Letters
		Commentaries
		Abstracts
		Reviews
Language restrictions	English only	Non-English
Abbreviations: HRQL, health-related quality of life; PNH, paroxysmal nocturnal haemoglobinuria.		

ERG comment: The eligibility criteria used by the company provide sufficient detail.

5.1.3 Identified studies

The company identified 339 records in the SLR, of which 21 met the inclusion criteria (Figure 6 of Appendix G of the CS).[21] After considering grey literature, three more studies were included. Of the 24 included, six reported outcomes of cost effectiveness (and met all other inclusion criteria relating to population, intervention, comparator and study design). Of these, two cost effectiveness models were identified that specifically assessed the cost effectiveness of ravulizumab compared with eculizumab for the treatment of PNH.

ERG comment: The company's reasoning for excluding cost effectiveness studies are considered appropriate given the defined in- and exclusion criteria. In the CS, two identified cost effectiveness models[31, 32] assessed the cost effectiveness of ravulizumab compared with eculizumab for the treatment of PNH. In the response to the clarification letter, the company explained that the published models and the company's model differ and that the identified studies do not address the current decision problem.[19]

5.1.4 Interpretation of the review

The CS provided an overview of the included cost effectiveness, utility and resource use and costs studies. None of the identified cost effectiveness studies were directly generalisable to the NICE decision problem.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

A summary of the economic evaluation conducted by the company is presented in Table 5.3.

Table 5.3: Summary of the company submission economic evaluation

	Approach	Source/justification in the company submission	Signpost (location in ERG report)
Model	The company developed in Excel a state transition model with 10 health states. The health states included in the model correspond to eight BTH-related health states, a mortality-related health state, and a spontaneous-remission health state.	The model captures the costs and consequences of the clinical events associated with PNH. The cost effectiveness model used in the studies by O'Connell et al. is similar to the one used in this appraisal.[32] However, the O'Connell model and the submitted model differ in the application of specific parameters and also the relevance of others to the NICE decision problem.	Section 5.2.2.
States and events	The health states included in the model correspond to eight BTH-related health states, one mortality-related health state, and a spontaneous-remission health state. Patients start the simulation in the 'No BTH' health state, from which they may transition to the BTH event health states (CAC-related or incomplete C5 inhibition-related) or die. The model can distinguish between first, second and subsequent incomplete C5 inhibition-related BTH events. After a second subsequent incomplete C5 inhibition-related BTH events, patients may transition to health states where they are treated with continuous eculizumab up-dosing. In the continuous eculizumab up-dose health states, only CAC-related BTH events are possible. Spontaneous remission is included for completeness but only used in scenario analyses.	The model is built in such a way that it is possible to model eculizumab up-dosing, even though this was not allowed in the clinical trials ALXN1210-PNH-301 and ALXN1210-PNH-302, to be more reflective of UK clinical practice. This functionality can be easily 'switched-off' to allow running the model under the clinical trial settings (no eculizumab up-dose).	Section 5.2.2.
Comparators	The comparator is eculizumab. In the company's base-case analysis, all patients start the simulation on the licensed 900mg eculizumab dose. A continuous up-dosing (1200mg and above) following two incomplete C5 inhibition-related BTH events was assumed. In the company's "equal effectiveness" scenario, [redacted]% of the patients start the simulation on a higher than licensed dose (1200mg and above) of eculizumab,	In ALXN1210-PNH-301 and ALXN1210-PNH-302 all patients received the licensed 900mg eculizumab dose and eculizumab dose-escalation/up-dosing was not permitted. In UK clinical practice, an increased dose of eculizumab is used to manage BTH due to incomplete C5 inhibition. The proportion of patients receiving a higher than license dose (1200 mg and above) of eculizumab was estimated as [redacted]% based on PNH national service data.[17]	Section 5.2.4.

	Approach	Source/justification in the company submission	Signpost (location in ERG report)
	while the rest of patients start on the licensed eculizumab dose (900mg).		
Natural history	PNH is caused by an acquired mutation in the *PIG-A* gene in haematopoietic stem cells,[1, 2 3] that results in a partial or absolute deficiency in proteins linked to the cell membrane by a glycosylphosphatidylinositol anchor. PNH is a rare condition, with an estimated 725 diagnosed cases in the UK (2018 figures).[4] PNH is a progressive, life-threatening haematological disorder that is characterised by uncontrolled activation of the terminal complement pathway, which can lead to intravascular haemolysis, anaphylaxis, inflammation and thrombosis.[1] The CS states that, *'without complement-inhibitor treatment, the majority of patients (up to 75%) die within 20 years of diagnosis, and the median survival time is estimated at approximately 10 years (from diagnosis)'*.[1, 5]		Section 2.2
Treatment effectiveness	The company used the data and the outcomes assessed in the pivotal trials ALXN1210-PNH-301 and ALXN1210-PNH-302. Patient-visit-level data was used to estimate the transition probabilities for each health state. A base-case analysis and an equal effectiveness scenario were developed by the company. In the latter, patients in the eculizumab arm receiving a clinically stable dose – and not the licensed dose (900mg) given in the pivotal trials – were assumed not to experience BTH due to incomplete C5 inhibition. Therefore, events other than incomplete C5 inhibitor-related BTH were assumed to be equal across arms, as per the ravulizumab arm.	The outcomes assessed in the trials were chosen as representative of the health-related benefits and potential side-effects expected with ravulizumab treatment in practice. The assumption of equal effectiveness when dosing of eculizumab is adopted as per UK clinical practice (i.e. no incomplete C5 inhibition-related BTH events in either arm) was considered clinically plausible.	Section 5.2.6

	Approach	Source/justification in the company submission	Signpost (location in ERG report)
Adverse events	Adverse events (AEs) were not included in the economic model.	EMA concluded that ravulizumab safety profile appeared to be similar to that of eculizumab. AEs observed in the clinical trials (headache and nasopharyngitis) were not considered for modelling purposes, as it was assumed to have a negligible impact on the cost effectiveness analysis.	Section 5.2.7
Health-related QoL	The company estimated utility values for events from mixed-effects regression models on the trial data. No significant HRQoL/utility benefit was obtained for frequency of administration, but the direction of the coefficient was in favour of ravulizumab. Results from a DCE were used to estimate treatment benefit of ravulizumab due to lower frequency administration.	The company argues that in ALXN1210-PNH-301 and ALXN1210-PNH-302 the benefit of reduced frequency of administration could not be measured as patients were still required, due to the trial protocol, to visit the study site.	Section 5.2.8
Resource utilisation and costs	A survey was developed to estimate inputs about the rates and causes of BTH and medical management for BTH in four categories: general ward hospitalisation, intensive care unit hospitalisation, medication and dialysis. Treatment acquisition costs, monitoring costs, health state costs, and miscellaneous costs for meningococcal infections and prophylactic antibiotics were included.	In the absence of resource use data, it is appropriate to source inputs from the survey. Unit prices were based on the NHS reference prices, British National Formulary, and Personal Social Services Research Unit.	Section 5.2.9
Discount rates	Cost and health outcomes discounted at 3.5%	As per NICE reference case	Section 5.2.5
Sensitivity analysis	Probabilistic, deterministic one-way sensitivity analysis and scenario analyses conducted	As per NICE reference case	Section 6.2

Based on the CS.[1]
AE = adverse event; BTH = breakthrough haemolysis; CS = company submission; DCE = discrete choice experiment; EMA = European Medicines Agency; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PNH = paroxysmal nocturnal haemoglobinuria; PSS = Personal Social Services; UK = United Kingdom

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.4: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	Direct health effects for patients included.
Perspective on costs	NHS and PSS.	NHS and PSS perspective taken.
Type of economic evaluation	Cost utility analysis with fully incremental analysis.	Cost utility analysis with fully incremental analysis undertaken.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	The model time horizon of 55 years for Cohort 1 and 52 years for Cohorts 2 and 3 is appropriate for a lifetime horizon. The average age of patients at the start of the simulation is 45 and 48 years, respectively.
Synthesis of evidence on health effects	Based on systematic review.	Systematic review conducted to identify additional evidence on health effects beyond trial data. However, none of the economic evaluations identified were conducted from a UK perspective.
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.	Health effects were expressed in QALYs. The EORTC QLQ-C30 was used to measure HRQoL in the ALXN1210-PNH-301 and ALXN1210-PNH-302 studies and mapped to EQ-5D-3L using the Longworth (2014) mapping algorithm.[33]
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	Obtained through a discrete choice experiment [redacted]

Element of health technology assessment	Reference case	ERG comment on company's submission
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	Representative sample of the UK population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No equity issues have been identified.
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.	The model includes the costs that relate to NHS and PSS resources, valued using the prices relevant to the NHS and PSS.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	Costs and health effects are discounted at 3.5%.

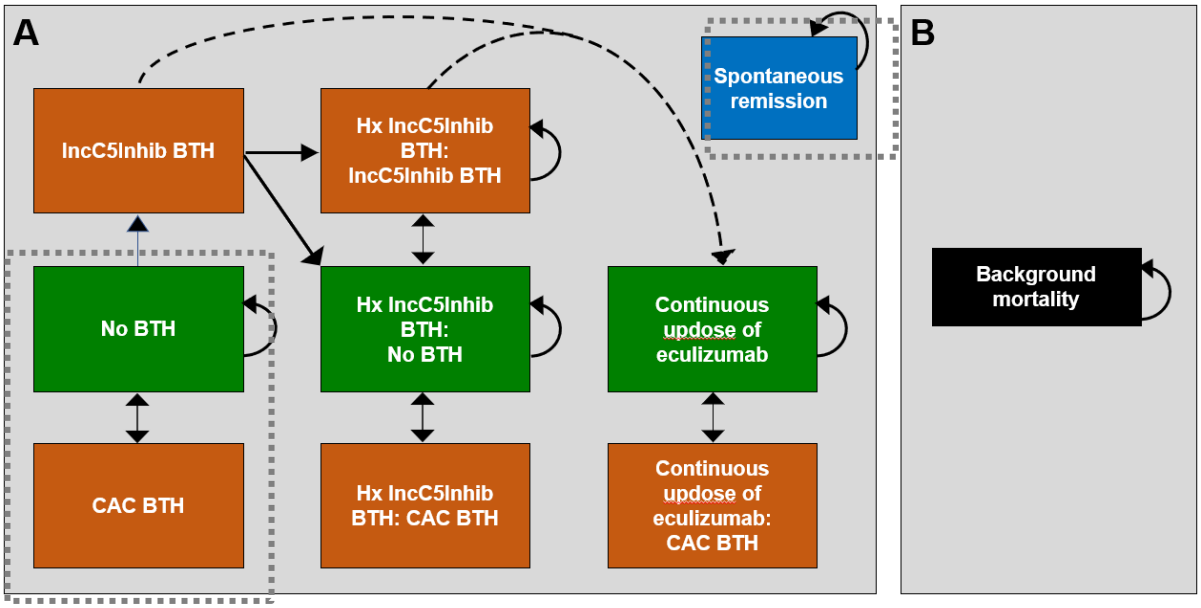
Abbreviations: EQ-5D = European Quality of Life-5 Dimensions; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ERG = Evidence Review Group; HRQoL = health related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality adjusted life year; UK = United Kingdom

5.2.2 Model structure

The company developed a state transition model in Excel with 10 health states. A schematic representation of the model is shown in Figure 5.1. The health states included in the model correspond to eight BTH-related health states, one mortality-related health state, and a spontaneous-remission health state. A detailed description of the health states is provided below. The model uses a cycle length of two weeks, which corresponds to the data collection time points in ALXN1210-PNH-301 and ALXN1210-PNH-302, and the treatment schedule for eculizumab. Given the short cycle length, the company did not apply a half-cycle correction to the model results. Costs and utilities are applied to each health state of the model (except death) to calculate per-cycle costs and quality adjusted life-years (QALYs).

ERG comment: The model captures the costs and consequences of the clinical events associated with PNH and its structure was deemed appropriate by experts consulted by the company at a July 2018 Advisory Board meeting.[16] The cost effectiveness model used in the studies by O'Connell et al. was similar to the one used in this appraisal.[31, 32]

Figure 5.1: Schematic representation of the model structure



Source: Figure 14 in CS.[1]
Abbreviations: BTH = breakthrough haemolysis; CAC = complement-amplifying condition; Hx = history of; IncC5Inhib = incomplete C5 inhibitor.

BTH-related health states

As explained in Section 2.3 of this report, two main types of BTH events were considered in ALXN1210-PNH-301 and ALXN1210-PNH-302: incomplete C5 inhibitor-related BTH and CAC-related BTH. Additionally, an undetermined BTH event was defined as those "*deemed to have neither incomplete C5 inhibition nor concomitant infection*" and, since undetermined events did not show free or high C5 levels, the clinical experts consulted by the company were "*confident that these events were not incomplete C5 inhibition-related BTH events*".[1] Even though a CAC was not reported, the experts considered that the cause of the event might not have been adequately captured and, therefore, a CAC-related cause was not ruled out. Based on this, the company modelled undetermined BTH events as CAC-related BTH events. Transition probabilities were estimated from ALXN1210-PNH-301 and ALXN1210-PNH-302 data. Further details are provided in Section 5.2.6 and Appendix 1.

ERG comment: Based on the information presented in the CS, the ERG is unclear how patients with undetermined BTH events were treated in the clinical trials. This was part of clarification question B11, but no clear answer regarding undetermined BTH events was provided.[19] Therefore, the ERG is unable to judge the appropriateness of modelling undetermined BTH events as CAC-related BTH events. If undetermined BTH events were indeed treated as CAC-related events, then the ERG would agree with this assumption. Otherwise, it would be more appropriate to model undetermined BTH events separately.

Up-dosing due to BTH

As explained in Section 3.3 of this report, in UK clinical practice, an increased dose of eculizumab is used to manage BTH due to incomplete C5 inhibition. However, eculizumab dosing changes were not allowed in ALXN1210-PNH-301 and ALXN1210-PNH-302. In order to include eculizumab up-dosing in the economic model, the following assumptions were made:

- CAC-related BTH events (base-case analysis and "equal effectiveness" scenario):
    - In the eculizumab arm, one single up-dose was required to re-establish the blockade.[16]

  - In the ravulizumab arm, an additional dose of eculizumab, as opposed to ravulizumab, was assumed because there are no available data on the effectiveness or safety of up-dosing ravulizumab. The latter assumption was "*discussed and felt to be appropriate as a potential treatment strategy in the December 2018 Advisory Board meeting*" held by the company.[11]
- Incomplete C5 inhibition-related BTH events (base-case analysis):
  - In the eculizumab arm, a permanent (continuous) eculizumab up-dosing was assumed, as this was considered to be in line with the management algorithm adopted in UK clinical practice by the clinical experts consulted by the company.[11] The continuous up-dosing was assumed for the rest of the model time horizon after a second incomplete C5 inhibition-related BTH event. For the first and second incomplete C5 inhibition-related BTH event, a single up-dose was assumed, similar to the approach used for treating CAC-related BTH events.
  - In the ravulizumab arm, continuous up-dosing to resolve incomplete C5 inhibition-related events was not needed because incomplete C5 inhibition-related events were not observed in the ravulizumab arm in either of the clinical trials. Therefore, in the model it is assumed that these events do not occur in the ravulizumab arm.

ERG comment: In order to model UK clinical practice, where eculizumab up-dosing is used, the company made the assumptions presented above. While the ERG acknowledges the importance of modelling up-dosing to treat BTH events, there are several concerns regarding the way this was operationalised in the model.

The ERG is unclear why the company assumed that CAC-related BTH events were treated with a single eculizumab up-dose in the eculizumab arm, and with an additional dose of eculizumab in the ravulizumab arm. Page 83 of the CS states that "*infection was the most common aetiology of CAC-related BTH events and resolved with treatment of the infection*".[1] This suggests that CAC-related BTH events would be resolved by treating the infection. The same statement also suggests that there were other causes that triggered CAC-related BTH events, but it is not mentioned which ones and how these were treated. Furthermore, in response to clarification question B11, the company indicated that "*BTH may occur due to suboptimal C5 inhibition, and/or complement-amplifying conditions (CACs) such as infection, surgery, or pregnancy that may lead to increased complement activation resulting from higher C3b density*".[19] Therefore, CAC-related events and incomplete C5 inhibition events might also occur simultaneously. The response to clarification question B11 also states that "i*n some patients with suboptimal C5 inhibition or complement-amplifying conditions, BTH may be ameliorated by shortening the 2-week dosing interval and/or increasing the dose of eculizumab*".[19] Furthermore, "*where a CAC is driving the BTH (e.g. an infection), there may not be suboptimal C5 inhibition and the underlying condition should primarily be managed – i.e. the infection treated*".[19] Finally, "i*n the non-clinical trial setting the BTH caused by a CAC would have required the infection to be treated*".[19] Thus, the response to clarification question B11 seems to suggest, even though it is not completely clear to the ERG, that some (but not all) CAC-related events might be treated with an eculizumab up-dose, while some (but not all) might be resolved by treating only the infection. However, it is not mentioned under which circumstances one option would be preferred over the other. The ERG considers that the rationale to assume that all CAC-related events should be treated with an eculizumab up-dose should have been better justified. With the evidence presented in the CS and the response to the clarification letter, the ERG preferred to assume that CAC-related BTH events would not be treated with an eculizumab up-dose, in line with what was observe in the clinical trials in which up-dose was not allowed. The opposite would result in higher costs for the eculizumab arm

of the model since CAC-related events were more frequent in the eculizumab arm than in the ravulizumab arm. Nevertheless, given the low frequency of such events in both arms, the impact on the model results is minor.

Regarding incomplete C5 inhibition-related BTH events, in response to clarification question A5, the company indicated that "*eculizumab administered at higher doses than the standard dose […] would likely prevent the breakthrough haemolysis due to incomplete C5 inhibition events observed in the eculizumab arm of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials*".[19] Therefore, the ERG is uncertain whether the base-case approach to eculizumab up-dosing would completely capture the additional effects associated with up-dosed eculizumab, as there are no clinical data to validate the base-case results. Furthermore, as will be explained in Section 5.2.3 of this report, this assumption seems to result in an overestimation of the number of patients requiring an up-dose in the eculizumab arm. For these reasons, the ERG does not agree with this assumption. Finally, the model assumes that incomplete C5 inhibition-related events do not occur in the ravulizumab arm. This is in line with the observations of no incomplete C5 inhibition-related in the clinical trials and, therefore, the ERG agrees with this assumption.

In conclusion, the ERG has several concerns regarding how eculizumab up-dosing was implemented in the model. Other concerns regarding up-dosing will be explained in sections "Equal effectiveness scenario" and 5.2.3. Based on all these concerns and the fact that in the two clinical trials up-dosing was not allowed, the ERG prefers a base-case scenario based completely on the clinical trials, thus, no eculizumab up-dose included in the model, even though it is acknowledged that this will not be completely representative of UK clinical practice.

Spontaneous remission

There is some evidence to support that long-term spontaneous remission can occur in PNH patients. The study by Hillmen et al. 1995 reported that, from a cohort of 35 patients who survived 10 years or more, 12 had a spontaneous clinical recovery.[5] The study by Socie et al. 1996 reported a 5% of spontaneous remission on a sample of 220 patients.[34] Finally, the study by Pulini et al. 2011 provided a case report of a male patient who discontinued eculizumab and achieved PNH spontaneous remission.[35] Given the lack of robust evidence, the company did not include spontaneous remission in their base-case analysis. The impact of this assumption was explored in an additional scenario, in which it was assumed that patients achieving spontaneous remission would stop PNH-related treatment (including complement-inhibitor therapy). The same rate of spontaneous remission was assumed in both treatment arms.

ERG comment: The ERG agrees with this approach. The impact of spontaneous remission on the cost effectiveness results was deemed minor and, therefore, was not explored by the ERG in their additional scenario analyses.

Background mortality

Overall survival was not a pre-specified endpoint in ALXN1210-PNH-301 and ALXN1210-PNH-302. Deaths were captured as a safety outcome. In ALXN1210-PNH-301 one death event was reported but this was not treatment-related.[28, 30] The company sought additional evidence around excess mortality associated with PNH from published literature and clinical experts. According to the company, this evidence suggests that "*the clinical consequences of uncontrolled complement activity are diverse, but in severe instances include outcomes such as thrombotic events, endothelial damage, inflammation and ischaemia*".[36] Also, "*persistent BTH events may lead to long-term uncontrolled haemolysis if they are left untreated*".[14] Chronic haemolysis is the underlying cause of premature

mortality in PNH (Page 12, CS).[1] However, eculizumab treatment has aligned the life expectancy of PNH patients to that of the general population (Page 14, CS).[1] Therefore, the company base-case analysis only includes age-adjusted general population mortality risk.[37] In an additional scenario, the company explored the impact of modelling an excess mortality risk associated with BTH events, which is assumed to be equal in both treatment arms.

ERG comment: In clarification question B12, the ERG asked the company to provide further evidence to justify the assumption that mortality with ravulizumab equals mortality with eculizumab. The company referred back to the results from the clinical trials and "*the fact that ravulizumab was derived from eculizumab and the technologies share over 99% homology*".[19] The company concluded that there is no clinical rationale as to why mortality should differ between eculizumab and ravulizumab. Additional data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trial Extension Phases will report clinical outcomes up to 104 weeks. The company expects these to be available in [redacted]. When the new data become available, the company will conduct an analysis of overall survival. The company also expects that the new data will support the outcomes observed over the 52-week period. With the current evidence, the ERG agrees with the company's approach to mortality.

Equal effectiveness scenario

As discussed in Section 3.3 of this report, the company states in the CS that the lack of "up-dosing" in the two trials compared with UK clinical practice may result in worse clinical outcomes for patients in the eculizumab arms. In response to clarification question A5, the company indicated that "*UK clinical practice demonstrates that the majority of PNH patients (~ [redacted]%) are managed at the standard dose of eculizumab. However, approximately [redacted]% of UK PNH patients require an eculizumab dosing adjustment to achieve complete terminal complement inhibition. Therefore, eculizumab administered at higher doses than the standard dose […] would likely prevent the breakthrough haemolysis due to incomplete C5 inhibition events observed in the eculizumab arm of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials*".[19] This is the rationale for considering the so-called "equal effectiveness" scenario, in which only CAC-related BTH events (in the three cohorts) were included in the analysis. Thus, this scenario considers a simplified version of the model where only the transitions within the dashed boxes in Figure 5.1 are possible. Also, a cohort of patients (further referred to as Cohort 3) was assumed to be eculizumab up-dosed from the start of the model, to reflect current clinical practice (i.e., approximately 20% of the PNH population as mentioned above). Further details about Cohort 3 and the equal effectiveness scenario are provided in Section 5.2.3 of this report.

ERG comment: The ERG considers that the equal effectiveness scenario provides a better representation of UK clinical practice than the company base-case scenario because it seems to overcome the main ERG concern regarding modelling eculizumab up-dose: the overestimation of the number of patients requiring an up-dose in the eculizumab arm. Nevertheless, as discussed in Section 5.2.3 of this report, the ERG is also concern that the trial population might not be representative of the UK PNH population and, for that reason, the ERG prefers a base-case scenario based completely on the clinical trials, thus, no eculizumab up-dose included in the model, even though it is acknowledged that this will not be completely representative of UK clinical practice.

5.2.3 Population

The population considered in the cost effectiveness analyses is adults with PNH who have haemolysis with clinical symptom(s) indicative of high disease activity or whose disease is clinically stable after

having eculizumab for at least six months. This is the population discussed in Section 3.1 of this report.

Three different cohorts were included in the economic analyses depending on whether patients were either complement inhibitor naïve (or simply treatment – ravulizumab or eculizumab – naïve, referred to as Cohort 1 in the economic analyses) or treatment experienced. Additionally, treatment experienced patients (and clinically stable on eculizumab) were classified as patients on the licensed dose of eculizumab (900 mg – referred to as Cohort 2 in the economic analyses) and patients on a higher-than-labelled dose (1200 mg – referred to as Cohort 3 in the economic analyses).[11] Note that patients in Cohort 3 were not included in ALXN1210-PNH-301 or ALXN1210-PNH-302. The rationale for including Cohort 3 in the economic analyses was already discussed in the "equal effectiveness scenario" section above. In summary, despite eculizumab dosing changes for patients who experienced BTH events not being allowed in ALXN1210-PNH-301 and ALXN1210-PNH-302, PNH National Service data suggests that an increased dose of eculizumab is used in UK clinical practice to achieve complete terminal complement inhibition in [redacted]% of the patients receiving label dose of eculizumab (900mg) treatment (reported range: 5%–29%).[12-15, 38] Thus, Cohort 3 was included in the model to reflect the proportion of patients who receive an eculizumab dose greater than 900mg, which is consistent with UK clinical practice.

The proportion of patients in each cohort was estimated as follows. Based on company data,[38] as of May 2020, eculizumab is being used to treat [redacted] patients in England, [redacted] of whom started treatment in 2019 and, therefore, were classed as treatment naïve. Additionally, [redacted] patients in England are receiving ravulizumab through the ALXN1210-PNH-301 or ALXN1210-PNH-302 extension.[27, 29] This yields a total of [redacted] PNH patients in England. For their base-case analysis, the company assumed a mixture of Cohort 1 and Cohort 2 using a weighted average based on the previous figures. Thus, the proportion of patients in Cohort 1 (treatment naïve patients) was estimated as [redacted] and it was further assumed that that the proportion of patients starting treatment remains the same each year. The proportion of patients in Cohort 2 (treatment experienced and on eculizumab label dose) was estimated as [redacted]. Additionally, the company assumed that eculizumab-treated patients with a history of two incomplete C5 inhibition BTH events, were allowed to "transition" into Cohort 3 during the course of the simulation. In the so-called "equal effectiveness scenario" the company assumed that a proportion of patients in Cohort 2 were allowed to start the simulation on higher-than-labelled eculizumab dose, thus in Cohort 3. Therefore, at the start of the simulation in the equal effectiveness scenario, the proportions of patients in each cohort were [redacted]% in Cohort 1, [redacted]% in Cohort 2 and [redacted]% in Cohort 3. In this scenario, the company additionally assumed that patients receiving their eculizumab dose as per clinical practice, would not experience incomplete C5 inhibition-related BTH events. Therefore, clinical outcomes were assumed to be the same as for the ravulizumab treatment arm in Cohort 2.

ERG comment: Cohorts 1 and 2 were defined to reflect the profiles of patients in ALXN1210-PNH-301 and ALXN1210-PNH-302, respectively. As mentioned above, eculizumab dosing changes to manage BTH events were not allowed in these two studies. Therefore, the lack of "up-dosing" in the two trials compared with UK clinical practice may result in worse clinical outcomes for patients in the eculizumab arms (e.g. Section 4.6).

In order to include eculizumab up-dose in the economic analyses, the company made a number of assumptions as discussed in previous sections. For example, in the company's base-case analysis, patients who experienced a CAC-related BTH event or an incomplete C5 inhibition BTH, were assumed to receive one single up-dose of eculizumab to re-establish the blockade. Additionally,

eculizumab patients with a history of one incomplete C5 BTH event, and who experienced a second incomplete C5 BTH event, transitioned to a continuously higher dose of eculizumab, which according to the company aligning would align to UK clinical practice. However, as shown in Table 6.4 (see Section 6.1 for further details), the proportion of time spent in the continuous up-dose health states across the complete model time horizon is [redacted]%, which is approximately twice as much as the [redacted]% reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice and, therefore, a large overestimation of the number of patients requiring an up-dose in the eculizumab arm. On pages 81 and 142 of the CS, the company indicated that "*across the model time horizon of 20 years*", patients spend 24.3% of their time in the continuous up-dose health states.[1] The company further concluded that this 24.3% closely aligns with the [redacted]% from the PNH National Service (used for Cohort 3 in the equal effectiveness scenario) which, according to the company, provides a measure of external validation. However, the ERG is unclear why the company has reported the previous comparison "*across the model time horizon of 20 years*" and not across the complete model time horizon (55 years for Cohort 1 and 52 years for Cohorts 2 and 3) where the proportion of time spent in the continuous up-dose health states is approximately two times larger.

In the equal effectiveness scenario, the proportion of time spent in the continuous up-dose health states *across the complete model time horizon* was assumed to be exactly [redacted]% (Cohort 3), thus, matching the PNH National Service estimate of the proportion of patients expected to receive an increased dose of eculizumab in UK clinical practice. The ERG understands, that the proportion of patients expected to receive an increased dose of eculizumab in UK clinical practice refers to the complete time horizon. Therefore, the assumption in the equal effectiveness scenario is in line with the ERG expectations. In clarification question B7, the ERG asked the company to clarify the clinical plausibility of the base-case and the equal effectiveness scenario analyses and which scenario provides a better representation of UK clinical practice.[19] The company answered that "*both pharmacoeconomic analyses incorporate the clinical practice of up-dosing and are therefore reflective of the disease pathway and clinical management of PNH patients who meet the criteria for complement-inhibitor treatment in the UK. As such, both analyses are equally clinically plausible*".[19] The ERG does not agree with the company's interpretation of the plausibility of the scenarios for the reasons explained above and prefers the equal effectiveness scenario over the company's base-case. However, the ERG considers that it is up to the Committee to decide which scenario is clinically more plausible. In any case, the impact of both assumptions on the cost effectiveness results was explored by the ERG in their additional scenario analyses in Section 7.1.3 of this report.

Page 78 of the CS states that "*while the eligibility criteria of the trial were not explicitly matched to the PNH service specification criteria for treatment initiation, they were designed to identify patients requiring active treatment to manage their disease versus those who do not. Patients in the trial were therefore considered representative of the population for whom ravulizumab is intended and for whom eculizumab is currently used*".[1] While the ERG has no reasons to disagree with this statement, the ERG is concerned that the sub-population of patients who would require an eculizumab up-dose might be underestimated in the trials and, therefore, these trial populations might not be representative for the UK. In response to clarification question B6,[19] the company explained that "c*hanging the dose of eculizumab to reflect UK up-dosing clinical practice would be expected to affect the clinical effectiveness as observed in the trial, allowing more patients in the eculizumab arm to achieve complete and sustained inhibition of terminal complement and thereby avoid associated BTH events".* In particular, "*changing the dose of eculizumab would alter the clinical effectiveness in the 11 eculizumab arm patients who experienced incomplete C5 inhibition related BTH events across the clinical trials; 7 patients in ALXN1210-PNH-301 and 4 patients in ALXN1210-PNH-302*.[19] Note that

11 out of a total of 219 patients is approximately 5% of patients in the trial population who would need an eculizumab up-dose, which is approximately [redacted] lower than the [redacted]% estimate from the PNH National Service. While we agree with the company that this "*would not be expected to impact on the conclusion of the clinical trial (non-inferiority criteria met) as no patients in the ravulizumab arm of either trial experienced BTH due to incomplete C5 inhibition*",[19] it might indicate that the population in the trials was not representative of the UK population. Therefore, the ERG wonders whether the conclusions from the trials, in which only 5% of patients would be "eligible" for an eculizumab up-dose, would be the same if there were approximately [redacted]% of patients who would need such an up-dose (as in UK clinical practice). In clarification question A10,[19] the ERG suggested that acknowledged differences between the trial and UK populations, as presented in Section B.2.13.2 of the CS,[1] appear to indicate more severe disease in the UK treated population. In response to the question of the ERG to provide evidence to support the assertion that the trial data are generalisable to UK clinical practice, the company indicated that "*the differences are not indicative of more severe disease in one population than another, hence why we conclude there are no clear clinical indications that the characteristics of patients enrolled are not generalizable to UK patients*".[19] The fact that only 5% of patients would be "eligible" for an eculizumab up-dose in the trials, as opposed to approximately [redacted]% in UK clinical practice might suggest otherwise. Additional data may help reducing the uncertainty regarding this aspect of the analysis. The study ALXN1210-PNH-401 has been designed to investigate the clinical effectiveness of ravulizumab in UK patients who are stable on a higher-than-licensed eculizumab dose, planned to switch to ravulizumab and observed for 52 weeks. The estimated start and completion dates are January 2021 and February 2022, respectively. However, but the study may be delayed due to a pause in recruitment relating to the COVID-19 pandemic.[39].

It is important to emphasise that throughout the CS and the responses to the clarification letter, the company have made it clear that 'up-dosing' is only necessary in approximately [redacted]% of the population and that most patients would achieve an adequate terminal complement inhibition on the licensed eculizumab dose. However, despite being a minority, the assumptions about patients who would require an eculizumab up-dose are crucial for the results of the cost effectiveness analyses. As will be shown in Chapter 7 of this report, this is the main driver of the cost effectiveness results. In conclusion, the ERG prefers a base-case scenario based completely on the clinical trials, without modelling eculizumab up-dose. Even though it is acknowledged that this will not be completely representative of UK clinical practice, the ERG considers that, with the current evidence, neither the company base-case nor the equal effectiveness scenario would provide a better representation of UK clinical practice. The three approaches are explored by the ERG in Chapter 7 of this report.

5.2.4 Interventions and comparators

The intervention considered in this appraisal was ravulizumab. Ravulizumab is administered intravenously in eight week dosing intervals, following a weight-based dosing regimen, as described in Section 3.2 of this report.

As explained in Section 3.3 of this report, the comparator technology is eculizumab. As described in the previous section, in the company's base-case analysis, all patients start the simulation on the licensed 900mg eculizumab dose, which is in line with ALXN1210-PNH-301 and ALXN1210-PNH-302. In UK clinical practice, an increased dose of eculizumab is used to manage BTH due to incomplete C5 inhibition. However, in both ALXN1210-PNH-301 and ALXN1210-PNH-302, eculizumab dose-escalation/up-dosing was not permitted. In the cost effectiveness model, the company assumed a continuous up-dosing (1200mg and above) following two incomplete C5

inhibition-related BTH events, as explained in previous sections. Doses above 1200mg are funded by the company and, therefore, the cost of a 1200mg was assumed for higher doses.

In the company's equal effectiveness scenario, [redacted]% of the patients start the simulation on a higher than licensed dose (1200mg and above) of eculizumab, while the rest of patients start on the licensed eculizumab dose (900mg).

5.2.5 Perspective, time horizon and discounting

The economic analyses were conducted from an NHS and Personal Social Services (PSS) perspective and adopted a lifetime time horizon. Total costs and QALYs were discounted at a 3.5% annual rate, as recommended in the NICE Reference Case.[40]

5.2.6 Treatment effectiveness and extrapolation

The company used the data and the outcomes from the two Phase III trials ALXN1210-PNH-301 (NCT02946463) and ALXN1210-PNH-302 (NCT03056040) to model ravulizumab and eculizumab clinical effectiveness for the three different patient cohorts included in the model, as discussed in Section 5.2.3. The outcomes assessed in the trials were chosen as representative of the health-related benefits and potential side effects expected with ravulizumab treatment in practice. They included BTH events and blood transfusions. Table 5.5 shows the source and main assumptions for the model inputs in both the base-case and the equal effectiveness scenario analysis. The company assumed that ravulizumab treatment effect remains constant over time based on opinion from an Advisory Board held in December 2018.[11] This is modelled by assuming the same transition matrices throughout the complete model time horizon.

The company base-case analysis is aligned with the trial population and observed outcomes from ALXN1210-PNH-301 and ALXN1210-PNH-302,[27, 29] with the exception of modelling eculizumab up-dose to treat BTH events, as explained in Sections 5.2.2 and 5.2.3. Given that eculizumab was administered at its licensed dose in the pivotal trials, the efficacies of eculizumab and ravulizumab were taken directly from the respective clinical trials and treatment arms. In contrast, the equal effectiveness scenario aligns with the non-inferiority trial designs and assumes that, when for the management of BTH due to incomplete C5 inhibition patients receive an up-dose of eculizumab as per clinical practice, the efficacy of ravulizumab and eculizumab is equivalent. More details are provided in the following sections.

Table 5.5: Base-case analysis and equal effectiveness scenario - model inputs

Model input	Base-case analysis	Equal effectiveness scenario	Justification
CAC-related BTH Events	CAC-related BTH events that occurred in Study ALXN1210-PNH-301 and ALXN1210-PNH-302 were modelled per trial.	CAC-related BTH events were assumed to be the same in the eculizumab and ravulizumab arms.	In the base-case, given that the population is the same as the populations from the trials, the observed events from the trials were also used. In the equal effectiveness scenario, non-inferiority is assumed when all eculizumab patients are on a clinically stable dose; hence, events are assumed to be equal across arms, as per the ravulizumab arm.
Incomplete C5 inhibition-related BTH events	Incomplete C5 inhibition-related BTH events that occurred in Study ALXN1210-PNH-301 and ALXN1210-PNH-302 were modelled.	Incomplete C5 inhibition-related BTH events were not modelled or assumed to be zero.	In the base-case, given that the population was the same as the populations from the trials, the observed events from the trials were also used. In the equal effectiveness scenario, all patients in the eculizumab arm were assumed to receive a clinically stable dose (i.e. UK dosing was used) – and not the licensed dose (900mg) given in the pivotal trials. At the clinically stable dose, it was assumed that patients would not experience BTH due to incomplete C5 inhibition.
Blood transfusions	Transfusions reported in Study ALXN1210-PNH-301 and ALXN1210-PNH-302 were modelled per trial.	Transfusions were not modelled or assumed to be zero.	In the base-case, given that the population is the same as the populations from the trials, the observed events from the trials were also used. In the equal effectiveness scenario, transfusion was not modelled (assumed same on both arms so will cancel out).
Spontaneous remission	Included as a model scenario.	Included as a model scenario.	Evidence of spontaneous remission was derived from the literature; given the uncertainty, this is not considered in the base-case.

Source: Table 21 in CS.[1]
Abbreviations: BTH = breakthrough haemolysis, CAC = complement-amplifying condition, UK = United Kingdom.

BTH events and transitions probability matrices

BTH event rates from ALXN1210-PNH-301 and ALXN1210-PNH-302 were used to determine the transitions to and from BTH events in the model.[27, 29] In the base-case analysis both incomplete C5 inhibition-related and CAC-related BTH events were modelled. In the equal-effectiveness scenario, only CAC-related BTH events were modelled. Table 5.6 to Table 5.9 present the transition probabilities by cohort and by treatment arm for the base-case analysis, and Table 5.10 to Table 5.11 for the equal effectiveness scenario. Transition probabilities were based on patient visit-level data from the two clinical studies. The rationale for estimating the transition probabilities is described in Appendix 1.

Table 5.6: Transition matrix Cohort 1 – eculizumab

IncC5Inhib BTH history	No BTH	IncC5Inhib BTH	CAC BTH
No history	[redacted]	[redacted]	[redacted]
History, no current BTH	[redacted]	[redacted]	[redacted]
History, current BTH	[redacted]	[redacted]	[redacted]

Source: economic model.[41]

Abbreviations: IncC5Inhib = incomplete C5 inhibition; BTH = breakthrough haemolysis; CAC, complement-amplifying condition

Table 5.7: Transition matrix Cohort 1 - ravulizumab

IncC5Inhib BTH history	No BTH	IncC5Inhib BTH	CAC BTH
No history	[redacted]	[redacted]	[redacted]
History, no current BTH	[redacted]	[redacted]	[redacted]
History, current BTH	[redacted]	[redacted]	[redacted]

Source: economic model.[41]

Abbreviations: IncC5Inhib = incomplete C5 inhibition; BTH = breakthrough haemolysis; CAC, complement-amplifying condition

Table 5.8: Transition matrix Cohort 2 - eculizumab

IncC5Inhib BTH history	No BTH	IncC5Inhib BTH	CAC BTH
No history	[redacted]	[redacted]	[redacted]
History, no current BTH	[redacted]	[redacted]	[redacted]
History, current BTH	[redacted]	[redacted]	[redacted]

Source: economic model.[41]

Abbreviations: IncC5Inhib = incomplete C5 inhibition; BTH = breakthrough haemolysis; CAC, complement-amplifying condition

Table 5.9: Transition matrix Cohort 2 – ravulizumab

IncC5Inhib BTH history	No BTH	IncC5Inhib BTH	CAC BTH
No history	[redacted]	[redacted]	[redacted]
History, no current BTH	[redacted]	[redacted]	[redacted]
History, current BTH	[redacted]	[redacted]	[redacted]

Source: economic model.[41]

Abbreviations: IncC5Inhib = incomplete C5 inhibition; BTH = breakthrough haemolysis; CAC, complement-amplifying condition

Table 5.10: Transition matrix Cohort 1 – ravulizumab and eculizumab (equal effectiveness scenario)

IncC5Inhib BTH history	No BTH	IncC5Inhib BTH	CAC BTH
No history	[redacted]	[redacted]	[redacted]
History, no current BTH	[redacted]	[redacted]	[redacted]
History, current BTH	[redacted]	[redacted]	[redacted]

Source: economic model.[41]

Abbreviations: IncC5Inhib = incomplete C5 inhibition; BTH = breakthrough haemolysis; CAC, complement-amplifying condition

Table 5.11: Transition matrix Cohort 2 and 3* – ravulizumab and eculizumab (equal effectiveness scenario)

IncC5Inhib BTH history	No BTH	IncC5Inhib BTH	CAC BTH
No history	[redacted]	[redacted]	[redacted]
History, no current BTH	[redacted]	[redacted]	[redacted]
History, current BTH	[redacted]	[redacted]	[redacted]

Source: economic model.[41]

* The same transition probabilities as in Cohort 2 were assumed to model Cohort 3 (higher-than-licensed dose eculizumab patients).

Abbreviations: IncC5Inhib = incomplete C5 inhibition; BTH = breakthrough haemolysis; CAC, complement-amplifying condition

ERG comment: The company derived the transition probabilities from patient-visit-level data from the two clinical studies. Since these data have not been provided in the CS, the ERG could not validate the calculations.

Excess mortality risk of BTH

Considering that a BTH event may be accompanied by severe outcomes, such as thrombosis (see e.g. Section B.3.2.6 of CS [1]), the model allowed for the specification of excess mortality risk associated with BTH events.

In the base-case model analyses, no excess mortality risk of BTH events was specified. The application of higher mortality risk to that of the age- and gender-adjusted background mortality rate was identified in the literature. No evidence was available for a UK population or a comparable disease following a targeted search, therefore, data from an alternative source was used. A study of patients enrolled in the Korean PNH registry by Jang et al. (2016) found that the standard mortality ratio associated with LDH ≥1.5 x ULN was 4.81.[36] Given the similarity in LDH threshold to the definition of BTH events in ALXN1210-PNH-301 and ALXN1210-PNH-302, a hazard ratio (HR) of 4.81 applied to patients experiencing BTH events was tested in the scenario analysis.

Transfusion requirements

Transfusion requirements were included in the base-case analysis, due to their impact on HRQoL and cost and resource use when differential effectiveness is assumed as per the trials. The economic model allows for the specification of packed red blood cell transfusion requirements, by treatment arm and presence of incomplete C5 inhibition-related or CAC-related BTH event. These transfusion requirements were used to estimate mean transfusion-related cost and utility impacts. In the equal effectiveness scenario, transfusion requirements were assumed to be equal in the comparison, therefore cancelling each other out; consequently, these were not included in the analysis.

The probabilities of requiring a transfusion in each two week cycle, as well as the mean number of units of red blood cells required, were calculated based on patient-level data from ALXN1210-PNH-301 and ALXN1210-PNH-302. Details of transfusions requirement are reported in Appendix 2. Of note, as no patient was observed to require multiple transfusions between visits in the clinical studies, it was assumed that while multiple units of red blood cells may have been required per transfusion, only one transfusion procedure would occur in a model cycle.

In the 'permanent up-dosing as per clinical practice dose' scenario, the rate of transfusions and the number of packed red blood cell units required were assumed to be equal to those of the ravulizumab arm.

Spontaneous remission

Spontaneous remission was incorporated as a scenario analysis. To model this scenario, the transition probability of spontaneous remission was calculated from data in Hillmen et al. (1995), which provided patient-level data on 80 PNH patients treated with supportive measures, such as oral anticoagulant therapy after established thromboses, and transfusions in the UK between 1940-1970.[5]

5.2.7 Adverse events

Based on the conclusion from EMA that the safety profile appeared to be similar to that of eculizumab,[25] the company did not model any of the adverse events (AEs) that occurred (including headache and nasopharyngitis) in the two clinical trial studies, as it was assumed not to have an impact on the cost effectiveness analysis.

ERG comment: Adverse events were observed in the clinical trials as shown in Tables 6 and 7 of Appendix F to the CS.[21] These seem to be balanced between the two treatment arms and occurring at

low frequencies. Thus, the ERG agrees with the company that including adverse events in the model is likely to have a minor impact on the model results.

5.2.8 Health-related quality of life

Health related quality of life was measured from baseline to week 26 in the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C-30). Data was collected on Day 1, 8, 29, 71 and then twice between Day 71 and the end of study, resulting in a mean of 5.9 observations per patient in ALXN1210-PNH-301 and 5.7 in ALXN1210-PNH-302. EQ-5D data was not collected (section B3.4.1 CS page 100).[1]

Baseline health on the Global health scale (0 – 100, where 100 is better health) of QLQ-C30 was 56.13 for ravulizumab and 57.51 for eculizumab in ALXN1210-PNH-301. In the ALXN1210-PNH-302 trial, global health in the ravulizumab arm was higher with a mean of 75.25 vs 69.47 in the eculizumab arm (Appendix R of CS, Table 31 page 96 and clarification question B14 Table 5 as amended).[19, 21]

Utility impact of breakthrough haemolysis and transfusion

The QLQ-C30 was mapped to EQ-5D-3L to predict response levels on the five items. using the Longworth et al (2014) response mapping algorithm.[33] The mapped response probabilities were converted to utilities using the 3L UK tariff of Dolan (1997).[42]

In the base-case, utilities from a mixed-effects regression model were used to estimate the impact on utility of BTH events and transfusions. The model was estimated separately on the two trials and the values are presented in the Table 5.12 and Table 5.13 below.

Table 5.12: Mixed-effects model utility input for trial ALXN1210-PNH-301

Covariate	Coefficient	Standard error	Z	P>|z|	[95% CI]	
BTH indicator	-0.1143	0.0376	-3.0400	0.0020	-0.1881	-0.0406
Transfusion indicator	-0.0678	0.0131	-5.1700	0.0000	-0.0935	-0.0421
Individual-level linear trend	0.0212	0.0015	14.3000	0.0000	0.0183	0.0241
Constant	0.7592	0.081	93.3500	0.0000	0.7432	0.7751

Source: Table 26 in CS.[1]
Abbreviations: CI, confidence interval, BTH, breakthrough-haemolysis event experienced since last visit; individual-level linear trend, time trend (number of visits); transfusion, protocol guidelines for transfusion met since last visit.

Table 5.13: Mixed-effects model utility input for trial ALXN1210-PNH-302

Covariate	Coefficient	Standard error	Z	P>|z|	[95% CI]	
BTH indicator	-0.1828	0.0490	-3.7300	0.0000	-0.2789	-0.0868
Transfusion indicator	-0.0716	0.0189	-3.7800	0.0000	-0.1087	-0.0345
Individual-level linear trend	0.0028	0.0012	2.2800	0.0230	0.0004	0.0052

Covariate	Coefficient	Standard error	Z	P>|z|	[95% CI]	
Constant	0.8471	0.0098	86.5700	0.0000	0.8280	0.8633

Source: Table 27 in CS.[1]
Abbreviations: CI, confidence interval, BTH, breakthrough-haemolysis event experienced since last visit; individual-level linear trend, time trend (number of visits); transfusion, protocol guidelines for transfusion met since last visit.

Linear regressions were also estimated where predictor variables included a treatment arm. In those analyses, the treatment arm parameters favoured ravulizumab with utility increments ranging from 0.0098 to 0.0178 (ALXN1210-PNH-301) and 0.0037 to 0.022 (ALXN1210-PNH-302) depending on the selected covariates. None of the treatment arm parameters reach statistical significance in the presented models ($p > 0.1$). In a response to the clarification letter question B15,[19] exploratory mixed-effects models that did include treatment arm parameters were presented that displayed no statistical significance (Table 5.14 and Table 5.15).

Table 5.14: Exploratory mixed-effects model utility input for trial ALXN1210-PNH-301

Covariate	Coefficient	Standard error	Z	P>|z|	[95% CI]	
BTH indicator	-0.1142	0.0376	-3.0300	0.0020	-0.1880	-0.0404
Treatment*	0.0103	0.0128	0.8100	0.4210	-0.0147	0.0353
Transfusion indicator	-0.0674	0.0131	-5.1500	0.0000	-0.0931	-0.0418
Individual-level linear trend	0.0212	0.0015	14.3000	0.0000	0.0183	0.0241
Constant	0.7540	0.0104	72.5900	0.0000	0.7336	0.7743

Source: Table 6 in response to clarification letter.[19]
Abbreviations: CI, confidence interval, BTH, breakthrough-haemolysis event experienced since last visit; individual-level linear trend, time trend (number of visits); transfusion, protocol guidelines for transfusion met since last visit.
*Treatment, ravulizumab =1, eculizumab = 0

Table 5.15: Exploratory mixed-effects model utility input for trial ALXN1210-PNH-302

Covariate	Coefficient	Standard error	Z	P>|z|	[95% CI]	
BTH indicator	-0.1816	0.0490	-3.7100	0.0000	-0.2777	-0.0856
Treatment*	0.0197	0.0176	1.1200	0.2630	-0.0148	0.0543
Transfusion indicator	-0.0717	0.0189	-3.7800	0.0000	-0.1088	-0.0345
Individual-level linear trend	0.0028	0.0012	2.2800	0.0230	0.0004	0.0052
Constant	0.8373	0.0131	63.8400	0.0000	0.8116	0.8630

Source: Table 7 in response to clarification letter.[19]
Abbreviations: CI, confidence interval, BTH, breakthrough-haemolysis event experienced since last visit; individual-level linear trend, time trend (number of visits); transfusion, protocol guidelines for transfusion met since last visit. *Treatment, ravulizumab =1, eculizumab = 0

Utility impact of treatment burden

The majority of the ravulizumab HRQoL benefit is derived from the benefit of the infusion schedule of ravulizumab over eculizumab. It is argued that the impact of ravulizumab on treatment burden could not be fully captured in the trial because patients still needed to attend the research site for other trial protocol obligated reasons. Therefore, the company stated that "*patients did not experience the potential HRQL benefit of less frequent visits, although they did experience the benefit of less frequent infusion visits*".[1] In order to address the benefit of less visits and the benefit of less infusions, data from a discrete choice experiment (DCE) were applied in the model [43].

[redacted]

Adverse event disutilities

Adverse event disutilities were not incorporated in the cost effectiveness model.

ERG comment: NICE Technical Support Document TSD 10 and TSD 11 request the use of EQ-5D unless it is demonstrably insensitive or invalid in a particular condition, which would open the door for alternatives, such as mapping exercises.[45, 46] As no EQ-5D data have been collected in PNH patients, the validity of the instrument in this condition is unknown. However, due to the event related quality of life losses, it is conceivable that the instrument with a recall period of 'today' may not be optimal for capturing events. Hence, the relatively generic QLQ-C30, mapped to EQ-5D is an acceptable alternative due to its longer recall period in the absence of EQ-5D but cannot replace EQ-5D. The utilised mapping algorithm is consistently tested among the best functioning algorithms for estimating EQ-5D-3L UK utility values and is, therefore, a sensible choice.

There is evidence that patients prefer ravulizumab over eculizumab due to the lower treatment frequency.[23] However, that preference did not result in improved quality of life measurable in the trials. There are concerns regarding the validity of the estimated disutility related to treatment frequency. These concerns focus on two elements: the mixed-effect models and the DCE study. Firstly, no significant treatment effect with regards to quality of life could be estimated in any of the ordinary least-squares (OLS) or mixed-effects models (CS appendix R, table 33 and 34, page 99 and

100).[21] The company argued that this is due to the trial design, in which patients could not benefit from differential visit schedule but would benefit from the reduced infusion frequency itself. Hence, the only utility benefit that the trial design could not capture is the reduced burden of visits. The size of such potential disutility is unknown.

Secondly, as the design of the trials could not demonstrate statistically significant health-related quality of life (HRQoL) benefit due to its design, the company resorts to using data external to the trial from a DCE study. Following the reasoning of the company submission, this DCE data would only need to supply disutility data for reduced burden of frequency of visits, as the trial itself shows no statistically significant HRQoL benefit of the infusion frequency, possibly due to the increased length of infusion time with ravulizumab. The DCE, however, has several methodological concerns. [redacted]. Indeed, this time preference can to some extent be observed by the increase in the disutility by using parameters for shorter losses in life expectancy, which would in effect occur closer to the end of life and thus later. Hence, the ERG is of the opinion that the DCE should not be used when trial data on HRQoL are available.

However, the common-sense argument that there is value to patients in having a reduced treatment frequency is substantiated by the fact that patients themselves have indicated that they prefer ravulizumab over eculizumab due mainly to reduced treatment frequency. Therefore, the ERG prefers a base-case that takes this benefit into account, using the non-significant treatment effect from the mixed-effects models. While this point estimate is uncertain, its application in the model including the PSA captures benefit while taking uncertainty into account as well.

5.2.9 Resources and costs

A list price of £4,533 per 300mg vial was approved for ravulizumab by the Department of Health and Social Care. A patient access scheme (PAS) price of [redacted] per 300mg for ravulizumab (representing a discount of [redacted] on the list price) has been submitted by the company to reduce [redacted].[1] The cost of eculizumab was sourced from the Monthly Index of Medical Specialities (MIMS).[47]Pack costs for ravulizumab and eculizumab are listed in Table 5.16.

Table 5.16: Drug unit size, pack size, and pack cost

Treatment	Unit size	Pack size	Cost per pack	Source
Ravulizumab	300mg	1	List price: £4,533 PAS price: [redacted]	Company
	1100mg	1	List price: £16,621 PAS price: [redacted]	Company
Eculizumab	300mg	1	£3,150	MIMS[47]

Source: Table 31 in CS.[1]
Abbreviations: MIMS, Monthly Index of Medical Specialities; PAS, patient access scheme.

For ravulizumab, the recommended dosing regimen for adult patients (≥18 years) consists of an initial loading dose (2700mg) followed by maintenance doses (3300mg). Maintenance doses are administered every eight weeks, starting at two weeks after the initial loading dose. The dosing was weight based and the proportion of patients within each weight band was estimated using age- and gender-specific weights that were derived from the 'NHS Health Survey for England 2017: Adult health tables.[48] All patients from the survey was within the ≥60 kg to <100 kg band. In the first year, patients received the loading dose at Week 0, and commenced the maintenance dose at Week 2; which was given every eight weeks and equated to seven doses in the first year of treatment. In subsequent years, the number of doses per year alternates between six and seven; but for simplicity, 6.5 doses were used. Table 5.17 lists annual costs of ravulizumab by weight.

Table 5.17: Ravulizumab annual cost calculations by weight

Patient body weight	Loading phase: dose	Maintenance phase: annual dose	Annual cost (first year)	Annual cost (subsequent years)
≥60 kg to <100 kg	9 x 300mg	First year: 11 x 300mg X 7	List: £389,838	List: £324,110
		Subsequent years: 11 x 300mg X 6.5	PAS: [redacted]	PAS: [redacted]

Source: Table 33 in CS.[1]
Note: [redacted]
Abbreviations: PAS, patient access scheme.

For eculizumab, the dosing regimen for adult patients consists of a four week initial phase followed by a maintenance phase. In the initial phase, 600mg of eculizumab was given intravenously every week for the first four weeks. In the maintenance phase, 900mg of eculizumab was administered every two weeks starting at Week 5, with higher doses used if patients continue to experience incomplete C5 inhibition-related BTH. Given that patients may receive a higher-than-licensed eculizumab dose, the annual cost for a 900mg or 1200mg maintenance dose was presented in Table 5.18. For Cohort 2 and 3, it was assumed that these patients would not require the initial phase doses; therefore, the first-year costs were equal to the subsequent year costs. This assumption was not applied to the ravulizumab arm because treatment-experienced patients would switch from eculizumab and hence a ravulizumab loading dose would be required.

Table 5.18: Eculizumab annual cost calculations

Loading phase: dose received	Maintenance phase: dose received	Maintenance phase: annual dose	Annual cost (first year)a	Annual cost (subsequent years)
2 x 4 x 300mg	900mg	First year: 3 x 300mg vials for 24 doses Subsequent years: 3 x 300mg vials for 26 doses	£252,000	£245,700
Not applicable	1200mg or over	4 x 300mg vials for 26 doses	£327,600	£327,600

Source: Table 34 in CS.[1]
[a] Cohort 2 and 3 do not require a loading dose (as these are patients continuing treatment on eculizumab), therefore, first year costs are equal to subsequent year costs for these patients.

In the model, no cost of spontaneous remissions was applied given that the patients achieving spontaneous remission discontinue complement inhibitor therapy.

Drug administration costs

The intravenous infusion costs associated with the first loading dose and first maintenance dose of eculizumab, and the loading dose and first maintenance dose of ravulizumab are included within the scheme of NHS England. When patients receive infusions at home through the homecare infusion services, then these costs are funded by the company. Therefore, the NHS-administered infusion costs were the only administration costs included in the model. However, the company indicated that the clinical practice is changing and that the first maintenance dose would also be administered at patients' home. For the cost of administration, before receipt of the homecare service, the cost per hour of Band 7 pharmacist specialist time (£57) and Band 6 nurse specialist time (£113) was derived from the Personal Social Services Research Unit (PSSRU).[49] The duration of administration (for both the loading dose and maintenance dose) were derived from the summary of product characteristics (SPCs).[26] Where a range was given, (i.e., a 25–45-minute infusion), the mid-point was used. The cost of nurse time was applied over these durations, and an additional one-hour observation time was included.

For the company base-case (100 mg/mL formulation), the following infusion durations were assumed for ravulizumab and eculizumab: Loading dose: 35 minutes nurse time + 15 minutes pharmacist time (£193.17), Maintenance dose: 35 minutes nurse time + 15 minutes pharmacist time (£193.17). For the model scenario (10mg/mL formulation), the following infusion durations were assumed: Loading dose: 110 minutes nurse time + 30 minutes pharmacist time, Maintenance dose: 130 minutes nurse time + 30 minutes pharmacist time.

BTH events

PNH patients can experience BTH events throughout complement-inhibitor treatment. This can occur as a result of incomplete C5 inhibition or in patients with CACs. Based on the expert survey, the resource use associated with a BTH event is presented in Table 5.19.

Table 5.19: Resource use associated with BTH

	BTH due to incomplete C5 inhibition		BTH due to CAC	
	First event*	Subsequent event*	First event*	Subsequent event*
Hospital stays				
General ward (days)	15%/1	15%/1	23%/3	23%/3
Intensive care (days)	1%/1	1%/1	1%/1	1%/1
Dialysis				
Dialysis (days)	4%/7	4%/7	4%/7	4%/7

Source: Table 37 in CS.[1]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement-amplifying condition.
Notes: *Frequency of management strategy (%) / number of units used per treated episode.

Health-state costs applied in the model

A survey was developed to estimate inputs about the rates and causes of BTH and medical management for BTH.[11] The survey was administered in the context of an Advisory Board meeting, to 10 clinicians who were experts in the treatment of PNH with both eculizumab and ravulizumab. Clinical experts were asked to estimate the proportion of patients requiring the resource and average duration of resource for four categories: general ward hospitalisation, intensive care unit (ICU) hospitalisation, medication and dialysis. Table 5.20 presents the per cycle (two-weekly) costs associated with each health state applied in the model.

Table 5.20: Health states and associated costs in the model

Health states	Cost Items	Costs	
No BTH	Haematology specialist visit	£8.48	
	Transfusion - Cohort 1; Ravulizumab | Eculizumab	£14.00 Ravulizumab	£20.61 Eculizumab
	Transfusion – Cohort 2 & 3; Ravulizumab | Eculizumab	£5.46 Ravulizumab	£4.59 Eculizumab
CAC-related BTH	General ward admission	£364.00	
	Intensive care admission	£14.67	
	Dialysis	£37.41	
	Haematology specialist visit	£164.80	
	Transfusion - Cohort 1; Ravulizumab | Eculizumab	£40.41 Ravulizumab	£85.64 Eculizumab
	Transfusion – Cohort 2 and 3; Ravulizumab | Eculizumab	N/A Ravulizumab	£131.24 Eculizumab
Incomplete C5 inhibition-related BTH	General ward admission	£79.13	
	Intensive care admission	£14.67	
	Dialysis	£37.41	

Health states	Cost Items	Costs	
	Haematology specialist visit	£164.80	
	Transfusion - Cohort 1;	£40.41 Ravulizumab	£85.64 Eculizumab
	Ravulizumab | Eculizumab		
	Transfusion – Cohort 2 and 3; Ravulizumab‡ | Eculizumab	N/A Ravulizumab	£131.24 Eculizumab
History of Incomplete C5 inhibition-related BTH, No BTH	Haematology specialist visit	£12.63	
	Transfusion - Cohort 1;	£14.00 Ravulizumab	£20.61 Eculizumab
	Ravulizumab | Eculizumab		
	Transfusion – Cohort 2 and 3; Ravulizumab | Eculizumab	£5.46 Ravulizumab	£4.59 Eculizumab
Subsequent Incomplete C5 inhibition-related BTH	General ward admission	£79.13	
	Intensive care admission	£14.67	
	Dialysis	£37.41	
	Haematology specialist visit	£164.80	
	Transfusion - Cohort 1;	£40.41 Ravulizumab	£85.64 Eculizumab
	Ravulizumab | Eculizumab		
	Transfusion – Cohort 2 and 3; Ravulizumab‡ | Eculizumab	N/A Ravulizumab	£131.24 Eculizumab
History of incomplete C5 inhibition-related BTH, CAC-related BTH	General ward admission	£364.00	
	Intensive care admission	£14.67	
	Dialysis	£37.41	
	Haematology specialist visit	£164.80	
	Transfusion - Cohort 1;	£40.41 Ravulizumab	£85.64 Eculizumab
	Ravulizumab | Eculizumab		
	Transfusion – Cohort 2 and 3; Ravulizumab‡ | Eculizumab	N/A Ravulizumab	£131.24 Eculizumab
History of incomplete C5 inhibition-related BTH, Cont. up-dose	Haematology specialist visit	£12.63	
	Transfusion - Cohort 1;	£14.00 Ravulizumab	£20.61 Eculizumab
	Ravulizumab | Eculizumab		
	Transfusion – Cohort 2 and 3; Ravulizumab | Eculizumab	£5.46 Ravulizumab	£4.59 Eculizumab
Cont. up-dose, CAC-related BTH	General ward admission	£364.00	
	Intensive care admission	£14.67	
	Dialysis	£37.41	
	Haematology specialist visit	£164.80	

Health states	Cost Items	Costs	
	Transfusion - Cohort 1; Ravulizumab| Eculizumab	£40.41 Ravulizumab	£85.64 Eculizumab
	Transfusion – Cohort 2 and 3; Ravulizumab‡ | Eculizumab	N/A Ravulizumab	£131.24 Eculizumab
Spontaneous remission	Haematology specialist visit	£12.63	

Source: Table 39 in CS.[1]
* Health state costs relevant to the equal effectiveness scenario; ‡ no BTH events were observed in the ravulizumab arm of ALXN1210-PNH-302, thus no transfusion costs were estimated for Cohort 2 and 3.
Key: BTH, breakthrough haemolysis; CAC, complement-amplifying condition; Cont., continuous.

Adverse reaction unit costs and resource use

No adverse event costs or resource use were included.

Miscellaneous costs and resource use

To reduce the risk of infection, patients must be vaccinated against meningococcal infections and receive additional prophylactic antibiotics, at least two weeks before receiving eculizumab or ravulizumab. Costs and dosing for the two vaccines, MenACWY (£60, one dose) and MenB (£115, two doses) , were derived from information from Hampstead Health Pharmacy.[50] Following the advice of the PNH National Service in Leeds a booster vaccination of MenACWY and MenB (one dose only) are assumed to be given every five years for patients receiving complement-inhibitor treatment.[51] As the vaccination history was assumed unknown for treatment experienced patients, a booster vaccine was given at the start of model for Cohorts 2 and 3 and thereafter every 5 years.

Prophylactic antibiotics, specifically penicillin, are required in all treated patients, while on treatment. The drug cost was derived from the drugs and pharmaceutical electronic market information tool (eMIT). [52] It was assumed that the pack providing the cheapest cost per mg (250mg tablets/pack size 28) would be used. It was assumed that prophylactic penicillin would be given at a dose of 500mg, twice daily. This resulted in a cost per cycle amount of £0.72 and was applied to both treatment arms.

Equal effectiveness scenario

The company only included direct drug-related costs in the equal effectiveness scenario. The differences in cost and resource use inputs modelled for the base-case and equal effectiveness scenario are listed in Table 5.21.

Table 5.21: Differences in cost/resource use inputs modelled for the base-case analysis and equal effectiveness scenario

Model input	Base-case analysis	Equal effectiveness scenario
Drug acquisition and administration costs	Included	Included – these are direct drug-related costs
Meningococcal vaccine cost	Included	
Prophylactic antibiotics	Included	
Transfusion costs	Included	Not included
BTH event costs	All CAC-related BTH and incomplete C5 inhibition costs included	Only the cost of an additional dose of eculizumab was included after a CAC-related BTH event
Other costs (consultant-led haematology follow-up)	Included	Not included

Source: Table 30 in CS.[1]
Key: BTH, break-through haemolysis; CAC, complement amplifying condition.

ERG comment: The company indicated that the regulatory review of two new vial sizes (3mL and 11mL) containing 100mg/mL of ravulizumab is ongoing with marketing authorisation expected to extend to these vial sizes by [redacted]£4,533 for 3mL vial (100 mg/mL), £16,621 for 11mL vial (100mg/mL). 100mg/mL formulation was used in the model base-case analysis as this formulation is expected to be approved by the time of the first appraisal committee meeting. The company also indicated that the increased drug concentration in these new vial sizes reduces the infusion times for ravulizumab. With the new vial sizes, the minimum infusion time is expected to range from 25–45 minutes for the loading dose and 30–55 minutes for maintenance doses.[26] The company assumed that the administration time for each infusion of ravulizumab 100mg/ml (infused at a 50mg/ml concentration) would be reduced to approximately the same administration time as each infusion of eculizumab. A scenario was modelled using the currently licensed 10mg/ml formulation. However, the ERG prefers to use the currently licensed 10mg/mL formulation in the ERG base-case analysis.

In the model, costs were sourced either from year 2018/2019 or 2020, except for the costs associated with transfusion administration. This was derived from a publication which reported costs from year 2014/15.[53] In response to the clarification letter, the company updated the model with the transfusion administration cost, which was inflated to year 2019, using the healthcare indices published in Unit Costs of Health and Social Care.[49]

A survey was developed to estimate inputs about the rates and causes of BTH and medical management for BTH.[11] Ten clinical experts were asked to estimate the proportion of patients requiring the resource use and average duration of resource use for four categories: general ward hospitalisation, intensive care unit (ICU) hospitalisation, medication and dialysis. In the absence of resource use data, the ERG thinks it is appropriate to source inputs from the survey.

6. COST EFFECTIVENESS RESULTS

6.1 Company's cost effectiveness results

Table 6.1 shows the key cost effectiveness results of the company's base-case analysis. Results are reported with the confidential PAS price assumed and discounted. Results indicated that ravulizumab accrued [redacted] incremental QALYs and was cost saving compared to eculizumab.

Table 6.1: Base-case cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Eculizumab	[redacted]	35.08	[redacted]	[redacted]	0.00	[redacted]	Ravulizumab dominates
Ravulizumab	[redacted]	35.08	[redacted]				

Source: Table 43 in CS [1]

Abbreviations: ICER, incremental cost effectiveness ratio; Inc., incremental; LYG, life years gained; QALY, quality-adjusted life year.

The disaggregated discounted QALYs by health state are shown in Table 6.2 and the disaggregated discounted costs by cost category are given in Table 6.3. The difference in QALYs between treatment arms is due to modelled ravulizumab benefit over eculizumab. The largest differences in costs across treatment arms are due to acquisition costs in the "No BTH" health state, which resulted in [redacted] difference for ravulizumab compared to eculizumab. However, these costs are outweighed by eculizumab due to patients requiring eculizumab up-dose. Thus, in the health state "continuous up-dose with history of incomplete C5 inhibition-related BTH event", the costs for eculizumab are [redacted], while there are no costs for ravulizumab in this health state (no incomplete C5 inhibition-related BTH events and no up-dose in the ravulizumab arm). This explains why in the company's base-case ravulizumab is cost saving compared to eculizumab.

Table 6.2: Summary of QALY gain by health state (base-case analysis)

Health state	QALY ravulizumab	QALY eculizumab	Increment	Absolute increment	% absolute increment
No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, Cont. up-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cont. up-dose, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spontaneous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state	QALY ravulizumab	QALY eculizumab	Increment	Absolute increment	% absolute increment
remission					
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	100%

Source: Table 15 in Appendix J to the CS.[19]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement amplifying condition; IncC5Inhib, incomplete C5 inhibition; QALY, quality-adjusted life year.

Table 6.3: Summary of costs by health state (base-case analysis)

Health state	Cost ravulizumab	Cost eculizumab	Increment	Absolute increment	% absolute increment
No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, Cont. up-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cont. up-dose, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spontaneous remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	100%

Source: Table 16 in Appendix J to the CS.[19]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement amplifying condition; IncC5Inhib, incomplete C5 inhibition.

Finally, Table 6.4 shows the estimated proportion of time spent in each of the model's health states in the company's base-case analysis. In the ravulizumab arm, since no incomplete C5 inhibition-related BTH events occurred, patients spent most of the time in the "No BTH" health state, with a small proportion of patients ([redacted]%) in the "CAC BTH" health state. In the eculizumab arm, on the contrary, patients may experience incomplete C5 inhibition-related BTH events and, as a consequence, receive eculizumab continuous up-dose. The company's base-case estimated that [redacted]% of patients would require eculizumab continuous up-dose, almost exclusively due to managing incomplete C5 inhibition-related BTH events. The company's base-case also estimated that [redacted]% of eculizumab patients spent their time in the "No BTH" health state. Thus, the "No BTH" and the

continuous up-dose health states account for almost 100% of the time eculizumab patients spent on the company's base-case analysis.

Table 6.4: Proportion of time spent in each health state by treatment arm (base-case analysis)

Health state	Eculizumab	Ravulizumab
No BTH	[redacted]	[redacted]
CAC BTH	[redacted]	[redacted]
IncC5Inhib BTH	[redacted]	[redacted]
Hx IncC5Inhib BTH, No BTH	[redacted]	[redacted]
Subsequent IncC5Inhib BTH	[redacted]	[redacted]
Hx IncC5Inhib BTH, CAC BTH	[redacted]	[redacted]
Hx IncC5Inhib BTH, Cont. up-dose	[redacted]	[redacted]
Cont. up-dose, CAC BTH	[redacted]	[redacted]
Spontaneous remission	[redacted]	[redacted]

Source: economic model.[41]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement amplifying condition; IncC5Inhib, incomplete C5 inhibition.

ERG comment: As previously discussed in Section 5.2.3 of this report and as shown in Table 6.4, the company's base-case seems to result in an overestimation of the number of patients requiring an up-dose in the eculizumab arm. The proportion of time spent in the continuous up-dose health states across the complete model time horizon is [redacted]%, which is approximately twice as much as the [redacted]% reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice. As a consequence, the company's base-case results might be biased against eculizumab.

6.2 Company's sensitivity analyses

The company conducted a number of sensitivity and scenario analyses. Sensitivity analyses included probabilistic sensitivity analyses (PSA), deterministic one-way sensitivity analyses (DSA) and additional scenario analyses to test the impact of model assumptions on the model results. The results of all these analyses are summarised below. Only discounted results are presented here.

6.2.1 Probabilistic sensitivity analysis

The company conducted a PSA in which all inputs were varied simultaneously over 1,000 iterations, based upon their distributional information. The parameters and the probability distributions used in the PSA are shown in Appendix T to the CS.[21] The PSA results are summarised in Table 6.5**,** and presented on a cost effectiveness (CE) plane in Figure 6.1, from which a cost effectiveness acceptability curve (CEAC) was calculated and plot in Figure 6.2.

The mean PSA results are consistent with the deterministic results shown in Table 6.1 and show that ravulizumab is also dominant compared to eculizumab with a similar QALY gains and cost savings as in the deterministic base-case analysis. As shown in Figure 6.1, every PSA iteration indicated that ravulizumab [redacted]. Therefore, as illustrated in Figure 6.2, the estimated probability that ravulizumab is a cost effective alternative to eculizumab [redacted].

Table 6.5: Mean probabilistic sensitivity analysis results

Technologies	Mean costs	Mean QALYs	Incremental		ICER
			Mean costs	Mean QALYs	
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
Ravulizumab	[redacted]	[redacted]			

Source: Table 43 in CS.[1]
Key: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Figure 6.1: Probabilistic sensitivity analysis cost effectiveness plane

Source: Figure 15 in CS.[1]
Abbreviations: QALY, quality-adjusted life year.

Figure 6.2: Probabilistic sensitivity analysis cost effectiveness acceptability curve

Source: Figure 16 in CS.[1]

ERG comment: Following the ERG request in the clarification letter,[19] additional parameters were included in the model submitted in response to the ERG clarification questions. These are summarised in Table 7.1 of this report. While parameter uncertainty is thus likely to be underestimated in the company's base-case analysis, it is also likely that this would have no impact on decision uncertainty, since all PSA outcomes in the company's base-case analysis are expected to remain in the south eastern quadrant of the CE-plane, even after these additional parameters are included in the PSA.

6.2.2 Deterministic sensitivity analysis

The results of the deterministic one-way sensitivity analysis are presented in Figure 6.3. One-way analyses were performed to evaluate the sensitivity of the ICER to individual inputs, holding all else constant. In the deterministic sensitivity analysis, the upper and lower bounds of a parameter were taken from their 95% confidence intervals if these were available from the data source. When such information was not available, the upper and lower bounds were assumed to be within ±25% for cost values and ±10% of the other base-case values. These are reported in Appendix T of the CS.[21]

In this analysis, conducted in terms of net monetary benefit (NMB), it was shown that the NMB was most sensitive to the probability of an incomplete C5 inhibition in eculizumab patients with no history of incomplete C5 inhibition BTH events. This was followed by the utility for ravulizumab and eculizumab patients with no history of BTH, the probability of a subsequent incomplete C5 inhibition BTH event in eculizumab patients with a history of incomplete C5 inhibition BTH event and the utility related to transfusion burden for patients on treatment. None of them resulted in a situation where the NMB was negative.

Figure 6.3: Cost effectiveness analysis – tornado diagram

Source: Figure 17 in CS.[1]
Abbreviations: BTH, break-through haemolysis; CH, cohort; NMB, Net Monetary Benefit; PAS, patient access scheme; Prob., probability; RBC, red blood cells.
Note: £30,000 willingness to pay threshold used

6.2.3 Scenario analysis

The company ran several scenario analyses to test the sensitivity of the cost effectiveness results to methodological, parameter and structural uncertainties in the economic analysis. A key scenario was built under the assumption of equal effectiveness of ravulizumab and eculizumab, as explained in Section 5.2.2 and 5.2.3 of this report. This analysis is, according to the company, consistent with the non-inferiority trial designs and provides a more conservative viewpoint. Given its importance within the current submission, the equal effectiveness scenario is presented separately below.

Equal effectiveness scenario

The results of the equal efficacy scenario are presented below in Table 6.6. At PAS price, ravulizumab is associated with incremental cost savings of [redacted]. The lower predicted savings estimated in this scenario compared to the base-case analysis are largely due to the assumed constant proportion of patients who receive the higher than licensed dose of eculizumab ([redacted]). In the base-case analysis, patients can transition into the continuous up-dosing health state at each model cycle, which results in a greater proportion of patients receiving the higher (and thus more costly) eculizumab dose over the total model time horizon.

Table 6.6: Equal effectiveness scenario – deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Eculizumab	[redacted]	35.08	[redacted]				
Ravulizumab	[redacted]	35.08	[redacted]	[redacted]	0.00	[redacted]	Dominant

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; Inc., incremental; LYG, life years gained; QALY, quality-adjusted life year.

Since no incomplete C5 inhibition BTH events were modelled in this scenario, all QALYs in the ravulizumab arm correspond to the "No BTH" health state, except for a very small proportion of patients in the "CAC BTH" health state. In the eculizumab arm, there were also no incomplete C5 inhibition BTH events but since continuous up-dose since the start of the simulation is assumed for [redacted]% of patients, [redacted] QALYs are accrued in the continuous up-dose health state, and the remaining QALYs in the "No BTH" health state (and a small proportion in the CAC-related health states). The disaggregated discounted costs by cost category can be interpreted in a similar way as it was done for the costs in the company's base-case presented in Table 6.3. The largest differences in costs across treatment arms are due to acquisition costs in the "No BTH" health state, where ravulizumab resulted in [redacted] additional costs compared to eculizumab. Also, in the equal effectiveness scenario, these costs are outweighed by eculizumab patients requiring an up-dose. Thus, in the health state "continuous up-dose with history of incomplete C5 inhibition-related BTH event", the costs for eculizumab are [redacted], while there are no costs for ravulizumab in this health state. Again, this explains why also in the equal effectiveness scenario ravulizumab is cost saving compared to eculizumab. Note, however, that in the equal effectiveness scenario, ravulizumab is less cost saving ([redacted]) than in the company's base-case ([redacted]). This is because, as shown in Table 6.7, in the equal effectiveness scenario [redacted]% of patients spent their time in the continuous up-dose health state, while in the base-case analysis this was [redacted]%, which is approximately two times larger (and probably an overestimation). Therefore, in the company's base-case analysis, eculizumab is a more expensive option than in the equal effectiveness scenario.

Table 6.7: Proportion of time spent in each health state by treatment arm (equal effectiveness scenario)

Health state	Eculizumab	Ravulizumab
No BTH	[redacted]	[redacted]
CAC BTH	[redacted]	[redacted]
IncC5Inhib BTH	[redacted]	[redacted]
Hx IncC5Inhib BTH, No BTH	[redacted]	[redacted]
Subsequent IncC5Inhib BTH	[redacted]	[redacted]
Hx IncC5Inhib BTH, CAC BTH	[redacted]	[redacted]
Hx IncC5Inhib BTH, Cont. up-dose	[redacted]	[redacted]
Cont. up-dose, CAC BTH	[redacted]	[redacted]
Spontaneous remission	[redacted]	[redacted]

Source: economic model.[41]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement amplifying condition; IncC5Inhib, incomplete C5 inhibition.

ERG comment: The proportion of time spent in the continuous up-dose health states across the complete model time horizon is [redacted]% in the company's base-case, which is approximately twice as much as the [redacted]% assumed in the equal effectiveness scenario and reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice. For this reason, the ERG prefers the equal effectiveness scenario over the company's base-case. However, for the reasons discussed in Section 5.2.3 regarding the generalisability of the trial populations to UK clinical practice, the ERG prefers a base-case scenario based completely on the clinical trials, without modelling eculizumab up-dose. Even though it is acknowledged that this will not be completely representative of the UK clinical practice.

Company's additional scenario analyses

The results of all other scenarios are presented in Table 6.8 at the ravulizumab PAS price. Despite the relatively large number of scenarios run by the company, the results were relatively insensitive in most of these analyses with ravulizumab remaining more effective and cost saving in all.

Table 6.8: Company's additional scenario analyses results

Scenario	Base-case	Scenario	Incremental costs	Incremental QALYs	ICER	NMB	% change from base-case NMB
Base-case			[redacted]	[redacted]	Dominant	[redacted]	0.0%
Time horizon	Lifetime	10 years	[redacted]	[redacted]	Dominant	[redacted]	-84.7%
Time horizon	Lifetime	20 years	[redacted]	[redacted]	Dominant	[redacted]	-54.1%
Discount rate (costs and QALYs)	3.50%	0.00%	[redacted]	[redacted]	Dominant	[redacted]	127.2%
Discount rate (costs and QALYs)	3.50%	6.00%	[redacted]	[redacted]	Dominant	[redacted]	-39.4%
Utility increment of ravulizumab vs eculizumab	0.0570	0.000	[redacted]	[redacted]	Dominant	[redacted]	-5.8%
Utility increment of ravulizumab vs eculizumab	0.0570	0.025	[redacted]	[redacted]	Dominant	[redacted]	-3.1%
Utility increment of ravulizumab vs eculizumab	0.0570	0.050	[redacted]	[redacted]	Dominant	[redacted]	-0.7%
EORTC to EQ-5D mapping (value set)	Longworth et al. (2014)	McKenzie and van der Pol. (2009)	[redacted]	[redacted]	Dominant	[redacted]	0.1%
HRQL regression population	Separate	Pooled	[redacted]	[redacted]	Dominant	[redacted]	0.0%
Utility: general population age adjustment	Applied	Not applied	[redacted]	[redacted]	Dominant	[redacted]	0.5%
Utility: general population cap	Applied	Not applied	[redacted]	[redacted]	Dominant	[redacted]	0.3%
BTH excess mortality (HR) vs background	1.00	4.81	[redacted]	[redacted]	Dominant	[redacted]	-1.7%
CAC BTH up-dosing	Yes	No	[redacted]	[redacted]	Dominant	[redacted]	-1.1%
Spontaneous remission rate (per cycle)	0.0000	0.0005	[redacted]	[redacted]	Dominant	[redacted]	-24.4%

Scenario	Base-case	Scenario	Incremental costs	Incremental QALYs	ICER	NMB	% change from base-case NMB
Spontaneous remission rate (per cycle)	0.0000	0.0006	[redacted]	[redacted]	Dominant	[redacted]	-28.8%
Spontaneous remission rate(per cycle)	0.0000	0.0010	[redacted]	[redacted]	Dominant	[redacted]	-42.1%
Incomplete C5 inhibition BTH duration (days)	2	3	[redacted]	[redacted]	Dominant	[redacted]	0.0%
Incomplete C5 inhibition BTH duration (days)	2	7	[redacted]	[redacted]	Dominant	[redacted]	0.0%
Ravulizumab formulation	100mg/ml	10mg/ml	[redacted]	[redacted]	Dominant	[redacted]	-0.1%
Permanent eculizumab up-dosing per clinical practice dose	Licensed dose at model entry	English clinical practice dosing and no incomplete C5 inhibition BTH events	[redacted]	[redacted]	Dominant	[redacted]	-37.5%

Source: Table 46 in CS.[1]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement-amplifying condition; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life year.

ERG comment: The results of the additional scenarios presented by the company showed that ravulizumab was more effective and cost saving compared to eculizumab in all of them. This is expected given that all scenarios resulted from variations in the company's base-case where proportion of time spent in the continuous up-dose health states across the complete model time horizon was [redacted]%, twice as much as the [redacted]% assumed in the equal effectiveness scenario and reported by the company to be expected in patients receiving an increased dose of eculizumab in UK clinical practice. In previous sections of this report, it has been discussed that the proportion of patients requiring an eculizumab up-dose is the main driver of the cost effectiveness results. This will be further explored by the ERG in Chapter 7 of this report. Since in all scenarios presented in Table 6.8 the assumption about the number of patients requiring an eculizumab up-dose remain unchanged with respect to the company's base-case, it is logical that these scenarios keep showing ravulizumab as a dominant option compared to eculizumab. For this reason, the ERG feels that the impact of some key assumptions on the model results was not sufficiently tested by the company. In particular, a scenario completely based on the trials' settings, where eculizumab up-dose was not allowed seems to be of great importance and it was not explored in the CS. Also, explorations on the equal effectiveness scenario instead of the company's base-case or the duration of ravulizumab treatment effect seem to represent key sources of uncertainty to be addressed in detail. These uncertainties were explored by the ERG in their additional scenario analyses in Section 7.1.3 of this report.

6.3 Model validation and face validity check

Several aspects of validation were discussed by the company in the validation section of the CS (B.3.10).[1] The validation of the conceptual model was assessed by three clinicians and one health economics expert at an Advisory Board meeting conducted by the company.[11] At the same meeting, all input parameters considered in the economic model were also validated.

Additionally, the company discussed in the CS validation regarding overall survival and utilities (as input parameters of the model) in more detail. In particular, the company assumed that (overall) survival was equal to that of the age- and gender-matched general population. To support this assumption the company referred to the studies by Socie et al. (1996) and Kelly et al. (2008).[34, 54] Socie et al. (1996) studied survival of 2,356 PNH patients who were enrolled in the International PNH registry. The study aimed to determine the prognosis of patients with aplastic anaemia, an underlying bone marrow disorder. In total, 16% of the patients included in the study were presented with aplastic anaemia, and 1% of these died of causes that were related to aplastic anaemia in the study follow-up period.[34] Kelly et al. (2008) conducted a study in 79 patients in Leeds, thus, an UK patient cohort. The study reported the presence of bone marrow disorders in a minority of patients. However, the study concluded that "*survival of patients treated with eculizumab was not different from age- and sex-matched normal controls*".[54] The utilities used in the economic analyses were derived from EQ-5D data mapped from EORTC-QLQ-C30 data collected in both ALXN1210-PNH-301 and ALXN1210-PNH-302. The company compared these utilities with the utilities reported in Coyle et al. (2014), a study which was identified in the economic systematic literature review.[55] In this study, the following three utilities were reported based on transfusion requirement: transfusion independent (utility value 0.84), reduced transfusion requirement (utility value 0.77) and transfusion dependent (utility value 0.60). The (mapped) utilities used in the company's economic analyses, resulted in a baseline utility of 0.82 in ALXN1210-PNH-301 and 0.86 in ALXN1210-PNH-302. A utility decrement of -0.07 (estimated from the mixed effects regression in the trial) was applied to account for the need for transfusion. This decrement is the same as the difference in the utilities for reduced transfusion requirement and transfusion independent reported in Coyle et al. (2014).[55]

Regarding the verification of the electronic model, the company indicated that, after the model was finalised, internal modellers (not mentioned how many) undertook its validation. A programmer who was not involved in building the model reviewed all formulae and labelling in the model. Further details on the model verification efforts were not reported.

Finally, the company discussed validation of several model outcomes (both final and intermediate). As mentioned in Section 5.2.3 of this report, across the model time horizon of 20 years, patients spent 24.3% of their time in the eculizumab up-dosed states, which is similar to the [redacted]% reported by the PNH National service and the [redacted]% derived from UK data from the International PNH Registry, of patients who require eculizumab maintenance dosing higher than the labelled 900mg to achieve and maintain efficacy.[38]

The modelled rate of transfusion, which was also derived from ALXN1210-PNH-301 and ALXN1210-PNH-302, was validated using the results of a survey on BTH and medical management strategies conducted by the company with a group of 10 clinicians who were experts in treating PNH. According to the company, the experts indicated that patients would receive a transfusion in approximately 30%–35% of incomplete C5 inhibition-related BTH events and in approximately 15% of CAC-related BTH events. These frequencies are in line with the probabilities derived from ALXN1210-PNH-301 and ALXN1210-PNH-302.

The incremental QALY benefit of ravulizumab compared to eculizumab obtained in the base-case, was compared to the results reported in the O'Connell et al. studies,[31, 32] which were obtained from the same model used in this submission but under the US and Germany settings. The incremental QALYs reported in the US and German studies were 1.67 and 0.53, respectively. The company's base-case resulted in [redacted] incremental QALY, [redacted]. The company explained that this was expected because a smaller utility benefit due to the reduced dosing frequency of ravulizumab was used in the German analysis, which was published prior to the availability of the DCE results used in this submission. In the US and German analyses no age-adjustment to the utility values or utility capping were applied. Additionally, the US analysis used a different mapping algorithm (McKenzie et al. 2009[56]) and included treatment arm as a covariate in the regression equation used to estimate utilities. These two different assumptions led to increased incremental QALYs according to the company.

Health state costs were based on the results of a survey of 10 clinicians, experts in the treatment of PNH with both eculizumab and ravulizumab. The results of this survey were also used to inform a separate cost analysis in the US. This analysis estimated that a total annual cost of BTH management of $386 per ravulizumab-treated patient and $3,472 per eculizumab-treated patient, excluding pregnant women.[57] This shows that BTH management costs for ravulizumab were approximately 11% of BTH management costs for eculizumab. As shown in Table 6.3, in the company's base-case this was approximately 9%, which is in line with what was observed in the US study.

ERG comment: The company discussed important validation aspects in the CS. Furthermore, in response to clarification B25,[19] a filled-in version of the validation tool AdViSHE was included as part of the response.[58] All validation aspects in the tool were covered to some extent.

As discussed, in Section 5.2.3 of this report, the ERG is concerned that the company's base-case analysis overestimates the number of patients in the continuous up-dose health states, which as will be explained in Chapter 7 of this report, has a major impact on the model results. The company indicated that "*across the model time horizon of 20 years*",[1] patients spend 24.3% of their time in the continuous up-dose health states and that this closely aligns with the [redacted]% from the PNH National

Service, which, according to the company, provides a measure of external validation. However, the ERG is unclear why the company has reported the previous comparison "*across the model time horizon of 20 years*" and not across the complete model time horizon where the proportion of time spent in the continuous up-dose health states is [redacted]% (see Table 6.4), which is approximately twice as much as the [redacted]% reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice and, therefore, a large overestimation of the number of patients requiring an up-dose in the eculizumab arm. In the equal effectiveness scenario, the proportion of time spent in the continuous up-dose health states *across the complete model time horizon* was assumed to be exactly [redacted]%, which is equal to the proportion of patients expected to receive an increased dose of eculizumab in UK clinical practice. The ERG understands that the proportion of patients expected to receive an increased dose of eculizumab in UK clinical practice refers to the complete time horizon. Therefore, the assumption in the equal effectiveness scenario is in line with the ERG expectations. In response to clarification question B7,[19] the company indicated that "*both pharmacoeconomic analyses incorporate the clinical practice of up-dosing and are therefore reflective of the disease pathway and clinical management of PNH patients who meet the criteria for complement-inhibitor treatment in the UK. As such, both analyses are equally clinically plausible*".[19] The ERG does not agree with the company's interpretation of the plausibility of the scenarios seeing that they greatly differ in this very important aspect. However, the ERG considers that it is up to the Committee to decide which scenario is clinically more plausible.

7. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

7.1 Exploratory and sensitivity analyses undertaken by the ERG

7.1.1 Explanation of the company adjustments after the request for clarification

In their response to clarification question B27,[19] the company explained what changes were made in response to the ERG clarification questions. These are summarised in Table 7.1. These changes did not impact the base-case results, except for the update of the cost for transfusion administration. The impact of this change on the overall results was negligible.

Table 7.1: Summary of model changes and impact on the base-case results

Change	Model change (sheetname:cellname)	Impact on base-case ICER
Inclusion of Bayesian prior distribution option in response to question B5	Inputs:H67 [IO]_Model_BayesPrior Addition of model option to include Bayesian prior in response to question B5	No change (not included in base-case analysis)
Inclusion of a treatment arm utility option in response to question B15	Input:H160 [IO]_HU_InclTxArm Addition of model option to include treatment arm in response to question B15	No change (not included in base-case analysis)
Update of the cost for transfusion administration	Inputs:H259 Update on cost in response to question B22	ICER remains dominant
Inclusion of parameters into OSWA and PSA Weight for age Cohort proportions Utility regression coefficients Bayesian priors in response to question B5	Analysis parameters: K17:K123, N17:N123, K206:K217 K206,K212 – text change to Yes Analysis parameters:N175:N185 – text change to No Updated in response to question B 24	No change (not included in base-case analysis)
Inclusion of option to model joint variance	PSA:K8 PSA_Jointvar_include Updated to include option to test joint variance in the PSA (applies to utility covariates and Ara and Brazier general population utility variance)	No change (not included in base-case analysis)
Source: Table 10 in clarification letter response.[19]		

7.1.2 Explanation of the ERG adjustments

The changes made by the ERG (to the model received with the response to the clarification letter) were subdivided into the following three categories, according to Kaltenthaler et al. 2016:[59]

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to).

- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred).

After these changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

Fixing errors

1. Error in the model "Output" sheet in the ca1culation of the proportion of time spent in the model health states. This has no impact on the model cost effectiveness results, but it is important for clinical validation.

Fixing violations

2. No violations to the NICE reference case, scope or best practice were identified by the ERG.

Matters of judgement

3. Eculizumab up-dose: based completely on the clinical trials ALXN1210-PNH-301 and ALXN1210-PNH-302. Thus, without modelling eculizumab up-dose.
4. Utilities: ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate.
5. Utilities: additional utility benefit for treatment frequency set to 0 (instead of 0.057, as derived from the DCE).
6. Ravulizumab currently licensed 10mg/ml formulation (instead of 100mg/ml).

The overview of the changes and the bookmarks for the justification of the ERG changes are presented in Table 7.2.

Table 7.2: Company and ERG base-case preferred assumptions

Base-case preferred assumptions	Company	ERG	Justification for change
Eculizumab up-dose	Eculizumab up-dose per UK clinical practice (without continuous up-dose from the start). Continuous up-dose from start in the "equal effectiveness" scenario.	No eculizumab up-dose. Based completely on ALXN1210-PNH-301 and ALXN1210-PNH-302.	The ERG is concerned that, in the company's base-case, the proportion of time spent in the continuous up-dose health states largely overestimates what is expected in clinical practice (Section 5.2.3). The ERG is concerned that the patients requiring eculizumab up-dose were underrepresented in the trials. Trial data suggests that approximately 5% of patients in the trial population would need an eculizumab up-dose, which is approximately [redacted] lower than what is expected in UK clinical practice. The ERG wonders whether the conclusions from the trials would be the same if there were approximately [redacted]% of patients who would need an up-dose (Section 5.2.3).
Utilities – assumption 1	Ravulizumab utility derived from a mixed-effects regression model without treatment as covariate.	Ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate.	The ERG prefers a non-significant utility benefit of 0.0103 and 0.0197 estimated from trials ALXN1210-PNH-301 and ALXN1210-PNH-302 respectively for ravulizumab, derived from a mixed-effects regression model, as the source of HRQoL benefit in the cost effectiveness model. The ERG prefers not to use the utility benefit for treatment frequency of 0.057 as derived from the DCE. The ERG is concerned that the benefit derived from the DCE overestimates ravulizumab benefit (Section 5.2.8).
Utilities – assumption 2	Ravulizumab utility benefit for treatment frequency (0.057) derived from DCE.	Additional utility benefit for treatment frequency set to 0.	
Ravulizumab formulation	Ravulizumab 100mg/ml	Ravulizumab currently licensed	Ravulizumab 10mg/ml is the currently

Base-case preferred assumptions	Company	ERG	Justification for change
	formulation	10mg/ml formulation (instead of 100mg/ml)	licensed formulation (Section 5.2.9)
Abbreviations: DCE = discrete choice experiment; ERG = Evidence Review Group			

7.1.3 Additional scenarios conducted by the ERG

The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. These key uncertainties were related to the number of patients requiring eculizumab up-dose, the utilities and BTH excess mortality. A list of scenario analyses conducted by the ERG is given below.

Scenario analysis 1: Alternative distribution of patients in Cohort 3 in the "equal effectiveness" scenario

Cohort 3 is assumed to reflect UK clinical practice, where a continuous increased dose of eculizumab is used to manage BTH events. The reported range of PNH patients requiring this up-dose is between 5% and 29%, with an estimated mean value of [redacted]%.[12-15] In this scenario, the impact of assuming a smaller population (5%) in Cohort 3 was explored by the ERG. The rationale for this scenario is to consider a lower percentage of patients requiring continuous up-dose to align with the proportion of these patients that is suspected to be in the trials (see Section 5.2.3) and that is still within the limits provided by the company. Therefore, the ERG feels that this "equal effectiveness" scenario would be more reflective of what might occur in the trials, should eculizumab up-dose be allowed.

Scenario analysis 2: Alternative utilities and ravulizumab formulation in the company's "equal effectiveness" scenario

The assumptions on utilities and costs used in the ERG base-case as explained in Section 7.1.2, were explored in the company's "equal effectiveness scenario". Thus, in this scenario, the ERG assumed [redacted]% of patients in Cohort 3, the ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate, the additional utility benefit for treatment frequency set to 0 and the ravulizumab formulation of 10mg/ml.

Scenario analysis 3: Alternative utilities and ravulizumab formulation in the company's base-case

The assumptions on utilities and costs used in the ERG base-case as explained in Section 7.1.2, were explored in the company's base-case. Thus, in this scenario, the ERG assumed eculizumab up-dose as in the company's base-case (continuous after second incomplete C5 inhibition-related BTH event), the ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate, the additional utility benefit for treatment frequency set to 0 and the ravulizumab formulation of 10mg/ml.

Scenario analysis 4: ERG base-case with alternative utility values

In these scenarios, the ERG explored the impact of assuming the utility decrement of 0.057 (instead of 0) as in the company base-case, and half of this value (0.029). The remaining ERG preferred assumptions were as in ERG base-case. Thus, in this scenario, the ERG also assumed no eculizumab up-dose and the ravulizumab formulation of 10mg/ml.

Scenario analysis 5: ERG base-case with BTH excess mortality

In this scenario, the ERG base-case was run with the assumption of BTH excess mortality as reported by Jang et al. (2016).[36] A standard mortality ratio of 4.81 was thus applied for this scenario.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

7.2.1 Results of the ERG preferred base-case scenario

The results of the ERG preferred base-case are provided in Table 7.3. After the implementation of the ERG's preferred assumptions, the ICER was £38,290. Ravulizumab was estimated to provide [redacted] additional QALYs at an incremental cost of £[redacted] compared to eculizumab. As can be seen in Table 7.4, the incremental QALY gains for ravulizumab stemmed from the incomplete C5 inhibition-related BTH events modelled in the eculizumab arm. Finally, in Table 7.5 it is observed that the largest differences in costs across treatment arms are due to acquisition costs in the "No BTH" health state, which resulted in £[redacted] difference for ravulizumab compared to eculizumab. Eculizumab costs associated to management of incomplete C5 inhibition-related BTH events (with no up-dose as in the trials) add up to £[redacted], which unlike the company base-case and equal effectiveness scenario, do not outweigh the higher costs of eculizumab in the "No BTH" health state. This explains why in the ERG base-case (when eculizumab up-dose is not modelled as in the clinical trials) ravulizumab is not cost saving compared to eculizumab.

Table 7.3: ERG base-case deterministic results (no eculizumab up-dose)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Eculizumab	[redacted]	35.08	[redacted]	[redacted]	0.00	[redacted]	£38,290
Ravulizumab	[redacted]	35.08	[redacted]				

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Table 7.4: ERG base-case disaggregated discounted QALYs (no eculizumab up-dose)

Health state	QALY ravulizumab	QALY eculizumab	Increment	Absolute increment	% absolute increment
No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, Cont. up-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cont. up-dose, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spontaneous remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state	QALY ravulizumab	QALY eculizumab	Increment	Absolute increment	% absolute increment
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	100%

Source: economic model.[41]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement amplifying condition; IncC5Inhib, incomplete C5 inhibition; QALY, quality-adjusted life year.

Table 7.5: ERG base-case disaggregated costs (no eculizumab up-dose)

Health state	Cost ravulizumab	Cost eculizumab	Increment	Absolute increment	% absolute increment
No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, Cont. up-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cont. up-dose, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spontaneous remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	100%

Source: economic model.[41]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement amplifying condition; IncC5Inhib, incomplete C5 inhibition.

7.2.2 Results of the ERG preferred sensitivity analysis

The ERG also conducted a PSA using their preferred base-case assumptions. As shown in Table 7.1, the company included in the PSA additional parameters, following the ERG request in the clarification letter.[19] No further adjustments were made to the PSA by the ERG. The PSA results obtained after the ERG adjustments can be seen in Table 7.6. The probabilistic ICER was £46,976 per QALY gained (incremental costs were £[redacted] and incremental QALYs were [redacted]), thus, £8,686 larger than the ERG deterministic ICER. Even though the ERG was unable not retrieve PSA results disaggregated per health state (it is unclear whether this is possible in the company's model), the ERG considers that this relatively large difference might be explained by the inclusion of a prior distribution in the transition probabilities associated to experiencing incomplete C5 inhibition-related BTH events in the ravulizumab arm. Thus, unlike the deterministic ERG base-case, the ERG PSA

allows a proportion of patients in the ravulizumab arm to transition to the incomplete C5 inhibition-related BTH events related health states. The estimated size of this proportion of patients is unknown to the ERG but it is expected to be small. The CE-plane and CEAC resulting from the ERG PSA are shown in Figure 7.1 and 7.2, respectively. The CE-plane shows approximately [redacted]% of the simulations (according to the CEAC) in the south eastern quadrant, in which ravulizumab is dominant, with a few simulations showing large savings in costs. The remaining simulations are in the north eastern quadrant of the CE-plane, where ravulizumab is both more effective and more costly than eculizumab. The CEAC shows that the probability of ravulizumab being cost effective was [redacted]% at a threshold ICER of £30,000 per QALY gained.

Table 7.6: Mean PSA results - ERG base-case (no eculizumab up-dose)

Technologies	Mean costs	Mean QALYs	Incremental		ICER
			Mean costs	Mean QALYs	
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	£46,976
Ravulizumab	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 7.1: ERG preferred cost effectiveness plane (no eculizumab up-dose)

Source: economic model.[41]
QALY = quality-adjusted life year

Figure 7.2: ERG preferred cost effectiveness acceptability curve (no eculizumab up-dose)

Source: economic model.[41]

The adjustments made by the ERG to the company's base-case also had an impact on the univariate sensitivity analyses. As shown in Figure 7.3, in general the NMB was most sensitive to utilities and to the probability of an incomplete C5 inhibition-related events in eculizumab patients. These parameters resulted in NMB ranges including both negative and positive values.

Figure 7.3: ERG tornado diagram (no eculizumab up-dose)

Source: economic model.[41]
Abbreviations: BTH, break-through haemolysis; CH, cohort; NMB, Net Monetary Benefit; PAS, patient access scheme; Prob., probability; RBC, red blood cells.
Note: £30,000 willingness to pay threshold used

7.2.3 Results of the ERG additional exploratory scenario analyses

Scenario analysis 1: Alternative distribution of patients in Cohort 3 in the "equal effectiveness" scenario

Assuming 5% of patients in Cohort 3 in the "equal effectiveness" scenario had a substantial impact on the model results. As can be seen in Table 7.7, ravulizumab became a cost saving option compared to eculizumab under this assumption. The incremental QALYs predicted by the model in this scenario were [redacted] and the incremental costs [redacted].

Table 7.7: ERG scenario analyses on Cohort 3 patients in the equal effectiveness scenario

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	0.33	Ravulizumab dominates
Ravulizumab	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Scenario analysis 2: Alternative utilities and ravulizumab formulation in the company's "equal effectiveness" scenario

Assuming the ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate, with the additional utility benefit for treatment frequency set to 0 and the ravulizumab formulation of 10mg/ml, while keeping the proportion of patients in Cohort 3 as in the company's "equal effectiveness" scenario ([redacted]%), did not change the conclusions drawn from the "equal effectiveness" scenario as run by the company. As can be seen in Table 7.8, in this scenario ravulizumab is associated with incremental cost savings of [redacted] and [redacted] incremental QALYs. Incremental cost savings were nearly identical to those in the company's "equal effectiveness" scenario ([redacted]) where the incremental QALYs were larger ([redacted]), as can be seen in Table 6.6. This shows the impact of assuming a different approach to utilities but overall ravulizumab remained a dominant option over eculizumab in both scenarios.

Table 7.8: ERG scenario analyses on alternative utilities and costs in the equal effectiveness scenario

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
Ravulizumab	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Scenario analysis 3: Alternative utilities and ravulizumab formulation in the company's base-case

Assuming the ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate, with the additional utility benefit for treatment frequency set to 0 and the ravulizumab formulation of 10mg/ml, under the assumptions of the company's base-case (continuous after second incomplete C5 inhibition-related BTH event), did not change the conclusions drawn from the company's base-case. As can be seen in Table 7.9, in this scenario ravulizumab is associated with incremental cost savings of [redacted] and [redacted] incremental QALYs. Incremental cost savings were nearly identical to those in the company's base-case ([redacted]) where the incremental QALYs were larger ([redacted]), as can be seen in Table 6.1. This shows the impact of assuming a different approach to utilities but overall ravulizumab remained a dominant option over eculizumab in both scenarios.

Table 7.9: ERG scenario analyses on alternative utilities and costs in the company's base-case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
Ravulizumab	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Scenario analysis 4: ERG base-case with alternative utility values

The impact of assuming the utility decrement of 0.057 (instead of 0) as in the company base-case, and half of this value (0.029) can be seen in Table 7.10 and 7.11, respectively. In both scenarios, the difference with respect to the ERG base-case was on the incremental QALYs only, since the costs were unchanged, as can be seen in Table 7.3. The two scenarios explored in this section resulted in larger QALY gains for ravulizumab because an additional utility benefit for treatment frequency was assumed. The larger the assumed benefit, the larger the incremental QALYs, which were [redacted] and [redacted], respectively; both larger than the [redacted] incremental QALYs in the ERG base-case. The ICERs were £11,790 and £17,688, respectively; both below the common threshold ICER of £30,000 per QALY gained.

Table 7.10: ERG scenario analyses with alternative utilities – decrement 0.057

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	£11,790
Ravulizumab	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Table 7.11: ERG scenario analyses with alternative utilities – decrement 0.029

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	0.92	£17,688
Ravulizumab	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Scenario analysis 5: ERG base-case with BTH excess mortality

The impact of assuming BTH excess mortality by applying the standard mortality ratio of 4.81 by Jang et al. (2016),[36] can be seen in Table 7.12. The ICER in this scenario was £124,433, more than three times larger than the ERG base-case. Despite resulting in more incremental QALYs than the ERG base-case ([redacted] vs. [redacted]), the increased incremental costs was the main cause for this large ICER.

This can be explained by the life years gained in the eculizumab arm. In the company base-case, eculizumab resulted in 35.08 life years, whereas in the scenario with BTH excess mortality eculizumab resulted in 34.42 life years, which in turn, had a great impact on eculizumab total costs compared to ravulizumab where the difference in life years with respect to the ERG base-case was only 0.01.

Table 7.12: ERG scenario analyses with BTH excess mortality

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Eculizumab	[redacted]	34.32	[redacted]		0.75	[redacted]	£124,433
Ravulizumab	[redacted]	35.07	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

7.3 ERG's preferred assumptions

The ERG preferred changes to the updated company base-case were described in Section 7.1.2 of this report. The cost effectiveness results of the ERG preferred base-case are presented in Table 7.13 in four steps. In each step, the cumulative impact on the model results is shown. Additionally, in Table 7.14, the individual impact of each change on the model results is shown.

Table 7.13: ERG's preferred model assumptions – cumulative impact on results

Preferred assumption	Section in ERG report	Ravulizumab		Eculizumab		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case (after clarification)	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
ERG change 1: no eculizumab up-dose	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,798
ERG change 2: utilities (treatment arm as covariate)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,538
ERG change 3: utilities (no additional utility benefit for treatment frequency)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,474
ERG change 4: ravulizumab 10mg vial	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,290

Based on the CS and the electronic model of the CS.[1, 41]
Abbreviations: ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; QALY = quality adjusted life year

Table 7.14: ERG's preferred model assumptions – individual impact on results

Preferred assumption	Section in ERG report	Ravulizumab		Eculizumab		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
ERG change 1: no eculizumab up-dose	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,798
ERG change 2: utilities (treatment arm as covariate)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
ERG change 3: utilities (no additional utility benefit for treatment frequency)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
ERG change 4: ravulizumab 10mg vial	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates

Based on the CS and the electronic model of the CS.[1, 41]
Abbreviations: ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; QALY = quality adjusted life year

7.4 Conclusions of the cost effectiveness section

The company developed a state transition model in Excel with eight BTH-related health states, one mortality-related health state, and a spontaneous-remission health state. Two main types of BTH events were considered in ALXN1210-PNH-301 and ALXN1210-PNH-302 and included in the model: incomplete C5 inhibitor-related BTH and CAC-related BTH. Additionally, undetermined BTH events, defined as those deemed to have neither incomplete C5 inhibition nor concomitant infection, were considered as CAC-related BTH events in the analyses. In UK clinical practice, an increased dose of eculizumab is used to manage BTH events. However, eculizumab dosing changes were not allowed in ALXN1210-PNH-301 and ALXN1210-PNH-302. In order to include eculizumab up-dosing in the economic model, the company assumed in their base-case analysis that CAC-related BTH events were managed with one single up-dose in both treatment arms. Incomplete C5 inhibition-related BTH events were only modelled in the eculizumab arm. A single eculizumab up-dose was assumed for the first two incomplete C5 inhibition-related BTH events. A continuous up-dose was assumed for the rest of the model time horizon after a second incomplete C5 inhibition-related BTH event.

Three different patient cohorts were included in the economic analyses depending on whether patients were either complement inhibitor naïve (Cohort 1) or treatment experienced. Treatment experienced patients (and clinically stable on eculizumab) were classified as patients on the licensed dose of eculizumab (900mg – Cohort 2) and patients on a higher-than-labelled dose (1200mg – Cohort 3). Despite eculizumab dosing changes for patients who experienced BTH events not being allowed in ALXN1210-PNH-301 and ALXN1210-PNH-302, PNH National Service data suggests that an increased dose of eculizumab is used in UK clinical practice to achieve complete terminal complement inhibition in [redacted]% of the patients receiving label dose of eculizumab (900mg) treatment.[12-15, 38] Thus, Cohort 3 was included in the model to reflect the proportion of patients who receive an eculizumab dose greater than 900mg from the start of the model, which is consistent with UK clinical practice. This is the rationale for considering Cohort 3 in the "equal effectiveness" scenario, in which only CAC-related BTH events were included in the analysis. The proportion of patients in each cohort was estimated as [redacted] in Cohort 1 (treatment naïve patients) and [redacted] in Cohort 2 (treatment experienced and on eculizumab label dose). Only these two cohorts were included in the company's base-case. Additionally, in the "equal effectiveness scenario" the company assumed that a proportion of patients in Cohort 2 were allowed to start the simulation on higher-than-labelled eculizumab dose, thus in Cohort 3. Therefore, in the equal effectiveness scenario, the proportions of patients in each cohort were [redacted] in Cohort 1, [redacted] in Cohort 2 and [redacted] in Cohort 3.

The company used the data and the outcomes assessed in the two pivotal trials in the economic model for the different patient cohorts included. The base-case is aligned with the trial population and observed outcomes. Given that eculizumab was administered at its licensed dose in the pivotal trials, the efficacies of eculizumab and ravulizumab were taken directly from the respective clinical trials and treatment arms. However, up-dosing of eculizumab was included in the base-case analysis to reflect UK clinical practice.

HRQoL benefit in terms of utilities was assessed by mapping the QLQ-C30 to EQ-5D-3L. The company argued that the HRQoL benefit of ravulizumab could not be assessed in the trials and, therefore, used utility values in the cost effectiveness model that were sourced from a discrete choice experiment.

A list price of £4,533 per 300mg vial was approved for ravulizumab by the Department of Health and Social Care. A patient access scheme (PAS) price of [redacted] per 300mg for ravulizumab (representing

a discount of [redacted] on the list price) has been submitted by the company to reduce [redacted].[1]

The company's base-case results indicated that ravulizumab accrued [redacted] incremental QALYs and was cost saving compared to eculizumab. The disaggregated discounted costs by health state showed that the largest differences in costs across treatment arms were due to acquisition costs in the "No BTH" health state, which resulted in [redacted] difference for ravulizumab compared to eculizumab. However, these costs were outweighed by eculizumab due to patients requiring eculizumab up-dose. Thus, in the health state "continuous up-dose with history of incomplete C5 inhibition-related BTH event", the costs for eculizumab are [redacted], while there are no costs for ravulizumab in this health state (no incomplete C5 inhibition-related BTH events and no up-dose in the ravulizumab arm). This explains why in the company's base-case ravulizumab was cost saving compared to eculizumab. However, the proportion of time spent in the continuous up-dose health states across the complete model time horizon was [redacted]%, which is approximately twice as much as the [redacted]% reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice. As a consequence, the company's base-case results might be biased against eculizumab. The results of the additional scenarios presented by the company (including the PSA) did not change the conclusions drawn from the company's base-case.

The ERG is unclear how patients with undetermined BTH events were treated in the clinical trials. Therefore, the ERG was unable to judge the appropriateness of modelling undetermined BTH events as CAC-related BTH events. Also, the ERG feels that the rationale to assume to treat all CAC-related events with an eculizumab up-dose should have been better justified. With the evidence presented in the CS and the response to the clarification letter, the ERG preferred to assume that CAC-related BTH events would not be treated with an eculizumab up-dose, in line with what was observe in the clinical trials in which up-dose was not allowed.

As mentioned above, the ERG is concerned that the company's base-case analysis might overestimate the proportion of time spent in the continuous up-dose health states and consequently the results might be biased against eculizumab. In the "equal effectiveness" scenario, the proportion of time spent in the continuous up-dose health states *across the complete model time horizon* was assumed to be exactly [redacted]%, matching the PNH National Service estimate of the proportion of patients expected to receive an increased dose of eculizumab in UK clinical practice. This is the main reason why the ERG prefers the "equal effectiveness" scenario over the company's base-case. However, the ERG considers that it is up to the Committee to decide which scenario is clinically more plausible.

The ERG is also concerned that the sub-population of patients who would require an eculizumab up-dose might be underestimated in the trials. In response to clarification question B6,[19] the company explained that 11 out of a total of 219 patients (approximately 5%) in the trial population would need an eculizumab up-dose, which is approximately [redacted] lower than the [redacted]% estimate from the PNH National Service. This might indicate that the population in the trials was not representative of the UK population. Furthermore, the ERG wonders whether the conclusions from the trials, in which only 5% of patients would be "eligible" for an eculizumab up-dose, would be the same if there were approximately [redacted]% of patients who would need such an up-dose (as in UK clinical practice). The fact that only 5% of patients would be "eligible" for an eculizumab up-dose in the trials, as opposed to

approximately [redacted]% in UK clinical practice might indicate more severe disease in the UK treated population. Additional data may help reducing the uncertainty regarding this aspect of the analysis.

In conclusion, the ERG considers that the "equal effectiveness" scenario provides a better representation of UK clinical practice than the company's base-case scenario because it seems to overcome the main ERG concern regarding modelling eculizumab up-dose: the overestimation of the number of patients requiring an up-dose in the eculizumab arm. Nevertheless, the ERG is also concerned that the trial population might not be representative of the UK PNH population and, for that reason, the ERG prefers a base-case scenario based completely on the clinical trials, thus, with no eculizumab up-dose included in the model, even though it is acknowledged that this will not be completely representative of UK clinical practice. The ERG considers that, with the current evidence, neither the company base-case nor the equal effectiveness scenario would provide a better representation of UK clinical practice.

The ERG is also concerned about the company's assumption of a constant lifelong ravulizumab treatment effect. In response to clarification question B13,[19] the company refused to model a decline in treatment effect over time as this was not considered clinical plausible. However, it might be argued that data from over 10 years are available only for eculizumab and the long-term effects of ravulizumab are unknown. Given the time constraints associated to this project, the ERG was unable to run a scenario where a decline in treatment effect over time was included in the model. Additionally, the ERG could not validate the transition probabilities that the company derived from patient-visit-level data from the pivot trials, since the data needed for that were not provided to the ERG.

The ERG disagrees that HRQoL could not be assessed in the trial, as the administration frequency for ravulizumab was lower in the trial and substantial benefits, other than time of the patient, ought to be captured in the trial. Furthermore, the ERG argues that the methodological challenges of the discrete choice experiment outweigh its benefit as an external source for utility values. The ERG prefers a non-significant utility benefit of 0.0103 and 0.0197 from the trials ALXN1210-PNH-301 and ALXN1210-PNH-301 respectively for ravulizumab, derived from a mixed-effects regression model, as the source of HRQoL benefit in the cost effectiveness model and prefers not to use the utility benefit for treatment frequency of 0.057 as derived from the discrete choice experiment.

The company indicated that the regulatory review of two new vial sizes (3mL and 11mL) containing 100mg/mL of ravulizumab is ongoing with marketing authorisation expected to extend to these vial sizes by [redacted]: £4,533 for 3mL vial (100mg/mL), £16,621 for 11mL vial (100mg/mL). 100mg/mL formulation was used in the model base-case analysis as this formulation is expected to be approved by the time of the first appraisal committee meeting. The company also indicated that the increased drug concentration in these new vial sizes reduces the infusion times for ravulizumab. With the new vial sizes, the minimum infusion time is expected to range from 25–45 minutes for the loading dose and 30–55 minutes for maintenance doses.[26] The company assumed that the administration time for each infusion of ravulizumab 100mg/ml (infused at a 50mg/ml concentration) would be reduced to approximately the same administration time as each infusion of eculizumab. However, the ERG prefers to use the currently licensed 10mg/mL formulation in the ERG base-case analysis.

In response to the ERG clarification questions, the company made several changes to the originally submitted model. However, these changes did not have any impact on the base-case results except for the updated cost for transfusion administration. The impact was negligible. Additionally, the ERG changed various assumptions with respect to the company's base-case. The most important deviation

from the company's base-case was to assume no eculizumab up-dose to align the cost effectiveness analyses with the clinical trials. As mentioned above, the ERG acknowledged that this assumption is not completely representative of UK clinical practice. However, as the company stated in the CS, the majority (about [redacted]%) of PNH patients in UK clinical practice are managed at the standard eculizumab dose for whom an additional eculizumab up-dose is not needed. Additionally, the ERG proposed a different approach to utilities under the assumption that the ravulizumab quality of life benefit due to reduced treatment frequency might be captured by the treatment effect coefficient included in the mixed-effects regression equations used by the company to estimate utilities. This also implied that the additional ravulizumab utility for reducing treatment frequency, which was estimated from an external DCE and included in the company's base-case, was not used (set equal to 0) in the ERG preferred base-case. Finally, for the cost calculations, the ERG assumed the currently licensed 10mg/ml ravulizumab formulation, as opposed to 100mg/ml assumed by the company. The impact of this assumption was minor. These changes led to a situation where ravulizumab was not cost saving compared to eculizumab, unlike the company's base-case. The ICER from the ERG base-case was £38,290, obtained from the estimated [redacted] incremental QALYs gained by ravulizumab at an incremental cost of [redacted] compared to eculizumab. The differences with respect to the company's base-case were mostly explained by the assumption of no eculizumab up-dose. The ERG also conducted a PSA based on its preferred assumptions. The probabilistic ICER was £46,976 per QALY gained (incremental costs were [redacted] and incremental QALYs were [redacted]), thus, £8,686 larger than the ERG deterministic ICER. The ERG considers that this relatively large difference might be explained because the ERG PSA allows a (small) proportion of patients in the ravulizumab arm to transition to the incomplete C5 inhibition-related BTH events related health states. The CE-plane showed approximately [redacted]% of the simulations in the south eastern quadrant, in which ravulizumab is dominant. The remaining simulations were in the north eastern quadrant. The CEAC showed that the probability of ravulizumab being cost effective was [redacted]% (as opposed to [redacted]% in the company's PSA) at a threshold ICER of £30,000 per QALY gained. The ERG also conducted additional scenario analyses to explore important areas of uncertainty in the model. These key uncertainties were related to the so-called "equal effectiveness" scenario, utilities and BTH mortality. Other sources of uncertainty were deemed less important and were not explored in this section. The results of these analyses showed that when eculizumab up-dose was included in the analysis, ravulizumab becomes a cost saving (and more effective) option compared to eculizumab. These analyses highlight the large impact that the proportion of patients treated with eculizumab up-dose has on the overall cost effectiveness results, even though this sub-population represents a minority (approximately [redacted]%) of the total PNH patients. The other assumptions tested by the ERG had an impact on the model results only when up-dose was not included in the analyses, thus under the ERG preferred assumption. The choice of non-zero values for the additional ravulizumab utility for reducing treatment frequency, had a relatively large impact on the ERG preferred base-case ICER. When the value estimated from the DCE and used by the company in their base-case, was used (0.057), the ICER decreased to £11,790 and when this utility value was halved (0.029) the ICER was £17,688. Thus, in both cases below the £30,000 threshold ICER. Finally, when excess mortality risk of BTH events was added to the ERG preferred analysis, by applying a hazard ratio of 4.81 to patients experiencing BTH events, sourced from the Korean PNH registry by Jang et al. 2016,[36] the ICER increased to £124,433. This scenario highlights the impact of BTH excess mortality on the ERG base-case results. Additional data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trial Extension Phases reporting clinical outcomes up to 104 weeks are expected to be available in [redacted]. When the new data become available, the company will conduct an analysis of overall survival, which might be useful in reducing the uncertainty regarding BTH excess mortality.

The ERG feels it is important to emphasise that throughout the CS and the responses to the clarification letter, the company have made it clear that 'up-dosing' is only necessary in approximately [redacted]% of the population and that most patients would achieve an adequate terminal complement inhibition on the licensed eculizumab dose. However, despite being a minority, the assumptions about patients who would require an eculizumab up-dose are the main driver of the cost effectiveness results, as shown in Chapter 7 of this report.

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Appendix 1: Derivation of the transition probabilities in the cost effectiveness model

As explained in the CS,[1] trial data allowed for the identification of BTH events that occurred since the previous visit, and information on the type of event experienced. Events were 'adjudicated' to take one of the following five values: 1) 'Free C5 ≥0.5 µg/mL', 2) 'Free C5 ≥0.5 µg/mL and CAC', 3) 'CAC', 4) 'Undetermined' or 5) 'Missing value' (i.e. not 'adjudicated').

Internal clinical experts were consulted by the company to confirm the meaning of 'adjudication' values and it was concluded that BTH events were classified as missing values when a patient experienced a BTH event in the previous visit, and the event had continued. In these instances, missing values were imputed to reflect the most recent adjudicated event. Based on this, BTH events were subsequently assigned to one of the following three health states: 1) No BTH – no BTH event occurred, 2) Incomplete C5 inhibition-related BTH – a BTH event occurred and was associated with adjudication of one of: 'Free C5 ≥0.5 µg /mL' or 'Free C5 ≥0.5 µg /mL and CAC', or 3) CAC-related BTH – a BTH event occurred and was associated with adjudication of one of: 'CAC' or 'Undetermined'.

As depicted in Figure 5.1 of this report, in the model, a patient's history of incomplete C5 inhibition-related BTH impacts the likelihood of experiencing a subsequent BTH event. Consequently, separate transition probabilities were estimated conditional on whether a patient had a history of incomplete C5 inhibition-related BTH events. Persistence of incomplete C5 inhibition-related BTH events was defined as the probability of an incomplete C5 inhibition-related BTH event in the current cycle of the model, conditional on having experienced an incomplete C5 inhibition-related BTH event in the previous cycle (i.e. whether there is a history of incomplete C5 inhibition-related BTH). This was not relevant to the company's "equal effectiveness scenario" but it was modelled in the company's base-case analysis based on the persistence data observed in the clinical studies ALXN1210-PNH-301 and ALXN1210-PNH-302.

Transitions to initial CAC-related BTH events

Transition matrices were constructed based on the observed probability of experiencing CAC-related BTH events. These were calculated using patient – visit-level data from the trials. The estimation model produced a transition equation for each (initial state–follow-up state) pair that related the predictors to the probability of transitioning, through the estimated coefficients of time between visits and treatment arm. The time-between-visits covariate was held constant at a value of 14 days, to generate two-weekly transition probabilities aligning with the model cycle length. Transition probabilities were calculated for both values of the treatment covariate, a binary indicator for whether the patient received ravulizumab or eculizumab in the randomised period (i.e. first 26 weeks) and the extension period (Week 27–52) of the clinical study.

Transitions to initial incomplete C5 inhibition-related BTH events

The company's base-case analysis included incomplete C5 inhibition-related BTH events in the eculizumab arm. The steps outlined above for CAC-related BTH were also applied for determining the transitions to initial incomplete C5 inhibition-related BTH events.

In the "equal effectiveness" scenario, the company assumed that the same clinical outcomes would be experienced in both treatment arms when the permanent eculizumab up-dosing, as per UK clinical practice, was used. Therefore, no incomplete C5 inhibition-related BTH events were modelled for either eculizumab or ravulizumab.

Transitions to subsequent incomplete C5 inhibition-related BTH events

In the company's base-case analysis, transitions to subsequent incomplete C5 inhibition-related BTH events (occurring when there is a history of previous BTH events) were also modelled. These transition probabilities differed from those observed for initial BTH events. The approach used to derive them is outlined below.

Transition matrices for *subsequent* incomplete C5 inhibition-related BTH events were determined in the same manner as for the *initial* incomplete C5 inhibition-related and CAC-related BTH event transitions, with the following exceptions:

- To determine the likelihood of subsequent incomplete C5 inhibition-related BTH events, the sample was restricted to patients with a history of incomplete C5 inhibition-related BTH events.
- Only observations that occurred after the first incomplete C5 inhibition-related BTH event were included in the estimation.
- These selection criteria substantially limited the sample for the ALXN1210-PNH-302 clinical study and, thus, could only be derived for ALXN1210-PNH-301.
- Since no patient in the ravulizumab arm of either clinical study experienced an incomplete C5 inhibition-related BTH event, the estimation was only performed for patients in the eculizumab arm.

This estimation allowed for two initial states, either 'No BTH' or 'Incomplete C5 inhibition-related BTH' and observed the subsequent health states from either of these starting states

Persistence of incomplete C5 inhibition-related BTH events

'Persistence' refers to the probability of experiencing an incomplete C5 inhibition-related BTH event in the current cycle of the model, conditional on having experienced an incomplete C5 inhibition-related BTH event in the previous cycle. This was modelled based on observed persistence in the trials.[23]

Duration of BTH (incomplete C5 inhibition-related and CAC-related) symptoms

In modelling the utility impact of incomplete C5 inhibition-related and CAC-related BTH events separately, the model accounts for the duration of each event type of event within the two-week model cycle. Specifically, the company assumed, based on internal medical opinion, that symptoms and complications of CAC-related BTH events would be incurred for the full cycle (14 days), and the duration of an incomplete C5 inhibition-related BTH event may be specified as between 1–14 days. CAC-related BTH events required an additional eculizumab dose until the infection or CAC has resolved. However, incomplete C5 inhibition-related BTH events occur in patients receiving eculizumab as a result of incomplete C5 inhibition.[16] This is often observed in the last one to two days of the 14-day dosing interval; a pattern that is repeated across dosing cycles. The assumed duration of an incomplete C5 inhibition-related BTH event is two days. Since the time from a BTH event at a given visit was not reported in the trials, the company consulted published literature to estimate the duration of symptoms and complications of an incomplete C5 inhibition-related BTH event. According to Kelly et al. (2008) and Brodsky (2014), BTH symptoms due to incomplete C5 inhibition often occurred one to two days before the next dose in a 14-day dosing schedule.[60, 61] By extrapolation, it was assumed that incomplete C5 inhibition-related BTH symptoms due to incomplete

C5 inhibition would last for two days in the base-case analysis. Variation of the duration was considered in sensitivity analyses.

Appendix 2: Probabilities of transfusions and estimation of units of RBC per transfusion

Table A2.1: Transfusion requirements – observed events by trial and treatment arm

		Trial ALXN1210-PNH-301		Trial ALXN1210-PNH-302	
		Eculizumab	Ravulizumab	Eculizumab	Ravulizumab
Patients not experiencing BTH					
Visits with no BTH		[redacted]	[redacted]	[redacted]	[redacted]
Visits with transfusion and no BTH		[redacted]	[redacted]	[redacted]	[redacted]
Prob. transfusion in 2-week period	Mean	[redacted]	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	[redacted]
Units of RBC per transfusion	Mean	[redacted]	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	[redacted]
Patients experiencing BTH					
Visits with BTH		[redacted]	[redacted]	[redacted]	[redacted]
Visits with transfusion and BTH		[redacted]	[redacted]	[redacted]	[redacted]
Prob. transfusion in 2-week period	Mean	[redacted]	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	[redacted]
Units of RBC per transfusion	Mean	[redacted]	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 28, Appendix P to CS.[21]
Abbreviations: BTH, breakthrough haemolysis; RBC, red blood cell; SE, standard error.