CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report

Ravulizumab for atypical Haemolytic Uremic Syndrome

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Georgios Nikolaidis, Research Fellow, CHE, University of York Alexis Llewellyn, Research Fellow, CRD, University of York Laetitia Schmitt, Research Fellow, CHE, University of York Nick Meader, Research Fellow, CRD, University of York Simon Walker, Senior Research Fellow, CHE, University of York Melissa Harden, Information specialist, CRD, University of York Claire Rothery, Senior Research Fellow, CHE, University of York Alison Eastwood, Professor of Research, CRD, University of York
Correspondence to	Alison Eastwood alison.eastwood@york.ac.uk
Date completed	08/12/2020

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR131389.

Declared competing interests of the authors

None

Acknowledgements

We would like to thank Carol Inward, Consultant Paediatric Nephrologist at Bristol Royal Hospital for Children, David Kavanagh, Professor of Complement Therapeutics and Honorary Consultant Nephrologist National Renal Complement Therapeutics Centre, Newcastle University, and Neil

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Sheerin, Professor of Nephrology, Institute of Cellular Medicine, Newcastle University, for their clinical advice throughout this project. David Kavanagh and Neil Sheerin also acted as clinical advisers to the company for this submission; Neil Sheerin advised the company on the indirect treatment comparison analyses.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Nikolaidis, G., Llewellyn, A., Schmitt, L., Meader, N., Walker, S., Harden, M., Rothery, C., Eastwood, A. Ravulizumab for atypical Haemolytic Uremic Syndrome: A Single Technology Appraisal. CRD/CHE University of York ERG Report, 2020.

Contributions of authors

Georgios Nikolaidis critiqued and performed the economic analyses and wrote Sections 4, 5 and 6 of the report.

Alexis Llewellyn critiqued the clinical effectiveness review and wrote Section 3 of the report.

Laetitia Schmitt performed the economic analyses and contributed to Sections 4, 5 and 6 of the report.

Nick Meader critiqued the clinical effectiveness review and wrote Sections 2 and 3 of the report.

Simon Walker provided expert advice on the economic analyses and the report as a whole.

Melissa Harden critiqued the company search strategies and provided information support.

Claire Rothery critiqued the economic analyses, contributed to Sections 4, 5 and 6 of the report, led the overall economic analyses and takes joint responsibility for the report as a whole.

Alison Eastwood provided advice, commented on drafts of the report, led the overall clinical effectiveness sections and takes joint responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been redacted, all academic-in-confidence (AIC) data are redacted, all depersonalised data (DPD) redacted.

Copyright statement

Copyright belongs to the University of York

Copyright is retained by Alexion for Table 8, Table 14 to Table 17, Table 19, Figure 2, Figure 3, Figure 4 and text referenced in Section 4.2.3. and Section 4.2.10.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table of Contents

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table of Tables

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table of Figures

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

List of abbreviations

AE	Adverse event
aHUS	Atypical haemolytic uraemic syndrome
CI	Confidence interval
CKD	Chronic kidney damage
CS	Company submission
CSR	Clinical study report
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D	Euroqol 5-Dimensions
ERG	Evidence Review Group
ESRD	End stage renal disease
FAS	Full analysis set
HRQoL	Health-related quality of life
HST	Highly Specialised Technologies
HUS	Haemolytic uraemic syndrome
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
LOCF	Last observation carried forward
LYG	Life year gained
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OLS	Ordinary least squares
ONS	Office for National Statistics
PE/PI	Plasma exchange/infusion
PICO	Population, intervention, comparators, outcomes

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

PNH	Paroxysmal nocturnal haemoglobinuria
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
RCT	Randomised controlled trial
SAE	Serious adverse event
SmPC	Summary of product characteristics
SOC	Standard of care
TA	Technology appraisal
TMA	Thrombotic microangiopathy
TTO	Time trade-off
TTP	Thrombotic thrombocytopenic purpura

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

1.1 Overview of the ERG's key issues

Table 1 Summary of key issues

ID1530	Summary of issue	Report sections
1.	Generalisability of the ravulizumab trials to NHS practice Most of the ravulizumab trial population is not representative of patients who would be eligible in UK clinical practice. Most trial evidence includes eculizumab naïve patients; however, it is expected that nearly all eligible patients in clinical practice would initially receive eculizumab treatment for at least 3 months and only after a response has been demonstrated (or correct diagnosis determined) these patients would switch to ravulizumab treatment.	3.2.1 and 3.2.2
2.	Relative efficacy of ravulizumab versus eculizumab Despite the substantial biological similarity between ravulizumab and eculizumab, there is insufficient evidence to support the assumption that these treatments have equivalent efficacy and safety. All aHUS evidence for ravulizumab and eculizumab is based on single-arm trials. Clinically relevant differences between the ravulizumab and eculizumab trial populations, limitations of the indirect treatment comparison between the two treatments, and significant study quality concerns mean that indirect comparisons between the two treatments are highly uncertain and at high risk of bias. The data are too limited to predict the direction and magnitude of this bias. Equivalence in efficacy and safety between the two treatments is a key assumption of the company's economic model.	3.4, 4.2.7 (item 8), and 6.1.2.1
3.	Long-term efficacy and safety of ravulizumab There is insufficient follow-up data to conclude on the long-term safety and efficacy of ravulizumab. In the company model, long-term efficacy and safety of ravulizumab are assumed to be equivalent. Although this is clinically plausible, there is no evidence to support this assumption.	3.2.3 and 3.2.4
4.	Relapse rate following treatment discontinuation The company assumes that patients who discontinue treatment experience a risk of relapse that is constant through time. However, evidence from the literature suggests that the risk of relapse is higher shortly after treatment withdrawal and is substantially reduced after around one year of sustained disease control. This issue has important implications for the proportion of patients in the model who are back on -lifelong- treatment in the long-term.	Section 4.2.3 (item 3)

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 1 continued.		
5.	Possibility of providing treatment `on demand' and allowing for multiple treatment discontinuations. The company assumes that patients who discontinue treatment and their disease subsequently relapses will re-initiate treatment and receive it for the remainder of their lifetime (and are not permitted to discontinue treatment again). It is likely that clinical practice will soon switch from lifelong treatment to treating aHUS patients `on-demand'. As a result, patients who re-initiate may only be on treatment during a proportion of their lifetime.	Section 4.2.3 (item 4)
6.	Treatment discontinuation due to renal response Although current guidelines suggest that treatment should be given lifelong, there are several arguments presented in the literature opposing this view when adequate renal response has been achieved, and several trials have attempted to discontinue treatment in patients who respond to complement-inhibitor treatment. The ERG expects that once the SETS study reports, current practice is likely to change, and lifelong complement-inhibitor treatment will not be standard in patients who show adequate renal response.	Section 4.2.3 (item 1)
7.	The submission does not consider the potential use of eculizumab biosimilar treatments that may become available in the future. Despite that eculizumab (Soliris) is currently the only complement-inhibitor treatment option for patients with aHUS, its patent is set to expire in the next 3 years[1] and biosimilar eculizumab treatments are likely to enter the market.	Section 4.2.5

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are: (i) the inclusion of renal response as a reason for treatment discontinuation, (ii) the use of time-dependent relapse rates, and (iii) addressing the potential for using complement-inhibitor treatment only `on demand'.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is not modelled to affect QALYs as the company's base case comprises a cost-minimisation analysis.

Overall, the technology is modelled to affect costs by:

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

[redacted]

The modelling assumption that has the greatest effect on the ICER is:

- The proportion of a patient's lifetime over which they would receive treatment after the first disease relapse.

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

The population defined in the NICE scope includes patients who have had eculizumab treatment for at least 3 months and whose disease has responded to eculizumab, as well as eculizumab treatment-naïve patients. It is expected that nearly all patients who would be eligible for ravulizumab in the NHS would have shown prior response to eculizumab. However, most of the evidence from the ravulizumab trials includes eculizumab treatment-naïve patients and the economic analysis explicitly considers treatment-naïve patients due to the lack of evidence on patients who have switched from eculizumab. This is further discussed in Section 1.4.

Eculizumab is the only comparator in the company's analyses. Although eculizumab is currently the only complement-inhibitor treatment option for patients with aHUS, its patent is set to expire in the next 3 years and biosimilar treatments may enter the market. This is further discussed in Section 1.6.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

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

Issue 1 Generalisability of the ravulizumab trials to NHS practice

Report section	3.2.1 and 3.2.2
Description of issue and why the ERG has identified it as important	The ravulizumab trial population is not representative of the NHS aHUS population who would be eligible for ravulizumab therapy. All of the trial evidence in adults and most of the paediatric evidence for ravulizumab is based on eculizumab-naïve patients. However, it is expected that nearly all eligible patients in NHS practice would receive ravulizumab treatment only after they have received eculizumab for at least 3 months and who have shown response to eculizumab. There are significant differences in baseline characteristics between treatment naïve patients and eculizumab-experienced patients switching to ravulizumab. In addition, a significant proportion of patients in the ravulizumab trials may not have aHUS. This significantly limits the generalisability of the trial evidence to the NHS.
What alternative approach has the ERG suggested?	There is insufficient evidence to inform outcomes in patients who have switched from eculizumab to ravulizumab.
What is the expected effect on the cost-effectiveness estimates?	Total costs for ravulizumab would be expected to increase because of the increased number of infusions associated with receiving prior eculizumab treatment, while the impact on QALYs is unknown due to the lack of evidence on outcomes for patients who have switched from eculizumab.
What additional evidence or analyses might help to resolve this key issue?	Additional ravulizumab evidence in eculizumab-experienced adult and paediatric patients with a confirmed diagnosis of aHUS.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Issue 2 Relative efficacy of ravulizumab versus eculizumab

Report section	3.4, 4.2.7 (item 8), 6.1.2.1
Description of issue and why the ERG has identified it as important	Despite the substantial biological similarity between ravulizumab and eculizumab, there is insufficient evidence to support the assumption that these treatments have equivalent efficacy and safety. All aHUS evidence for ravulizumab and eculizumab is based on single-arm trials. Therefore, the company conducted prognostic score matching using stabilized weights to reduce baseline differences observed between the eculizumab and ravulizumab trial populations. Indirect treatment comparison (ITC) analyses did not match for the presence of pathogenic variants, despite substantial differences between treatments, and results showed that differences in effectiveness between treatments cannot be ruled out. The absence of RCT evidence, clinically relevant differences between the ravulizumab and eculizumab trial populations, limitations of the ITC and significant study quality concerns mean that indirect comparisons between the two treatments are highly uncertain and at high risk of bias. The data are too limited to predict the direction and magnitude of this bias. Equivalence in efficacy and safety between the two treatments is a key assumption of the company's economic model.
What alternative approach has the ERG suggested?	The ERG conducted an analysis assuming differential efficacy based on the company's ITC analysis. Further details are provided in Section 6.1.2.1.
What is the expected effect on the cost-effectiveness estimates?	Assuming differential efficacy reduced the cost-effectiveness of ravulizumab because the ITC analysis implies that ravulizumab is less effective than eculizumab. The impact is minimal though, and ravulizumab remains cost-effective. However, the ERG highlights that the insensitivity of the conclusions is reliant on key assumptions employed in the economic model. Specifically, if more information was available regarding the relapse rates, the possibility of providing treatment `on demand', and the potential availability of biosimilar treatments, the impact of differential efficacy on cost-effectiveness could be substantial.
What additional evidence or analyses might help to resolve this key issue?	Randomised evidence of ravulizumab versus eculizumab in aHUS patients would help clarify whether the assumption of equal efficacy and effectiveness is justified. However, the ERG acknowledges that given the ultra-rare nature of the disease, this evidence may never become available. Where possible, establishing non-inferiority between the treatments in a trial programme for aHUS may be required.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Issue 3 Long-term safety and efficacy of ravulizumab

Report section	3.2.3 (efficacy), 3.2.4 (safety)
Description of issue and why the ERG has identified it as important	There is no follow-up data to inform the long-term safety and efficacy of ravulizumab. In the company model, long-term efficacy and safety of ravulizumab are assumed to be equivalent. Although this is clinically plausible, there is no evidence to support this assumption.
What alternative approach has the ERG suggested?	Alternative assumptions on discontinuation, relapse rates and alternative long-term treatment strategies are explored (see section 1.5, Issue 4 to Issue 6.
What is the expected effect on the cost-effectiveness estimates?	See section 1.5, Issue 4 to Issue 6.
What additional evidence or analyses might help to resolve this key issue?	Longer-term efficacy and safety follow-up data of patients currently enrolled in trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312, and long-term efficacy (including recurrence and quality of life) and safety data for eculizumab experienced patients who switched to ravulizumab. As with eculizumab, long-term studies on treatment withdrawal and alternative treatment strategies for ravulizumab are required. The duration of the ongoing trial extension period may be dependent on approval of ravulizumab in the NHS and other healthcare systems and may therefore not be sufficient to resolve this issue.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

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

Issue 4 Relapse rate following treatment discontinuation

Report section	4.2.3 (item 3)
Description of issue and why the ERG has identified it as important	The company assumes that patients who discontinue treatment experience a risk of relapse that is constant through time. However, evidence from the literature suggests that the risk of relapse is higher shortly after treatment withdrawal and is substantially reduced after around one year of sustained disease control. This issue has important implications for the proportion of patients in the model who are back on lifelong treatment in the long-term.
What alternative approach has the ERG suggested?	The ERG considers time-dependent relapse rates to be a more appropriate approach. The ERG conducted time-to-event analysis to estimate the risk of relapse over time using evidence from UK patients enrolled in the global aHUS registry. This is described in detail in Section 6.1.1.2
What is the expected effect on the cost-effectiveness estimates?	Implementing time-dependent relapse rates in the model increased the incremental costs and potential cost-savings associated with ravulizumab compared with eculizumab. This was because the estimated relapse rates were higher than the company's constant relapse rate for the first 7.6 years in adults and 6.6 years in children, and lower only thereafter. The model also assumes that once patients' relapse, they are re-initiated on lifelong treatment. The ERG highlights that the time-to-event analysis is based on a small number of UK patients and therefore the derived relapse rates over time are surrounded by considerable uncertainty.
What additional evidence or analyses might help to resolve this key issue?	Conducting time-to-event analysis using the full cohort of patients enrolled in the aHUS registry who discontinued treatment could significantly reduce uncertainty and help inform the economic model with more appropriate time-dependent relapse rates.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Issue 5 Possibility of providing treatment `on demand' and allowing for multiple treatment discontinuations

Report section	4.2.3 (item 4)
Description of issue and why the ERG has identified it as important	The company assumes that patients who discontinue treatment and their disease subsequently relapses will re-initiate treatment and receive it for the remainder of their lifetime (and are not permitted to discontinue treatment again). The ERG considers it likely that clinical practice will soon switch from lifelong treatment to treating aHUS patients `on-demand'. As a result, patients who re-initiate may only be on treatment during a proportion of their lifetime.
What alternative approach has the ERG suggested?	The ERG acknowledges that there is a paucity of evidence surrounding second and subsequent treatment discontinuations and highlights that this as an area of considerable uncertainty with high potential impact on incremental costs and cost-effectiveness. To reflect the plausibility of providing treatment `on-demand', the ERG assumed that patients who relapse and re-initiate treatment would receive treatment only for a proportion of their remaining lifetime. The ERG presents cost-effectiveness estimates for a wide range of possibilities from 50% - 100%. In the former, patients who relapse receive treatment only for 50% of their remaining lifetime, whilst in the latter they receive treatment for 100% (i.e. lifelong treatment as assumed in the company's base case). More details are provided in Section 6.1.1.3.
What is the expected effect on the cost-effectiveness estimates?	Accounting for the potential of multiple discontinuations by reducing the proportion of a patient's lifetime that they are on treatment after disease relapse implies a substantial reduction in the total incremental costs and potential cost-savings of ravulizumab compared with eculizumab. However, ravulizumab remains a cost-saving treatment option compared with eculizumab based on the modelled assumptions and evidence available.
What additional evidence or analyses might help to resolve this key issue?	Once the SETS study[2] reports, a similar study could be designed that would seek to evaluate whether patients who relapse following disease relapse and treatment re-initiation can safely be withdrawn from treatment for a second or further time.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Issue 6 Treatment discontinuation due to renal response

Report section	4.2.3. (item 1)
Description of issue and why the ERG has identified it as important	The company's base-case did not consider treatment discontinuation due to adequate renal response. Although current guidelines suggest that treatment should be given lifelong, there are several arguments presented in the literature opposing this view when adequate renal response has been achieved, and several trials have attempted to discontinue treatment in patients who respond to complement-inhibitor treatment. The ERG expects that once the SETS study reports, current practice is likely to change, and lifelong complement-inhibitor treatment will not be standard in patients who show adequate renal response.
What alternative approach has the ERG suggested?	The ERG suggests that discontinuation due to adequate renal response is considered as a reason for treatment discontinuation
What is the expected effect on the cost-effectiveness estimates?	The total incremental costs of ravulizumab compared with eculizumab are reduced by [redacted] in the ERG's base case analysis, which is relatively small compared to the impact of the other assumptions in the model.
What additional evidence or analyses might help to resolve this key issue?	None required.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

1.6 Other key issues: summary of ERG's view

Issue 7 The submission does not consider eculizumab biosimilars

Report section	4.2.5.
Description of issue and why the ERG has identified it as important	The company compares ravulizumab (Ultomiris) with eculizumab (Soliris). Although eculizumab (Soliris) is currently the only complement-inhibitor treatment option for patients with aHUS, its patent is set to expire in the next 3 years[1] and biosimilar eculizumab treatments are likely to enter the market.
What alternative approach has the ERG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	The introduction of eculizumab biosimilars could reduce the costs of eculizumab and therefore could also reduce the cost-effectiveness of ravulizumab. Depending on the actual discount that a biosimilar would offer compared to eculizumab, ravulizumab may or may not still be the cost-effective option.
What additional evidence or analyses might help to resolve this key issue?	1. A detailed list of the eculizumab biosimilar treatments that are currently under development, their expected time of entering the market, and their expected prices. 2. An assessment of whether it can be realistically expected that a switch in practice from eculizumab to ravulizumab would not discourage a proportion of patients switching back to eculizumab.

1.7 Summary of ERG's preferred assumptions and resulting ICER

Table 2 Summary of the ERG's preferred assumptions and ICERs

	Incremental costs (£)	Incremental QALYs	ICER for RAV vs ECU
Company's base-case	[redacted]	[redacted]	[redacted]
1. Include renal response as a reason for treatment discontinuation	[redacted]	[redacted]	[redacted]
2. Analysis 1 + Assume time-dependent relapse rates following treatment discontinuation	[redacted]	[redacted]	[redacted]
3. Analysis 2 + Account for the potential of multiple treatment discontinuations (The presented ranges correspond to treatment re-initiation for a proportion of 50% and 100% of a patient's remaining lifetime) **ERG's PREFERRED BASE-CASE**	[redacted]	[redacted]	[redacted]
ERG's base case + assuming differential efficacy*	[redacted]	[redacted]	[redacted]

*This scenario corresponds to Scenario 1b in Table 22, which does not include the additional QALY increment for RAV based on the company's discrete choice experiment.
ǂ ICER in the South-West quadrant of the Incremental cost-effectiveness plane with higher values indicating that RAV is more likely to be cost-effective compared to eculizumab. RAV: ravulizumab; ECU: eculizumab

For further details of the exploratory and sensitivity analyses conducted by the ERG, see Section 6.1.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

EVIDENCE REVIEW GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Background

2.1.1 Previous NICE appraisals on complement-inhibitor therapies for aHUS

NICE has previously appraised eculizumab, which is a complement-inhibitor treatment functioning through the same mechanism as ravulizumab, as a highly specialised service in HST1 for the treatment of aHUS. HST1 recommends the use of eculizumab for the treatment of both adult and paediatric patients with aHUS.[3]

2.1.2 Disease Background

The ERG agrees that the company's summary of atypical haemolytic uremic syndrome (aHUS) provides an appropriate and relevant background to the decision problem.

The underlying pathophysiology of aHUS is uncontrolled terminal complement activation in the alternative pathway (AP) of complement. Complement regulatory gene/protein mutations or autoantibodies are detected in approximately 50-70% of patients.[4] In the UK, genetic or acquired complement abnormalities were identified in 69% of patients with aHUS.[5]

Since there is no specific test, aHUS is a clinical diagnosis of complement-mediated thrombotic microangiopathy (TMA) and requires exclusion of thrombotic thrombocytopenic purpura (TTP) and STEC (Shiga toxin-related Escherichia coli) infection.

Critique

Although historically life-long treatment has been proposed for eculizumab, there is very limited evidence to support this practice.[6] In response to NICE recommendations, the Stopping Eculizumab Treatment Safely (SETS) trial[7] is currently investigating the impact of eculizumab withdrawal and is expected to be completed in 2022.

A recent review found nine case-reports studying the impact of withdrawing eculizumab in patients who had responded to treatment.[6] Overall, 27% of patients relapsed in these studies. The median time to relapse across studies was 3 months, suggesting that those who relapsed were more likely to do so soon after discontinuation.[6]

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

The CS stated (based on an advisory board meeting of clinical experts) that patients who relapsed were expected to remain on treatment indefinitely. However, minutes from one of the company advisory board meetings indicate greater uncertainty: "[redacted]."[8]

2.1.3 **The technology and the company's anticipated positioning of ravulizumab**

The ERG considers the company's description of the technology to be appropriate. Ravulizumab is a monocolonal antibody (mAB) treatment that acts as a complement inhibitor. Ravulizumab is a re-engineering of eculizumab to extend the half-life of the drug. Both ravulizumab and eculizumab bind to complement protein C5 inhibiting terminal complement-mediated inflammation and preventing immune activation and haemolysis. Although both treatments function through the same mechanism, ravulizumab binds to its substrate with higher affinity and achieves a quadruple half-life; thus, requiring less frequent administration. Therefore, adults require ravulizumab every 8 weeks compared with every 2 weeks for eculizumab (and 4 weeks vs 2 weeks for paediatric patients <20 kg).

The CS positioned ravulizumab as an alternative treatment option to eculizumab (with the exception of paediatric patients weighing less than 10kg). In response to question A2 of points for clarification (PFCs), the company expected ravulizumab to be offered as either:

- first-line treatment option for complement-inhibitor treatment naïve population, or
- second-line/maintenance treatment in people who had received eculizumab for at least three months and had evidence of response.

Points for critique

Clinical advice provided to the ERG, suggested that in nearly all cases, ravulizumab would be provided as a second-line/maintenance treatment for people who had responded to eculizumab. Because aHUS is a diagnosis of exclusion, the shorter half-life of eculizumab is beneficial at the initiation of treatment since there is a shorter duration time required to discontinue treatment when evidence of an alternative diagnosis becomes available. Although, clinical advisers pointed out in some paediatric patients, where it is challenging to maintain central lines for a long period of time, ravulizumab may potentially be a first-line treatment option. However, most of the evidence from the ravulizumab trials included eculizumab treatment-naïve patients and the economic analysis explicitly considered treatment-naïve patients due to the lack of evidence on patients who had switched from eculizumab.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

A further factor impacting the positioning of ravulizumab, not mentioned in the CS, is the likely availability of several biosimilars (oral and subcutaneous treatments), potentially within the next five years. Therefore, the positioning of ravulizumab may change as these alternative treatments become available.

2.2 Critique of company's definition of decision problem

The company submission generally reflected the NICE decision problem, although the ERG has concerns about the trial population not being reflective of most patients who would receive ravulizumab in clinical practice, and the expected availability of biosimilar comparators in the relatively near future. A summary and critique of the company's definition of the decision problem is presented in Table 3.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 3 Summary and critique of decision problem

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**	**ERG comment**
Population	People who weigh 10kg or more with atypical haemolytic uremic syndrome (aHUS) and: • who have not had complement inhibitor treatment, or • who have had eculizumab for at least 3 months and whose disease has responded to eculizumab	People who weigh 10kg or more with atypical haemolytic uremic syndrome (aHUS) and: • who are complement inhibitor treatment-naive, or • have received eculizumab for at least 3 months and have evidence of response to eculizumab	Wording has been aligned to the market authorisation.	The evidence presented by the company largely reflected the NICE decision problem. However, the ERG identified some concerns: • Very limited evidence presented on aHUS patients who responded to eculizumab (data was only available for 10 paediatric patients). This is an important limitation, since ERG clinical advisers expected almost all patients in UK clinical practice would receive ravulizumab after responding to eculizumab. • According to clinical advisers to the ERG, the low prevalence of identified genetic variants in some of the ravulizumab trials suggested many of the patients did not have aHUS.
Intervention	Ravulizumab	Ravulizumab	Not applicable	The intervention described in the company's submission matches the intervention described in the final scope.
Comparator(s)	Eculizumab	Eculizumab	Not applicable	Comparators described in the company's submission matched the comparators described in the final scope. However, clinical advisers to the ERG pointed out that current practice for aHUS is likely to change substantially in the next 3-5 years. As discussed above, although eculizumab is currently the only available comparator, as eculizumab biosimilars become available this is likely to have a substantial impact on

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

				the positioning of ravulizumab in NHS practice in the relatively near future.
Outcomes	The outcome measures to be considered include: • Overall survival • Disease recurrence • Response to treatment • Cessation or avoidance of dialysis • Maintenance or improvement of kidney function • Other major non-renal clincal outcomes • Eligibility for/success of transplantation • Development of antibodies and resistance • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Disease recurrence • Response to treatment • Cessation or avoidance of dialysis • Maintenance or improvement of kidney function • Other major non-renal clincal outcomes • Eligibility for/success of transplantation • Development of antibodies and resistance • Adverse effects of treatment • Health-related quality of life	The company noted that some outcomes (overall survival, disease re-currence, and eligibility for/success of transplantation) included in the final scope were not pre-specified in the ravulizumab trial programme. Overall survival was modelled in the pharmacoeconomic analyses and death was captured as a safety outcome. Because follow up for ravulizumab trials were of insufficient duration, disease recurrence was not collected. However, TMA parameters were included in these trials. Disease recurrence in the CS was modelled in the pharmacoeconomic analyses using longer term data from eculizumab trials. Eligibility for/success of transplantation was not measured in trials. However, CKD stage was captured in trials and included in economic modelling.	The outcomes largely match the final scope. The company appropriately pointed out some outcomes were not available in the ravulizumab trials.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an	The economic analysis base case assumes equal efficacy and effectiveness between ravulizumab and eculizumab and only compares the differences in treatment costs. A scenario analysis considered differential effectiveness based solely upon CKD stage outcomes, and models the differences between QALYs and costs for ravulizumab and eculizumab. The cost-effectiveness of treatments in the scenario analysis is expressed in terms of cost per QALY. A lifetime time horizon is used and costs are considered from an NHS and Personal Social Services perspective.	Not applicable	The CS is in line with the final scope issued by NICE. The appropriateness of the cost-minimisation analysis for evaluating the cost-effectiveness of ravulizumab is dependent on the clinical equivalence of ravulizumab and eculizumab in terms of efficacy, safety, and health-related quality of life (and uncertainty surrounding these outcomes). Adult and child populations were modelled separately with the cost-effectiveness results weighted based on the proportion of adults versus children currently treated in clinical practice. This approach is considered appropriate given the evidence available.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

	NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups	N/A	N/A	N/A	N/A
Special considerations including issues related to equity or equality	N/A	N/A	N/A	N/A

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic review to identify the available clinical evidence for the current treatment options for patients with atypical haemolytic uremic syndrome (aHUS), including eculizumab and ravulizumab. The systematic review methods are reported in the CS Document B, Appendix D. This section provides a brief summary and critique of the systematic review methods.

Overall, the ERG found that the review methods for searching, extracting and quality assessing studies were broadly appropriate. However, the ERG believes the selection of studies was too restrictive and excluded relevant studies on the safety of ravulizumab and eculizumab.

3.1.1 **Searches**

Literature search methodology is reported in CS Document B, Appendix D.1.1. Searches included key databases (MEDLINE, EMBASE and Central Register of Controlled Trials) up to April 2020. An OVID search strategy was reported, and relevant conference proceedings were consulted. The search strategy was designed to pick up any interventions for aHUS. No reference checking was reported, and it does not appear that validated filters for study designs were used.

3.1.1.1 Points for critique

Despite some limitations, the ERG believes that the review search strategy was broadly appropriate and is unlikely to have missed relevant studies up to April 2020. Appendix A, Table 23 contains the ERG appraisal of the searches.

3.1.2 **Study selection**

The study selection process is reported in CS Document B, Appendix D.1.2. Eligibility criteria are presented in CS Document B, Appendix D, Table 2. Participants with a diagnosis of aHUS receiving ravulizumab, eculizumab, plasma therapy, kidney transplantation, liver-kidney transplantation, immunosuppression therapy or dialysis were included. Any efficacy and safety outcomes were included. Eligible study designs included randomised, non-randomised, single-arm, prospective and retrospective studies. Studies reported in a non-English language were excluded. A PRISMA flow diagram was reported in CS Document B, Appendix D, Figure 1. A total of 55 unique studies were included. A list of references with a brief description of the design and intervention is presented in CS Document B, Appendix D, Table 3. Two studies of ravulizumab were included (the single-arm trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312), and 37 non-comparative studies of eculizumab, of which four were single-arm trials (aHUS-C08-002, aHUS-C08-003, aHUS-C10-003, aHUS-C10-004).

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Following initial study selection, a feasibility analysis was conducted to determine which trials identified in the systematic review were appropriate for inclusion in an indirect treatment comparison. Details of the selection process are presented in CS Document B, Appendix D, Section D.1.4. Only studies with individual patient datasets "available to Alexion" were considered for inclusion in the indirect treatment comparisons. The company did not state whether any attempts were made to retrieve individual patient datasets not already held by them. The feasibility analysis included 'cleaning' of individual patient level data, tabulation of patient characteristics and outcomes measures, qualitative comparison of data available and identification of key differences between studies and homogeneous subgroups. A number of additional exclusions resulted from the feasibility analysis, notably: clinically stable patients following eculizumab therapy (as all patients enrolled in eculizumab trials were complement inhibitor treatment-naïve); patients who were clinically stable following long-term plasma therapy (such as those included in trial aHUS-C08-003, as they are not represented in the ravulizumab trials); and the global aHUS registry of 1,794 participants due to data quality concerns (no formal monitoring of data collection, only six month intervals assessments) and risk of double counting (overlap with eculizumab trial population).

Of the 55 studies included in the systematic review, only five single-arm trials were included following the feasibility analysis: two ravulizumab trials (ALXN1210-aHUS-311 and ALXN1210-aHUS-312) and three eculizumab trials (aHUS-C08-002, aHUS-C10-003 and aHUS-C10-004). Patient characteristics and outcomes of studies included in the systematic review but subsequently excluded from the indirect treatment comparison were not presented.

3.1.2.1 Points for critique

Although the systematic review eligibility criteria were generally appropriate to identify relevant studies of aHUS participants, the feasibility analysis conducted by the company led to the exclusion of most aHUS studies (50 out of 55 identified), and to the inclusion of only a subset of ravulizumab and eculizumab single-arm trials with individual patient data (total N=139). In particular, all observational evidence on eculizumab, including data on long-term efficacy and safety from the aHUS global registry data of 1,794 participants was not presented in the CS.

As no comparative trials were found and selection of studies was restricted to aHUS patients, broadening the selection criteria to include head-to-head randomised comparisons of ravulizumab against eculizumab, such as trial 301[9] would have identified broader indirect evidence informing the relative safety profiles of these treatments. Language restrictions mean that the risk of missing relevant non-English language studies cannot be excluded.

3.1.3 Data extraction

The data extraction process is described in CS Document B, Appendix D, Section D.1.3.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

The CS stated that double data extraction was performed for all data of interest from the eligible studies, and that summary tables and summary tables and a narrative description of the study designs used, data collected, and outcomes reported were assembled into a final report. Extracted data were only presented for the five studies included in the indirect treatment comparison.

3.1.3.1 Points for critique

The process for conducting data extraction was generally appropriate. Where available, appropriate disease characteristics and outcomes were extracted. However, extracted data were only presented for the five studies that were included in the indirect treatment comparison.

3.1.4 Quality assessment

Quality assessment of single-arm studies identified through the systematic review was conducted using the STROBE statement for observational studies,[10] and risk of bias was considered in an adapted version of the Cochrane Risk of Bias assessment tool for ravulizumab trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312. Risk of bias was assessed for seven items including: participant selection, representativeness of the trial participants, blinding of participants and study personnel, attrition, missing data, outcomes reporting, and other concerns.

Results of the quality assessment were reported for ravulizumab trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312 in CS Document B, Appendix D, Section D.3, and for eculizumab trials used in the ITC in CS Document B, Appendix D, Section D.1.4.8. The internal validity and applicability of the ravulizumab trials were also discussed in CS Document B, Section 2.5.

3.1.4.1 Points for critique

The risk of bias tool used is not reflective of the Cochrane Risk of Bias assessment tool (v2.0)[11] but a modified version of an out-of-date prior edition[12] and is not adapted to single-arm trials. The STROBE assessment decisions were not supported by relevant text or specific cross-references, making results difficult to interpret. The CS did not state whether quality assessment was conducted in duplicate. Overall, given these limitations the ERG believes that the CS quality assessment may not be valid.

3.1.5 Evidence synthesis

Results from ALXN1210-aHUS-311 (conducted in complement-inhibitor naïve adult patients) and ALXN1210-aHUS-312 (complement inhibitor treatment naïve and eculizumab experienced children and adolescents) were appropriately not combined in a meta-analysis due to their distinct populations. Results from ravulizumab and eculizumab trials included in the ITC are discussed in sections 3.2 and 3.3, and the ERG critique and summary of the ITC is reported in section 3.4.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The company systematic review included two multi-centre ongoing single arm open-label trials of ravulizumab, ALXN1210-aHUS-311 and ALXN1210-aHUS-312. Both were described by the company as phase III. ALXN1210-aHUS-311 was conducted in adults with aHUS who are complement inhibitor treatment-naïve, and ALXN1210-aHUS-312 in children and adolescents with aHUS who are complement inhibitor treatment-naïve or clinically stable following ≥90 days treatment with eculizumab. This section provides a summary and critique of each trial.

3.2.1 **ALXN1210-aHUS-311**

3.2.1.1 Design

The study design is summarised in CS Document B, Section B.2.3.1, with further details reported in the clinical study report (CSR).[13] ALXN1210-aHUS-311 is an ongoing single-arm open-label ongoing trial designed to assess the efficacy and safety of ravulizumab in adults with a diagnosis of aHUS who are naïve to complement inhibitor therapy. Patients were recruited across 41 sites in 14 countries ([redacted] patients were recruited in the UK). Participants aged 12 or older were eligible, although enrolment of eligible adolescent patients was deferred to a paediatric trial (Study ALXN1210-aHUS-312). Diagnosis of aHUS was determined by evidence of TMA, haemolysis and kidney injury (platelet count of < 150,000/μL, LDH ≥ 1.5 × ULN, haemoglobin, ≤ lower limit of normal [LLN], and serum creatinine level ≥ ULN) without ADAMTS13 deficiency, Shiga toxin, a positive direct Coombs test or systemic bacterial infection. Selection criteria are reported in CS Document B, Table 5.

The study consists of a Screening Period (≤ 7 days), a 26-week Initial Evaluation Period, and an Extension Period, which is planned to "last until the product is registered or approved (in accordance with country-specific regulations) or for up to 4.5 years, whichever occurs first" (CS Document B, p22 and CSR p28). The first study patient started treatment in March 2017, and data presented by the company runs up to the cut-off date of July 2019, when all patients had at least 52 weeks of follow-up.

Dosages are presented in CS Document B, Table 5. Loading dose was given on Day 1 with maintenance doses on Day 15 and once every eight weeks thereafter by IV infusion. Loading dosages ranged from 2,400mg to 3,000mg and maintenance doses from 3,000mg to 3,600mg based on patient body weight, as per the licence indication. No dose-response studies were conducted for ravulizumab in aHUS.[14] Weight-based dosage was determined by early development studies in healthy volunteers and ongoing Phase 1b and Phase 2 studies in PNH patients (see CSR Section 9.4.4). Discontinuation and retreatment protocols are described in the trial CSR, Section 9.3.3.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

The following co-treatments were prohibited at any time after the first dose of study drug for all patients in the study (including those who discontinued ravulizumab but remained in study) until completion of the study or early termination: eculizumab or other complement inhibitors, intravenous immunoglobulin, rituximab, plasma exchange/plasma infusion. Dialysis was permitted, including new dialysis within the first 48-hour period following the first dose of ravulizumab if there was 'a compelling medical need'. Further details are reported in the study CSR, p37.

The primary efficacy endpoint was complete TMA response during the Initial Evaluation Period by central laboratory assessment. Complete TMA response was defined as simultaneous normalization of haematology parameters, which included platelet count and lactate dehydrogenase [LDH] and ≥25% improvement in serum creatinine at two separate assessments obtained at least 28 days apart, and any measurement in-between. All analyses were based on results from a central laboratory.

Secondary endpoints included: time to complete TMA response; complete TMA response status over time; dialysis requirement status at endpoint; observed value and change from baseline in eGFR; CKD stage; observed value and change from baseline in haematological parameters (platelets, LDH, Hb); increase in Hb of ≥ 20 g/L from baseline; change from baseline in QoL (EQ-5D-3L and FACIT-Fatigue). Overall survival was not a pre-specified endpoint, although deaths were captured as a safety outcome. Similarly, major non-renal outcomes (such as cardiac events and thrombosis) were monitored as safety outcomes. Disease recurrence was not a pre-specified outcome; TMA parameters were collected in trial participants, including those who discontinued treatment, although the company stated that no data on recurrence are available yet due the limited follow-up to date. Eligibility for and success of transplantation were not pre-specified endpoints.

The planned sample size was 55. Based on an assumed proportion of Complete TMA response of 65%, the company estimated that 50 patients would yield a 95% confidence interval for the proportion of response with a half-width of approximately 15%; the target sample size was increased to 55 patients to account for drop-out (CS Document B, Table 7 and CSR, Section 16.1).

Methods for dealing with missing data for the primary outcome and its components were reported in CS Document B, Table 7. Patients missing an efficacy assessment that was part of the definition of Complete TMA Response while still on study, had their last observation carried forward, although when all Complete TMA Response criteria were met, confirmatory result could not be from an assessment that was carried forward from the initial assessment.

A protocol amendment in July 2017 (four months after treatment of the first study patient was initiated) required that at least 30 patients (rather than the total study population, as initially planned) enrolled met all four TMA requirements at Day 1 (platelet count of < 150,000/μL, LDH ≥ 1.5 × ULN,

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

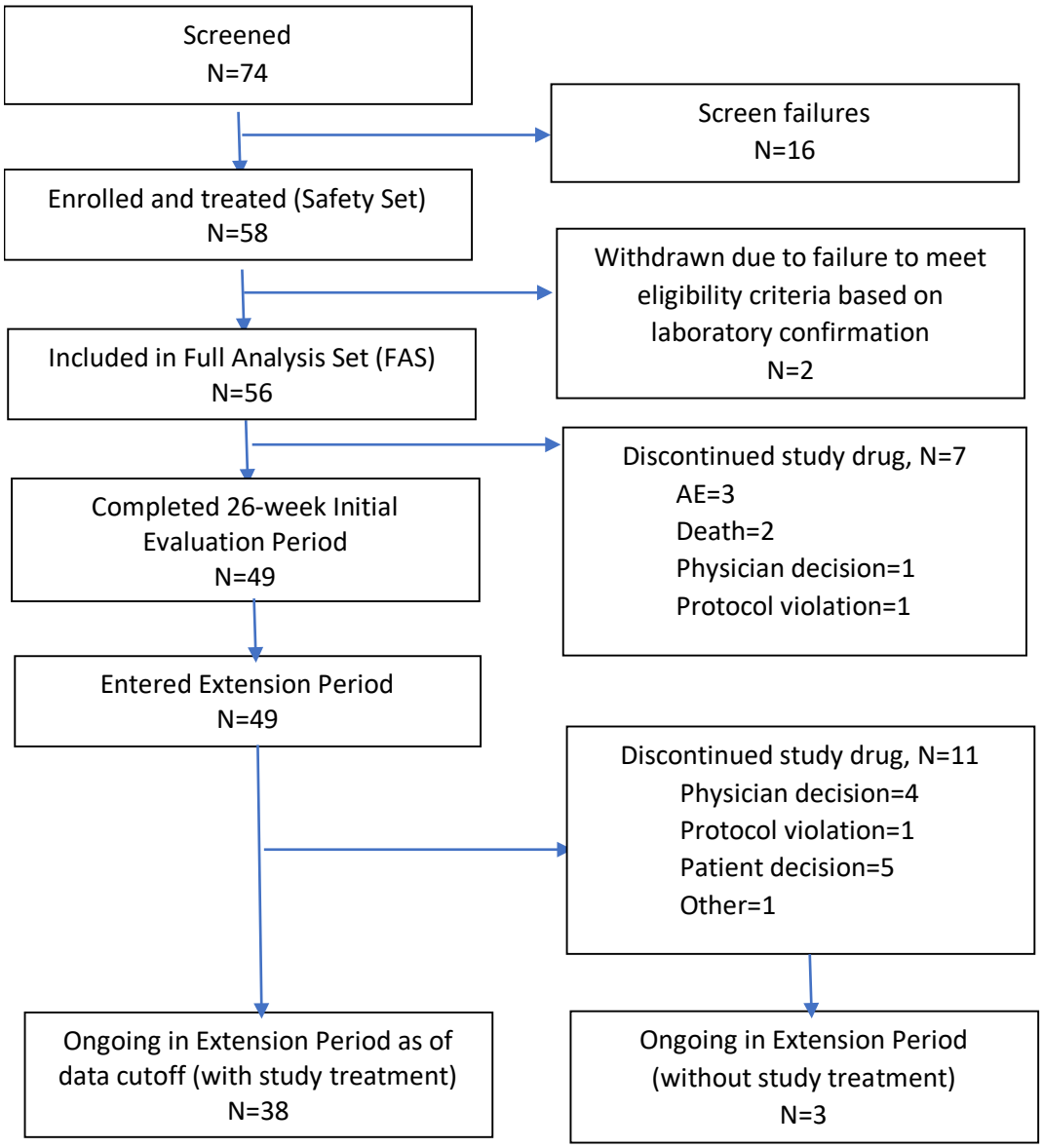
haemoglobin ≤ LLN, and serum creatinine level ≥ ULN) to ensure that a majority of patients enrolled had abnormal baseline laboratory values.

Out of 74 patients screened, a total of 58 patients were enrolled and received at least one dose of ravulizumab (Safety Set). Two patients from the Safety Set were subsequently excluded for testing positive to Shiga toxin-related HUS. The remaining 56 patients were included in the Full Analysis Set (FAS). The FAS was defined as patients who received at least one dose of ravulizumab and had at least one efficacy assessment, a serum creatinine level upper limit of normal (ULN) during screening and no known familial or acquired ADAMTS13 deficiency or STEC-HUS. Of the 56 patients included in the FAS, 49 completed the Initial Evaluation Period.

As of data cut-off (2 July 2019), [redacted] patients are still treated with ravulizumab in the Extension Period, and [redacted] patients continue to be monitored without receiving ravulizumab. Reasons for discontinuation in the Extension Period included physician or patient choice (n=[redacted]), primarily due to complete TMA response and low risk of disease recurrence/relapse (n=[redacted] including [redacted] patients who had onset of TMA post-partum). Following request for clarification, the company reported that [redacted] patients discontinued drug treatment due to physician decision; [redacted] of those were complete TMA responders, [redacted] remained with ESRD, and [redacted] had an alternative non-aHUS diagnosis. Further details are reported in the company's response to points for clarification (PFC), Table 2. A flow diagram is presented in the CSR, Figure 2 and reproduced below in Figure 1.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Figure 1 Flow diagram of trial ALXN1210-aHUS-311 participants as of Data July 2019 cut-off



Source: Adapted from CSR Figure 2, p62.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Points for critique

ALXN1210-aHUS-311 is the only known trial of ravulizumab in an adult aHUS population. Although described as a Phase III clinical trial, study 311 only included 56 patients in its FAS and no comparator arm, and to the ERG's knowledge, no earlier phase trials of ravulizumab in an aHUS population exist. As 311 is a non-comparative trial, it is not designed to assess the relative efficacy and safety of ravulizumab against eculizumab, and the sample size is unlikely to have been sufficient to inform indirect analyses of non-inferiority.

The trial was designed to only include patients who were complement-inhibitor treatment naïve; therefore there is no direct evidence for the efficacy and safety of ravulizumab in patients previously treated with eculizumab. The ERG agree with the company that, as noted in response to PFC, clinicians and patients may want the option of treatment with eculizumab or ravulizumab based on their individual circumstances. However, clinical advisers to the ERG noted that their preference for management of complement-therapy naïve patients in the NHS would almost always involve initiating eculizumab as first-line treatment for approximately three months, until aHUS diagnosis is confirmed, after which patients may switch to ravulizumab. This management strategy is based on the rationale that, due to its shorter half-life, eculizumab is eliminated faster than ravulizumab for those patients who are started on treatment and subsequently receive a non-aHUS diagnosis. The UK advisory board to the company also agreed that nearly all treatment-naïve patients would be initiated on eculizumab and could be considered for treatment switching after 3 months if they were deemed to need long-term therapy, and that "one or two patients" per year with known mutations may be initiated on ravulizumab.[8] There are significant differences in population characteristics between eculizumab treatment-naïve patients and those switching to ravulizumab following response to eculizumab, as shown for instance by the respective baseline characteristics of the treatment naïve and eculizumab experienced cohorts of trial ALXN1210-aHUS-312 (see Table 4). Patients switching to ravulizumab following response to three months of eculizumab therapy will be expected to have their disease stabilized and a confirmed diagnosis of aHUS. This limits the applicability of the adult trial evidence to UK clinical practice.

In the company's response to points for clarification, they noted clinical evidence to support a recommendation of ravulizumab use in adults with aHUS who have received eculizumab for at least 3 months and have evidence of response to eculizumab; this included data from 10 paediatric patients in Cohort 2 of trial ALXN1210-aHUS-312 (described in Table 4 and Section 3.2.2) and data from trial ALXN1210-PNH-302 in PNH patients who were clinically stable following ≥6 months treatment with eculizumab and maintained target complement C5 inhibition and disease control after switching to ravulizumab. Further details are discussed in the company response to PFCs, Section A. The ERG agree that these results are promising. However, as noted by clinical advisers to the ERG, the

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

paediatric aHUS population and PNH patients are clinically different from adults with aHUS; notably, the paediatric aHUS population has a significantly better prognosis, and PNH patients are a clinically distinct population. Therefore it is uncertain whether the results of trials ALXN1210-aHUS-312 and ALXN1210-PNH-302 may apply to the adult aHUS population.

The screening period of seven days is unlikely to have been sufficient to exclude non-aHUS patients. However, as aHUS diagnosis is challenging and is usually made by ruling out other potential causes of TMA (for example, Shiga toxin-related haemolytic uraemic syndrome [STEC-HUS]); due to this and potential benefits of early initiation of eculizumab therapy, patients in clinical practice may be initiated on complement-inhibitor treatment for aHUS while screening for differential diagnosis continues.[15] Of 58 patients enrolled and treated, two were excluded for testing positive to Shiga toxin-related HUS, which is reflective of clinical practice. As noted in the CS Section B.1.3.2, diagnosis of aHUS is by exclusion and can be challenging. Given this, and due to likely heterogeneity across study centres in participant selection, the ERG is concerned that not all 56 remaining patients included in the FAS may have met the UK criteria for aHUS diagnosis and eligibility for treatment, and that a significant number of patients included in the 311 study may not be reflective of UK patients eligible for complement-therapy. This is further discussed in Section 3.2.1.2.

The trial selection criteria reflected the licence indication and clinical advisers to the ERG considered were broadly acceptable. However, the ERG is concerned that, following a protocol amendment after the start of the study, a large proportion (46%) of participants included in the FAS did not fulfil all four pre-specified TMA criteria at Day 1 of treatment. These patients may have had more favourable prognosis (such as likelihood of complete TMA response at follow-up) compared to patients with TMA at baseline. The company presented subgroup analyses to account for this and showed higher complete TMA results for patients without TMA at Day 1; results are presented in 3.2.3.1.

Clinical advisers to the ERG also noted that the low rate of pathogenic mutation rate observed in the ravulizumab evidence meant that it was not clear that the selection criteria at the discretion of the treating physician were implemented appropriately. Implications are further discussed in Section 3.2.1.2.

The company did not provide evidence on the efficacy and safety of alternative dosing to that described in the licence. The same issue was raised in the EPAR and ERG report for eculizumab. Although at the time of licencing, the company agreed to discuss the feasibility of a further study investigating the efficacy and safety of lower eculizumab doses following approval. The lack of long-term safety evidence for ravulizumab means the risk of long-term safety due to overdosing cannot be excluded. However, clinical advisers to the ERG were not aware of evidence suggesting that lower

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

doses of ravulizumab may have a better benefit/risk balance, and did not raise any specific concerns due to dosing based on eculizumab safety evidence other than the risk of meningococcal sepsis.

Clinical advisers confirmed that the primary endpoint, although not routinely used in clinical practice, is clinically relevant. The ERG agrees with the company that duration of follow-up is likely to capture a clinically meaningful recovery in the acute phase in aHUS patients following initiation of anti-C5 therapy. Clinical advisers to the ERG noted that recovery in the acute period would be expected in three to six months following treatment initiation if successful; recovery beyond this period would probably not be related to resolution of the original TMA. The follow-up duration to date is insufficient to inform the risk of recurrence following treatment response or long-term safety. The ERG is concerned that the trial Extension Period duration is dependent on registration or approval (in accordance with country-specific regulations) of ravulizumab and may therefore last less than the period required to inform long-term efficacy and safety outcomes. The company did not provide further details and it is not clear whether a NICE approval would affect the duration of the planned Extension Period.

The ERG notes that the lack of a randomised control trial design means that a causal relationship between ravulizumab exposure and complete TMA resolution (or any of the secondary outcomes) cannot be demonstrated. In study 311, observed improvements in renal function or haematological parameters following complement-therapy therapy are not equivalent to a response to treatment. Clinical advisers to the ERG noted that the low rate of pathogenic variants in complement regulation in the 311 trial population suggested that some FAS patients did not have complement-mediated aHUS and may have experienced an improvement in renal function or haematological endpoints due to other factors, such as co-interventions for co-occurring morbidities (e.g. infection, hypertension).

3.2.1.2 Population

Demographic and clinical characteristics of the patients in the FAS of ALXN1210-aHUS-311 are presented in Table 4.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 4 Baseline characteristics of patients included in trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312 (FAS population)

	ALXN1210-aHUS-311 NCT02949128	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=56)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Male, n (%)	19 (33.9)	8 (44.4)	9 (90.0)
Race, n (%)			
White/Caucasian	29 (51.8)	9 (50.0)	5 (50.0)
Asian	15 (26.8)	5 (27.8)	4 (40.0)
Undisclosed	8 (14.3)	1 (5.6)	0
Other	4 (7.1)	4 (22.2)	1 (10.0)
Age at time of first aHUS symptoms		[redacted]	[redacted]
Median years (range)	40.1 (9.3–76.6)		
Age at first infusion of study drug			
Median years (range)	40.1 (19.5–76.6)	[redacted]	12.5 (1.2–15.5)
<2 years, n (%)	0	2 (11.1)	1 (10.0)
2 to <6 years, n (%)	0	9 (50.0)	1 (10.0)
6 to <12 years, n (%)	0	5 (27.8)	1 (10.0)
12 to <18 years, n (%)	0	2 (11.1)	7 (70.0)
18 to <30 years, n (%)	11 (19.6)	0	0
30 to <40 years, n (%)	17 (30.4)	0	0
40 to <50 years, n (%)	15 (26.8)	0	0
50 to <60 years, n (%)	5 (8.9)	0	0
≥60 years, n (%)	8 (14.3)	0	0
Weight at first infusion of study drug	n=[redacted]	[redacted]	
Median kg (range)	[redacted]		47.8 (9–69)
<10 kg			[redacted]
10 to <20 kg			
20 to <30 kg			
30 to <40 kg			
40 to <60 kg			
60 to <100 kg			
≥100 kg		[redacted]	
Unknown			
Platelets (normal: 130–400 10^9/L)			281.8
Median x 10^9/L (range)	95.3 (18–473)	51.3 (14–125)	(207–416)
LDH (normal: 120–246 U/L)		1,963	
Median U/L (range)	508 (230–3,249)	(772–4,985)	207 (139–356)
Serum creatinine	n=58[a]	Not available	Not available
Median µmol/L (range)	284 (51–1,027)		
Haemoglobin (normal: 130–175 g/L)			
Median g/L (range)	85 (60.5–140)	74.3 (32–106)	132 (115–148)
eGFR (normal: ≥ 60 mL/min/1.73 m^2)			
Median mL/min/1.73 m^2 (range)	10 (4–80)	22 (10–84)	100 (54–137)

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 4 continued.	**ALXN1210-aHUS-311 NCT02949128**	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=56)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Dialysis within 5 days of first dose n (%)	29 (51.8)	6 (33.3)	0
Kidney transplant prior to enrolment Any transplant, n (%) Related to aHUS, n (%)	8 (14.3)	1 (5.6)	1 (10.0)
Onset of TMA post-partum, n (%)	8 (14.3)		
CKD stage, n (%) 1 2 3A 3B 4 5 Missing	n=54 0 3 (5.4) 1 (1.8) 2 (3.6) 9 (16.1) 40 (71.4) 1 (1.8)		8 (80.0) 1 (10.0) 1 (10.0) 0 0 0 0
Systolic blood pressure, mmHg Median (range)			
Patients with ≥1 known pathogenic variant or autoantibody, n (%) C3 CD46 CFB CFH CFH autoantibody	n=39 8 (20.5) 1 (2.6) 2 (5.1) 1 (2.6) 2 (5.1) 2 (5.1)	n=10 2 (20.0)	Not available
Extra-renal signs or symptoms Cardiovascular, n (%) Pulmonary, n (%) Central nervous system, n (%) Gastrointestinal, n (%) Skin, n (%) Skeletal muscle, n (%)	39 (69.6) 25 (44.6) 29 (51.8) 35 (62.5) 17 (30.4) 13 (23.2)		1 (10.0) 0 0 0 0 0
Medical history prior to study[b], n (%) Hypertension Acute kidney injury Headache Renal failure Nausea Constipation			
PE/PI before first dose of study drug and related to current TMA, n (%)	n=54 48 (82.8)		

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 4 continued.	**ALXN1210-aHUS-311 NCT02949128**	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=56)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Hospitalization history prior to study Emergency room visit, n (%) Other hospitalization, n (%) ICU stay, n (%)	[redacted]	[redacted]	[redacted]
Length of ICU stay N Median days (range)	[redacted]	[redacted]	[redacted]
FACIT-Fatigue score[c] at baseline Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]
EQ-5D-3L score[d] at baseline Mean VAS (SD) Mean TTO (SD)	[redacted]	Not collected	Not collected

Key: aHUS, atypical haemolytic uremic syndrome; C3, Complement 3; CD46, cluster of differentiation 46; CFB, Complement Factor B; CFH, Complement Factor H; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EQ-5D-3L, EuroQol-5 Dimension-3 Level; FACIT, Functional Assessment of Chronic Illness Therapy; ICU, intensive care unit; LDH, lactate dehydrogenase; PE, plasma exchange; PI, plasma infusion; SD, standard deviation; TMA, thrombotic microangiopathy, TTO, time trade-off; VAS, visual analogue scale.
Notes: [a], data reported for the safety set; [b], reported in >20% of patients – dashes represent this criteria not being met in individual trials/cohorts; [c], paediatric FACIT-Fatigue questionnaire used to assess HRQL in patients ≥5 years of age in ALXN1210-aHUS-312. The FACIT-Fatigue score ranges from 0 to 52, with higher score indicating less fatigue; [d], the EQ-5D VAS has end points of 0 and 100 with higher scores indicating better quality of life. TTO value set for the US.
Sources: ALXN1210-aHUS-311 CSR[13]; ALXN1210-aHUS-312 CSR.[16]; EMA Variation Assessment Report[17]; Rondeau et al. 2020.[18]

Overall, characteristics of the trial 311 population differed from the global aHUS adult cohorts for a number of variables.[19] For instance, the proportion of patients with prior kidney transplant was also significantly lower in study 311 (14.3%) compared with treatment naïve adults in the aHUS registry (26.7%), although patients in study 311 had lower fatigue scores and higher rates of extra-renal signs or symptoms. The median age of patients in study 311 (40.1 years) was somewhat younger than the global treatment naïve population (41.9 years) although this may have limited clinical significance. Comparisons with the global aHUS population are limited by the limited number of variables reported in the aHUS registry (such as kidney disease severity, pathogenic variants) and differences in eligibility criteria.

Points for critique

Most patients initiating ravulizumab would be expected to have undergone prior treatment with eculizumab. TMA parameters (including thrombocytopenia, haemolysis, and kidney injury) in

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

treatment-naïve adult patients are expected to differ significantly from eculizumab treatment-experienced patients who switch to ravulizumab, as shown in the paediatric trial 312 evidence (Table 4). The absence of eculizumab-experienced patients from study 311 significantly limits the applicability of the study population to the NHS.

The low rate of pathogenic variants in complement regulatory gene/protein mutation or anti-CHF autoantibody in the 311 trial population (20.5%, compared with 45-70% in observational data [20-23] and in eculizumab trial evidence 49–76%)[24-26] suggests that a significant proportion of trial patients included in the FAS may not have aHUS, as noted by clinical advisers to the ERG. The risk of inclusion of non-aHUS patients was potentially even higher in adults, due to a much wider differential diagnosis than in children.

As noted above (Section 3.2.1.1), a significant proportion of patients (46%) enrolled in the FAS did not meet all four TMA requirements at Day 1 (platelet count of < 150,000/μL, LDH ≥ 1.5 × ULN, haemoglobin ≤ LLN, and serum creatinine level ≥ ULN). Trial 311 also included severely critically ill patients (including three FAS patients who died) and late presenters (with lower likelihood of renal function recovery) who may not have been eligible for anti-complement therapy based on current NHS practice, as noted by clinical advisers to the ERG. The proportion of patients with prior kidney transplant (14.3%) is also relatively low compared with the trial target (10 to 25 patients) and the global aHUS eculizumab-treatment naïve population (26.7%).[19]

Study 311 included a large proportion of Asian patients, who showed lower rates of complete TMA response in a subgroup analysis (see Section 3.2.3.1). Clinical advisers to the ERG and to the company suggested that these observed differences may be associated with different diagnostic and management strategies rather than ethnic differences, although there is insufficient evidence to confirm this. The company noted that these differences in diagnosis and management may have introduced bias against ravulizumab when compared to UK clinical practice.

Overall, the ERG has a number of concerns about the generalizability of the study 311 population to NHS practice. Interpretations on the direction and magnitude of bias due to differences in population characteristics between trial 311 and the adult aHUS population who would be eligible for ravulizumab in the NHS are difficult to ascertain, due to limited evidence and potentially conflicting or uncertain sources of confounding. The inclusion of a large proportion of patients without TMA at baseline is likely to have positively biased TMA endpoints, as suggested by a subgroup analysis reported in Section 3.2.3.1; on the other hand, the inclusion of severely and critically ill patients that would not have been eligible in NHS practice is likely to have negatively biased ravulizumab efficacy and safety outcomes. Differences in management strategies across trial centres, or the risk that some trial 311 patients did not have aHUS may not necessarily lead to worse efficacy outcomes, contrary to

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

the discussion in CS Document B, Section 2.13.2.2. Although response to complement-therapy is consistent with an aHUS diagnosis (as response to complement pathway blockade confirms complement medicated aHUS), it is also clinically plausible that improvements in TMA parameters may have been confounded by disease natural history and concomitant therapies for non-aHUS related pathologies (e.g. treatments for infection or hypertension), as confirmed by clinical advisers to the ERG.

3.2.2 **ALXN1210-aHUS-312**

3.2.2.1 Design

The study design is summarised in CS Document B, Section B.2.3.1, with further details reported in the CSR.[16] ALXN1210-aHUS-312 is an ongoing single-arm open-label ongoing trial designed to assess the efficacy and safety of ravulizumab in children and adolescents with a diagnosis of aHUS. Both eculizumab-treatment experienced and treatment-naïve patients were included. Patients were recruited across 20 sites in eight countries ([redacted] patients were recruited in the UK). Participants aged <18 years were eligible. Patients were split into two cohorts: Cohort 1 were complement-inhibitor therapy naïve, and Cohort 2 included patients who had been treated with eculizumab for at least 90 days prior to screening. For Cohort 2, patients were excluded if they had any known abnormal TMA parameters within 90 days prior to screening.

Diagnosis of aHUS was determined by the same criteria as with trial 311, and there were no restrictions on kidney transplant status or dialysis status, except for patients with chronic dialysis needs who were excluded. Selection criteria are reported in CS Document B, Table 5. Study periods were aligned except for the screening period for Cohort 2 that could continue for up to 28 days. The first study patient started treatment in September 2017, and the latest cut-off data available is December 2019, when all patients had at least 52 weeks follow-up.

Dosages are presented in CS document B, Table 5. Loading doses on Day 1 with maintenance doses on Day 15 and once every eight weeks thereafter for patients weighing ≥ 20 kg, or once every four weeks for patients weighing < 20 kg administered by IV infusion. For Cohort 2 patients, Day 1 occurred 14 days from the patient's last dose of eculizumab. Co-treatment restrictions were broadly aligned with those described in trial 311.

The primary endpoint (complete TMA response) definition was the same as for trial 311, although it was only measured in the treatment-naïve Cohort. Secondary endpoints included Time to complete TMA response and complete TMA response status over time (for Cohort 1) and dialysis requirement status (both Cohorts).

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

As with trial 311, overall survival was not a pre-specified endpoint, although no deaths were recorded. Similarly, major non-renal outcomes (such as cardiac events and thrombosis) were monitored as safety outcomes. Disease recurrence was not a pre-specified outcome, and no data on recurrence are available yet due the limited follow-up to date. Eligibility for and success of transplantation were not pre-specified endpoints.

In line with trial 311, the FAS population for Cohort 1 included patients who received at least one dose of ravulizumab and had at least one efficacy assessment, a serum creatinine level ≥ upper limit of normal (ULN) during screening and had no known familial or acquired ADAMTS13 deficiency or STEC-HUS. The FAS for Cohort 2 included all patients who received at least 1 dose of ALXN1210 and had at least 1 postbaseline efficacy assessment.

The original protocol had a planned sample size of 16 patients. Following a protocol amendment, the total planned sample size was increased to include approximately 23 to 28 patients to account for the addition of Cohort 2. The company stated that this sample size was deemed appropriate to obtain "proper representation in each of the four planned age groups and provide adequate safety information and precision level for the planned estimation." The study protocol provided in response to clarification did not provide further details on how the sample size was derived including any power calculations.

Methods for dealing with missing data for the primary outcome and its components were aligned with those of trial 311 and reported in CS Document B, Table 7.

In Cohort 1, [redacted] patients were screened, enrolled, and treated with ravulizumab (safety set). Of those, three discontinued due to failure to meet eligibility criteria based on laboratory confirmation. The FAS for Cohort 1 included [redacted] patients. [redacted] discontinued treatment due to an AE and the remaining [redacted] completed the Initial Evaluation Period and entered the Extension Period. Of those, one patient discontinued due to physician decision and follow-up of remaining [redacted] was still ongoing as of the latest data cut-off. A flow diagram is presented in the trial CSR, Figure 2. Ten patients from Cohort 2 were screened, enrolled, and treated with ravulizumab in the study, and all 10 patients completed the Initial Evaluation Period and were ongoing in the Extension Period as of the December 2019 cut-off date. Hence the total number of patients included in the FAS was 28.

Points for critique

ALXN1210-aHUS-312 is the only known trial of ravulizumab in a paediatric aHUS population. Although described as a Phase III clinical trial, study 312 only included 28 patients in its FAS and no comparator arm, and no earlier phase trials in children with aHUS exist. Like trial 311, it is not

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

designed to assess the relative efficacy and safety of ravulizumab against eculizumab, and the sample size is unlikely to have been sufficient to inform indirect analyses of non-inferiority.

As discussed in 3.2.1.1, there is no evidence for the use of alternative dosing of complement-therapy in aHUS. A clinical adviser to the ERG noted there was insufficient evidence to support the use of a full adult dose for patients above 40kg, or for a more flexible approach to dosing and infusion frequency in the paediatric population.

3.2.2.2 Population

Demographic and disease characteristics of patients included in trial 312 are presented in Table 4.

Eculizumab experienced patients enrolled in Cohort 2 had laboratory values within normal ranges at baseline and normal kidney function, whereas treatment-naïve patients included in Cohort 1 had laboratory values outside of normal ranges at baseline and significantly impaired kidney function. Just three patients did not fall under the marketing authorization due to their low weight (under <10 kg).

Points for critique

As with trial 311, trial 312 included a lower proportion of patients with a known pathogenic variant or autoantibody than expected in UK clinical practice. Therefore, there is a risk that a significant number of patients included in trial 312 did not have aHUS.

Trial 312 included a minority (37%) of patients with experience of eculizumab therapy before switching to ravulizumab. As with adults, clinical advisers to the ERG expect that most paediatric aHUS patients would receive eculizumab as first-line prior to switching to ravulizumab, with the exception of some children for whom it may be hard to maintain central lines for long periods of time and who may be preferred for ravulizumab treatment as first-line. The fact that most patients included in the FAS were eculizumab treatment-naive limits the generalisability of the trial population to the aHUS population who would receive ravulizumab in the NHS.

3.2.3 Effectiveness

3.2.3.1 ALXN1210-aHUS-311

Efficacy results for the FAS population of ALXN1210-aHUS-311 during the Initial Evaluation Period (26 weeks) and Extension Period (available up to 2 July 2019 when all participants had received at least 52 weeks of treatment) are presented in CS Document B Table 8, and reproduced in Table 5 below. The median follow-up duration at data cut-off was [redacted] weeks (range: [redacted] weeks).

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 5 Summary of efficacy results from ALXN1210-aHUS-311: Initial Evaluation and Extension Period (up to 2 July 2019 cut-off) (FAS)

	Initial Evaluation Period	Extension Period
Complete TMA response, n (%) [95% CI]	30 (53.6) [39.6–67.5]	[redacted]
Platelet count normalization, n (%) [95% CI]	47 (83.9) [73.4–94.4]	[redacted]
Change in platelet count, Median x10^9/L (range)	125 (-126, 338)	Day 407 [redacted]
LDH normalization, n (%) [95% CI]	43 (76.8) [64.8–88.7]	[redacted]
Change in LDH, Median U/L (range)	-310.8 (-3,072, 9)	Day 407 -[redacted]
≥25% improvement in serum creatinine, n (%) [95% CI]	33 (58.9) [45.2–72.7]	[redacted]
Haematologic normalization[a], n (%) [95% CI]	41 (73.2) [60.7–85.7]	[redacted]
Haemoglobin response[b], n (%) [95% CI]	40 (71.4) [redacted]	[redacted]
Change in haemoglobin, Median g/L (range)	35 (9, 69)	Day 407 [redacted]
Time to complete TMA response, median days (95% CI)	86.0 [redacted]	NR
eGFR (normal range ≥ 60) Median mL/min/1.73 m^2 (range)	[redacted]	**Day 407** [redacted]
Change in eGFR, Median mL/min/1.73 m^2 (range)	29 (-13, 108)	Day 407 [redacted]
Dialysis requirement status Discontinuation from baseline, n/N (%) Initiation from baseline, n/N (%)	17/29 (58.6) 6/27 (22.2)[c]	[redacted]
CKD stage improvement, n/N (%)	32/47 (68.1)	[redacted]
CKD stage worsening, n/N (%)	2/47 (4.3)	[redacted]
Change in FACIT-Fatigue score[d], Median (range) Mean (SD)	20.0 (-16, 48) [redacted]	Day 351 [redacted]
≥3-point improvement in FACIT-Fatigue score[d], n/N (%)	37/44 (84.1)	Day 351 [redacted]
Change in EQ-5D-3L score[e], Mean VAS (SD) (IEP: n=45; EP: n=41) Mean TTO (SD) (IEP: n=46; EP: n=42)	[redacted]	[redacted]

Key: aHUS, atypical haemolytic uremic syndrome; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EQ-5D-3L, EuroQol-5 Dimension-3 Level; FACIT, Functional Assessment of Chronic Illness Therapy; HRQL, health-related quality of life; LDH, lactate dehydrogenase; SD, standard deviation; TMA, thrombotic microangiopathy; TTO, time trade-off; VAS, visual analogue scale.

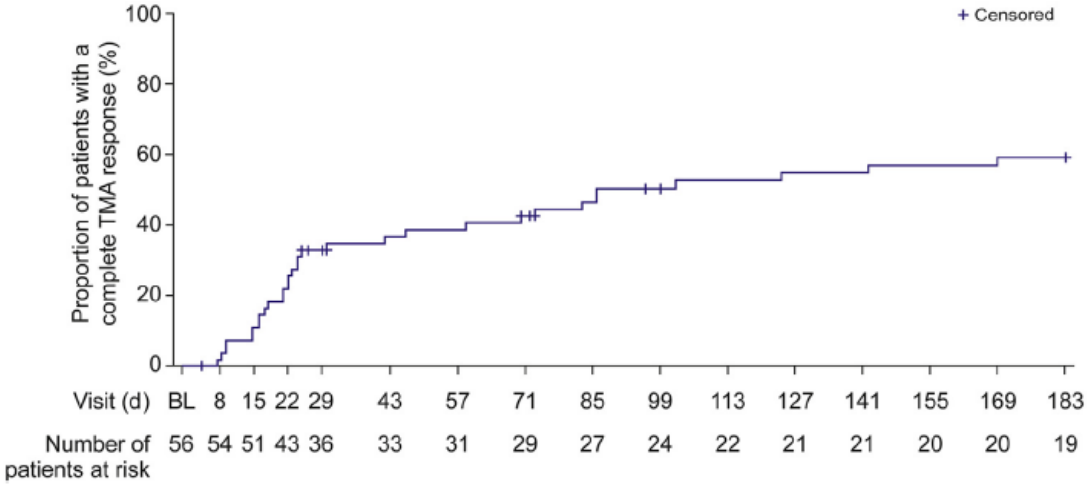
Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

	Initial Evaluation Period	Extension Period
Notes: [a], platelet count and LDH normalization; [b], ≥ 20 g/L increase; [c], one additional patient initiated and discontinued dialysis within the Initial Evaluation Period; [d], paediatric FACIT-Fatigue questionnaire used to assess HRQL in patients ≥5 years of age in ALXN1210-aHUS-312. The FACIT-Fatigue score ranges from 0 to 52, with higher score indicating less fatigue; [e], the EQ-5D VAS has end points of 0 and 100 with higher scores indicating better quality of life. TTO value set for the US.		

Complete TMA response

Complete TMA response was attained by 53.6% (95% CI 39.6 to 67.5) of patients in the Initial Evaluation Period, in a median time of 86 days ([redacted]); Figure 2 shows that the number of patients with a complete TMA response continued to increase over time during the Initial Evaluation Period, although most complete TMA responses were observed between day 7 and 29 approximately. [redacted] additional patients to those who achieved the primary endpoint achieved a complete TMA response in the Extension Period up to data cut-off (2 July 2019), making a total of [redacted] (95% CI [redacted] of patients attaining complete TMA response. As noted above (Section 3.2.1.1), it is unlikely that these later events are directly related to complement inhibition.

Figure 2 Kaplan–Meier plot of time to complete TMA response in ALXN1210-aHUS-311: Initial Evaluation Period (FAS)



Key: BL, baseline; d, day; FAS, full analysis set; TMA, thrombotic microangiopathy.
Notes: Patients who did not have a response were censored on the day of their last study visit or at study discontinuation.
Source: CS Document B, Figure 5.

Subgroup analysis results for the primary endpoint are reproduced in Figure 3 below. It does not appear that any of these subgroups were pre-specified. The subgroup analysis results show notably higher rates of complete TMA response in patients treated in Europe, and in patients without kidney

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

transplant history, although the small number of patients and overlapping confidence intervals mean that these results may not be reliable.

Figure 3 Forest plot of cTMA response rate in subgroups of ALXN1210-aHUS-311: Initial Evaluation Period

Source: CS Document B, Appendix E, Figure 5.

Renal endpoints

Renal function improvement (≥25% reduction in serum creatinine from baseline) was observed in 59% of patients in the Initial Evaluation Period, and by [redacted] in the Extension Period. A median increase of 29 mL/min/1.73 m^2 in the estimated glomerular filtration rate (eGFR) from baseline was observed by the end of the Initial Evaluation Period, and by [redacted] mL/min/1.73 m^2 at day 407. CKD stage improvement was observed in 68% of patients in the Initial Evaluation Period and [redacted] in the Extension Period, and two participants had worsening in CKD stage (from stage 4 to 5) during the Initial Evaluation Period. CKD stage shift from baseline in the Initial Evaluation and Extension Periods are presented in CS Document B, Table 9 and 13 respectively.

Of the patients on dialysis at baseline, 59% discontinued renal replacement therapy (RRT) during the Initial Evaluation Period and [redacted] in the Extension Period; 22% of those without dialysis at baseline initiated RRT during the Initial Evaluation Period, [redacted] during the Extension period.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Haematological endpoints

Seventy-three percent of participants achieved haematological normalization; 84% of patients had platelet count normalization during the Initial Evaluation Period, and [redacted] during the extension period. LDH normalisation was achieved by 77% in the Initial Evaluation Period, and by [redacted] in the Extension Period. Further details are reported in Table 5.

Health-related quality of life (HRQL)

Fatigue scores were measured using the FACIT-Fatigue scale, ranging from 0 to 52, with a maximum score indicating no fatigue, and with improvements of ≥3 considered to be clinically meaningful.[27] Of the 44 patients with FACIT-Fatigue data at baseline and at the end of the Initial Evaluation Period, 84% reported a ≥3-point improvement in FACIT-Fatigue score, and a mean improvement of [redacted] was observed during the Initial Evaluation Period. Clinically significant improvements in EQ-5D-3L scores from baseline were recorded and are reported in Table 5.

Overall mortality, disease recurrence, major non-renal outcomes, eligibility for/success of transplantation

Overall survival was not reported as an efficacy outcome but deaths were reported as part of the safety assessment. Similarly, major non-renal clinical outcomes such as thrombosis or cardiac events were captured as safety events. The CS stated that no data on disease recurrence are available yet due to limited follow-up to date. Eligibility for/success of transplantation was not captured in the ravulizumab trials. Data on drug resistance is reported in the safety results section.

Points for critique

Results from trial 311 provide promising evidence that ravulizumab may be effective for the management of complement-therapy naïve adult patients with aHUS. Improvements in renal function observed at 26 weeks follow-up were generally maintained at the latest data cut-off.

Due to significant limitations in the design of the study, the ERG has a number of concerns about the generalisability of the trial results to NHS clinical practice. All patients included in trial 311 were complement-therapy naïve, where it is expected that nearly all patients who would be likely to receive ravulizumab in clinical practice would have received eculizumab as first-line treatment. Due to challenges and likely heterogeneity in patient selection across study centres, and notably the relatively low prevalence of pathogenic variants in the trial population, the ERG is concerned that a significant number of patients included trial 311 may not have had aHUS.

Given the small sample size and as evidenced by the large confidence intervals in most of the efficacy endpoints reported, the precision of efficacy estimates is uncertain. In addition, the lack of randomised design and concerns about inclusion of non-aHUS patients mean that the causal relation between

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

ravulizumb exposure and observed clinical outcomes is largely uncertain. The likely direction and magnitude of bias associated with these limitations are too uncertain to predict. Lack of blinding means that self-reported HRQL outcomes should be interpreted with caution.

3.2.3.2 ALXN1210-aHUS-312

Efficacy results for the FAS population of ALXN1210-aHUS-312 during the Initial Evaluation Period (26 weeks) and Extension Period when all participants had received at least 52 weeks of treatment are presented in CS Document B Tables 8 and 12, and reproduced in Table 6 below. The median follow-up duration at data cut-off was [redacted] weeks (range: [redacted]weeks) for Cohort 1, and [redacted] weeks (range: [redacted]) for Cohort 2.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 6 Summary of efficacy results from ALXN1210-aHUS-312: Initial Evaluation and Extension Period (up to 3 December 2019 cut-off) (FAS)

	Initial Evaluation Period		Extension Period	
	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)	Ravulizumab Cohort 1 (n=18)	Ravulizumab Cohort 2 (n=10)
Complete TMA response, n (%) [95% CI]	14 (77.8) [52.4–93.6]	Not relevant	[redacted]	Not relevant
Platelet count normalization, n (%) [95% CI]	17 (94.4) [72.7–99.9]	Platelet count remained stable	[redacted]	[redacted]
Change in platelet count, Median x10^9/L (range)	[redacted]	[redacted]	[redacted]	[redacted]
LDH normalization, n (%) [95% CI]	16 (88.9) [65.3–98.6]	LDH remained stable	[redacted]	[redacted]
Change in LDH, Median U/L (range)	[redacted]	[redacted]	[redacted]	[redacted]
≥25% improvement in serum creatinine, n (%) [95% CI]	[redacted]	Not relevant	[redacted]	Not relevant
Haematologic normalization[a], n (%) [95% CI]	16 (88.9) [65.3–98.6]	Not relevant	[redacted]	Not relevant
Haemoglobin response[b], n (%) [95% CI]	16 (88.9) [65.3–98.6]	Hb remained stable	[redacted]	[redacted]
Change in haemoglobin, Median g/L (range)	[redacted]	[redacted]	[redacted]	[redacted]
Time to complete TMA response, median days (95% CI)	[redacted]	Not relevant	Not applicable	Not relevant
eGFR (normal range ≥ 60) Median mL/min/1.73 m^2 (range)	108 [redacted]	[redacted]	**Day 407** [redacted]	**Day 351** [redacted]
Change in eGFR, Median mL/min/1.73 m^2 (range)	80 [redacted]	[redacted]	Day 407 [redacted]	Day 351 [redacted]

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 6 continued.				
Dialysis requirement status Discontinuation from baseline, n/N (%) Initiation from baseline, n/N (%)	[redacted]	Not relevant [redacted]	[redacted]	Not relevant [redacted]
CKD stage improvement, n/N (%)	15/17 (88.2)	[redacted]	[redacted]	[redacted]
CKD stage worsening, n/N (%)	0/17 (0.0)	[redacted]	[redacted]	[redacted]
Change in FACIT-Fatigue score[d], Median (range) Mean (SD)	10.0 [redacted]	[redacted]	**Day 351** [redacted]	**Day 351** [redacted]
≥3-point improvement in FACIT-Fatigue score[d], n/N (%)	[redacted]	Not relevant	Day 351 [redacted]	Not relevant
Change in EQ-5D-3L score[e],	Not collected	Not collected	Not collected	Not collected

Key: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EQ-5D-3L, EuroQol-5 Dimension-3 Level; FACIT, Functional Assessment of Chronic Illness Therapy; HRQL, health-related quality of life; LDH, lactate dehydrogenase; SD, standard deviation; TMA, thrombotic microangiopathy; TTO, time trade-off; VAS, visual analogue scale.
Notes: [a], platelet count and LDH normalization; [b], ≥ 20 g/L increase; [c], one additional patient initiated and discontinued dialysis within the Initial Evaluation Period; [d], paediatric FACIT-Fatigue questionnaire used to assess HRQL in patients ≥5 years of age in ALXN1210-aHUS-312. The FACIT-Fatigue score ranges from 0 to 52, with higher score indicating less fatigue; [e], the EQ-5D VAS has end points of 0 and 100 with higher scores indicating better quality of life. TTO value set for the US.

Complete TMA response

Cohort 1

Complete TMA response was attained by 78% (95% CI 52 to 94) of patients in the Initial Evaluation Period, in a median time of [redacted] days; Figure 2 shows that the number of patients with a complete TMA response outcome increased over time during the Initial Evaluation Period. [redacted] additional patients to those who achieved the primary endpoint achieved a complete TMA response in the Extension Period up to data cut-off, making a total of [redacted] (95% CI [redacted]) complete TMA response rate.

Renal endpoints

Cohort 1

Renal function improvement (≥25% reduction in serum creatinine from baseline) was observed in [redacted] of patients in the Initial Evaluation Period, and by [redacted] in the Extension Period. A median increase of 80 mL/min/1.73 m^2 in eGFR from baseline was observed by the end of the Initial Evaluation Period, and by [redacted] mL/min/1.73 m^2 at day 407. CKD stage improvement was observed in 88% of patients in

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

the Initial Evaluation Period and [redacted] in the Extension Period, and no patients had worsening in CKD stage. CKD stage shift from baseline in the Initial Evaluation and Extension Periods are presented in CS Document B, Table 10 and 14 respectively.

Of the patients on dialysis at baseline, [redacted] discontinued dialysis during the Initial Evaluation Period and [redacted] in the Extension Period. [redacted] patients initiated dialysis during the study periods in either cohort.

Cohort 2

Renal function remained mostly stable in patients switching from eculizumab to ravulizumab, although [redacted] during the Initial Evaluation period. [redacted].

Haematological endpoints

In Cohort 1, 89% of participants achieved haematological normalisation, 94% had platelet count normalisation, and 89% had LDH normalisation during the Initial Evaluation Period. In Cohort 2, haematological endpoints remained stable overall. Further details are reported Table 6.

HRQoL

In Cohort 1, [redacted] (of [redacted] patients) reported a ≥3-point improvement in FACIT-Fatigue score, and a mean improvement of [redacted] points was observed during the Initial Evaluation Period. EQ-5D scores were not collected.

Overall mortality, disease recurrence, major non-renal outcomes, eligibility for/success of transplantation

Trial 312 reported no deaths. Similarly to study 311, major non-renal clinical outcomes were captured as safety events, no data on disease recurrence are available yet due to limited follow-up to date, and eligibility for/success of transplantation was not captured. Data on drug resistance is reported in the safety results section.

Points for critique

Results from trial 312 provide promising evidence that ravulizumab may be effective for the management of complement-therapy naïve and eculizumab experienced paediatric patients with aHUS. As with trial 311, improvements in renal function in eculizumab-naïve patients observed at 26 weeks follow-up were generally maintained at the latest data cut-off.

The precision of efficacy estimates in both trial cohorts is uncertain, as evidenced by the large confidence intervals in most of the efficacy endpoints reported. In addition, the lack of randomised design and concerns about inclusion of non-aHUS patients mean that the causal relation between

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

ravulizumb exposure and observed clinical outcomes is largely uncertain. As with trial 311, the likely direction and magnitude of bias associated with these limitations are too uncertain to predict. Lack of blinding means that self-reported HRQL outcomes should be interpreted with caution.

3.2.4 **Safety**

Table 7 presents a summary of safety results as of the latest available data cut-off for ALXN1210-aHUS-311 and ALXN1210-aHUS-312.

Table 7 Summary of adverse events from ALXN1210-aHUS-311 and ALXN1210-aHUS-312 (Safety Populations, Extension Period as of December 2019 cut-off dates)

	ALXN1210-aHUS-311 NCT02949128	**ALXN1210-aHUS-312 NCT03131219**	
	Ravulizumab (n=58)	Ravulizumab Cohort 1 (n=21)	Ravulizumab Cohort 2 (n=10)
Patients with any AE, n (%)	[redacted]	[redacted]	[redacted]
Common adverse events[a], n (%)	[redacted]	[redacted]	[redacted]
Headache	[redacted]		
Diarrhoea			
Vomiting	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Peripheral oedema	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Otitis media	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]
AE severity, n (%)			
Grade 1	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]	[redacted]

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Patients with any treatment-related AE, n (%)	[redacted]	[redacted]	[redacted]
Patients with any serious adverse event, n (%)	[redacted]	[redacted]	[redacted]
Common SAEs[b], n (%) Hypertension Pneumonia Malignant hypertension Urinary tract infection Septic shock aHUS Viral gastroenteritis Abdominal pain	[redacted]	[redacted]	[redacted]
Meningococcal infections, n (%)	[redacted]	[redacted]	[redacted]
Discontinuation due to AE, n (%)	[redacted]	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]	[redacted]
Death due to AE, n (%)	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; aHUS, atypical haemolytic uremic syndrome; SAE, serious adverse event.
Notes: [a], Defined as ≥ 15% of patients – dashes represent events not meeting these criteria in individual trials/cohorts; [b], Defined as >1 patient – dashes represent events not meeting these criteria in individual trials/cohorts.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

3.2.4.1 ALXN1210-aHUS-311

[redacted]

AEs deemed to be treatment-related were assessed by the study investigator, and the CS did not report that causality between treatment and safety outcomes were also assessed by an independent endpoint assessment adjudication panel. In response to clarification, the company stated that their UK advisory group had reviewed death narratives based on short summaries.

Four patients died during the study (three patients from the FAS and one from the safety analysis set). Table 4 presents of summary of the four deaths. Following request for clarification, the company provided narratives for deaths and serious adverse events from the CSR to the ERG. The three deaths from the FAS resulted from a fatal treatment-emergent AE; two patients died from a septic shock and one from a cerebral haemorrhage. The other death occurred in a patient who had been discontinued from the study after a single dose of ravulizumab following differential diagnosis (positive STEC test) from a cerebral artery thrombosis. All four patients had significant comorbidities and were critically ill at treatment initiation; three (including two FAS patients) were receiving mechanical ventilation at baseline and two patients were receiving antibiotics for an existing infection.

The company concluded that the four deaths were unrelated to ravulizumab, as per the CSR and the trial publication.[13, 18] This view differs from the conclusions of the company's UK advisory board (ref. 24 in CS Document B, page 160) which stated that it was "difficult to draw any definitive conclusion from the data presented and not possible to say with certainty that these deaths were not treatment-related." Clinical advisers to the ERG also agreed that it was not possible to conclude with certainty that these deaths were not treatment-related, although they concurred with the company that, given their presentation at baseline, these patients may not have had aHUS and would likely not have been treated with ravulizumab in UK clinical practice.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 8 Summary of deaths in patients treated with ravulizumab in ALXN1210-aHUS-311 (from CS Document B, Appendix F, Table 23)

Cause of death	**Age**	**Time on treatment**	**Key timepoints**
Septic shock	73	Onset of event Day 2 Patient received 1 dose Death on Day 3	**Prior to the first dose:** history of diabetes, coronary heart disease, congestive heart failure. Recent ischemic stroke, encephalopathy, respiratory failure, and on multiple antibiotics for infection. **On day of the first dose:** receiving mechanical ventilation, *pseudomonas* in pulmonary aspirate. **Additional points:** CRP and white cell count were elevated prior to ravulizumab treatment and clotting assays were normal. No genetic analysis was performed.
Septic shock	76	Onset of event Day 6 Patient received 2 doses Death on Day 25	**Prior to the first dose:** history of diabetes, kidney transplant in 2010 (kidney disease due to diabetes), myelofibrosis (cytopenia) diagnosed in 2016. Recent shock (septic or hypovolemic), acute respiratory distress syndrome, multiple infections (*Pneumocystis carinii* and CMV pneumonia). Patient was on antibiotics, cardiovascular medications, insulin, sirolimus, prednisolone and inotropes. **On day of the first dose:** receiving mechanical ventilation. **Day 6:** new septic shock due to *Corynebacterium* and *Candida lusitaniae* in the catheter (tip taken for culture prior to the first dose). **Additional points:** clotting assays were normal prior to ravulizumab treatment, while CRP was elevated, and white cell count low. No pathogenic variant found.
Cerebral haemorrhage	46	Onset of event Day 93 Patient received 3 doses Death on Day 107	**Prior to the first dose:** uncontrolled hypertension (multiple drugs); Stage 4 CKD >2 months that had progressed to CKD Stage 5, requiring dialysis at initiation of study drug; thrombocytopenia; anaemia; and hypercalcemia. **Day 93:** patient experienced headache, nausea, vomiting, left side weakness and dysarthria, and was admitted with loss of consciousness. Right intraventricular haemorrhage and intracranial haemorrhage were identified. Following surgery, the patient was transferred to neurosurgery ICU. However, hypertension and loss of consciousness persisted, and supportive care was withdrawn. No pathogenic variant found.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 8 continued.			
Cerebral artery thrombosis	77	Onset of event prior to treatment Patient received 1 dose but was excluded from efficacy analysis due to positive *Shiga* toxin test Death on Day 15	**Prior to the first dose:** in ICU for cerebral arterial thrombosis and seizures. **On day of the first dose:** receiving mechanical ventilation. **Additional points:** white cell count and CRP were elevated prior to ravulizumab treatment. Seizures and cortical infarcts approximately 10 days later, supportive care was withdrawn. No genetic analysis was performed.
Key: ARDs, acute respiratory distress syndrome; CKD, chronic kidney disease; CMV, cytomegalovirus; CRP, C-reactive protein; ICU, intensive care unit. **Source:** Rondeau et al. 2020.[18]			

One patient had a treatment-emergent antidrug antibody positive test on Day 68 although there was no apparent impact on safety and efficacy.[13]

Targeted AEs for this study were meningococcal infections. In one country, the targeted AEs also included sepsis, serious infections, *Aspergillus* infection, infusion reactions, serious cutaneous adverse reactions, cardiac disorders (including ventricular fibrillation), and angioedema.[13, 16]

CS Document B, p.96 states that ravulizumab "could reduce the risk of vein damage" compared with eculizumab. In response to clarification, the company noted that although there are no specific data demonstrating a lower risk of vein damage with ravulizumab compared to eculizumab, long-term intravenous (IV) therapy is associated with complications which include among others, venous depletion over time. [28, 29] The company quoted evidence from a survey of 34 aHUS patients suggesting that venous access was a difficulty with eculizumab for approximately a third or respondents (12/34), and that given the expected significant reduction in number of annual ravulizumab infusions compared to eculizumab, it was reasonable to expect a corresponding reduction in the risks associated with frequent IV infusions.

3.2.4.2 ALXN1210-aHUS-312

Table 7 (Section 3.2.4) presents a summary of safety results as of the latest available data cut-off for ALXN1210-aHUS-312. [redacted] experienced an AE, and [redacted] patient in [redacted] discontinued the study to an AE [redacted] patients died during the study, [redacted] cases of meningococcal infections, and [redacted] treatment-emergent ADA positive samples were observed in [redacted] Treatment related AEs and serious adverse events in Cohort 1 were [redacted] and [redacted] respectively.

As in trial 311, AEs deemed to be treat-related were assessed by the study investigator, and it does not appear that causality between treatment and safety outcomes were also assessed by an independent endpoint assessment adjudication panel.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Points for critique

AEs deemed to be treatment-related were assessed by the study investigators, and the CS did not report that causality between treatment and safety outcomes were also assessed by an independent endpoint assessment adjudication panel. Due to the absence of data beyond the 2019 cut-off, the long-term safety of ravulizumab is uncertain. As meningococcal infections were the only targeted adverse event except in one country, the risk that other serious infection may not have been captured cannot be excluded.

The ERG believes that in view of the evidence provided, it is not possible to conclude whether the deaths recorded in trial 311 were not treatment-related, although the ERG agrees with the company that it is likely that the patients who died would not have been eligible for ravulizumab in NHS practice.

The ERG agrees with the company that is clinically plausible that the reduced need for infusions with ravulizumab may be associated with a lower risk of infusion-related adverse events compared with eculizumab; there is currently no evidence to support this.

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

Due to the lack of direct evidence comparing ravulizumab with eculizumab, the company conducted indirect treatment comparison (ITC) analyses. Since both treatments were developed by the company, the ERG judged it unlikely that any relevant comparator data were missed. Clinical advisors to the ERG confirmed that eculizumab was the only relevant comparator.

3.3.1 **Summary of included studies**

Five single arm trials were included in the ITC (see Table 9).

Table 9 Single arm trials of ravulizumab and eculizumab in aHUS patients included in the ITC analyses*

Trial ID	Population	Sample size	Treatment	Mutation and/or auto-antibodies identified
ALXN1210-aHUS-311	Complement Inhibitor naïve adults	N=58	Ravulizumab	8/39 (20.5%)
ALXN1210-aHUS-312	Complement Inhibitor naïve children and adolescents	N=21	Ravulizumab	9/10 (90%)
aHUS-C08-002	Complement Inhibitor naïve and plasma therapy-resistant	N=17 (n=16 adults, n=1 adolescents)	Eculizumab	13/17 (76%)
aHUS-C10-003	Complement inhibitor naïve paediatric patients	N=22	Eculizumab	11/22 (50%)
aHUS-C10-004	Complement Inhibitor naïve adults	N=44	Eculizumab	20/41 (49%)

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

*Adapted from CS Document B, Table 16, and company response to question A10 of PFCs

Points for critique

Limited evidence

All evidence included in the ITC analyses were from single arm trials with relatively small sample sizes. The ERG considers that the company have made adequate justification for including these sources of evidence. However, there are substantial uncertainties when evaluating the comparative effectiveness of ravulizumab and eculizumab that are inherent to single arm trials with small sample sizes. Without randomized controlled trials, it is not possible to rule out the impact of confounding on comparisons between these treatments (see section 3.4.1 for further details on the potential impact of confounding). In addition, the trials were not designed to test whether ravulizumab and eculizumab are similar in effectiveness. The sample sizes of these trials are unlikely to be large enough to draw firm conclusions on comparative effectiveness (see section 3.4.2 for further details).

Comparability of trials at baseline

The ERG identified several important concerns regarding the comparability of the eculizumab and ravulizumab trials. There is a substantial possibility that the population recruited in one of the ravulizumab trials is different from that recruited in the eculizumab trials. Moreover, standard practice may have differed between centres in the ravulizumab trial which raises further issues in comparisons with eculizumab. These uncertainties are summarised below.

First, there was a substantial difference of pathogenic variants (20.5%) for ravulizumab patients recruited in the ALXN1210-aHUS-311 study compared with the eculizumab trials (aHUS-C10-003: 70%, aHUS-C10-004: 49%).[24, 26] Because aHUS is a diagnosis of exclusion, there is a risk that patients with similar symptoms but alternative conditions will be recruited to trials. The low mutation rate suggests this may have been the case with the ravulizumab trial.[30]

Second, the definition of aHUS was more restrictive 10 years ago when the eculizumab trials were conducted.[30] Therefore, patients recruited to the current ravulizumab trials using broader definitions of aHUS are likely to differ from patients in eculizumab trials recruited according to earlier definitions.

Third, there were important differences between treatment centres recruited to the ravulizumab (20-29% of patients were recruited in Taiwan, Japan and South Korea) and eculizumab (no patients were recruited in Asia) trials. Data from the ravulizumab trials suggests treatment may have differed between Asian and non-Asian treatment centres. All patients recruited outside Asia were treated

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

within 4 weeks from the start of the TMA episode. However, 11/14 patients treated in Asia received treatment at least 4 weeks after the start of the current TMA episode.[30]

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

3.4.1 Matching of baseline patient characteristics

The company conducted prognostic score matching using stabilized weights to reduce baseline differences observed between the ravulizumab and eculizumab trials.

Since the company had access to individual patient data for all included trials, they combined all trial data into one dataset and conducted separate analyses for adult non-transplant, adult transplant, and paediatric patients (see Table 10).

Table 10 Baseline differences between ravulizumab and eculizumab prior and after application of stabilized weighting*

	Adult non-transplant patients		**Adult transplant patients**		**Paediatric patients**	
Outcomes	**Ravulizumab**	**Eculizumab**	**Ravulizumab**	**Eculizumab**	**Ravulizumab**	**Eculizumab**
Dialysis status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR in non-dialysis patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients recruited in Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Proportion of patients aged 65 years or over	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age in years: mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*sample sizes quoted for all data reported after application of stabilized weights refer to effective sample size (ESS), SD= standard deviation, n=sample size, eGFR=estimated Glomerular Filtration Rate

Points for Critique

Dialysis status and eGFR values

Dialysis status at baseline and eGFR values were identified by clinical advisers to the ERG as key prognostic factors (company analyses concur). Prognostic score matching generally reduced imbalances in dialysis status at baseline and eGFR values between ravulizumab and eculizumab trials in adult non-transplant and paediatric patients. Although there may have been baseline differences for these measures in transplant patients, it is difficult to tell the impact of these imbalances given the small numbers in this population [redacted]

Pathogenic variant or autoantibody rates

It is well accepted that the course of aHUS is impacted by the presence of genetic variants. Therefore, the low mutation rate (20.5%) for adult ravulizumab patients compared with mutation rates in the eculizumab trials is a major limitation of the ALXN1210-aHUS-311 study. The proportion of genetic variants identified in the adult eculizumab trials (aHUS-C10-004= 49%; aHUS-C08-002=76%)[24, 26] is similar to that found in the wider literature and in aHUS patients currently treated in the NHS (69%)[5] (see Table 9). As discussed above, commentaries in the literature[30] and clinical advice provided to the ERG raise important questions on whether a substantial proportion of patients included in this ravulizumab trial were correctly diagnosed with aHUS.

Despite the potential importance of these differences between trials, the company did not address these in their ITC analyses. In response to question A10 in points for clarification (PFCs), the company provided two main justifications:

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

- genetic analyses were not mandatory in the ravulizumab trials (39/56 (70%) patients received genetic testing)
- the company's clinical advisers did not consider genetic variants or autoantibodies to be an important prognostic factor
- genetic analysis has moved on since the eculizumab trials therefore a 'like-for-like' comparison is not possible

The ERG judged this justification to be insufficient. First, it has been pointed out that genetic testing is standard practice for many treatment centres, therefore it is likely the company could have obtained most of these missing data on genetic variants by contacting treatment centres.[30] Even if it was not possible to obtain these genetic data, matching could have been conducted in patients with available data for this covariate in a similar way to other prognostic factors included in the ITC analyses. Alternatively, the impact of including this factor in the matching analyses could have been assessed in sensitivity analyses.

The second justification provided by the company was also considered insufficient. Clinical advice to the ERG highlighted substantial differences in proportion of patients with genetic variants between eculizumab and ravulizumab trials as one of the major uncertainties of the ITC analyses.

The ERG noted several issues with the third justification. First, this reasoning is not applied consistently across the submission. As noted above, various aspects of practice (e.g. diagnosis of aHUS) have changed since the eculizumab trials but this did not prevent the company from comparing ravulizumab with these eculizumab trials. Second, although the ERG accepts that genetic analyses have developed over time, the company did not provide evidence that changes in genetic analyses would substantially impact comparisons of pathogenic variants/autoantibody rates across trials. Pathogenic variants/autoantibody rates in the eculizumab trials were similar to that reported in current UK clinical practice.

Patients recruited in Asia

In adult non-transplant patients, the proportion of patients recruited in Asia was higher in ravulizumab than eculizumab ([redacted] trials. The difference was slightly larger when applying stabilized weights [redacted] Similar imbalances were observed in adult transplant and paediatric patient populations. Sensitivity analyses excluding patients recruited in Asia are considered in section 3.4.2.

Age

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

In adult non-transplant patients, mean age was higher for ravulizumab patients compared with eculizumab patients both prior to weighting ( ) and after application of stabilized weights ( ). Similar baseline imbalances were observed for adult transplant patients. Sensitivity analyses excluding patients 65 years and over are considered in section 3.4.2.

Other

Additional baseline differences between ravulizumab and eculizumab for adult transplant patients were identified for gender (after application of stabilized weights, ravulizumab patients were much more likely to be male: and systolic blood pressure (after application of stabilized weights, eculizumab patients had much higher systolic blood pressure:). Systolic blood pressure differences are potentially important as this factor was identified as a potential confounder by clinical advisers to the company. But it is difficult to predict what magnitude and direction of bias would be expected from these baseline differences.

3.4.2 **Results of Indirect Comparison**

Table 11 Summary of aHUS related outcomes in adult non-transplant, adult transplant, and paediatric patients*

	Adult non-transplant patients		**Adult transplant patients**		**Paediatric patients**	
Outcomes	**Ravulizumab (ESS=46)**	**Eculizumab (ESS=39)**	**Ravulizumab (ESS=9.3)**	**Eculizumab (ESS=12.7)**	**Ravulizumab (ESS=10.7)**	**Eculizumab (ESS=21.3)**
Change in CKD stage: Improved Unchanged Worsened						
eGFR, mean (SD)						
Dialysis at endpoint						
cTMA response						
Improvement in creatinine						
Platelet count normalisation						
LDH normalisation						
Haematological normalisation						
EQ-5D VAS, mean (SD)						

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

FACIT-fatigue, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Died in trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ESS= effective sample size, SD=standard deviation, eGFR=estimated Glomerular Filtration Rate

* Adapted from CS Document B, Tables 21 and 22

Results from the ITC analyses are summarised in Table 11. The CS concluded that there were no statistically significant or clinically relevant differences in effectiveness between ravulizumab and eculizumab.

Completed TMA (cTMA) response

Meeting criteria for cTMA response was less likely for adult non-transplant patients ([redacted]) receiving ravulizumab compared with eculizumab, but more likely in adult transplant patients ([redacted]and paediatric non-transplant patients ([redacted]

Renal endpoints

Adult transplant ([redacted]and adult non-transplant ([redacted]patients receiving ravulizumab were less likely than patients receiving eculizumab to experience an improvement in CKD stage. A similar proportion of ravulizumab ([redacted]) and eculizumab ([redacted]) paediatric non-transplant patients experienced an improvement in CKD stage.

There may also be differences between ravulizumab and eculizumab for patients requiring dialysis at endpoint. There was an approximately [redacted]increased risk for requiring dialysis at endpoint for ravulizumab compared with eculizumab in adult non-transplant patients ([redacted] ravulizumab vs eculizumab [redacted]). Paediatric non-transplant populations receiving ravulizumab were also more likely to require dialysis at endpoint ([redacted]) However, less ravulizumab patients in the adult transplant population required dialysis at endpoint ([redacted]

Haematological endpoints

Haematological (ravulizumab [redacted] vs eculizumab [redacted]LDH (ravulizumab [redacted] vs eculizumab [redacted]), and platelet count (ravulizumab [redacted] vs eculizumab [redacted]normalization rates were higher for eculizumab in non-transplant populations.

Haematological (ravulizumab [redacted] vs eculizumab [redacted]and LDH (ravulizumab [redacted] vs eculizumab [redacted]) normalisation rates were slightly higher in eculizumab transplant patients. In paediatric non-transplant

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

patients, haematological (ravulizumab [redacted] vs eculizumab [redacted]) and LDH (ravulizumab [redacted] vs eculizumab [redacted]) normalization rates were higher for ravulizumab. Platelet count normalisation rates were [redacted] for all transplant and paediatric non-transplant patients.

Quality of life

Ravulizumab patients reported [redacted] fatigue than eculizumab in adult non-transplant and transplant patients. While in paediatric non-transplant patients fatigue was [redacted] in both groups. [redacted] quality of life (EQ-5D VAS) was reported for ravulizumab in non-transplant patients but [redacted] quality of life for eculizumab in transplant patients.

Deaths

The ITC analyses included data from the full analysis set (FAS), where there were [redacted] deaths in non-transplant patients receiving ravulizumab. As discussed in more detail in section 3.2, the safety population included [redacted]. No deaths were reported in the eculizumab trials. Although this evidence may be of limited generalisability to the UK, differences regarding the safety of ravulizumab in comparison with eculizumab cannot be ruled out.

Sensitivity analyses

Sensitivity analyses excluding patients recruited in Asia, reduced differences between eculizumab and ravulizumab for most outcomes. However, ravulizumab patients were still [redacted] as likely to need dialysis at endpoint compared with eculizumab patients ([redacted]**).** Excluding patients 65 years or over had less of an impact on results.

Non-inferiority trial of ravulizumab vs eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PNH)

In addition, to the data in aHUS patients, the CS also pointed out a trial in patients with PNH found that ravulizumab met criteria for non-inferiority with eculizumab across a range of outcomes (see CS section B2.13.2.1 for further discussion).

3.4.2.1 Points for Critique

The ERG accepts the company's argument that non-inferiority trials were not feasible in aHUS patients. However, the lack of a non-inferiority trial means that, although it is biologically plausible ravulizumab and eculizumab are associated with similar clinical effectiveness, this remains uncertain despite being a key assumption of the submission.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

The CS states, "[redacted]." (see section B2.9.9.2). However, the results of the ITC analyses (summarised in 3.4.2) suggest for some outcomes (e.g. number of patients on dialysis at endpoint in non-transplant patients, change in CKD stage in transplant patients), ravulizumab may be [redacted] than eculizumab. Whether these potential differences are reflective of genuine differences in effectiveness or residual confounding is highly uncertain:

1) The company's claim that there were no statistically significant differences between treatments doesn't accurately reflect the outcome data. For example, table 22 of the CS shows [redacted]

2) Failure to meet the threshold for statistical significance does not necessarily imply the treatments are of similar effectiveness since sample sizes were small for all populations in the ITC analyses. Although formal power calculations are needed to assess the required sample size for non-inferiority analyses in aHUS patients, it is likely there were insufficient sample sizes for all three populations in the ITC analyses ([redacted]). For example, the non-inferiority trial comparing eculizumab and ravulizumab in patients with PNH included a far larger sample size (195 patients).

   Therefore, where differences were not statistically significant, this may just reflect that sample sizes were of insufficient magnitude to detect important differences. There were several differences between groups approaching statistical significance. For example, in non-transplant patients, data on proportion of patients on dialysis at endpoint (ravulizumab [redacted] vs eculizumab [redacted]), and LDH, U/L (ravulizumab [redacted] vs eculizumab [redacted]), favoured eculizumab. Given limitations in sample size, genuine differences cannot be ruled out.

3) The CS stated that there were [redacted] between treatments. However, clinical advisers to the ERG judged this highly uncertain based on the data presented by the company as the sample sizes in trials were not large enough to rule out a clinically significant difference.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

4) Although, there is evidence of non-inferiority between ravulizumab and eculizumab in PNH patients, clinical advice to the ERG concluded that extrapolation of these findings to aHUS patients is highly uncertain as they are different disorders.

3.4.3 Comparing safety data in ravulizumab and eculizumab

The company's response to question A15 of the PFCs provided naïve comparisons of safety data on ravulizumab and eculizumab (see table 5 of the company's response to question A15 of the PFC for full details).

The company argued that the safety data appeared similar across treatments. For example, all patients reported experiencing an adverse event (with the exception of aHUS-C10-003 where 20/22 (91%) reported any adverse events for eculizumab). There were a similar proportion of treatment-related adverse events in ravulizumab (ALXN1210-aHUS-311: 20/58 (34.5%), ALXN1210-aHUS-312 (Cohort 1): [redacted]) and eculizumab (aHUS-C08-002: 12/17 (71%), aHUS-C10-003: 9/22 (41%), aHUS-C10-004: [redacted]trials. Additionally, there were a similar number of serious adverse events in ravulizumab (ALXN1210-aHUS-311: 33/58 (56.9%), ALXN1210-aHUS-312 (Cohort 1): [redacted]) and eculizumab (aHUS-C08-002: [redacted]aHUS-C10-003: 13/22 (59%), aHUS-C10-004: 18/41 (44%)) trials.

In response to points for clarification, the company presented safety results for eculizumab from the aHUS global registry for 535 adult and 330 paediatric patients over 5 years.[19] Results are summarised in the company response to points for clarification document, Table 5. Rates of serious infection were 8.6% in adults and 9.7% in children, and deaths due to AE (all infections) were 1.5% in adults and 0.6% in children. Although this data is based on a significantly larger sample size than the trial evidence, comparability with eculizumab and ravulizumab trial evidence is limited by the observational nature of the data and significantly different follow-up durations.

3.4.3.1 Points for Critique

Given important differences between populations included in the ravulizumab and eculizumab trials, these findings are subject to even further uncertainty than the ITC analyses since the company did not attempt to match baseline population characteristics for safety data.

In addition, limitations in reporting of data made it difficult to draw comparison between treatments. For example, the severity of adverse events were graded differently in the ravulizumab and eculizumab trials.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Although results from trial 301 (PNH naïve) found that the safety of razulizumab is non-inferior to that of eculizumab, due to clinically relevant differences between PNH and aHUS populations, the applicability of these results to the decision problem is uncertain.

Although the assumption that ravulizumab and eculizumab have similar safety profiles is clinically plausible, there is insufficient data to confirm this.

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG verified the company's ITC methods and code. No additional analyses were carried out.

3.6 Conclusions of the clinical effectiveness section

Due to their biological homology and similar mechanism of action, it is clinically plausible that ravulizumab and eculizumab have equivalent efficacy and safety in aHUS patients. However, the limited data means there is insufficient evidence to support this assumption.

The lack of randomised evidence for ravulizumab and eculizumab in aHUS patients, clinically relevant differences between the ravuzliumab and eculizumab trial populations and small sample sizes mean that indirect comparisons between the two treatments are at high risk of confounding and highly uncertain. ITC analyses did not include presence of pathogenic variants, despite substantial differences between treatments, as a factor to balance characteristics across groups. Results also show differences in effectiveness between treatments cannot be ruled out. However, due to multiple and potentially conflicting sources of confounding, the likely direction and magnitude of bias in the indirect comparisons are highly uncertain.

The generalisability of the ravulizumab trial population to the NHS is significantly limited. All of the ravulizumab adult trial population evidence and most of the paediatric evidence includes first-line/complement-therapy naïve patients. This differs from clinical practice, where for clinical reasons, it is expected that nearly all eligible patients would receive ravulizumab as second-line treatment following response to eculizumab therapy. In addition, the low prevalence of pathogenic variants in the ravulizumab trial population means that a potentially significant number of patients did not have aHUS. Therefore, most of the trial evidence is not representative of the population who would receive ravulizumab in NHS practice.

Due to limited follow-up, the long-term safety and efficacy of ravulizumab is uncertain. The ERG is concerned that the trial Extension Period duration is dependent on registration or approval (in accordance with country-specific regulations) of ravulizumab rather than for appropriate clinical reasons, and may therefore be insufficient to inform long-term efficacy and safety outcomes. The company did not provide further details and it is not clear how the approval of ravulizumab in the UK

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

(or abroad) may affect the duration of follow-up of trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312.

Disease recurrence following response to treatment was not captured in the ravulizumab trial evidence. Although the frequency of complement-therapy infusions is lower with ravulizumab compared with eculizumab, there is insufficient evidence to show that ravulizumab use translates into safety and quality of life benefits. In their clarification response, the company referred to a US based qualitative study of ten adult patients and three carers of paediatric patients who had switched to ravulizumab (from eculizumab) 4 to 10 months before study participation.[31] All respondents in the Global Action research study considered the longer infusion intervals as a key benefit of ravulizumab treatment. Although these results are encouraging, they are based on a very small sample size and these views may not be representative of UK patients.

Additional long-term ravulizumab efficacy and safety evidence in eculizumab-experienced adult and paediatric patients with a confirmed diagnosis of aHUS is needed, including robust monitoring of disease recurrence, and treatment discontinuation and reinitiation.

Randomised evidence of ravulizumab versus eculizumab in aHUS patients would help clarify whether the assumption of equal efficacy and effectiveness is justified. However, the ERG acknowledges that given the ultra-rare nature of the disease, this evidence may never become available. Where possible, establishing non-inferiority between the treatments in a trial programme for aHUS may be required.

Additional long-term ravulizumab efficacy and safety evidence in eculizumab-experienced adult and paediatric patients with a confirmed diagnosis of aHUS is also needed, including robust monitoring of disease recurrence, and treatment discontinuation and reinitiation. Once the SETS study [2] reports, a similar study could be designed that would seek to evaluate whether patients who relapse following disease relapse and treatment re-initiation can safely be withdrawn from treatment for a second or further time. Given the lack of evidence for alternative dosing of ravulizumab and eculizumab, studies evaluating a more flexible approach to dosing and infusion frequency, notably in the paediatric and adolescent population (<18 years), may be warranted. Evidence of quality of life benefits and patient preferences associated with switching to ravulizumab relevant to the NHS is required.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company's methods for reviewing the cost-effectiveness literature are outlined in Appendix G of the CS (pages 80-84). The CS included a combined search to identify economic evaluations, health-related quality of life studies, and cost and resource use studies in patients with aHUS. The company identified seven studies reporting only costs or HRQoL and two cost-effectiveness studies evaluating the use of eculizumab for aHUS against Standard of Care (summarised in Table 25 of the CS). Of the two cost-effectiveness studies, only one was conducted in the UK and was relevant to this appraisal. This study, which was the ERG's critique of eculizumab for treating aHUS as part of the NICE Appraisal of eculizumab (HST1), described a state-transition model with five mutually exclusive health states reflecting kidney function. The company used the ERG's critique as the basis for the development of the decision model submitted in this appraisal.

Points for critique

The ERG is satisfied with the company's review of the cost-effectiveness evidence (see Table 24 in Appendix B for a detailed appraisal of the company's searches for economic evidence). The searches are expected to have identified relevant cost-effectiveness studies on the treatment of aHUS. Given the rare nature of aHUS, it is not surprising that HST1 is the only study that matches the decision-making context of this appraisal (UK NHS and Personal Social Services perspective); hence the ERG agrees with the company's use of HST1 as a starting point to inform their submission.

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

The company submitted a state-transition model that analysed adult and child populations separately and presented overall cost-effectiveness results weighted based on the proportion of adults ([redacted]) versus children ([redacted]currently treated in clinical practice. The company assumed equal efficacy and effectiveness between ravulizumab and eculizumab and, as a result, their base case corresponds to a cost-minimisation analysis. Differential efficacy in terms of CKD stage was assumed by the company in a sensitivity analysis that was based on the ITC analysis, and the results are presented under the company's 'worst-case scenario'.

4.2.1 **NICE reference case checklist**

Table 12 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.	The CS is appropriate.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Perspective on costs	NHS and PSS.	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis.	The company assumed in their base case that eculizumab and ravulizumab are equally efficacious and conducted a cost-minimisation analysis. Fully incremental analysis, assuming differential efficacy, is presented by the company in their `worst-case scenario' analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	The CS is appropriate. Adult patients enter the model at an average age of 38.3 years old, whilst children enter at the average age of 5.8 years old. A maximum age of 100 years is assumed.
Synthesis of evidence on health effects	Based on systematic review.	The CS 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.	The company compares ravulizumab and eculizumab in terms of HRQoL only in their `worse-case scenario' analysis. This scenario is using EQ-5D-3L data. Children are assumed to have the same utility values as the adult population. The company applies a HRQoL increment, derived in a discrete choice experiment, to patients receiving ravulizumab to reflect the reduced frequency of infusions.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	EQ-5D-3L data were directly obtained from patients in the ravulizumab and eculizumab studies that enrolled adults.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	The CS is appropriate. Although, it should be noted that only 5/56 patients in ALXN1210-aHUS-311 study and 2/28 patients in ALXN1210-aHUS-312 study were from the UK.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	The CS is appropriate.
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 CS is appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	The CS is appropriate.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

EQ-5D, standardised instrument for use as a measure of health outcome. HRQOL, health-related quality of life; PSS, personal social services; QALYs, quality-adjusted life years;

4.2.2 **Model structure**

The company submitted a state-transition Markov model that simulates the long-term outcomes of aHUS patients over their lifetime. Patients receive either ravulizumab or eculizumab and no other treatment option is considered. The model uses a 14-day cycle length, without a half-cycle correction. The company justified their model structure based on consistency with the previous economic model submitted for HST1, which was considered representative of the aHUS pathway [3].

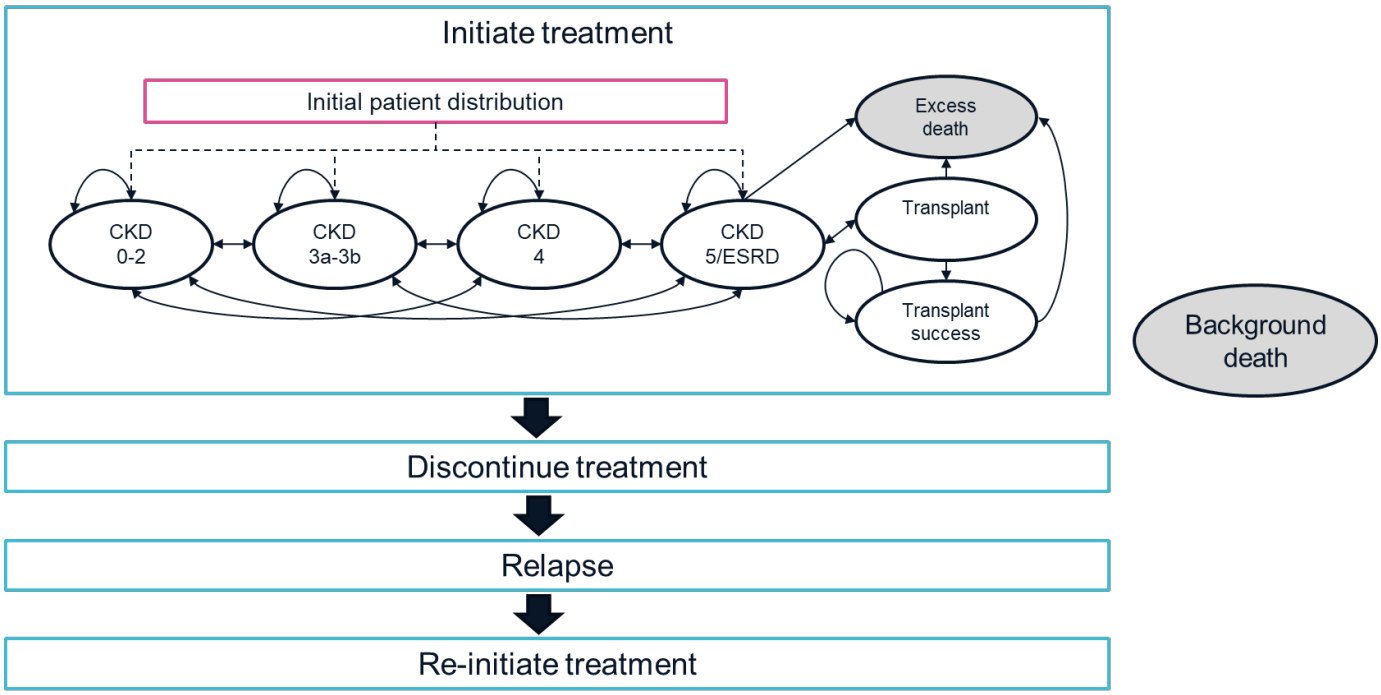
In HST1, the committee highlighted that the company's model assumed that patients would receive lifelong treatment with eculizumab, although the evidence on the optimal treatment duration was unclear [32]. Since then, studies have been investigating the potential for treatment discontinuation [7], and lifetime treatment will not necessarily be considered standard practice in the UK in the future. To accommodate the feedback received in the previous appraisal and recent changes to clinical practice in the UK, the company expanded the model submitted in HST1 to explicitly account for treatment discontinuation. As a result, the model developed for this appraisal included four mutually exclusive health states around treatment discontinuation: (1) Initiate treatment, (2) Discontinue treatment, (3) Relapse, and (4) Re-initiate treatment. Within each health state, there are eight sub-health states reflecting aHUS progression on renal outcomes: CKD Stages 0–2, 3a–3b, 4, 5/ESRD, transplant, transplant success, excess death, and background death. The transplant health state is a tunnel state that lasts for 1 model cycle only, after which if the transplantation is successful, patients transition to `transplant success', whilst if the transplantation failed they either move back to `CKD 5/ESRD' or die due to the excess death incurred in the process.

Transitions were allowed between any two CKD health states. To calculate transition probabilities the company fitted ordinal probit models (a form of regression analysis that is used to estimate relationships between an ordinal dependent variable and a set of independent variables) that treat CKD stage as the ordered categorical dependent variable. The independent variables included time and a lag variable describing a patient's CKD stage at the previous time-period (see Appendix P in the CS Document B for further details). The company used data from all available ravulizumab and eculizumab aHUS studies; however, only evidence from patients included in the FAS with complete data were included. Analyses were restricted to the first 52 weeks and to 5.5 years for the ravulizumab and the eculizumab studies respectively. In the company's base case, trial outcomes were pooled irrespective of treatment. However, in the company's main ITC analysis ('worst case scenario'), the same cut-off was applied to both ravulizumab and eculizumab, and transition probabilities were assumed to be time-dependent only during the first year and constant beyond that. The company presents further scenario analyses using a 1 year cut-off for ravulizumab and a 5.5 years cut-off for

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

eculizumab studies in Table 51 of the Appendix to Document B (page 130). The initial patient distribution across the sub-health states was derived using evidence from all the existing studies and was conditional on the population under consideration (i.e. adults or children). A schematic representation of the model is provided in Figure 4. The company cites feedback from clinicians to justify that the adapted model structure is appropriate.

Figure 4: Economic model diagram.



Key: aHUS, atypical haemolytic uremic syndrome; CEA, cost-effectiveness analysis; CKD, chronic kidney disease; ESRD, end-stage renal disease.
Figure adapted from CS Document B, Figure 16).

Points for critique

The economic model is largely consistent with the model submitted in HST1. However, the company reflected on the feedback received by the ERG and the committee during HST1, and made the following adaptations in this submission:

- The model was modified to consider both adults and children separately to appropriately calculate treatment dosages based on age and weight distributions, and subsequently weight the results of the two populations to produce the overall cost-effectiveness results.
- The model was adapted to reflect recent developments in UK practice and does not model lifelong treatment. Instead, it assumes that treatment may be discontinued once, and reinitiated in those patients whose disease relapses.
- The model was adapted to apply time-dependent transition probabilities (for the first year) amongst CKD health states in the ITC analysis. These were based on an ordered probit model.
- The derivation of the transition probabilities is based on a multi-stage modelling approach.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

The ERG notes that the company's model makes the following key assumptions about the model's structure and key drivers of the transitions between health states:

Transitions

- ravulizumab and eculizumab patients can improve or worsen in terms of CKD stage.
- Transition probabilities are time-dependent during the first year but remain constant beyond that.

Treatment discontinuation

- Patients may discontinue treatment due to four reasons: misdiagnosis, no renal response, adequate renal response, general reasons including AEs and patient preferences.
- Patients can discontinue treatment only once in the model.
- General discontinuation rates do not differ between ravulizumab and eculizumab.
- Patients who discontinue due to adequate renal response, do so only at 6 months after treatment initiation, which is the minimum treatment duration for ravulizumab and in line with the minimum treatment duration within the SETS protocol. In other words, it is assumed that all the patients who achieve renal recovery do so by six months.

Disease relapse

- Patients face a constant risk of relapse throughout their treatment discontinuation period.

Treatment re-initiation

- All patients who relapse after treatment discontinuation, re-initiate treatment (irrespective of whether they had discontinued treatment for no renal response, renal response or general reasons) and remain on treatment for the remainder of their lifetime

Populations

- Adults and children are modelled separately, and their results are subsequently weighted based on the proportion of adults ([redacted]) and children ([redacted] treated in clinical practice.

The ERG considers the model structure to be generally appropriate. A minor point which was raised by the ERG's clinical advisors is that CKD stage is generally non-reversible, unless a patient receives transplant, and hence patients' CKD stage is not expected to improve but only deteriorate or remain stable. Given that the model aims to reflect renal function which retains the potential to improve, the health states could have been better defined in terms of Acute Kidney Injury (AKI) instead of CKD. This labelling would not affect the model structure, which would remain largely unchanged.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

4.2.3 Treatment discontinuation, relapse and re-initiation

4.2.3.1 Treatment discontinuation

The company's model captures four reasons for treatment discontinuation: (1) misdiagnosis, (2) general discontinuation due to AEs or patient choice, (3) no renal response, and (4) adequate renal response. The company's modelling approach to the various reasons for discontinuation is detailed in Section B.3.3.1. (page 117 of Document B).

For misdiagnosis, the company adopts a simplified approach that takes account of the fact that around 17% of patients are misdiagnosed and discontinue treatment during the first month based on NRCTC reports. The company uplifts the costs of the first month in the model by 20% for both ravulizumab and eculizumab. For general discontinuation due to AEs or patient choice, the company fits parametric survival curves to the pooled eculizumab and ravulizumab trial data assuming that general discontinuation rates would not differ between eculizumab and ravulizumab. Parametric models were fitted separately for adults without a prior transplant, adults with prior transplant, and children. Model choice was primarily informed by the non-transplant data as more information was available for that subgroup. All parametric models were shown to fit similarly in terms of AIC/BIC and differences in their predictions were observed primarily in the extrapolation period. The company chose an exponential model for their base case analysis because the curve sat between the lower and upper predicted curves and assumed a constant rate of discontinuation over time. The company presented results of scenario analyses using alternative parametric models, which were demonstrated to have minimal impact on the cost-effectiveness of ravulizumab.

For no renal response, the model assumes that the proportion of patients who do not respond to treatment, and therefore discontinue, is 23% based on NRCTC reports.[5, 33, 34] Although the same proportion of patients is assumed to discontinue due to no renal response for both ravulizumab and eculizumab, the time point for discontinuation differs between the two treatments. Current clinical practice discontinues patients on eculizumab with no renal response after 3–4 months. However, to align with the minimum treatment duration for ravulizumab, outlined in the Summary of Product Characteristics, the company assumes that ravulizumab patients without renal response discontinue treatment after 6 months[35], whilst eculizumab patients discontinue after 3.5 months based on current practice.Finally, the company did not include discontinuation due to adequate renal recovery in their base-case analysis, but it was included as a scenario analysis. The company's justification for not including it in the base case is because of the lack of reliable data to inform the proportion of patients who would discontinue after having achieved stabilization, if not normalization, of renal function. Patients being considered for discontinuation for this reason are part of the SETS study, which is designed to assess the safety and impact of eculizumab withdrawal [2]. In the scenario analysis, the company explored the inclusion of discontinuation due to renal response by varying the proportion of

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

patients with adequate renal response. The scenario used a minimum treatment duration of 6 months for both ravulizumab and eculizumab based on the SETS protocol and assumed that either 65% of patients on treatment would discontinue based on preliminary assessment of SETS protocol, or 25% of patients would discontinue based on clinical opinion from a UK advisory board meeting.

4.2.3.2 Relapse and treatment re-initiation

The company's model assumes that patients who discontinue treatment for any cause except misdiagnosis and their disease subsequently relapses are eligible for treatment re-initiation. Specifically, in the base-case, the model assumes that 42.3% of adults and 50% of children who discontinued treatment will relapse and restart treatment at 3.56 and 3.99 years respectively, and that the corresponding probability of relapse is constant throughout the discontinuation period. These estimates are based on evidence obtained from UK patients in the aHUS registry, who were treated with eculizumab [37] and are consistent in the company's view with the long-term evidence from C11-003 study, whereby 50% of patients relapsed and resumed eculizumab treatment over a period of 5.25-5.45 years[38]. Crucially, once patients re-initiate treatment, they are not permitted to discontinue again and are assumed to remain on treatment for the remainder of their lifetime.

Points for critique

As noted by the company, clinical practice in the UK has evolved since the introduction of eculizumab, with lifelong treatment no longer considered as standard. Therefore, the ERG considers it important to model treatment discontinuation and welcomes the company's attempt to incorporate discontinuation in their analyses. There are several arguments against lifelong treatment. First, there is not adequate evidence to support lifelong treatment in every aHUS patient; instead, there is a growing literature suggesting that aHUS patients who discontinue treatment may not relapse, and that even when they do relapse, treatment is rapidly re-initiated and patients could recover their baseline renal function. For instance, in Fakhouri et al., 2017 all relapsing patients reinitiated treatment and recovered their baseline renal function[39]. Second, complement-inhibitor treatment is associated with potential adverse events such as susceptibility to infections and especially meningococcal disease [40, 41]. Third, recent evidence suggests that eculizumab may cause hepatotoxicity, leading to liver enzyme abnormalities and potentially drug-induced liver injury [42, 43]. Fourth, eculizumab, in particular, is associated with high administration burden and frequent infusions impact on patients Health Related Quality of Life (HRQoL). Fifth, lifelong treatment may increase the risk of immune-mediated drug reactions which may ultimately lead to the development of neutralising anti-drug antibodies [44]. Finally, complement-inhibitor treatment is associated with very high treatment costs; indicatively, the cost of ravulizumab for the first year is estimated to be around [redacted].

In terms of deriving estimates for the general discontinuation rate for eculizumab and ravulizumab, the ERG and its clinical advisors support the company's approach that pools the trial evidence for

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

eculizumab and ravulizumab. The ERG is also satisfied that the model incorporates all potential reasons for discontinuation of treatment. However, the ERG has a number of concerns in relation to the appropriateness of the assumptions and evidence used to inform the overall discontinuation rate:

1. Discontinuation due to adequate renal response is not included in the company's base case analysis

In the CS (page 110; Document B) the company states that *"Clinical practice in the UK has evolved since the introduction of eculizumab, with lifelong treatment no longer considered as standard for all patients."*. However, the company did not include discontinuation due to renal response in their base-case and justified their approach based on the lack of adequate data to inform the proportion of patients who would be eligible for treatment discontinuation due to renal recovery. The ERG acknowledges that the existing evidence base on discontinuation is limited to case-reports [6] and that the SETS study [45] which is designed to shed more light on this question has not yet reported results. Yet, the ERG considers that the company's base case should aim to reflect the likely changes in clinical practice.

Furthermore, the company's base-case assumes that adults and children who discontinue treatment are subject to a constant 0.59% and 0.66% probability of relapse and re-initiation of treatment in each two-weekly model cycle, respectively. This implies that around 50% of patients who discontinue treatment will re-initiate treatment within five years. The ERG believes that if discontinuation due to adequate renal response is excluded (as per the company's base case), it may not be realistic to assume that such a high proportion of patients would re-initiate treatment. This is because it is likely that the preponderance of patients who re-initiate treatment do so because they have evidence that complement-inhibitor treatment adequately controls their disease. As a result, the ERG deems that it is unlikely that 50% of patients who discontinued treatment due to reasons other than adequate renal response would re-initiate treatment within five years, and therefore it is unrealistic to exclude renal response from the base-case analysis.

item 1. Discontinuation due to adequate renal response is not included in the company's base-case analysis

2. Rate of relapse and re-initiation of treatment may be overestimated in the company's base-case analysis

The ERG highlights that the company's base-case analysis assumes that among adults and children who discontinue treatment, 42.3% and 50.0%, will relapse within 3.56 years and 3.99 years, respectively, and will require treatment re-initiation. The company derived these estimates from UK patients included in the aHUS registry in which 11/26 adult patients and 7/14 children relapsed and

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

re-initiated eculizumab treatment [37]. Similar estimates were also reported by Menne et al. (2019) for patients who relapsed and resumed eculizumab treatment [38].

The CS also indicates that these estimates are in line with TMA recurrence after discontinuation of eculizumab from other published studies ranging from 20 to 67%. The ERG notes that these estimates are based on 8 case-series studies which are shown in Table 13. All studies, except one, report a proportion of patients who discontinued treatment that is equal or lower than 31%. A higher proportion is only reported by the authors' case-reports of Macia et al., 2017 but it pertains to a very low number of patients (n = 6). Interestingly, the same study's summary of clinical series reports a much lower proportion of relapse of 20%. Furthermore, an analysis of the evidence from the global aHUS registry that included the global number of patients with aHUS by August 2014 estimated a relapse rate of 10% for adults and 25% for children [46]. Also, a recent retrospective review analysed 194 patients who discontinued eculizumab and found that 56 patients (i.e. 28.8%) relapsed. This review highlighted that there is substantial heterogeneity across genetic mutations with patients not having any genetic mutations relapsing only rarely, whilst patients with 'high-risk' mutations relapsing in more than 80% of cases [47]. Similarly, a recent update of the French STOPECU study found that out of the 55 patients who discontinued treatment, 13 (23%) relapsed and re-initiated and concluded that eculizumab can be safely discontinued once complement genetics are taken into consideration [48].

Table 13: Studies in which patients discontinued eculizumab treatment.

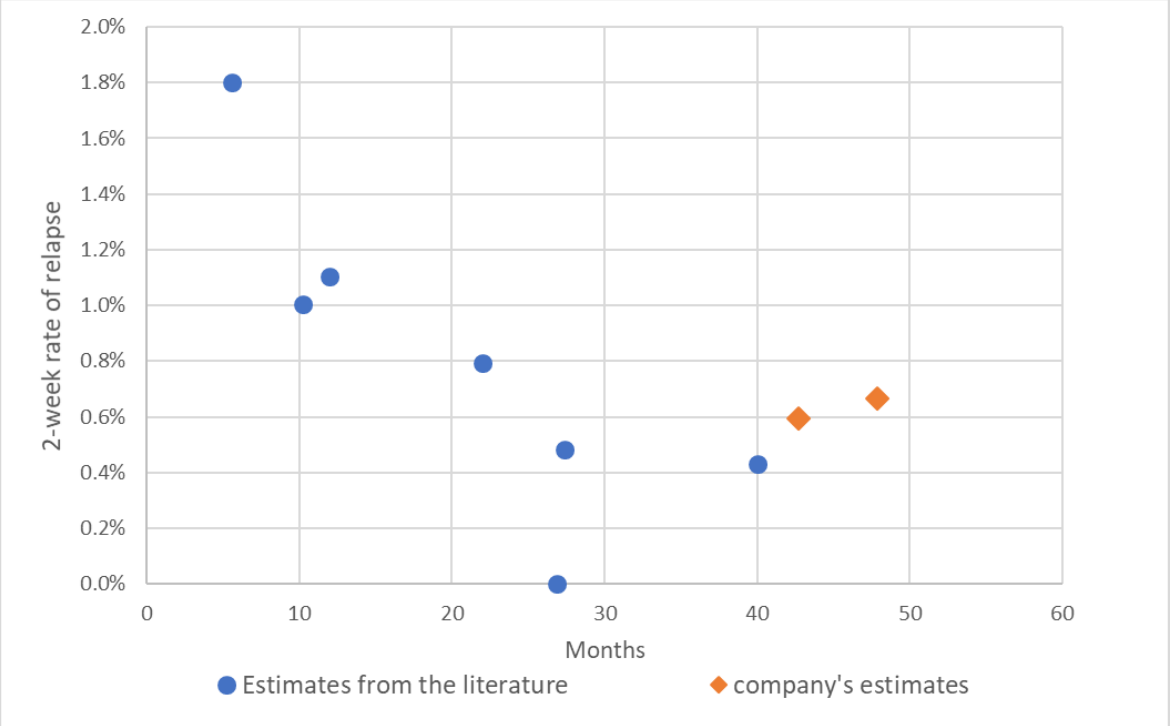
Study	Number of patients who relapsed / Number of patients who discontinued (%)	Mean follow-up (months)	2-week relapse rate
Company's base case (adults)	11/26 (42.3%)	42.72	0.59%
Company's base case (children)	7/14 (50.0%)	47.88	0.67%
Ardissino 2014 and Ardissino et al., 2015[44, 49]	5/16 (31%)	40	0.43%
Sheerin, 2016[50]	3/12 (25%)	12	1.10%
Fakhouri, 2017 [39]	12/38 (31%)	22	0.79%
Merrill., 2017 [51]	3/15 (20%)	10.2	1.01%
Macia, 2017[52] - summary of authors' case-reports	4/6 (67%)	NA	NA
Wijnsma, 2018[53]	5/20 (25%)	27.4	0.48%
Ardissino, 2018 [54]	0/9 (0%)	26.9	0.00%
Macia, 2017 [52]- summary of clinical series	12/61 (20%)	5.6	1.80%

Adapted from Wijnsma et al., 2018 [6]

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

The ERG notes that when the mean follow-up period of each study is taken into account, the company's calculated 2-week relapse rate is not too dissimilar from those reported in the literature. However, comparing the 2-week relapse rates from a set of studies with considerably different follow-up periods makes the implicit assumption that relapse rates are constant through time (which will be discussed later). Though, the current evidence from the literature suggest that relapse rates are not constant; instead, they are higher shortly after treatment discontinuation and significantly lower after around one year of sustained disease control [6, 20]. Figure 5 compares 2-week relapse rate estimates between the company's base case and the studies reported in Table 13. The figure clearly shows that the longer a study's follow up, the lower its reported relapse rate, and the company's estimates seem to deviate from the overall trend and therefore potentially overestimates the expected 2-weeks relapse rate.

Figure 5: Two-week relapse rates according to mean follow-up periods in the company's model and the available studies in the literature.



The ERG sought further advice from its clinical advisors on the potential reasons for the observed discrepancy between the UK and global estimates of relapse and re-initiation of treatment. The clinicians suggested that non-UK countries may follow a more `sensitive' approach and initially treat more patients who end up not having aHUS. As a result, a lower proportion of patients who discontinue stand to benefit from treatment re-initiation in non-UK countries compared to the UK. The clinicians could not identify any other reasons to expect higher relapse rates in the UK.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

In response to the ERG's points for clarification document, question B2, the company highlighted a recent study (accepted but publication pending) that analysed patient outcomes after treatment discontinuation using the global aHUS registry. Importantly, patients who had an alternative diagnosis as a reason for discontinuation were excluded from this analysis so the aforementioned justification for differential relapse rates would not apply [55]. Out of the 151 patients who discontinued treatment and had a median follow-up of 2.3 years, 30 (i.e. 19.9%) restarted treatment, implying a probability of relapse of 0.37% within each two-week model cycle [56]. This estimate is based on considerably more patients (i.e. 151 patients who discontinued eculizumab globally) than the company's estimate which is based on only 40 UK patients and is better aligned with the estimates provided in the evolving literature around this topic. The ERG notes that the company's sensitivity analyses varied the 2-week probability of relapse in a range of 0.48% – 0.71% for adults and 0.54% - 0.8% for children (see tornado plot in Figure 23 of the CS Document B; page 151); hence, no results have been presented for relapse rates similar to those suggested by the updated analyses by Ariceta et al., 2020. The ERG considers the estimate of 19.9% (that is equivalent to a 2-week probability of relapse of 0.37%) to be a more accurate reflection of the relapse rates for patients who discontinue treatment, that is more aligned with several of the estimates from studies reported in Table 13. In the absence of a separate estimate of relapse rate for adults and children, the ERG considers it appropriate to use the same relapse rate as an approximation for both age groups.

item 2. The rate of relapse following treatment discontinuation may be overestimated in the company's base-case analysis

3. Rate of relapse is assumed to be constant through time

In the company's model, patients who discontinue treatment are subject to a constant relapse rate based on evidence from UK patients in the aHUS registry over 3.56 years for adults and 3.99 years for children. The company derives the estimate of the probability of relapse over the follow-up period by dividing the total number of patients who relapsed over the follow-up period by the total number of patients who discontinued treatment with eculizumab. The corresponding two-week relapse probabilities are then applied in each model cycle over the duration of the model's time horizon. Therefore, the company assumes that the same relapse rate that applied during the first 3.56 years for adults (or 3.99 years for children) would apply constantly in the model. As a result, within 10 years from discontinuing treatment, around 80% of adults (86% of children) have relapsed and started lifelong treatment.

The ERG notes that the company's method of estimating the relapse rate by just dividing the number of patients who relapsed over a specific time period may not be considered appropriate because it

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

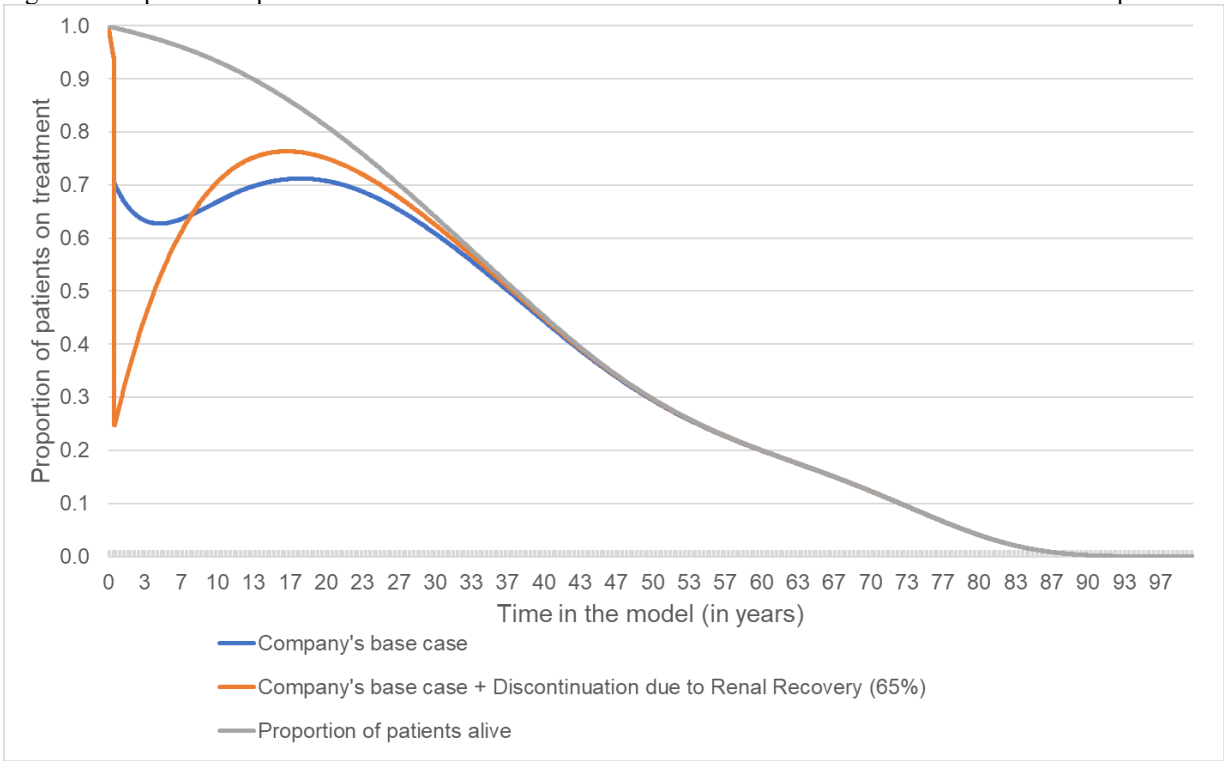
cannot appropriately account for censoring. Therefore, a survival modelling approach based on UK patients in the aHUS registry would have been more suitable.

Importantly, the company's assumption of constant relapse rate is not supported by the existing literature. Indicatively, Wijnsma et al., 2019 report that across nine case-report studies (shown in Table 13), the median (range) time to relapse was 3 months (1–29.5 months). The ERG's clinical advisors also indicated that the risk of relapse is higher shortly after treatment discontinuation and is considerably reduced in later years, conditional on sustained remission. This is also in agreement with reports from the pre-eculizumab era, which indicated that 57–82% of relapses occurred during the first year of follow-up and that risk decreased from >80% to around 25% in almost all aHUS patients after the first year [20].

The ERG highlights that the company's assumption of a constant relapse rate based on a short follow-up of around 3.5 – 4 years is likely to overestimate the proportion of patients who relapse over the model's time horizon. This is illustrated in Figure 6 which shows the proportion of patients who are on treatment over time across a number of scenarios. The grey line corresponds to a no discontinuation scenario, where patients discontinue treatment only due to mortality effects (this is just shown as a reference to demonstrate the impact of discontinuation in the model), the blue line corresponds to the company's base-case assumption, where there is no discontinuation due to renal recovery (only reasons for discontinuation are no renal recovery and general causes), and the orange line corresponds to the scenario where 65% of patients who are still on treatment at 6 months discontinue due to adequate renal response (company's scenario analysis). Interestingly, although in the scenario analysis the proportion of patients on treatment initially falls sharply, it quickly recovers and surpasses that of the company's base case analysis at around 8 years. Indicatively, 70% of patients who discontinued treatment at 6 months in the scenario analysis have returned to lifelong treatment within 8.5 years. This is because the company's model assumes a 2-week probability of relapse rate of 0.59% (0.66% for children) that is equivalent to a 54% chance of relapse (58% for children) over 5 years and a 71% (75% for children) over 8 years. Consequently, the proportion of patients who discontinue treatment due to adequate renal response has little effect on the company's overall cost-effectiveness results because the majority of patients who discontinue get back on treatment relatively quickly and for their remaining lifetime.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Figure 6: Proportion of patients on treatment over time with and without discontinuation due to renal response



Graph obtained using the company's submitted economic model.

item 3. A constant relapse rate may overestimate the proportion of patients who relapse in the long-term

4. Second and subsequent treatment discontinuations

The company's approach assumes that once a patient discontinues treatment and their disease subsequently relapses, they will receive complement inhibitor therapy for the remainder of their lifetime. Therefore, the model allows patients to discontinue only once and does not provide sufficient flexibility to model multiple treatment discontinuations/re-initiations.

To evaluate the plausibility of this assumption, the ERG sought advice from clinical advisors. There was a consensus among clinical advisors that practice in aHUS is rapidly changing as the literature evolves around the use of complement-inhibitor treatments. It is likely that for the majority of patients practice will soon change from lifelong treatment and instead aHUS will be managed as a treatment/relapse disease, i.e. patients who relapse would receive a new treatment course until they subsequently discontinue again. The ERG acknowledges that the literature has not yet matured on this topic, and the clinicians' expectations may not necessarily be confirmed. However, the ERG notes that the probability of discontinuation and subsequent relapse, as well as the number of possible discontinuations/re-initiations, are important drivers of drug acquisition costs and hence cost-effectiveness of complement-inhibitor treatments. Indicatively, if we were to assume that patients

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

never discontinue treatment, the incremental costs of ravulizumab vs. eculizumab would amount to around [redacted]. In contrast, in the current version of the company's model that allows for only one discontinuation the incremental costs amount to around [redacted]. This means that the impact of the assumptions surrounding treatment discontinuation has a substantial effect on cost-effectiveness. The ERG expects that modelling additional discontinuations would lead to considerable further reductions in the incremental costs, albeit of a lower magnitude.

In response to ERG's points for clarification document, question B2, which requested a more flexible economic model that can accommodate multiple discontinuations, the company did not provide an updated model structure for two reasons: first, because there is very limited evidence from patients who discontinued treatment more than once, and therefore it is challenging to inform the relapse rates of subsequent discontinuations, as well as the criteria that would be met for a patient to discontinue for a second time; and second, because it deemed that "*Adding in another layer of treatment discontinuation would have added additional complexity to the structure, and based on little data and clinical backing, was considered unnecessary*."

The ERG agrees with the company that there is very limited evidence to inform an analysis of multiple discontinuations. However, the potential for complement-inhibitor treatments to be used `on-demand' has been discussed in the recent literature as potential future practice. Indicatively, Wijnsma et al., 2019 mentions that amongst 17 patients who relapsed and re-initiated eculizumab after an initial eculizumab discontinuation, 3 patients with pathogenetic mutations discontinued for a second time and no relapses had been reported [6]. The authors then clearly state that "*This suggests that even in a proportion of patients with disease recurrence, lifelong treatment is not necessary*". In their response to question B2, the company also indicated that in the long-term eculizumab study (C11-003), 21 patients restarted treatment after discontinuation and, of those, 6 discontinued treatment for a second time (for reasons other than end of study period).

The ERG notes that the company's simplified model structure that assumes lifelong treatment following a single treatment discontinuation is potentially overestimating the cost savings of using ravulizumab instead of eculizumab.

item 4. The company's approach to treatment discontinuation may overestimate incremental costs if more than one discontinuation is permitted in clinical practice.

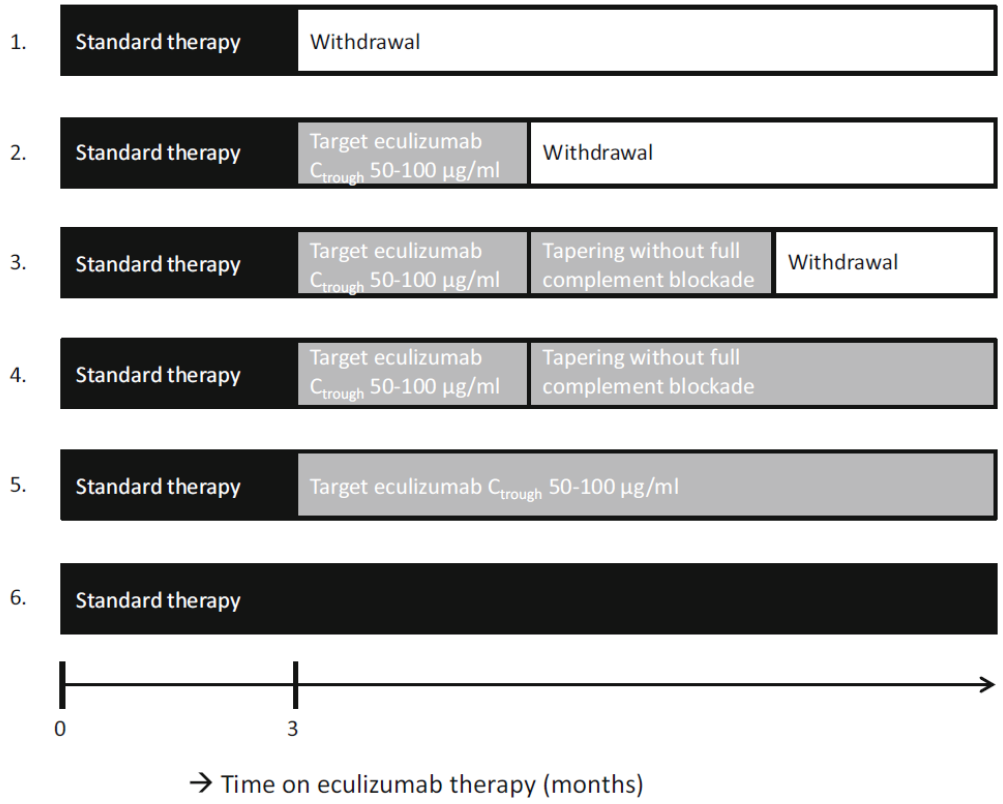
5. Alternative treatment strategies

Finally, the ERG notes that following an initial treatment period, treatment discontinuation is not the only strategy. Instead, several restrictive treatment strategies have recently been described [6]. For

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

example, one option is to adapt the dosage of the complement-inhibitor to target trough levels of 50–100 µg ml−1 with complete blockade of the complement system. Another option includes tapering with incomplete complement blockade. Also, prolonging the period between eculizumab infusions has been attempted [53]. Other options include combinations of the above strategies with or without treatment withdrawal. A list of the potential restrictive treatment strategies is provided in Figure 7. The ERG acknowledges that there is very limited evidence on the effectiveness of each of the possible treatment strategies and therefore the best strategy is currently unknown. However, strategies 2-5 sit between the two extremes and may considerably avoid the disadvantages of prolonged treatment, whilst also achieving a reduced relapse rate compared to strategy 1 that is considered in the company's model. These restrictive strategies may therefore offer adequate disease control and play a role in facilitating a second or subsequent treatment discontinuation.

Figure 7: Possible treatment strategies for aHUS patients.



Adapted from [6].

item 5. The optimal treatment strategy for complement-inhibitor treatments is uncertain.

4.2.4 Population

The population considered by the decision problem is adults and children 10 kg or above with aHUS who are complement-inhibitor treatment-naïve or have received eculizumab for at least 3 months and have shown evidence of response to eculizumab. The company's model considers only treatment-

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

naïve patients due to the lack of data from patients who switched from eculizumab and assumes that ravulizumab would be equally efficacious in treatment-naïve and treatment-experienced patients.

In the company's model, the population corresponds to the pooled ravulizumab and eculizumab trial data after 'stabilised weights' were applied to balance the characteristics of the two groups (Section 3.4). A summary of the baseline characteristics of the adult and children populations is provided in Table 14. It should be noted that Table 14 is based only on patients who weighed more than 10kg. However, despite not being included in the licenced population, the company's base case-analysis includes the data of seven patients who weighed less than 10kg (three patients who received ravulizumab in ALXN1210 -aHUS-312 - 8.5 kg, 8.8 kg and 9.1 kg - and four patients who received eculizumab in C10-003 - 6.7 kg, 8.3 kg, 8.5 kg and 9.9 kg). The company justifies the inclusion of these patients in their base-case analysis based on the fact that their weight was close to 10 kg and that excluding them would decrease the sample size.

Table 14: Baseline characteristics by population

Patient demographic	Adults	Children	Source
Age, mean	[redacted]	[redacted]	311 312 C08-002 C10-003 C10-004
Percentage female	[redacted]	[redacted]	
Weight, mean (kg)	[redacted]	[redacted]	
Weight distribution (kg)			
≥ 10 to < 20	[redacted]	[redacted]	
≥ 20 to < 30	[redacted]	[redacted]	
≥ 30 to < 40	[redacted]	[redacted]	
≥ 40 to < 60	[redacted]	[redacted]	
≥ 60 to < 100	[redacted]	[redacted]	
≥ 100	[redacted]	[redacted]	
CKD stage distribution			
0–2	[redacted]	[redacted]	
3a–3b	[redacted]	[redacted]	
4	[redacted]	[redacted]	
5/ESRD	[redacted]	[redacted]	

Key: CKD, chronic kidney disease; ESRD, end-stage renal disease.

Table adapted from CS Table 27.

Adult and children are analysed separately in the model using different sources of evidence to inform each analysis. Overall cost-effectiveness results for ravulizumab are then presented by weighting the two populations according to the current number of patients in each population treated for aHUS in the (NRCTC) in Newcastle upon Tyne i.e. [redacted] adult ([redacted]%) and [redacted] children ([redacted]%) patients.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Points for critique

As discussed in detail in Sections 3.2.1.2 and 3.2.2.2., the ERG considers there to be uncertainty in the generalisability of the patients included in the ravulizumab studies to patients who would be expected to be eligible for ravulizumab treatment in the UK.

An important characteristic of study ALXN1210-aHUS-311 was that four patients in the adult, non-transplantation, group died. However, the company's `worst-case scenario' analysis was based on an ITC that excluded the data pertaining to these four patients. The company justified this approach based on the fact that these patients presented in a critical condition, would be considered high-risk, and would *not* be treated with complement-inhibitor treatment in the UK. The ERG's clinical advisors shared this same opinion. Therefore, the ERG accepts the company's rationale and deems that the results of the analysis that excludes these patients is more likely to represent patients eligible for treatment in the UK. In response to the ERG's points for clarification document, question B3, the company provided an analysis of an extreme scenario where these deaths were included for ravulizumab and no deaths for eculizumab. The results of this scenario did not have a material impact on cost-effectiveness.

The ERG further notes that the patients included in the ravulizumab studies were primarily eculizumab-naïve. However, the ERG's clinical advisors indicated that it is likely that in the majority of cases ravulizumab would be used only after an initial period in which patients would receive eculizumab. Therefore, the question of whether ravulizumab is equally effective in eculizumab-naïve patients and in patients who switch after receiving eculizumab remains uncertain. The company supports the recommendation of ravulizumab for eculizumab-experienced patients based on a subgroup of n=10 children included in ALXN1210-aHUS-312 who switched after at least 90 days of treatment with eculizumab and remaining clinically stable. These patients maintained disease control after switching to ravulizumab and continued to have evidence of complement blockade. The company also provides evidence from a Phase III trial enrolling n=197 PNH patients (ALXN1210-PNH-302). After at least six months receiving eculizumab and being clinically stable, these patients switched to ravulizumab and maintained disease control with evidence of complement blockade.

item 6. The generalisability of the populations included in the ravulizumab trials to UK clinical practice is uncertain.

4.2.5 Intervention and comparator

As per the decision problem, the intervention considered in the model is ravulizumab, whilst the comparator is eculizumab. This differs from the decision problem in HST1 which considered eculizumab as the intervention and supportive care as the comparator. Both ravulizumab and eculizumab bind to complement protein C5 inhibiting terminal complement-mediated inflammation

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

and preventing immune activation and haemolysis. Although both treatments function through the same mechanism, ravulizumab binds to its substrate with higher affinity and achieves a quadruple half-life; thus, requiring less frequent administration.

Treatment with ravulizumab starts with a loading dosage, followed by the first maintenance dose 2 weeks later and subsequent maintenance dosages every 8 weeks. In contrast, eculizumab treatment requires weekly infusions for an initial period of 4 weeks, followed by the first maintenance dosage on week 5 and further maintenance dosages every 2 weeks. The dosing schedules for the ravulizumab and eculizumab according to the patient's weight are provided in Table 15.

Table 15: Dosing schedules of ravulizumab and eculizumab for adults and children.

Treatment	Population	Body weight (kg)	Dose	Source
Ravulizumab	Adults	≥ 40 to < 60 ≥ 60 to < 100 ≥ 100	2,400 mg followed by 3,000 mg every 8 weeks 2,700 mg followed by 3,300 mg every 8 weeks 3,000 mg followed by 3,600 mg every 8 weeks	SmPC[35]
	Children[a]	≥ 10 to < 20 ≥ 20 to < 30 ≥ 30 to < 40	600 mg followed by 600 mg every 4 weeks 900 mg followed by 2,100 mg every 8 weeks 1,200 mg followed by 2,700 mg every 8 weeks	
Eculizumab	Adults	NA	900 mg weekly for four doses and 1,200 mg for the fifth week followed by 1,200 mg every 2 weeks	SmPC[36]
	Children*	≥ 10 to < 20 ≥ 20 to < 30 ≥ 30 to < 40	600 mg weekly for one dose followed by 300 mg every 2 weeks 600 mg weekly for two doses followed by 600 mg every 2 weeks 600 mg weekly for two doses followed by 900 mg every 2 weeks	
Key: SmPC, summary of product characteristics; kg, kilograms; NA, not applicable. **Note**: [a] Children over 40 kg have the same dosing schedule as adults.				

Table adapted from CS Table 30.

Points for critique

The ERG considers the company's approach with respect to the intervention to be appropriate and consistent with the decision problem. The ERG notes that the company's model considers ravulizumab only for complement-inhibitor naïve patients. However, the ERG's clinical advisors indicated that in most cases they would expect ravulizumab would be used after an initial 3-month period when patients would receive eculizumab. As a result, the ERG considers it more representative

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

of UK clinical practice to model eculizumab and ravulizumab as a treatment sequence in the intervention arm with patients first receiving eculizumab for an initial period; however, the ERG acknowledges that the impact of modelling this treatment sequence on the cost-effectiveness results would be expected to be minor.

Regarding the comparator, the use of eculizumab (Soliris) is appropriate. Since the advent of eculizumab, which was a step change in the management of aHUS patients, practice has changed and best supportive case including plasma therapy is only rarely considered in some countries and under specific circumstances. However, the ERG notes that other treatments are expected to become available within the next few years. Specifically, an eculizumab biosimilar, ABP 959, is already being developed by Amgen. Studies have already demonstrated pharmacokinetics (PK) and pharmacodynamics (PD) bioequivalence, as well as similarity of ABP 959 to Soliris in terms of safety and immunogenicity profiles [57]. Currently, ABP 959 is at Phase III for PNH and Phase I for HUS [58]. Since the current patent for Soliris is expected to expire on November 2023 [1], it is not unlikely that eculizumab biosimilar treatments will be available for aHUS patients by then.

The ERG highlights that if an eculizumab biosimilar is offered at an adequate discount, then ravulizumab may not be cost saving anymore. Furthermore, if ravulizumab were to be approved, current practice would potentially switch from eculizumab to ravulizumab. Therefore, once the patent for Soliris expires and eculizumab biosimilars enter the market, it may be challenging for clinicians and patients to switch back to a treatment like eculizumab that has different pharmacokinetic properties and is associated with increased treatment administration burden compared to ravulizumab.

item 7. Eculizumab biosimilar treatment are likely to become available within the next five years.

4.2.6 Perspective, time horizon and discounting

The model adopts the NHS and Personal Social Services perspective. In the company's base-case, the model discounts costs and outcomes at 3.5%, in line with the NICE reference case, and adopts a lifetime time horizon. Sensitivity analyses using lower discount rates for costs, and shorter time horizons were considered but the company did not make a case for lower discount rates to be applied.

Points for critique

The ERG considers the company's approach to perspective, time horizon, and discounting to be appropriate. The ERG notes that in HST1 a discount rate of 1.5% was considered appropriate as eculizumab was likely to restore people to near full health and sustain it for over a long time-period compared to the alternative treatment, which was best supportive care. In contrast, in this appraisal the company compares ravulizumab against eculizumab and both treatments are likely to achieve similar

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

health benefits. Therefore, the company correctly opted for a 3.5% discount rate in their base-case analysis. The company explored higher and lower discount rates in scenario analyses which led to considerable changes in incremental costs. However, the ERG believes that the discount rate used in the company's base case is more appropriate and in line with NICE methods guide [59].

4.2.7 Treatment effectiveness and extrapolation

The company's base-case assumes that ravulizumab and eculizumab are equally efficacious. The company justifies their approach based on four main arguments:

1. The ITC analysis did not yield any statistically significant or clinically relevant differences (see Section 3.4.2.1.),

2. Eculizumab and ravulizumab share over 99% homology and function through the same mechanism of action,

3. Non-inferiority studies in PNH showed that ravulizumab is non-inferior to eculizumab [9, 60], and

4. The EMA has accepted that the two treatments have similar efficacy [17].

Based on these arguments the company adopts a cost-minimisation approach in their base-case analysis, where the transition probabilities in the model are assumed equivalent for both ravulizumab and eculizumab and the only difference between the two treatments is the time point for treatment discontinuation due to no renal response (6 months for ravulizumab and 3.5 months for eculizumab).

The company also presents a scenario analysis (termed 'worst-case scenario' in CS) where differential efficacy is assumed between ravulizumab and eculizumab. It should be noted that for this scenario the model does not apply a relative effect on the transition probabilities of the baseline treatment. This is because there is no direct relative effectiveness evidence from an RCT comparing ravulizumab and eculizumab, or evidence from studies comparing ravulizumab and eculizumab with a common comparator. Instead, the company applies transition probabilities for changes between CKD health states based on absolute effects observed in single-arm non-randomised eculizumab and ravulizumab trials. Therefore, the absolute effects of ravulizumab and eculizumab and their uncertainty are separately analysed and subsequently compared. This scenario is based on the ITC analysis which combined the two ravulizumab and the three eculizumab trials and used stabilised weights to balance the two treatment groups according to important patient characteristics (Section 3.4.1.). Importantly, the ITC results that were carried forward in the economic model excluded four adult patients who died during the study period because these patients presented in a critical condition and died from AEs that were considered unrelated to the study drug (see page 92 in the CS Document B). Finally, it

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

should also be noted that this scenario only captures differences in one outcome (i.e. CKD stage) and no other endpoints are considered in the model.

Points for critique

As discussed in detail in Section 3.4.2., there are a number of uncertainties associated with the company's approach to treatment efficacy and relative effectiveness. First, there are currently no direct head-to-head randomised studies of ravulizumab vs. eculizumab and the evidence base is limited to single-arm studies using ravulizumab or eculizumab. Although the ERG acknowledges that the ultra-rare nature of the disease prevents the production of randomised evidence, we highlight that any conclusions regarding the relative effectiveness of ravulizumab and eculizumab are prone to bias.

In the absence of comparative evidence, the company implements propensity score matching methods that balance the eculizumab and ravulizumab treatment groups according to a set of important observed patient characteristics. The ERG notes that this approach is reasonable; however, propensity scoring has the potential to produce unbiased estimates only when conditioned on the all relevant patient characteristics. When there are any unobserved important prognostic characteristics, the estimates may be biased. The company tried to alleviate this issue by seeking extensive clinical input to inform the characteristics but given that the scientific community has not reached a consensus on an exhaustive list of prognostic factors, it cannot be guaranteed that all important patient characteristics were included. For example, the company's ITC analysis did not match patients on their genetic mutations or the presence of anti-CHF antibodies, despite the fact that these parameters are known prognostic factors for aHUS [39, 53]. In response to ERG points for clarification, question A10, the company justified the exclusion of these factors based on the following reasons: these parameters were not raised by the clinicians in the company's clinical validation process; less than 70% of patients currently treated with eculizumab for aHUS have an identified genetic variant; and new genetic mutations have been identified and characterised recently, rendering the older evidence from eculizumab trials and the more recent evidence from ravulizumab trials incomparable.

The company justified the cost-minimisation (equal efficacy and effectiveness) approach adopted in their base-case based on the absence of any statistically significant differences between treatment groups for any outcomes after the application of propensity score methods, as well as other reasons detailed at the beginning of this section. The ERG notes that these analyses are based on a low number of patients (65 ravulizumab and 74 eculizumab patients) which were further split into three subgroups according to age and whether patients had received a transplant, and separate analyses were run within each subgroup. Therefore, any differences in outcomes between ravulizumab and eculizumab may not have been detected due to low statistical power.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

The ERG also notes that there were differences in the way that ravulizumab and eculizumab studies defined a 'dialysis' patient. Specifically, in the ravulizumab studies this was defined as a dialysis within 5 days of a baseline/endpoint measure, whilst in eculizumab studies, this was within 7 days of a baseline/endpoint measure. The ERG sought input from clinical advisors who thought that this difference is unlikely to considerably affect results.

Finally, the company's analyses use the evidence reported in ravulizumab and eculizumab studies at 52 weeks and 5.5 years respectively, and project them through the patients' lifetime. The ERG notes that a period of 26 weeks is adequate to establish that ravulizumab and eculizumab are effective treatments for aHUS; however, given that in both the ravulizumab and the eculizumab studies patients experienced considerable improvements, it is uncertain whether the effect of treatment was stabilised within 26 weeks and whether the magnitude of the effect could differ in the long term.

item 8. It is uncertain whether ravulizumab and eculizumab can be considered equally efficacious.

4.2.8 Adverse events

The company's model does not account for AEs in their base-case or scenario analyses. The company justified this approach based on clinical feedback indicating that it is expected that the two treatments would have similar AEs profiles [61] and on a previous head-to-head assessment of ravulizumab and eculizumab for PNH that demonstrated similar safety profiles [9, 60]. A comparison of AEs across the ravulizumab and the eculizumab trials can be found in the CS (Appendix F of Document B; page 78).

Points for critique

As detailed in Section 3.4.3., the ERG considers there to be uncertainty with respect to the similarity of the AEs profiles of ravulizumab and eculizumab. However, in the absence of further evidence, the ERG considers the company's approach to exclude AEs from the economic model as appropriate.

4.2.9 Health related quality of life

Given that the company's base-case analysis considers ravulizumab and eculizumab to be equally efficacious and effective on all aspects of outcome, no differences in HRQoL were considered. However, in the company's `worse-case scenario', differential efficacy is assumed and HRQoL differences are included.

The company conducted a systematic review to identify HRQoL evidence for patients with aHUS (see CS Appendix H of Document B). Besides the ravulizumab trials, this systematic review identified only two studies reporting HRQoL for eculizumab [3, 62] (see Table 35 of the CS Document B). The company concluded that the HRQoL data in these studies were not well reported.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Given the lack of adequate information on HRQoL in the literature, the company preferred to use the HRQoL data reported in the eculizumab and ravulizumab studies. These studies directly collected EQ-5D-3L data; hence, no mapping algorithm was required. However, since HRQoL data were not routinely collected in these studies for children, they were assumed to have the same HRQoL as adults. The company notes that this assumption is consistent with previous appraisals [63, 64] but highlights that it is likely to underestimate the HRQoL of children because renal function generally improves more, haematologic outcomes are better, and levels of fatigue are lower in treated children relative to adults.

The company fitted mixed-effects models to estimate health-state specific utilities accounting for the repeated measurements within patients. Their selected model, shown in Table 34 of the CS (Document B; page 130), adjusts for baseline utility to account for the fact that the patients enrolled in the ravulizumab studies had lower utilities at baseline and hence showed greater improvement post-baseline than patients receiving eculizumab. Age-matched general population utilities were based on the Ara and Brazier algorithm [65]. To account for the fact that the trial-derived utilities for CKD Stage 0-2 were higher than the age-matched utility of the general population, a cap was introduced to ensure that it does not exceed the general population value for adults.

Patients receiving a transplant were assumed to experience the same utility as patients in the CKD5/ESRD state, whilst patients who had a successful transplant were assigned the average utility across CKD Stage states 0-4. A utility decrement of 0.1 was assumed to apply for patients who discontinued treatment and their disease subsequently relapsed, whilst a 5.5% utility reduction was explored in a scenario analysis. Once patients who relapsed reinitiated treatment, they were assumed to experience the same utility that they had before discontinuation. Finally, to account for the improved dosing schedule of ravulizumab and the need for less frequent infusions, a utility increment of 0.013 was assumed to apply for patients receiving ravulizumab based on a Discrete Choice Experiment (DCE) conducted by the company in the UK [66].This increment was applied as an increase in the HRQoL score of the CKD stage related health states of patients receiving ravulizumab i.e. pre-discontinuation patients and patients resuming after relapse. A summary of the utility values used in the company's `worst-case scenario' analysis is shown in Table 16.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 16: Summary of utility values used in the company's `worst case scenario' analysis

State	Adults – utility value	Children – utility value	Justification
CKD 0–2	0.895	0.904	EQ-5D values derived from a relevant patient population and model specific health states – adjusted for general population utilities
CKD 3a–3b	0.844	0.852	
CKD 4	0.742	0.750	
CKD 5/ESRD	0.685	0.692	
Transplant	0.685	0.692	
Transplant success	0.827	0.835	
Reduced burden of treatment (ravulizumab increment versus eculizumab)	0.013	0.013	To account for the differences in administration frequencies
Relapse	-0.1	-0.1	Decrement assumed for patients whose treatment progresses
Key: CKD, chronic kidney disease; EQ-5D, EuroQol-5 Dimension, ESRD, end-stage renal disease.			

Adapted from Table 43 of the CS (Appendix N of Document B; page 117)

Points for critique

The ERG considers that informing the HRQoL based on the pooled EQ-5D-3L data from the ravulizumab and eculizumab studies (aHUS-311, C08-002 adults, C08-003 adults -not included in the ITC-, and C10-004) is appropriate and meets the NICE reference case [59]. The ERG had some concerns regarding the company's approach to missing data. In response to ERG points for clarification, question B4, the company clarified that of the 1,575 utility records, 125 (8%) were removed from the mixed effects models that used data on CKD stage due to an unknown or missing CKD stage at the date of utility record. Of these 125 records, 25 pertained to a single patient whilst 49, 21, and 3 patients had 1, 2, and 3 records missing, respectively. The company also highlighted that there were not any substantial differences between patients who had and did not have any utility records removed due to missing data (see Table 7 of the company's response to ERG points for clarification; page 30). Therefore, given the low level of missing data (125/1575 utility records) and the similarity between patients with and without missing data, the company did not attempt to impute missing data and instead based the utility model only on complete records. To demonstrate the robustness of their estimates, the company conducted a scenario analysis employing a Last Observation Carried Forward (LOCF) approach which resulted in very similar estimates with their preferred approach (see Table 8 of company's response to PfC; page 32). The ERG does not expect the missing data to have a material impact on cost-effectiveness results.

The company applied a HRQoL increment on the CKD stage health states of patients receiving ravulizumab. This QALY increment was added to reflect the utility gain attributed to the reduced frequency of regular infusions with ravulizumab compared with eculizumab and amounted to 0.013 (95% CI: 0.007–0.020) based on the company's DCE [66]. The ERG notes that EQ-5D is NICE's preferred instrument for measuring HRQoL, and any potential utility gains under ravulizumab may

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

have already been reflected in the EQ-5D data collected in the ravulizumab trials. The company's mixed effects model that considered a treatment covariate did not find a statistically significant effect for treatment (see Table 37 of the CS Appendix M to Document B; page 103). Therefore, it is unclear whether it is appropriate to incorporate a QALY increment for ravulizumab treatment in the company's 'worst-case' scenario analysis.

item 9. The company's use of a QALY increment in patients receiving ravulizumab based on a DCE may not be appropriate.

4.2.10 Resource use and costs

In addition to health state-specific costs, the company's model includes costs relating to drug acquisition, drug administration, protective meningococcal vaccination, treatment monitoring, discontinuation, and relapse. The company conducted a systematic search to identify published cost and healthcare resource evidence (see CS Appendix I of Document B). The identified studies reported only US costs and therefore could not be used to inform the company's model.

To calculate the drug acquisition costs per cycle, the model considers both the drugs' dosing schedules and the patient weight distribution. To account for the increasing weight of children less than 18 years old, the company applies a constant 3.2 kg per 6-month increase to the children's baseline weight distribution. This estimate is based on fitting a linear model to growth charts data obtained from the Royal College of Paediatrics and Child Health (RCPCH) UK-World Health Organization (WHO). A cap is also imposed on the children's weight distribution to ensure that the children's overall mean weight does not exceed the overall mean weight of adults. Once children reach adulthood, they are assumed to maintain a constant weight.

In calculating administration costs, the model includes a 15-minute preparation time and infusion time, which differs between eculizumab and ravulizumab, and a combination of specialist nurse and pharmacist time. For patients who respond to treatment, the company assumes that further administrations would be carried out at home through Alexion's homecare programme. For eculizumab, patients are assumed to switch to the homecare programme after their fifth dose, whilst for ravulizumab after the initial loading dose and two subsequent maintenance doses. Based on the company's communications with NRCTC, the company assumes that [redacted] of patients would switch to the homecare programme. No administration costs are considered for these patients as these are covered by the company.

For both treatments, the costs of continuous prophylactic antibiotics were included, as well as meningococcal vaccinations with MenACWY and MenB, which would take place once before the start of the treatment and then every five years for patients remaining on treatment. With regards to

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

treatment monitoring, the model includes monthly blood tests and testing for complement blockade initially every 3 months and annually after the first year.

For patients who discontinue treatment, the company assumes frequent monitoring in line with the SETS protocol (see Table 44 of the CS Document B for a detailed list of costs). Also, the model assumes that in patients whose disease relapses after treatment discontinuation, patients would present with Acute Kidney Injury (AKI) and would therefore be subject to AKI-related inpatient costs. In the model, these patients reinitiate treatment and, therefore, also incur treatment acquisition, administration, vaccination, and prophylactic antibiotics costs. The total re-initiation costs over a patient's lifetime are applied upfront, after discounting, upon entering the re-initiation health state. Finally, CKD Stage, dialysis, and kidney transplantation costs were based on Kent et al [67], which was identified through a literature review. A summary of the costs applied in the company's model is provided in Table 17.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 17: Healthcare and resource use costs.

Health state	Cost	Source/justification
Drug acquisition[a]	First year: Ravulizumab: [redacted] (adults), [redacted] (children) Eculizumab: £352,800 (adults), £168,407 (children)	MIMS [68] Costs are based on patient weight distribution dosing frequency as per their SmPC [35, 36]
Administration costs[b]	Ravulizumab: Average £208 per dose Eculizumab: £195	PSSRU (2019 [69]) Combination of associated nurse specialist (£113) and pharma specialist (£57). Infusion times as per SmPC with additional 1-hour nurse observation time [35, 36]
Meningococcal vaccine	£290	Hampstead Health Pharmacy [70] Combination of MenACWY (£60) and MenB vaccine (£115) (see Table 41 of the CS -Document B; page 137- for further details)
Treatment monitoring	£69.70 (first year per 2-week cycle) £69.57 (after first year per 2-week cycle)	NRCTC [71] NHS ref 18/1[72] NHS 2015. [73]
Discontinuation cost	£98.87 (per 2-week cycle)	SETS protocol [2] NHS ref 18/1 [72] NHS 2015 [73]
Relapse cost	£1,272.84 (per 2-week cycle)	Silver 2017 [74], cost of diagnosis of acute kidney injury, inflation adjusted
Health state costs (per 2-week cycle)		
CKD 0–2	£17.35	Costs are calculated based on annual hospital care costs in the absence of diabetes and cardiovascular complications (Kent et al. [2015]) [67]
CKD 3a–3b	£17.35	
CKD 4	£16.92	
CKD 5/ESRD	£22.61	
Transplant	£1,059.38	
Transplant success	£49.43	
Key: CKD, chronic kidney disease; ESRD, end-stage renal disease; MIMS, Monthly Index of Medical Specialities; NRCTC, National Renal Complement Therapeutics Centre; PSSRU, Personal Social Services Resource Unit; SmPC, summary of product characteristics. **Note:** [a] Drug costs shown exclude VAT, are based on PAS price for ravulizumab and list price for eculizumab (no PAS applies) and assume no discontinuation. [b] Administration costs are only applied to patients who do not receive homecare – [redacted] of patients (funded by Alexion).		

Table adapted from CS, Document B, Table 36.

Points for critique

The ERG believes that all relevant sources of resource use and costs have been considered and the methods used to estimate the cost of treatment with ravulizumab and eculizumab are broadly appropriate. Figure 8 compares the discounted cumulative drug acquisition and total costs for adults receiving ravulizumab over the model's time horizon. It can easily be observed that compared to the drug acquisition costs, all other cost parameters are negligible; therefore, the only cost parameter that is likely to materially impact cost-effectiveness is the treatment price.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Figure 8: Total and treatment acquisition costs for ravulizumab over the model time horizon.

The ERG notes that in HST1, the committee concluded that *"it had not been presented with sufficient justification for the high cost per patient of eculizumab in light of the manufacturing, research and development costs of a medicinal product for the treatment of a very rare condition."* and that "*the overall cost of eculizumab was materially higher than the overall cost of other highly specialised technologies.*". In response to ERG points for clarification, question B5, the company highlighted that under the company's PAS (% simple discount), ravulizumab is less expensive than eculizumab and could save the NHS a total of £ over a patient's lifetime, or as much as £ across all aHUS patients over the first five years.

The ERG acknowledges that ravulizumab's cost is lower than eculizumab, however it is still a considerably expensive treatment in absolute terms, costing on average around £ per patient in the first year. Also, ravulizumab is currently being considered by NICE for PNH [ID 1457] and therefore research, development, and manufacturing costs of ravulizumab would not need to be recovered solely by aHUS patients.

The high estimates of incremental costs and potential cost-savings for ravulizumab compared with eculizumab depend critically on the company's model structure and, in particular, on the assumptions associated with treatment discontinuation, relapse and re-initiation of treatment. Specifically, the company's model assumes that a high proportion of patients who discontinue treatment would relapse (42.3% for adults and 50% for children), and that all these patients would receive complement-inhibitor treatment for the remainder of their lifetime. The ERG notes that if a lower proportion of

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

patients relapse, as suggested by Wijnsma et al (2019) [6], or treatment is provided `on-demand' instead of over a lifetime following relapse, the incremental costs and cost-savings of ravulizumab compared with eculizumab would considerably decrease and other model parameters beyond the drug acquisition costs could start having a larger impact on cost-effectiveness.

4.2.11 **Summary**

Overall, a summary of the key assumptions of this model is provided in Table 45 of the CS (Document B; page 144) and a comparison of the main features of this economic analysis against HST1 in Table 26 of CS (Document B; page 105).

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The cost-effectiveness results of the company's base-case are shown in Table 18. The company conducted a cost-minimisation analysis for their base-case, where ravulizumab was found to be cost-saving compared to eculizumab with incremental costs [redacted] (deterministic) and [redacted] (probabilistic). In response to ERG points for clarification, question B10, the company reviewed and updated the confidence intervals used for some model parameters for the probabilistic sensitivity analysis (See Table 12 of the Company's response to PfC). Although the company did not report the average incremental costs of the updated PSA, the ERG does not expect these changes to have a material impact on cost-effectiveness.

Table 18: Company's base-case deterministic and probabilistic results.

Technologies	Total costs	Incremental costs
Base-case results (Deterministic)		
Eculizumab	[redacted]	[redacted]
Ravulizumab	[redacted]	[redacted]
Base-case results (Probabilistic)		
Eculizumab	[redacted]	[redacted]
Ravulizumab	[redacted]	[redacted]

The company also evaluated a scenario where differential efficacy for CKD stage was assumed for ravulizumab and eculizumab. This scenario used the estimated effects from the ITC analysis and resulted in an ICER of £[redacted] per QALY (South-West quadrant of the cost-effectiveness plane with negative incremental costs and QALYs for ravulizumab compared with eculizumab) as shown in Table 19.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 19: Cost-effectiveness results of the company's ITC analysis scenario.

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

Key: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; iNMB, incremental net monetary benefit; WTP, willingness to pay.
Notes: Adults represent 75.2% of the combined adult and children population.

Table adapted from CS Document B, Table 51.

5.2 Company's sensitivity analyses

The company conducted several sensitivity analyses to their cost-minimisation base-case (see Table 52 of the CS Document B; page 153 and response to Tables 6 and 10 of the response to ERG points for clarification). Only sensitivity analyses exploring alternative discount rates for costs and model time horizons had a material impact on incremental costs. ravulizumab was found to yield cost savings compared to eculizumab under all analyses. A tornado diagram of the most influential parameters is shown in Figure 23 of the CS. The diagram indicates that the relapse rates for adults and children, the length of the aHUS diagnosis period, and the proportion of patients who discontinue treatment due to misdiagnosis are the most influential parameters.

5.3 Model validation and face validity check

The company describes the model validation process in Section B 3.10 of the CS. The ERG undertook further validation checks and identified some inconsistencies between the results of the ERG's analyses and the company's reported results. In response to ERG points for clarification, question B11, the company corrected a minor technical error in the economic model. No face validity issues were identified with the model.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

A summary of the main issues identified and critiqued in Section 4 along with the Section where the ERG addresses each issue in its additional analyses is shown in Table 20.

Table 20: Summary of the main issues identified by the ERG

	Dealt with in the		

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Critique item and description The ERG considers that:		ERGs base case	ERG's Scenario analyses	Area of remaining uncertainty	Significant impact on ICER
item 1	***Discontinuation due to adequate renal response is not included in the company's base-case analysis***	An.1	Sc.3		
item 2	***The rate of relapse following treatment discontinuation may be overestimated in the company's base-case analysis***		Sc.2		x
item 3	***A constant relapse rate may overestimate the proportion of patients who relapse in the long-term***	An.2			x
item 4	***The company's approach to treatment discontinuation may overestimate incremental costs if more than one discontinuation is permitted in clinical practice.***	An.3			x
item 5	***The optimal treatment strategy for complement-inhibitor treatments is uncertain.***			x	Uncertain
item 6	***The generalisability of the populations included in the ravulizumab trials to UK clinical practice is uncertain.***			x	
item 7	***Eculizumab biosimilar treatment are likely to become available within the next five years.***			x	x
item 8	***It is uncertain whether ravulizumab and eculizumab can be considered equally efficacious.***		Sc.1	x	
item 9	***The company's use of a QALY increment in patients receiving ravulizumab based on a DCE may not be appropriate.***		Sc.1b		

6.1 Exploratory and sensitivity analyses undertaken by the ERG

As shown in Table 20, the ERG identified a number of limitations and areas of uncertainty in the company's cost-minimisation and cost-effectiveness analysis. Where the ERG considered that there was a more appropriate alternative approach, modifications were implemented in a cumulative manner and formed part of the ERG's preferred base case (analyses 1 - 3). Areas of remaining uncertainty were explored as sensitivity analyses to the ERG's base case (scenarios 1 - 4). Thorough descriptions of the analyses that form part of the ERG's base case and sensitivity analyses are presented in Section 6.1.1. and Section 6.1.2. respectively, and the impact on the ICER is detailed in Section 6.3.

6.1.1 **Building the ERG base case**

6.1.1.1 Analysis 1: Inclusion of discontinuation due to renal response in the base-case

As discussed in relation to item 1, the company acknowledged in the CS that current practice is changing, and lifelong treatment is unlikely to be considered standard. However, discontinuation due to adequate renal response does not form part of the company's base case analysis. As a result, the company's base case assumes that patients discontinue treatment only for reasons related to negative

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

aspects of the treatment i.e. no renal response, AEs, or patient preferences, while potential positive aspects of treatment such as its ability to induce renal response and adequately control the disease are not reflected. The ERG considers it counter-intuitive to consider treatment re-initiation following disease relapse unless renal response is also considered as a viable reason for discontinuation. Furthermore, the evidence supporting lifelong treatment in patients who show renal response is limited, and several case-series studies have demonstrated that treatment can be discontinued after renal response in a large proportion of patients [6]. The evolving literature on this topic has stimulated the design and conduct of an observational study, which is currently ongoing, and aims to demonstrate that patients with adequate renal response can be safely withdrawn from eculizumab treatment and re-introduced only after relapse [45]. Preliminary assessments of the SETS study estimated that around 60-70% of patients would be able to participate in the study after receiving treatment for a minimum of 6 months [2]. Therefore, the ERG incorporates discontinuation due to renal response in the ERG's base-case, assuming that 65% of patients would be eligible for treatment discontinuation due to adequate renal response. The uncertainty around the proportion of patients who would discontinue due to renal response is further explored in scenario 3.

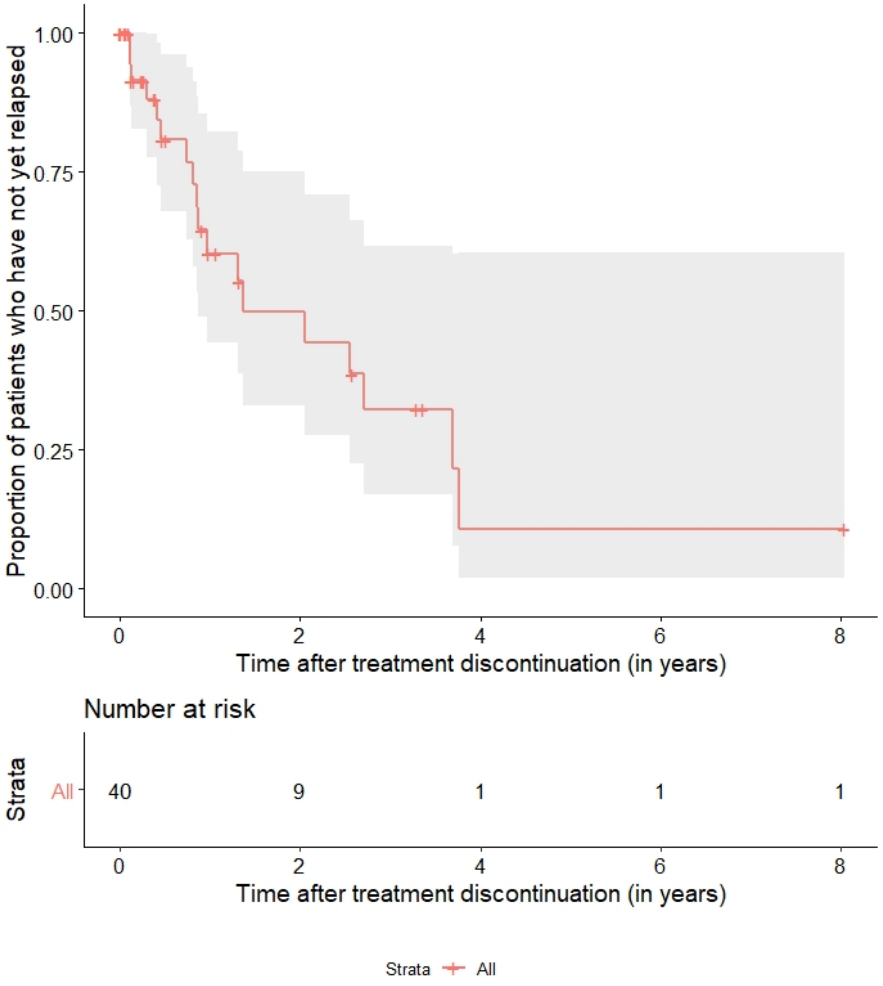
6.1.1.2 Analysis 2: Implementing time-dependent relapse rates after treatment discontinuation

As discussed in relation to item 3, patients who discontinue treatment are subject to disease relapse and treatment re-initiation. To calculate the relapse rates, the company used evidence from the global aHUS registry pertaining to 40 UK patients with a mean follow up of around 3.5 – 4 years. Based on the proportion of patients who relapsed within the follow-up period, the company derived the two-week relapse rate and applied it as a constant rate in all model cycles for the duration of the model's time-horizon. The ERG highlights that this approach does not appropriately deal with censoring, and also assumes that relapse rates are constant through time. The latter is in contradiction to existing evidence suggesting that relapse rates are high shortly after treatment discontinuation and considerably reduced after one year, conditional on sustained remission [6, 20].

To appropriately account for censoring and to reflect the time-dependent nature of relapse rates, the ERG digitised the evidence provided by the company on the 40 UK patients from the global aHUS registry who discontinued eculizumab treatment and re-initiated following relapse up to April 2020 [37]. Given the low sample size and the fact that the log-rank test did not show a statistically significant difference between adults and children in terms of the probability of relapse (*P-value* = 0.57 – see Appendix B; Figure 11), the ERG pooled the evidence on the two groups and conducted time-to-event analysis in the overall population. Figure 9 shows the Kaplan-Maier data for the combined populations.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

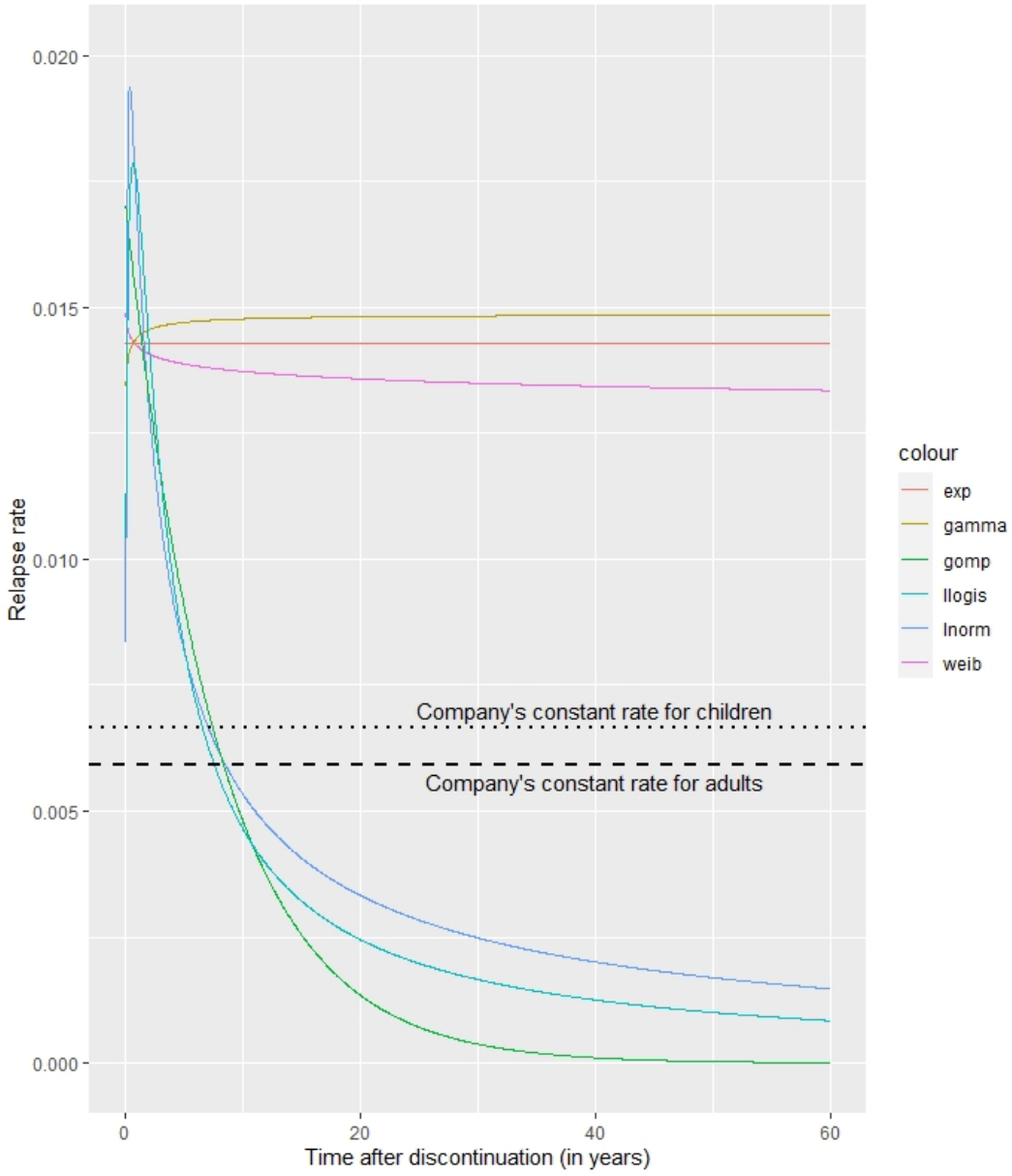
Figure 9: Kaplan Meier curve for time from eculizumab treatment discontinuation to restart –All UK discontinued patients in global aHUS registry.



Standard parametric survival models (exponential, weibull, gamma, gompertz, log-normal, log-logistic) were fitted to the data. The models fitted very similarly (see Appendix; Figure 12) with AIC values ranging between 73.3 and 75.3. The extrapolated hazards across the fitted models are shown in Figure 10. The only models that reflected the 'a priori' expectation of decreasing hazard rates through time were the gompertz, the log-normal, and the log-logistic. These models fitted similarly and suggested similar relapse rates over time. As a result, for its base case, the ERG chose the log-logistic model, which sits between the gompertz and the log-normal curves; sensitivity analyses were conducted using the two remaining parametric models.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Figure 10: Predicted relapse rates, per two-week model cycle, over time for different parametric models



6.1.1.3 Analysis 3: Accounting for the potential of multiple treatment discontinuations over the model time horizon

As discussed in item 4, the company's model assumes that patients who discontinue treatment and subsequently experience a relapse will re-initiate lifelong treatment and are not permitted to discontinue treatment again. Although this is in line with current treatment guidelines, some studies have suggested that these patients may be able to discontinue treatment for a second time [6, 39]. The ERG acknowledges that there is a paucity of evidence surrounding second and subsequent treatment discontinuations and highlights that this as an area of considerable uncertainty with high potential impact on incremental costs and cost-effectiveness. To reflect the plausibility of providing treatment `on-demand', the ERG assumed that patients who relapse and re-initiate treatment would receive treatment only for a proportion of their remaining lifetime. This assumption was implemented

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

homogenously across the model time-horizon by applying a percentage reduction to the treatment acquisition costs incurred at each model cycle following treatment re-initiation. Since it was not possible to know whether and when patients would discontinue for a second time and re-initiate treatment during the course of their lifetime, a constant percentage reduction was applied to drug acquisition costs. Given the uncertainty in the appropriate proportion of patients' lifetime during which patients who relapse will receive treatment, the ERG considered a wide range of possible values from 50% to 100% and presents incremental costs and ICERs resulting from this range. The analysis that is using the 100% value effectively adopts the company's preferred assumption of lifetime treatment, whilst the analysis that is using the 50% value implies that patients who re-initiate treatment would only actually receive treatment for half of their remaining lifetime following a subsequent discontinuation that may or may not, be followed by a second period of treatment re-initiation. Despite the uncertainty in the appropriate value, the ERG considers this a useful approach to provide an indication of the potential impact on lifetime costs from restricting the model structure to permit treatment discontinuation only once.

6.1.2 Scenario analyses to the ERG's base-case

6.1.2.1 Scenario 1: Assuming differential efficacy between ravulizumab and eculizumab

As discussed in relation to item 8, the company assumes in their base case that ravulizumab and eculizumab are equally efficacious. However, due to the lack of randomised evidence comparing ravulizumab and eculizumab directly or with a common comparator, the relative efficacy of ravulizumab compared with eculizumab remains uncertain. Therefore, the ERG conducted sensitivity analysis on the ERG's base case using differential efficacy for CKD stage. This scenario was based on the company's ITC analysis that excluded the four deaths in the ravulizumab group and used propensity score matching methods to balance the treatment groups.

The ERG notes that the company's model also applied an additional utility increment based on a DCE, for ravulizumab to reflect the quality of life gain due to the reduced frequency of infusions. As detailed in item 9, the ERG has some concern regarding the appropriateness of this approach because EQ-5D is the preferred instrument based on the NICE methods guide[59], and the utility gains may already be reflected in the EQ-5D data collected in the ravulizumab and eculizumab studies; although it should be noted that no statistically significant difference in EQ-5D score was found between treatments. Therefore, the ERG conducted the scenario of differential efficacy with and without the utility increment.

6.1.2.2 Scenario 2: Deriving the relapse rate based on all patients included in the aHUS registry

As detailed in relation to item 2, the company's estimate of relapse rate was based on 40 UK patients (26 adults and 14 children) enrolled in the aHUS registry from 2012 onwards who had discontinued

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

treatment with eculizumab at different time points after treatment initiation. Since 11/26 (42.3%) adults and 7/14 (50.0%) children relapsed over a mean follow up of 3.5 - 4 years, the company assumed that these rates also applied to their base-case. The ERG highlights that these rates are considerably higher than the estimates provided in the literature [6]. The ERG considers a scenario where the evidence on all UK and non-UK patients enrolled in the aHUS registry were considered. This analysis was based on 151 patients who discontinued eculizumab treatment, 30 of whom (i.e. 19.9%) re-initiated treatment over a median follow-up of 2.3 years [55]. Importantly, patients who had an alternative diagnosis (i.e. non-aHUS) as a reason for eculizumab or registry discontinuation were not included, and therefore between-countries variation in the proportion of patients who are initially treated and discontinue due to alternative diagnosis would not affect the estimates. Time-to-event data for the cohort of the 151 patients were not available, therefore, the ERG could not conduct survival analysis to obtain time-dependent relapse rates. As a result, a constant relapse rate was assumed, in line with the assumption of constant rates used in the company's base-case, to enable us to explore the impact of using an estimate of relapse based on data on all patients from the global aHUS registry.

6.1.2.3 Scenario 3: Assuming alternative values for the probability of discontinuing treatment due to renal response

In the CS, the company conducted scenario analyses assuming that 65% and 25% of patients who are still on treatment at 6 months discontinue due to adequate renal response (see Table 52 of the CS Document B; page 153). The impact of this parameter on incremental costs was minimal. This was due to the assumption of a constant relapse rate which implied that, regardless of the proportion of patients who discontinue at 6 months (about 25% under the company's base case and 75% when including renal recovery as a source of discontinuation), most patients are back on treatment - for their remaining lifetime - within 8-10 years (see Section 4.2.3.2 for more details). However, under the ERG's base case relapse rates are time-dependent; therefore, the ERG conducted scenarios to explore whether the impact of the proportion of patients discontinuing due to renal response would be different under time-dependent relapse rates.

6.1.2.4 Scenario 4: Using alternative parametric models to reflect the time-dependent relapse rates

As discussed in Section 6.1.1.2., the ERG's base case implemented time-dependent relapse rates based on a time-to-event analysis that considered the 40 UK patients in the global aHUS registry (as explained in section 6.1.2.2. time-to-event was not available for the non-UK patients in the registry). Three parametric models (log-normal, log-logistic, gompertz) predicted relapse rates for the long-term that broadly aligned with the ERG's and clinical advisor's expectations based on the existing literature. In the absence of adequate evidence to evaluate the plausibility of the three models, the ERG chose the log-logistic model for its base-case and conducted additional scenario analyses using the log-normal and the gompertz models.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

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

All results for the ERG scenarios are based on deterministic analyses because of the substantial amount of time required to run the model probabilistically. However, the company's deterministic and probabilistic analyses yielded very similar results, suggesting reasonable linearity within the model. The ERG did compare the results of probabilistic and deterministic analyses across a number of scenarios and confirmed that the results were similar.

This section presents the results of the ERG's analyses that formed the ERG's base case in Section 6.2.1. and the results of the ERG's sensitivity analyses, applied to the ERG's base case, in Section 6.2.2. All analyses consider the company's PAS price which offers a [redacted] discount to ravulizumab vials.

6.2.1 **Results of analyses building the ERG's base-case**

Table 21 illustrates the results of the analyses that the ERG undertook as separate steps to form the ERG's base case. Across all analyses incremental costs remained very high, suggesting that ravulizumab has the potential to result in considerable cost-savings compared to eculizumab. Interestingly, assuming that relapse rates are time-dependent (analysis 2) increased the incremental costs of ravulizumab compared to eculizumab. This was because the estimated relapse rates were higher than the company's constant relapse rates for the first 7.6 years in adults and 6.6 years in children, and lower only thereafter. As a result, in the ERG's base case, 72.6% of adults and 71.3% of children who discontinued treatment were estimated to relapse and re-initiate lifelong treatment within 8 years compared to analysis 1, where 56.8% of adults and 59.8% of children had relapsed and reinitiated lifelong treatment within the same period.

Table 21: ERG's preferred assumptions (ERG base-case)

	Discounted costs (£)		Incremental costs (£)	ICER for RAV vs ECU
	RAV	ECU		
CS base-case	[redacted]	[redacted]	[redacted]	[redacted]
1. Include renal response as a reason for treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
2. Analysis 1 + Assume time-dependent relapse rates following treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
3. Analysis 2 + Account for the potential of multiple treatment discontinuations (The presented ranges correspond to the cases of receiving treatment after relapse and treatment re-initiation for a portion of 50% and 100% of a patient's remaining lifetime.) **ERG's PREFERRED BASE-CASE**	[redacted]	[redacted]	[redacted]	[redacted]

All analyses were run deterministically. Key. RAV: Ravulizumab, ECU: Eculizumab

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

The ERG's analysis 3 demonstrates that a second and subsequent treatment discontinuation has the potential to significantly affect the incremental costs of ravulizumab compared with eculizumab. Specifically, if we assume that patients who relapse would not receive lifelong treatment but instead would only receive treatment for 50% of their remaining lifetime, the incremental costs fall to [redacted]. However, despite the considerable reduction in incremental costs, ravulizumab remains cost-saving compared to eculizumab. The ERG highlights that given the assumption of equal efficacy and that ravulizumab is overall less expensive than eculizumab, ravulizumab would most likely remain cost saving under any scenario and the only factor that would affect incremental costs is the actual amount of treatment required throughout a patient's lifetime.

6.2.2 **Results of the scenario analyses to the ERG's base-case**

The results of the sensitivity analyses that were conducted on the ERG's base case are shown in Table 22. Among the scenarios that considered equal efficacy for ravulizumab and eculizumab (scenarios 2, 3 and 4), only scenario 2 that used a constant relapse rate based on all patients in the global aHUS registry (i.e. including non-UK patients) resulted in a substantial reduction in incremental costs (between [redacted] and [redacted]). [redacted] The only scenario where ravulizumab was not dominant was when differential efficacy was assumed (scenario 1 [redacted] This analysis was based on the company's ITC analysis which used single-arm eculizumab and ravulizumab studies and compared their absolute effects based on propensity score weighting methods. The ERG highlights that the relative efficacy between ravulizumab and eculizumab is highly uncertain and appropriate evaluation of the relative effectiveness would require randomised evidence. However, the rare nature of aHUS poses significant challenges in the acquisition of such evidence.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Table 22: ERG scenario analyses

Scenario	Discounted costs (£)		Discounted QALYs		ICER for RAV vs ECU (Incremental costs, £)
	RAV	ECU	RAV	ECU	
ERG's preferred base-case (i.e. analysis 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Differential efficacy between RAV and ECU (i.e. ITC)					
a) With HRQoL increment applied in the RAV arm based on DCE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) Without HRQoL increment applied in the RAV arm based on DCE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Using all 151 patients who discontinued treatment in the global aHUS registry (both UK and non-UK) to derive a two-week relapse rate of 0.37% that is applied as a constant rate throughout the model time horizon for both adults and children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Assuming that only 25% of patients discontinue treatment due to renal response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Using alternative parametric models to derive the time-dependent relapse rates					
a) Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

All analyses were run deterministically. The presented ranges correspond to the cases of receiving treatment after relapse and treatment re-initiation for a portion of 50% and 100% of a patient's remaining lifetime. Key. RAV: Ravulizumab, ECU: Eculizumab, DCE: Discrete Choice Experiment, IC: Incremental Costs

*Cost-minimization analysis where QALYs are assumed equivalent between RAV and ECU.

ǂ ICER in the South-West quadrant of the Incremental cost-effectiveness plane with higher values indicating that RAV is more likely to be cost-effective

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

6.3 Conclusions of the cost effectiveness section

The company submitted a cohort state-transition model that simulates the long-term outcomes of aHUS patients over their lifetime. The model was based on the economic model submitted in HST1 and included health states around treatment discontinuation and sub-health states reflecting aHUS-associated renal function and transplant. Where the model was adapted to reflect the feedback received by the ERG and the committee in HST1, the company outlines these changes in their submission (see Table 26 in the CS Document B; page 105). The ERG considers that the company's approach is appropriate and accurately reflects the decision problem defined in the final NICE scope.

There are, however, limitations and areas of remaining uncertainty (see Table 20). The main areas of uncertainty are: whether patients who respond to treatment and have their renal function restored can safely discontinue treatment and re-initiate only after disease relapse without a considerable risk to the patients' renal function and overall health (item 1); the proportion of UK patients who would relapse following treatment discontinuation and require treatment re-initiation (item 2); whether relapse rate is constant through time or is higher immediately after discontinuation and then decreases over time (item 3); whether complement-inhibitor treatment should be provided only `on demand' i.e. whether patients whose disease is adequately controlled following a relapse and a second treatment course could safely discontinue treatment again (item 4); whether ravulizumab and eculizumab can be considered equally efficacious in the absence of comparative evidence (item 8); whether the evidence of the ravulizumab trials are generalisable to patients expected to be treated for aHUS in the UK (item 6); and finally, whether eculizumab biosimilar treatments, which are expected to become available in the next 5 years should be considered as alternative treatment options (item 7).

To address these issues, the ERG made a number of changes to the company's base-case (see Section 6.1). First, the ERG included renal response as a reason for treatment discontinuation and used preliminary assessments of the SETS study [2] to inform the proportion of patients who discontinue treatment for this reason. Second, instead of a constant rate of relapse which was assumed in the company's model, the ERG conducted time-to-event analysis to derive time-dependent relapse rates based on UK patients enrolled in the global aHUS registry. Finally, given the uncertainty in the plausibility of providing treatment `on demand', - essentially allowing multiple treatment discontinuations -, the ERG presents a range of plausible estimates of incremental cost based on assumptions about the lowest and highest proportion of patients' lifetime during which they may receive treatment after their first relapse (see Section 6.1.1.3.). The ERG's base case was based on the cost-minimisation analysis (due to limitations in the indirect treatment comparison and limited data to inform the relative effectiveness of ravulizumab and eculizumab) and estimated a range of incremental costs between [redacted] per patient; this implies that ravulizumab could offer considerable cost-savings compared with eculizumab in the NHS. However, it must be noted

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

that it is highly uncertain whether the clinical effectiveness of ravulizumab and eculizumab are equivalent.

Despite the ERG's attempt to address the key uncertainties, limitations in the evidence base mean that some of the uncertainties remain. First, as discussed in Section 4.2.7., there is no comparative evidence assessing the relative effectiveness of ravulizumab and eculizumab. Hence, the plausibility of the company's assumption of equal efficacy is questionable. In the absence of better evidence, the company assessed a scenario assuming differential efficacy employing an ITC approach that sought to match patients in the single-arm ravulizumab and eculizumab trials using propensity score weighting methods. This approach was also carried forward by the ERG in scenario 1a and 1b. [redacted] Indicatively, under the most extreme conditions of ERG's scenario 1 (i.e. where patients who relapsed after a discontinuation received treatment only for 50% of their remaining lifetime [redacted]. Hence, the ERG concludes that although there is uncertainty relating to the relative effect of ravulizumab and eculizumab, given the company's model structure, the decision to adopt ravulizumab is unlikely to be affected by more or better quality relative effectiveness evidence.

The ERG highlights that in the company's model the cost-effectiveness of ravulizumab is primarily driven by the incremental costs; hence, if the incremental costs were considerably reduced, there could be a significant impact in the cost-effectiveness of ravulizumab. This could happen in two main ways: first, if current practice changed and complement inhibitor treatments were given only 'on demand' such as in 6-month courses following a relapse. In such a scenario, some patients may end up receiving treatment only for a small proportion of their lifetime; therefore, much lower quantities of complement-inhibitor treatments would be needed for these patients over their lifetime and the total incremental costs would substantially reduce because the treatment acquisition cost is the main driver of the incremental costs. Second, if a cheaper alternative complement-inhibitor treatment became available, such as an eculizumab biosimilar (see section 4.2.5.). Although outside of the scope of this appraisal, the ERG notes that eculizumab biosimilar treatments are expected to be available in the next 5 years; therefore, given that the market exclusivity for eculizumab (Soliris) for aHUS is set to expire in November 2023 [1], the latter scenario may soon materialise.

Overall, the ERG's preferred base case suggests that ravulizumab is highly cost-effective and none of the ERG's sensitivity analyses suggested otherwise. These conclusions are contingent on a number of key structural assumptions employed by the company that relate to the relapse rates estimates, the plausibility of providing treatment only 'on demand', and the potential of eculizumab biosimilars,

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

which could offer a discount compared to eculizumab (Soliris), entering the market. Although the current model structure suggests that more evidence on the relative efficacy of ravulizumab compared with eculizumab would be unlikely to impact cost-effectiveness, the ERG highlights that once key structural uncertainties have been addressed, relative efficacy may have a considerable influence on conclusions.

7 END OF LIFE

End-of-life considerations do not apply to this appraisal.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

8 REFERENCES

1. *Union Register of medicinal products for human use - Soliris*. European Commission; 2020. URL: https://ec.europa.eu/health/documents/community-register/html/h393.htm (accessed 23rd November 2020).

2. National Institute for Health Research (NIHR). *SETS aHUS protocol*. 2020. URL: https://fundingawards.nihr.ac.uk/award/15/130/94 (accessed 07 July 2020.

3. National Institute for Health and Care Excellence (NICE). *HST 1: Eculizumab for treating atypical haemolytic uraemic syndrome*. 2015. URL: https://www.nice.org.uk/guidance/hst1 (accessed 3 April 2020.

4. Berger BE. Atypical hemolytic uremic syndrome: a syndrome in need of clarity. *Clinical Kidney Journal* 2019;**12**:338-47.

5. National Renal Complement Therapeutics Centre (NRCTC). *The Annual Report of the National Renal Complement Therapeutics Centre 2018/19*. 2019. URL: http://www.atypicalhus.co.uk/wp-content/uploads/2019/12/Annual-Report-Final-Version-2018-2019.pdf (accessed 25 May 2020.

6. Wijnsma KL, Duineveld C, Wetzels JF, van de Kar NC. Eculizumab in atypical hemolytic uremic syndrome: strategies toward restrictive use. *Pediatr Nephrol* 2019;**34**:2261-77. 10.1007/s00467-018-4091-3

7. National Renal Complement Therapeutics Centre (NRCTC). *National Renal Complement Therapeutics Centre: Clinical trials*. 2016. URL: http://www.atypicalhus.co.uk/clinical-trials/sets-ahus-2/ (accessed 15 June 2020.

8. Alexion Pharmaceuticals Inc. Ravulizumab for Atypical Haemolytic Uraemic Syndrome: UK Advisory Board Report. In; 2019.

9. Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, Pessoa V, Gualandro S, Füreder W*, et al.* Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood* 2019;**133**:530-9. 10.1182/blood-2018-09-876136

10. von Elm E, Altman DG, Egger M, Pocock S, Gotzsche PC, Vandenbroucke JP*, et al.* Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;**335**:806-8.

11. Cochrane. *RoB 2: A revised Cochrane risk-of-bias tool for randomized trials*. 2018. URL: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials (accessed 25th March 2020).

12. Higgins JPT, Altman DG, Sterne JAC. Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. 0 (updated March 2011). The Cochrane Collaboration, 2011. *Available from handbookcochraneorg* 2011.

13. Alexion Pharmaceuticals Inc. Single arm study of ALXN1210 in complement inhibitor treatment-naive adult and adolescent patients with atypical hemolytic uremic syndrome (aHUS). In: Clinical Study Report (52-week). Data on file; 2020.

14. European Medicines Agency (EMA). *Ultomiris: European Public Assessment Report*. 2019. URL: https://www.ema.europa.eu/en/documents/assessment-report/ultomiris-epar-public-assessment-report_en.pdf (accessed 25 February 2020.

15. National Renal Complement Therapeutics Centre (NRCTC). *Eculizumab in the treatment of aHUS*. NRCTC; 2016. URL: http://www.atypicalhus.co.uk/ahus/eculizumab-in-the-treatment-of-ahus/ (accessed 15th June 2020).

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

16. Alexion Pharmaceuticals Inc. A Phase 3, open-label, multicenter study of ALXN1210 in children and adolescents with atypical hemolytic uremic syndrome (aHUS). In: Clinical Study Report (52-week). Data on file; 2020.

17. European Medicines Agency (EMA). *Ultomiris: European Public Assessment Report - Variation*. 2020. URL: https://www.ema.europa.eu/en/documents/variation-report/ultomiris-h-c-004954-ii-0002-epar-assessment-report-variation_en.pdf (accessed 21 July 2020.

18. Rondeau E, Scully M, Ariceta G, Barbour T, Cataland S, Heyne N*, et al.* The long-acting C5 inhibitor, Ravulizumab, is effective and safe in adult patients with atypical hemolytic uremic syndrome naive to complement inhibitor treatment. *Kidney Int* 2020;**97**:1287-96. 10.1016/j.kint.2020.01.035

19. Rondeau E, Cataland SR, Al-Dakkak I, Miller B, Webb NJA, Landau D. Eculizumab safety: five-year experience from the Global Atypical Hemolytic Uremic Syndrome registry. *Kidney International Reports* 2019;**4**:1568-76. https://doi.org/10.1016/j.ekir.2019.07.016

20. Fremeaux-Bacchi V, Fakhouri F, Garnier A, Bienaime F, Dragon-Durey MA, Ngo S*, et al.* Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. *Clin J Am Soc Nephrol* 2013;**8**:554-62. 10.2215/cjn.04760512

21. Longhi S, Del Vecchio L, Martelli L, Ardissino G. FP106RISK OF aHUS IN FAMILIES MEMBERS WITH COMPLEMENT GENES MUTATIONS. *Nephrol Dial Transplant* 2019;**34**. 10.1093/ndt/gfz106.FP106

22. Noris M, Caprioli J, Bresin E, Mossali C, Pianetti G, Gamba S*, et al.* Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. *Clin J Am Soc Nephrol* 2010;**5**:1844-59. 10.2215/cjn.02210310

23. Schaefer F, Ardissino G, Ariceta G, Fakhouri F, Scully M, Isbel N*, et al.* Clinical and genetic predictors of atypical hemolytic uremic syndrome phenotype and outcome. *Kidney Int* 2018;**94**:408-18. 10.1016/j.kint.2018.02.029

24. Fakhouri F, Hourmant M, Campistol JM, Cataland SR, Espinosa M, Gaber AO*, et al.* Terminal Complement Inhibitor Eculizumab in Adult Patients With Atypical Hemolytic Uremic Syndrome: A Single-Arm, Open-Label Trial. *Am J Kidney Dis* 2016;**68**:84-93. 10.1053/j.ajkd.2015.12.034

25. Greenbaum LA, Fila M, Ardissino G, Al-Akash SI, Evans J, Henning P*, et al.* Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome. *Kidney Int* 2016;**89**:701-11. 10.1016/j.kint.2015.11.026

26. Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C*, et al.* Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome. *N Engl J Med* 2013;**368**:2169-81. 10.1056/NEJMoa1208981

27. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage* 2002;**24**:547-61. 10.1016/s0885-3924(02)00529-8

28. Dychter SS, Gold DA, Carson D, Haller M. Intravenous therapy: a review of complications and economic considerations of peripheral access. *J Infus Nurs* 2012;**35**:84-91. 10.1097/NAN.0b013e31824237ce

29. Ingram P, Lavery I. Peripheral intravenous therapy: key risks and implications for practice. *Nurs Stand* 2005;**19**:55-64. 10.7748/ns2007.09.22.1.44.c4613

30. Menne J. Is ravulizumab the new treatment of choice for atypical hemolytic uremic syndrome (aHUS)? *Kidney Int* 2020;**97**:1106-8. 10.1016/j.kint.2020.03.011

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

31. aHUS Alliance. *A report on the comparative experiences of the impact on ahus patients following a transition from eculizumab to ravulizumab for the treatment of aHUS.*: aHUS Alliance; 2020.

32. National Institute for Health and Care Excellence. *Final evaluation determination. Eculizumab for treating atypical haemolytic uraemic syndrome*: NICE; 2014.

33. National Renal Complement Therapeutics Centre (NRCTC). *The National aHUS Service Annual Report 2016/17*. 2017. URL: http://www.atypicalhus.co.uk/wp-content/uploads/2018/03/NRCTC-Annual-Report.pdf (accessed 05 May 2020.

34. National Renal Complement Therapeutics Centre (NRCTC). *The Annual Report of the National Renal Complement Therapeutics Centre 2017/18*. 2018. URL: http://www.atypicalhus.co.uk/wp-content/uploads/2018/10/NRCTC-Annual-report-2017_18.pdf (accessed 15 May 2020.

35. Alexion Pharmaceuticals Inc. Ravulizumab (Ultomiris). In: Summary of Product Characteristics; 2020.

36. Alexion Pharmaceuticals Inc. Eculizumab (Soliris). In: Summary of Product Characteristics; 2012.

37. Alexion Pharmaceuticals Inc. aHUS registry patient-level data (United Kingdom of Great Britain and Northern Ireland). In; 2020.

38. Menne J, Delmas Y, Fakhouri F, Licht C, Lommelé Å, Minetti EE*, et al.* Outcomes in patients with atypical hemolytic uremic syndrome treated with eculizumab in a long-term observational study. *BMC Nephrol* 2019;**20**:125. 10.1186/s12882-019-1314-1

39. Fakhouri F, Fila M, Provôt F, Delmas Y, Barbet C, Châtelet V*, et al.* Pathogenic variants in complement genes and risk of atypical hemolytic uremic syndrome relapse after eculizumab discontinuation. *Clin J Am Soc Nephrol* 2017;**12**:50-9. 10.2215/cjn.06440616

40. Benamu E, Montoya JG. Infections associated with the use of eculizumab: recommendations for prevention and prophylaxis. *Curr Opin Infect Dis* 2016;**29**:319-29.

41. Konar M, Granoff DM. Eculizumab treatment and impaired opsonophagocytic killing of meningococci by whole blood from immunized adults. *Blood* 2017;**130**:891-9. 10.1182/blood-2017-05-781450

42. Hayes W, Tschumi S, Ling SC, Feber J, Kirschfink M, Licht C. Eculizumab hepatotoxicity in pediatric aHUS. *Pediatr Nephrol* 2015;**30**:775-81. 10.1007/s00467-014-2990-5

43. Oruc A, Ayar Y, Vuruskan BA, Yildiz A, Aktas N, Yavuz M*, et al.* Hepatotoxicity associated with eculizumab in a patient with atypical hemolytic uremic syndrome. *Nefrología* 2018;**38**:448-50. https://doi.org/10.1016/j.nefro.2017.10.001

44. Ardissino G, Testa S, Possenti I, Tel F, Paglialonga F, Salardi S*, et al.* Discontinuation of eculizumab maintenance treatment for atypical hemolytic uremic syndrome: a report of 10 cases. *Am J Kidney Dis* 2014;**64**:633-7. 10.1053/j.ajkd.2014.01.434

45. National Renal Complement Therapeutics Centre (NRCTC). *Welcome to SETS aHUS*. 2020. URL: http://www.atypicalhus.co.uk/clinical-trials/sets-ahus-2/ (accessed 06 July 2020.

46. Licht C, Ardissino G, Ariceta G, Cole A, Gasteyger C, Cohen DJ*, et al.* Characteristics of 521 adult and pediatric patients in the global aHUS registry. Poster SA-PO510. Paper presented at: American Society of Nephrology (ASN) Kidney Week 2014 Annual Meeting, 11–16 November 2014; Philadelphia, PA.

47. Acosta-Medina AA, Moyer AM, Go RS, Willrich MA, Alkhateeb HB, Bourlon De Los Rios C*, et al.* Determination of relapse risk by complement gene variants after eculizumab discontinuation in complement-mediated thrombotic microangiopathy: a retrospective review (1675). Paper presented

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

at: Virtual 62nd American Society of Hematology (ASH) Annual Meeting and Exposition, 5-8 December.

48. Fakhouri F, Fila M, Hummel A, Ribes D, Sellier-Leclerc A-L, Ville S*, et al.* Eculizumab discontinuation in children and adults with atypical haemolytic uremic syndrome: a prospective multicentric study. *Blood* 2020. 10.1182/blood.2020009280

49. Ardissino G, Possenti I, Tel F, Testa S, Salardi S, Ladisa V. Discontinuation of eculizumab treatment in atypical hemolytic uremic syndrome: an update. *Am J Kidney Dis* 2015;**66**:172-3. 10.1053/j.ajkd.2015.04.010

50. Sheerin NS, Kavanagh D, Goodship TH, Johnson S. A national specialized service in England for atypical haemolytic uraemic syndrome - the first year's experience. *QJM* 2016;**109**:27-33. 10.1093/qjmed/hcv082

51. Merrill SA, Brittingham ZD, Yuan X, Moliterno AR, Sperati CJ, Brodsky RA. Eculizumab cessation in atypical hemolytic uremic syndrome. *Blood* 2017;**130**:368-72. 10.1182/blood-2017-02-770214

52. Macia M, de Alvaro Moreno F, Dutt T, Fehrman I, Hadaya K, Gasteyger C*, et al.* Current evidence on the discontinuation of eculizumab in patients with atypical haemolytic uraemic syndrome. *Clin Kidney J* 2017;**10**:310-9. 10.1093/ckj/sfw115

53. Wijnsma KL, Duineveld C, Volokhina EB, van den Heuvel LP, van de Kar NC, Wetzels JFM. Safety and effectiveness of restrictive eculizumab treatment in atypical haemolytic uremic syndrome. *Nephrol Dial Transplant* 2018;**33**:635-45. 10.1093/ndt/gfx196

54. Ardissino G, Tel F, Sgarbanti M, Cresseri D, Giussani A, Griffini S*, et al.* Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome: an update. *Pediatr Nephrol* 2018;**33**:457-61. 10.1007/s00467-017-3813-2

55. Ariceta G, Fakhouri F, Sartz L, Miller B, Nikolaou V, Cohen D*, et al.* Risk of TMA recurrence and renal outcomes after eculizumab discontinuation in aHUS. Results from the global aHUS registry. Poster TH-PO802. Paper presented at: American Society of Nephrology (ASN) Kidney Week 2019 Annual Meeting, 5–10 November 2019 Washington, DC.

56. Ariceta G, Fakhouri F, Sartz S, et al. Eculizumab discontinuation in atypical hemolytic uremic syndrome: TMA recurrence risk and renal outcomes (unpublished). In; 2020.

57. Chow V, Pan J, Chien D, Mytych DT, Hanes V. A randomized, double-blind, single-dose, three-arm, parallel group study to determine pharmacokinetic similarity of ABP 959 and eculizumab (Soliris) in healthy male subjects. *Eur J Haematol* 2020;**105**:66-74. 10.1111/ejh.13411

58. Adis Insight. *Eculizumab biosimilar - Amgen (ABP 959)*. 2020. URL: https://adisinsight.springer.com/drugs/800045569 (accessed 24 Nov 2020).

59. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013*: NICE; 2013.

60. Kulasekararaj AG, Hill A, Rottinghaus ST, Langemeijer S, Wells R, Gonzalez-Fernandez FA*, et al.* Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood* 2019;**133**:540-9. 10.1182/blood-2018-09-876805

61. Alexion Pharmaceuticals Inc. Ravulizumab in aHUS: UK virtual advisory board. In; 2020.

62. van den Brand JA, Verhave JC, Adang EM, Wetzels JF. Cost-effectiveness of eculizumab treatment after kidney transplantation in patients with atypical haemolytic uraemic syndrome. *Nephrol Dial Transplant* 2017;**32**:i115-i22. 10.1093/ndt/gfw353

63. National Institute for Health and Care Excellence. *Immunosuppressive therapy for kidney transplant in children and young people. Technology appraisal guidance [TA482]*: NICE; 2017.

64. National Institute for Health and Care Excellence. *Omalizumab for treating severe persistent allergic asthma. Technology appraisal guidance [TA278]*: NICE; 2013.

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

65. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;**13**:509-18. 10.1111/j.1524-4733.2010.00700.x

66. Alexion Pharmaceuticals Inc. A discrete choice experiment to explore preferences for treatments for atypical hemolytic uremic syndrome (aHUS): All countries study report. In; 2020.

67. Kent S, Schlackow I, Lozano-Kuhne J, Reith C, Emberson J, Haynes R*, et al.* What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease? *BMC Nephrol* 2015;**16**:65. 10.1186/s12882-015-0054-0

68. MIMS. *Soliris*. 2020. URL: https://www.mims.co.uk/drugs/cardiovascular-system/anaemia-neutropenia/soliris (accessed 06 July 2020.

69. Curtis L, Burns A. *PSSRU: Unit Costs of Health and Social Care 2019*. 2019. URL: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/ (accessed 05 June 2020.

70. Hampstead Heath Pharmacy. *Meningitis Vaccines*. 2020. URL: https://hhpharmacy.co.uk/meningitis-vaccine/ (accessed 01 July 2020.

71. National renal Complement Therapeutics Centre (NRCTC). *Monitoring of patients receiving eculizumab* 2020. URL: http://www.atypicalhus.co.uk/ahus/eculizumab-in-the-treatment-of-ahus/monitoring-of-patients-receiving-eculizumab/ (accessed 06 July 2020.

72. NHS Inprovement. *National Cost Collection for the NHS*. 209. URL: https://improvement.nhs.uk/resources/national-cost-collection/ (accessed 01 August 2020.

73. National Institute for Health and Care Excellence (NICE). *NICE guideline NG45: Preoperative tests (Update): Routine preoperative tests for elective surgery*. 2016. URL: https://www.nice.org.uk/guidance/ng45/evidence/appendix-m-economic-considerations-for-delphi-pdf-87258149464 (accessed 15 July 2020.

74. Silver SA, Chertow GM. The Economic Consequences of Acute Kidney Injury. *Nephron* 2017;**137**:297-301. 10.1159/000475607

Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

9 APPENDICES

9.1 Appendix A

Table 23 ERG appraisal of evidence identification for the clinical effectiveness review

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	YES	
Were appropriate sources searched?	PARTLY	- Sources of both published and unpublished studies were included in the search. MISSING: - Reference checking of previous reviews or included studies was not reported as a search method. - Trial registers containing ongoing or completed but unpublished studies (e.g. ClinicalTrials.gov) were not searched. - The HTA database was not searched.
Was the timespan of the searches appropriate?	YES	Database inception to 3rd April 2020.
Were appropriate parts of the PICOS included in the search strategies?	YES	aHUS(P) AND various study designs (S). OR aHUS(p) AND adverse events (O).
Were appropriate search terms used?	YES	
Were any search restrictions applied appropriate?	PARTLY	Database search results were restricted to studies published in English.
Were any search filters used validated and referenced?	UNCLEAR	The source of the search terms used to restrict retrieval by study design (Line 5 – 16, Table 1, Appendix D) or by adverse events (Lines 17 and 18, Table 1, Appendix D) is not reported or referenced. Therefore, it is unclear if validated search filters were used in the search strategies.

9.2 Appendix B

Table 24: ERG appraisal of economic evidence identification

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	YES	The search strategy was missing for EconLit, however the ERG checked and no studies on aHUS patients would have been found with a search via EconLit.
Were appropriate sources searched?	YES	- MEDLINE, Embase, CENTRAL, CDSR, DARE, EconLit, NHS EED, and HTA database. - Relevant conference abstracts from conferences taking place in the past 2 years were searched.

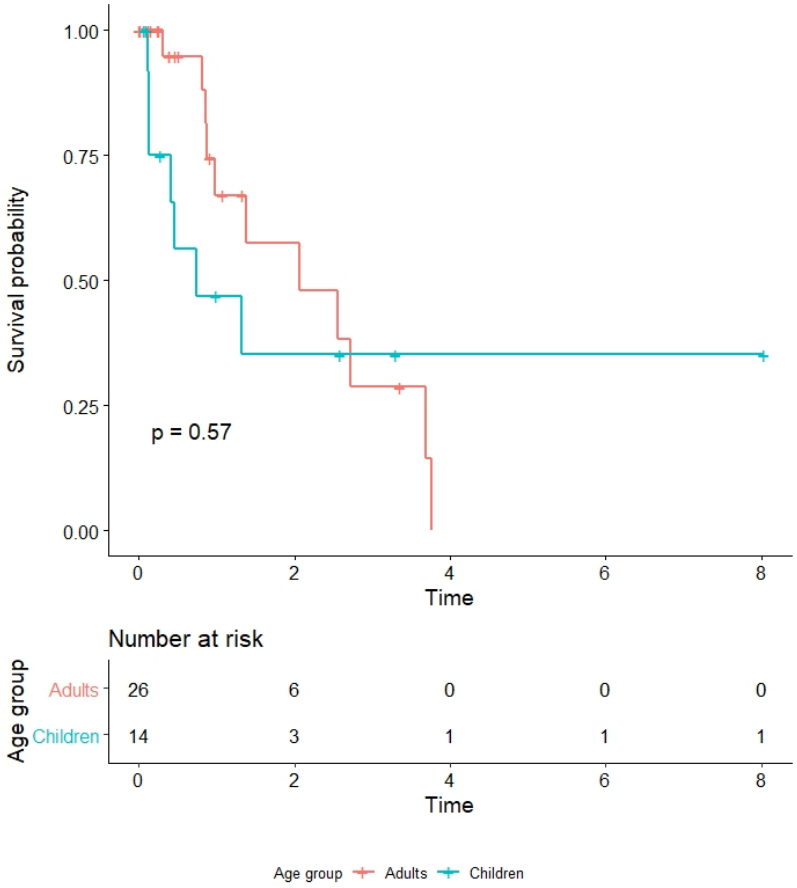
Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Was the timespan of the searches appropriate?	YES	The databases were searched on 3rd April 2020 and date limits were not applied.
Were appropriate parts of the PICOS included in the search strategies?	YES	aHUS (P) AND Economic evaluations (S) OR costs (O) OR health-state utility values (O)
Were appropriate search terms used?	YES	However, further terms to capture studies about resource use would have increased comprehensiveness.
Were any search restrictions applied appropriate?	PARTLY	Searches were restricted to those studies published in English.
Were any search filters used validated and referenced?	UNCLEAR	Retrieval was restricted to economic evaluations, cost or health related quality of life studies. No references were provided for any study design search filters, therefore it is unclear if validated search filters were used.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

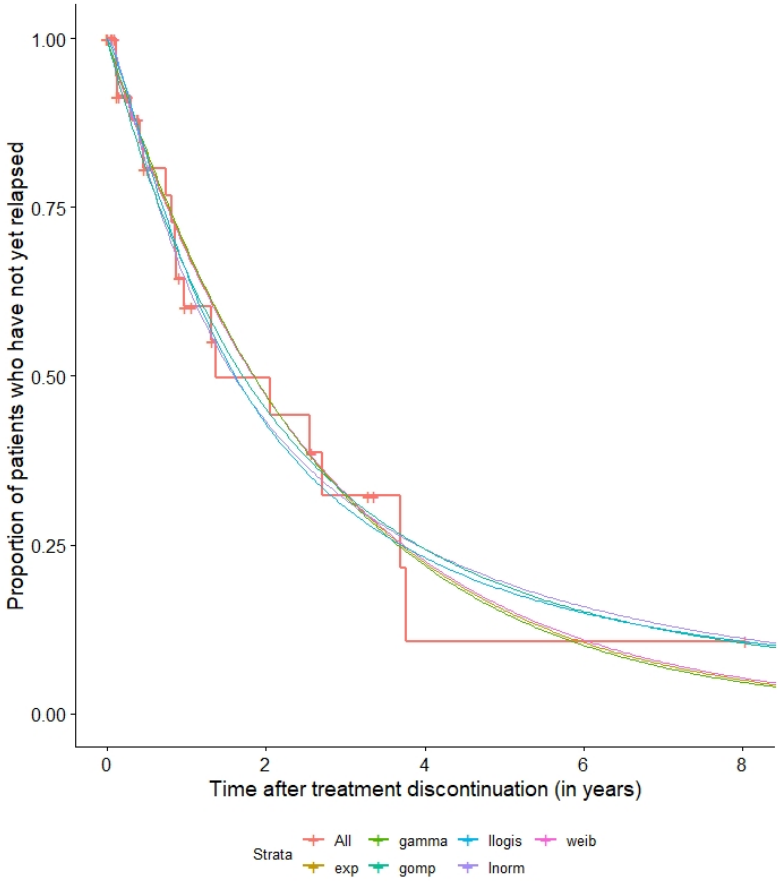
Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Figure 11: Kaplan Meier curve for time from eculizumab treatment discontinuation to restart – adult and children UK discontinued patients in global aHUS registry.



Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.

Figure 12: Kaplan Meier curve for time from eculizumab treatment discontinuation to restart – All UK discontinued patients in global aHUS registry. Lines represent the fitted survival models.



Copyright 2021 Queen's Printer and Controller of HMSO. All rights reserved.