Single Technology Appraisal

Danicopan with ravulizumab or eculizumab for treating paroxysmal nocturnal haemoglobinuria [ID5088]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Danicopan with ravulizumab or eculizumab for treating paroxysmal nocturnal haemoglobinuria [ID5088]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from** Alexion

2. **Consultee and commentator comments on the Draft Guidance** from:
    a. Novartis

There were no comments on the Draft Guidance received through the NICE website

3. **External Assessment Group critique of company response to the DG**

4. **External Assessment Group post-committee analyses**

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

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Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 19 June 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Alexion Pharmaceuticals

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Executive summary Alexion appreciate the opportunity to respond to the draft guidance document (DGD) prepared by the National Institute for Health and Care Excellence (NICE) for the evaluation of danicopan with ravulizumab or eculizumab for treating paroxysmal nocturnal haemoglobinuria (PNH). In response to the initial decision not to recommend danicopan in this indication, Alexion are eager to work with the evaluation committee in order to address key concerns and resolve any remaining uncertainty associated with the submission, in order to provide patients in England and Wales access to this therapy. It is important to consider this response in the context of the unmet needs faced by patients with PNH in UK clinical practice. While complement component 5 (C5) inhibitors provide a complete and sustained control of intravascular haemolysis (IVH), reducing the risk of life-threatening

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	manifestations of PNH, an unmet need continues to exist for a subset of patients who experience clinically significant extravascular haemolysis (csEVH) whilst receiving eculizumab or ravulizumab. Clinical experts in PNH consulted during a UK advisory board estimated the proportion of patients treated with C5 inhibition experiencing csEVH to be around 30%, noting that in this population, severe fatigue represents a key unmet need.[1] Fatigue has been demonstrated throughout the published literature to have a profound impact on health-related quality of life (HRQoL) of affected patients.[1-3] Furthermore, residual anaemia and continued dependence on blood transfusions are other common manifestations experienced by patients that contribute to the humanistic and economic burden associated with csEVH.[1, 4-8] As noted by the evaluation committee, PNH can substantially affect HRQoL.[9] Pegcetacoplan, a complement component 3 (C3) inhibitor, is recommended for the treatment of adults with PNH who have anaemia after at least three months of treatment with a C5 inhibitor.[1, 10] Following a crossover period, patients are required to discontinue ongoing treatment with eculizumab or ravulizumab to receive pegcetacoplan as a monotherapy, and therefore subsequently receive no C5 inhibitor backbone treatment.[11] Treatment with a proximal complement inhibitor monotherapy, such as pegcetacoplan, therefore risks a lapse in control of IVH in the absence of complete terminal complement inhibition.[12] As such, breakthrough haemolysis (BTH), a lapse in disease control, may occur.[13-15] BTH events pose a substantial risk to patients' health due to the potential recurrence of life-threatening symptoms of IVH.[12, 16] The Patriquin et al. 2024 and Griffin et al. 2024 studies provide long-term evidence on patient outcomes with pegcetacoplan.[17, 18] The Griffin et al. 2024 study presents data in a real-world setting for 48 patients with PNH receiving pegcetacoplan in the UK and France. In this study, a total of 32 BTH events had occurred in 13/48 (approximately 27%) patients, indicating suboptimal disease control.[18] The Patriquin et al. 2024 study, an open-label extension study, provides safety and efficacy data for 64 patients who completed the PEGASUS trial and who were followed-up for an additional 48 weeks. In this study, a total of 14/64 patients reported BTH events, corresponding to approximately 22% of patients.[17] Furthermore, the published literature indicates that pegcetacoplan is associated with more severe BTH events when compared with C5 inhibitors, with reports of BTH events on pegcetacoplan featuring lactate dehydrogenase (LDH) levels of up to 10–15 times the upper limit of normal (ULN).[12] Comparatively, LDH level increases of more than five times the ULN are rare amongst patients treated with a C5 inhibitor.[12] There is therefore an unmet need for a treatment to effectively address the symptoms associated with csEVH whilst maintaining sufficient disease control that is essential to preventing life-threatening IVH. Danicopan is positioned to address this unmet need. This is supported by clinical experts consulted as part of the aforementioned advisory board, who stated that danicopan add-on treatment provides reassurance of continued control of IVH due to the presence of the C5 inhibitor backbone.[1] The patient expert statement provided for this evaluation also supports the efficacy of danicopan add-on treatment: "*The biggest advantage I have found from the danicopan is the quality of life I have. I can manage my tiredness much better and often forget that I am living with PNH. They have stabilised my blood levels consistently and I am able to work full time along with continuing to have an active social life*".[19] While danicopan is an add-on treatment to intravenous infusions of eculizumab or ravulizumab, its oral formulation is convenient, permitting travel and accommodating employment and educational needs as noted in the patient organisation submission for this evaluation.[19] Conversely, subcutaneous pegcetacoplan treatment places a time and administration burden on patients, and would exclude any patients with csEVH with visual difficulties, dexterity issues, mental health issues or minimal subcutaneous fat.[1] Overall, danicopan presents an efficacious and convenient add-on treatment to address the needs of patients with PNH experiencing csEVH.

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	In order to facilitate patient access to danicopan add-on treatment in UK clinical practice, Alexion have provided a response in which several areas of uncertainty and additional analyses requested by the evaluation committee in the DGD have been addressed. This response provides: 1. Transition probabilities and health state utility values (HSUVs) derived from the interim analysis 3 (IA3) data cut of the ALPHA trial 2. Long-term BTH event rates modelled using the Kulasekararaj et al. 2023 publication for the danicopan treatment arm, and the Griffin et al. 2024 and Patriquin et al. 2024 publications for the pegcetacoplan treatment arm. Additionally, clarity is provided on the definitions for BTH events used in all relevant studies, and the approach taken for the cost-effectiveness model[17, 18, 20] 3. Clarity on the dose escalation regimens (and corresponding costs) associated with BTH events for patients receiving pegcetacoplan. Additionally, the rationale behind excluding one-off costs of eculizumab in the economic model is provided 4. Scenario analyses varying the long-term (Year 1+) discontinuation rate of danicopan add-on treatment and pegcetacoplan between 0–1% per cycle 5. Recently collected clinical validation on the proportion of patients anticipated to discontinue danicopan add-on therapy and transition to pegcetacoplan in UK clinical practice Alexion have also provided an updated model which allows the following EAG preferences to be selected by the user: • Setting the transition probabilities for pegcetacoplan equal to danicopan add-on treatment • Setting the long-term probability for BTH events for pegcetacoplan equal to danicopan add-on treatment • Setting the probability for BTH events on C5 inhibitor treatment from Week 25+ equal to danicopan add-on treatment • An alternative calculation for the probability of alanine aminotransferase (Weeks 1–12) for patients receiving danicopan add-on treatment • Allowing differing proportions of patients discontinuing danicopan add-on treatment to receive pegcetacoplan or C5 inhibitor monotherapy o The model has been updated to ensure that patients who discontinue to pegcetacoplan are assigned the correct treatment-related administration disutility, rates of BTH events and transition probabilities o The model has also been updated with the functionality to model subsequent discontinuation of treatment from pegcetacoplan to C5 inhibitor monotherapy; rates of discontinuation are based on the rate of non-BTH event related discontinuation and are aligned with the rates assigned to the pegcetacoplan arm • Correcting the EAG model to ensure that patients who discontinue from danicopan as an add-on to eculizumab and ravulizumab to pegcetacoplan receive three doses of pegcetacoplan upon the event of BTH, which may have been unintentionally omitted from the EAG model

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Alongside this response, Alexion have submitted an updated company base case, which includes the following inputs and assumptions:

- Transition probabilities and HSUVs for danicopan and placebo as an add-on to eculizumab and ravulizumab derived from the IA3 data cut of the ALPHA trial
- Long-term BTH events rates for patients receiving pegcetacoplan derived from the Patriquin et al. 2024 publication[17]
- Upon experiencing a BTH event, 53% of patients receiving pegcetacoplan will temporarily dose escalate for three cycles, supported by the de Latour et al. 2024 publication[21]
- The long-term (Year 1+) non-BTH discontinuation rate is constant at 0% in both treatment arms
- 60% of all patients who discontinue danicopan as an add-on to eculizumab or ravulizumab will receive pegcetacoplan; the remaining patients receiving eculizumab or ravulizumab monotherapy

Results of the updated base case, and all relevant scenario analyses, are presented in Appendix A.

1

Interim analysis 3 data cut off

Following the EAG report, Alexion provided top-line results from IA3 of the ALPHA trial. IA3, corresponding to a 31st March 2023 data cut, provides efficacy data for all patients randomised to treatment in the ALPHA trial (the modified randomised set, N=[redacted] patients), resulting in data for an additional n=[redacted] patients randomised to the danicopan arm and n=[redacted] patients randomised to the placebo arm.

The primary and key secondary endpoints of the ALPHA trial (assessed at Week 12) were presented for IA3 in an addendum, with results at Week 24 also provided for completeness. Efficacy results for IA3 were [redacted] with respect to the data cut used to inform the company submission, IA2. Specifically, the primary and key secondary endpoints (the difference between danicopan add-on treatment and pegcetacoplan at Week 12) varied in magnitude by <[redacted]% of the IA2 endpoints presented in the company submission.

Transition probabilities

Updated transition probabilities and HSUVs were estimated taking the same approach as used in the company submission and updating the mean age of the patients in IA3 to [redacted] years. Updated transition probabilities for the 9.5 g/dL haemoglobin level threshold from the ALPHA trial are presented in Table 1 and Table 2, for danicopan as an add-on and placebo as an add-on to eculizumab and ravulizumab, respectively.

Transition probabilities for patients receiving danicopan as an add-on to eculizumab or ravulizumab informed by IA3 were broadly consistent with the transition probabilities informed by IA2; the proportion of patients in the transfusion ending health state is [redacted] between the data cuts, with a slightly [redacted] proportion of patients in the low haemoglobin ending health state for the IA3 transition probabilities.

Table 1: IA3 transition probabilities (danicopan as an add-on to eculizumab or ravulizumab)

Beginning health state	Ending health state		
	Low Hb (No Tr.)	Moderate Hb (No Tr.)	Transfusion

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Low Hb (No Tr.)	[redacted]	[redacted]	[redacted]
Moderate Hb (No Tr.)	[redacted]	[redacted]	[redacted]
Transfusion	[redacted]	[redacted]	[redacted]

Abbreviation: Hb: haemoglobin; IA3: interim analysis 3; Tr.: transfusion.

Table 2: IA3 transition probabilities (placebo as an add-on to eculizumab or ravulizumab monotherapy)

Beginning health state	Ending health state		
	Low Hb (No Tr.)	**Moderate Hb (No Tr.)**	**Transfusion**
Low Hb (No Tr.)	[redacted]	[redacted]	[redacted]
Moderate Hb (No Tr.)	[redacted]	[redacted]	[redacted]
Transfusion	[redacted]	[redacted]	[redacted]

Abbreviation: Hb: haemoglobin; IA£: interim analysis 3; Tr.: transfusion.

Health state utility values

Updated HSUVs are presented in Table 3. Utility values for all health states were slightly improved for IA3 versus IA2.

Table 3: Updated IA3 HSUVs (EQ-5D-3L derived from ALPHA; 9.5 g/dL threshold)

Health state	Utility
Low Hb (No Tr.)	0.8207
Moderate Hb (No Tr.)	0.8692
Transfusion	0.7107

Abbreviations: Hb: haemoglobin; HSUV: health state utility value; IA3: interim analysis 3; Tr: transfusion.

As shown by Table 4, inclusion of transition probabilities and HSUVs calculated from the IA3 data cut of the ALPHA trial had a minimal impact on cost-effectiveness results versus the original company base case, which was informed by IA2 of the ALPHA trial, also slightly improving cost-effectiveness estimates. The updated company base case uses the updated transition probabilities and HSUVs presented above in addition to a number of other changes; model results are provided in Appendix A.

Table 4: Cost-effectiveness results incorporating data from IA3 of the ALPHA trial

Model update	Incremental costs	Incremental QALYs	ICER	Incremental NHB	% change from original company base case
Transition probabilities and HSUVs	[redacted]	0.424	Dominant	[redacted]	+3.61

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	informed by IA3 | | | | | |
	Abbreviations: IA3: interim analysis 3; HSUV: health state utility value; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.
2	**Long-term rates and definitions for breakthrough haemolysis** As noted in the executive summary of this response document, BTH events, which can result in a return of key symptoms of IVH, represent a substantial risk to patients' health. For example, a BTH event may lead to thrombosis, which is associated with an increased risk of mortality.[12, 16, 22] Additionally, clinical experts consulted during the evaluation noted that patients receiving pegcetacoplan have a higher likelihood of experiencing BTH events relative to ravulizumab. As noted in the committee papers for this evaluation, clinical experts *"expect there would be less breakthrough haemolysis with C5i and danicopan (especially with ravulizumab) given it is a combination of two complement inhibitors used*".[19] As such, BTH events were a key clinical outcome captured in the cost-effectiveness model developed for this evaluation. As noted in Page 13, Section 3.8 of the DGD, clinical experts in the committee meeting requested further details about the criteria used to classify BTH events in the relevant trials and their comparability with the criteria implemented in the model.[9] Therefore, details on the approach to modelling BTH events are provided below. ***Classification of breakthrough haemolysis*** The following definitions were used for BTH events in the ALPHA trial for danicopan and the PEGASUS trial for pegcetacoplan: • The ALPHA trial: *"BTH events were based on the clinical judgement of the Investigator".*[23] • The PEGASUS trial: *"BTH events were defined as at least one new or worsening symptom or sign of IVH (fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia [haemoglobin level < 10 g/dL], major adverse vascular event including thrombosis, dysphagia or erectile dysfunction) in the presence of elevated LDH ≥2 x ULN after prior LDH reduction to ≤1.5 x ULN on therapy".*[24] In order to validate clinical assumptions and definitions associated with BTH events in the submission, Alexion conducted several interviews with UK clinical experts in PNH. During these meetings, the clinical experts confirmed that the following definition, used in the ravulizumab trials Study 301 and Study 302, aligns with that used to identify BTH events in clinical practice:[25, 26] • Study 301 and 302: *"at least one new or worsening symptom or sign of intravascular haemolysis (fatigue; haemoglobinuria; abdominal pain; shortness of breath [dyspnoea]; anaemia; major adverse vascular events, including thrombosis; dysphagia; or erectile dysfunction) in the presence of elevated LDH ≥2 × ULN after prior LDH reduction to <1.5 × ULN on therapy*".[27, 28] The definition of BTH events agreed on by UK clinical experts aligns with the criteria used to classify BTH events in the PEGASUS trial.[24] While a BTH event in the ALPHA trial was investigator defined and therefore more broadly defined than UK clinical expert opinion and the PEGASUS trial definition, the LDH levels at the time of the event were reported during the ALPHA trial and thus allowed for a common BTH definition to be used. In order to ensure alignment with UK clinical practice and consistency between danicopan add-on treatment and pegcetacoplan, the BTH event

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rate from the ALPHA trial (Weeks 1–24 and Weeks 25+) utilised in the cost-effectiveness model was calculated based on patients that had an LDH elevation ≥2 x ULN during these events. This simple adjustment was made to ensure the criteria used to define BTH events in the model were consistent; furthermore, using a ≥2 x ULN threshold for LDH was considered to be a reasonable approach by clinical experts in PNH consulted to support this evaluation.[27, 29]

Long-term breakthrough haemolysis rates

As noted in Page 12, Section 3.8 of the DGD, clinical experts in the committee meeting stated that BTH event rates for patients receiving danicopan as an add-on to eculizumab and ravulizumab are expected to be lower than pegcetacoplan due to the presence of the C5 inhibitor backbone.[9]

Rates of BTH for patients receiving danicopan add-on treatment and pegcetacoplan were therefore derived from the ALPHA trial and the PEGASUS trial, respectively, in order to reflect this anticipated difference in risk of BTH events between the two treatments.

In recognition of the evaluation committee's request, the economic model submitted alongside this response has been updated to present scenario analyses in which long-term BTH event rates are calculated from the Kulasekararaj et al. 2023 publication for ravulizumab, and the Griffin et al. 2024 publication for pegcetacoplan.[18, 20] Sales data procured by Alexion indicates that the majority of patients (█%) receive ravulizumab compared to eculizumab (█%) in UK clinical practice; these figures were also validated by clinical experts from the PNH National Service in the UK. Therefore, the BTH event rate observed in the Kulasekararaj et al. 2023 publication can be considered generalisable to patients in UK clinical practice who would be eligible for treatment with danicopan.

The Kulasekararaj et al. publication reports results after a four-year duration of Study 302 (NCT03056040), which investigates ravulizumab in C5 inhibitor experienced patients with PNH.[20] In the Griffin et al. 2024 publication, patients had received treatment with pegcetacoplan for a mean duration of 20.2 months.[18] As such, the BTH event rate for ravulizumab is applied from Week 25+ in the scenario analysis, whereas the BTH event rate for pegcetacoplan is applied from Week 17+ in the scenario analysis.

It should be noted that while the definitions for BTH events vary slightly between these two sources, clinical experts consulted in advance of submitting this response confirmed that these definitions are highly consistent and do not equate to any significant clinical difference.[29] The studies used the following definitions:

- (As noted above), Study 302 defined BTH events as: *"at least 1 new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnoea], anaemia [haemoglobin <10 g/dL], major adverse vascular event [including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥2 x ULN after prior reduction of LDH to <1.5 x ULN on treatment"*.[27]

- The Griffin et al. 2024 publication defined BTH rates as: *"an LDH rise above twice the upper limit of normal in patients with LDH predominantly controlled below 1.5 x ULN and a recurrence of PNH symptoms or a thrombotic event"*.[18 29]

In addition to the Griffin et al. 2024 publication, longer-term BTH event data was recently published in the Patriquin et al. 2024 study. This was an open-label extension study reporting on 64 patients over 48 weeks, following the first 48-week period of the PEGASUS trial. Patients were also recruited from other parent studies for pegcetacoplan. A total of 14/64 patients reported BTH events in this study, corresponding to approximately 22% of patients (2.04% as a 4-weekly probability).[17]

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Clinical experts consulted ahead of the submission of this response believe that the annual long-term BTH event rates for pegcetacoplan are likely to be between rates from the PEGASUS trial and the real-world evidence study by Griffin et al. 2024 (Table 5). Specifically, the clinicians noted that the PEGASUS trial recruited a more severely ill population than the Griffin et al. 2024 study, which accounts for the slightly higher BTH rate observed in the PEGASUS trial.[29] One clinical expert estimated that the annual rate of BTH events on pegcetacoplan would be approximately 25%.[29] Thus, the long-term data from the Patriquin et al. 2024 study may be considered as reflective of the BTH event rates expected in UK clinical practice.

As such, the long-term rate for BTH events for patients receiving pegcetacoplan observed in the Patriquin et al. 2024 study has been incorporated into the updated company base case, presented in Appendix A.

Table 5: Observed BTH event rates for pegcetacoplan

Publication	Trial	4-weekly probability	Annual probability
Latour et al. (2022)[14]	PEGASUS trial (post-16 weeks)	2.67%	29.68%
Patriquin et al. (2024)[17]	307 Open label extension study (PEGASUS)	2.04%	23.47%
Griffin et al. (2024)[18]	Real-world evidence (France & UK)	1.55%	18.35%

Abbreviations: BTH: breakthrough haemolysis; UK: United Kingdom.

In the original company base case, long-term rates of BTH for patients receiving danicopan as an add-on to eculizumab or ravulizumab were informed by the long-term extension period of the ALPHA trial, in which 1/60 patients who entered the long-term extension at the 20th September 2022 DCO experienced a BTH event with LDH ≥2 × ULN.[30] These patients received either eculizumab or ravulizumab background C5 inhibition.

As requested by the appraisal committee, the observed long-term BTH event rates for patients receiving ravulizumab in Study 302 are presented in Table 6. As a conservative assumption, the long-term BTH event rate derived from the ALPHA trial is maintained for patients receiving danicopan add-on treatment in the updated base case, however, the long-term BTH event rate derived from the Kulasekararaj et al. 2023 publication (Study 302) is presented as a scenario analysis in Appendix A.

Table 6: Observed BTH event rates for C5 inhibition

Publication	Trial	4-weekly probability	Annual probability
Data on File;[30] danicopan + C5 inhibitor	The ALPHA trial	0.24%	3.07%
Kulasekararaj. et al (2023);[20] ravulizumab	Study 302	0.13%	1.69%

Abbreviations: BTH: breakthrough haemolysis; C5: complement component inhibitor.

It should be noted that pegcetacoplan has only been available for approximately two years for use in UK clinical practice; a lack of long-term data on rate of BTH events on this treatment is therefore an unavoidable limitation that it will not be possible to resolve within the near future.[10] However, Alexion has provided an updated base case incorporating data from the Patriquin et al. 2024 study, providing an additional 48 weeks of follow-up than the source used in the original company base case, also presenting the scenario analysis requested by the appraisal committee for which danicopan add-on treatment remains dominant versus pegcetacoplan.

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	Alexion hope that these analyses alleviate the evaluation committee's concerns regarding uncertainty with long-term rates of BTH for both danicopan add-on treatment and pegcetacoplan.
3	**Management of breakthrough haemolysis in clinical practice** Alexion wish to provide clarity on the approach used to model management of BTH events for patients receiving pegcetacoplan in the economic model. Two types of BTH events may occur in patients with PNH receiving complement inhibition: • **Pharmacodynamic BTH:** A BTH may occur as a result of a temporary event, such as an infection or vaccination. These events are also termed a complement amplifying condition (CAC), where the body's immune system triggers complement amplification in response. The therapeutic response to a pharmacodynamic BTH is a temporary increase in drug dosing.[18] • **Pharmacokinetic BTH:** Alternatively, a BTH may occur as a result of insufficient levels of complement inhibitors in the plasma, such as insufficient dosing levels.[31] The therapeutic response to a pharmacokinetic BTH is a permanent increase in drug dosing.[18] ***Treatment of BTH events in clinical practice: pegcetacoplan dose escalation*** For patients receiving pegcetacoplan, pharmacokinetic BTH events are treated with dose escalations in clinical practice, as noted above.[25, 26] During interviews conducted ahead of submitting this response, UK clinical experts stated that if the BTH event is pharmacokinetic, with no identifiable cause, patients will remain on the escalated dose.[29] The experts also stated that in the case of pharmacodynamic BTH, that is, an event with an identifiable trigger, pegcetacoplan dosing may be escalated for approximately three months following which the patient may return to the previous dose level.[29] Since submission, the Griffin et al. 2024 publication has been published.[18] This publication outlines the management of patients with PNH receiving pegcetacoplan in the UK and France, and was produced by the PNH National Service lead in the UK. Therefore, management of PNH observed in this publication can be considered as highly representative of current clinical practice in the UK. Figure 1 in this publication, which is reproduced in Appendix B, outlines the management of patients receiving pegcetacoplan experiencing a BTH event.[18] As shown by this figure, if a patient experiences a BTH event, they receive intensive pegcetacoplan therapy consisting of one dose per day for three days consecutively (administered subcutaneously), or a single intravenous dose. This is then followed by an increase of pegcetacoplan dosing (every 3 days or if already on every 3 days, switch to 3 times a week). Aligned with the approach suggested by clinicians above, a patient will temporarily increase pegcetacoplan dosing for three months, reverting back to base pegcetacoplan dosing after this time, if the BTH event is pharmacodynamic. However, if the BTH event is pharmacokinetic, the patient will increase pegcetacoplan dosing permanently.[18] ***Treatment of BTH events in clinical practice: eculizumab dosing*** On Page 15, Section 3.9 of the DGD, the evaluation committee note that it may be appropriate to assume that some patients receive a one-off dose of eculizumab in response to a BTH event whilst on-treatment with pegcetacoplan, rather than dose escalation of pegcetacoplan treatment. The Griffin et al. 2024 publication also provides guidance on the use of eculizumab in response to BTH events.[29] As indicated by the management flowchart for BTH events in clinical practice, an immediate C5 inhibitor dose is utilised only in the uncommon event of thrombosis or another life-threatening event occurring as a result of BTH. For a thrombosis, the patient would revert back from

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	pegcetacoplan treatment to C5 inhibition, or initiate dual therapy. Alternatively, a C5 inhibitor dose can be used if a patient does not respond to the initial intensive pegcetacoplan monotherapy outlined above (subcutaneous pegcetacoplan for three days or single intravenous dose of pegcetacoplan), and their LDH level continues to rise. Thus, in current UK clinical practice, C5 inhibition on pegcetacoplan is reserved for use in rare cases of severe BTH events, and does not present typical management for patients receiving pegcetacoplan.[18] This management pathway was also validated by two UK clinical experts in PNH consulted ahead of submitting this response document.[29] In line with clinical opinion and the BTH event management pathway outlined in Griffin et al. 2024, costs of one-of doses of eculizumab have not been incorporated into the model, as they are not used as an alternative to dose escalations of pegcetacoplan and are reserved for rare, severe cases of BTH. ***Cost-effectiveness model: pegcetacoplan dose escalation*** In the original company base case, all patients who receive pegcetacoplan who experienced a BTH event were dose escalated permanently. In recognition of the evaluation committee's preferences, the economic model has been updated with the functionality to allow a proportion of patients receiving pegcetacoplan who experience a BTH event to temporarily dose escalate for three cycles (12 weeks). These patients therefore represent the proportion of patients experiencing a pharmacodynamic BTH event. Sequential escalations from twice weekly dosing of pegcetacoplan to the following two dose levels are permitted: • A dose of pegcetacoplan once every three days • A dose of pegcetacoplan three times each week, following a BTH event on the previous dose level In order to model temporary dose escalation for patients receiving pegcetacoplan, tunnel states were built into the cost-effectiveness model. The use of tunnel states enables patients who experience a pharmacodynamic BTH to be tracked within the model and assigned the appropriate pegcetacoplan dosing regimen in line with UK clinical practice as described above. It should be noted that a proportion of the total number of patients receiving pegcetacoplan were modelled to escalate temporarily, as patients experiencing pharmacokinetic BTH events may require permanent dose escalation as confirmed by clinical experts.[29] Those who escalate permanently are modelled as per the original company submission. Clinical experts consulted ahead of submitting this response document were asked to estimate the proportion of patients receiving pegcetacoplan that would temporarily dose escalate upon experiencing a BTH event. The clinical experts confirmed that around 50% of patients would temporarily dose escalate, with the remaining half of patients permanently remaining on an escalated dose.[29] This estimate is supported by the de Latour et al. 2024 study investigating haemolysis events in the PEGASUS study, in which 9/19 patients (47%) experienced a BTH event not associated with a CAC.[32] As such, the updated company base case presented in Appendix A assumes that 53% of patients receiving pegcetacoplan who experience a BTH event are temporarily dose escalated, then returning to their previous dose level after a period of three cycles. A scenario in which 100% of patients experiencing a BTH event on pegcetacoplan are temporarily dose-escalated is also provided for completeness. In both the updated base case and this scenario, danicopan add-on treatment remains dominant versus pegcetacoplan.

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4	**Long-term <u>non</u>-breakthrough haemolysis related discontinuation** Alexion has substantial concerns with modelling long-term, non-BTH event associated discontinuation rates using arbitrary values with no underlying clinical justification. When consulting clinical experts in PNH ahead of submitting this response document, the experts re-iterated the clinical expert position at the first committee meeting, that patients are less likely to discontinue treatment for non-BTH event reasons beyond the first year.[29] This is further supported by the Patriquin et al. 2024 open-label extension study, indicating that no patients during the 48-week follow-up period after completion of the PEGASUS trial discontinued treatment for non-BTH reasons.[17] This is in line with the modelling assumption accepted in TA778, in which discontinuations on pegcetacoplan were only expected to occur during a 'settling' period – the first 16 weeks of pegcetacoplan treatment.[10] Overall, the clinical consensus suggest discontinuation due to non-BTH reasons would be very infrequent.[29] There are limited data on long-term discontinuation rates for treated patients with PNH, however Study 301 and 302 provide the longest-term evidence available for treatment discontinuation for PNH patients. Of the 192 patients who received ravulizumab in the 302 study, 11 (5.7%) discontinued treatment, of which three were due to death during the study period.[20] These data result in a 4-weekly discontinuation rate on ravulizumab of 0.08%, and an annual probability of 1.1%. This is also consistent with discontinuation rate observed in the 301 study, in which patients discontinued for the following reasons death (n=8), patient choice (n=7), physician decision (n=5), pregnancy (n=4), adverse event (n=3), lost to follow-up (n=1) and other (n=5). These data equate to a 4-weekly rate of 0.14%, with an annual probability of 1.77%.[33] Overall, the data from the ravulizumab studies suggest the proportion of patient that will discontinue over long period of time is negligible, thus assuming a sustained discontinuation rate beyond the first year of treatment for any treatment is potentially overestimating the number of patients stopping treatment. However, in recognition of the evaluation committee's preferences, six scenarios exploring differing long-term rates of discontinuation (per cycle) not occurring due to BTH events have been provided in **Appendix A**. The scenarios assume the following: • A sustained life-long discontinuation following Year 1 and onwards, modelled at 0.1% per cycle for both treatment arms • A sustained life-long discontinuation following Year 1 and onwards, modelled at 0.2% per cycle for both treatment arms • A sustained life-long discontinuation following Year 1 and onwards, modelled at 0.4% per cycle for both treatment arms • A sustained life-long discontinuation following Year 1 and onwards, modelled at 0.6% per cycle for both treatment arms • A sustained life-long discontinuation following Year 1 and onwards, modelled at 0.8% per cycle for both treatment arms • A sustained life-long discontinuation following Year 1 and onwards, modelled at 1% per cycle for both treatment arms

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For ease of interpretation of the discontinuation rates modelled in the scenario analyses, the corresponding annual probabilities are presented in Table 7 below.

Table 7: Annual and per cycle rates of discontinuation used in the scenario analyses

Per cycle probability	Annual Probability
0.1%	1.29%
0.2%	2.57%
0.4%	5.08%
0.6%	7.53%
0.8%	9.92%
1.0%	12.25%

In all scenario analyses, danicopan as an add-on to eculizumab or ravulizumab remains dominant versus pegcetacoplan.

While Alexion have provided these analyses for the evaluation committee's consideration, Alexion wish to reiterate concerns with modelling an arbitrary lifelong discontinuation rate from Year 1 of after initiation of treatment until death without any clinical justification for the values used. The clinical expert opinion gathered by Alexion supports that the majority of non-BTH discontinuation on danicopan add-on treatment or pegcetacoplan is anticipated to take place within the first six months–first year of initiation of treatment, for example, due to adverse events.[29] Therefore, Alexion maintain that the assumption of no discontinuation for danicopan add-on treatment and pegcetacoplan after Year 1 of treatment remains the most appropriate approach to take in the model and consistent with TA778.[10]

5

Discontinuation of patients receiving danicopan as an add-on to eculizumab or ravulizumab

Clinical expert opinion

In recognition of the evaluation committee's request to provide an estimate for the proportion of patients expected to discontinue treatment with danicopan add-on treatment to pegcetacoplan, additional clinical validation interviews were conducted by Alexion prior to submitting this response.

One clinician consulted during the interview indicated that treatment choice following discontinuation of danicopan would depend on whether the patient was pegcetacoplan-naïve or experienced. One clinician stated that of patients discontinuing treatment with danicopan as an add-on to eculizumab or ravulizumab, approximately 50-60% of patients would receive pegcetacoplan.[29]

This estimate is supported by the clinical expert statements provided in the committee papers for this evaluation (Page 288 and 300), in which clinicians were asked to estimate the proportions of subsequent treatments received by patients discontinuing danicopan as an add-on to eculizumab or ravulizumab. These estimates are presented in Table 8.

Table 8: Clinical expert estimates of subsequent treatment following danicopan as an add-on to eculizumab or ravulizumab

	Clinical Expert #1	Clinical Expert #2

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C5 inhibitor monotherapy	30%	20%
Pegcetacoplan	50%	30%
Other	20%	50%

Abbreviations: C5: complement component 5.

As the 'Other' row displayed above only includes treatments accessed via a clinical trial or compassionate use, Alexion is not able to include these treatments within the model.

Therefore, by reweighting the percentages of treatments which are commercially available in England, the proportion of subsequent treatments estimated by clinical experts are illustrated in Table 9:

Table 9: Reweighted clinical expert estimates of subsequent treatment following danicopan as an add-on to eculizumab or ravulizumab

	Clinical Expert #1	Clinical Expert #2
C5 inhibitor monotherapy	$\frac{30\%}{30\% + 50\%} = 37.5\%$	$\frac{20\%}{20\% + 30\%} = 40\%$
Pegcetacoplan	$\frac{50\%}{30\% + 50\%} = 62.5\%$	$\frac{30\%}{20\% + 30\%} = 60\%$

Abbreviations: C5: complement component 5.

When reweighting the proportions of subsequent treatments estimated by clinical experts to only include treatments available within the ALPHA and PEGASUS trials, ~60% of patients discontinuing treatment with danicopan as an add-on to eculizumab or ravulizumab are expected to receive pegcetacoplan.[19]

Modelling updates

In the EAG model, a proportion of patients were modelled to discontinue danicopan as an add-on to eculizumab or ravulizumab to pegcetacoplan, with the relevant costs and BTH event rates for pegcetacoplan applied after this treatment switch. In the updated model provided by the company, patients who discontinue from danicopan as an add-on to eculizumab or ravulizumab to pegcetacoplan have the relevant administration disutilities, BTH event rates and transition probabilities for pegcetacoplan applied.

It should also be noted that patients who discontinue danicopan as an add-on to eculizumab or ravulizumab to pegcetacoplan may also subsequently discontinue to C5 inhibitor monotherapy in the economic model. The rate at which these patients discontinue is modelled from the rate of non-BTH related discontinuation events.

The updated company base case assumes that 60% of patients who discontinue danicopan as an add-on to eculizumab or ravulizumab subsequently receive pegcetacoplan, with the remaining patients receiving C5 inhibitor monotherapy, in line with clinical opinion. For completeness, a scenario is presented in Appendix A, whereby 50% of patients discontinue to pegcetacoplan and 50% of patients discontinue to C5 inhibitor monotherapy.

Both the updated company base case and the scenario analysis varying the proportion of patients discontinuing from danicopan to pegcetacoplan result in danicopan add-on treatment dominating pegcetacoplan.

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Appendix A: Updated company base case and scenario analyses

In recognition of the evaluation committee's preferences, analyses requested within the DGD have been conducted and are provided below in Table 10.

Alexion wish to provide an updated company base case which incorporates the following changes and assumptions:

- Transition probabilities and HSUVs for danicopan and placebo as an add-on to eculizumab and ravulizumab are informed by the IA3 data cut of the ALPHA trial
- Long-term BTH events rates for patients receiving pegcetacoplan derived from the Patriquin et al. 2024 publication[17]
- 53% of patients receiving pegcetacoplan will temporarily dose escalate for three cycles upon the event of BTH, derived from the de Latour et al. 2024 publication[21]
- The long-term (Year 1+) non-BTH discontinuation rate is constant at 0% in both treatment arms
- 60% of all patients who discontinue danicopan as an add-on to eculizumab or ravulizumab will receive pegcetacoplan; the remaining patients receiving eculizumab or ravulizumab monotherapy

The results of the updated company base case are presented in Table 10. In the deterministic analyses, danicopan as an add-on to eculizumab or ravulizumab was found to be a cost-effective use of NHS resources when compared to pegcetacoplan at a WTP threshold of £20,000–30,000/QALY. The resulting net health benefit (NHB) with danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan in the updated company base case is positive, with a value of [redacted] in the deterministic analysis.

Furthermore, danicopan as an add-on to eculizumab or ravulizumab remains dominant versus pegcetacoplan in all scenario analyses, which explored alternative rates of long-term BTH and dose escalations for patients receiving pegcetacoplan, alternative rates of long-term (Year 1+), non-BTH discontinuation rates and an alternative proportion of patients who discontinued danicopan as an add-on to eculizumab or ravulizumab to pegcetacoplan.

Table 10: Economic model results

Model update	Incremental costs	Incremental QALYs	ICER	Incremental NHB	% change from updated company base case
Updated company base case	[redacted]	0.423	Dominant	[redacted]	NA
Issue 2: Long-term rates of BTH					
Committee requested sources for BTH (Griffin et al. 2024 and Kulasekararaj et al. 2023)	[redacted]	0.394	Dominant	[redacted]	−10.68
Issue 3: Temporary dose escalation on pegcetacoplan					
100% of patients receiving pegcetacoplan temporarily dose escalate upon a BTH event	[redacted]	0.423	Dominant	[redacted]	−69.22
Issue 4: Long-term non-BTH discontinuation					
Sustained discontinuation in Year 1+ at 0.1% per cycle	[redacted]	0.339	Dominant	[redacted]	−36.69

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Sustained discontinuation in Year 1+ at 0.2% per cycle	[redacted]	0.388	Dominant	[redacted]	−52.43
Sustained discontinuation in Year 1+ at 0.4% per cycle	[redacted]	0.340	Dominant	[redacted]	−76.22
Sustained discontinuation in Year 1+ at 0.6% per cycle	[redacted]	0.296	Dominant	[redacted]	−87.50
Sustained discontinuation in Year 1+ at 0.8% per cycle	[redacted]	0.260	Dominant	[redacted]	−93.06
Sustained discontinuation in Year 1+ at 1% per cycle	[redacted]	0.232	Dominant	[redacted]	−95.90
Issue 5: Discontinuation of danicopan add-on treatment to pegcetacoplan					
50% of patients who discontinue danicopan add-on treatment receive pegcetacoplan	[redacted]	0.417	Dominant	[redacted]	+2.32

Abbreviations: BTH: breakthrough haemolysis; HSUV: health state utility value; IA3: interim analysis 3; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

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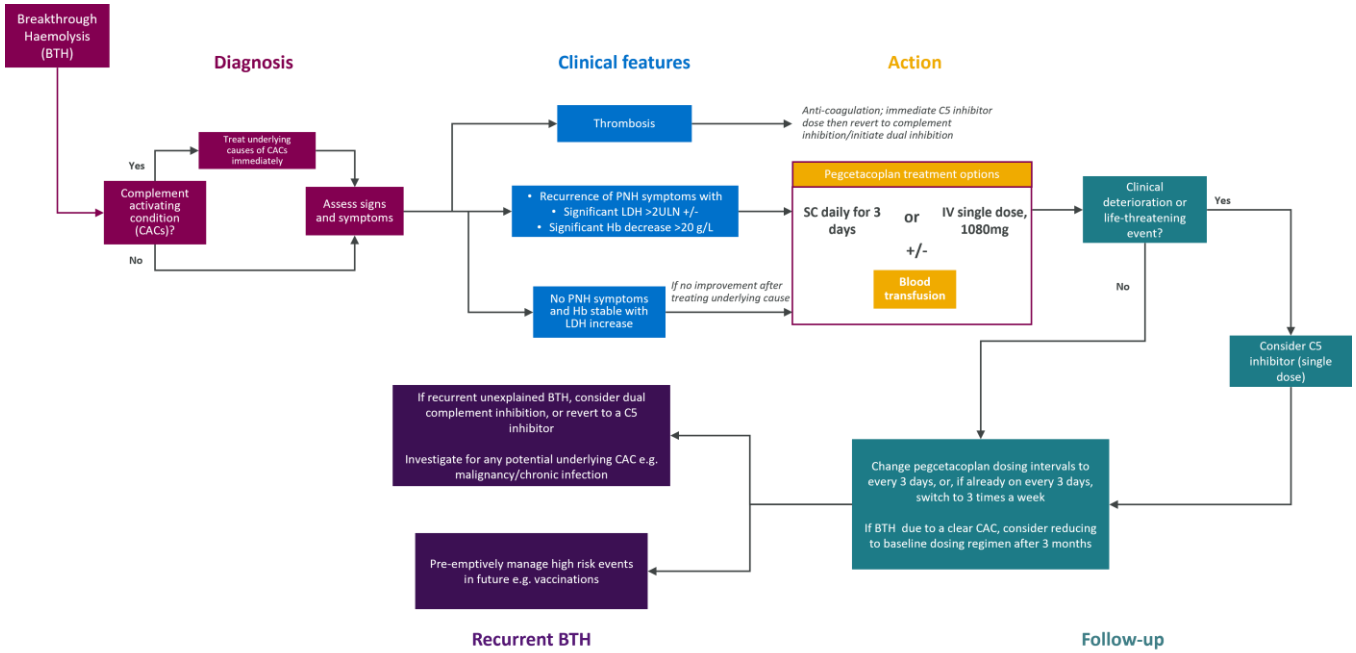
Appendix B: Management of BTH events in clinical practice

Figure 1 illustrates the management of BTH for patients receiving pegcetacoplan in clinical practice, informed by the Griffin 2024 real-world study.[18] The original flowchart for BTH management may be located in Figure 1, Page 6 of the publication.

Figure 1: Management flowchart for BTH in clinical practice



Abbreviations: BTH: breakthrough haemolysis; C5: complement component 5; CAC: complement amplifying condition; Hb: haemoglobin; LDH: lactate dehydrogenase; PNH: paroxysmal nocturnal haemoglobinuria; SC: subcutaneous; ULN: upper limit of normal.
Source: Griffin, et al. (2024).[18]

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	regarding such impacts and how they could be avoided or reduced**.**	
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Novartis Pharmaceuticals UK Limited	

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NICE National Institute for Health and Care Excellence

Danicopan with ravulizumab or eculizumab for treating paroxysmal nocturnal haemoglobinuria [ID5088]

Draft guidance comments form

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Name of commentator person completing form:	[redacted]	
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.	
1	With regards to appropriate comparators, we agree that staying on a C5 inhibitor would not address clinically significant extravascular haemolysis. However, both the appraisal of danicopan [ID5088; Draft guidance section 3.3] and the appraisal of iptacopan [ID6176; Final draft guidance section 3.2] have established that in UK clinical practice some people with residual anaemia on a C5 inhibitor may not switch to pegcetacoplan, and instead remain on a C5 inhibitor. In the NICE final draft guidance for iptacopan published on 17th May 2024 (after the danicopan NICE committee meeting was held on 7th May 2024), the committee concluded that ravulizumab and pegcetacoplan are the most relevant comparators for people with residual anaemia on C5 inhibitor treatment (Final draft guidance section 3.16). The conclusion in the danicopan draft guidance (section 3.3) that only pegcetacoplan is the appropriate comparator thus creates an inconsistency between appraisals for the same population.	
2	It may be helpful to clarify the company's modelling of pegcetacoplan: in particular, whether or not the impact of dose increases on pegcetacoplan efficacy is considered, rather than the impact on cost alone.	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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Danicopan with ravulizumab or eculizumab for treating paroxysmal nocturnal haemoglobinuria [ID5088]

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submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.

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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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External Assessment Group Response to Company Comments on Draft Guidance for danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria

Produced by	*Warwick Evidence*
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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.

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Contributions of authors
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In this document the EAG summarises and critiques the information submitted by the company in their comments on the draft guidance following the first appraisal committee meeting.

The company submitted a response to 5 key points raised the committee, have presented an updated economic model with additional specification and have also revised the assumptions making up the company base case analysis.

The EAG still has considerable concerns surrounding the suitability of the evidence for a comparison of danicopan + C5 inhibitors (C5i) to pegcetacoplan. The lack of direct comparison, small sample sizes and differences in underlying populations means any comparison is at very high risk of bias. This opinion is shared by a recent ICER report where all 13 panellists concluded the evidence is not adequate to demonstrate a benefit of danicopan + C5i over pegcetacoplan.[1]

Whilst pegcetacoplan is the most relevant clinical comparator, the evidence does not permit a robust comparison to be performed.

In this appraisal, the benefits of danicopan over pegcetacoplan in the company base case continue to come from a decreased BTH event rate and the lack of a treatment disutility compared with pegcetacoplan. The disutility is taken from TA778 where a disutility of 0.025 is applied annually to the patient utility to account for the intravenous eculizumab infusion given every two weeks.

In reviewing this information, the EAG has noticed a further important inconsistency between the current appraisal and the appraisal of pegcetacoplan (TA778). In this current appraisal of danicopan the same disutility is applied for eculizumab and pegcetacoplan, where the latter is administered 2-3 times/week by subcutaneous infusion and can be self-administered at home. In TA778, the disutility is only applied for eculizumab, with neither pegcetacoplan and ravulizumab incurring a disutility. In this current appraisal, the company justify applying the disutility for eculizumab and pegcetacoplan by citing the increased frequency of pegcetacoplan administration over ravulizumab. The EAG has major concerns about this inconsistency across appraisals and the lack of supporting evidence for this assumption of equivalence of eculizumab and pegcetacoplan and difference between pegcetacoplan and danicopan. The EAG does not rule out the possibility of a disutility being relevant, however the current approach appears flawed and so the EAG removes the disutility for pegcetacoplan from the EAG preferred assumptions.

This is in addition to the previously identified inconsistency regarding the dose-escalation for pegcetacoplan modelled by the company, which was not reflected in TA778.

The EAG now responds to each of the company's points in turn.

1. **Transition Probabilities and Utility Values from interim analysis 3 of ALPHA Trial**

As requested, the company provided transition probabilities estimated from the more recent interim analysis 3 (IA3), rather than from IA2 as previously submitted. As predicted by the EAG, substituting in the updated probabilities for the danicopan efficacy slightly reduces the total QALYs for danicopan. The company also updated the transition probabilities for C5i monotherapy, which applies to patients in the model when discontinuing their initial therapy. Whilst these are now more similar to the transition probabilities for the equivalent group from Hakimi et al., (PEGASUS) there is still considerable difference over the transitions for patients in the Hb ≥9.5 mg/dL health-state (Table 1), suggesting the populations may have important differences.

Overall the impact of the updated transition probabilities on the ICER is very minor.

Table 1: Comparison of transition probabilities for C5 inhibitors

Beginning Health State	Ending Health State		
	Source: ALPHA IA3		
	Hb <9.5 mg/dL	**Hb ≥9.5 mg/dL**	**Transfusion**
Hb <9.5 mg/dL	[redacted]	[redacted]	[redacted]
Hb ≥9.5 mg/dL	[redacted]	[redacted]	[redacted]
Transfusion	[redacted]	[redacted]	[redacted]
	Source: Hakimi et al (PEGASUS)		
	Hb <9.5 mg/dL	**Hb ≥9.5 mg/dL**	**Transfusion**
Hb <9.5 mg/dL	0.652	0.001	0.347
Hb ≥9.5 mg/dL	0.742	0.030	0.228
Transfusion	0.404	0.001	0.595

The company also presented updated utility values from IA3, which are slightly higher than for IA2 across all health-states (see Table 2). This could be attributable to attrition bias rather than the more recent values providing a more reliable estimate of health quality. The EAG were previously satisfied with the company's utility values and do not have any new concerns. The impact of the updated values has a very minor impact on the cost-effectiveness analyses.

Table 2: Comparison of utility values across ALPHA data-cuts

Health State	Interim Analysis 2	Interim Analysis 3
Low Hb	0.8181	0.8207
Moderate Hb	0.8644	0.8692
Transfusion	0.7018	0.7107

2. Long term rates of breakthrough haemolysis

Previously the company's modelling assumptions for long term breakthrough haemolysis (BTH) on either danicopan + C5i or pegcetacoplan resulted in markedly different rates. The per cycle rate for pegcetacoplan was over ten times than that for danicopan+C5i or C5i alone.

The company describe how the definitions of a BTH event differ across the ALPHA and PEGASUS trials, but that they were able to replicate the PEGASUS definition (lactate dehydrogenase (LDH) rise ≥ 2.0 x upper limit of normal (ULN)) when calculating the BTH rate from ALPHA.

The EAG accepts that the definitions of BTH have been aligned for the purposes of the economic model inputs, however is still concerned at underlying differences in the populations. Within the randomised period of the PEGASUS and ALPHA trials, the BTH events were experienced by 9 (23%) and 0 (0%) people on the respective C5i arms. This suggests that the populations have a different underlying risk of experiencing a BTH event and a naïve comparison is not appropriate.

The company presented newly identified sources to support their approach to modelling substantially different long term BTH rates. Due to time constraints, the EAG has not been able to verify the company's calculation of BTH rates from the alternative sources. The non-ALPHA source of information for BTH event rates for C5i, by Kulasekararaj et al. 2023,[2] is only a conference abstract and the EAG notes this work has not been peer-reviewed. In summary, the two new studies of pegcetacoplan[3, 4] show a higher BTH rate than studies of C5i. The EAG considers that sources may underestimate BTH event rates as these studies generally report the number of people rather than number of events, meaning repeat events are excluded. Demonstrating this difference, the Griffin et al.[4] reports 13 people experienced 32 BTH events. The Griffin study also includes one BTH event where the LDH rise was 1.8 x ULN, outside of the threshold mentioned by the company.

The EAG expects that the definitions and underlying risk of BTH are likely to vary further across these studies.

The EAG still considers there to be a lack of evidence of a long-term difference between danicopan+C5i and pegcetacoplan in BTH event rates. If dose escalation of pegcetacoplan (considered later) is appropriate and accurately modelled, then the EAG anticipates this should reduce the BTH rate for pegcetacoplan over time. This is supported by the reducing BTH rate across the studies identified by the company, whose BTH rates decrease as the length of study follow-up increases (Table 3).

Table 3: Company estimated BTH event rates for pegcetacoplan from other sources

Study	Population	People experiencing BTH events	Length of Follow-up	Company Derivation
Latour (post randomisation PEGASUS)	Pegcetacoplan	15 / 77	32 weeks	2.67% / 4 weeks
Patriquin (OLE PEGASUS and other studies)	Pegcetacoplan	23 / 137	48 weeks	2.04% / 4 weeks
Griffin (UK/France trial/RWE)	Pegcetacoplan	13 / 48	20.2 months	1.55% / 4 weeks

Hence, the EAG considers it plausible that the BTH rates across pegcetacoplan and danicopan+C5i may begin to converge over time.

Whilst the BTH rate may be expected to be lower for danicopan+C5i than pegcetacoplan, there remains no reliable estimate of relative effect on this parameter which is highly influential on the cost-effectiveness analyses. For the EAG preferred assumptions, the EAG set the long term BTH rate for pegcetacoplan to be twice the rate for danicopan + C5i used by the company in the model from 25 weeks (as the long-term rate is defined in the model). This works out at 2 x 0.24% = 0.48% per 4 week cycle, and is based on the assumption that the rates will become more similar over time but maintains a benefit for danicopan. Applying from 25 weeks may be slightly earlier than occurs in practice, however the EAG does not anticipate the difference is to remain high long into the [redacted] year model time horizon, especially considering that if dose escalations are not providing sufficient control for a patient, then returning to C5i may be preferred, with discontinuation modelled separately.

3. Management of Breakthrough Haemolysis.

In their original submission, the company assumed that every BTH event that occurred whilst on pegcetacoplan resulted in a permanent dose escalation of pegcetacoplan, which led to people moving from the starting dose (2/week), to every 3 days, and eventually to 3/week. This is shown in

Figure *1*.

Figure 1: Company dose escalation for pegcetacoplan from original company base case.

In response to the committee's comments, the company describes how there are two kinds of BTH events: pharmacodynamic and pharmacokinetic where the former is managed with a temporary dose uplift, whilst the latter is managed with a permanent dose uplift.

The company then cites a BTH management plan by Griffin et al.[4] to support their modelling of dose escalation. The EAG accepts some escalation is expected, however the company fail to consider the possibility of BTH events being observed without any dose escalation, which is a possibility according to the management plan, and evidenced by the Griffin data discussed below.

Based on a paper published by de Latour et al. the company presents a new base case analysis which assumes that 53% of BTH events incur a temporary dose increase, rather than a permanent one which is modelled through a series of tunnel states.[5] This aligned with views from their clinical experts who state around 50% of patients would have a temporary dose escalation. It is not clear why or how the de Latour study was used as the basis for the company's analysis. De Latour presented results of 26 haemolysis events from 19 patients, with 19 events having LDH ≥ 2 x ULN. 13 patients had their dose escalated, however only 6 of these were reported to demonstrate a benefit from the escalated dose. The EAG is not clear how the company has obtained the percentage of 53% which it has implemented in its modelling. The relates to 10 of 19 patients (or alternatively 9 out of 19), however the only statistic matching this proportion the EAG can find relates to dosing of eculizumab and appears irrelevant.

In

Figure 2, the EAG presents the equivalent figure for the company's new base case. This shows the impact of the company's changes have had a small impact on the resulting modelled doses, with the majority of people receiving pegcetacoplan receiving the maximum dose from being on three doses before [redacted].

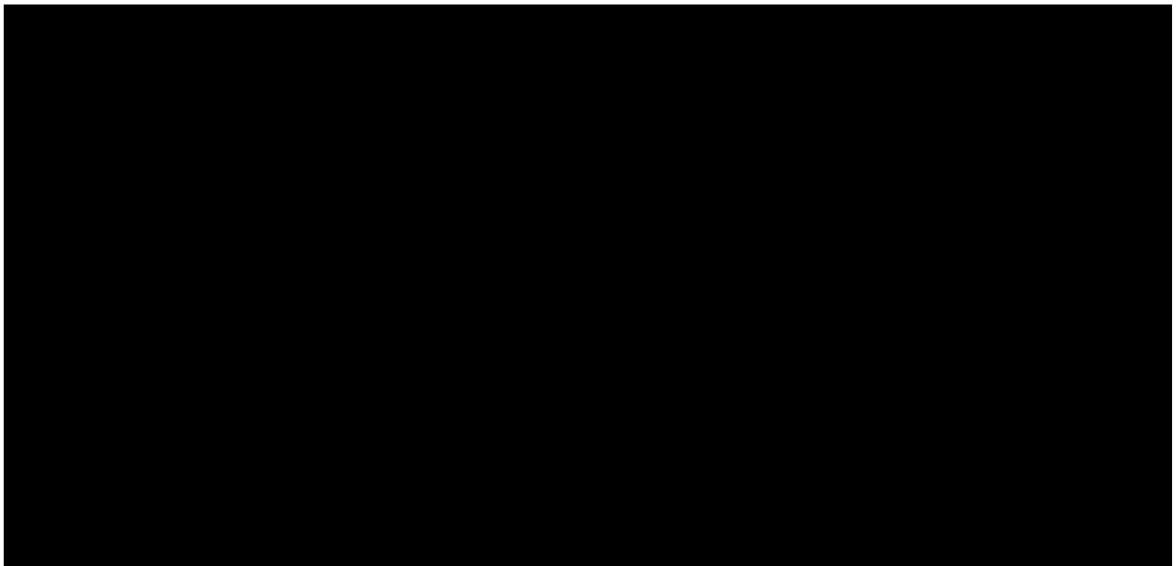

Figure 2: Company dose escalation for pegcetacoplan from new company base case.

The EAG notes that the Griffin et al.[4] study reports management details for 18 BTH events that were not managed within clinical trials. Four events resulted in permanent dose increases, with three of these also having temporary dose increase. Six others only had temporary dose increases. Eight had no changes to their pegcetacoplan dosing. Hence, the EAG concludes that the company's modelling of BTH-related dose escalation to be unsupported by the literature.

Furthermore, the EAG considers the company's combined modelling of dose-escalation and BTH event rates to be inconsistent, as the average dosing for pegcetacoplan increases over time, whilst BTH event rate remains constant.

Within the economic model, BTH events for pegcetacoplan result in either a temporary or permanent dose escalation, with no option for no dose escalation. Hence the EAG preferred analysis applies 14/18 (78%) as a temporary dose escalation for pegcetacoplan BTH events based on data from Griffin et al., however the EAG considers this could still substantially overestimate treatment costs for pegcetacoplan as the BTH event rate does not reduce over time, and the modelling does not account for events with no dose escalation. The impact on the dosing of this change alone is shown in Figure 3. The EAG show it combined with their preferred BTH event rate and discontinuation rate for pegcetacoplan in

Figure ***4***.

Figure 3: EAG preferred dose escalation

Figure 4: EAG preferred dose escalation combined with EAG preferred BTH event rate and discontinuation rate

4. **<u>Long term treatment discontinuation unrelated to breakthrough haemolysis.</u>**

In defence of the previous and current base-case assumption of no discontinuation of pegcetacoplan or danicopan after 1 year of therapy for non-BTH reasons, the company report results from Patriquin et al.[3] where there were no discontinuations in the open label extension of PEGASUS. The EAG notes this study only provides information for up to 48 weeks of follow-up, and so caution should be taken when extrapolating for the full model time-horizon (48 years).

As highlighted by the company, further data for is available for discontinuation long-term therapy for C5i. The EAG has been unable to verify the calculation of these rates, but the company state that follow-up from studies 301 and 302 produces estimates of annual discontinuation rates of 1.10% and 1.77%.[2, 6] Whilst discontinuation is likely linked to the specific treatment being received and the availability of alternative therapies, these outputs suggest that applying a zero long term rate is implausible.

The company is critical of any rate of discontinuation being applied, stating it would be arbitrary, however the EAG understand that the company's modelling basis of zero events can be considered equally arbitrary.

The EAG preference is to apply a 0.1% cycle (1.29% annual) discontinuation rate to both danicopan+C5i and pegcetacoplan, reflecting similarity to the long-term follow-up from studies 301 and 302.

5. **Subsequent treatment following discontinuation.**

In the original company base case, the company assumed that all patients discontinuing danicopan would switch and receive C5i, as was assumed for pegcetacoplan. The EAG questioned why patients for whom C5i therapy was ineffective and thus are eligible for danicopan+C5i, would then revert back to C5i therapy when pegcetacoplan was also available.

The company conducted interviews to gauge clinical expert opinion on this matter. One expert stated that it would depend whether a patient had received prior pegcetacoplan. The EAG agrees, and presumes that almost all pegcetacoplan naïve patients would then move to pegcetacoplan. However, for those who have received pegcetacoplan and have also received C5i, the path is less clear. The EAG is unsure whether retreatment with pegcetacoplan would be permitted in the NHS.

Based on further expert elicitation the company report that they estimate 60% of people who discontinue danicopan+C5i will switch to pegcetacoplan, which is used in their base case. The EAG welcomes this improvement, however considers this parameter to be highly uncertain and explores alternative values.

Cost-effectiveness results

The EAG has reproduced the company's original and new base case analyses in Table 4 and Table 5 respectively.

Table 4: Original Company Base Case

Intervention	Total Costs	Total LY	Total QALY	Inc' Costs	Inc' QALY	ICER	Inc' NHB @ 30k/QALY
Danicopan + C5i[a]	[redacted]	17.86	14.21				
Pegcetacoplan	£7,711,022	17.86	13.78	[redacted]	0.429	Dominant	[redacted]

Table 5: New Company Base Case

Intervention	Total Costs	Total LY	Total QALY	Inc' Costs	Inc' QALY	ICER	Inc' NHB @ 30k/QALY
Danicopan + C5i[a]	[redacted]	18.478	14.758				
Pegcetacoplan	£7,436,252	18.478	14.335	[redacted]	0.423	Dominant	[redacted]

The EAG notes a change in the total life-years associated with both arms. This is down to a change in the company's starting age in the economic model from [redacted] to [redacted]. From inspection of the CSR, the new starting age reflects the age of the interim safety population which is the more complete trial population, whilst the previously used and accepted starting age is from the interim efficacy population. The EAG presents the new company base case analysis removing the age change in Table 6. The incremental costs and benefits both reduce as a result.

Table 6: New Company Base Case without starting age change

Intervention	Total Costs	Total LY	Total QALY	Inc' Costs	Inc' QALY	ICER	Inc' NHB
Danicopan + C5i[a]	[redacted]	17.864	14.280				
Pegcetacoplan	£7,163,441	17.864	13.870	[redacted]	0.410	Dominant	[redacted]

The company conducted a series of alternative scenarios building on their base-case assumptions, and the EAG can confirm it has been able to replicate each one using the economic model.

The following section presents analyses conducted by the EAG.

In Table 7 are results from analyses using the company's base case assumptions, but comparing each of danicopan+C5i and pegcetacoplan to C5i. This is achieved by starting all patients in the alternative arm of the model in the switched-to-C5i group. The EAG is not able to establish why there is a minor disagreement between the QALYs in the C5i arms, however this is unlikely to be consequential in this appraisal.

More importantly, the results in Table 7 demonstrate the inconsistency between the assumptions and conclusions across appraisals. The EAG recommends caution when using a reference treatment that is potentially not cost-effective under current implementation.

In Table 8 are the EAG's preferred assumptions if a comparison to pegcetacoplan is still preferred by the committee. Table 9 contains analyses building on the combined EAG preferred assumptions which explore the modelling uncertainty. Probabilistic results of the EAG preferred assumptions showed close similarity to the deterministic results (**Table 10**).

Table 7: Analyses comparing Danicopan and Pegcetacoplan to C5i using Company Base Case Assumptions

Assumptions	Intervention	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	Incremental NHB @ 30k/QALY
Company Base Case	Danicopan + C5i	[redacted]	[redacted]				
	C5i	[redacted]	[redacted]	[redacted]	[redacted]	£496,643	[redacted]
Company Base Case	Pegcetacoplan	[redacted]	[redacted]				
	C5i	[redacted]	[redacted]	[redacted]	[redacted]	£5,074,696	[redacted]

Table 8: Impact of EAG preferred analyses

EAG change to company base case	Intervention	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	Incremental NHB @ 30k/QALY
New Company Base Case	Danicopan + C5i	[redacted]	14.758				
	Pegcetacoplan	£7,436,252	14.335	[redacted]	0.423	Dominant	[redacted]
1. Set long term BTH rate for pegcetacoplan to double danicopan rate	Danicopan + C5i	[redacted]	14.767				
	C5i	£6,422,214	14.434	[redacted]	0.333	Dominant	[redacted]
2. Set 78% of pegcetacoplan dose escalations to be temporary	Danicopan + C5i	[redacted]	14.758				
	Pegcetacoplan	£6,980,064	14.335	[redacted]	0.423	Dominant	[redacted]
3. Apply 0.1%/cycle discontinuation rate for non-BTH events to both arms	Danicopan + C5i	[redacted]	14.665				
	Pegcetacoplan	£6,963,499	14.256	[redacted]	0.409	Dominant	[redacted]
4. Removal of pegcetacoplan disutility	Danicopan + C5i	[redacted]	14.793				[redacted]
	Pegcetacoplan	£7,436,252	14.746	[redacted]	0.047	Dominant	[redacted]

5. 1-4 combined	Danicopan + C5i	[redacted]	14.739				
	Pegcetacoplan	£5,932,322	14.692	[redacted]	0.048	Dominant	[redacted]
6. 1-3 combined	Danicopan + C5i	[redacted]	14.680				
	Pegcetacoplan	£5,932,322	14.340	[redacted]	0.340	Dominant	[redacted]

Table 9: Additional EAG analyses

Change from EAG preferred assumptions	Intervention	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	Incremental NHB
EAG preferred assumptions (1-4)	Danicopan + C5i	[redacted]	14.739				
	Pegcetacoplan	£5,932,322	14.692	[redacted]	0.048	Dominant	[redacted]
Set long term BTH rate for pegcetacoplan equal to danicopan	Danicopan + C5i	[redacted]	14.742				
	C5i	£5,809,783	14.704	[redacted]	0.037	Dominant	[redacted]
Set long term BTH rate for pegcetacoplan to triple danicopan rate	Danicopan + C5i	[redacted]	14.737				
	Pegcetacoplan	£6,056,316	14.679	[redacted]	0.058	Dominant	[redacted]
Set BTH dose escalation temporary to 70%	Danicopan + C5i	[redacted]	14.739				
	Pegcetacoplan	£5,998,289	14.692	[redacted]	0.048	Dominant	[redacted]
Set BTH dose escalation temporary to 90%	Danicopan + C5i	[redacted]	14.739				
	Pegcetacoplan	£5,822,411	14.692	[redacted]	0.048	Dominant	[redacted]
	Danicopan + C5i	[redacted]	14.739				

Set BTH dose escalation temporary to 95%	Pegcetacoplan	£5,772,272	14.692	[redacted]	0.048	Dominant	[redacted]
Change discontinuation rate on both arms to 0.05% per cycle	Danicopan + C5i	[redacted]	14.771				
	Pegcetacoplan	£6,046,409	14.763	[redacted]	0.009	Dominant	[redacted]
Change discontinuation rate on both arms to 0.15% per cycle	Danicopan + C5i	[redacted]	14.707				
	Pegcetacoplan	£5,832,765	14.629	[redacted]	0.077	Dominant	[redacted]
Change danicopan discontinuation to 50% pegcetacoplan	Danicopan + C5i	[redacted]	14.716				
	Pegcetacoplan	£5,932,322	14.692	[redacted]	0.024	Dominant	[redacted]
Change danicopan discontinuation to 70% pegcetacoplan	Danicopan + C5i	[redacted]	14.763				
	Pegcetacoplan	£5,932,322	14.692	[redacted]	0.072	Dominant	[redacted]
Change danicopan discontinuation to 80% pegcetacoplan	Danicopan + C5i	[redacted]	14.787				
	Pegcetacoplan	£5,932,322	14.692	[redacted]	0.096	Dominant	[redacted]

Table 10: EAG Preferred Assumptions Probabilistic Sensitivity Analysis.

	Intervention	**Total costs**	**Total QALYs**	**Incremental Costs**	**Incremental QALYs**	**ICER**	**Incremental NHB**
EAG preferred assumptions PSA	Danicopan + C5i	[redacted]	14.805				
	Pegcetacoplan	£5,900,627	14.745	[redacted]	0.060	Dominant	[redacted]

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Change from EAG preferred assumptions	Intervention	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	Incremental NHB @ 30k/QALY
EAG preferred assumptions at AC2	Danicopan + C5i	[redacted]	14.739				
	Pegcetacoplan	£5,932,322	14.692	[redacted]	0.048	Dominant	[redacted]
1) adjust temporary escalation to 72%	Danicopan + C5i	[redacted]	14.739				
	C5i	£5,982,302	14.692	[redacted]	0.048	Dominant	[redacted]
2) (1) + 10% annual Peg BTH event rate [0.808% per cycle]	Danicopan + C5i	[redacted]	14.736				
	Pegcetacoplan	£6,176,283	14.674	[redacted]	0.062	Dominant	[redacted]
3) (1) + 14% annual Peg BTH event rate [1.154% per cycle]	Danicopan + C5i	[redacted]	14.733				
	Pegcetacoplan	£6,357,126	14.656	[redacted]	0.077	Dominant	[redacted]
4) (1) + 18% annual Peg BTH event rate [1.515% per cycle]	Danicopan + C5i	[redacted]	14.730				
	Pegcetacoplan	£6,516,267	14.637	[redacted]	0.093	Dominant	[redacted]
PSA of (4)	Danicopan + C5i	[redacted]	14.856				
	Pegcetacoplan	£6,504,709	14.752	[redacted]	0.104	Dominant	[redacted]