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

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Contents:
The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Alexion Pharma UK

2. **Company summary of information for patients (SIP)** from Alexion Pharma UK

3. **Clarification questions and company responses**

4. **Patient group, professional group and NHS organisation submissions** from:
   a. PNH Support
   b. PNH National Service
   c. NHS England

5. **Expert personal perspectives** from:
   a. Kate Monan – patient expert, nominated by PNH Support
   b. Maria Piggin, Chair of PNH Support – patient expert, nominated by PNH Support
   c. Dr Talha Munir, Consultant Haematologist – clinical expert, nominated by Alexion Pharma UK
      i. Part 1
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   d. Dr Richard Kelly, Consultant Haematologist – clinical expert, nominated by National PNH Service

6. **External Assessment Report** prepared by Warwick Evidence Review Group

7. **External Assessment Report – factual accuracy check**

8. **Company submission addendum**

9. **External Assessment Report addendum** prepared by Warwick Evidence Review Group

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria

ID5088

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
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Abbreviations

Abbreviation	Definition
ADA	Antidrug antibodies
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ARC	Absolute reticulocyte count
AST	Aspartate aminotransferase
BMI	Body mass index
BNF	British National Formulary
BTH	Breakthrough haemolysis
C3	Complement component 3
C5	Complement component 5
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trails
COVID-19	Coronavirus disease
csEVH	Clinically significant extravascular haemolysis
CSR	Clinical study report
DAN	Danicopan
DCO	Data cut-off
DSA	Deterministic sensitvity analyses
EAG	External assessment group
ECDRP	European Commission Decision Reliance Procedure
ECU	Eculizumab
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	EuroQol 5-dimensions
ESS	Effective sample size
EVH	Extravascular haemolysis
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FAS	Full analysis set
GLM	Generalised linear model
GP	General practitioner
GPI	Glycosylphosphatidylinositol
Hb	Haemoglobin
HCRU	Healthcare resource utilisation
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life

HSC	Haematopoetic stem cells
HSCT	Haematopoietic stem cell transplantation
HSUV	Health state utility value
IAS	Interim efficacy analysis set
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient level data
IRT	Interactive response technology
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IVH	Intravascular haemolysis
LDH	Lactate dehydrogenase
LS	Least squares
LTE	Long-term extension
MAC	Membrane attack complex
MAIC	Matching-adjusted indirect comparison
MAR	Missing-at-random
MHRA	Medicines and Healthcare Regulatory Agency
MMRM	Mixed model for repeated measures
N/A	Not applicable
NCGC	National Clinical Guideline Centre
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NR	Not reported
OS	Overall survival
PAS	Patient Access Scheme
PBO	Placebo
PD	Pharmacodynamic
PIG	Phosphatidylinositol glycan
PKAS	Pharmacokinetic analysis set
PNH	Paroxysmal nocturnal haemoglobinuria
PPS	Per-protocol set
PRISMA	Preferred Reporting Items for Systematic Literature Review and Meta-Analyses
PRO	Patient-reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RAV	Ravulizumab

RBC	Red blood cell
RCT	Randomised clinical trial
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SCHAAR	Sheffield Centre for Health and Related Research
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TID	Three times daily
TP1	Treatment period 1
TP2	Treatment period 2
TSD	Technical Support Document
ULN	Upper limit of normal
WPAI:ANS	Work Productivity and Activity Impairment Questionnaire: Anaemic Symptoms
WTP	Willingness-to-pay

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

B.1.1 *Decision problem*

The objective of this evaluation is to determine the clinical and cost-effectiveness of danicopan as an add-on to a complement component 5 (C5) inhibitor (eculizumab or ravulizumab) within its full marketing authorisation:

[redacted]

The decision problem addressed within this submission is broadly consistent with the National Institute of Health and Care Excellence (NICE) final scope for this appraisal, and any differences between the decision problem addressed within this submission and the NICE final scope are outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with paroxysmal nocturnal haemoglobinuria who have signs and symptoms of extravascular haemolysis while on treatment with a C5 inhibitor (eculizumab or ravulizumab).	Adult patients with PNH who have csEVH while on treatment with a C5 inhibitor (eculizumab or ravulizumab).	The population is in line with the final NICE scope, however, further detail is provided as follows. Some patients with PNH treated with C5 inhibitors will experience EVH to a varying degree. A subgroup of these patients will require treatment for their symptoms; these patients are defined as having csEVH. Published literature indicates that around 10–20% of patients develop csEVH.[1, 2] Clinical experts in the United Kingdom (UK) consulted at an advisory board estimated the prevalence of csEVH to be approximately 30%.[3, 4] Clinical experts noted that csEVH has no standardised definition and is evaluated based on a range of parameters in clinical practice, including anaemia, need for blood transfusions, bilirubin and reticulocyte levels, as well as patient-reported fatigue and impact on HRQoL.[4]
Intervention	Danicopan as an add-on treatment to a C5 inhibitor (eculizumab or ravulizumab).	Danicopan as an add-on to a C5 inhibitor (eculizumab or ravulizumab)	N/A
Comparator(s)	• Pegcetacoplan • Eculizumab • Ravulizumab • Iptacopan (subject to NICE ongoing appraisal)	Pegcetacoplan	At present, pegcetacoplan is the only therapy recommended by NICE for the treatment of PNH patients with uncontrolled anaemia after treatment with a C5 inhibitor.[5] CsEVH is characterised by persistent residual anaemia and its accompanying symptoms following C5 inhibitor treatment.[6-9] As such, pegcetacoplan is a relevant comparator in the indication under consideration in this evaluation.

			Eculizumab and ravulizumab are licensed for the treatment of PNH in patients who experience haemolysis with clinical symptoms indicative of high disease activity.[10, 11] They are administered to address intravascular haemolysis (IVH), the lysis of red blood cells (RBCs) within blood vessels, which is the underlying cause of morbidity and mortality in PNH; uncontrolled IVH results in thrombosis which is the leading cause of death in PNH.[12] Eculizumab and ravulizumab reduce IVH by inhibiting C5 and consequently the terminal complement pathway.[10, 11] By reducing IVH, eculizumab and ravulizumab therefore reduce the risk of thromboembolic events and death. The manifestation of EVH, the destruction of RBCs in the liver and spleen, subsequently only becomes apparent upon terminal complement inhibition by C5 inhibitors.[13] In the setting of treatment with C5 inhibitors, PNH RBCs are no longer subject to IVH, but instead may become opsonised (marked for destruction) with C3 fragments, making them susceptible to destruction in the liver or spleen (EVH).[6, 14] Accordingly, eculizumab and ravulizumab do not address EVH and are not licensed nor recommended in UK clinical practice for the treatment of csEVH, and therefore are not considered as relevant comparators for the evaluation of danicopan. Further details of the pathogenesis of PNH, including the different complement pathways, are provided in Section B.1.3.1 of Document B. Iptacopan has not been included as a comparator as it has not received a positive recommendation from

			NICE at the time of submission, and final publication of NICE guidance is not expected until mid-2024.[15] Accordingly, iptacopan is not considered established practice for the treatment of csEVH in the NHS.
Outcomes	• Overall survival (OS) • Intravascular haemolysis • EVH • Breakthrough haemolysis (BTH) • Transfusion avoidance • Haemoglobin • Thrombotic events • Adverse effects (AEs) of treatment • HRQoL	• IVH • EVH • BTH • Transfusion avoidance • Haemoglobin • Thrombotic events • AEs of treatment • HRQoL	As described above, when haemolysis of RBCs occurs inside blood vessels, it is known as IVH.[16] Complement-mediated IVH is the main contributor to morbidity and mortality associated with PNH, and leads to symptoms such as fatigue, anaemia, and haemoglobinuria, and can be life-threatening.[12, 17-22] However, the development of C5 inhibitors has led to the control of IVH, and thus control of the occurrence of life-threatening events.[22] The indication of focus for this evaluation is patients with csEVH following treatment with a C5 inhibitor. Accordingly, IVH is not considered a key outcome of interest for this decision problem. The effectiveness of C5 inhibitors in managing IVH has been established in prior clinical trials.[23, 24] Nevertheless, data on lactate dehydrogenase (LDH) levels, which are indicative of RBC destruction and IVH, are presented for completion.[25] Similarly, OS is not considered a key outcome for this decision problem since life-threatening symptoms of IVH are controlled by C5 inhibitors.[22] Furthermore, EVH is not life-threatening to patients and does not impact survival outcomes of patients.[25, 26] The incidence of death is therefore only reported as safety data for danicopan in the ALPHA trial.[27]

			The occurrence of csEVH is captured through haemoglobin levels and the requirement for blood transfusions in the ALPHA trial.[16] Finally, data on BTH and thrombotic events are available in the AE reporting of the ALPHA trial. BTH was determined by the investigator's clinical judgement.[27] As discussed in Section B.1.3.1 of Document B, BTH is the phenomenon whereby sustained control of IVH is suboptimal; the maintenance of IVH control alongside treatment of EVH as part of PNH patients' care is extremely important.[4]
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 (QALY) • 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 a National Health Service (NHS) and Personal Social Services (PSS) perspective • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	As per the NICE final scope	N/A

Abbreviations: AE: adverse event; BTH: breakthrough haemolysis; C5: complement component 5; csEVH: clinically significant EVH; EVH: extravascular haemolysis; HRQoL: health-related quality of life; IVH: intravascular haemolysis; LDH: lactate dehydrogenase; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PNH: paroxysmal nocturnal haemoglobinuria; QALY: quality-adjusted life year; RBC: red blood cell; UK: United Kingdom.

B.1.2 *Description of the technology being evaluated*

A summary of the mechanism of action, indication, administration requirements and costs associated with danicopan is provided in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Danicopan (Voydeya™)
Mechanism of action	Danicopan (ALXN2040) is an investigational, oral factor D inhibitor in development as an add-on to C5 inhibitor therapy (eculizumab or ravulizumab) for patients with PNH who experience csEVH.[28] Danicopan selectively inhibits factor D, a complement system protein that plays a key role in the amplification of the complement system response in the alternative pathway.[28, 29] The inhibition of this complement amplification-loop leads to a reduction in the production of C3 cleavage products (C3 fragments) and C3-mediated EVH.[12,] The complement system forms part of the body's innate immune system, comprising over 30 proteins in the plasma, and is essential for the destruction and removal of pathogens from the body.[30-32] In the presence of pathogens, complement proteins are activated sequentially in a cascade of enzymatic reactions, leading to the opsonisation of pathogens and formation of the membrane attack complex (MAC), and the subsequent destruction of pathogens by phagocytes.[32] However, uncontrolled activation of the complement system, which underlies the pathogenesis of PNH, can lead to the damage of healthy cells.[30-32] In PNH, a somatic mutation in the phosphatidylinositol glycan class A (*PIG-A)* gene results in the production of abnormal blood cells that are deficient in the cell surface complement regulatory proteins CD55 and CD59, which protect blood cells against uncontrolled complement-mediated lysis.[33, 34] • A deficiency of CD59 causes the uncontrolled cleavage of C5 proteins into C5 fragments and subsequently the formation of the MAC on affected blood cells. The MAC then causes the lysis and death of circulating blood cells, such as RBCs, leading to IVH (Figure 1).[12, 35, 36] This represents the predominant mechanism of destruction of PNH cells among patients with untreated PNH. • A deficiency of CD55 causes the uncontrolled activation of the C3 convertase, and C3 proteins are cleaved into C3 fragments which bind to affected blood cells. Macrophages in the spleen and liver then recognise and destroy these blood cells, such as RBCs, leading to the occurrence of EVH (Figure 1).[12, 37] In the absence of C5 inhibition, PNH RBCs are predominantly destroyed by uncontrolled IVH. Therefore it is only following C5 inhibitor treatment that PNH RBCs survive long enough to become opsonised by C3 fragments and are subject to destruction in the liver and spleen, leading to csEVH.

	The mechanism of action of danicopan addresses EVH through binding to factor D to prevent the cleavage of factor B, thereby inhibiting the synthesis of C3 convertase, and consequently, the formation of C3 fragments that lead to opsonisation of PNH cells and subsequent EVH.[29, 38] The proximal inhibition of the alternative complement pathway with danicopan also impairs terminal (C5) complement activation, providing maximum protection from BTH. Furthermore, by targeting factor D, danicopan selectively inhibits the alternative pathway, allowing the classical and lectin pathways to remain undisrupted to respond to infections (Figure 1).[38, 39]
Marketing authorisation/CE mark status	A marketing authorisation application was submitted to the European Medicines Agency (EMA) in [redacted] with licence anticipated to be granted in [redacted]. [redacted]
Indications and any restriction(s) as described in the SmPC	The anticipated UK marketing authorisation wording for danicopan (subject to approval) is "[redacted]" **Contraindications** Danicopan should not be initiated for those patients who have: • Unresolved *Neisseria meningitidis* infection • An unknown history of vaccination or who are not up to date on their meningococcal vaccines as per local guidelines, unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination Full details on contraindications may be found in Section 4.3 of the draft Summary of Product Characteristics (SmPC).[40]
Method of administration and dosage	The starting dose of danicopan is 150 mg, administered orally three times daily (TID), approximately 8 hours apart (±2 hours). Depending on clinical response, the dose can be increased to 200 mg TID. Treatment with danicopan is recommended to continue for a patient's lifetime, unless the discontinuation of danicopan is clinically indicated.[40]
Additional tests or investigations	Liver enzyme tests may be conducted prior to starting treatment to assess the patient's liver function. Following treatment initiation, routine chemistry laboratory monitoring as per PNH standard of care is recommended.[40]
List price and average cost of a course of treatment	The list price of danicopan is [redacted]
Patient access scheme (if applicable)	N/A

Abbreviations: CE: Conformité Européene; C3: complement component 3; csEVH: clinically significant EVH; EMA: European Medicines Agency; EVH: extravascular haemolysis; IRP: International Recognition Procedure; MHRA: Medicines and Healthcare products Regulatory Agency; N/A: not applicable; PNH: paroxysmal nocturnal haemoglobinuria; RBC: red blood cell; SmPC: summary of product characteristics; TID: three times daily; UK: United Kingdom.

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

Overview of PNH

- PNH is an extremely rare and life-threatening blood disorder, characterised by uncontrolled activation of the terminal complement system, which leads to IVH, the underlying cause of morbidity and mortality in PNH.[6, 12, 22, 41]
- IVH is characterised by the destruction of blood cells inside blood vessels, and is associated with a high risk of life-threatening complications such as thrombosis, chronic kidney disease and renal failure.[13, 42] IVH is also associated with symptoms such as anaemia, fatigue, dyspnoea, haemoglobinuria, erectile dysfunction, abdominal pain, chest pain and dysphagia.[17-21]
- EVH is a mechanistic consequence of treatment with C5 inhibitors, and is characterised by the destruction of blood cells in the liver, spleen, bone marrow and lymph nodes.[12, 16, 43] Following treatment with C5 inhibitors, defective PNH RBCs are no longer destroyed via IVH; the RBCs that are no longer subject to lysis may become opsonised with C3 fragments, making them susceptible to EVH through phagocytosis (RBCs are engulfed by white blood cells) in the liver or spleen.[6, 14]
- EVH becomes clinically significant in a subgroup of patients with EVH, manifesting as persistent anaemia and often dependence on blood transfusions, in addition to other debilitating symptoms.[14] This subset of patients therefore require treatment. Fatigue is reported in high proportions of patients treated with C5 inhibitors; the substantial decrement on HRQoL as a result of fatigue has been highlighted in both the published literature and through clinical expert opinion.[2, 4, 44]
    - As noted above, the debilitating symptoms experienced due to PNH lead to a substantial decrement in patient HRQoL. Approximately 76% of patients with PNH who took part in a 2007 multi-national study were patients who required to modify their normal daily activities to manage disease symptoms.[45] While C5 inhibitor treatment has improved outcomes for PNH patients, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) global health scores indicate that C5 inhibitor treated patients have a lower HRQoL score (62.9–68.7) than the general population (75.0).[44]
- PNH has a predicted prevalence in the UK of approximately 1 in 62,000. The UK National PNH service reported that there were 926 individuals in England living with the condition in 2022.[3] In UK clinical practice, the standard of care treatment for PNH, and therefore IVH, is C5 inhibition with ravulizumab or eculizumab; see Section B.1.3.3 below).[46] However, according to the PNH National Service, only approximately 30.35% of patients with PNH receive complement inhibition in England, excluding those enrolled in clinical trials.[3]
- For those patients receiving C5 inhibitor treatment, it is estimated in the literature that around 10–20% patients will subsequently experience csEVH.[1, 2] Clinicians consulted as part of a UK advisory board noted this proportion may be closer to approximately 30%.[2, 4]

Treatment pathway

- Current first-line treatment for PNH in UK clinical practice is the administration of C5 inhibitors, eculizumab or ravulizumab, which prevent IVH through terminal complement inhibition.[10, 47]
    - Eculizumab is available through the NHS Highly Specialised Service and ravulizumab was recommended for use by NICE in 2021 [TA698].[11, 46, 48] Based on Alexion's sales data which were validated by UK clinical experts, the proportions of patients receiving eculizumab and ravulizumab are approximately [redacted] and [redacted], respectively.[49, 50]
    - Pegcetacoplan is recommended by NICE for patients with PNH who remain anaemic after at least three months of treatment with a C5 inhibitor [TA778].[5, 51] Pegcetacoplan is a C3 inhibitor, addressing both IVH and EVH through inhibition of the alternative and classical pathways in the complement system.[47, 51, 52]

Unmet need and danicopan

- Around 30% of patients receiving C5 inhibitor treatment experience the emergence of csEVH, confirmed by UK clinical experts in PNH consulted during an advisory board.[4] Pegcetacoplan is the only available treatment for patients who remain anaemic following treatment with eculizumab or ravulizumab. However, as pegcetacoplan is a monotherapy, after an initial 4-week overlap period, patients must discontinue treatment with eculizumab or ravulizumab to continue receiving pegcetacoplan. Due to the lack of sustained control of IVH in some patients treated with pegcetacoplan, they may experience severe BTH (LDH levels up to 10–15 times the upper limit of normal [ULN]), whereas BTH with LDH levels >5 times the ULN are rare with eculizumab or ravulizumab.[53]
- Danicopan is an oral, first in class, small molecule factor D inhibitor positioned as an alternative treatment to pegcetacoplan and designed as an add-on therapy to eculizumab or ravulizumab, specifically addressing EVH through the inhibition of the alternative pathway, whilst maintaining control of IVH.[40]

B.1.3.1 Paroxysmal nocturnal haemoglobinuria

Overview of PNH

PNH is an extremely rare, chronic and life-threatening blood disorder characterised by persistent and uncontrolled activation of the terminal complement system (part of the body's immune system).[22, 54-56] As a result, the normal functioning of RBCs, white blood cells and platelets are impaired which leads to the premature destruction of RBCs (haemolysis), thrombotic events and ultimately death.[57, 58] Haemolysis in PNH takes two forms, each associated with differing manifestations, severity, and treatment.[12, 59] IVH occurs in RBCs in circulation (i.e. within blood vessels) and is associated with a high risk of life-threatening complications, including thrombosis.[12] As IVH is the underlying cause of mortality and morbidity in PNH, the treatment goal of PNH is the complete and sustained elimination of IVH via terminal complement inhibition (C5 inhibitors).[12, 20, 22, 35, 57, 60-62] Following the availability of the C5 inhibitors ravulizumab and eculizumab, it is possible for IVH, and accordingly life-threatening symptoms such as thrombosis, to be controlled in patients with PNH.

However, patients achieving disease control with a C5 inhibitor may experience EVH. Of these patients, a small proportion will experience csEVH, whereby EVH becomes symptomatic and requires treatment. This is a mechanistic consequence of treatment with C5 inhibitors, whereby RBCs that are no longer being destroyed through IVH are surviving and becoming opsonised by C3 fragments. These opsonised RBCs are targeted for destruction outside of blood vessels, in the liver, spleen, bone marrow and lymph nodes in the process of EVH, which is associated with a loss of energy and fatigue.[12, 63] These symptoms are not life-threatening but result in a poorer HRQoL and represent a key unmet need for patients with csEVH, as supported by clinical expert opinion.[4, 44] The two primary clinical manifestations of PNH are described further below. People with csEVH is the indication of interest for this evaluation.

The predicted prevalence of PNH in Great Britain is approximately 1 in 62,500 people.[41] In 2022, the UK National PNH service reported that there were 926 individuals in England living with the condition.[3] However, according to the annual report published by the PNH National Service in the UK, only 30.35% of patients with PNH receive treatment with complement inhibitors in England, excluding those enrolled in clinical trials.[3] Following treatment with C5 inhibitors, many patients still experience residual anaemia due to EVH.[8, 64] While most patients with EVH are asymptomatic, a subgroup of patients with EVH are symptomatic and require treatment, having csEVH.[65] The published literature indicates that around 10–20% of patients who receive C5 inhibitors for treatment of IVH develop csEVH, based on the clinical trial of ravulizumab (Study 302) and real-world data from the multi-national Adelphi Disease Specific Programme.[1, 2] Clinical experts consulted as part of a UK advisory board suggested that the prevalence of csEVH is slightly higher, at approximately 30%.[2, 4] While PNH is an acquired condition and can occur at any age, the mean age of onset of PNH is reported as 39.3 years by the international PNH registry.[55, 66-68] The incidence of PNH is broadly similar between males and females; incidence rates indicate a slightly higher female predominance, though this varies by geographical region.[55, 66 67, 68]

The gold standard for the diagnosis of PNH involves a flow cytometric analysis to detect cells that are deficient in glycosylphosphatidylinositol (GPI)-anchored proteins (see 'Pathogenesis of PNH' below).[69] In addition, the screening process includes a complete blood count, reticulocyte count, determination of iron stores, assessment of biochemical markers of haemolysis (serum concentration of LDH, bilirubin, and haptoglobin), biopsy, bone marrow aspirate, cytogenics, and a Coombs test.[8, 70-73]

Clinical manifestation of PNH

Intravascular haemolysis

Many of the common symptoms that patients with PNH present with can be attributed to IVH, including anaemia (88–94%), fatigue (~80% of patients), dyspnoea (64%), haemoglobinuria (62%), erectile dysfunction (62%), abdominal pain (44%), chest pain (33%), and dysphagia (24%).[17-21] Debilitating and potentially life-threatening consequences of IVH include thrombosis, chronic kidney disease, renal and hepatic failure, infection/septicaemia and malignancy.[12, 20, 22, 60, 74] The introduction of C5 inhibitors in UK clinical practice, beginning with eculizumab in 2007, has largely led to the successful management of patients' IVH, allowing control of the debilitating and often life-threatening symptoms associated with PNH. Indeed, survival in patients with PNH has substantially improved since the introduction of C5 inhibitor treatment, with published

evidence indicating that the lifespan of treated patients with PNH now approaches that of the general population.[8, 12]

The phenomenon whereby sustained control of IVH is suboptimal is known as BTH. Elevated LDH level is a key biomarker for IVH and is associated with an increased risk of thrombosis; reducing LDH to <1.5× ULN is critical and a recognised goal of IVH treatment. In the clinical trials of ravulizumab (Study 301 and Study 302), the most recently licensed C5 inhibitor, BTH was defined as at least one new or worsening sign or symptom of IVH (fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia, major adverse vascular events [thrombosis], dysphagia or erectile dysfunction) in the presence of LDH levels twice the ULN) following a prior reduction of LDH levels to <1.5 times ULN.[24, 75] There are two distinct types of BTH depending on their pathogenic mechanism, pharmacokinetic BTH and pharmacodynamic (PD) BTH.[6] Pharmacokinetic BTH arises from having insufficient levels of complement inhibitors in the plasma (e.g. through insufficient dosing levels). PD BTH is due to a large amount of complement activation resulting from an infectious episode or other clinical conditions. In PD BTH, the amplified complement activation exceeds the inhibitory activity of complement inhibitors, and occurs regardless of plasma levels of complement inhibitors.[6]

Of the symptoms associated with IVH, thrombosis (a blood clot) is a frequent complication and the leading cause of morbidity and mortality in PNH.[12] Published literature indicates that prior to the advent of C5 inhibitors, 29% to 44% of patients with PNH would experience a thromboembolic event during their disease course, with the relative risk of death upon presentation of thrombosis increasing 5–15.4 fold.[20] Following the introduction of C5 inhibitors, the risk of thrombosis has been reduced. Based on an extension study of clinical trials studying eculizumab as a treatment for PNH, eculizumab treatment significantly reduced the rate of thromboembolic events to 1.07 events/100 patient-years from 7.37 events/100 patient-years.[61] Given this, it is particularly important to achieve a sustained control of IVH whilst addressing symptoms of EVH, as discussed further in the 'Unmet need' section.

Other leading causes of death in PNH include chronic kidney disease and renal damage, leading to mortality in 2%–18% of patients with PNH who are naïve to treatment with C5 inhibitors.[18, 60]

Extravascular haemolysis

Although treatment of PNH with C5 inhibition has transformed outcomes for patients, a proportion of patients still experience residual anaemia.[8, 64] A 2019 study conducted among 182 patients with PNH reported that approximately one-third of patients with PNH treated with eculizumab or ravulizumab experienced suboptimal haemoglobin values.[76] This residual anaemia is caused by EVH, which is a mechanistic consequence of effective treatment with C5 inhibition. Blood cells that are no longer subject to lysis (the breakdown of cell structure, leading to cell death), as a result of C5 inhibition, may subsequently be destroyed through a separate mechanism via the proximal complement pathway (described further below in 'Pathogenesis of PNH').[6, 14] Accordingly, the resulting haemolysis outside of circulation of blood vessels, EVH, manifests as anaemia.[12, 14]

The presentation and severity of EVH is variable, and many patients experiencing EVH are asymptomatic.[65] However, a subgroup of patients with EVH are symptomatic and require treatment, which is defined as clinically significant (csEVH). Based on feedback from UK clinical experts, approximately 30% of patients with EVH have csEVH.[4] The clinical experts agreed that

csEVH is assessed on an individual patient basis, in the absence of a standardised definition.[4] A range of parameters may be used to define csEVH, and biomarkers such as bilirubin and reticulocyte levels, the deposition of C3 fragments on RBCs (measured via flow cytometry), as well as patient reported factors including the level of fatigue and impact of the PNH on patients' day-to-day life, will be taken into consideration.[4, 7] Relatedly, a continued need for blood transfusions, despite C5 inhibitor therapy, is an additional common manifestation of csEVH. Published literature indicates that 20% of patients with PNH require occasional transfusions despite receiving treatment with C5 inhibitors.[77] Guidance from the PNH National Service indicates that blood transfusions are used for patients who have symptomatic anaemia; for these patients, visits to hospitals or outpatient clinics for transfusions may be required in addition to C5 inhibitor treatment administration.[78, 79]

Among patients treated with C5 inhibitors who experience EVH, anaemia, loss of energy and fatigue are the most frequently reported physical symptoms with a subset of patients requiring transfusions.[63] Indeed, clinical experts in PNH consulted at a UK advisory board highlighted that fatigue is a key symptom used to understand whether a patient has csEVH.[4,8] Whilst EVH also risks complications such as iron overload, general consensus suggests that EVH, and its associated symptoms, do not impact mortality in patients with PNH.[12]

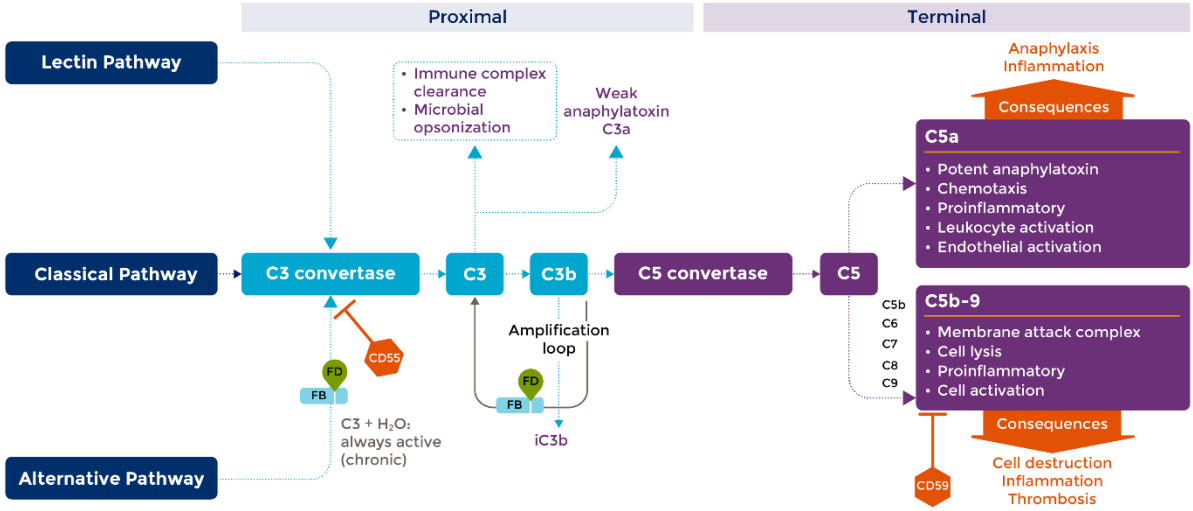
Whilst the effect of EVH on patient HRQoL has not been formally evaluated, the common association of EVH and fatigue implies a detrimental impact on patient HRQoL; in the published literature, fatigue substantially impacts the HRQoL of affected individuals, as described further in Section B.1.3.2.[6, 12] Given that csEVH becomes unmasked upon treatment with C5 inhibitors, there is an outstanding clinical unmet need for the treatment of this aspect of PNH that is yet to be addressed. During the UK advisory board discussed above, the clinical experts identified that the severe fatigue observed in patients with csEVH represents a key unmet need.[4]

Pathogenesis of PNH

PNH is caused by somatic mutations in the *PIG-A* gene within haematopoietic stem cells (HSC), leading to the production of abnormal blood cells that are lacking CD55 and CD59 that are susceptible to destruction by the complement system.[12, 30]

The complement system, also referred to as the complement cascade, comprises of over 30 proteins forming part of the body's innate immune system.[32] The complement cascade is responsible for the recognition, marking and clearance of pathogens and damaged cells from the body, as well as promoting inflammation in response to infection and/or other events initiating complement activation.[30, 31] The complement cascade can be separated into three distinct pathways activated by distinct triggers: the classical pathway (activated by immune complexes), the lectin pathway (activated by microbial-related triggers) and the alternative pathway (automatic activation), shown in Figure 1.[80, 81] The three pathways converge at the point at which C3, a protein responsible for amplifying and co-ordinating immune response, is activated.[30, 82, 83]

Figure 1: The complement system in PNH



Abbreviations: C3: complement component 3; C5: complement component 5; FB: factor B ; FD: factor D. PNH: paroxysmal nocturnal haemoglobinuria.
Source: Walport 2001,[84] Murphy et al. 2016,[85] Kelly et al. 2009,[86] Merle et al. 2015,[87] Hill et al. 2017.[12]

While the complement system plays a key role in defence against infection, overactivation of this system can lead to damage of healthy cells.[88] The acquired *PIG-A* gene mutation in PNH leads to production of abnormal blood cells, referred to as 'PNH clones', which are characterised by either a partial or complete deficiency in GPI, molecules serving as membrane anchors for two surface proteins, CD55 and CD59.[12, 33, 89, 90] CD55 and CD59 proteins, which are homogeneously expressed on healthy blood cell surfaces, regulate complement activity and protect against uncontrolled complement-mediated lysis (breaking down of the cell membrane and subsequent cell death).[33, 34]

The lack of GPI and the subsequent deficiency in CD55 and CD59 in PNH plays a role in both terminal and proximal complement activation.[12] CD59 acts on the downstream (terminal) complement cascade, preventing cleavage of C5 through C5 convertase and subsequent formation of the membrane attack complex, a complex of proteins formed on cell surfaces leading to cell lysis and death.[12, 35, 36] CD55 mediates C3 convertase in the proximal section of the pathway, preventing cleavage to C3 fragments.[12] Deficiency in these proteins due to PNH causes C3 and C5 to become unregulated, leading to dysregulation of complement activity. Consequently, otherwise healthy blood cells are recognised as damaged by the body and are susceptible to destruction by the complement system, leading to haemolysis.[12, 30, 37]

PNH is treated by inhibiting C5 activity (through C5 inhibitors, ravulizumab or eculizumab), as discussed in Section B.1.3.3, during which CD59 deficiency is compensated for and IVH is prevented. However, CD55 deficiency then remains unaddressed, leading to the accumulation of C3 fragments on affected cells. These cells are recognised by macrophages (white blood cells of the innate immune system) expressed in the spleen and liver, and are susceptible to destruction, leading to EVH caused by activation of the proximal complement pathway.[12, 30, 37]

B.1.3.2 Disease burden

Patient and carer burden

Though C5 inhibitors have improved symptom control and HRQoL among patients with PNH, there remains an unmet need to further improve symptom control and subsequently HRQoL of patients.

A larger European burden of illness study conducted in the UK, France, and Germany, recruiting 71 patients with PNH treated with eculizumab or ravulizumab, reported statistically significant greater levels of fatigue, and lower HRQoL, in this population compared to the general population.[44] Fatigue was the most common symptom reported (eculizumab: 61.2%; ravulizumab: 68.2%). Fatigue scores, measured via the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) questionnaire (ranging 0–52, with 52 as the best possible score), were lower for eculizumab (35.6) and ravulizumab (33.8) compared to the general population (43.5).[44] Furthermore, poorer HRQoL, measured via EORTC-QLQ-C30 global health scores (ranging 0–100, with 100 as the highest possible HRQoL), were observed for eculizumab treated patients (68.7) and ravulizumab treated patients (62.9) compared to the general population (75.0).[44] Preliminary evidence (derived from a small study of 25 patients with PNH and csEVH) also suggests that csEVH may impact the HRQoL of patients with PNH: 56% of patients with csEVH who were clinically stable on C5 inhibitor treatment had good to excellent quality of life, compared with 79% of patients without csEVH.[2]

PNH patients with fatigue may experience the need to sleep for prolonged hours during the day, experience brain fog and have difficulty in walking, climbing stairs, leaving the house or working.[44, 91-93] As such, it is anticipated that carers will also be impacted by the caregiving responsibilities for these affected individuals. If caregiving takes the form of informal assistance through family and friends, this may strain patient relationships with their immediate family network. Carers also experience a high administration burden considering the travel requirements associated with blood transfusions, for which the proportion of patients with PNH experiencing csEVH may be dependent upon.[2, 4, 78]

Economic burden of disease

PNH is associated with considerable healthcare resource utilisation (HCRU), including high rates of hospitalisations from PNH associated symptoms. This is supported by a US study conducted in 2021 studying HCRU in 151 patients with PNH receiving eculizumab; all-cause hospitalisation costs were $168,783 for transfusion-dependent individuals versus $20,275 for transfusion-free individuals.[94] Although IVH is typically well-controlled in patients receiving treatment with C5 inhibitors in UK clinical practice, episodes of BTH can still occur, and additional HCRU costs are incurred due to management of these events.[53, 95] An American study conducted in 2020, examining the cost burden of BTH on healthcare systems, found that incremental costs for management of BTH for eculizumab and ravulizumab were $9,379 and $407, respectively.[94, 96] While the literature is limited to US studies on the HCRU in PNH, the publications support the high costs incurred through suboptimal disease control. Pegcetacoplan is the only available treatment in UK clinical practice for the treatment of residual anaemia while on treatment with C5 inhibitors.

Blood transfusions, for which a sizeable proportion of patients with PNH experiencing csEVH may be dependent upon, are associated with an economic burden. Patients with PNH in the UK may require hospital visits to receive transfusions; the length of time to receive one unit of blood in a transfusion varies from 1.5–2 hours to up to 4 hours, as reported by the NHS.[97, 98] Patients are also monitored regularly during transfusions to check for reactions or any other side effects, implying a further burden on healthcare professional time.[97] Among 141 patients with PNH experiencing EVH treated under the UK PNH National Service, 36% of patients received at least one transfusion and 16% of patients required three or more blood transfusions within a 12-month period.[7] Blood transfusions thus represent a significant burden of treatment in the management of PNH, restricting patients' flexibility and planning for work and family life.[10, 11]

In addition to the burden on HRQoL, PNH is associated with substantial economic burdens from the perspective of patients, arising from productivity losses. Among patients receiving C5 inhibitors in the UK, only 57.7% of patients are employed.[44] Of these patients, almost all patients (97.6%) reported PNH-related work impairment and the majority (70.3%) reported presenteeism (working while unwell, physically, mentally or emotionally).[44]

B.1.3.3 Current treatment pathway

There are no clinical guidelines published by NICE for the management of PNH in England and Wales. Guidelines on the management of PNH have been previously outlined by the International PNH Interest Group, and a consensus statement for the diagnosis and treatment of PNH was published in 2021.[8, 99, 100] However, these guidelines and consensus statement are outdated and mainly focus on the management with eculizumab. Since their publication, ravulizumab and pegcetacoplan have been recommended by NICE as new treatment options for PNH.[5, 46] The current treatment pathway presented in Figure 2 is informed by NICE's recommendations on treatments for PNH and the guidelines published by the PNH National Service.[5, 46, 101] The current treatment pathway is also in line with feedback received from UK clinical experts consulted as part of an advisory board, who are part of the PNH National Service.[4]

First-line treatments: C5 inhibitors

As IVH triggered by terminal complement activation represents the underlying cause of mortality and morbidity in PNH, the goal of treatment for PNH is to achieve a complete and sustained elimination of IVH.[20, 22, 35, 60] This is achieved through the standard of care treatment, C5 inhibitors. However, not all patients will have disease activity at a sufficient level to require treatment. It has been estimated that up to 30% of the total number PNH patients requiring treatment in England receive C5 inhibitors.[3] There are two C5 inhibitors available to patients in UK clinical practice:

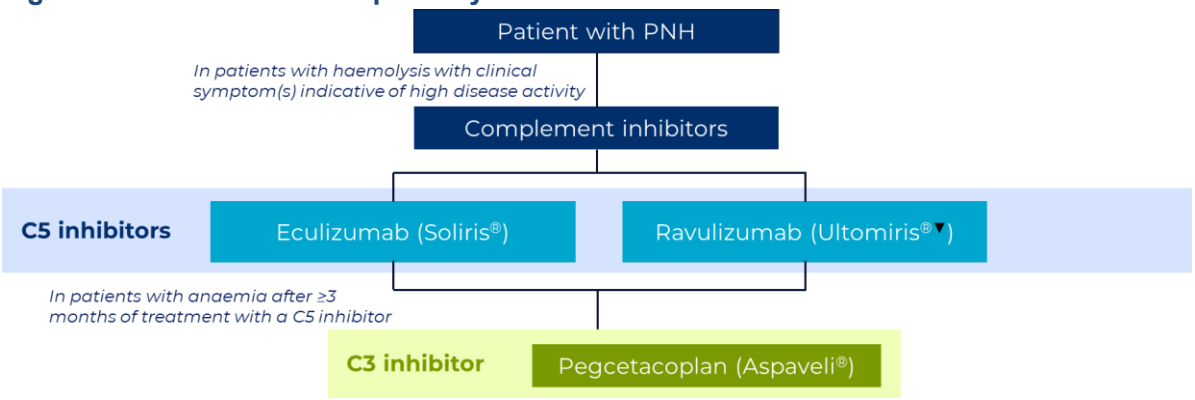
- Eculizumab is an intravenous (IV) infusion administered every two weeks, and it is a monoclonal antibody which binds to C5 proteins with high affinity. By binding to C5 proteins, eculizumab prevents the formation of the MAC, thus terminally inhibiting the complement pathway and preventing IVH.[10, 47] Eculizumab is available through the NHS Highly Specialised Services, and is used by [redacted] of patients receiving C5 inhibitor treatment (i.e., eculizumab or ravulizumab) based on Alexion's sales data validated by UK clinical experts[49, 50]
- Ravulizumab is an IV infusion which is administered every eight weeks with a similar mechanism of action as eculizumab. Ravulizumab was recommended by NICE [TA698] in

2021, and has since become the standard of care in the UK with [redacted] of patients being treated with ravulizumab based on Alexion's sales data validated by UK clinical experts[46, 49, 50]

Second-line treatment: C3 inhibitor

Pegcetacoplan was approved by the EMA in 2021 and was subsequently recommended by NICE [TA778] in 2022.[5, 51] Based on NICE's recommendation, patients with PNH who remain anaemic after at least three months of treatment with a C5 inhibitor may then receive pegcetacoplan monotherapy in the second-line treatment setting.[5] However, clinical experts consulted at a UK advisory board indicated that in clinical practice, patients would typically not switch to receive pegcetacoplan until at least six months of treatment with a C5 inhibitor.[4] Pegcetacoplan is a C3 inhibitor that is administered twice weekly by subcutaneous (SC) injection. In patients who have a LDH level of more than twice the ULN, pegcetacoplan may be administered every third day instead.[51] It is a pegylated pentadecapeptide that binds to proximal C3 proteins, inhibiting the alternative and classical pathways of the complement system and thereby addressing both EVH and IVH.[47, 51, 52]

Figure 2: Current treatment pathway of PNH



Abbreviations: C3: complement component 5; C5: complement component 5; PNH: paroxysmal nocturnal haemoglobinuria.
Source: Adapted from Cançado (2021).[99]

Unmet need

As discussed in Section B.1.3.1, approximately 30% of patients receiving C5 inhibitors experience the emergence of csEVH.[4] Following at least 3 months of treatment with a C5 inhibitor, patients who continue to have anaemia may be treated with pegcetacoplan in UK clinical practice, although UK expert advisors noted patients are typically treated with a C5 inhibitor for 6 months before an attempt to switch to pegcetacoplan is made.[4]

In UK clinical practice, should a patient require an alternative treatment to a C5 inhibitor as a result of csEVH, patients will discontinue treatment with their C5 inhibitor treatment after a four-week overlap period in order to receive pegcetacoplan monotherapy. This discontinuation risks a potential lapse in sustained control of IVH in some patients, warranting dosing adjustments, and/or rescue treatment with a C5 inhibitor or treatment discontinuation.[52, 102, 103] Additionally, in an international survey conducted with clinicians from various national PNH referral centres, a proportion of patients experiencing BTH require hospitalisation (general ward stay: 10–23%; intensive care stay: 1–13%).[96] In the PEGASUS trial, after 16 weeks of treatment with pegcetacoplan, four patients (10%) experienced BTH, of whom three patients discontinued treatment (switched back to receive eculizumab) and one patient's dosing regimen was

increased to every 3 days.[37] Real world data from a compassionate use study showed that patients with pegcetacoplan experience repeated BTH events; mean BTH event/patient was every 8 months (mean duration on pegcetacoplan was 13.8 months per patient).[104] Additionally, patients with pegcetacoplan experience rapid haemolysis, with a mean haemoglobin level drop of 2.9 g/dL one day from the start of symptoms.[104]

Relative to C5 inhibitors, pegcetacoplan is associated with more severe episodes of BTH. Patients on treatment with pegcetacoplan who experience BTH have reported LDH levels up to 10–15 times the ULN.[53] Comparatively, LDH level increases of more than five times the ULN are rare amongst patients treated with a C5 inhibitor.[53] Noting the confidence in IVH control provided by C5 inhibition, clinical experts at the advisory board indicated that any decision to switch patients from C5 inhibitor monotherapy to pegcetacoplan monotherapy would require careful consideration.[4] Hence, there is an unmet need for an alternative novel treatment regimen that effectively and reliably controls both IVH and EVH.

UK clinical experts highlighted that fatigue is a key symptom associated with EVH.[4] As C5 inhibitors do not address EVH, patients who receive C5 inhibitor treatments can experience severe fatigue, with a statistically significant lower FACIT-F scores (eculizumab: 35.6; ravulizumab: 33.8) compared with the general population (43.5).[44] UK clinical experts indicated that current treatments therefore do not sufficiently address fatigue, and emphasised that the severe fatigue observed in patients with csEVH is an important unmet need in this population.[4]

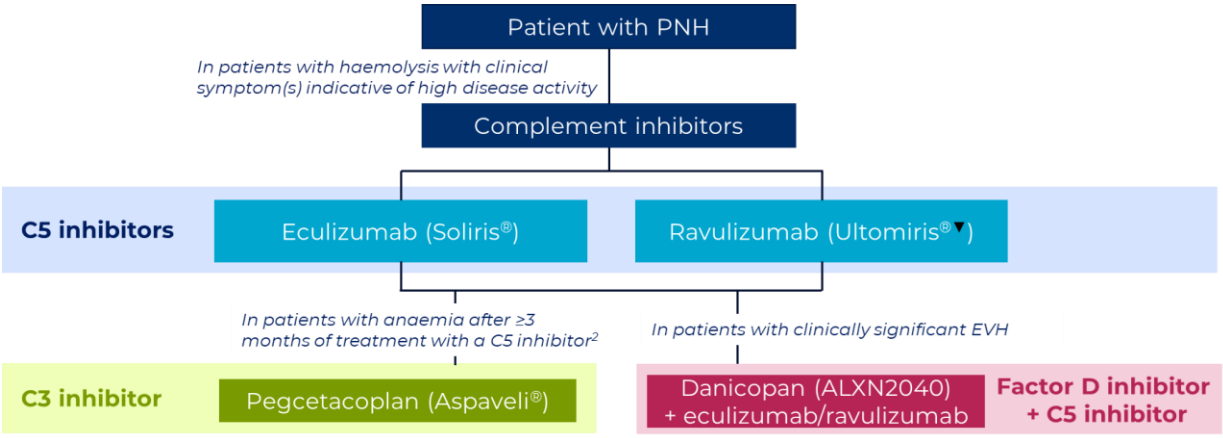
Eculizumab and ravulizumab are both IV infusions which require administration by a trained healthcare professional and are administered once every 2 weeks and 8 weeks, respectively.[10, 11] Pegcetacoplan is associated with a higher administration burden, having a higher dosing frequency of twice a week, with each administration taking 30–60 minutes via a commercially available syringe system infusion pump, as shared by UK clinical experts.[4, 51] Although pegcetacoplan is a SC injection that may be self-administered, patient training to self-inject is required, and there are 10 steps which patients need to follow for each administration.[51] The UK clinical experts further commented that a proportion of patients with dexterity or sight-related issues may not be capable of self-administering pegcetacoplan. Furthermore, patients with minimal SC tissues, mental health issues, and other visual difficulties, may be unable to self-administer pegcetacoplan. Therefore, the UK clinical experts concluded there is a need for a new treatment with an alternative method of administration to pegcetacoplan to enable patient choice, with the burden associated with the need for regular SC infusions and difficulties with self-administration (due to dexterity and sight-related issues) representing key unmet needs.[4]

In summary, there remains an unmet need for a treatment approach that effectively manages both IVH and csEVH, thus minimising symptoms that substantially reduce patient HRQoL (such as fatigue), which also provides an alternative method of administration to pegcetacoplan.

Proposed positioning of danicopan

Danicopan as an add-on to eculizumab or ravulizumab therapy is designed as an alternative to pegcetacoplan in the treatment pathway for PNH for the management of csEVH. As EVH only becomes clinically significant following treatment with eculizumab or ravulizumab and neither treatment address EVH, they are not considered relevant comparators to danicopan in this indication. The positioning of danicopan as an add-on therapy in the treatment pathway is provided in Figure 3 below.

Figure 3: Proposed treatment pathway for PNH with danicopan



Abbreviations: C3: complement component 5; C5: complement component 5; EVH: extravascular haemolysis; PNH: paroxysmal nocturnal haemoglobinuria.
Source: Adapted from Cançado (2021)[99]

Eculizumab and ravulizumab are proven treatments for the control of IVH, for which clinicians in the UK have substantial in-practice experience, and danicopan functions as an add-on to them and presents a novel mechanism of action.[105, 106] As such, danicopan addresses the unmet need for a new treatment which directly targets EVH, whilst ongoing C5 inhibitor treatment with ravulizumab and eculizumab provides complete and sustained terminal complement inhibition, essential to prevent life-threatening IVH and manage disease activity. By providing an immediate, complete and sustained blockade of terminal complement, danicopan provides effective disease control.[11, 25] UK clinical experts at the advisory board highlighted that danicopan as an add-on therapy provides reassurance that IVH remains well-controlled.[4] As a specific treatment for EVH, danicopan is anticipated to lead to a reduction in fatigue, and accordingly lead to significant improvements in patient HRQoL. Furthermore, danicopan is orally administered, and eculizumab and ravulizumab are administered intravenously at home by a trained healthcare professional. Eculizumab and ravulizumab also have a lower frequency of administration than pegcetacoplan. Danicopan as an add-on to eculizumab or ravulizumab therefore provides a more convenient method administration, and more importantly, an alternative method of administration for patients who have difficulties with self-administration of pegcetacoplan SC injection.

In summary, danicopan as an add-on treatment to eculizumab or ravulizumab offers a novel mechanism of action and method of administration. It provides dual inhibition of terminal and proximal components of the complement pathway, thus helping to control the IVH while offering quality of life benefits to patients experiencing csEVH, by reducing persistent symptomatic anaemia, need for transfusion, and improving levels of fatigue.[2, 14, 107] Danicopan thus represents a valuable new treatment option that addresses the current unmet needs associated with csEVH.

B.1.4 *Equality considerations*

No equality issues are anticipated for the appraisal of danicopan in this indication.

B.2 Clinical effectiveness

Summary of clinical and safety evidence for danicopan for the treatment of csEVH

- The clinical efficacy and safety base for danicopan as an add-on to eculizumab or ravulizumab for the treatment of csEVH was informed by the ALPHA trial[108]
- The ALPHA trial is an ongoing, multiple-region, Phase III, randomised, double-blind, placebo-controlled study in 86 patients (as of the 20th September 2022 data cut-off [DCO]) comparing danicopan as an add-on to ongoing eculizumab or ravulizumab treatment versus placebo as an add-on to ongoing eculizumab or ravulizumab treatment for the treatment of csEVH in PNH[1, 27]

Efficacy

Primary endpoint

- The primary endpoint of the ALPHA trial was change in haemoglobin level from baseline to Week 12. Danicopan (N=42) resulted in a statistically significant (p<0.0001) and clinically meaningful increase in least squares (LS) mean haemoglobin level from baseline (2.94 g/dL) compared to placebo (0.50 g/dL) (N=21), thereby meeting the primary endpoint of the trial[27, 109]
    - Low levels of haemoglobin are associated with symptoms such as fatigue, shortness of breath, headache and heart palpitations.[110] The clinically meaningful improvements in haemoglobin level demonstrated by danicopan are therefore expected to alleviate burdensome symptoms experienced by patients with EVH

Key secondary endpoints

- The key secondary endpoints (all assessed at Week 12) investigated in the ALPHA trial included the proportion of patients with an increase in haemoglobin level of ≥2 g/dL, transfusion avoidance, change from baseline in FACIT-F scores and change in absolute reticulocyte count (ARC) from baseline. Danicopan led to statistically significant improvements in all key secondary endpoints versus placebo[27, 109]
    - Transfusion avoidance was achieved by 83.3% of patients in the danicopan treatment arm, compared to 38.1% of patients in the placebo treatment arm. A statistically significant (p=0.0004) difference of 41.7% (95% confidence interval [CI]: 22.7%, 60.8%) was achieved with danicopan, versus placebo
    - The treatment arm difference in FACIT-F scores of 6.12 indicated that danicopan led to statistically significant (p=0.0021) and clinically meaningful improvements FACIT-F scores, translating to a reduction in fatigue symptoms versus placebo. Fatigue has been identified as a key burden to the HRQoL of patients with csEVH by UK clinical experts in PNH[4]

Efficacy at Week 24

- After Week 12, all patients receiving placebo switched to receive danicopan whilst continuing the same C5 inhibitor received up to Week 12. All patients receiving danicopan continued with this treatment[27]

- Analyses conducted at Week 24 indicated that the change from baseline in haemoglobin level, proportion of patients achieving transfusion avoidance and decrease from baseline in ARC were maintained for those patients continuing on treatment with danicopan.[1] [redacted][27]
- For those patients who switched from placebo to danicopan at Week 12, a meaningful change from baseline in haemoglobin levels (2.26 g/dL) was observed, along with an increase in transfusion avoidance from 38.1% of patients (Week 12) to 90.0% of patients (Week 24)[1, 27]

Safety

- Safety results are presented in this submission for the interim safety analysis set, including the N=86 patients who had received at least one dose of study intervention (including placebo) at the 20th September 2022 DCO[27]
- At Week 12, 73.7% patients of receiving danicopan and 62.1% of patients receiving placebo had experienced a treatment-emergent adverse event (TEAE), demonstrating the comparable safety profile of the two treatments. Serious adverse events (SAEs) were uncommon and comparable between danicopan (5.3%) and placebo (6.9%)
    - The safety profile of danicopan was maintained in the long-term with similar safety trends observed through Week 24 and the long-term extension (LTE)
    - Overall, danicopan was demonstrated to be well-tolerated and to have a similar safety profile to placebo, with no indication of an increased treatment burden upon the addition of danicopan

Indirect treatment comparison

- Due to the lack of head-to-head data available for danicopan and the relevant comparator in United Kingdom (UK) clinical practice, pegcetacoplan monotherapy, matching-adjusted indirect comparisons (MAICs) were used to generate relative efficacy estimates for the two treatments
- Four methodological approaches for the MAIC were explored as part of a feasibility analysis, including combinations of naïve or adjusted and anchored or unanchored analyses. For the adjusted MAICs, baseline haemoglobin level and reticulocyte count were the covariates adjusted for between the relevant patient populations[111]
- Due to the considerable uncertainty associated with the MAIC results, arising from the unadjusted heterogeneity between the ALPHA and PEGASUS trials, the results of all analyses were not considered suitable for informing the base case of the economic model

Conclusion

- The results of the ALPHA trial demonstrate that danicopan leads to statistically significant improvements across a range of key outcomes for EVH, improving haemoglobin levels, reducing fatigue and improving rates of transfusion avoidance, compared to placebo [27]
    - Reduction in fatigue symptoms, in addition to avoidance of burdensome transfusion requirements through treatment with danicopan are expected to

translate to improvements in patient HRQoL, whilst offering a comparable safety profile to eculizumab or ravulizumab monotherapy

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted in November 2022, with a subsequent update conducted in June 2023, to identify relevant evidence on the efficacy and safety of danicopan add-on treatment to eculizumab or ravulizumab and the relevant comparators for the treatment of csEVH.[112] The SLR identified 63 studies reporting on clinical, humanistic and economic outcomes, in addition to cost-effectiveness analyses, for synthesis. Of the included clinical articles, 32 described a PNH patient population that was previously treated with a C5 inhibitor, 13 described a mix of previously C5 inhibitor-treated and treatment-naïve patients, and 13 described only treatment-naïve patients. Full details of the SLR, including the search strategy, study selection process and detailed results are provided in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

The SLR identified a randomised clinical trial (RCT) investigating the efficacy and safety of danicopan as an add-on to ongoing C5 inhibitor treatment for csEVH in PNH; ALPHA (NCT04469465).[112, 113] The ALPHA trial forms the principle clinical evidence base for danicopan add-on treatment for patients with PNH with csEVH, the indication of interest to the decision problem of this evaluation.

The ALPHA trial is an ongoing, multiple-region, Phase III, randomised, double-blind, placebo-controlled study. The study was initiated on 6th January 2021 (with the first participant randomised at this date) with the latest DCO corresponding to 20th September 2022.[27] Unless otherwise noted, the results presented and analysed in this submission are based on this DCO.

Efficacy results in this submission are based on the interim efficacy analysis set (IAS). At a prior DCO (28th June 2022), a prespecified IAS was defined as the first 75% of patients out of the total planned enrolment of the trial (N=84) who had completed treatment period 1 (TP1 – the initial 12-week randomised period, see Table 3), totalling N=63 patients.[113] By definition of the interim efficacy analysis, all of the N=63 patients in the IAS had completed treatment period 2 (TP2 – a further 12-week treatment period, see Table 3) at the 20th September 2022 DCO.[27]

The information in this submission has been derived from the ALPHA trial Clinical Study Report (CSR)[27], the ALPHA trial protocol (Version 6.0)[114], the publications by Kulasekararaj, *et al.* (2020)[108] and Lee *et al.* (2023),[107]and the conference proceedings by Kulasekararaj, *et al.* (2023)[1] and Lee *et al* (2023).[107]

A summary of the clinical effectiveness evidence presented in this submission is provided in Table 3.

Table 3: Clinical effectiveness evidence

Study	ALPHA (NCT04469465)

Study design	An ongoing multiple-region, Phase III, randomised, double-blind, placebo-controlled, multiple-dose study in patients with PNH who have csEVH, consisting of several parts:
	• A screening period (up to 45 days in duration), followed by two treatment periods:
	  ○ TP1: patients were randomised with a 2:1 ratio of danicopan to placebo (and ongoing C5 inhibitor treatment in each arm) for a double-blind period of 12 weeks
	  ○ TP2: At Week 12, patients who received placebo (and ongoing C5 inhibitor treatment) at randomisation were switched to receive danicopan and ongoing C5 inhibitor treatment. Patients who were randomised to the danicopan arm continued to receive danicopan (and ongoing C5 inhibitor treatment), for a further 12 weeks[a]
	• An optional 2-year LTE[a]

Population	Patients with PNH who fulfil the following criteria:
	• Age 18 years or older
	• Clinically evident EVH defined by
	  ○ Anaemia (defined as haemoglobin ≤9.5 g/dL)
	  ○ ARC ≥120 × 10^9 /L
	• Receiving an approved C5 inhibitor for at least 6 months prior to Day 1 of the study
	• Platelet count ≥30,000/μL without the need for platelet transfusions
	• Absolute neutrophil count (ANC) ≥500/μL
	• With or without transfusion history[b]

Intervention(s)	Danicopan as an add-on to ongoing eculizumab or ravulizumab treatment
Comparator(s)	Placebo as an add-on to ongoing eculizumab or ravulizumab treatment
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem[c]	• OS • IVH • **EVH** • **BTH**

	• **Transfusion avoidance** • **Haemoglobin** • **Thrombotic events** • **AEs of treatment** • **HRQoL**
All other reported outcomes[d]	**Key secondary outcomes:** • Changes from baseline in ARC **Other secondary outcomes:** • Changes in red blood cell (RBC) units transfused and transfusion instances • Change in bilirubin level • Changes in PNH RBC clone size and C3 fragment deposition on PNH RBCs • Change in LDH

[a] TP2 and the LTE were open label, meaning that all patients received danicopan add-on treatment, and treatment allocation in TP1 was known to patients and Investigators. This unblinding was done at the time of the primary interim analysis.
[b] Patients in the ALPHA trial were required to have at least one transfusion within the 6 months before randomisation prior to a protocol update (V6.0) in February 2022.[114] After this time, patients with no prior history of transfusion were permitted to enrol in the ALPHA trial, based on clinical expert opinion supporting that danicopan add-on treatment may benefit patients regardless of their requirements for transfusion.[114]
[c] Bolded outcomes signify those included in the cost-effectiveness model.
[d] Other exploratory endpoints assessed in the ALPHA trial are not included in this table but may be found in the ALPHA trial CSR (20th September 2022 DCO).[27]
Abbreviations: AE: adverse event; ARC: absolute reticulocyte count; BTH: breakthrough haemolysis; CSR: clinical study report; EVH: extravascular haemolysis; HRQoL: health-related quality of life; IVH: intravascular haemolysis; LDH: lactate hydrogenase;LTE: long-term extension; N/A: not applicable; OS: overall survival; PNH: paroxysmal nocturnal haemoglobinuria; RBC: red blood cell; TP: treatment period.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27]

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

B.2.3.1 Trial methodology

A summary of the methodology used in the ALPHA trial is provided in Table 4.

Table 4: ALPHA trial methodology

Methodology	TP1	TP2	LTE (Y1 and Y2)
Location	A multi-regional study, including 80 centres across 18 countries in Europe (including three UK trial centres),[113] Asia, North America and South America.		
Trial design	An ongoing, Phase III, multi-region, multiple-dose study consisting of three distinct treatment periods: • A randomised, double-blind and placebo-controlled 12-week treatment period (TP1) • A 12-week treatment switch period. During this treatment period, all patients receiving placebo were switched to receive danicopan. Patients receiving danicopan in TP1 continued with this treatment in this period (TP2) • An LTE period, consisting of two distinct 1-year long treatment periods, for which all patients continued on danicopan A detailed overview of the ALPHA trial design is provided in Section B.2.3.2.		
Duration of study	12 weeks	12 weeks	• LTE Year 1: 1-year duration • LTE Year 2: 1-year duration
Method of randomisation	• Randomised – patients were randomised via interactive response technology (IRT) in a 2:1 ratio to receive either danicopan or placebo	• Non-randomised – all patients in TP2 received danicopan ○ All patients receiving placebo were switched to receive danicopan	• Non-randomised – all patients enrolled into the LTE continued with danicopan, as received during Week 24 of TP2
Method of blinding	• TP1 was a double-blind treatment period; both patients and the Sponsor were blinded to treatment allocation ○ Pharmacokinetic (PK) and PD data considered to risk unblinding of the study were not reported (NR) to investigative sites or blinded personnel ○ Dose escalation was performed in a similar manner for both placebo add-on and danicopan add-on treatment groups, to maintain blindness of the trial	• During TP2, LTE Year 1 and LTE Year 2, all patients received danicopan[a]	

Trial drugs and method of administration	**Intervention**
	Danicopan as an add-on to eculizumab or ravulizumab treatment
	• Administered as an oral tablet, 150 mg TID
	  ○ Dose escalations to 200 mg TID were permitted based on haemoglobin response and transfusion requirements
	Ongoing eculizumab or ravulizumab treatment
	• Eculizumab or ravulizumab were administered as an IV infusion once every two or once every eight weeks, respectively
	Comparator
	Placebo as an add-on to eculizumab or ravulizumab treatment
	• Administered as an oral tablet, 150 mg TID
	  ○ Dose escalations to 200 mg TID were performed similarly to danicopan treatment, to maintain blinding
	Ongoing eculizumab or ravulizumab treatment
	• Eculizumab or ravulizumab were administered as in the danicopan treatment arm
		Intervention
		Danicopan as an add-on to eculizumab or ravulizumab treatment
		• Administered as an oral tablet, 150 mg TID
		  ○ Dose escalations to 200 mg TID were permitted based on haemoglobin response and transfusion requirements
		Ongoing eculizumab or ravulizumab treatment
		• Eculizumab or ravulizumab were administered as an IV infusion once every two or once every eight weeks, respectively
		Comparator
		• N/A – all patients in the LTE received danicopan

Permitted and disallowed concomitant medication	**Permitted concomitant medications** • Folic acid, and/or erythropoiesis-stimulating agents were permitted if patients were receiving stable doses for at least 30 days prior to Day 1 of the study; patients must have been maintained on stable doses (without any modifications of quantity or frequency) of these agents through to Week 24 • Steroids or other immunosuppressants were permitted in the trial if the dosage regimen was stable for at least 12 weeks	

	before Day 1 of the study and if the patient remained on stable doses through to Week 24 • Oral, injectable, implantable, transdermal, or intravaginal hormonal therapies were allowed for either contraception or hormonal replacement therapy • Prophylactic antibiotics may have been administered if deemed appropriate by a local clinical practice and/or guidelines for treatment with a complement inhibitor **Disallowed concomitant medications** • No concomitant medications were specifically prohibited in the protocol		
Primary endpoints (including scoring methods and timings of assessments)	• Change in haemoglobin relative to baseline after 12 weeks of treatment with danicopan compared to placebo		
Secondary endpoints (including scoring methods and timings of assessments)	**Key secondary endpoints** • The proportion of patients with haemoglobin increase of ≥ 2 g/dL (≥ 2.0 g/dL) at Week 12 in the absence of transfusion • The proportion of patients with transfusion avoidance, defined as patients who remain transfusion free and do not require a transfusion as per protocol-specified guidelines through Week 12 • The change from baseline in FACIT-Fatigue scores at Week 12 • The change from baseline in ARC at Week 12 **Other secondary endpoints[b]** • The change in the number of RBC units transfused and transfusion instances during the 12 weeks of treatment with danicopan compared to the 12 weeks while receiving placebo • The change from baseline of danicopan-	**Key secondary endpoints** • N/A – key secondary endpoints of the ALPHA trial were all assessed at Week 12 of TP1 **Other secondary endpoints[b]** • The proportion of patients with haemoglobin increase of ≥ 2 g/dL (≥ 2.0 g/dL) at Week 24 in the absence of transfusion • The percentage of patients who have transfusion avoidance through 24 weeks of treatment • The change from baseline in FACIT-Fatigue scores at Week 24 in all patients • The change in the number of RBC units transfused and transfusion instances during the 24 weeks of treatment with danicopan compared to the 24 weeks prior to initiation of	• N/A – key and other secondary endpoints of the ALPHA trial were all assessed at either Week 12 of TP1 or Week 24 of TP2

	treated patients compared to placebo in total and direct bilirubin at 12 weeks • The changes in PNH RBC clone size and C3 fragment deposition on PNH RBCs at 12 weeks of treatment with danicopan compared to placebo • The changes in LDH at 12 weeks • The percentage of patients with haemoglobin normalisation at 12 weeks	treatment with danicopan • The percentage of patients with haemoglobin stabilisation during the last 12 weeks of treatment in patients receiving 24 weeks of danicopan • The percentage of patients with haemoglobin normalisation at 24 weeks	
Exploratory objectives	**HRQoL measures** • The change from baseline relative to placebo in Three-level EuroQoL 5 Dimensions 3 Level (EQ-5D-3L) scores at Week 12 • The change from baseline relative to placebo in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30) at Week 12 • The change from baseline relative to placebo in Work Productivity and Activity Impairment Questionnaire: Anaemic Symptoms (WPAI:ANS) at Week 12 • The change from baseline relative to placebo in HCRU at Week 12 **PK and PD measures** • Plasma concentrations of danicopan over time • The changes from baseline in PD biomarkers	**HRQoL measures** • The change from baseline in EQ-5D-3L scores at Week 24 • The change from baseline in EORTC QLQ-C30 scale at Week 24 • The change from baseline in WPAI:ANS scores at Week 24 • The change from baseline in HCRU scores at Week 24 **PK and PD measures** • Plasma concentrations of danicopan over time • The changes from baseline in PD biomarkers	**HRQoL measures** • LTE Year 1: Patient-reported outcomes (PRO) and HRQoL questionnaires applied at Weeks 32, 40, 48, 56, 64 • LTE Year 2: PRO and HRQoL questionnaires applied at Weeks 88 and 104
Safety objectives	• Incidence of TEAEs, SAEs, laboratory abnormalities, and events leading to discontinuation of study drug during TP1 and TP2 **In countries where ravulizumab is not approved**		• Incidence of TEAEs, SAEs, laboratory abnormalities, and events leading to

	• The proportion of patients on ravulizumab who develop antidrug antibodies (ADAs)		discontinuation of study drug
Pre-specified subgroup analyses	Subgroup analyses were performed on the primary analysis, change from baseline in haemoglobin at Week 12, by: • Haemoglobin at screening • Transfusion history • Japanese/non-Japanese patients Subgroup analyses were performed for primary and key secondary endpoints by: • Sex • Race • Region • Age (<65 years and ≥65 years) • Background C5 inhibitor (ravulizumab or eculizumab)	• N/A – no primary or key secondary endpoints were assessed during TP2 therefore no subgroup analyses were performed.	• N/A – No efficacy endpoints were assessed in the LTE and therefore no subgroup analyses were performed.

[a] TP2 and the LTE were open-label, meaning that all patients received danicopan add-on treatment, and treatment allocation in TP1 was known to patients and Investigators. This unblinding was done at the time of the primary interim analysis.
[b] Only the primary and key secondary endpoints (also including changes in PNH clone size) of the ALPHA trial are presented in this submission. This is with the exception of key secondary endpoints assessed instead at Week 24 (rather than Week 12) and changes in PNH clone size. For the other key secondary endpoints in the ALPHA trial, see the ALPHA CSR (20th September 2022 DCO, Tables and Figures)[27]
Abbreviations: ADA: antidrug antibodies; ARC: absolute reticulocyte count; C5: complement component 5; -QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale; EQ-5D-3L: EuroQol-5 dimensions- 3 level; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; HCRU: healthcare resource utilisation; IRT: interactive response technology; IV: intravenous; LDH: lactate dehydrogenase; LTE: long-term extension; N/A: not applicable; NR: not reported; PD: pharmacodynamic; PK: pharmacokinetic; PNH: paroxysmal nocturnal haemoglobinuria; PRO: patient-reported outcomes; RBC: red blood cell; SAE: serious adverse events; TEAE: treatment-emergent adverse events; TID: three-times-daily; TP: treatment period; WPAI:ANS: Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Alexion Data on File. ALPHA Protocol (Protocol ALXN2040-PNH-301 Amendment 6.0)[114]

B.2.3.2 Trial design

The ALPHA trial is an ongoing, multiple-region, Phase III, randomised, double-blind, placebo-controlled, multiple-dose study in patients with PNH who have csEVH whilst receiving treatment with eculizumab or ravulizumab.[27] The ALPHA trial is comprised of three distinct treatment periods: a double-blind, randomised 12-week treatment period comparing danicopan versus placebo (TP1), a further 12-week treatment period for which all patients receiving placebo switched to danicopan (TP2), and an open-label extension of up to 2 years (LTE, Years 1 and 2). In the LTE, all patients received danicopan. A trial schematic is presented in Figure 4, illustrating the three treatment periods.

Screening

Over a period of up to 45 days, patients were screened for inclusion in the ALPHA trial. Inclusion in the trial was assessed based on the eligibility criteria presented in Table 5.

Ultimately, 86 patients were then randomised in the ALPHA trial.[1, 27]

Treatment period 1 (TP1)

Eligible patients progressed to TP1, a double-blind, randomised, 12-week treatment period which comprised of two treatment arms:

- Danicopan and ongoing eculizumab or ravulizumab treatment
- Placebo and ongoing eculizumab or ravulizumab treatment

Patients were randomised into the two treatment arms in a 2:1 ratio of danicopan and placebo. Randomisation of patients to treatment group was facilitated by IRT and stratified by transfusion history (>2 or ≤2 transfusions within six months of screening), haemoglobin level at screening (<8.5 g/dL and ≥8.5 g/dL) and Japanese versus non-Japanese patients. Patients received the same C5 inhibitor (i.e. eculizumab or ravulizumab) in the ALPHA trial that they had been receiving for a minimum of 6 months prior to Day 1 in the study.

The starting dose of danicopan in the ALPHA trial was selected as 150 mg TID based on efficacy and safety data observed in a proof-of-concept Phase II study (ACH471).[29] During TP1, TID dosing of danicopan was permitted to be escalated to 200 mg TID, after a minimum of 4 weeks at each dosing level, based on haemoglobin level response (escalated if the response had not increased by ≥2 g/dL from baseline value) and blood transfusion requirements (escalated if the patient required a transfusion during the previous four weeks of treatment).

Treatment period 2 (TP2)

At the end of Week 12 of the trial (TP1) patients entered TP2, which was comprised of an additional 12 weeks of non-randomised treatment. In TP2, all patients randomised to receive placebo up to Week 12 were switched to receive danicopan. Patients randomised to danicopan remained on this treatment for the further 12-week treatment period. All patients in TP2 received danicopan; the treatment period was open-label and the treatment group assignment for TP1 was known to patients and Investigators. Unblinding was performed at the time of primary interim analysis.

In TP2, TID dosing of danicopan could be escalated at Week 12 and Week 18. Dose escalation was permitted if, at Week 10 and Week 16, respectively, the patient's haemoglobin level had not normalised from the patient's baseline level to at least the midpoint of the normal range relevant to the patient's sex. Alternatively, dose escalation was permitted if the patient had received a transfusion in the last four weeks of treatment.

Long-term extension periods

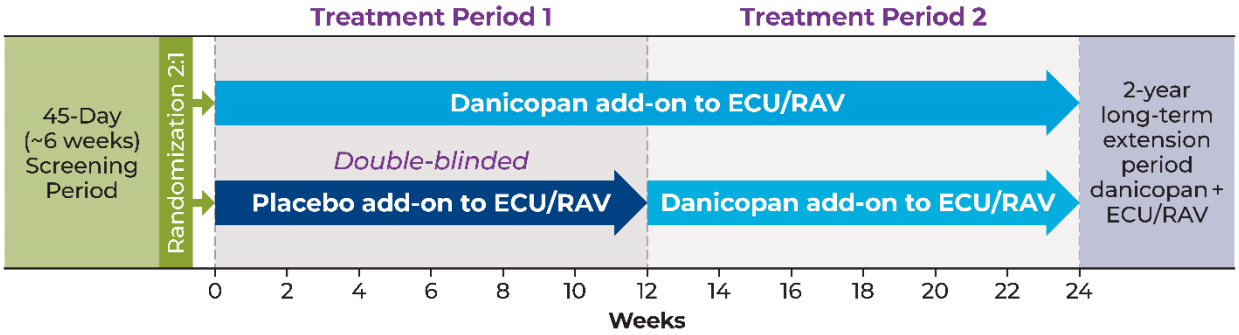
Following the completion of Week 24 (TP2) patients were able to enrol in an LTE study.

The LTE of the ALPHA trial was comprised of two distinct periods:

- LTE Year 1: After completing TP2, participants were able to enrol in a one-year extension, receiving the same danicopan dose received at Week 24 in TP2 along with continued eculizumab or ravulizumab treatment
- LTE Year 2: After LTE Year 1, participants were able to either complete participation in the study, or, continue into the optional LTE Year 2 treatment period, which monitored patients for a further year

In both LTE Year 1 and LTE Year 2, patients were permitted to escalate to the maximum dose of danicopan 200 mg TID provided they had been on their previous dose for a minimum of four weeks.

Figure 4: Trial schematic for the ALPHA trial



[a] After TP1, all patients receiving placebo add-on to C5 inhibitor treatment were switched to danicopan and remained on danicopan throughout the study.
[b] As of the interim analysis DCO (20th September 2022), 86 participants were randomised and 63 patients were included for interim efficacy analysis.[1, 109]
Abbreviations: D: day; DAN: danicopan; DCO: data cut-off; ecu: eculizumab; EVH: extravascular haemolysis; F/U: follow-up; LTE: long-term extension; PBO: placebo; rav: ravulizumab; TID: three-times-daily; TP: treatment period; W: week.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Lee, *et al.* (2023)[109]

The key eligibility criteria used to screen patients for inclusion into the ALPHA trial is summarised in Table 5.

Table 5: Summary of key inclusion and exclusion criteria of the ALPHA trial

Eligibility criteria[a]	
Key inclusion criteria	Participants were eligible for inclusion in the study if the following criteria applied:

	• A diagnosis of PNH
	• CsEVH, defined by:
	  ○ Anaemia (defined as haemoglobin ≤9.5 g/dL) with ARC ≥120 × 10^9/L
	• Receiving an approved C5 inhibitor for at least 6 months prior to Day 1 of the study at an approved dose (or higher), with no change in the prescribed dose or interval for at least 24 weeks preceding Day 1 of study[b]
	• Age 18 years or older (or greater than or equal to minimum adult age in accordance with local legal requirements)
	• A platelet count ≥30,000/μL without the need for platelet transfusions
	• An ANC ≥500/μL
	• Documentation of vaccination for *Neisseria meningitidis*:
	  ○ All patients must have been vaccinated against meningococcal infections within 3 years prior to, or at the time of initiating study drug
	  ○ Patients who initiated the study drug treatment less than 2 weeks after receiving a meningococcal vaccine were required to receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination
	• Patients who are on iron, folic acid, and vitamin B12 supplementation are eligible for the study if on a stable dose for at least 30 days prior to Day 1 (see Table 4)

Key exclusion criteria	Patients were excluded from entry into the study if any of the following criteria applied:
	• History of a major organ transplant (e.g., heart, lung, kidney, liver) or haematopoietic stem cell transplantation (HSCT)
	• Known aplastic anaemia or other bone marrow failure that requires HSCT or other therapies including anti-thymocyte globulin and/or immunosuppressants, unless the dosage regimen of immunosuppressant was stable for at least 12 weeks before Day 1 of the study, for which the patient was expected to remain on stable doses through Week 24
	• A known or suspected complement deficiency
	• Known underlying bleeding disorders (e.g. coagulation factor deficiencies, idiopathic thrombocytopenic purpura, Von Willebrand disease) or any conditions leading to anaemia that are not primarily due to PNH
	• History or presence of any clinically relevant co-morbidities that would make the patient inappropriate for the study
	• Laboratory abnormalities at screening, including:
	  ○ Alanine aminotransferase (ALT) >2 × ULN (>3 × ULN in the case of patients with documented liver iron overload defined by serum ferritin values ≥500 ng/mL); discussion with the Medical Monitor was permitted
	  ○ Direct bilirubin >2 × ULN, with the exception of:
	  ▪ Patients who, in the opinion of investigator, had direct bilirubin >2 × ULN due to EVH

	▪ Patients with documented Gilbert's syndrome (if Gilbert's syndrome was suspected, the patient was tested for this condition at screening) ○ Any other clinically significant laboratory abnormality as judged by the Investigator that, in the opinion of the Principal Investigator, would make the patient inappropriate for the study or put the patient at undue risk • Females who are pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration • Current evidence of biliary cholestasis • Evidence of hepatitis B or hepatitis C viral infection, except for patients with documented successful treatment and documented sustained virologic response at Screening • Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 and/or are on dialysis

[a] Full eligibility criteria may be found in the ALPHA trial protocol (Amendment 6.0).[114] Patients in the ALPHA trial were required to have at least one transfusion within the 6 months before randomisation prior to a protocol update (V6.0) in February 2022.[114] After this time, patients with no prior history of transfusion were permitted to enrol in the ALPHA trial, based on clinical expert opinion supporting that danicopan add-on treatment may benefit patients regardless of their requirements for transfusion.[114]
[b] Further criteria on the use of C5 inhibitor therapy are provided in the ALPHA SAP (Amendment 6.0).[114]
Abbreviations: ALT: alanine aminotransferase; ANC: absolute neutrophil count; ARC: absolute reticulocyte count; C5: complement component 5; csEVH: clinically significant EVH; eGFR: estimated glomerular filtration rate; EVH: extravascular haemolysis; HSCT: haematopoietic stem cell transplantation; PNH: paroxysmal nocturnal haemoglobinuria; ULN: upper limit of normal. **Source:** Alexion Data on File. ALPHA Protocol (Protocol ALXN2040-PNH-301 Amendment 6.0)[114]

Definitions for the endpoints assessed in the ALPHA trial are provided in Table 6. The change in haemoglobin levels from baseline to Week 12 is an important indication of improvement in EVH, as an increase in haemoglobin levels demonstrates a reduction in haemolysis in the spleen and liver. Furthermore, improvements in haemoglobin levels in the absence of blood transfusion demonstrate the actual improvements in haemoglobin levels as a result of treatment with danicopan. These improvements in haemoglobin levels are anticipated to translate into reductions in the need for blood transfusions (a higher proportion of transfusion avoidance), fatigue levels and ARC, which are assessed by the key secondary endpoints. In particular, ARC is considered an important indicator of EVH, and is typically elevated as a compensatory response to haemolysis to increase the production of RBCs.[7, 115, 116] Reductions in ARC thus illustrate recovery from haemolysis.[115]

Table 6: Summary of efficacy, safety, and other assessments used in the ALPHA trial

Assessment	Definition/Details
Primary efficacy	
Change in haemoglobin relative to baseline	Haemoglobin levels from baseline to Week 12. For this analysis, baseline haemoglobin was defined as the lowest haemoglobin value observed between and including screening and Day 1 of the study A change of haemoglobin level of ≥2 g/dL (≥20 g/L) was considered clinically meaningful based on a study by Cella et al., across 5 RCTs in anaemic cancer patients (Cella, et al., 2004)[117]
Secondary efficacy	

Haemoglobin improvement in the absence of transfusion	Proportion of participants with a haemoglobin increase of ≥2 g/dL (≥20 g/L) at Week 12 and Week 24 in the absence of transfusion
Transfusion avoidance	Proportion of participants who remain transfusion free and not requiring a transfusion as per protocol-specified guidelines[a] through Week 12 and 24 weeks of treatment
FACIT-F scores[b]	Analysis of participants with an improvement of at least 5 points in FACIT-F scores during the 12-week TP1 was performed. A change from baseline of 5 or more points is considered clinically meaningful as assessed by the scale originator (Cella et al., 2004)[117] in a PNH population
ARC	Reticulocyte counts at baseline and Week 12
Transfusion requirements	Number of RBC units transfused and number of transfusion instances
PNH-related laboratory markers	PNH RBC clone size
Safety	
TEAEs, SAEs, AEs leading to discontinuations	Evaluation, definitions, recording, follow up, and reporting of safety events, as defined in the protocol[114]
AESIs	• Meningococcal infections. MedDRA Preferred Terms of: ○ Meningococcal bacteraemia ○ Meningitis meningococcal ○ Meningococcal infection ○ Meningococcal sepsis ○ Meningococcal carditis ○ Encephalitis meningococcal ○ Endocarditis meningococcal ○ Myocarditis meningococcal ○ Optic neuritis meningococcal ○ Pericarditis meningococcal • Liver enzyme elevations: MedDRA Preferred Terms fall under the following two standardised MedDRA queries (SMQ): ○ SMQ Drug-related hepatic disorders - severe events only ○ SMQ Liver
Quality of Life	
EQ-5D-3L	The EQ-5D descriptive system uses 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with 3 response options (no problems, moderate problems, severe problems). The system defines a total of 243 unique health states[118] For the health state index, scoring algorithms derived for the United Kingdom (UK) general population were applied using individual health profiles D
EORTC-QLQ-C30	The questionnaire includes the following subscales: global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), symptom scales (fatigue, nausea and vomiting, and pain), and single items (dyspnoea, insomnia, loss of appetite, constipation, and diahorrea) and financial difficulties

	Each subscale has a range of 0% to 100%, with a high score representing a higher response level. A high score for a functional scale represents a high level of functioning, but a high score for a symptom scale represents a high level of symptomatology/problem (Version 3.0). A change of ≥ 10 points is considered clinically significant and meaningful[119]

This table summarises the safety, efficacy and other assessments presented within in this submission. Definitions for all other assessments performed during the ALPHA trial may be found in Table 5 of the CSR provided alongside this submission.
[a] Protocol-specified guidelines before and during the study recommended the administration of a pRBC transfusion if a patient had 1) haemoglobin level <7 g/dL regardless of presence of clinical signs and symptoms, or 2) haemoglobin level <9 g/dL with signs or symptoms of sufficient severity to warrant a transfusion.
[b] A 13-item questionnaire scored on a 5-point Likert scale (0 = not at all, 4 = very much) that assesses self-reported fatigue and its impact on daily activities and function. Total scores range from 0 to 52 with a higher score indicating better HRQoL.
Abbreviations: AESI: adverse events of special interest; ARC: absolute reticulocyte count; CSR: clinical study report; C3: complement component 3; C5: complement component 5; EORTC: European Organization for Research and Treatment of Cancer; EQ-5D-3L: European Quality of Life Health 5-item questionnaire dimensions 3 level; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; HRQoL: health-related quality of life; LDH: lactate dehydrogenase; LS; least squares; PNH: paroxysmal nocturnal haemoglobinuria; RBC: red blood cell; RCT: randomised controlled trial; TP: treatment period.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27]

B.2.3.3 Participant flow

A summary of patient disposition in the ALPHA trial as of the 20th September 2022 DCO is presented in Figure 5, and is summarised below by treatment period.[27]

Treatment period 1

As of the 20th September 2022 DCO, enrolment was complete with N=86 patients randomised in a 2:1 ratio of danicopan (N=57) or placebo (N=29).[1, 27]

At the DCO, 71 patients had completed TP1 (12 weeks of randomised treatment), corresponding to 48 patients in the danicopan treatment arm and 23 patients in the placebo treatment arm. Discontinuation of treatment was consistent between these treatment arms; 2 (3.5%) patients in the danicopan treatment arm discontinued treatment, both due to AEs, while 2 (6.9%) patients in the placebo treatment arm discontinued treatment due an AE (N=1) or withdrawal by participant (N=1).[1] All discontinuations were TEAEs related to liver abnormalities; discontinuation in one patient was due to SAEs of blood bilirubin increased and pancreatitis. [27]

Treatment period 2

At the 20th September 2022 DCO, 60 patients had completed TP2 corresponding to 40 (70.2%) patients who continued with danicopan through Day 1 to Week 24 (DAN/DAN), and 20 (69.0%) patients in the placebo treatment arm (TP1) who switched to receive danicopan in TP2 (Week 12–24) (PBO/DAN).[1] One occurrence of treatment discontinuation was reported in TP2; a patient in the DAN/DAN treatment arm discontinued treatment due to an AE beginning in TP1.[1, 27]

Long-term extension

While no patients had completed the LTE Year 2 at the 20th September 2022 DCO, [redacted] patients in the DAN/DAN treatment arm had completed LTE Year 1, with [redacted] patients in the PBO/DAN treatment arm completing this trial period.

In summary, there were 11 patients ongoing in TP1, 10 patients ongoing in TP2 and 55 patients ongoing in the LTE at the 20th September 2022 DCO.[1] At this time, the IAS (N=63 – see section B.2.4 for a definition of this analysis set) was comprised of [redacted] patients who had completed TP1 and [redacted] of patients who had completed TP2.[27]

Figure 5: CONSORT diagram for patient disposition in the ALPHA trial as of the 20th September 2022 DCO (all randomised participants)

A patient may contribute to more than one disposition category, In the case of the LTE, patients who have completed LTE1 ([redacted]) may be ongoing in the LTE overall ([redacted]). The LTE period is optional, therefore, patients completing TP2 may optionally end participation in the study.
Abbreviations: DAN/DAN: patients received danicopan in TP1 and continued with treatment in TP2; DCO: data cut-off; LTE: long-term extension; N: total number of patients; n: number of patients in subgroup; PBO/DAN: patients received placebo in TP1 and were subsequently treatment switched to danicopan in TP2; PNH: paroxysmal nocturnal haemoglobinuria; TP: treatment period.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.1.1.1, 14.1.1.2, 14.1.1.4.3 and 14.3.1.1.4.

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

Patient populations grouped for the purpose of analyses in the ALPHA trial are presented, and described, in Table 7.[27]

The IAS, defined as the first 75% of patients randomised to treatment with respect to the enrolment target (N=84), was used to analyse the primary, key secondary, and all other efficacy endpoints for the interim analysis of the ALPHA trial.

All safety analyses were analysed using the interim safety analysis set, comprised of all patients who received at least one dose of the study intervention by the 20th September 2022 DCO date.

Table 7: Analysis sets used in the ALPHA trial

Analysis set	Description	Number of patients at the 20th September 2022 DCO
Full analysis set (FAS)	All enrolled patients that were randomised to either the danicopan treatment arm or the placebo treatment arm.	86
Interim efficacy analysis set (IAS)	The IAS was comprised of the first 75% of patients (N=63) of the target enrolment of N=84 patients) The first interim analysis, taking place on 28th June 2022, occurred when the N=63 patients in the IAS all completed TP1 (either completed or discontinued) The second interim analysis of relevance to this submission and taking place on the 20th September 2022, occurred when the N=63 patients in the IAS all completed TP2 (either completed or discontinued)	63
Interim safety analysis set	All patients (N=86) who received at least one dose of study intervention by the 20th September 2022 interim DCO date.	86
Pharmacokinetic analysis set (PKAS)	All patients who received at least one dose of danicopan and who had evaluable PK data.	• DAN/DAN: [redacted] patients • PBO/DAN: [redacted] patients

Abbreviations: DAN/DAN: patients received danicopan in TP1 and continued with this treatment in TP2; DCO: data cut-off; FAS: full analysis set; N: number of patients; PBO/DAN: patients received placebo in TP1 and switched to danicopan in TP2; pRBC: packed red blood cell; TP: treatment period; PKAS: pharmacokinetic analysis set; PPS: per-protocol set; TP: treatment period.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.1.1.2. Kulasekararaj *et al.* (2023).[1] Lee *et al.* (2023).[109]

The statistical methods used to assess endpoints in the ALPHA trial are summarised in Table 8 below. Full details of the statistical methods used may be found in the statistical analysis plan (SAP) provided within the accompanying reference pack for this submission.[120] Unless otherwise stated, all endpoints were assessed using the IAS.

Table 8: Statistical methods for analyses in the ALPHA trial

	ALPHA
Null hypothesis	The improvement in haemoglobin level from baseline at Week 12 for danicopan is similar to the improvement for placebo; defined as the difference in mean change from baseline between danicopan and placebo at Week 12 is zero.

Statistical analysis	**Primary efficacy endpoint**
	• Statistical analysis of the primary endpoint, change in haemoglobin level from baseline at Week 12, was carried out on the IAS using a two-sided Cochran-Mantel-Haenszel (CMH) test at the 0.046 level of significance
	• Longitudinal changes from baseline in haemoglobin were analysed using a mixed model for repeated measures (MMRM)
	  ○ The model included the fixed, categorical effects of treatment, study visit and study visit by treatment group
	  ○ The continuous, fixed covariate of baseline haemoglobin was also included in the model
	  ○ The stratification randomisation indicator of transfusion history and baseline haemoglobin level (as a continuous variable) was also included in the model:
	  ▪ To address the impact of transfusion on haemoglobin levels, patients who received a transfusion on or after Week 8 of TP1 did not have Week 12 haemoglobin levels included in the primary efficacy analysis
	• The LS mean estimate and its associated standard error (SE) was calculated along with a 2-sided 95% CI
	Key secondary endpoints
	• Key secondary endpoints were assessed using a hierarchical fixed sequence test procedure, used to determine the statistical significance at a 2-sided level for each endpoint, sequentially, in the following order:
	  1. Difference in proportion of patients with haemoglobin increase of ≥2 g/dL at Week 12 in the absence of transfusions
	  2. Difference in proportion of patients with RBC transfusion avoidance between danicopan and placebo groups during the 12 weeks of treatment
	  3. Difference in changes from baseline in FACIT-F scores between danicopan and placebo groups at Week 12
	  4. Difference in changes from baseline in ARC between danicopan and placebo groups at Week 12
	  ▪ For key secondary endpoints 1) and 2), the CMH test was used to compare the danicopan and placebo treatment arms. For key secondary endpoints 3) and 4) The MMRM model, as specified for analysis of the primary endpoint, was used to compare the mean difference between danicopan add-on and placebo add-on treatment
	• The key secondary endpoints are listed above by clinical importance. In order to test the significance of the next hypothesis, the current hypothesis must be rejected; the p-value for the test statistic must be <0.05
	Other secondary and exploratory endpoints

	• Results of the remaining secondary and exploratory endpoints were analysed as follows:
	  ○ Changes in the number of transfusions units and instances (12 weeks prior and 12 weeks after initiation of study treatment) were compared between treatment groups via an analysis of covariance (ANCOVA) model
	  ○ For change from baseline to Week 12 in bilirubin, direct bilirubin, PNH RBC clone sizes (Types II and III), C3 fragment deposition on PNH RBCs and LDH, the longitudinal changes observed over TP1 were analysed using the same MMRM method used to assess the key secondary endpoints
	  ○ The number of patients with haemoglobin normalisation at Week 12 was summarised and compared between the treatment arms using the same CMH test as used to analyse the key secondary endpoints
	Subgroup/sensitivity analyses
	• In the US, a local protocol amendment necessitated the primary endpoint to be analysed via re-randomisation test. Thus, in non-US countries, a sensitivity analyses was conducted for the primary endpoint using the same re-randomisation test. For the US, the primary analyses and sensitivity analyses were reversed, that is, MMRM was used as the sensitivity analyses
	• Sensitivity analyses were conducted for the primary and key secondary endpoints using the per-protocol set (PPS), to examine the impact on results due to major protocol deviations
	• Sensitivity analyses were also conducted to assess the treatment effect of alternative missing data mechanism assumptions

Sample size, power calculations	Assuming the target enrolment of 84 patients are enrolled into the trial, and using an assumption that approximately 10% of patients would discontinue the study prior to the primary endpoint, the following power calculations applied: • For the primary endpoint, the statistical power using a two-sample t-test was 99% to detect the difference in mean change from baseline of 2 g/dL (alternative hypothesis), assuming the statistical significance level of 0.05 (two-sided) and the SD of 1.6 g/dL, which was estimated from study ACH471-101[121] • For the key secondary endpoint of patients with Hgb increase of ≥2 g/dL at Week 12 in the absence of transfusions, the study had >95% power assuming at least 35% of patients in the danicopan arm and 5% of patients in the placebo arm met the criterion • For the key secondary endpoint of patients with transfusion avoidance, the study had 70% power for the transfusion avoidance endpoint assuming that 90% of patients in the danicopan arm and 64% of patients in the placebo arm had transfusion avoidance • For the key secondary endpoint of change from baseline to Week 12 in FACIT-Fatigue score, the study had 91% power with a two-sample t-test to detect a 9-point difference between treatment arms in mean change from baseline, which is considered clinically meaningful. The power calculation was based on the assumption of a SD of 11 for FACIT-F change,

	which was observed in Study ALXN1210-PNH-301 in PNH patients. The power was 80% based on the SD assumption of 13, which was observed in Study ACH471-101[121] ○ A separate power calculation was not calculated for the IAS, as it was believed this clinical effect may be observed in smaller sample sizes
Data management, patient withdrawals	• The IAS was used as the primary population for all efficacy analyses ○ For the primary endpoint, missing haemoglobin assessments for a specific patient at each particular visit were not imputed; the MMRM can still produce valid statistical inference under the missing-at-random (MAR) missing data mechanism assumption ○ For the key secondary endpoint of transfusion avoidance at Week 12, patients who withdrew from study treatment early and/or had a missing transfusion occurrence assessment during TP1 were considered not to have achieved transfusion avoidance for this period. For the key secondary endpoint of haemoglobin increase ≥2 g/dL at Week 12 in the absence of transfusion, patients who withdrew from the study early and/or had a missing haemoglobin value at Week 12 were considered as not achieving the criterion for this endpoint. ○ For other key secondary and exploratory endpoints such as change from baseline in ARC, FACIT-F and PNH RBC clone sizes it was assumed that data were MAR and the same MMRM method as used for the primary endpoint was applied.

Abbreviations: ANCOVA: analysis of covariance; ARC: absolute reticulocyte count; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; DCO: data cut-off**;** FACIT-F: The Functional Assessment of Chronic Illness Therapy – Fatigue; FAS: full analysis set; IAS: interim efficacy analysis set; MMRM: mixed model of repeated measures; LS; least squares; PPS; per protocol set; RBC: red blood cell; SD: standard deviation; SE: standard error; TP: treatment period; US: United States.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Alexion Data on File. ALPHA Protocol (Protocol ALXN2040-PNH-301 Amendment 6.0).[114]

B.2.5 *Baseline characteristics*

Baseline characteristics split by demographics, disease characteristics and prior eculizumab or ravulizumab therapy for patients in the ALPHA trial are presented below for the IAS (N=63), the analysis set informing the efficacy results of this submission.[27]

Demographic characteristics

The baseline demographics by treatment arm, and for the total IAS, are summarised in Table 9.[27]

The mean age of patients in the IAS was 54.3 years, with a wide range of patient ages (25–80 years). The IAS also included slightly more females (37 patients [58.7%]) than males (26 patients [41.3%]). Patients were predominantly White (44.4%) or Asian (39.7%).[27, 107]

Demographic characteristics were well-balanced between the danicopan and placebo treatment arms, including the mean age at informed consent (55.0 years versus 53.1 years, respectively), distribution of race (predominantly White or Asian for both treatment arms), the mean body mass index (BMI) (26.7 kg/m^2 and 24.8 kg/m^2, respectively) and the proportion of patients with Japanese ancestry (11.9% and 9.5%, respectively). The only notable heterogeneities between treatment arms were the proportion of female patients in the danicopan treatment arm (54.8%) versus the placebo treatment arm (66.7%), along with the representation of patients with Hispanic or Latino ethnicity in each treatment arm (9.5% and 0.0%, respectively) though this difference may be partly attributable to unreported data.[27]

In terms of the generalisability of the ALPHA trial population to patients seen in clinical practice, data from the International PNH Registry indicates that the majority of registered patients are White, also indicating a slight predominance of female patients, though this varies by geographical region.[12, 66] Thus, in the absence of UK specific data, the IAS in the ALPHA trial has been demonstrated to broadly represent the global PNH population across key demographic characteristics.

Table 9: Baseline demographics of patients in the IAS in the ALPHA trial

	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=21	Total N=63
Sex, n (%)			
Female	23 (54.8)	14 (66.7)	37 (58.7)
Age (years) at informed consent, n (%)			
Mean (standard deviation [SD])	55.0 (15.6)	53.1 (14.3)	54.3 (15.1)
Median (min, max)	57.5 (25, 80)	53.0 (29, 75)	57.0 (25, 80)
Age group (years) at informed consent, n (%)			
< 65	30 (71.4)	17 (81.0)	47 (74.6)
≥ 65 to < 85	12 (28.6)	4 (19.0)	16 (25.4)
Race, n (%)			
American Indian or Alaska Native	1 (2.4)	0 (0.0)	1 (1.6)
Asian	18 (42.9)	7 (33.3)	25 (39.7)

Black or African American	1 (2.4)	0 (0.0)	1 (1.6)
White	19 (45.2)	9 (42.9)	28 (44.4)
Other	1 (2.4)	0 (0.0)	1 (1.6)
NR	2 (4.8)	4 (19.0)	6 (9.5)
Unknown	0 (0.0)	1 (4.8)	1 (1.6)
Ethnicity, n (%)			
Hispanic or Latino	4 (9.5)	0 (0.0)	4 (6.3)
Not Hispanic or Latino	34 (81.0)	17 (81.0)	51 (81.0)
NR	4 (9.5)	4 (19.0)	8 (12.7)
BMI (kg/m^2)			
Mean (SD)	26.7 (5.4)	24.8 (4.9)	26.1 (5.3)
Min, max	19.7, 49.3	18.4, 37.1	18.4, 49.3
Japanese ancestry, n (%)			
No	37 (88.1)	19 (90.5)	56 (88.9)
Yes	5 (11.9)	2 (9.5)	7 (11.1)

[a] Eculizumab or ravulizumab.
Abbreviations: BMI: body mass index; C5i: complement component 5 inhibitor; N: number of patients in treatment group; n: number of patients; NR: not reported; SD: standard deviation.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Tables 14.1.2.1.1 and 14.1.2.1.2. Lee, *et al.* EHA conference (2023).[107]

Disease characteristics

Baseline disease characteristics for the IAS are presented in Table 10.[27]

The mean age at PNH diagnosis in the IAS was 43.1 years; the mean number of years from diagnosis to informed consent was 11.8 years. When considering baseline fatigue scores (a mean FACIT-F score of 33.6), the baseline haemoglobin level (7.69 g/dL) and the baseline ARC (0.2 x 1012/ L) of the IAS, these data are strongly indicative of a patient population experiencing csEVH in the absence of a definitive clinical criteria. Furthermore, the baseline LDH level of the IAS was 292.1 U/L, within the reference range (135–330 U/L) reflecting control of IVH through C5 inhibitor treatment).[27, 122]

The majority of the baseline disease characteristics were broadly aligned between the danicopan and the placebo treatment arms, including age at diagnosis (44.2 years and 40.8 years, respectively), age from diagnosis to informed consent (11.3 years and 12.8 years, respectively), baseline haemoglobin levels (7.66 g/dL and 7.74 g/dL, respectively), baseline FACIT-F scores (33.5 and 33.9, respectively) and baseline ARC (0.2 x 10^{12}/L in both treatment arms).[107] However, the danicopan treatment arm had slightly elevated LDH levels at baseline (298.7 U/L) compared to the placebo treatment arm (278.3 U/L).[107] Baseline PNH RBC clone sizes also varied slightly between the treatment arms, however, these differences were not consistent across the PNH RBC clone types.

In terms of the generalisability of baseline disease characteristics in the ALPHA trial to clinical practice, the baseline FACIT-F score in the IAS was aligned with values previously reported in the published literature for patients with PNH.[44, 123] As described in Table 6 (Section B.2.3.2), a lower FACIT-F score indicates greater fatigue, expected to translate to a reduction in patient

HRQoL as indicated in the published literature.[12, 17, 124] Comparing to general population norms for FACIT-F scores reported for European countries and the US in the published literature (43.5 for Germany and 43.6 for the US),[123, 125] fatigue in the ALPHA trial population was substantially increased compared to the general public, as expected. Indeed, UK clinical experts in PNH consulted as part of an advisory board confirmed that the impact of fatigue on patients' daily lives is often taken into consideration when determining whether a patient has csEVH.[4] Thus, low FACIT-F scores are in line with clinical expectations for this population. Furthermore, a retrospective analysis of 509 PNH patients receiving eculizumab or ravulizumab in the UK between May 2002 to July 2022, found the mean age at diagnosis of PNH was 43 years and 11 months.[106] The average age at diagnosis of PNH for the IAS is therefore aligned with that observed in UK clinical practice. The clinical experts in PNH also highlighted that the mean baseline haemoglobin value for the IAS was low, indicating a trial population with severe anaemia, as expected for a population experiencing csEVH.[4]

The same retrospective analysis discussed above reported a median PNH granulocyte clone size of 85.5% prior to initiation of C5 inhibitor treatment, though larger clone sizes prior to initiation of eculizumab (96.4%) were reported in an alternative retrospective analysis conducted in 79 patients with PNH in the UK.[106, 126] A case series recruiting a smaller sample size of N=20 patients diagnosed with PNH (and Budd-Chiari syndrome) in the UK receiving eculizumab reported a median PNH RBC granulocyte size of 90% (range: 59.7–99.5%).[127] Thus, baseline RBC PNH granulocyte size of patients in the ALPHA trial (98.2 (63.5, 100.0) may be considered broadly aligned, albeit slightly higher, than both treated and untreated patients with PNH in UK clinical practice. Upon initiation of C5 or C3 inhibitor treatment, PNH clone sizes are typically monitored 3 monthly, then 6 monthly to detect any unexpected changes.[49, 50]

Table 10: Baseline disease characteristics of patients in the IAS in the ALPHA trial

	Danicopan + C5 inhibitor N=42	Placebo + C5 inhibitor N=21	Total N=63
Age (years) at PNH diagnosis			
n	42	21	63
Mean (SD)	44.2 (16.6)	40.8 (16.3)	43.1 (16.4)
Median (min, max)	45.0 (11.6, 76.4)	41.0 (18.0, 69.8)	43.6 (11.6, 76.4)
Years from diagnosis to informed consent			
n	42	21	63
Mean (SD)	11.3 (10.6)	12.8 (10.4)	11.8 (10.5)
Median (min, max)	7.3 (0.9, 49.6)	10.8 (1.2, 39.6)	8.8 (0.9, 49.6)
Haemoglobin at Baseline (g/dL)			
n	42	21	63
Mean (SD)	7.66 (0.94)	7.74 (1.04)	76.69 (0.96)
Median (min, max)	77.5 (57, 94)	78.0 (54, 93)	78.0 (54, 94)
FACIT-Fatigue scores at Baseline			
n	42	21	63
Mean (SD)	33.5 (11.1)	33.9 (10.8)	33.6 (10.9)
Median (min, max)	36.0 (9.0, 51.0)	37.0 (12.0, 52.0)	37.0 (9.0, 52.0)

ARC at Baseline (10^{12}/L)			
n	42	20	62
Mean (SD)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)
Median (min, max)	0.2 (0.1, 0.5)	0.2 (0.1, 0.5)	0.2 (0.1, 0.5)
PNH Clone Size at Baseline			
Total PNH RBC Clone Size (Type II + Type III) (%)			
n	14	9	23
Mean (SD)	51.6 (25.4)	65.5 (29.6)	57.1 (27.3)
Median (min, max)	51.5 (14.1, 87.8)	69.6 (19.3, 100.0)	60.5 (14.1, 100.0)
PNH RBC Type III Clone Size (%)			
n	24	10	34
Mean (SD)	47.5 (22.2)	51.7 (29.0)	48.8 (24.0)
Median (min, max)	49.0 (11.6, 92.7)	47.2 (17.1, 99.9)	47.2 (11.6, 99.9)
PNH RBC Type II Clone Size (%)			
n	14	8	22
Mean (SD)	6.9 (12.6)	6.1 (5.3)	6.6 (10.4)
Median (min, max)	0.8 (0.1, 36.8)	6.0 (0.1, 14.5)	1.2 (0.1, 36.8)
PNH Granulocyte Clone Size (%)			
n	29	10	39
Mean (SD)	94.6 (9.6)	96.6 (4.9)	95.1 (8.6)
Median (min, max)	98.2 (63.5, 100.0)	98.3 (83.7, 100.0)	98.2 (63.5, 100.0)
C3d PNH Type 3 Cells (%)[a]			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
LDH at Baseline (U/L)			
n	42	20	62
Mean (SD)	298.7 (105.7)	278.3 (68.4)	292.1 (95.2)
Median (min, max)	261.0 (165.5, 734.5)	257.3 (180.0, 404.0)	261.0 (165.5, 734.5)

[a] C3d is a fragment of complement factor C3.
Abbreviations: ARC: absolute reticulocyte count; C5: complement component 5; IAS; interim efficacy analysis set; LDH: lactate dehydrogenase; N: number of patients in treatment group; n: number of patients; PNH: paroxysmal nocturnal haemoglobinuria; RBC: red blood cell; SD: standard deviation.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.1.3.1.1. Lee et al. EHA conference (2023).[107]

Prior treatments

Details of the prior treatments received by patients in the IAS in terms of C5 inhibitors (eculizumab or ravulizumab) and blood transfusions are provided in Table 11.[27]

In the IAS, patients had been receiving their current eculizumab or ravulizumab treatment for a mean duration of 4.1 years up to the first dose of study intervention, increasing to 5.9 years from their initial eculizumab or ravulizumab treatment. This indicates that the IAS comprised a population of patients stable on eculizumab or ravulizumab therapy for a substantial amount of

time. Mean age at first eculizumab or ravulizumab infusion was 49.1 years. The number of patients receiving a pRBC transfusion in the 24 weeks prior to first study dose (55 patients, 87.3%) and the mean number of transfusion instances in the same timeframe (2.6) for the IAS indicates a population dependent on occasional transfusions. Transfusion requirements have been used in prior trials in PNH to characterise csEVH.[4, 14, 77] Overall, slightly more patients in the IAS received ravulizumab (58.7%) compared to eculizumab (41.3%).

Baseline prior treatment characteristics were broadly similar between the danicopan and placebo treatment arms in terms of age at first eculizumab or ravulizumab infusion (50.1 and 47.1 years, respectively), duration of current eculizumab or ravulizumab treatment (3.9 years and 4.5 years, respectively), proportion of patients receiving a pRBC transfusion in the 24 weeks prior to the first study dose (90.5% and 81.0%, respectively) and mean transfusion instances during this time (2.5 and 2.6, respectively). Furthermore, patients had received a mean number of 4.3 and 4.4 units transfused within this timeframe, respectively. Slight differences between the treatment arms were observed in the durations of initial and current eculizumab or ravulizumab treatment to first dose of study intervention, as 5.5 and 3.9 years for the danicopan and 6.7 and 4.5 years in the placebo treatment arms, respectively. Furthermore, eculizumab use was higher in the placebo treatment arm (52.4% of patients) versus the danicopan treatment arm (35.7% of patients). A clinical expert consulted to support this submission stated that these differences in prior C5 inhibitor treatment were not clinically relevant.[49, 50]

Whilst a discrepancy exists between treatment arms, the predominant use of ravulizumab over eculizumab in the IAS and both treatment arms aligns with data from the retrospective analysis of PNH patients treated with eculizumab or ravulizumab in the UK, Kelly et al. (2022) whereby 53.4% and 46.6% of patients received ravulizumab and eculizumab, respectively.[106] Age of initiation of C5 inhibitor treatment in the ALPHA trial is supported data observed in UK clinical practice; Kelly et al. (2011)[126] reported a median age of initiation of eculizumab as 46 years, from 76 patients with PNH consulted at the Leeds Teaching Hospitals PNH Centre, UK.

Table 11: Prior treatments received by patients in the IAS in the ALPHA trial

	Danicopan + C5i[a] N=42	Placebo + C5i[a] N= 21	Total N=63
Current C5i, n (%)			
n	42	21	63
Ravulizumab	27 (64.3)	10 (47.6)	37 (58.7)
Eculizumab	15 (35.7)	11 (52.4)	26 (41.3)
Age (years) at first C5i infusion			
n	42	21	63
Mean (SD)	50.1 (15.3)	47.1 (14.6)	49.1 (15.0)
Median	53.5	47.6	50.6
Min, max	20.9, 76.9	20.5, 70.4	20.5, 76.9
Duration (years) from initial C5i to first dose of study intervention			
n	42	21	63
Mean (SD)	5.5 (3.9)	6.7 (4.6)	5.9 (4.1)
Median	4.3	5.2	4.5

Min, max	0.8, 15.8	0.7, 16.8	0.7, 16.8
Duration (years) from start of current C5i to first dose of study intervention			
n	42	21	63
Mean (SD)	3.9 (3.3)	4.5 (4.0)	4.1 (3.5)
Median	3.6	3.7	3.7
Min, max	0.5, 14.2	0.7, 16.8	0.5, 16.8
Number of patients with pRBC transfusions during the 24 weeks prior to first dose			
n (%)	38 (90.5)	17 (81.0)	55 (87.3)
Number of transfusion instances within 24 weeks prior to receiving study intervention			
Mean (SD)	2.5 (2.2)	2.6 (2.1)	2.6 (2.1)
Median (min, max)	2.0 (0, 8)	3.0 (0, 8)	2.0 (0,8)
Number of units transfused within 24 weeks prior to receiving study intervention			
Mean (SD)	4.3 (4.7)	4.4 (3.8)	4.3 (4.4)
Median (min, max)	2.0 (0, 20)	4.0 (0, 12)	3.0 (0, 20)

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; IAS: interim efficacy analysis set; n: number of patients; pRBC: packed red blood cell; SD: standard deviation.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Tables 14.1.3.1.1 and 14.1.3.1.5. Lee *et al.* EHA conference (2023)[107]

B.2.6 *Critical appraisal of the relevant clinical effectiveness evidence*

The ALPHA trial was assessed for the risk of bias and generalisability using the Cochrane Risk of Bias tool. Using the Lee et al. (2023) conference abstract and the ALPHA CSR (20th September 2022 DCO) and protocol (V.6) (Alexion Data on File), a quality assessment of the ALPHA trial is summarised below in Table 12.[27, 107, 114]

Table 12: Overview of the quality assessment of the ALPHA trial

Criteria	Outcome	Justification	Relevant section in Document B
Was randomisation carried out appropriately?	Yes	The methods of randomisation were not described in the conference abstract, however, details on randomisation were provided in the protocol for the ALPHA trial (stochastic dynamic allocation rules using IRT).	Section B.2.3.2.
Was the concealment of treatment allocation adequate?	Yes	Methods of blinding were not described in conference abstract, however, details on adequate concealment were provided in the protocol and CSR. Patients were randomised via IRT in a 2:1 ratio to receive either danicopan and placebo. Dose escalations were performed in both treatment arms to maintain blinding until	Section B.2.3.2.

		Week 12 of the trial, after which all patients received danicopan add-on treatment.	
Were the trial arms similar at the outset of the study in terms of prognostic factors?	Partially	Baseline characteristics between the trial arms appear similar, however, no analysis was presented within the conference abstract. The CSR states that demographic and disease characteristics were generally balanced between treatment arms.	Section B.2.5.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	The ALPHA trial was randomised and double-blind, during the initial 12 weeks of treatment for which the primary and key secondary outcomes were assessed during, with a 2:1 parallel assignment as described in the conference abstract.	Section B.2.3.2.
Were there any unexpected imbalances in drop-outs between trial arms?	No	As of 28th June 2022, N=73 patients were randomised and N=63 patients were included in the IAS. No additional information was provided in the conference abstract regarding any drop-outs or missing data between arms. However, as discussed in Section B.2.3.3, the CSR reports that discontinuations taking place during TP1 and TP2 of the ALPHA trial were infrequent and broadly aligned between treatment arms.	Section B.2.3.3.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Partially	There was no evidence in the conference abstract to suggest that additional outcomes were measured outside of the primary and secondary endpoints. The CSR lists all exploratory endpoints that were assessed in the ALPHA trial.	Section B.2.3.1.
Did the analysis include an	Yes	No ITT analysis was performed in the conference abstract.	Section B.2.4.

intention-to-treat (ITT) analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		However, the CSR states that the FAS (at 20th September 2022, the N=63 patients who completed TP2) were analysed using the ITT principle.	

Abbreviations: CSR: clinical study report; IAS: interim efficacy analysis set; IRT: interactive response technology; ITT: intention to treat; TP: treatment period.

B.2.7 *Clinical effectiveness results of the relevant studies*

B.2.7.1 Efficacy endpoints at Week 12

Unless otherwise specified, the data presented in this section are based on the 20th September 2022 DCO.[27] All efficacy analyses were performed using the IAS, defined as the first 75% of randomised patients out of the enrolment target (63 patients, out of the N=84 target enrolment) (Section B.2.4, Table 7).

The primary efficacy endpoint in the ALPHA trial was change in haemoglobin level from baseline at Week 12, with all key secondary endpoints also assessed at Week 12, corresponding with the end of the placebo-controlled initial TP1. The results of the primary and all key secondary efficacy endpoints of the ALPHA trial are summarised below, with a summary of secondary efficacy endpoints assessed at Week 24, corresponding to the end of TP2, provided in Section B.2.7.3.

Due to the known correlation between the mechanism of action of danicopan (proximal complement inhibition) and the subsequent increase of PNH RBC clone size,[53] changes from baseline across PNH RBC clone size types at Week 12 were also investigated, and presented in the following section, as a secondary endpoint in the ALPHA trial.

Definitions for each endpoint are provided in Section B.2.3.2, Table 6.

Primary endpoint: Change in haemoglobin from baseline to Week 12

Danicopan resulted in a statistically significant and clinically meaningful increase in haemoglobin from baseline to Week 12, when compared with placebo ($p<0.0001$), as shown in Table 13.[27] The LS mean changes in haemoglobin from baseline to Week 12 in the danicopan treatment arm and the placebo treatment arm were 2.94 g/dL and 0.50 g/dL, respectively. Accordingly, the ALPHA trial met its primary endpoint.[109]

Table 13: Change in haemoglobin from baseline to Week 12 (IAS)

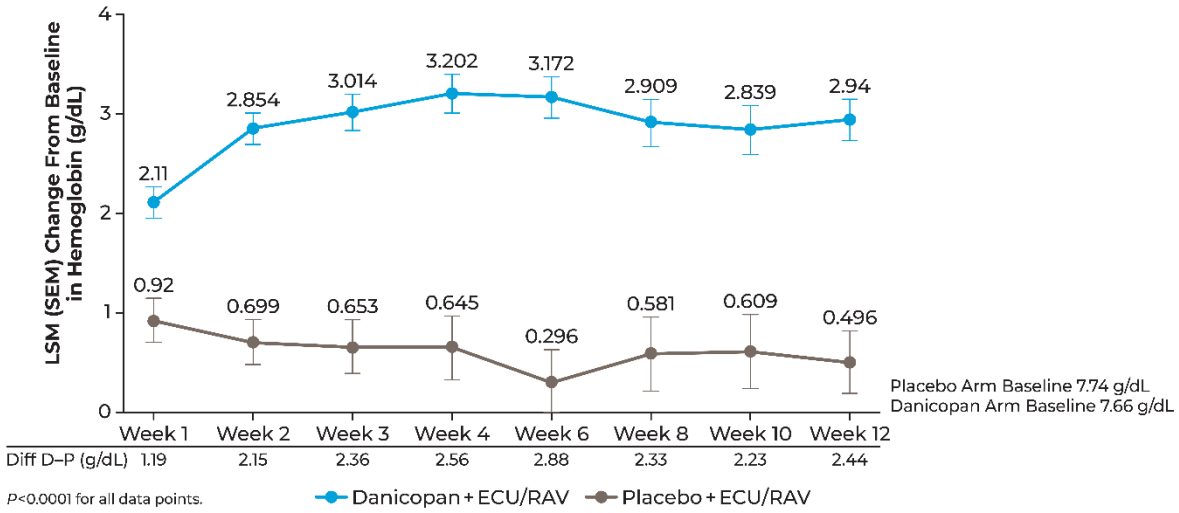
	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=21	Difference (Danicopan - Placebo)	p-value
LS mean (SE), g/dL	2.94 (0.21)	0.50 (0.31)	2.44 (0.38)	<0.0001 (MMRM)[a,b]
95% CI for LS mean	2.52, 3.36	-0.13, 1.12	1.69, 3.20	

[a] Eculizumab or ravulizumab.
[b] For non-US countries, the test for treatment group differences directly from the MMRM using the actual treatment assignments was considered as the primary analysis. The re-randomisation test for treatment group differences was considered as a sensitivity analysis.
[c] For the US, the primary test for statistical significance of the treatment group difference between danicopan and placebo was conducted via a re-randomisation test method. The test for treatment group differences from the MMRM was considered as a sensitivity analysis. P-value for the re-randomisation test method was p=0.0007
Abbreviations: C5i: complement component 5 inhibitor; CI: confidence interval; IAS: interim efficacy analysis set; LS: least squares; MMRM: mixed model for repeated measures; N: number of patients; SE: standard error; US: United States.
Source: Lee *et al.* (2023).[109]

A change in haemoglobin level by ≥2 g/dL was considered as clinically meaningful based on the study by Cella, et al. in 2004, conducted across five RCTs in anaemic cancer patients.[117] The same study demonstrated that an increase in haemoglobin by ≥2 g/dL resulted in increases of FACIT-F scores between 2.8–5.8, depending on patient subgroup. The clinically significant increase in haemoglobin levels due to danicopan is therefore anticipated to translate to reduced fatigue, a key symptom of csEVH,[4] and a key driver of reduction in patient HRQoL as indicated in the published literature.[17, 124, 128]

Change from baseline in haemoglobin level by study visit (by week) is illustrated by Figure 6.[27] Baseline haemoglobin levels were comparable between treatment arms, with this figure illustrating the rapid onset of the treatment effect of danicopan. At Week 1, differences in change from baseline in haemoglobin levels due to danicopan were statistically significant (p<0.0001) and clinically meaningful, and remaining stable throughout TP1.[109]

Figure 6: LS mean change from baseline in haemoglobin through Week 12 (IAS)

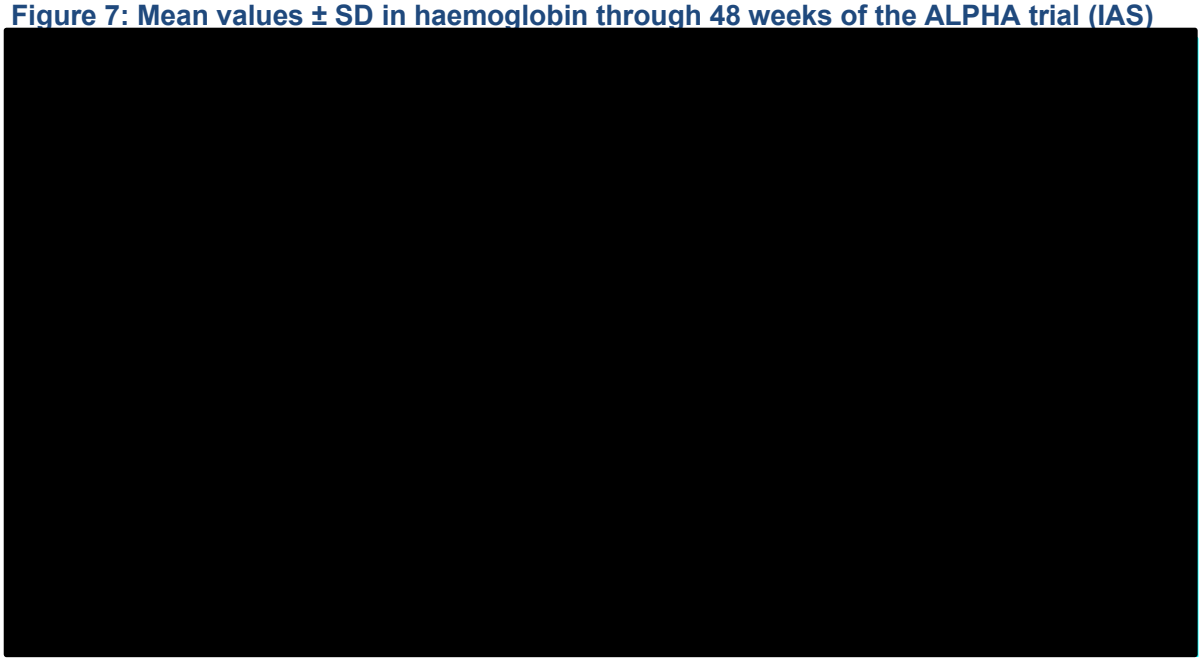


Abbreviations: D – P: danicopan – placebo; ECU: eculizumab; IAS: interim efficacy analysis set; LSM: least squares mean; RAV: ravulizumab; SEM: standard error of the mean; TP: treatment period; W: week.

Source: Lee *et al.* EHA conference (2023).[107, 109]

The mean absolute values of haemoglobin level for each treatment arm, by study visit, are presented in Figure 7, as supportive evidence for the comparative treatment effect of danicopan on patient haemoglobin levels.[27] As shown below, mean haemoglobin levels for both treatment arms were similar at baseline, with danicopan treatment resulting in higher mean haemoglobin levels from Week 2 and onwards in the randomised period (to Week 12). At Week 12, upon switching patients from placebo to danicopan, a rapid improvement in haemoglobin levels was observed. In both treatment arms, haemoglobin levels were subsequently maintained up to Week 48.[107]

Figure 7: Mean values ± SD in haemoglobin through 48 weeks of the ALPHA trial (IAS)



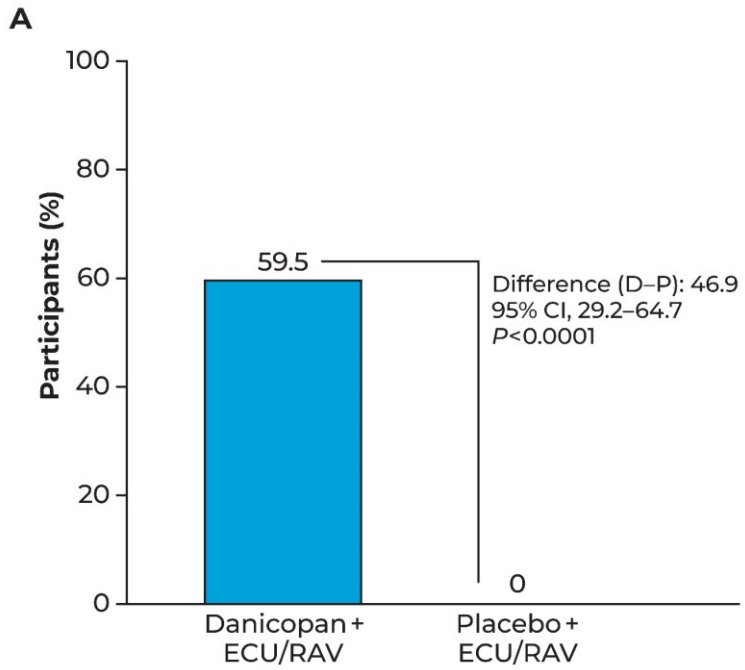
Abbreviations: IAS: interim efficacy analysis set; N: number of patients at study visit; SD: standard deviation.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Figure 14.2.1.1.4, Figure 14.2.1.1.4.1.

Key secondary endpoint: Proportion of patients with a haemoglobin increase of ≥2 g/dL at Week 12 in the absence of transfusion

The proportion of patients with a haemoglobin increase of ≥2 g/dL in the absence of transfusion was assessed, in order to differentiate changes in haemoglobin level due to danicopan add-on treatment from changes in haemoglobin level due to the receipt of blood transfusions.

At Week 12, over half of all patients in the IAS (59.5%) receiving danicopan had achieved a clinically significant increase in haemoglobin of ≥2 g/dL in the absence of transfusion,[117] compared to no patients receiving placebo, as presented in Table 14.[27] The difference in haemoglobin level increase in the absence of transfusion between the danicopan and placebo treatment arms was statistically significant ($p<0.0001$), and is illustrated by Figure 8.[109]

Figure 8: Comparative proportion of patients with haemoglobin increase ≥ 2 g/dL at Week 12 in the absence of transfusion (IAS)



Abbreviations: CI: confidence interval; D–P: Danicopan – placebo; ECU: eculizumab; IAS: interim efficacy analysis set; RAV: ravulizumab.
Source: Lee *et al.* EHA conference (2023).[107, 109]

This key secondary endpoint supported the superiority of danicopan versus placebo in helping to restore haemoglobin levels in patients with EVH. Anaemia resulting from EVH is associated with symptoms such as fatigue, dyspnoea, headache and weakness.[129] Accordingly, corresponding HRQoL benefits to patients through effective anaemia treatment are expected with danicopan add-on treatment.

Table 14: Proportion of patients with haemoglobin increase of ≥2 g/dL at Week 12 in the absence of transfusion (IAS)

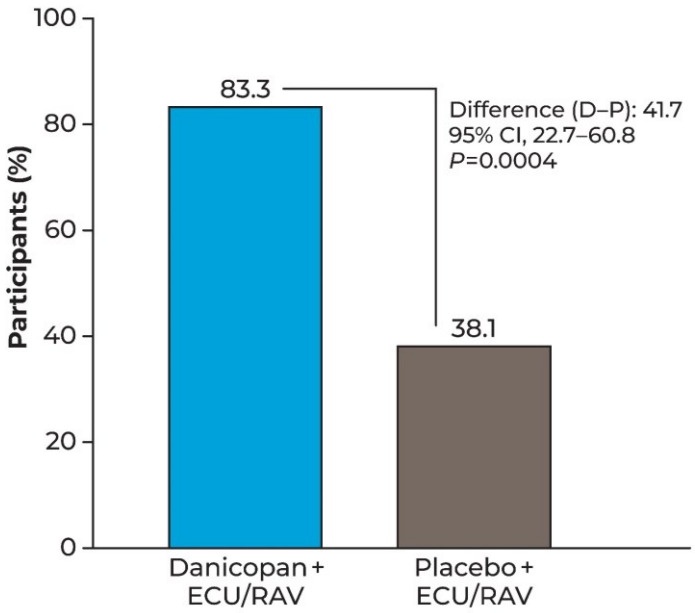
	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=21	Treatment Difference (Danicopan - Placebo)
Number of participants (n)	25	0	N/A
Percentage (%)	59.5	0	46.9
95% CI	43.3, 74.4	0.0, 16.1	29.2, 64.7
Stratified CMH p-value			<0.0001

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; IAS: interim efficacy analysis set; N: number of patients in treatment group; n: number of patients; N/A: not applicable.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.2.2.1.1. Lee, *et al.* (2023).[109]

Key secondary endpoint: Proportion of patients with transfusion avoidance at Week 12

Transfusion avoidance was defined as a patient remaining transfusion free and not requiring a transfusion as per protocol specified guidelines (provided in Section B.2.3.2, Table 6).[27] At Week 12, danicopan resulted in a statistically significant (p=0.0004) increase in transfusion avoidance (83.3%) compared to placebo (38.1%), as illustrated by Figure 9 and shown by Table 15.

Figure 9: Comparative proportion of patients with transfusion avoidance through Week 12 (IAS)



Abbreviations: CI: confidence interval; D–P: Danicopan – placebo; ECU: eculizumab; IAS: interim efficacy analysis set; RAV: ravulizumab.
Source: Lee *et al.* EHA conference (2023).[107]

Transfusion dependence is prevalent across the PNH population treated with eculizumab or ravulizumab, with 20% of treated patients requiring occasional transfusions.[95] In a retrospective study of 509 patients with PNH treated with eculizumab or ravulizumab in the UK, 27.6% of patients required blood transfusions in the most recent 12 months, of which 76.4% required three of more transfusions.[106] As discussed in Section B.1.3.2, transfusions are associated with a high administration-related burden for patients and logistical challenges for the NHS.[77-79] Further, transfusion dependence can lead to iron overload and accompanying complications.[100, 130] Improvements in transfusion avoidance can therefore be expected to reduce the treatment burden on affected patients as well as the healthcare system.

Table 15: Proportion of patients achieving transfusion avoidance through Week 12 (IAS)

	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=21	Treatment Difference (Danicopan - Placebo)
Number of participants (n)	35	8	N/A
Percentage	83.3	38.1	41.7
95% CI	68.6, 93.0	18.1, 61.6	22.7, 60.8
Stratified CMH p-value			0.0004

[a] Eculizumab or ravulizumab.

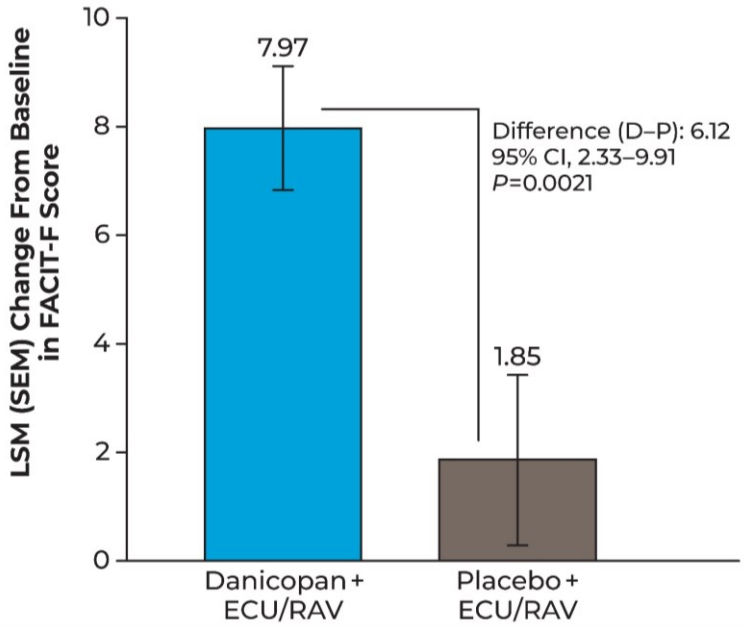
Abbreviations: C5i: complement component 5; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; IAS: interim efficacy analysis set; N: number of patients in treatment group; n: number of patients; N/A: not applicable.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.2.2.2.1. Lee, *et al.* (2023).[109]

Key secondary endpoint: change from baseline in FACIT-F scores at Week 12

Treatment with danicopan resulted in a statistically significant (p=0.0021) and clinically meaningful improvement in change from baseline in FACIT-F score (7.97) versus placebo (1.85), as illustrated in Figure 10.[27]

These results (Table 16) support the treatment effect of danicopan in reducing fatigue in patients with csEVH, a key unmet need in this indication, as confirmed by UK clinical experts in PNH.[4] Indeed, at baseline, [redacted] of patients in each treatment arm reported fatigue, indicating the prevalence of this symptom across the patient population.[27]

Figure 10: Comparative change from baseline in FACIT-F scores at Week 12 (IAS)



Abbreviations: CI: confidence interval; D–P: Danicopan – placebo; ECU: eculizumab; FACIT-F: The Functional Assessment of Chronic Illness Therapy – Fatigue; IAS: interim efficacy analysis set; LSM: least square mean; RAV: ravulizumab; SEM: standard error of the mean.
Source: Lee, *et al.* EHA conference (2023).[107, 109]

Table 16: Change from baseline in FACIT-F scores at Week 12 (IAS)

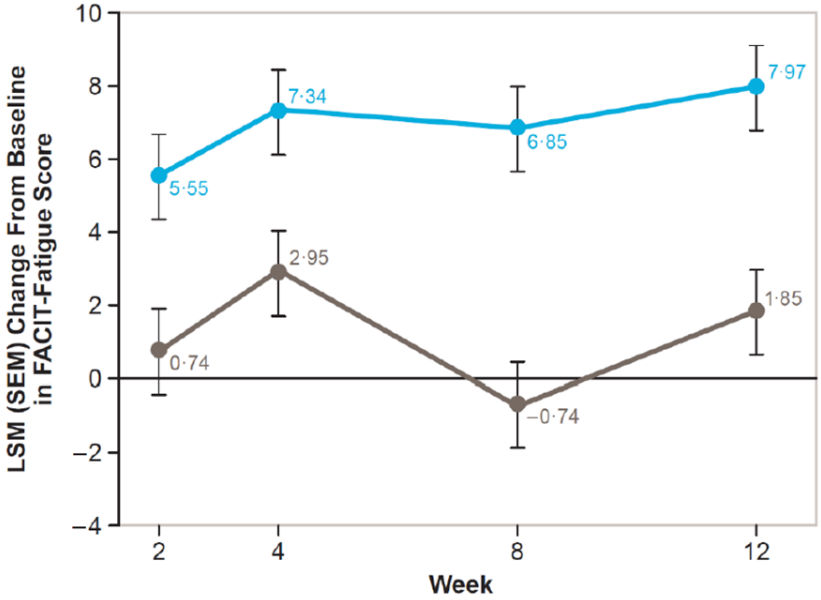
	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=21	Difference (Danicopan-Placebo)	p-value
LS mean (SE)	7.97 (1.13)	1.85 (1.58)	6.12 (1.89)	0.0021
95% CI for LS mean	5.72, 10.23	−1.31, 5.02	2.33, 9.91	

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; CI: confidence interval; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; IAS: interim efficacy analysis set; LS: least squares; N: number of patients in treatment group; SE: standard error.

Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.2.2.3.1.Lee, *et al.* (2023).[109]

Change from baseline in FACIT-F score by visit is illustrated in Figure 11.[27] A change in FACIT-F score of ≥5 is considered to be clinically meaningful, according to Cella et al. 2021, a study conducted specifically in PNH patients.[131] Thus, clinically meaningful differences between danicopan and placebo were observed from [redacted] onwards. At Week 12, [redacted] of the patients in the danicopan treatment arm had a clinically meaningful change in fatigue score (improvement of at least 5 points), compared with [redacted] in the placebo treatment arm. Danicopan therefore reduced fatigue, a key symptom and key unmet need in csEVH, by [redacted] compared to placebo.[4]

Figure 11: Change from baseline in FACIT-F scores through Week 12 (IAS)

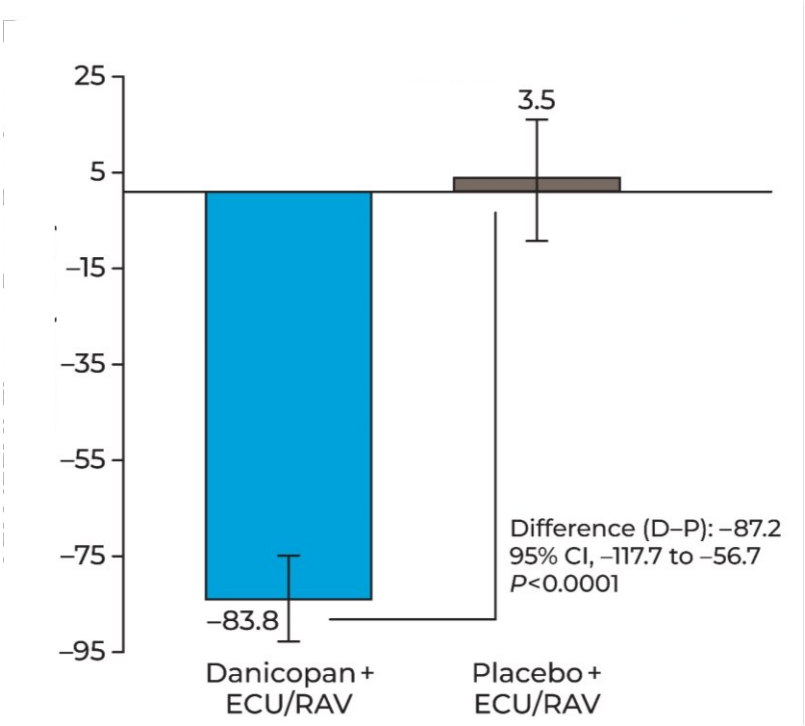


Footnotes: The blue line represents the danicopan treatment arm and the grey line represents the placebo treatment arm.
Abbreviations: FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; IAS: interim efficacy analysis set; LSM: least squares mean; SEM: standard error of the mean.
Source: Lee *et al.* (2023) Supplementary materials.[107]

Key secondary endpoint: Change from baseline in ARC at Week 12

At Week 12, danicopan resulted in a statistically significant decrease from baseline in ARC ($p<0.0001$) (Table 17) compared with placebo, as illustrated in Figure 12.[27]

Figure 12: Comparative change from baseline in ARC at Week 12 (IAS)[a]



Footnotes: [a]Units of ARC in this figure are expressed as 10^9/L.
Abbreviations: ARC: absolute reticulocyte count; CI: confidence interval; D–P: Danicopan – placebo; ECU: eculizumab; IAS: interim efficacy analysis set; LSM: least squares mean; RAV: ravulizumab; SEM: standard error of the mean..
Source: Lee, *et al.* EHA conference (2023).[107]

A 2017 study conducted in 141 patients with PNH treated with eculizumab concluded that reticulocyte counts are a better indicator of EVH than LDH levels.[7] Reticulocyte counts are typically elevated in haemolysis as a compensatory response to decreased RBC levels, and a decrease in reticulocyte count is an important marker of recovery from haemolysis,[115, 116] Thus, these data indicate that danicopan results in improved control of EVH versus.

Table 17: Change from baseline in ARC at Week 12 (IAS)

	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=20	Difference (Danicopan – Placebo)	p-value
LS mean (SE), 10^9/L	−83.8 (8.93)	3.5 (12.7)	−87.2 (15.3)	<0.0001
95% CI for LS mean	−101.6, -65.9	−21.9, 28.8	−117.7, -56.7	

[a] Eculizumab or ravulizumab.
Abbreviations: ARC: absolute reticulocyte count; C5i: complement component 5 inhibitor; CI: confidence interval; IAS: interim efficacy analysis set; LS: least squares; SE: standard error.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.2.2.4.1. Lee *et. al* (2023).[109]

Overall, clinical experts in PNH consulted as part of a UK advisory board found that the key secondary results of the ALPHA trial, including change in baseline of FACIT-F scores, ARC and transfusion avoidance, were positive and reassuring in terms of patient improvements of csEVH.[4]

B.2.7.2 Changes in PNH red blood cell clone size at Week 12

Table 18 presents the resulting changes in PNH RBC clone size at Week 12 for danicopan versus placebo.[27] Changes in size are presented for type II clones (partial GPI-anchored protein deficiency) and type III clones (complete GPI-anchored protein deficiency).

In line with clinical expectations for the mechanism of action (MoA) of danicopan, which addresses EVH through proximal complement inhibition, PNH RBC clone sizes are anticipated to increase after initiation of treatment. This effect has also been observed with pegcetacoplan, an alternative proximal complement inhibitor, for which patients have reported increases in PNH RBC clone size of up to 98% after initiating treatment.[53]

Changes in PNH RBC clone size at Week 12 were therefore studied as a secondary endpoint in the ALPHA trial. As expected, clone size increased from baseline to Week 12 for total (24.60% versus -3.04%) and Type III ([redacted] versus [redacted]) PNH RBC size for danicopan versus placebo.[27, 109] For PNH RBC Type II clone sizes, a reduction in clone size from baseline was reported at 12 weeks for danicopan, compared with an increase in clone size for placebo ([redacted] versus [redacted]). The absolute PNH RBC clone cell sizes observed at Week 12 upon treatment with danicopan ([redacted] of total PNH RBC clones [type II and type III]) are therefore lower than those reported for relevant comparator treatments (pegcetacoplan) previously accepted for use for anaemia in PNH.[53]

As highlighted by Notaro et al. (2022), if a haemolysis event were to occur in a patient treated with a proximal inhibitor, a more severe episode of BTH may occur due to the higher proportion of PNH RBCs present (an increase in PNH clone size is observed with proximal complement inhibition).[53] The increase in PNH RBC clone observed is due to the proximal complement inhibition, allowing a higher proportion of PNH RBCs to survive in the blood, leading to a larger haemoglobin drop in the event of BTH.[53]

Due to the efficacy of danicopan add on treatment to eculizumab or ravulizumab in preventing serious BTH events, as demonstrated in Section B.2.11.4, the known effect of the MoA of danicopan add on treatment on PNH RBC clone size is not considered a concern, as C5 complement inhibition provides sustained inhibition of IVH. This was supported by feedback received during several validation meetings held with UK clinical experts; changes seen in the clone size for danicopan are similar or lesser to those observed in clinical practice for pegcetacoplan, and clone size is not considered a substantial concern for C5 inhibitor treated patients, due to the low risk of BTH. Monitoring of clone sizes will take place on a 3–6 monthly basis in clinical practice.[49, 50]

Table 18: Change from baseline in PNH RBC clone size (%) at Week 12 (IAS)

	Danicopan + C5i[a]	Placebo + C5i[a]	Difference (Danicopan – Placebo)	p-value
Total PNH RBC Clone Size (Type II + Type III)				
Week 12	[redacted]	[redacted]	[redacted]	
LS mean (SE)	24.60 (4.18)	−3.04 (5.86)	27.63 (6.91)	0.0010
95% CI for LS mean	15.78, 33.42	−15.32, 9.25	13.03, 42.24	
PNH RBC Type III Clone Size				

Week 12	[redacted]	[redacted]	[redacted]	
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
PNH RBC Type II Clone Size				
Week 12	[redacted]	[redacted]	[redacted]	
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	

[a] Eculizumab or ravulizumab.
[b] While samples were collected, some could not be analysed due to quality issues.
Abbreviations: C5i: complement component 5 inhibitor; CI: confidence interval; IAS: interim efficacy analysis set; LS: least squares; N: number of patients; N/A: not applicable; PNH: paroxysmal nocturnal haemoglobinuria; RBC: red blood cell; SE: standard error.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.2.3.4.1. Lee *et al.* Supplementary materials (2023).[27]

B.2.7.3 Efficacy endpoints at Week 24

Change in haemoglobin from baseline to Week 24

For those patients who continued on treatment with danicopan through Weeks 12–24 (DAN/DAN), improvements in haemoglobin were maintained from Week 12–24, as shown by Figure 13.[27] At Week 24, LS mean change from baseline in haemoglobin was 3.17 (SE: 3.02) g/dL in this treatment arm. For those patients who treatment switched from placebo to danicopan (PBO/DAN) at Week 12, change from baseline in haemoglobin at Week 24 was 2.26 (SE: 3.40) g/dL, indicating sustained meaningful improvements in haemoglobin levels.[1]

Figure 13: LS change from baseline in haemoglobin through Week 24 (IAS)

Abbreviations: C5: complement component 5; D>D: patients received danicopan in TP1 and continued with treatment in TP2; D>P: patients received placebo TP1 and switched to danicopan in TP2; IAS: interim efficacy analysis set; LS: least squares; SE: standard error; TP: treatment period.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27]

Other secondary endpoints assessed at Week 24

Efficacy results from Week 24 demonstrate that the treatment effect of danicopan was maintained in the DAN/DAN treatment arm, whilst leading to distinct improvements across a range of endpoints in the PBO/DAN treatment arm.[27] As shown in Table 19, at Week 24, 46.3% of patients in the DAN/DAN treatment arm achieved a clinically meaningful increase from baseline haemoglobin level of ≥2 g/dL, additionally, transfusion avoidance and decrease in ARC was also maintained through Weeks 12–24. At Week 24, 35.0% of patients in the PBO/DAN treatment arm achieved the ≥2 g/dL haemoglobin target, with a substantial increase in transfusion avoidance of 90.0% of patients in the treatment arm. Decreases in ARC were also observed in the PBO/DAN treatment arm.[1]

Table 19: Secondary endpoints assessed at Week 24 in the ALPHA trial (IAS)

	DAN/DAN + C5i[a] N=41	PBO/DAN + C5i[a] N=20
Patients with haemoglobin increase of ≥2 g/dL at Week 24 in the absence of transfusion		
Number of participants (n)	19	7
Percentage (%)	46.3	35.0
95% CI	30.7, 62.6	15.4, 59.2
Change in haemoglobin from baseline to Week 24		
Number of participants (n)	[redacted]	[redacted]
Mean (g/dL) (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Proportion of patients with haemoglobin stabilisation from Week 12 to Week 24		
Number of participants (n)	[redacted]	[redacted]
Percentage (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Achieving pRBC/whole blood transfusion avoidance from Week 12 to Week 24		
Number of participants (n)	32	18
Percentage (%)	78.0	90.0
95% CI	62.4, 89.4	68.3, 98.8
Change from baseline in FACIT-F scores at Week 24		
Number of participants (n)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Change from baseline in ARC scores at Week 24		
Number of participants (n)	37	19
LS mean (SE), 10^{12}/L	−0.0802 (0.0088)	−0.0652 (0.0127)
95% CI for LS mean	−0.0977, -0.0627	−0.0909, -0.0395

[a] Eculizumab or ravulizumab.
Abbreviations: ARC: absolute reticulocyte count; C5i: complement component 5 inhibitor; CI: confidence intervals; DAN/DAN: patients received danicopan in TP1, and continued with treatment in TP2; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue; IAS: interim efficacy analysis set; NR: not reported; PBO/DAN: patients received placebo in TP1 and switched to danicopan in TP2; pRBC: packed red blood cell; SD: standard deviation; SE: standard error; TP: treatment period.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.2.4.2.1, 14.2.4.3.1, 14.2.4.7.1, 14.2.4.9.1, 14.2.4.11.1, 14.2.6.1.1 14.2.6.2.1. Kulasekararaj, *et al.* (2023).[1]

B.2.7.4 Patient reported outcomes: EQ-5D-3L

EQ-5D-3L scores were collected across several treatment visits during TP1, a MMRM was then used to generate UK health state index scores as presented in Table 20.[27] Differences in the change from baseline in UK health state index scores collected up to Week 12 for danicopan versus placebo were [redacted]. With change from baseline EQ-5D-3L UK health state index scores ranging from [redacted] from Week 2–12 in the danicopan treatment arm, patient HRQoL is shown to be [redacted] despite additional administration requirements of danicopan add-on treatment.

EQ-5D-3L UK health state index scores did not indicate [redacted] from Weeks 12–24, as shown by Table 21 presenting a summary of the change in baseline in EQ-5D-3L scores through these treatment periods. Observed trends in HRQoL data may have been limited by small patient numbers; by Week 72, just [redacted] and [redacted] patients from the DAN/DAN treatment arm and PBO/DAN treatment arm had reported EQ-5D-3L data.

Table 20: UK health state index scores by treatment visit through Week 12 (IAS)

	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=21	Difference (D-P)	P-value
Week	Change from baseline LS mean (SD)	Change from baseline LS mean (SD)		
2	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; DAN/DAN: patients received danicopan in TP1 and continued with danicopan in TP2; LS: least squares; IAS: interim efficacy analysis set; LTE: long-term extension; SD: standard deviation; UK: United Kingdom.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.2.5.1.1.

Table 21: UK health state index scores by treatment visit through Week 24 and during the LTE (IAS)

	DAN/DAN + C5i[a] N=42		PBO/DAN + C5i[a] N=21	
Week	N	Change from baseline mean (SD)	N	Change from baseline mean (SD)
14	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
LTE				
40	[redacted]	[redacted]	[redacted]	[redacted]
56	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]

[a] Eculizumab or ravulizumab.

Abbreviations: C5i: complement component 5 inhibitor; DAN/DAN: patients received danicopan in TP1 and continued with danicopan in TP2; IAS: interim efficacy analysis set; LTE: long-term extension; SD: standard deviation; TP: treatment period; UK: United Kingdom.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.2.5.3.1.

B.2.8 *Subgroup analysis*

As discussed in Section B.2.3.1, pre-specified subgroup analyses were performed for the primary efficacy endpoint by the stratification factors of haemoglobin at screening, transfusion history and by Japanese and non-Japanese patients. Subgroup analysis were also performed by sex, race, region, age and background C5 inhibitor treatment (eculizumab or ravulizumab) for the primary endpoint and key secondary endpoints. Subgroup analyses were performed to assess the consistency of results across subgroups based on baseline and demographics; all analyses were conducted using the IAS.[27]

Primary efficacy endpoint

Subgroup analyses for the primary endpoint of change in haemoglobin level from baseline at Week 12 are presented in Table 22.[27] Results remained broadly consistent with respect to the primary analyses, in terms of the magnitude of treatment effect for each treatment arm and the improved change from baseline in haemoglobin level resulting from treatment with danicopan versus treatment with placebo. Subgroup analyses by Japanese/non-Japanese patients showed differing results, however these analyses may have been limited by small patient numbers.

Table 22: Subgroup analyses for the change from baseline in haemoglobin at Week 12 for the IAS – stratification factors

Subgroup analysis	Danicopan + C5i[a]		Placebo + C5i[a]	
	N	Change from baseline	N	Change from baseline
Primary analysis: Change from baseline in haemoglobin at Week 12, LS mean (SE), g/dL				
N/A	[redacted]	[redacted]	[redacted]	[redacted]
Transfusions (n) during 6 months prior to screening, mean (SD), g/dL				
>2	[redacted]	[redacted]	[redacted]	[redacted]
≤2	[redacted]	[redacted]	[redacted]	[redacted]
Screening haemoglobin level at baseline, mean (SD), g/dL				
<8.5 g/dL	[redacted]	[redacted]	[redacted]	[redacted]
≥8.5 g/dL	[redacted]	[redacted]	[redacted]	[redacted]
Japanese patients (Yes/No), mean (SD), g/dL				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; IAS: interim efficacy analysis set; LS: least squares; N; number of patients in group; N/A: not applicable; SD: standard deviation; SE: standard error.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Tables 14.2.7.1.1, 14.2.7.1.2 and 14.2.7.1.3.

Subgroup analyses for the primary efficacy endpoint by demographic subgroups are also presented in Table 23; change from baseline in haemoglobin at Week 12 remained broadly

consistent between the subgroups, with small patient numbers potentially influencing results.[27] For each subgroup, the improvement in change from baseline in haemoglobin level was demonstrated for danicopan versus placebo.

Table 23: Subgroup analyses for change from baseline in haemoglobin at Week 12 for the IAS set – demographic data

Subgroup analysis	Danicopan + C5i[a]		Placebo + C5i[a]	
	N	Change from baseline	N	Change from baseline
Primary analysis: Change from baseline in haemoglobin at Week 12, LS mean (SE), g/dL				
N/A	[redacted]	[redacted]	[redacted]	[redacted]
Sex, mean (SD), g/dL				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Race, mean (SD), g/dL				
America Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Region, mean (SD), g/dL				
Europe	[redacted]	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]	[redacted]
Latin America	[redacted]	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]	[redacted]
Rest of Asia Pacific	[redacted]	[redacted]	[redacted]	[redacted]
Age (years) at informed consent, mean (SD), g/dL				
<65	[redacted]	[redacted]	[redacted]	[redacted]
≥65	[redacted]	[redacted]	[redacted]	[redacted]
Background C5i therapy, mean (SD), g/dL				
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; IAS: interim efficacy analysis set; LS: least squares; N: number of patients in group; N/A: not applicable; NR: not reported; SD: standard deviation; SE: standard error.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Tables 14.2.7.1.4, 14.2.7.1.5, 14.2.7.1.6, 14.2.7.1.7 and 14.2.7.1.8.

Secondary efficacy endpoints

Results for the subgroup analyses conducted for key secondary endpoints assessed at Week 12 such as the proportion of patients with haemoglobin level increase of ≥2 g/dL in the absence of transfusion and transfusion avoidance remained [redacted] with respect to the primary analysis for key subgroups such as sex and age at informed consent.[27] While FACIT-F scores from baseline to Week 24 did vary with subgroup analyses, treatment with danicopan resulted in [redacted] changes from baseline in FACIT-F scores versus placebo between subgroups. For completeness, subgroup analyses for the key secondary endpoints are presented in Appendix E.

B.2.9 *Meta-analysis*

The clinical evidence base informing the efficacy and safety of danicopan is the Phase III RCT, ALPHA. The only other trial investigating danicopan add-on treatment in this indication is a Phase II dose-finding trial recruiting N=12 patients.[29] Due to the lack of substantial evidence at the licensed dose of danicopan, and the small patient numbers associated with this trial, a meta-analysis was not performed.

B.2.10 *Indirect and mixed treatment comparisons*

B.2.10.1 Identification and selection of relevant studies for the clinical SLR

As the ALPHA trial does not provide direct data on the relative efficacy of danicopan add-on therapy versus the relevant comparator for csEVH, pegcetacoplan, the possibility of conducting an indirect treatment comparison (ITC) was considered in order to generate the comparative efficacy estimates for danicopan add-on treatment in this indication.[27, 111]

An SLR was conducted in November 2022 and updated in August 2023 to identify all relevant clinical evidence on the efficacy and safety of danicopan and all other relevant therapies for the treatment of EVH in PNH.[112] In the original SLR, 35 relevant studies were identified, with 28 new articles included in the review update. In total, 63 studies reporting on clinical, humanistic and economic outcomes, along with cost-effectiveness analyses, were included in the final review. Full details on the SLR may be found in Appendix D.

B.2.10.2 Studies included in the ITC

As discussed in Section B.1.1, pegcetacoplan is considered the only relevant comparator to danicopan add-on therapy for the treatment of csEVH. Pegcetacoplan is the only treatment recommended by NICE for patients with uncontrolled anaemia after treatment with eculizumab or ravulizumab.[5] As csEVH commonly manifests as persistent residual anaemia after eculizumab or ravulizumab treatment,[6-9] and SoC treatments (eculizumab and ravulizumab) are used in UK clinical practice for the treatment of PNH by targeting IVH, pegcetacoplan is the only relevant comparator to danicopan in the indication of relevance to this submission.

As pegcetacoplan is the only relevant comparator to this submission, only studies reporting on pegcetacoplan or danicopan were considered for an ITC. The SLR identified two such trials, ALPHA (reporting on danicopan add-on treatment to eculizumab or ravulizumab) and PEGASUS

(reporting on pegcetacoplan). As such, these two trials alone were used to assess the feasibility of conducting ITC analyses.

B.2.10.3 Feasibility assessment

The available evidence for danicopan add-on therapy and pegcetacoplan was reviewed to understand the feasibility of conducting ITC analyses to generate estimates of relative efficacy between the two interventions. A rigorous qualitative and quantitative assessment of between-trial heterogeneity was conducted based on trial design, trial endpoints, patient eligibility criteria and baseline patient characteristics, as described further below.[111]

Trial design

Whilst the ALPHA[27] and PEGASUS[37] trials are both Phase III RCTs recruiting adult patients with PNH who were stable on eculizumab or ravulizumab treatment (see *trial eligibility criteria* below for more details), the feasibility assessment identified several key differences in design between the two trials.

Trial comparators

The ALPHA trial allowed patients in both treatment arms to receive either eculizumab or ravulizumab as an add-on treatment, whilst the PEGASUS trial limited patients to eculizumab treatment only.[27, 37] This difference between the control arms of each trial has the potential to complicate any planned anchored ITC analyses, the underlying assumption for which is a common comparator arm.[132] However, the clinical equivalence of ravulizumab and eculizumab has been demonstrated in prior PNH studies and appraisals,[24, 46, 75] thus, this methodological limitation was not anticipated to substantially bias results of any subsequent analyses.

Trial blinding

A key source of heterogeneity in the treatment periods of the ALPHA and PEGASUS trials was the difference in blinding; the 12-week randomised period in the ALPHA trial was double-blind, whereas the 16-week treatment period in the PEGASUS trial was open label.[27, 37] Open label trial designs are associated with an increased risk of bias, particularly for patient reported outcomes, such as FACIT-F. This is due to the subjective nature of assessments, risking the under- or over-estimation of results if patients are aware of their treatment allocation.[133]

Run-in period

The PEGASUS trial comprised a 4-week run-in period for which all patients received co-administration of pegcetacoplan and eculizumab prior to switching to pegcetacoplan monotherapy or eculizumab monotherapy for the 16-week randomised period.[37] This run-in period may have resulted in a residual treatment effect of pegcetacoplan for those patients subsequently randomised to receive eculizumab monotherapy, impacting the comparative efficacy estimates. Feedback received from several validation meetings held with UK clinical experts suggested that the run-in period in the PEGASUS trial may have impacted results in the eculizumab treatment arm; noting the steep drop in haemoglobin values (below baseline) observed after withdrawal of pegcetacoplan treatment. As it may take time for haemoglobin levels to stabilise and return to baseline levels, the run-in period may have biased ITC results, specifically in the anchored analyses (described below).

Timepoints of assessment

The timepoints used to assess the efficacy of danicopan as an add-on to ongoing eculizumab or ravulizumab treatment and pegcetacoplan monotherapy differed; for the ALPHA trial, efficacy results were assessed at the end of the initial 12-week randomised treatment period.[27] For the PEGASUS trial, data were reported at the end of the 16-week randomised treatment period that had immediately followed a 4-week run-in period during which pegcetacoplan and eculizumab were co-administered according to the usual dosing schedules for each medicine.[37]

The differences in timepoints for assessment of the primary and key secondary endpoints may introduce bias into the planned ITC, as the relative treatment effect of danicopan would be estimated from the ALPHA trial data at 12 weeks post-baseline versus data from the PEGASUS trial, where efficacy of pegcetacoplan monotherapy was assessed at 20 weeks after randomisation (comprised of the 4-week run-in period and a 16-week randomised controlled period). Differences in the duration of the initial assessment period may also impact key secondary endpoints such as transfusion avoidance, for which exposure time to treatment should be adjusted for. Simple adjustments, such as assuming a constant rate of transfusion, were considered strong and challenging to validate during the feasibility assessment due to differences in trial designs between the ALPHA and the PEGASUS trials, including the run-in period featured in the PEGASUS trial. Consequently, these adjustments were considered inappropriate for inclusion in the ITC.

Trial eligibility criteria

A summary of the key inclusion and exclusion criteria for the ALPHA and PEGASUS trials is provided in Table 24, illustrating key differences in eligibility criteria between the two trials.[37, 114]

Table 24: Comparison of inclusion/exclusion criteria for the ALPHA and PEGASUS trials

Category	ALPHA study	PEGASUS study
Age	✓ Adults, ≥18 years of age	✓ Adults, ≥18 years of age
Diagnosis	✓ Documented diagnosis of PNH ✓ CsEVH (haemoglobin level ≤ 9.5 g/dL and ARC ≥ 120 × 10^9/L	✓ Documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry ✓ Haemoglobin level <10.5 g/dL (despite stable treatment with eculizumab)
Treatment	✓ Received C5 inhibitor treatment for ≥6 months at approved dose before study entry ✓ No change in dosing (or frequency) for at least 24 weeks	✓ Received eculizumab treatment for ≥3 months prior to screening ✓ Treatment with stable doses of eculizumab

Labs	✓ Platelet count ≥ 30 x10^9/L ✓ ANC ≥ 0.5 x10^9/L ✓ Haemoglobin level <9.5 g/dL ✓ Reticulocytes ≥120 x10^9/L ×ALT >2 x ULN × Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2	✓ Platelet count >50 x10^9/L at screening ✓ Neutrophils >0.5 x10^9/L at screening ✓ BMI <40.0 kg/m^2 at screening ✓ Reticulocytes >1.0 x ULN = 120 x10^9/L at screening
Medical history	× History of major organ transplant or HSCT × History of aplastic anaemia or bone marrow failure requiring HSCT × Received another investigational product with specified timeframe × Complement deficiency × Bleeding disorders × Human immunodeficiency virus (HIV), hepatitis B or active hepatitis C × History of *N meningitidis* infection	× History of bone marrow transplantation × Active bacterial infection × Hereditary complement deficiency × Certain cardiac conduction abnormalities, including QTcF prolongation >470ms and PR interval >280ms × Personal or family history of long QT syndrome, torsade de pointes, or unexplained syncope
Adverse events		× History of myocardial infarction, stroke, or certain revascularisation procedures
Vaccinations	✓ Vaccinated against *N meningitidis (including* serotypes A, C, Y, W135, and B) <3 years before dosing or at the time of study drug initiation	✓ Vaccinated against *N meningitidis* types A, C, W, Y, and B, Streptococcus pneumoniae, and Hemophilus influenzae type B within the previous 2 years or within 2 weeks of starting study treatment
Contraception/ pregnancy	✓ Use of approved methods of contraception for the duration of the study and for specified duration after last dose ✓ Women of childbearing potential were required to have a negative pregnancy test prior to study entry	✓ Use of protocol-defined methods of contraception for the duration of the study and for 90 days after last dose ✓ Women of childbearing potential were required to have a negative pregnancy test prior to study entry

Abbreviations: ALT: alanine transaminase; ARC: absolute reticulocyte count; BMI: body mass index; C5: complement component 5; csEVH: clinically significant EVH; eGFR: estimated glomerular filtration rate; EVH: extravascular haemolysis; HIV: human immunodeficiency virus; HSCT: haematopoietic stem cell transplantation; PNH: paroxysmal nocturnal haemoglobinuria; pRBC: packed red blood cell; ULN: upper limit of normal
Source: Alexion Data on File. ALPHA trial protocol (Version 6.0)[114]. Hillmen et al. (2021)[37]

The ALPHA trial restricted the patient population to those with a haemoglobin level ≤9.5 g/dL, whilst the PEGASUS trial enrolled patients with a haemoglobin level <10.5 g/dL. Thus, the ALPHA trial did not include a subset of patients with baseline haemoglobin level in the range 9.5–10.5 g/dL. Furthermore, this eligibility criterion was noted by UK clinical experts to have resulted in the patient population in the ALPHA trial having more severe EVH versus the patient population in the PEGASUS trial.[4, 37, 114]

Differences in baseline haemoglobin level between the trials were considered as a potential factor introducing bias into the results of the planned ITCs, without population adjustment. Clinical validation was obtained in order to establish the significance of baseline haemoglobin

when considering the plausibility of the ITC results, the outputs of which are discussed further in Section B.2.10.5.

Patients in the ALPHA trial were required to have at least one transfusion within the 6 months before randomisation prior to a protocol update (V6.0) in February 2022.[114] After this time, patients with no prior history of transfusion were permitted to enrol in the ALPHA trial, based on clinical expert opinion supporting that danicopan add-on treatment may benefit patients regardless of their requirements for transfusion.[114] No such criteria were applied to patients in the PEGASUS trial.[37, 114] Prior history of transfusions was considered as a key factor determining the difficulty of treating a patient with EVH, representing an important potential covariate in the planned ITCs during a UK advisory board consulting clinical experts in PNH.[4] Specifically, patients with a prior history of transfusions were considered to be more severely ill.[4] This was further complicated by the difference in assessment timepoints between either trial, as previously discussed, for which an assumption of a constant rate of transfusions was considered to be too simplistic. The potential for imbalance in transfusion history between the trial populations and the differences in assessment timepoints can therefore be considered as a key source of heterogeneity and uncertainty in the planned ITCs.

Baseline characteristics

To account for the heterogeneity between the two studies identified by the feasibility assessment, including patient characteristics, MAICs were selected for analysis. The baseline characteristics of patients enrolled in the ALPHA and the PEGASUS trial are presented in Table 25.[27, 37]

Key differences in baseline characteristics were identified, and with a view to minimising any bias in the results of the MAIC, a trimmed population of the ALPHA trial (full population: N=63 patients) was created to align more closely with the eligibility criteria for the PEGASUS trial (N=80 patients) (Table 24). Patients were excluded from the trimmed ALPHA trial population used in the MAIC if they featured:

- A BMI ≥40 kg/m^2
- A platelet count ≤50,000/µL

These additional criteria reduced the patient population in the ALPHA trial used for comparison in the MAIC to [redacted] patients. For this reason, no further criteria were applied to the trimmed population, in order to maintain a suitable sample size in the analyses. A summary of the baseline characteristics of the full and trimmed ALPHA trial population, in addition to the full PEGASUS trial population, is provided in Table 25.

Despite the trimming process, the feasibility assessment identified several areas of heterogeneity between the ALPHA and PEGASUS trial populations:[111]

- **Demographic data:** Patients in the ALPHA trial were slightly older than in the PEGASUS trial. Furthermore, the trials had differing distributions of race with far more Asian patients in the ALPHA trial. However, the ALPHA trial had a smaller proportion of patients for which race was NR; this may, in part, account for some of these differences. Sex was well-balanced across the trials.
- **Prior transfusions:** Patients in the PEGASUS trial received a wider range of numbers of prior transfusions; 25% of patients in the PEGASUS trial had received no transfusions in the

past 12 months while, likely due to prior trial eligibility criteria, [redacted]% of patients in the ALPHA trial had received no transfusions. However, higher proportions of patients in the PEGASUS trial had received ≥4 transfusions in the past 12 months

- **Lab results:** In general, patients in the ALPHA trial had lower baseline haemoglobin levels and platelet counts, in addition to elevated ARC and LDH. The results are indicative of a more severely ill population than compared to patients in the PEGASUS trial
- **FACIT-F scores:** Baseline FACIT-F scores in the ALPHA population were marginally higher than those in the PEGASUS trial, despite lab results suggesting that the patients in the ALPHA trial may have been more severely ill

The clinical experts confirmed that the patients in the ALPHA trial appeared more severely ill than in the PEGASUS trial, based on the comparative lab results and other baseline characteristics of patients between the two trials.[4] Baseline haemoglobin levels were lower in the ALPHA trial, along with higher baseline reticulocyte counts. Accordingly, these two factors were considered for adjustment in the MAICs, as discussed in Section B.2.10.4

As expected from the difference in eligibility criteria for prior transfusions between the ALPHA and the PEGASUS trials, prior transfusion history differed substantially between the trial populations. As discussed previously, this difference was considered to be a key factor in determining the difficulty of treating patients for EVH.[4] Additionally, bilirubin levels were also lower in the ALPHA trial population when compared to the PEGASUS trial population.[27] As discussed in B.1.3.1, elevated bilirubin levels are correlated with haemolysis.[134] Furthermore, FACIT-F scores were marginally different between trial populations.

Table 25: Summary of baseline characteristics of patients in the ALPHA trial (full and 'trimmed' population) and the PEGASUS trial

Characteristic		ALPHA – full population (N=63)		ALPHA – subset meeting PEGASUS inclusion criteria (N=[redacted])		PEGASUS (N=80)	
		Danicopan + C5i[a] (n=42)	Placebo + C5i[a] (n=21)	Danicopan + C5i[a] (n=[redacted])	Placebo + C5i[a] (n=[redacted])	Pegcetacoplan (n=41)	Eculizumab (n=39)
Age (years) - mean (range)		55.0 (25-80)	53.1 (29-75)	[redacted]	[redacted]	50.2 (19–81)	47.3 (23–78)
Age >65 (years) - n (%)		12 (28.6)	4 (19.0)	[redacted]	[redacted]	10 (24)	7 (18)
Sex (female) - n (%)		23 (54.8)	14 (66.7)	[redacted]	[redacted]	27 (66)	22 (56)
Race - n (%)	Asian	18 (42.9)	7 (33.3)	[redacted]	[redacted]	5 (12)	7 (18)
	Black	1 (2.4)	0 (0.0)	[redacted]	[redacted]	2 (5)	0
	White	19 (45.2)	9 (42.9)	[redacted]	[redacted]	24 (59)	25 (64)
	Other	2 (4.8)	1 (4.8)	[redacted]	[redacted]	0	1 (3)
	NR	2 (4.8)	4 (19)	[redacted]	[redacted]	10 (24)	6 (15)
BMI - mean ± SD		26.7±5.4	24.8±4.9	[redacted]	[redacted]	26.7±4.3	25.9±4.3
No transfusions within previous 12 months - n (%)		0 (0.0)	0 (0.0)	[redacted]	[redacted]	10 (24)	10 (26)
Time since PNH diagnosis (years) – median (range)		7.3 (0.9-49.6)	10.8 (1.2-39.6)	[redacted]	[redacted]	6.0 (1–31)	9.7 (1–38)
Duration of prior treatment with eculizumab/C5 inhibitor (years) – median (range)		3.6 (0.5-14.2)	3.7 (0.7-16.8)	[redacted]	[redacted]	4.4 (0.4–17.1)	3.4 (0.3–13.8)
Platelets (x10^9/liter) – mean ± SD		131.5±64.1	138.0±76.8	[redacted]	[redacted]	166.6±98.3	146.9±68.8
≥4 transfusions in previous 12 months – n (%)		22 (52.4)	9 (42.9)	[redacted]	[redacted]	21 (51)	23 (59)
Haemoglobin (g/dl) – mean ± SD		7.7±0.9	7.7±1.0	[redacted]	[redacted]	8.69±1.08	8.68±0.89

Reticulocyte count (×10^{-9}/L) – mean ± SD (normal reference range)	236.4±91.4	240.6±120.3 (n=20)	[redacted]	[redacted]	217.5±75.0 (30–120)	216.2±69.1 (30–120)
LDH (U/L) - mean ± SD (normal reference range)	298.7±105.7	278.2±68.4	[redacted]	[redacted]	257.5±97.6 (113–226)	308.6±284.8 (113–226)
Total bilirubin (µmol/L) - mean ± SD (normal reference range)	32.5±21.8	34.2±21.0	[redacted]	[redacted]	42.5±31.5 (1.7–18.8)	40.5±26.6 (1.7–18.8)
Indirect bilirubin (µmol/L) - mean ± SD (normal reference range)	23.7±19.0	25.4±19.6	[redacted]	[redacted]	34.7±28.5	32.9±23.0
FACIT-F score - mean ± SD	33.5±11.1	33.9±10.8	[redacted]	[redacted]	32.2±11.4	31.6±12.5

[a] Eculizumab or ravulizumab.
Abbreviations: BMI: body mass index; C5i: complement component 5 inhibitor; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; LDH: lactate dehydrogenase; N: total number of patients in treatment arm; n: number of patients; NR: not reported; SD: standard deviation.
Source: Alexion Data on File. 2023.[111]

Outcomes

The primary and key secondary endpoints of the ALPHA and PEGASUS trials investigated similar clinically relevant outcomes in EVH, with the exception of the proportion of patients with a haemoglobin level increase of ≥2 g/dL at Week 12 in the absence of transfusion, which was investigated in the ALPHA trial but not the PEGASUS trial.[27] These endpoints are presented in Table 26.[27, 37]

However, as previously discussed, outcomes were assessed at Week 12 in the ALPHA trial and Week 16 of the randomised period in the PEGASUS trial (following four weeks of treatment with pegcetacoplan and eculizumab during the run-in period). This difference in the timepoints of assessment of endpoints was identified as a key source of heterogeneity in trial design, as described previously.[111]

BTH was not investigated as a formal endpoint in either trial, however, BTH events were collected in both trials as a measure of safety. BTH events were not consistently defined between either trial, with the following definitions used to inform safety data for either trial:

- The ALPHA trial: BTH events were based on the clinical judgement of the Investigator[114]
- 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[37]

Thus, comparative treatment effects of danicopan versus pegcetacoplan on rates of BTH cannot be feasibly conducted due to these differences.[111] As BTH events are considered uncommon, confirmed by clinical experts in PNH consulted as part of a UK advisory board,[4] and patient numbers were small in both trials, it is unlikely that an accurate comparison of the rates of BTH could be calculated via a MAIC regardless of the definition used for events.

Table 26: Primary and key secondary endpoints assessed in the ALPHA and PEGASUS trials

ALPHA	PEGASUS
Primary endpoint	
Change in haemoglobin level from baseline to Week 12	Change in haemoglobin level from baseline to Week 16 (g/dL)
Secondary endpoint	
Proportion of patients with transfusion avoidance through Week 12	Proportion of patients who did not require transfusion at Week 16
Change from baseline in ARC at Week 12	Change from baseline in ARC at Week 16
Change from baseline in FACIT-F scores at Week 12	Change from baseline in FACIT-F scores at Week 16
Proportion of patients with a haemoglobin level increase of ≥2 g/dL at Week 12 in the absence of transfusion	–
–	Change from baseline in LDH level at Week 16

Abbreviations: ARC: absolute reticulocyte count; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue; LDH: lactate dehydrogenase.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Hillmen, et al. (2021)[37]

Summary of the feasibility assessment

The ALPHA and PEGASUS trial designs are associated with key differences, such as the timepoints for assessment and differences in blinding for each treatment period. Other areas of heterogeneity between the trial designs included the 4-week run-in period used for the PEGASUS trial, and not the ALPHA trial, and restrictions on the use of ravulizumab in the PEGASUS trial.[111]

Key differences in trial eligibility criteria included restrictions on baseline haemoglobin level and prior history of transfusion.[4] Subsequently, differences in the baseline characteristics of patients between the ALPHA and the PEGASUS trial, in terms of haemoglobin levels, transfusion history and reticulocyte counts indicated that patients enrolled into the ALPHA trial had more severe disease, as supported by clinical experts in PNH.[4] Further heterogeneity included baseline bilirubin levels. Clinical experts consulted as part of a UK advisory board supported that transfusion history was a key factor determining the difficulty in treating patients experiencing EVH.[4]

For these reasons, MAICs were decided upon to account for the heterogeneity between the ALPHA and PEGASUS trials identified during the feasibility assessment. Despite the differences between the trials, the ALPHA and PEGASUS trials represent the most suitable trials informing the evidence base for danicopan and pegcetacoplan, respectively, and therefore in order to provide an indirect comparison of efficacy, these analyses proceeded despite the associated limitations.

B.2.10.4 MAIC methodology

Given that patient level data were available from the ALPHA trial,[27] with aggregate data only available from the PEGASUS trial,[37] a MAIC was considered suitable to obtain relative efficacy estimates for danicopan versus pegcetacoplan. The MAIC analyses were conducted in line with the guidance outlined in NICE Technical Support Document (TSD) 18.[135]

In a MAIC, weights are applied to patients of the intervention study population so that their baseline characteristics more closely align with the baseline characteristics of the comparator study population. The outcome analyses are then performed on the weighted patient population.[111] The methodologies proposed by Signorovitch et al. 2012 and Jackson et al. 2021 were considered in the analysis, which outline methods for adjustment between trials that have differing availability of data (individual patient level data [IPD] or aggregate data).[136, 137] In line with best practice (NICE TSD 18), the goal is to adjust for all potential prognostic factors and treatment effect variables that may confound the relationship between treatments and study outcomes.[132]

Adjustment for treatment effect modifiers and prognostic factors

Prior to adjusting for treatment effect modifier of prognostic factor variables, the subset of patients in the ALPHA trial who aligned with the inclusion criteria of the PEGASUS trial ([redacted]; all

patients in the trimmed population of the ALPHA trial who were randomised to danicopan add-on treatment [redacted] or placebo [redacted]; Table 25) was taken.[111]

The following two variables were identified for adjustment in the MAICs:

- Mean baseline haemoglobin level
- Mean baseline reticulocyte count

These variables were selected for adjustment based on clinical validation of the potential prognostic factors and treatment effect modifiers relevant to the patient populations in the ALPHA and PEGASUS trials. These variables are the only meaningful factors that may be controlled for based on the available data. The resulting effective sample size (ESS), limiting the number of variables able to be adjusted for in the analyses, were also taken into account.

Two alternative methodologies for adjustment were explored in order to balance the two covariates:[111]

- Using the methods outlined in Signorovitch et al. 2010,[136] for which the ESS of the danicopan and eculizumab or ravulizumab arm of the ALPHA trial was reduced to N=13.9 patients
- Using the methods outlined in Jackson et al. 2020,[137] chosen to maximise ESS, which reduced the patient population to N=15.3 in the danicopan and eculizumab or ravulizumab arm of the ALPHA trial

Further details on these methods of adjustment are provided in Appendix D.3.2.

Given the significant reduction in ESS for danicopan add-on treatment associated with adjustments in the MAIC, scenario analyses were also conducted where a naïve comparison was made between danicopan add-on therapy.[111] A naïve comparison involves the comparison of efficacy and safety results between relevant trials without any adjustment for baseline or other heterogenous characteristics between the trials, including covariates that may be considered prognostic factors or treatment effect modifiers.

Anchored and unanchored analyses

A MAIC can either be anchored or unanchored. An anchored MAIC produces comparative efficacy estimates by using a common comparator arm between the respective trials being compared. For example, this could involve comparing two study interventions versus a common placebo arm in two RCTs. Rather than directly comparing separate efficacy results between the intervention and comparator in either trial, an anchored MAIC only requires the estimates of relative treatment effect.[138] Unanchored MAICs do not require the same common comparator for the two treatment arms. However, when comparing absolute treatment effects, any MAIC-adjustment used requires the differences in both effect modifiers and prognostic variables to be accounted for.

In the anchored MAIC, an assumption of clinical equivalence between eculizumab and ravulizumab was made due to the danicopan add-on treatment arm in the ALPHA trial including both eculizumab and ravulizumab ([redacted]% versus [redacted]%, respectively).[27, 111] This approach was taken over selecting the patients in the ALPHA trial receiving eculizumab only, as this approach would

have substantially reduced the sample size available for comparison. To explore uncertainty around this assumption, scenario analyses were also run exploring unanchored analyses.

Outcomes and timepoints assessed

MAICs were attempted for the following outcomes to generate comparative efficacy estimates for danicopan and eculizumab or ravulizumab treatment versus pegcetacoplan:[111]

- Increase in haemoglobin level from baseline
- Increase in LDH level from baseline
- Increase in FACIT-F score from baseline
- Increase in ARC from baseline
- Proportion of patients with transfusion avoidance

As increased LDH and ARC levels are considered indicative of haemolysis,[7] an improved treatment effect would be observed with a lesser increase or greater negative (i.e., larger decrease) change in these endpoints.

All analyses compared danicopan and eculizumab or ravulizumab treatment at 12 weeks versus pegcetacoplan at 20 weeks (4-week run-in period and 16-week randomised period). This comparison was necessary for transfusion avoidance, due to the transfusion avoidance outcome only being reported at this timepoint in the published PEGASUS trial data.[37]

Overall, for each outcome, the adjusted and unadjusted analyses, each adopting both an anchored and unanchored approach were explored. This thorough and extensive approach was taken in attempt to overcome the challenges associated with balancing the treatment populations for danicopan add-on treatment and pegcetacoplan.

Full details of the methodology of the ITCs are provided in Appendix D.3.2 and the MAIC code is provided in Appendix D.3.4.

B.2.10.5 MAIC results

Due to key differences between trials designs and populations that could not be adjusted for as part of a MAIC, for example the run-in period, transfusion history, bilirubin levels and key demographic variables, the results of the MAICs were associated with considerable uncertainty. Furthermore, the small ESS after adjustment introduced further uncertainty to MAIC results. For this reason, the MAIC results were not considered suitable for drawing conclusions on relative efficacy between danicopan add-on therapy and pegcetacoplan. However, for the purposes of transparency, all results for the adjusted and unadjusted (naïve), and the anchored and unanchored, MAIC results are presented in Appendix D.3.3.

B.2.10.6 Uncertainties in the indirect and mixed treatment comparisons

After population adjustment through the balancing of baseline haemoglobin and reticulocyte count levels through the methodologies outlined above, prior transfusion history and baseline bilirubin levels remained unbalanced between the ALPHA and PEGASUS trial populations. Both of these characteristics can be considered highly relevant to EVH and indicative of disease severity, as discussed during an advisory board consulting UK experts in PNH. [4] Furthermore,

the ESS for the danicopan arm became very small with either adjustment method utilised (N=13.9 and N=15.3 with the Signorovitch et al. 2010[136] and Jackson et al. 2020[137] approaches, respectively).

As the MAICs remained with un-adjustable heterogeneity between patient characteristics and trial designs, further to their small ESS', the MAIC results were ultimately associated with considerable uncertainty and were not considered suitable for informing in the economic model, and naïve data were used to inform the model base case, accordingly (Section B.3.7).[111]

B.2.10.7 Conclusions of the MAIC

The results of the MAIC were not considered suitable for drawing conclusions on relative efficacy between danicopan add-on therapy and pegcetacoplan, owing to the substantial level of un-adjustable heterogeneity between the trial designs and the patient characteristics of the ALPHA and PEGASUS trials.[111] This conclusion is consistent with the NICE committee's conclusion in TA778 where they specified that the company's ITC was not robust for decision-making; the company's MAIC analyses were subject to significant differences in trial design as well as the inability to adjust for important variables including haemoglobin and transfusion history.[5]

B.2.11 *Adverse reactions*

At the 20th September 2022 DCO, safety data were available for TP1 (Week 12) and TP2 (Week 24). Additional longer-term safety data were also available from LTE. At TP1, TP2 and the LTE, safety data were available for N=86, N=71 and N=60 patients, respectively.[27]

Safety results are presented for the interim safety analysis set, defined in Table 7 as all patients who had received at least one dose of study intervention by the 20th September 2022 interim DCO date.[27] This analysis set consisted of N=86 patients, as of the 20th September 2022 DCO. Two participants randomised to placebo discontinued the study during TP1 and were not exposed to danicopan, while [redacted] patients receiving placebo had not yet progressed into TP2 at the 20th September 2022.

B.2.11.1 Treatment duration and dosage

Informed by a dose-finding Phase II study (ACH471),[29] the starting dose of danicopan in the ALPHA trial was 150 mg TID. As discussed in Section B.2.3.2, dosing of danicopan was permitted to be escalated to 200 mg TID, depending on haemoglobin response and occurrence of transfusions.

An overview of treatment duration by dose level is presented for TP1 and TP2 in Table 27.[27] In TP1, the majority of patients in the danicopan treatment arm (56/57) received the starting 150 mg dose. During TP2, a substantial proportion (33/48) of patients continuing with danicopan add-on treatment (DAN/DAN treatment arm) had received an increased dose of 200 mg danicopan TID. For those patients who received placebo and subsequently treatment switched to danicopan in TP2 (PBO/DAN), 13/23 patients received a higher 200 mg TID dose of danicopan during the study.

Table 27: Study intervention exposure duration in TP1 and TP2

	TP1		TP2		
	DAN + C5ia N=57	PBO + C5ia N=29	DAN/DAN + C5ia N=48	PBO/DAN + C5ia N=23	Total N=71
Treatment duration (days)					
n	57	29	48	23	71
Mean (SD)	79.2 (13.47)	76.7 (17.16)	78.2 (17.03)	78.4 (17.64)	78.3 (17.10)
Median	84.0	84.0	84.0	84.0	84.0
Min, max	23.0, 85.0	28.0, 86.0	12.0, 94.0	5.0, 85.0	5.0, 94.0
Danicopan treatment duration (days) by dose level					
100 mg					
n	3	N/A	1	0	1
Mean (SD)	56.0 (37.04)	N/A	28.0 (N/A)	N/A	28.0 (N/A)
Median	70.0	N/A	28.0	N/A	28.0
Min, max	14.0, 84.0	N/A	28.0, 28.0	N/A	28.0, 28.0
150 mg					
n	56	N/A	21	23	44
Mean (SD)	69.1 (21.35)	N/A	63.5 (24.22)	55.5 (22.82)	59.3 (23.57)
Median	84.0	N/A	83.0	42.0	46.0
Min, max	14.0, 97.0	N/A	15.0, 94.0	5.0, 85.0	5.0, 94.0
200 mg					
n	14	N/A	33	13	46
Mean (SD)	35.4 (13.08)	N/A	71.9 (19.76)	40.5 (6.16)	63.0 (22.20)

[a] Eculizumab or ravulizumab.
Abbreviations: DAN/DAN: DAN/DAN: patients received danicopan as an add-on to ongoing C5 inhibitor treatment in TP1 and continued with treatment in TP2; N/A: not applicable; PBO/DAN: patients received placebo as an add-on to ongoing C5 inhibitor treatment in TP1 and switched to danicopan as an add-on to ongoing C5 inhibitor treatment in TP2; SD: standard deviation; TP: treatment period.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Tables 14.3.1.1.1, 14.3.1.1.2, 14.3.1.1.3 and 14.3.1.1.4.

B.2.11.2 Treatment-emergent adverse events

Unless otherwise stated, all AEs described in the following sections were treatment-emergent, i.e., AEs that started during or after the first dose of study intervention.

An overview of TEAEs from the 20th September 2022 DCO of the ALPHA trial is provided in Table 28Table 28.[27] Safety data collected during TP1 demonstrate that danicopan has a tolerable safety profile, consistent with that observed in the placebo treatment arm. TEAEs occurred in 73.7% of patients in the danicopan treatment arm (DAN) and 62.1% of patients in the placebo (PBO) treatment arm in TP1. In both treatment arms in TP1, SAEs were infrequent, occurring in 5.3% and 6.9% of patients in the DAN and eculizumab or ravulizumab and PBO and eculizumab or ravulizumab treatment arms, respectively.

Safety data in TP2 and during the LTE remained consistent with data reported in TP1, with similar rates of TEAEs observed in the DAN/DAN and eculizumab or ravulizumab and PBO/DAN and eculizumab or ravulizumab treatments arms.

Table 28: Summary of TEAEs through TP1, TP2 and the LTE

	TP1		TP2			LTE		
	DAN + C5i[a] N=57[b]	PBO + C5i[a] N=29	DAN/DAN + C5i[a] N=48[b]	PBO/DAN + C5i[a] N=23	Total N=71	DAN/DAN + C5i[a] N=40	PBO/DAN + C5i[a] N=20	Total N=60
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	42 (73.7)	18 (62.1)	31 (64.6)	13 (56.5)	44 (62.0)	25 (62.5)	16 (80.0)	41 (68.3)
Any SAE	3 (5.3)	2 (6.9)	3 (6.3)	3 (13.0)	6 (8.5)	3 (7.5)	4 (20.0)	7 (11.7)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE leading to withdrawal of study intervention	3 (5.3)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (1.7)
SAE leading to withdrawal of study intervention	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE by relationship								
Related	12 (21.1)	8 (27.6)	2 (4.2)	6 (26.1)	8 (11.3)	0 (0.0)	3 (15.0)	3 (5.0)
Not related	35 (61.4)	18 (62.1)	30 (62.5)	13 (56.5)	43 (60.6)	25 (62.5)	16 (80.0)	41 (68.3)
SAE by relationship								
Related	1 (1.8)	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Not related	2 (3.5)	2 (6.9)	3 (6.3)	2 (8.7)	5 (7.0)	3 (7.5)	4 (20.0)	7 (11.7)
AE by toxicity								
Grade 1	33 (57.9)	16 (55.2)	27 (56.3)	12 (52.2)	39 (54.9)	20 (50.0)	14 (70.0)	34 (56.7)
Grade 2	23 (40.4)	15 (51.7)	12 (25.0)	7 (30.4) 12	19 (26.8)	12 (30.0)	10 (50.0)	22 (36.7)
Grade 3	10 (17.5)	4 (13.8)	6 (12.5)	3 (13.0)	9 (12.7)	3 (7.5)	3 (15.0)	6 (10.0)
Grade 4	1 (1.8)	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)	1 (2.5)	1 (5.0)	2 (3.3)

AE of Special Interest								
Meningococcal infections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver enzyme elevations[d]	8 (14.0)	3 (10.3)	3 (6.3)	3 (13.0)	6 (8.5)	1 (2.5)	1 (5.0)	2 (3.3)

[a] Eculizumab or ravulizumab.
[b] One patient in the DAN/DAN arm discontinued treatment in TP2 as a result of an AE that began in TP1. For this reason, the discontinuation is listed under TP1, as the time the AE was first recorded.
Abbreviations: AE: adverse event; AESI: adverse event of special interest; C5i: complement component 5 inhibitor; DAN/DAN: patients received danicopan as an add-on to ongoing C5 inhibitor treatment in TP1, and continued with treatment in TP2; DCO: data cut off; LTE: long-term extension; N: number of patients in treatment group; n: number of patients; PBO/DAN: patients received placebo as an add-on to ongoing C5 inhibitor treatment in TP1 and switched to danicopan as an add-on to ongoing C5 inhibitor treatment in TP2.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Tables 14.3.1.3.1.1, 14.3.1.3.1.2, 14.3.1.3.1.3 and Table 14.3.1.3.1.4.

B.2.11.3 Common treatment-emergent adverse events

A summary of the most common (occurring in ≥5% of patients) TEAEs observed during the ALPHA trial are presented in Table 29.[27] The most common TEAEs experienced by patients in TP1 were similar between treatment arms with headache, nausea, diarrhoea and arthralgia commonly experienced in both treatment arms. Asthenia was also commonly experienced in the placebo treatment arm. Furthermore, no serious TEAEs observed in the danicopan treatment arm in TP1 were deemed as to be related to the study intervention, supporting the tolerability of this treatment.[107]

The trends in the safety profile observed during TP1 were maintained during TP2 and into the LTE with headache and diarrhoea as a commonly observed TEAE in both treatment arms. Clinical experts in PNH consulted as part of a UK advisory board shared that occurrences of headache were not considered as a concern, rather, the occurrence of headaches was reported by several clinicians as an indication of treatment effect.[4] The long-term tolerability of danicopan was supported by the LTE; most TEAEs were Grade 1 or 2 and deemed as non-serious by the Investigator.

Table 29: TEAEs reported in ≥5% patients by MedDRA system organ class and preferred term in TP1, TP2 and during the LTE

	TP1		TP2		LTE	
System Organ Class Preferred Term	**Danicopan + C5i[a] N=57**	**Placebo + C5i[a] N=9**	**DAN/DAN + C5i[a] N=48**	**PBO/DAN + C5i[a] N=23**	**DAN/DAN + C5i[a] N=40**	**PBO/DAN + C5i[a] N=20**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**N (%)**
Blood and lymphatic system disorders						
Anaemia	1 (1.8)	4 (13.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders						
Nausea	5 (8.8)	3 (10.3)	1 (2.1)	3 (13.0)	0 (0.0)	0 (0.0)
Diarrhoea	4 (7.0)	3 (10.3)	6 (12.5)	2 (8.7)	1 (2.5)	2 (10.0)
Vomiting	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain upper	1 (1.8)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions						
Pyrexia	3 (5.3)	0 (0.0)	5 (10.4)	0 (0.0)	3 (7.5)	2 (10.0)
Asthenia	0 (0.0)	4 (13.8)	2 (4.2)	2 (8.7)	1 (2.5)	3 (15.0)
Fatigue	0 (0.0)	0 (0.0)	3 (6.3)	1 (4.3)	2 (5.0)	1 (5.0)
Infections and infestations						
Ear infection	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (22.5)	5 (25.0)
Injury, poisoning and procedural complications						
Contusion	1 (1.8)	3 (10.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations						
ALT increased	3 (5.3)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST increased	2 (3.5)	3 (10.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Musculoskeletal and connective tissue disorders						
Arthralgia	4 (7.0)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain in extremity	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.0)	1 (5.0)
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)	2 (10.0)
Nervous system disorders						
Headache	6 (10.5)	3 (10.3)	5 (10.4)	2 (8.7)	0 (0.0)	0 (0.0)
Dizziness	1 (1.8)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders						
Insomnia	1 (1.8)	3 (10.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders						
Hypertension	3 (5.3)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Eculizumab or ravulizumab.
Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; C5i: complement component 5 inhibitor; COVID-19: coronavirus disease; DAN/DAN: patients received danicopan as an add-on to ongoing C5 inhibitor treatment in TP1, and continued with treatment in TP2; LTE: long-term extension; MedRA: Medical Dictionary for Regulatory Activities; n: number of patients; PBO/DAN: patients received placebo as an add-on to ongoing C5 inhibitor treatment in TP1 and switched to danicopan as an add-on to ongoing C5 inhibitor treatment in TP2; TEAE: treatment-emergent adverse event.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Tables 14.3.1.3.2.2.1, 14.3.1.3.14.2 and 14.3.1.3.14.3.

B.2.11.4 Grade 3 and 4 treatment-emergent adverse events

In TP1, only a small proportion of patients in both treatment arms experienced a Grade 3 TEAEs, occurring in 15.8% of patients and 13.8% of patients in the DAN and eculizumab or ravulizumab and PBO and eculizumab or ravulizumab treatment arms, respectively (Table 30).[27] A Grade 4 TEAE of pancreatitis was experienced by 1 (1.8%) patient in the DAN and eculizumab or ravulizumab treatment arm that was deemed related to study intervention and resulted in treatment discontinuation. No occurrences of Grade 3 and above haemolysis or BTH events occurred in either treatment arm in TP1.

Trends in Grade 3 and 4 TEAEs were also broadly similar during TP2, with Grade 3 TEAEs occurring in 12.5% and 8.7% of patients in the DAN/DAN and eculizumab or ravulizumab treatment arm and PBO/DAN and eculizumab or ravulizumab treatment arms, respectively. In TP2, a Grade 3 BTH event [redacted] and haemolysis event occurred in the DAN/DAN and eculizumab or ravulizumab treatment arm and the PBO/DAN and eculizumab or ravulizumab arm, respectively. 1 (4.3%) patient in the PBO/DAN treatment arm experienced a Grade 4 TEAE of thrombocytopenia; while the TEAE was deemed by the Investigator as related to study intervention, the event was deemed as non-serious. The safety results thus support the long-term tolerability of danicopan.

Rates of Grade 3 and 4 TEAEs were low in both the DAN/DAN and eculizumab or ravulizumab and PBO/DAN and eculizumab or ravulizumab treatment arms in the LTE. In particular, only one patient reported a LDH level >2 times ULN in the trial, which is the definition of BTH used in other clinical trials. The BTH event occurred during the LTE and was due to a complement amplifying factor as a result of coronavirus disease (COVID-19), and was resolved without intervention. Overall, the rate of BTH throughout the ALPHA trial was low, demonstrating that danicopan provides a sustained control of IVH over time.

Table 30: TEAEs ≥Grade 3 through Week 12 and Week 24

System Organ Class Preferred term	Week 12			Week 24		
	Danicopan + C5i[a] N=57 n (%)		Placebo + C5i[a] N=29 n (%)	DAN/DAN + C5i[a] N=48 n (%)	PBO/DAN + C5i[a] N=23 n (%)	
	Grade 3	Grade 4	Grade 3	Grade 3	Grade 3	Grade 4
Participants with TEAEs	9 (15.8)	1 (1.8)	4 (13.8)	6 (12.5)	2 (8.7)	1 (4.3)
Blood and lymphatic system disorders	2 (3.5)	0 (0.0)	3 (10.3)	3 (6.3)	1 (4.3)	1 (4.3)
Haemolysis[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)
BTH[b]	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
Anaemia	1 (1.8)	0 (0.0)	2 (6.9)	2 (4.2)	0 (0.0)	0 (0.0)
Leukopenia	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	1 (1.8)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (4.3)
Gastrointestinal disorders	0 (0.0)	1 (1.8)	0 (0.0)	2 (4.2)	0 (0.0)	0 (0.0)
Pancreatitis	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dieulafoy's vascular malformation	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
Stomatitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.1)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Infections and infestations	1 (1.8)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
COVID-19	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	1 (4.3)	0 (0.0)
Allergic transfusion reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
Vaccination complication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)
Investigations	6 (10.5)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
ALT increased	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST increased	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White blood cell count decreased	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood pressure increased	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophil count decreased	1 (1.8)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4,3)	0 (0.0)

[a] Eculizumab or ravulizumab.
[b] Haemolysis events were reported by the site based on medical judgement of the principal investigator.
Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BTH: breakthrough haemolysis; C5i: complement component 5 inhibitor; COVID-19: coronavirus disease; DAN/DAN: patients received danicopan as an add-on to ongoing C5 inhibitor treatment in TP1, and continued with treatment in TP2 N: number of patients in treatment arm; n: number of patients experiencing TEAE; PBO/DAN: patients received placebo as an add-on to ongoing C5 inhibitor treatment in TP1 and switched to danicopan as an add-on to ongoing C5 inhibitor treatment in TP2; TEAE; treatment-emergent adverse; TP: treatment period.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.3.1.3.3.1 and 14.3.1.3.3.2.

B.2.11.5 Adverse events of special interest

Adverse events of special interest (AESIs) in the ALPHA trial included meningococcal infections and liver enzymes elevation.[27]

Patients receiving medicines that target the complement system (complement inhibitors, including ravulizumab, eculizumab, pegcetacoplan, and danicopan), part of the body's innate immune system, may be more susceptible to meningococcal infections (*N. meningitidis*). This is due to the inhibition of the formation of the membrane attack complex that eliminates encapsulated microorganisms, such as *N. meningitidis*, on its own. Thus, due to this increased susceptibility, meningococcal infections were considered an AESI. [140, 141] As of the 20th September 2022 DCO, no occurrences of meningococcal infections were reported in either treatment arm during any treatment period.[107]

Liver enzyme elevations were considered as AESIs based on toxicology data in dogs, in addition to ALT and aspartate aminotransferase (AST) elevations observed in two healthy volunteers after treatment completion in a multiple ascending dose study at the highest dose cohorts (ACH471-002 CSR). AESIs of liver enzymes elevation in observed during TP1 and TP2 are presented in Table 31.[27] In TP1, rates of any AESIs of liver enzymes elevation were comparable between the DAN and eculizumab or ravulizumab treatment and PBO and eculizumab or ravulizumab treatment arms; 14.0% of patients and 10.3% of patients experienced a liver enzyme elevation AESI, respectively. Similar rates of AESIs were also observed for those AEs grouped as 'Investigations' in Table 31 between the treatment arms, furthermore, most AESIs were deemed non-serious with most events resolved without treatment modification. No AESI of liver enzymes elevation were observed in TP2.[107] Additionally, just one occurrence of an AESI was reported in either treatment arm in the LTE, supporting the long-term tolerability of danicopan.

Table 31: AESI due to liver enzymes elevation through Week 12 and Week 24 for the interim safety analysis set

	Week 12		Week 24	
System Organ Class Preferred Term	**Danicopan + C5i[a] N=57**	**Placebo + C5i[a] N=29**	**DAN/DAN + C5i[a] N=48**	**PBO/DAN + C5i[a] N=23**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Any AESI of liver enzyme elevation	8 (14.0)	3 (10.3)	NR	NR
Hepatobiliary disorders	2 (3.5)	0 (0.0)	1 (2.1)	2 (8.7)
Hyperbilirubinemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)
Hepatic function abnormal	1 (1.8)	0 (0.0)	0 (0.0)	1 (4.3)
Liver disorder	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	6 (10.5)	3 (10.3)	2 (4.2)	1 (4.3)
ALT increased	3 (5.3)	1 (3.4)	0 (0.0)	0 (0.0)
Blood bilirubin increased	2 (3.5)	0 (0.0)	1 (2.1)	0 (0.0)
AST increased	2 (3.5)	3 (10.3)	1 (2.1)	1 (4,3)
Hepatic enzyme increased	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Transaminases increased	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)

[a] Eculizumab or ravulizumab.

Abbreviations: AESI: adverse event of special interest; ALT: alanine aminotransferase; AST: aspartate aminotransferase C5i: complement component 5 inhibitor; DAN/DAN: patients received danicopan in TP1 and continued with danicopan in TP2; N: number of patients in treatment arm; n: number of patients with reported AESI; PBO/DAN: patients received placebo as an add-on to ongoing C5 inhibitor treatment in TP1 and switched to danicopan as an add-on to ongoing C5 inhibitor treatment in TP2. TP: treatment period.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Tables 14.3.1.3.17.1 and 14.3.1.3.17.2.

B.2.12 *Ongoing studies*

The ALPHA trial is currently ongoing, with an estimated completion date of December 2023.[113] No further DCOs are currently planned for the ALPHA trial within the timeframe of this evaluation.

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1 Principle findings from the clinical evidence base

Danicopan as an add-on to ongoing eculizumab or ravulizumab treatment resulted in a statistically significant (p<0.0001) and clinically meaningful increase in haemoglobin level from baseline to Week 12 (2.94 g/dL) versus placebo (0.05 g/dL).[27] The magnitude of haemoglobin level increase observed in the danicopan treatment arm is expected to translate to improved levels of fatigue, as supported in the published literature.[117] Indeed, statistically significant (p=0.0021) and clinically meaningful changes in FACIT-F scores were demonstrated for danicopan versus placebo during TP1 of the ALPHA trial. With a 2021 study investigating patients enrolled in the international PNH registry concluding that a 5-point change in FACIT-F scores was meaningful to patients with PNH, the treatment group difference of 6.12 observed in TP1 can be considered as a positive outcome for patients with csEVH.[131] Clinical experts in PNH consulted as part of a UK advisory board identified that the severe fatigue associated with csEVH as a key unmet need in this patient population, thus, danicopan add-on treatment has been demonstrated to address a key need for patients experiencing csEVH who are receiving treatment with eculizumab or ravulizumab.[4]

Clinical benefit to patients was also observed via a statistically significant increase (p=0.0004) in transfusion avoidance at Week 12 for danicopan add-on treatment to eculizumab or ravulizumab versus placebo and eculizumab or ravulizumab.[27] In a retrospective real-world study in 509 patients with PNH treated with eculizumab or ravulizumab in the UK, 27.6% of patients required a transfusion in the previous 12 months, furthermore, 87.3% of patients in the IAS had received a transfusion in the 24 weeks prior to receiving study intervention.[106] Danicopan is therefore expected to reduce the occurrence of burdensome transfusion requirements commonly occurring in patients with csEVH, reducing hospital trips and logistical challenges for affected patients.[142] Improvements in haemoglobin level from baseline and transfusion avoidance were also maintained through Week 24, supporting the longer-term treatment effect of danicopan add-on treatment to a eculizumab or ravulizumab.

HRQoL, measured via the EQ-5D-3L UK health state index, [redacted] throughout TP1, and values [redacted].[27] Values also remained consistent between TP2 and the LTE, indicating that the addition of danicopan add-on treatment did not impact patient HRQoL, whilst resulting in improvements in fatigue and reduction in transfusion dependence.

Safety analyses conducted at Week 12 indicated that the safety profile of danicopan is comparable to that of placebo; any grade TEAEs were observed in 73.7% and 62.1% in the danicopan treatment arm and the placebo treatment arm, respectively.[27] The majority of TEAEs occurring in TP1 in either treatment arm were Grade 1 or Grade 2 in severity, non-serious, and not related to study intervention. Low rates of SAEs were also observed in the danicopan treatment arm (3.5%) and the placebo treatment arm (6.9%). Thus, the safety profile of danicopan treatment was shown to be well-tolerated through TP1.

Observed safety trends were consistent when assessed during TP2 and in the LTE, supporting the long-term safety of danicopan add-on treatment to a eculizumab or ravulizumab.[27] Headache, which commonly occurred between both treatment arms in TP1 and TP2, was not considered a concern by clinical experts in PNH consulted as part of a UK advisory board.[4] In particular, the rate of severe BTH (≥Grade 3) was low whereby no patients in TP1 and only one patient in TP2 experienced a Grade 3 BTH event (DAN/DAN treatment arm), which resolved without intervention. In summary, the available safety data across all treatment periods in the ALPHA trial supports the tolerable safety profile of danicopan with easily manageable AEs in clinical practice.

B.2.13.2 Strengths and limitations of the clinical evidence base

Strengths of the clinical evidence base

The evidence base informing the efficacy and safety of danicopan as an add-on treatment to a ravulizumab or eculizumab in this submission was identified through a comprehensive clinical SLR investigating the efficacy and safety of danicopan and relevant comparators for EVH in PNH, as discussed in Section B.2.1.[112] Results were reported in alignment with the Preferred Reporting Items for Systematic Literature Review and Meta-Analyses (PRISMA) statement.[143] The principle evidence for the safety and efficacy of danicopan as an add-on to ongoing eculizumab or ravulizumab treatment was provided by the ALPHA trial, a multiple-region, Phase III, randomised, double-blind, placebo-controlled study supporting the ongoing licence application for danicopan add-on therapy to eculizumab or ravulizumab for the treatment of csEVH.[27]

As a randomised, Phase III and double-blind study, reducing risks of bias, the ALPHA trial can be considered to have a high-quality trial design to support the clinical efficacy and safety of danicopan versus placebo.[27] The trial also comprehensively investigated endpoints of relevance to csEVH as investigated in prior studies in PNH,[24, 37] including haemoglobin levels, transfusion avoidance, change in FACIT-F scores and reticulocyte counts. The endpoints investigated in the ALPHA trial were broadly aligned with the NICE scope of relevance to this submission, using surrogate endpoints such as haemoglobin levels and blood transfusion requirements to measure control of EVH. Other endpoints specified in the scope, such as the survival of patients and BTH, were investigated as safety endpoints. Endpoints were also aligned with those investigated in prior appraisals in PNH that were accepted for decision making.[5]

The trial enrolled patients directly aligned with the patient population of relevance to this submission: adults with PNH experiencing csEVH.[27] As demonstrated in Section B.2.5 patient characteristics were well balanced between the treatment arms and were reflective of the anticipated UK population danicopan add-on therapy will be used in. For example, the majority of the IAS were White, closely followed by Asian individuals, with a slight female predominance, mirroring data reported by the International PNH registry.[12, 66] Age of onset of disease for the IAS

was closely aligned with that reported in a UK study of 80 patients with PNH.[74] Furthermore, the ALPHA trial included three trial centres located in the UK ([redacted] of IAS), a similar number as accepted in prior technology appraisals in PNH as generalisable to UK clinical practice.[46]

Limitations of the clinical evidence base

Limitations that should be acknowledged when interpreting the clinical evidence for the efficacy and safety of danicopan as an add-on to eculizumab or ravulizumab treatment are:[27]

- **Small sample size:** The interim efficacy analysis set of the ALPHA trial included 63 patients with csEVH, a relatively small sample size. Owing to the rarity of this condition, leading to the well recognised challenges associated with obtaining robust efficacy data in rare diseases, the sample size in this indication can be considered reasonable. Prior clinical trials (for example, PEGASUS) enrolling a subset of patients with PNH who remain anaemic after treatment with eculizumab or ravulizumab have been accepted for decision making despite a small sample size, supported by clinical experts consulted as part of the appraisal process.[5] The ALPHA trial enrolled a similar (N=86) number of patients to the PEGASUS trial (N=80), with efficacy data currently available from the ALPHA trial for N=63 patients (see Section B.2.2).
- **Eligibility criteria:** It was noted by clinical experts in PNH that the eligibility criteria of the ALPHA trial were strict, during a UK advisory board. For example, the ALPHA trial enrolled patients with baseline haemoglobin level ≤9.5 g/dL, in contrast to the ≤10.5 g/dL criteria used in the PEGASUS trial, potentially recruiting a more severely ill patient population.
- **Limited follow-up:** Efficacy data for danicopan is primarily derived from Week 12 of the ALPHA trial, thus, a relatively short treatment duration. However, supportive results from Week 24 indicate that the treatment effect of danicopan is maintained beyond this time. Though patient numbers in the LTE were comparatively small at the 20th September 2022 DCO, with data available for N=60 patients, these supportive data provide evidence that the efficacy and safety of danicopan is maintained in the long term.

As with many clinical trials in a rare disease, a key limitation of the evidence base was the lack of a direct comparison versus the relevant comparator to this appraisal, pegcetacoplan. To address this limitation, the feasibility of a MAIC, as discussed in Section B.2.10, was investigated to obtain relative efficacy estimates of danicopan versus pegcetacoplan.[111]

Substantial heterogeneity in the feasibility assessment between the ALPHA and PEGASUS trials was identified that could not be adjusted for, including prior transfusion history and baseline bilirubin levels. While adjusted analyses were performed, adjusting for baseline haemoglobin levels and reticulocyte counts, the resulting ESS for the danicopan arm became very small, thus, these results were considered no more reliable than a naïve comparison. The results of the MAIC were therefore associated with significant uncertainty and were therefore not deemed suitable for inclusion in the economic analysis.[111]

Conclusions

In summary, danicopan demonstrated statistically significant and clinically meaningful improvements in haemoglobin levels, transfusion avoidance and a number of other clinically relevant endpoints to EVH versus placebo.[27] Specifically, danicopan resulted in clinically meaningful improvements from baseline in FACIT-F scores versus placebo, correlating to improvements in fatigue symptoms in patients with csEVH.[4] Despite the currently available

treatment options for PNH, clinical experts have highlighted that csEVH leading to severe fatigue is a key unmet need in the PNH patient population. Danicopan as an add-on to eculizumab or ravulizumab has the potential to meet this unmet need as it has been demonstrated to lead to clinically meaningful benefits, including restoration of haemoglobin levels, reductions in transfusions and reductions in fatigue symptoms, whist maintaining a tolerable safety profile comparable to eculizumab or ravulizumab monotherapy.

B.3 Cost-effectiveness

B.3.1 *Published cost-effectiveness studies*

Summary of cost-effectiveness results

Cost-effectiveness model structure

- A *de novo* cost-effectiveness model was developed to evaluate the cost-effectiveness of danicopan as an add-on to ongoing treatment with eculizumab and ravulizumab versus pegcetacoplan monotherapy for the treatment of PNH patients with csEVH
- The Markov model comprised 4 health states defined based on haemoglobin levels, blood transfusion status and death: 'Low Hb (No Transfusion)', 'Moderate Hb (No Transfusion)', 'Transfusion' and 'Death'. In each haemoglobin level and transfusion-related health state, the patients may experience BTH, whilst patients in the 'Transfusion' health state may experience iron overload
- Haemoglobin level and transfusion status were used to define the health states as they are clinical manifestations of csEVH, and have strong associations with patients HRQoL and costs to the NHS. This model structure is consistent with the model used in NICE's evaluation of pegcetacoplan (TA778)[5]
- Given that the results of the MAIC were not suitable for informing the economic analysis, the comparative efficacy of danicopan and pegcetacoplan, in terms of transition probabilities, was based on the naïve results of the ALPHA and PEGASUS trials.
- A lifetime time horizon assuming a maximum age of 100 years (45.7 years) was adopted, with a model cycle length of 4 weeks
- The following costs were included in the model: drug acquisition costs, administration costs, monitoring, transfusion costs, BTH and iron overload management costs, and AE management costs, and were considered from the NHS and PSS perspective
- Cost inputs were obtained from the British National Formulary (BNF)[144-146], electronic market information tool (eMIT)[147], National Schedule for NHS (2021/2022)[148], and Personal Social Services Research Unit (PSSRU)[149]. Resource use inputs were aligned with the accepted inputs and assumptions used in TA778[5]
- Utilities reflecting the HRQoL of each health state were derived from HRQoL data collected from the ALPHA trial, and utility decrements were applied for PNH treatment administration, AEs, BTH and iron overload as informed by published literature and past evaluations by NICE

Base case cost-effectiveness results

- In the base case, danicopan as an add-on to eculizumab or ravulizumab dominated pegcetacoplan in the deterministic and probabilistic analyses. When compared with pegcetacoplan, danicopan as an add-on to eculizumab or ravulizumab led to incremental QALYs of 0.418 at an incremental cost of [redacted], and was therefore dominant. The resulting incremental NHB (INHB) is [redacted] (probabilistic analysis)

- At a willingness-to-pay (WTP) threshold of £30,000/QALY gained, danicopan as an add-on to eculizumab or ravulizumab represents a cost-effective use of NHS resources as compared with pegcetacoplan]

Sensitivity and scenario analyses

- The probability of danicopan as an add-on to eculizumab or ravulizumab being cost-effective was 100% and 100% at a WTP threshold of £20,000/QALY gained and £30,000/QALY gained, respectively
- A deterministic sensitivity analysis (DSA) was conducted and age of patients, the probability of pegcetacoplan patients experiencing a BTH from 17 weeks onwards, and the probability of patients discontinuing pegcetacoplan to eculizumab or ravulizumab monotherapy between 17 weeks and a year were the top 3 most influential parameters on the base case results.
- Scenario analyses were conducted to explore the impact of structural assumptions and alternative inputs on the results of the cost-effectiveness model, such as transition probabilities, utility values, treatment discontinuation, management of iron overload, proportions of use of eculizumab and ravulizumab, proportions of patients receiving an escalated dose of danicopan, and time horizon. The results of the scenario analyses were consistent with the base case results, demonstrating that the model's base case is robust to uncertainties in the model's inputs and assumptions

Conclusion

- There remains a considerably high unmet need amongst adult patients with PNH experiencing csEVH for a treatment that effectively addresses csEVH whilst maintaining control of IVH and thus avoiding BTH. Danicopan as an add-on to eculizumab or ravulizumab is a valuable new treatment option which addresses this unmet met need, and is a cost-effective use of NHS resources

An economic SLR was initially conducted in November 2022, and was subsequently updated using the same review protocol in June 2023 to identify all relevant literature published on the economic impact of danicopan add-on treatment to eculizumab or ravulizumab and the relevant comparators for the treatment of csEVH.[112] Full details of the economic SLR search strategy, study selection process and results are reported in Appendix G.

Among the 63 studies identified to report on the clinical, humanistic, and economic outcomes, 5 cost-utility analyses were identified which all evaluated the cost-effectiveness of pegcetacoplan compared with C5 inhibitors. Of these, 2 cost-effectiveness analyses were conducted in the UK setting as summarised in Table 32. No prior economic evaluations were identified for danicopan add-on treatment to eculizumab or ravulizumab in the population of relevance to this submission.

Table 32: Summary list of published cost-effectiveness studies (UK)

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Hakimi et al., 2022[150]	2022	• Cost-utility analysis • Markov cohort model • PEGASUS trial • UK healthcare and social services • 10- & 20-year time horizons • 0% & 6% discount rates	Adult patients with PNH and haemoglobin levels <10.5 g/dl despite eculizumab treatment	• Pegcetacoplan: 14.694 • Ravulizumab: 12.942 • Incremental (pegcetacoplan vs ravulizumab): 1.75	• Pegcetacoplan: £6,409,166 • Ravulizumab: £6,660,676 • Incremental (pegcetacoplan vs ravulizumab): -£251,510	• Pegcetacoplan vs. ravulizumab: Dominant
NICE 2021 [TA778][5]	2021	• Cost-utility analysis • Markov cohort model • PEGASUS trial • NHS and PSS • Lifetime horizon • 3.5% discount rate	Adult patients with PNH and haemoglobin levels <10.5 g/dl despite eculizumab treatment	• Eculizumab: Redacted • Ravulizumab: Redacted • Pegcetacoplan: Redacted • Incremental: Redacted	• Eculizumab: Redacted • Ravulizumab: Redacted • Pegcetacoplan: Redacted • Incremental: Redacted	• Eculizumab: Reference • Ravulizumab: £2,990,271/QALY • Pegcetacoplan: Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PNH: paroxysmal nocturnal haemoglobinuria; PSS: Personal Social Services; QALYs, quality-adjusted life years; TA: technology appraisal; UK: United Kingdom.

B.3.2 *Economic analysis*

As described in Section B.3.1, no economic evaluations of danicopan add-on treatment to eculizumab or ravulizumab in PNH patients with csEVH were identified in the economic SLR. As such, a *de novo* cost-effectiveness analysis has been conducted to inform this evaluation, with a cost-effectiveness model built in Microsoft Excel®. The model is described in the following sections.

The objective of this economic analysis is to evaluate the cost-effectiveness of danicopan add-on treatment to eculizumab or ravulizumab versus pegcetacoplan within the target population of this evaluation.

In line with the NICE reference case, the analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) in the United Kingdom (UK) and included direct medical costs over a lifetime horizon.

B.3.2.1 Patient population

The modelled patient population is in line with the intended indication for marketing authorisation: adult PNH patients who have csEVH. The patient population is similarly consistent with the decision problem (Section B.1.1).

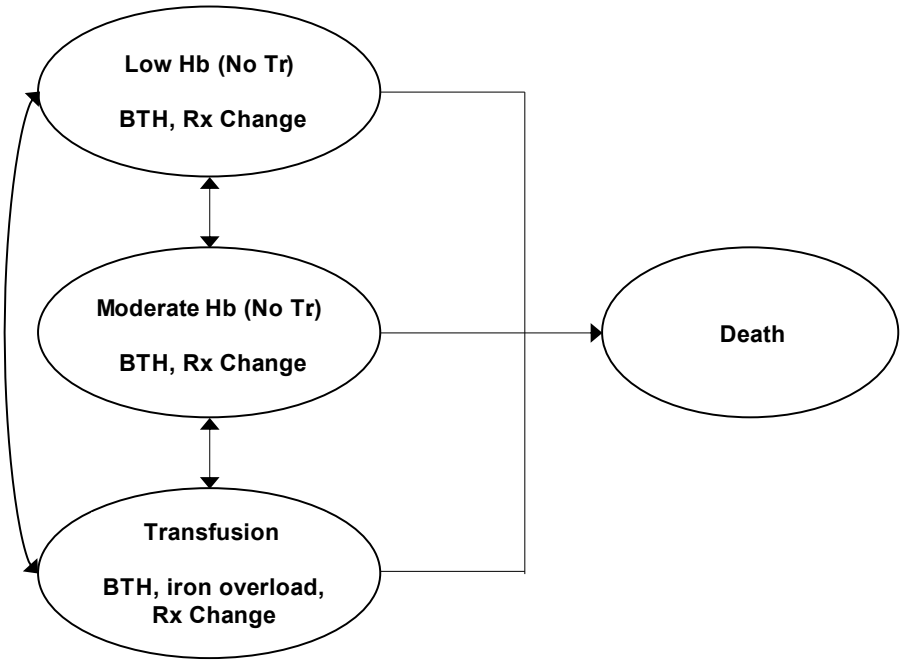
The modelled population was informed by data from the ALPHA trial, as detailed in Section B.3.3. At model entry, patients were characterised based on age and sex.

B.3.2.2 Model structure

A *de novo* Markov cohort model was developed, comprising health states defined according to haemoglobin levels ('Low Hb' and 'Moderate Hb'), blood transfusion status, and death. The model consists of four health states which are mutually exclusive and mutually exhaustive, and are outlined in Figure 14.

The model was structured based on haemoglobin level and blood transfusion status given that csEVH following treatment with a C5 inhibitor manifests as residual anaemia, indicated by a low level of haemoglobin, and the need for blood transfusions, as described in Section B.1.3.[8, 64, 77] The association between anaemia and fatigue has been established in the published literature and confirmed by UK clinical experts; a suboptimal level of haemoglobin can be expected to translate to a reduction in patient HRQoL.[151] Furthermore, published literature has demonstrated that blood transfusions have a negative impact on patient HRQoL due to their associated risks and complications such as iron overload, as well as lost productivity arising from travel time and time spent receiving the transfusions.[123, 152] Blood transfusions are also associated with a significant economic burden arising from the time and costs required (described further in Section B.1.3.2). Accordingly, given their impact on patients' HRQoL and costs to the NHS, they were used to define the health states in the model.[4] The model structure adopted is similar to the model accepted by the NICE committee in the evaluation of pegcetacoplan (TA778), the only treatment recommended for the treatment of PNH patients who remain anaemic following at least 3 months of treatment with a C5 inhibitor.[5]

Figure 14: Model structure



Footnotes: Rx change refers to the changes in PNH treatment dosing regimens patients receive upon experiencing a BTH event.
Abbreviations: BTH: breakthrough haemolysis; Rx: treatment; SAE: serious adverse event; Tr: transfusion.

The three haemoglobin level and transfusion-related health states are defined below. A haemoglobin cut-off at 9.5 g/dL was selected in line with the inclusion criteria of the ALPHA trial (Section B.2.3.2, Table 5).[114]

- Low Hb (No Tr.): Haemoglobin level <9.5 g/dL and not currently receiving a transfusion
- Moderate Hb (No Tr.): Haemoglobin level ≥9.5 g/dL and not currently receiving a transfusion
- Transfusion: Currently receiving a transfusion

All patients enter the model in the 'Low Hb (No Tr.)' state, based on the baseline haemoglobin levels in the ALPHA trial (Section B.2.5, Table 10). In each 4-week model cycle, patients can either remain in their current health state, move to a different health state, or move to 'death'. 'Death' is an absorbing health state in which patients remain for the rest of the model time horizon. The movement of patients between health states at the start of each new cycle is informed by health-state transition probabilities.

In each haemoglobin level and transfusion-related health state, the patients may experience BTH. When this occurs, patients may be assumed to change their PNH treatment regimen (increase in drug dose or frequency of administration) in order to address the BTH symptoms. Specific details of the changes in PNH treatment and treatment regimens patients receive upon experiencing a BTH event are provided in Section B.3.3.3.

As described in Section B.1.3.2, BTH represents the re-occurrence of IVH symptoms, and therefore poses a significant risk to patients' health and costs to the healthcare system. Danicopan is an add-on to ongoing treatment with eculizumab or ravulizumab; UK clinical experts have highlighted that danicopan add-on therapy provides reassurance that IVH remains well-controlled.[4] Patients receiving pegcetacoplan may be at greater risk of BTH as treatment

with eculizumab or ravulizumab will be discontinued (after an initial 4-week overlap period aimed to minimise the risk for suboptimal control of IVH and pharmacokinetic BTH). Thus, BTH is modelled to understand the comparative effects of danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan monotherapy. The event probabilities of experiencing BTH are presented in Sections B.3.3.3.

Frequent blood transfusions have been reported to result in the development of iron overload in patients with PNH, hence only patients in the 'transfusion' health state were modelled to be at risk of experiencing iron overload.[100, 130] The probabilities of iron overload are presented in Section B.3.3.4.

AEs observed in the ALPHA and PEGASUS trials were also included in the model, and may be experienced in any health state (Section B.3.3.5).

Treatment discontinuation was modelled in line with observations from the ALPHA and PEGASUS trials. Patients receiving danicopan as an add-on to eculizumab or ravulizumab may discontinue danicopan due to AEs, and subsequently receive eculizumab or ravulizumab monotherapy (Section B.3.3.6). Patients receiving pegcetacoplan may discontinue treatment to then receive either eculizumab or ravulizumab monotherapy as a result of BTH (B.3.3.3) or AEs (Section B.3.3.6).

Each haemoglobin and transfusion-related health state is assigned a utility value. To avoid double-counting, utility decrements were applied independent of health state utilities for BTH, iron overload, PNH treatment administration and SAEs. Costs considered in the model included drug acquisition and administration costs, monitoring costs, transfusion costs, BTH management costs, costs of iron overload, and AE management costs (described further in Section B.3.5). In each cycle, the number of costs and utilities were multiplied by the proportion of patients in each health state to calculate the weighted costs and QALYs. The weighted costs and QALYs per cycle were summed up for the entire model time horizon for each treatment arm, and the incremental costs and QALYs by treatment arm were subsequently calculated. As transition across health states may occur at any point within a model cycle, half-cycle correction was applied to both costs and health benefits.

B.3.2.3 Features of the economic analysis

Time horizon

A lifetime time horizon assuming a maximum age of 100 years (45.7 years) was considered. This is in line with the NICE reference case, which states that the time horizon should be sufficiently long to reflect all important differences in costs or outcomes between the technologies compared.[153] Hence, a lifetime time horizon was selected as PNH is a lifelong condition and patients would accumulate differential costs and QALYs until death. Alternative time horizons of 10 years and 20 years have been explored as scenario analyses (Section B.3.11.3).

As IVH, the leading cause of mortality in PNH, is managed with the ongoing treatment with eculizumab or ravulizumab and EVH does not impact the survival of patients, disease-related mortality is not included as an outcome in the model. Patients are thus assumed to follow the mortality rates observed in the general population, as informed by the UK life tables.[154] This is line with the approach taken in TA778.[5]

Discounting

Costs and utilities were discounted at 3.5% per annum, in line with the NICE reference case.[153] The annual discount rate was expressed and applied in the model on a per-cycle basis.

Perspective

A NHS and PSS perspective was chosen, in line with the NICE reference case.[153]

Table 33: Features of the economic analysis

	Previous evaluations	Current evaluation	
Factor	**TA778**	**Chosen values**	**Justification**
Time horizon	Lifetime (51 years)	Lifetime (45.7 years)	In line with the NICE reference case; the time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies compared.[153] Thus, a lifetime time horizon was selected. This approach is also consistent with TA778.
Treatment waning effect?	None	None	In line with previous NICE evaluation (TA778).
Source of utilities	Apellis data on file; EQ-5D utilities mapped from EORTC QLQ-C30 HRQoL data collected from the PEGASUS trial and mapped using Longworth et al.[155]	Health state utilities were estimated from EQ-5D-3L data collected from the ALPHA trial, using a generalised linear model (GEM) with a beta distribution.	In line with the NICE reference case, EQ-5D-3L data were directly collected from patients during the ALPHA trial.[153] This avoids any uncertainty associated with the mapping of HRQoL data to EQ-5D-3L as identified by the company in TA778.
Source of costs	• BNF for drug costs • NHS reference costs for disease management unit costs • Clinical expert opinion	Costs were sourced from the BNF[144-146], eMIT[147], National Schedule for NHS (2021/2022)[148], PSSRU[149], and TA778[5].	In line with the NICE reference case and previous NICE evaluation (TA778).[153]

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-3L: EuroQol Five-Dimension Three-Level; GLM: generalised linear model; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSSRU: Personal Social Services Research Unit; TA: technology appraisal
Source: NICE. Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria committee papers [ID3746]. 2021.[5]

Model outcomes

Outcomes generated by the model included the number of BTH events, and AEs, the average time spent in the 'transfusion' health state, transfusion-related iron overload, the time receiving PNH treatment (by drug/regimen), and the number of life years (LYs) and QALYs (discounted and undiscounted).

Discounted costs for each treatment arm were calculated on an overall basis and by the following cost components:

- PNH treatment costs (including drug acquisition costs, drug administration costs, training [in the first cycle only])
- BTH management costs
- Blood transfusion costs
- Iron overload management costs
- AE management costs
- Monitoring costs

Lastly, incremental LYs, QALYs and costs were calculated to generate an ICER and net health benefit (NHB) for danicopan add-on treatment to eculizumab or ravulizumab versus pegcetacoplan.

B.3.2.4 Intervention technology and comparators

Intervention and comparators

The intervention considered in the cost-effectiveness analysis was danicopan add-on treatment to eculizumab or ravulizumab, as described in Section B.1.2. In line with the draft Summary of Product Characteristics (SmPC), danicopan is administered orally at a starting dose of 150 mg three times a day, which may be increased to 200 mg depending on clinical response (Table 34).[40] The proportion of patients who receive the starting dose and escalated dose in Weeks 0–12 and Weeks 13+ were informed by TP1 and TP2 of the ALPHA trial, respectively.[27] This is in addition to ongoing treatment with eculizumab or ravulizumab. In order to ensure the proportion of patients receiving eculizumab and ravulizumab were aligned with UK clinical practice, the distribution of patients receiving eculizumab (■) or ravulizumab (■) at model entry was informed by Alexion sales data and was validated by UK clinical experts.[49, 50] Alternative distributions of patients receiving eculizumab (41.3%) or ravulizumab (58.7%) based on the ALPHA trial were explored in a scenario analysis (Section B.3.11.3). The proportions of use of each dose of eculizumab or ravulizumab were informed by the ALPHA trial patient population at baseline (Table 35). The dosing regimens used are consistent with the ALPHA trial and their SmPCs (Table 34).[10, 11, 27, 107]

The only relevant comparator considered in this evaluation is pegcetacoplan. As described in Section B.1.1 and Section B.1.3.3, pegcetacoplan is the only therapy recommended by NICE for the treatment of PNH patients who continue to have uncontrolled anaemia following treatment with a C5 inhibitor.[5] Given that csEVH only becomes apparent following treatment with a C5 inhibitor, eculizumab and ravulizumab do not treat EVH and are not licensed nor recommended for the treatment of EVH in UK clinical practice. Hence, eculizumab and ravulizumab are not considered to be relevant comparators for this evaluation. At model entry, pegcetacoplan was administered as a SC injection at a dose of 1,080 mg twice a week in line with the recommended dosing regimen in the SmPC (Table 34).[51] As the SmPC recommends a 4-week run-in period, in line with the PEGASUS trial,[37 37] patients receiving pegcetacoplan in this cost-effectiveness analysis were modelled to receive eculizumab or ravulizumab for the first 4 weeks upon model entry. As ravulizumab is administered once every 8 weeks, half the cost of one dose of

ravulizumab was applied. To ensure consistency with the danicopan as an add-on to eculizumab or ravulizumab treatment arm, the proportion of patients receiving eculizumab or ravulizumab in the pegcetacoplan arm was informed by the ALPHA trial and is presented in Table 35.

As noted in Section B.3.2.2, patients may require a dose escalation or change in treatments if they experience BTH, and the progressions in treatment regimens are detailed in Section B.3.3.3.

Table 34: Recommended dosing regimen in the SmPCs

Drug	Dosing regimen
Danicopan[40]	150 mg three times a day, approximately 8 hours apart (±2 hours) Depending on clinical response, the dose can be increased to 200 mg three times a day
Eculizumab[10a]	900 mg every 14±2 days
Ravulizumab[11a]	≥40 kg to <60 kg: 3,000 mg every 8 weeks ≥60 kg to <100 kg: 3,300 mg every 8 weeks ≥100 kg: 3,600 mg every 8 weeks
Pegcetacoplan[51]	1,080 mg twice weekly on Days 1 and 4 of each treatment week The dosing regimen may be change to 1,080 mg every third day (Day, 1, Day 4, Day 7, Day 10, Day 13, and so forth) For patients switching to pegcetacoplan from a C5 inhibitor, for the first 4 weeks, pegcetacoplan should be administered as twice weekly SC doses of 1,080mg in addition to the patient's current dose of C5 inhibitor treatment. After 4 weeks, the patient should discontinue the C5 inhibitor before continuing on monotherapy with pegcetacoplan.

[a] The dosing regimens of eculizumab and ravulizumab are based on their maintenance doses.
Abbreviation: SC: subcutaneous; SmPC: Summary of Product Characteristics.

Table 35: Distribution of patients receiving eculizumab or ravulizumab with danicopan or pegcetacoplan (initial 4 weeks of model entry for pegcetacoplan arm only)

Drug	Dose	Proportion of patients (%)
Eculizumab	900 mg	10.96
	1,200 mg	3.46
	1,500 mg	0.58
Ravulizumab	3,000 mg	29.86
	3,300 mg	50.54
	3,600 mg	4.59

Sources: Alexion Data on File, UK consultancy meeting with Dr Griffin;[49] Alexion Data on File, UK consultancy meeting with Dr Kulasekararaj;[50] Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.1.3.1.1 and 14.1.3.1.3.

B.3.3 *Clinical parameters and variables*

B.3.3.1 Baseline characteristics

The baseline characteristics for the model population are provided in Table 36. These inputs were based on the baseline characteristics of patients in the ALPHA trial. It was assumed that all patients had a haemoglobin level of <9.5 g/dL and did not receive a transfusion at model entry.

As noted in Section B.2.5, the baseline characteristics of the ALPHA trial were considered to be representative of patients in UK clinical practice.

Table 36: Baseline characteristics for population used in the economic model

Model parameter	Value
Mean age, years	54.30
Percentage male, %	41.27

Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 11.

B.3.3.2 Transition probabilities

Patients start in one of three health states and then, as described in Section B.3.2.2, may move from their current health state into another health state every 4 weeks, based on transition probabilities. It was assumed that these transition probabilities varied with PNH treatment, but do not vary according to the dose or frequency of administration.

Transition probabilities for patients receiving danicopan as an add-on to eculizumab or ravulizumab were derived from patient level data from all treatment periods (TP1 [Baseline–Week 12], TP2 [Week 13–24], and the LTE [Week 25–52]) of the ALPHA trial. To capture the outcomes of patients who receive eculizumab or ravulizumab monotherapy following discontinuation with danicopan or pegcetacoplan, their transition probabilities were also derived from the ALPHA trial data. The following approach was used in the derivation of transition probabilities:

- Patients were classified into appropriate health states depending on their medical characterisation on the planned visits during the ALPHA clinical trial period
- Transition probabilities between health states were estimated using a multinomial regression model with a log link, using R version 4.3.0, based on the approach employed by Hakimi et al. 2022:[150]

$$Health\ state_{current} = Health\ state_{previous} + T_x + Age$$

The probability of being in the current health state is calculated based on the previous health state (the previous 4 weeks), as well as covariates for treatment (danicopan as an add-on to eculizumab or ravulizumab, or eculizumab or ravulizumab monotherapy), treatment period in the ALPHA trial, and age.

Data for all randomised subjects from all treatment periods in the ALPHA trial were employed in the regression model.[27] Subject data for danicopan as an add-on to eculizumab or ravulizumab were censored to exclude subjects who discontinued and switched to receive eculizumab or ravulizumab monotherapy. Additionally, placebo data in the regression model included subjects who were receiving eculizumab or ravulizumab monotherapy before receiving danicopan. The transition probabilities for patients receiving danicopan as an add-on to eculizumab or ravulizumab and eculizumab or ravulizumab monotherapy, are presented in Table 37 and Table 38, respectively.

Table 37: Transition probabilities applied in base case (danicopan add-on to eculizumab or ravulizumab)

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; Tr.: transfusion.

Table 38: Transition probabilities applied in base case (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; Tr.: transfusion.

Transition probabilities for patients receiving pegcetacoplan were sourced directly from Hakimi et al. 2022, which were derived from IPD from the PEGASUS trial (Table 39).[150] In PEGASUS, all randomised patients had a baseline haemoglobin value of <10.5 mg/dL, while in ALPHA all randomised patients had a maximum baseline haemoglobin of <9.5 mg/dL. Owing to a lack of data availability from the PEGASUS trial, it was assumed that the values from Hakimi et al. 2022 were generalisable to a framework defining haemoglobin health states based on a threshold of 9.5 mg/dL. As discussed in Section B.2.10, feedback from clinical validation interviews was that baseline haemoglobin level is considered to be prognostic. The adopted approach to the transition probabilities framework assumes that current haemoglobin levels have a log-linear relationship with baseline haemoglobin levels. In light of the conclusion of the MAIC analyses, whereby it was not possible to produce a robust comparative effectiveness result through adjustment of relevant variables, this was considered the most suitable alternative approach without introducing undue complexity into the model. To explore the impact of this assumption, alternative transition probabilities for danicopan add-on to eculizumab or ravulizumab, informed by ALPHA trial data using a haemoglobin level threshold of 10.5 mg/dL, were explored in a MAIC scenario analysis. This analysis was restricted to the patients in the ITC analysis. The same multinomial regression model was used in this scenario analysis as in the main transition probabilities analysis, except that MAIC weights were fitted to the model.

Table 39: Transition probabilities applied in base case (pegcetacoplan)

Beginning health state	Ending health state		
	Low Hb (No Tr.)	Moderate Hb (No Tr.)	Transfusion
Low Hb (No Tr.)	0.4370	0.4900	0.0730[a]
Moderate Hb (No Tr.)	0.0310	0.9660	0.0030
Transfusion	0.2660	0.6120	0.1220

[a] The probability of transitioning from the 'Low Hb' state to the 'transfusion' state was 0.072 as reported by Hakimi et al. 2022,[150] and was adjusted in the model such that all transition probabilities for the 'Low Hb' state summed up to 1.
Abbreviation: Hb: haemoglobin; Tr.: transfusion.

B.3.3.3 Breakthrough haemolysis

The definition of BTH requiring clinical intervention which is accepted by UK clinical experts and used in previous ravulizumab pivotal clinical studies, is at least one new or worsening sign or symptom of IVH (fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia, major adverse vascular events [thrombosis], dysphagia or erectile dysfunction) in the presence of LDH levels >2 the ULN following a prior reduction of LDH levels to <1.5 times ULN.[24, 49, 75]

The probability of a BTH event occurring in patients receiving danicopan as an add-on to eculizumab or ravulizumab and pegcetacoplan per treatment cycle was derived from data from the ALPHA and PEGASUS trials, respectively (Table 40).[27, 37] It was assumed that patients receiving eculizumab or ravulizumab monotherapy have the same probability of BTH events as patients receiving danicopan as an add-on to eculizumab or ravulizumab.

Based on feedback received from clinical experts, it was modelled that all patients who experienced a BTH event in a given cycle had an adjustment made to their treatment dosing regimen in order to address the BTH, until no further treatment dosing options were available. When no further dosing regimens were available, patients remained on their final regimen.

An overview of the possible changes in treatment dosing over time is provided in Table 41. Regimen changes were assumed to occur at the next cycle in all instances. As danicopan is an add-on to eculizumab or ravulizumab, IVH and thus BTH, remain well-controlled with the ongoing treatment with eculizumab or ravulizumab. Therefore, patients do not discontinue danicopan treatment and no changes in danicopan's dosing regimen are made in response to a BTH event. Eculizumab and ravulizumab are instead dose escalated with an increased dosing frequency to manage BTH.

All patients on treatment with pegcetacoplan who experience a BTH event receive an escalated dosing frequency regimen of pegcetacoplan, as per Table 41. Although patients receiving pegcetacoplan were observed to discontinue treatment due to BTH in Weeks 1–16 of the PEGASUS trial, a UK clinical expert indicated that this does not typically occur in UK clinical practice.[50] The UK clinical expert noted that discontinuation due to BTH was observed in the PEGASUS trial given that dose modifications were not allowed.[50] Therefore, only changes to the

dosing frequency of pegcetacoplan were modelled in response to BTH. The modelled dose escalation for pegcetacoplan is in line with the approach adopted in an open-label extension study of pegcetacoplan and has been confirmed by UK clinical experts to reflect the management of BTH with pegcetacoplan in clinical practice.[49, 50, 156] A scenario was explored where a proportion of patients were modelled to discontinue pegcetacoplan due to BTH as observed in the PEGASUS trial (Weeks 1–16: 1 out of 4 patients; Weeks 17–52: 13 out of 15 patients).[37]

Table 40: Per model cycle probability of BTH events

Treatment	Value (%)	Source	Value (%)	Source
Danicopan + C5i[a]	**Weeks 1–24**		**Week 25+**	
	0.00	ALPHA trial: TP1 and TP2 (Week 0–24)[27]	0.24[b]	ALPHA: Long-term extension period (Week 25–52)[27]
Pegcetacoplan	**Weeks 1–16**		**Week 17+**	
	2.53	PEGASUS: Randomised controlled period (Week 4–16)[37]	2.67	PEGASUS: Open-label period (Week 17–48)[37]
C5i[a]	0.00	Assumed same as danicopan + C5i[a]	0.24	Assumed same as danicopan + C5i[a]

[a] Eculizumab or ravulizumab.
[b] In the ALPHA trial, only one patient across both treatment arms experienced BTH with a LDH level >2.2 times the ULN.
Abbreviations: BTH: breakthrough haemolysis; C5i: complement component 5 inhibitor; TP: treatment period; ULN: upper limit of normal.

Table 41: Progression of treatment regimens per BTH event

Starting treatment	Treatment escalation	
	First dose escalation	Second dose escalation
Pegcetacoplan 1,080 mg twice per week	Pegcetacoplan 1,080 mg daily for three consecutive days,[a] followed by once every three days	Pegcetacoplan 1,080 mg daily for three consecutive days,[a] followed by three times per week
Danicopan 150 mg three times a day + ravulizumab once every eight weeks	Ravulizumab once every seven weeks during the course of the BTH event. Following resolution of BTH, patients will revert to ravulizumab once every eight weeks.	
Danicopan 150 mg + eculizumab 900 mg once every two weeks	Eculizumab once every eleven days during the course of the BTH event. Following resolution of BTH, patients will revert to eculizumab once every two weeks.	

[a] Pegcetacoplan is administered as 1,080 mg daily for three consecutive days for the immediate treatment of BTH.
Abbreviation: BTH: breakthrough haemolysis.

B.3.3.4 Iron overload

All patients in the transfusion health state have a treatment-dependent per-cycle probability of having transfusion-related iron overload. Probabilities were derived from the ALPHA trial and Hakimi et al. 2022[150] for patients receiving danicopan as an add-on to eculizumab or ravulizumab

and pegcetacoplan, respectively (Table 42). The probability of having iron overload for patients receiving eculizumab or ravulizumab monotherapy was assumed to be the same as danicopan as an add-on to eculizumab or ravulizumab. Iron overload is associated with a utility decrement and management costs, as described in Sections B.3.4.6 and B.3.5.2, respectively.

Table 42: Per model cycle probability of transfusion-related iron overload

Treatment	Probability (%)	Source
Danicopan + C5i[a]	0.47	ALPHA CSR[27]
Pegcetacoplan	0.65	Hakimi et al. 2022[150]
C5i[a]	0.47	Assumed same as danicopan + C5i[a]

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor.
Sources: Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.3.1.3.2.2.2; Hakimi et al. 2022[150]

B.3.3.5 Adverse reactions

AEs included in the model comprised Grade ≥3 AEs, which occurred in >5% of patients in either treatment arm during the initial treatment period of the ALPHA or PEGASUS trial. In line with this criterion, only ALT increased is included as a relevant AE for danicopan as an add-on to eculizumab or ravulizumab. Based on the ALPHA trial, 5.3% of patients receiving danicopan as an add-on to eculizumab or ravulizumab experienced ALT increased in Weeks 1–12.[27] The per-cycle probability of ALT increased for patients receiving danicopan as an add-on to eculizumab or ravulizumab was thus 1.79% in Weeks 1–12, and no AEs were included in Weeks 13+. In the PEGASUS trial, no Grade ≥3 AEs were reported in >5% of patients receiving pegcetacoplan apart from haemolysis which has been accounted for under BTH (Section B.3.3.3).[103] The utility decrements associated with AEs and their management costs are described further in Sections B.3.4.4 and B.3.5.3.

B.3.3.6 Treatment discontinuation

In the ALPHA trial, patients receiving danicopan as an add-on to eculizumab or ravulizumab were observed to discontinue treatment due to reasons such as AEs.[27] As such, patients were modelled to discontinue treatment with danicopan as an add-on to eculizumab or ravulizumab and then continue receiving the same regimen of eculizumab or ravulizumab monotherapy. Treatment discontinuation of danicopan does not occur beyond Year 1.

In the PEGASUS trial, patients receiving pegcetacoplan were observed to discontinue treatment due to BTH in Weeks 1–16, and severe TEAEs from Weeks 17–48.[103, 150] As described in Section B.3.3.3, discontinuation of pegcetacoplan due to BTH is not common in UK clinical practice and was thus not modelled. The proportion of patients who discontinued treatment with pegcetacoplan due to severe TEAEs in Weeks 17–48 of the PEGASUS trial was then converted to a 4-week probability. Treatment discontinuation of pegcetacoplan does not occur beyond Year 1. Following discontinuation of pegcetacoplan, patients receive eculizumab or ravulizumab monotherapy based on the observed distribution of patients across eculizumab and ravulizumab doses in the ALPHA trial.

The probabilities of patients discontinuing danicopan as an add-on to eculizumab or ravulizumab and pegcetacoplan in Weeks 1–52 are presented in Table 43.

Table 43: Treatment discontinuation rates (Weeks 1–52)

Treatment	Value (%)	Source	Value (%)	Source	Value (%)	Source
Danicopan + C5i[a]	**Weeks 1–12**		**Weeks 13–24**		**Weeks 25–52**	
	1.58	ALPHA trial: TP1 (Weeks 0–12)	0.47	ALPHA trial: TP2 (Weeks 13–24)	1.24	ALPHA: LTE (Weeks 25–52)
Pegcetacoplan	**Weeks 1–16**		**Weeks 17–52**			
	0.00	PEGASUS: Random-ised controlled period (Week 4–16)	1.36	PEGASUS: Open-label period (Week 17–48)		

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; LTE: long-term extension; TP: treatment period.
Sources: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.3.1.1.1, Table 14.3.1.1.2 and Table 14.3.1.1.3; Hillmen et al. 2021;[37] de Latour et al. 2022[103]

As described above, no treatment discontinuation was assumed after Year 1 (i.e., Weeks 53+). This assumption is in line with NICE TA778.[5] Alternative treatment discontinuation rates were explored as a scenario, based on the treatment discontinuation rates from the ALPHA trial LTE and the PEGASUS trial open-label period (Table 44).

Table 44: Treatment discontinuation rates (Weeks 53+) – Scenario analysis

Treatment	Value (%)	Source
Danicopan + C5i[a]	1.24	ALPHA: LTE (Weeks 25–52)
Pegcetacoplan	1.36	PEGASUS: Open-label period (Week 17–48)

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; LTE: long-term extension.
Sources: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27] Table 14.3.1.1.3; de Latour et al. 2022[103]

B.3.3.7 Mortality

As described in Sections B.1.1 and B.1.3.1, mortality in patients with PNH is mainly attributed to thrombosis.[12] Given that current treatments such as eculizumab and ravulizumab are effective in managing IVH, the life-threatening complications of IVH such as thrombosis are well-controlled. Additionally, EVH is not life-threatening and does not impact patients' survival. Therefore, the probability of mortality was assumed to be equal between treatments and was estimated based on age and sex-matched general population mortality for England reported by the UK Office for National Statistics.[154]

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

As described in Section B.2.7.4, the ALPHA trial assessed HRQoL via the EQ-5D health utilities instrument. EQ-5D-3L scores were collected across several treatment visits during TP1 (Weeks 0–12), TP2 and LTE (Weeks 13–52). Multiplicative age adjustment was subsequently performed on data from the ALPHA trial, based on data from the Health Survey for England 2014.[157]

The following generalised linear model (GLM) (beta distribution with a logit link function) was used, incorporating data for all randomised subjects from TP1 (Baseline–Week 12), TP2 (Week 13–24), and LTE (Week 25–52):

EQ-5D-based utility = Health state + Tx + Age

The input EQ-5D-based adjusted utility values were adjusted to avoid bounds of 0 and 1 by inflating values by 0.001 and dividing by 1.0011. The values were then retransformed after the model was run to establish the health state utility values (HSUVs) employed in the model. With the Tobit model method utilised by Hakimi et al., values were not restricted between 0 and 1, making them unusable for the purpose of HSUVs.[37] Fixed effect covariates for health state, treatment (danicopan as an add-on to eculizumab or ravulizumab, or eculizumab or ravulizumab monotherapy), and age were included in the model. Due to lack of convergence, no random effect for individual was included in the analysis; this is expected to have minimal effect on the estimated mean utility values by health state. The HSUVs in the model are presented in Table 45. A scenario analysis was explored with HSUVs derived from a random effects model with a Normal distribution (Section B.3.11.3).

Alternative HSUVs were explored in the following scenario analyses (Section B.3.11.3):

- Values derived from arithmetic means from ALPHA (Table 50)
- Values based on a 10.5 g/dL haemoglobin level threshold from ALPHA with transition probabilities informed by the MAIC (Table 47)
- Values based on a 10.5 g/dL haemoglobin level threshold from ALPHA with transition probabilities informed by the MAIC, using the maximised effective sample size weights (Table 47)
- Values based on a 10.5 g/dL haemoglobin level threshold with transition probabilities informed by the MAIC, using utilities from Hakimi et al. 2022[150] (Table 48)

Table 45: Base case health state utility values (EQ-5D-3L derived from ALPHA; 9.5 g/dL threshold)

Health state	Utility	Source
Low Hb (No Tr.)	0.8181	Alexion Data on File
Moderate Hb (No Tr.)	0.8644	
Transfusion	0.7018	
Death	0.000	

Abbreviations: Hb: haemoglobin; Tr: transfusion.

Table 46: Scenario health state utility values (EQ-5D-3L derived from ALPHA; 9.5 g/dL threshold – arithmetic means)

Health state	Utility	Source
Low Hb (No Tr.)	0.8419	Alexion Data on File
Moderate Hb (No Tr.)	0.8507	
Transfusion	0.7080	
Death	0.000	

Abbreviations: Hb: haemoglobin; Tr: transfusion.

Table 47: Scenario health state utility values (EQ-5D-3L derived from ALPHA; 10.5 g/dL threshold)

Health state	Utility	Source
Low Hb (No Tr.)	0.8154	Alexion Data on File
Moderate Hb (No Tr.)	0.8798	
Transfusion	0.7015	
Death	0.000	

Abbreviations: Hb: haemoglobin; Tr: transfusion.

Table 48: Scenario health state utility values (HSUVs sourced from Hakimi et al. 2022;[150] 10.5 g/dL threshold)

Health state	Utility	Source
Low Hb (No Tr.)	0.7380	Hakimi et al. 2022 [150]
Moderate Hb (No Tr.)	0.8080	
Transfusion	0.6950	
Death	0.000	

Abbreviations: Hb: haemoglobin; Tr: transfusion.

B.3.4.2 Mapping

Since EQ-5D-3L outcomes were collected in the ALPHA trial, no mapping was required. However, a scenario analysis was explored whereby EORTC values from the ALPHA trial were mapped to the EQ-5D using the algorithm published by Longworth et al. 2014.[155] Once the mapped EQ-5D values were generated, the same GLM model as described in Section B.3.4.1 was used to produce utility values for each health state. Utility values were produced with an Hb threshold of 9.5 g/dL (Table 49)

Table 49: Scenario health state utility values (EORTC mapped to EQ-5D-3L;[155] 9.5 g/dL threshold)

Health state	Utility	Source
Low Hb (No Tr.)	0.7026	Alexion Data on File
Moderate Hb (No Tr.)	0.7480	
Transfusion	0.6518	
Death	0.000	

Abbreviations: Hb: haemoglobin; Tr: transfusion.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify relevant HRQoL data in patients with PNH experiencing EVH. Searches were conducted on 1st November 2022 and updated on 12th June 2023. The SLR was conducted following current best practices, as recommended by the Cochrane Collaboration.[158] The reporting of the methods and results of the SLR was done in line with the guidance provided by NICE[159] and following the PRISMA guidelines.[160, 161] Full details of the SLR search strategy, study selection progress and results are reported in Appendix H.

In total 13 unique studies were identified that reported on HRQoL data in patients with PNH experiencing EVH. Full results for all the identified studies are presented in Appendix H.

B.3.4.4 Adverse reactions

It is well-accepted that adverse events have a negative impact on patients' HRQoL. As described in Section B.3.3.5, only ALT increase is included as an AE in the model for patients receiving danicopan as an add-on to eculizumab or ravulizumab. A decrement in utility for ALT increase associated with treatment with danicopan as an add-on to eculizumab or ravulizumab was captured in the model. The annual utility decrement applied in the model was 0.05, as obtained from the NICE evaluation of lenalidomide for the treatment of multiple myeloma [TA171].[162] The AE was assumed to be independent of health state.

B.3.4.5 Drug administration

In line with the committee's preferences in TA778, an annual utility decrement of 0.025 was associated with the administration of eculizumab to account for the increased frequency of IV infusions versus ravulizumab.[5] Similarly, as pegcetacoplan has a higher frequency of administration than ravulizumab, the same annual utility decrement of 0.025 applied to eculizumab was assumed for pegcetacoplan. No other treatments included in the model were associated with administration-related utility decrement.

An alternative annual utility decrement for the administration of eculizumab and pegcetacoplan (0.057) was explored in a scenario analysis, based on NICE TA698.[46]

B.3.4.6 Other utility decrements

Apart from utility decrements associated with AEs and the administration of eculizumab and pegcetacoplan, the model accounted for utility decrements associated with BTH, and iron overload (chelation therapy) as summarised in Table 50.

In separate scenario analyses, the annual utility decrement for blood transfusions (0.695) based on NICE TA778 was applied,[5] and no utility decrement was applied for iron overload (Section B.3.11.3).

Table 50: Other utility decrements applied in the cost-effectiveness model

Event	Utility decrement	Source/Notes
BTH	0.40	O'Connell et al. 2020;[163] annual utility decrement
Iron overload (chelation therapy)	0.0300	Cherry et al. 2012;[164] utility decrement incurred over 3 months

Abbreviation: BTH: breakthrough haemolysis.

B.3.4.7 Health-related quality-of-life data used in the cost-effectiveness analysis

HSUVs and utility decrements used in the model are summarised in Table 51.

Table 51: Summary of utility values for cost-effectiveness analysis

Parameter	Utility value	95% CI	Reference in submission (section and page number)	Justification
Health state utility				
Low Hb	0.8181	N/A	Section B.3.4.1, page 114	EQ-5D-3L data were obtained directly from patients during the ALPHA trial.
Moderate Hb	0.8644	N/A		
Transfusion	0.7018	N/A		
Death	0.000	N/A		
AEs[a]				
ALT increased	−0.050	N/A	Section B.3.4.4, page 116	Assumption based on TA171[162]
Drug administration[a]				
Eculizumab	−0.025	N/A	Section B.3.4.5, page 116	Assumption based on TA778[5]
Pegcetacoplan	−0.025	N/A		
Other utility decrements[a]				
BTH	−0.400	N/A	Section B.3.4.6, page 116	O'Connell et al. 2020;[163] the disutility of BTH was not captured in EQ-5D-3L data from the ALPHA trial
Iron overload	−0.030	N/A		Assumption based on TA778[5]

[a] The utility decrements listed are on an annual basis, except for iron overload which is the utility decrement incurred over 3 months.
Abbreviations: ALT: alanine aminotransferase; BTH: breakthrough haemolysis; CI: confidence interval; Hb: haemoglobin; N/A: not applicable.

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

An SLR was conducted to identify relevant cost or resource use studies for incorporation in the model. The searches were run on 1st November 2022 and updated on 12th June 2023. In total, 2 unique studies reporting on cost or healthcare resource use in patients with PNH were identified. Full details of the SLR search strategy, study selection process and results are presented in Appendix I.

The following cost categories were included in the model:

- Drug acquisition costs
- Administration costs
- Monitoring
- Transfusion costs
- BTH management costs
- Iron overload management costs
- AE management costs

The economic analysis was conducted from an NHS and PSS perspective and therefore included only costs that would be incurred by the NHS and PSS. Cost inputs were based on BNF[144-146], eMIT[147], National Schedule for NHS (2021/2022)[148], and the PSSRU.[149]

B.3.5.1 Intervention and comparators' costs and resource use

Acquisition costs

Drug acquisition costs for treatment regimens were calculated based on the cost per pack and dosing regimens reported in the ALPHA and PEGASUS trials.[27, 37, 107] The list prices of danicopan, eculizumab and pegcetacoplan were used in the model, except for ravulizumab whereby the PAS price was used (Table 53).

Based on Alexion sales data which were validated by UK clinical experts, [redacted] of patients in the model received ravulizumab whilst [redacted] of patients received eculizumab.[49, 50] Similarly, in the initial 4-week run-in period where patients in the pegcetacoplan arm received eculizumab or ravulizumab, the same distribution of patients receiving eculizumab or ravulizumab was assumed. Dosing regimens and distribution of patients receiving each dose of eculizumab, ravulizumab and danicopan were taken from the ALPHA trial, whilst the dosing regimen for pegcetacoplan was taken from the PEGASUS trial.[27, 37, 107] The dosing regimens for danicopan, pegcetacoplan, ravulizumab and eculizumab are presented in Table 34, whilst the distribution of patients receiving each dose of ravulizumab and eculizumab in the danicopan and pegcetacoplan (4-week run-in period only) arms is presented in Table 35.

Treatment acquisition costs were determined by calculating the number of treatment administrations falling within a given cycle. Patients were assumed to receive treatment across a lifetime horizon, with treatment discontinuation as described in Section B.3.3.6. Patients

receiving danicopan as an add-on to eculizumab or ravulizumab were modelled to gradually receive a dose escalation to 200 mg, in line with observations from the ALPHA trial.[27] The proportion of patients who receive an increased dose of 200 mg of danicopan over time are presented in Table 52. A scenario analysis is also presented in Section B.3.11.3 where all patients in the danicopan as an add-on to eculizumab or ravulizumab arm are dose escalated to 200 mg after Week 52.

Table 52: Proportion of patients who dose escalate to 200 mg of danicopan

Treatment	Value (%)	Source	Value (%)	Source	Value (%)	Source	Value (%)	Source
Danicopan + C5i[a]	**Weeks 1–12**		**Weeks 13–24**		**Weeks 25–52**		**Weeks 52+**	
	[redacted]	ALPHA trial: TP1 (Weeks 0–12)	[redacted]	ALPHA trial: TP2 (Weeks 13–24)	0.00	ALPHA: LTE (Weeks 25–52)	0.00	Assumption

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; LTE: long-term extension; TP: treatment period.
Sources: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27]

Patients in the danicopan as an add-on to eculizumab or ravulizumab treatment arm who experienced BTH were managed by increasing the frequency of the administration of eculizumab (from once every 2 weeks to once every 11 days) or ravulizumab (from once every 8 weeks to once every 7 weeks) during the BTH event (Table 41). Following the resolution of BTH, patients revert to the normal dosing regimen. The only BTH event (LDH >2 times ULN, in line with the definition used in other clinical trials)[24, 75] observed in the ALPHA trial was due to a complement amplifying factor, and clinicians do not expect patients receiving ravulizumab (either concomitantly with danicopan or alone) to experience BTH, thus this was taken as a conservative approach.[49, 50] To reflect these increases in the administration frequencies of eculizumab and ravulizumab, a one-off cost of eculizumab and ravulizumab corresponding to the increase in frequency of administration is applied. The one-off cost was calculated by applying the proportional increase in frequency to the cost per dose. The costs per dose of treatment are presented in Table 53.

Table 53: Drug acquisition costs per cycle

Drug	Dose (mg)	Pack size	Pack unit, strength (mg)	Pack cost	Units per dose required	Cost per dose	Doses per model cycle	Cost per model cycle
Danicopan + C5i[a]								
Danicopan	150	90	50	[redacted]	3	[redacted]	84	[redacted]
	200				4	[redacted]		[redacted]
Eculizumab	900	1	300	£3,150.00	3	£9,450.00	2	£18,900
	1,200				4	£12,600.00		£25,200
	1,500				5	£15,750.00		£31,500
Ravulizumab[b]	3,000	1	300	[redacted]	10	[redacted]	0.5	[redacted]
	3,300	1	1,100	[redacted]	3	[redacted]		[redacted]
	3,600	1	1,100	[redacted]	3	[redacted]		[redacted]
			300	[redacted]	1			
Pegcetacoplan								
Pegcetacoplan	1,080	1	1,080	£3,100.00	1	£3,100.00	8	£24,800
Eculizumab (single 4-week cycle)	900	1	300	£3,150.00	3	£9,450.00	2	£18,900
	1,200				4	£12,600.00		£25,200
	1,500				5	£15,750.00		£31,500
Ravulizumab (one-off dose)[b]	3,000	1	300	[redacted]	10	[redacted]	0.5	[redacted]
	3,300	1	1,100	[redacted]	3	[redacted]		[redacted]
	3,600	1	1,100	[redacted]	3	[redacted]		[redacted]
			300	[redacted]	1			

[a] Eculizumab or ravulizumab.
[b] The pack cost of ravulizumab presented includes a PAS discount. Ravulizumab is available in two concentrations (1,100 mg/11 mL, or 300 mg/3 mL) at the same price (per mg).
Abbreviations: BNF: British National Formulary; C5i: complement component 5 inhibitor.
Source: BNF 2023[144-146]

Administration costs

In line with the accepted assumption in TA778, in the base-case analysis it was assumed that patients receiving pegcetacoplan receive their first administration in a clinic where they receive training on self-administration so that subsequent doses can be self-administered at home. The unit cost for SC administration training was estimated to be £17.67 (assuming 20 minutes of specialist nurse time, band 6).

No administration costs were associated with danicopan as it is administered orally. No administration costs were included for either eculizumab or ravulizumab as these costs are borne by the manufacturer and are therefore not incurred by the NHS.

Table 54: Administration resource use

Drug	Administration cost	Justification	Source
Danicopan +C5i[a]			
Danicopan	£0.00	Oral treatment	N/A
Eculizumab	£0.00	Costs borne by the manufacturer	N/A
Ravulizumab	£0.00	Costs borne by the manufacturer	N/A
Pegcetacoplan			
Pegcetacoplan initial dose (applied in cycle 1 only)	£17.67	First SC administration includes training for self-administration at home (20 minutes nurse specialist band 6 £53 per hour of contact time)	PSSRU 2022 (Table 11.2.2)[165]

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component inhibitor; N/A: not applicable; PSSRU: Personal Social Services Research Unit; SC: subcutaneous.

B.3.5.2 Health-state unit costs and resource use

Monitoring costs

Monitoring costs associated with general practitioner (GP) visits, haematologist visits, and blood tests differ by health state. Monitoring costs for each health state were calculated by multiplying the unit costs for each resource (Table 55) by the number of visits/tests required per health state per cycle (Table 56). Resource use frequencies were aligned with the accepted assumptions in NICE TA778.[5] Monitoring costs were applied as per cycle rates (Table 56).

Table 55: Unit costs of physician visits/tests

Health state	Unit cost (£)	Source
GP visit	41.00	PSSRU 2022, Table 9.4.2 (Outpatient GP consultation lasting 9.22 minutes)[165]
Haematologist visit	172.59	NHS Reference Costs 2021/2022, WF01C; national average unit cost[166]

Blood test	33.06	NCGC (2015); NG45

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

Table 56: Number of physician visits/tests per cycle

	Number of physician visits/tests per cycle			Source
	Low Hb (No Tr.)	Moderate Hb (No Tr.)	Transfusion	
GP visit	0.00	0.00	0.00	NICE TA778[5]
Haematologist	0.15	0.15	2.00	
Blood test	0.31	0.31	2.00	
Cost per cycle, £	**36.14**	**36.14**	**411.29**	**-**

Abbreviations: GP: general practitioner; Hb: haemoglobin; NICE: National Institute for Health and Care Excellence; TA: technology appraisal.

BTH

A one-off cost of £225.78 was applied to all BTH events occurring in any given model cycle. The derivation of this one-off cost is provided in Table 57 and is in line with the approach used in TA778.[5] The proportion of patients and number of days for each component of BTH management were directly obtained from TA778.[5]

Further to the cost of managing BTH, patients are assumed to change their PNH treatment or treatment regimen, as described in Section B.3.3.3.

Table 57: Derivation of BTH event cost

	% patients/ n days	Source	Cost (£)
General ward	15%/ 1 day	NHS Reference Costs 2021/2022 SA03G-H[166]	103.25
Intensive care	1%/ 1 day	NHS Reference Costs 2021/2022 XC01Z-7Z[166]	21.44
Dialysis	4%/ 7 days	NHS Reference Costs 2021/2022 LE01A, LE02A[166]	101.09
Total			**£225.78**

Abbreviations: BTH: breakthrough haemolysis; NHS: National Health Service.
Sources: NICE. Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria committee papers [ID3746]. 2021.[5]

Iron overload

In line with the accepted approach in TA778, patients receiving danicopan as an add-on to eculizumab or ravulizumab and pegcetacoplan in the 'transfusion' health state who experience iron overload receive phlebotomies and not chelation therapy.[5] This is because danicopan as an add-on to eculizumab or ravulizumab and pegcetacoplan can increase patients' haemoglobin levels sufficiently such that iron can be reduced by removing blood from these patients. Patients

were assumed to require an average of three phlebotomies per year.[5] These assumptions are in line with the accepted assumptions in TA778.[5]

Table 58: Cost of phlebotomies

Procedure	Unit cost	Average number in a year	Average number in a 4-week cycle	Cost per 4-week cycle	Source
Phlebotomy	£4.70	3	0.23	£1.08	NHS Reference Costs 2021/22 (DAPS08)[166]

Abbreviations: NICE: National Institute for Health and Care Excellence; TA: technology appraisal.

Patients in the 'transfusion' health state who have discontinued treatment (with either danicopan or pegcetacoplan) to receive eculizumab or ravulizumab monotherapy and experience iron overload are managed with chelation therapy. Chelation therapy consists of treatment with either deferasirox or deferoxamine mesilate. In line with TA778, it was assumed that 55% of patients receive deferasirox and 45% of patients receive deferoxamine mesilate.[5] The costs of deferasirox and deferoxamine mesilate were obtained from the BNF and a weighted average cost of chelation therapy was applied in the model as presented in Table 59. A scenario analysis was conducted in which patients receiving eculizumab or ravulizumab monotherapy who experience iron overload are managed by receiving phlebotomies (Section B.3.11.3).

Table 59: Cost of chelation therapy

Drug	Pack size	Dosage (mg)	Pack cost	Dosage (mg/kg)	Frequency	Cost per four-week cycle	Source
Deferasirox	30	360	£165.45	21	Once daily	£645.05	BNF 2023[167]
Deferoxamine mesilate	10	500	£40.54	35	Once daily	£681.07	BNF 2023[168]
Total average weighted cost per four-week cycle			**£661.35**				

Blood transfusions

Costs of blood transfusion were incurred by patients in the transfusion health state. Blood transfusion costs were estimated based on the unit cost per transfusion and transfusion frequency per cycle. The unit cost per transfusion was based on the accepted cost used in TA778 (£532.46 derived from 2020 NHS reference cost) inflated to 2022 prices.[5]

Table 60: Blood transfusion costs

Resource use	Unit cost	Source
Transfusions	£694.96	TA778 (NHS 2020 reference cost), inflated to 2022 prices

Abbreviations: NICE: National Institute for Health and Care Excellence; NHS: National Health Service; TA: technology appraisal.
Source: NICE. Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria committee papers [ID3746]. 2021.[5]

Antibiotic prophylaxis

Patients who are treated with complement inhibitors may be more susceptible to meningococcal infections, as described in Section B.2.11.5, and therefore all patients require prophylactic antibiotics. In line with NICE TA778, it was assumed that prophylactic penicillin is administered at a dose of 500 mg, twice daily.[5] The cost of penicillin was obtained from eMIT as presented in Table 61.[147]

Table 61: Cost of prophylactic antibiotic

Drug	Number in packet	Dose (mg)	Pack cost	Dosage description	Packets for 4-week cycle	Cost per four-week cycle
Penicillin	28	250	£1.63	500 mg twice daily	4.00	£6.53

Source: eMIT 2022. Phenoxymethylpenicillin 250mg tablets / Pack size 28.[147]

B.3.5.3 Adverse reaction unit costs and resource use

As described in Section B.3.3.5, the only AE included in the model is ALT increased for patients receiving danicopan as an add-on to eculizumab or ravulizumab. The per-cycle cost of managing ALT increased is £388.08 based on a weighted average of the total day case costs of liver failure disorders without interventions from the NHS Reference Costs 2021/22 (GC01E and GC01F)[166].

B.3.5.4 Miscellaneous unit costs and resource use

No further unit costs or resource use were included in the economic model.

B.3.6 *Severity*

The severity modifier tool developed by Sheffield Centre for Health and Related Research (SCHAAR) and Lumanity was used to calculate the absolute and proportional severity modifiers.[169] A summary of the features of the QALY shortfall analysis is provided in Table 62.

In line with the NICE reference case,[170] the Hernandez-Alava 2017 study[171] was used to inform the base case economic analysis with the discount rate of 3.5% applied and resulted in a QALY modifier of 1. This severity modifier was therefore applied to the base case economic analysis.

Table 62: Summary features of QALY shortfall analysis

Parameter	Input	Reference to section in submission
Sex distribution		
Female, %	58.7	Section B.3.3.1; Table 36
Starting age (years)	54.3	Section B.3.3.1; Table 36
HSUV		
Low Hb	0.8181	Section B.3.4.7; Table 51
Moderate Hb	0.8644	Section B.3.4.7; Table 51
Transfusion	0.7018	Section B.3.4.7; Table 51
Death	0.0000	Section B.3.4.7; Table 51

Abbreviations: Hb: haemoglobin; HSUV: health state utility value; QALY: quality-adjusted life year.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[27]

As the guidance for the only prior appraisal in this indication [NICE TA778] was published in 2022, no prior appraisals in the indication of interest to this submission used severity modifiers.[5]

The results of the QALY shortfall analysis are summarised in Table 63. The resulting QALY shortfall equates to a QALY weight of 1. No severity modifier was therefore applied to the base case economic analysis.

Table 63: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with the condition would be expected to have with current treatment (pegcetacoplan)	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
14.71	13.95	0.76	5.17%	x1

Abbreviations: QALY: quality-adjusted life year.
Source: University of York. QALY shortfall calculator[169]

B.3.7 *Uncertainty*

As described in Section B.1.3.1, PNH is an extremely rare condition occurring in approximately 1 in 62,500 people in the UK.[41] Furthermore, based on clinical expert opinion, around 30% of all patients with PNH develop csEVH.[4] The rarity of this condition introduces the well-known challenges for evidence generation associated with rare diseases.

The ALPHA trial had a small population size of 86 (Section B.2.3.3), potentially introducing bias to the trial's results and the clinical data used to inform the economic modelling. However, the PEGASUS trial used in NICE's evaluation of pegcetacoplan had a similar patient population size (N=80) and this was not raised as a key issue by the NICE committee in TA778.[5] Both the ALPHA trial and the PEGASUS trial have limited follow up data available; clinical data are available from Weeks 0–52 from the ALPHA trial and from Weeks 4–48 in the PEGASUS trial, making the prediction of long-term outcomes challenging. In TA778, the limited data available from the PEGASUS trial was not considered a key issue.[5]

Due to the lack of head-to-head data comparing the efficacy of danicopan as an add-on to eculizumab or ravulizumab and pegcetacoplan, an ITC using a MAIC was attempted. However, the ALPHA and PEGASUS trials had fundamental differences in study design, baseline characteristics and endpoint definitions. Thus, the MAIC was associated with significant uncertainty and was considered to be unsuitable for informing the treatment efficacy in the model, and the naïve results were used to inform the transition probabilities instead.

B.3.8 *Managed access proposal*

Danicopan is not a candidate for managed access.

B.3.9 *Summary of base-case analysis inputs and assumptions*

B.3.9.1 Summary of base-case analysis inputs

A summary of the variables applied in the base case economic analysis is presented in Table 64.

Table 64: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference and corresponding section in this submission
Model settings			
Discount rate costs, %	3.5	N/A	NICE reference case;[153] Section B.3.2.3
Discount rate benefits, %	3.5	N/A	
Time horizon	Lifetime	N/A	
Perspective	NHS and PSS	N/A	
Patient characteristics			
Baseline patient age, years (SD)	54.30	50.57, 58.03 (Normal)	ALPHA trial;[27] Section B.3.3.1
Proportion of males, %	41.27	39.74%, 42.81% (Beta)	
Clinical inputs			
Transition probabilities			
Danicopan add-on treatment to eculizumab or ravulizumab	Table 37	N/A	ALPHA trial;[27] Section B.3.3.2
Pegcetacoplan	Table 39	N/A	Hakimi et al. 2022;[150] Section B.3.3.2
Eculizumab or ravulizumab monotherapy	Table 38	N/A	ALPHA trial;[27] Section B.3.3.2
Probability of BTH events per model cycle, %			
Danicopan add-on treatment to eculizumab or ravulizumab	Weeks 1–24: 0.00	0%, 0% (Beta)	ALPHA trial;[27] Section B.3.3.3
	Weeks 25+: 0.24	0.11%, 0.42% (Beta)	
Pegcetacoplan	Weeks 0–16: 2.53	1.84%, 3.34% (Beta)	PEGASUS trial;[37] Section B.3.3.3
	Weeks 17+: 2.67	2.28%, 3.1% (Beta)	
Eculizumab or ravulizumab monotherapy	Weeks 1–24: 0.00	0%, 0% (Beta)	Assumed same as danicopan add-on treatment
	Weeks 25+: 0.24	0.11%, 0.42% (Beta)	
Probability of iron overload per model cycle, %			
Danicopan add-on treatment to	0.47	0.3%, 0.68% (Beta)	ALPHA trial;[27] Section B.3.3.4

eculizumab or ravulizumab			
Pegcetacoplan	0.65	0.32%, 1.09% (Beta)	Hakimi et al. 2022;[150] Section B.3.3.4
Eculizumab or ravulizumab monotherapy	0.47	0.3%, 0.68% (Beta)	ALPHA trial;[27] Section B.3.3.4
Probability of AEs per model cycle, %			
ALT increased: Danicopan add-on treatment to eculizumab or ravulizumab	Weeks 1–12: 1.79 Weeks 13+: 0.00	Weeks (1 –12): 1.36%, 2.27%, (Beta) Weeks 13+: 0%, 0%, (Beta)	ALPHA trial;[27] Section B.3.3.5
Treatment discontinuation, %			
Danicopan add-on treatment to eculizumab or ravulizumab	Weeks 1–12: 1.58	N/A	ALPHA trial;[27] Section B.3.3.6
	Weeks 13–24: 0.47	N/A	
	Weeks 25–52: 1.24	N/A	
	Weeks 53+: 0.00	N/A	
Pegcetacoplan	Weeks 0–16: 0.00	N/A	Hillmen et al. 2021,[37] de Latour et al. 2022;[103] Section B.3.3.6
	Weeks 17–52: 1.36	N/A	
	Weeks 53+: 0.00	N/A	
Utility inputs			
Health state utility			
Low Hb (No Tr.)	0.8181	0.63, 0.95 (Beta)	ALPHA trial;[27] Section B.3.4.7
Moderate Hb (No Tr.)	0.8644	0.66, 0.98 (Beta)	
Transfusion	0.7018	0.56, 0.83 (Beta)	
Death	0.000	N/A	
Utility decrements			
Annual utility decrement due to ALT increased	0.050	-0.06, -0.04 (Beta)	NICE TA171;[162] Section B.3.4.4
Annual utility decrement due to administration of eculizumab and pegcetacoplan	0.025	0.03, 0.02 (Beta)	NICE TA778;[5] Section B.3.4.5
Annual utility decrement due to BTH	0.400	0.405, 0.395 (Beta)	O'Connell et al. 2020;[163] Section B.3.4.6
Yearly utility decrement due to iron overload	0.120	0.14, 0.1 (Beta)	Cherry et al. 2012;[164] Section B.3.4.6
Cost and resource use inputs			
Drug acquisition cost per pack, £			

Danicopan (150 mg)	[redacted]	N/A	Alexion Data on File; Section B.3.5.1
Eculizumab (900 mg)	3,150.00	N/A	BNF 2023;[145] Section B.3.5.1
Ravulizumab (300 mg)	[redacted]	N/A	BNF 2023;[144] Section B.3.5.1
Ravulizumab (1,100 mg)	[redacted]	N/A	
Pegcetacoplan (1,080 mg)	3,100.00	N/A	BNF 2023;[146] Section B.3.5.1
Drug administration cost, £			
Danicopan	0.00	N/A	NICE TA778;[5] Section B.3.5.1
Eculizumab	0.00	N/A	
Ravulizumab	0.00	N/A	
Pegcetacoplan	17.67	£14.2, £21.13, (Gamma)	PSSRU 2020;[172] Section B.3.5.1
Health-state unit costs and resource use			
Monitoring costs			
Unit cost of GP visit, £	41.00	N/A	PSSRU 2022;[165] Section B.3.5.2
Unit cost of haematologist visit, £	172.59	N/A	NHS Reference Costs 2021/2022;[166] Section B.3.5.2
Unit cost of blood test, £	33.06	N/A	NCGC (2015); NG45; Section B.3.5.2
Monitoring cost per cycle: Low Hb health state	36.14	£29.05, £43.22, (Gamma)	NICE TA778;[5] Section B.3.5.2
Monitoring cost per cycle: Moderate Hb health state	36.14	£29.05, £43.22, (Gamma)	NICE TA778;[5] Section B.3.5.2
Monitoring cost per cycle: Transfusion health state	411.29	£330.68, £491.91, (Gamma)	NICE TA778;[5] Section B.3.5.2
BTH event cost	Table 57	181.53, 270.04, (Normal)	NICE TA778;[5] Section B.3.5.2
Iron overload management costs			
Unit cost of phlebotomy, £	4.70	N/A	NHS Reference Costs 2021/22 (DAPS08);[166] Section B.3.5.2
Pack cost of deferasirox, £	165.45	N/A	BNF 2023;[167] Section B.3.5.2
Pack cost of deferoxamine mesilate, £	40.54	N/A	BNF 2023;[168] Section B.3.5.2

Total average weighted cost per four-week cycle	£661.35	£531.72, £790.97, (Gamma)	See above; Section B.3.5.2
Blood transfusion costs			
Unit cost of blood transfusion, £	694.96	£558.74, £831.17, (Gamma)	NICE TA778;[5] Section B.3.5.2
Anaphylactic prophylaxis costs			
Pack cost of penicillin, £	1.63	N/A	eMIT 2022;[147] Section B.3.5.2
Per cycle cost of penicillin, £	6.53	£5.25, £7.82, (Gamma)	
AE management costs			
Per-cycle cost of ALT increased, £	388.08	£312.01, £464.14, (Gamma)	NHS Reference Costs 2021/22 (GC01E and GC01F);[166] Section B.3.5.3

Abbreviations: AE: adverse event; ALT: alanine aminotransferase; BNF: British National Formulary; BTH: breakthrough haemolysis; CI: confidence interval; Hb: haemoglobin; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; SD: standard deviation; TA: technology appraisal; Tr: transfusion.

B.3.9.2 Assumptions

The assumptions used in the base case analysis are described in Table 65.

Table 65: List of assumptions for the base case analysis model

Assumption	Justification	Reference to section in submission	Addressed in scenario analysis
A lifetime time horizon assuming a maximum age of 100 years (45.7 years) was adopted.	This approach is in line with NICE TA778.[5]	Section B.3.2.3	Scenario analyses of 10- and 20-year time horizons are explored.
The patient population in the ALPHA trial was assumed to be generalisable to clinical practice.	Data from the International PNH Registry indicates that the majority of registered patients are White, with a slight predominance of female patients, which is consistent with the baseline characteristics observed in the ALPHA trial (Section B.2.5, Table 10 of Document B).[12, 66] In the absence of UK-specific data, the IAS in the ALPHA trial has been demonstrated to broadly represent the global PNH population across key demographic characteristics. Furthermore, [redacted]% of participants in the ALPHA trial were from the UK (London, Airdrie and Leeds).[113] Therefore, it was assumed that the ALPHA trial population is generalisable to UK clinical practice.	Section B.3.2.1	N/A
Patients in the three haemoglobin level and transfusion-related health states may experience BTH, and were assumed to change their PNH treatment dosing regimen when this occurs.	This assumption is in line with feedback from UK clinical experts.[49, 50]	Sections B.3.2.2 and B.3.3.3	A scenario is performed whereby a proportion of patients discontinue treatment with pegcetacoplan in the management of BTH, in line with data from the PEGASUS trial
It was assumed that transition probabilities varied with PNH treatment, but did not vary	This approach is in line with NICE TA778.[5]	Section B.3.2.2	N/A

according to the dose or frequency of administration.			
Patients in the 'transfusion' state were assumed to be at risk of iron overload.	The assumption that patients in the 'transfusion' health state were at risk of iron overload is in line with the approach used in NICE TA778, which is based on clinical expert opinion.[5]	Sections B.3.2.2 and B.3.3.4	N/A
All patients were assumed have a haemoglobin level of <9.5 g/dL and did not receive a transfusion at model entry, and thus start in the 'Low Hb (No Tr.)' health state.	This assumption was based on the baseline haemoglobin levels reported in the ALPHA trial (Section B.2.5, Table 10 of Document B).[27, 107]	Sections B.3.3.1, B.3.2.2 and B.3.3.2	N/A
It was assumed that the transition probabilities from Hakimi et al. 2022 were generalisable to a framework defining haemoglobin health states based on a threshold of 9.5 mg/dL.	This assumption was made due to the lack of available data from the PEGASUS trial. Based on feedback from UK clinical experts, baseline haemoglobin level is considered to be prognostic. This approach to the transition probabilities framework makes a simple assumption that a log-linear relationship is present between baseline haemoglobin and haemoglobin level after treatment. In light of the conclusion of the MAIC analyses, whereby it was not possible to produce a robust comparative effectiveness result through adjustment of relevant variables, this was considered the most suitable alternative approach without introducing undue complexity into the model.	Section B.3.3.2	Transition probabilities informed by the MAIC are explored in scenario analyses for completeness.
It was assumed that patients receiving eculizumab or ravulizumab monotherapies have the same probability of BTH events as patients receiving danicopan as an add-on to eculizumab or ravulizumab.	As danicopan does not address IVH, it is expected that the addition of danicopan to eculizumab or ravulizumab will not result in changes in the probability of BTH.	Section B.3.3.3	N/A
No discontinuation for danicopan as an add-on to eculizumab or ravulizumab, and pegcetacoplan, was assumed beyond Year 1.	This assumption is in line with NICE TA778, whereby no treatment discontinuation was modelled beyond Year 1.[5]	Section B.3.3.6	Discontinuation for danicopan as an add-on to eculizumab or ravulizumab, and pegcetacoplan, was assumed beyond Year 1.

The probability of mortality was assumed to be equal between treatments and was estimated based on age and sex-matched general population mortality.	As described in Sections B.1.1 and B.1.3.1, thrombosis is the leading cause of mortality in patients with PNH.[12] As thrombosis is well-managed by the treatment of IVH with current available PNH treatments, it was assumed that mortality was equal between treatments and can be derived from the age and sex-matched general population mortality. This approach is in line with NICE TA778.[5]	Section B.3.3.7	N/A
AEs were assumed to be independent of health state.	Patients can experience any of the modelled AEs regardless of their health state. Furthermore, haemoglobin level and the receipt of blood transfusions do not influence the occurrence of an AE.	Section B.3.4.4	N/A
The administration of pegcetacoplan was assumed to have the same per-cycle disutility (0.025) as eculizumab.	Both pegcetacoplan and eculizumab have higher frequencies of administration than ravulizumab, and the disutility value of 0.025 is in line with the NICE committee's preference in TA778.[5]	Section B.3.4.5	An alternative utility decrement informed by TA698 (-0.057) was used in a scenario.
It was assumed that [redacted]% of patients received danicopan as an add-on to ravulizumab whilst [redacted]% of patients received danicopan as an add-on to eculizumab.	These proportions were informed by Alexion market research data. These proportions were also validated by UK clinical experts in PNH, during interviews conducted to support the development of this submission.[49, 50]	Section B.3.5.1	Proportions of ravulizumab and eculizumab use were based on the ALPHA trial: it was assumed that 58.73% of patients received danicopan as an add-on to ravulizumab whilst 41.27% of patients received danicopan as an add-on to eculizumab.[107]
The proportions of patients receiving 200 mg of danicopan were assumed to align with the ALPHA trial.	This assumption is based on observations from the ALPHA trial whereby [redacted] and [redacted] of patients in TP1 and TP2 increased to a 200 mg dose, respectively.	Section B.3.5.1	In a scenario it was assumed that all patients receiving danicopan as an add-on to eculizumab or ravulizumab would

			eventually receive 200 mg of danicopan after Week 52.
It was assumed that patients receiving pegcetacoplan receive their first administration in a clinic where they receive training on self-administration so that subsequent doses can be self-administered at home.	This approach is in line with NICE TA778.[5]	Section B.3.5.1	N/A
The management of iron overload was assumed to involve 3 phlebotomies per year for patients receiving danicopan as an add-on to eculizumab or ravulizumab and pegcetacoplan, whilst patients receiving C5i[a] monotherapy only were treated with chelation therapy.	This is because danicopan as an add-on to eculizumab or ravulizumab and pegcetacoplan can increase patients' haemoglobin levels sufficiently such that iron can be removed by removing blood from these patients, which is not assumed to be the case for C5i[a] monotherapy. This approach is in line with NICE TA778.[5]	Section B.3.5.2	Patients on C5i[a] monotherapy also receive phlebotomy for iron overload

Abbreviations: AE: adverse event; BTH: breakthrough haemolysis; EVH: extravascular haemolysis; Hb: haemoglobin; IAS: interim efficacy analysis set; IVH: intravascular haemolysis; NICE: National Institute of Health and Care Excellence; PNH: paroxysmal nocturnal haemoglobinuria; TA: technology appraisal; Tr: transfusion; UK: United Kingdom.

B.3.10 *Base-case results*

Results of the economic analysis are presented in Section B.3.10.1 below.

B.3.10.1 Base-case incremental cost-effectiveness analysis results

The base case deterministic and probabilistic cost-effectiveness results for danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan are presented in Table 66 and Table 67, respectively. In the model, the list prices of danicopan, eculizumab and pegcetacoplan, and PAS price of ravulizumab were used (Section B.3.5.1).

In both the deterministic and probabilistic 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 £30,000/QALY. Danicopan as an add-on to eculizumab or ravulizumab dominated pegcetacoplan in the deterministic and probabilistic analyses, respectively. The resulting net health benefit (NHB) with danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan is positive, with a value of [redacted] in the deterministic analysis, and [redacted] in the probabilistic analysis.

The clinical outcomes and disaggregated base case cost-effectiveness results (by cost category, including health states) and QALYs (by health state) are presented in Appendix J.

Table 66: Deterministic base-case results

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB
Danicopan + C5i[a]	[redacted]	17.864	14.207					
Pegcetacoplan	£7,711,022	17.864	13.778	[redacted]	0.000	0.429	Dominant	[redacted]

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 67: Probabilistic base-case results

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB
Danicopan + C5i[a]	[redacted]	17.896	14.373					
Pegcetacoplan	£7,722,911	17.896	13.954	[redacted]	0.000	0.418	Dominant	[redacted]

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

B.3.11 *Exploring uncertainty*

Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses, the results of which are presented in Sections B.3.11.1 and B.3.11.2, respectively. In addition, key assumptions in the model were explored in several scenario analyses, the results of which are presented in Section B.3.11.2. Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

B.3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order assess the simultaneous effect of uncertainty in the different model parameters and to demonstrate whether the model results are robust to those variations. A Monte-Carlo simulation with 1,000 iterations was performed where model inputs were randomly sampled from the specified probability distributions. Estimates of model parameters based on the uncertainty in the source data (where data availability permitted). Where no such data were available, the model applied a user-defined percentage of the mean value as the SE.

An ICER convergence plot is provided in Figure 15 below.

Figure 15: ICER convergence plot

Abbreviations: C5i: complement component 5 inhibitor; ICER: incremental cost-effectiveness ratio.

The probabilistic cost-effectiveness plane for danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan is presented in Figure 16.

The PSA found the probability of danicopan as an add-on to eculizumab or ravulizumab being a cost-effective use of NHS resources to be 100% and 100% at a WTP threshold of £20,000 and £30,000 per QALY gained, respectively.

Figure 16: Probabilistic cost-effectiveness plane for danicopan as an add-on to eculizumab or ravulizumab vs pegcetacoplan

B.3.11.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, DSAs were conducted by varying the input for each parameter in the model, whilst keeping all other inputs the same. For certain parameters where SEs of the mean were available, the lower and upper limits were defined by the 95% CI around the mean. In the absence of 95% CI, the inputs were varied by ±10% instead. The inputs used in the DSA are presented in Section B.3.9.1.

A tornado diagram showing the top 10 most influential parameters on the net health benefit for danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan is presented in Figure 17.

The NHB was most sensitive to the age of patients, the probability of pegcetacoplan patients experiencing a BTH from 17 weeks onwards and the probability of patients discontinuing pegcetacoplan to eculizumab or ravulizumab monotherapy between 17 weeks and a year. Patient age was sourced directly from the ALPHA trial, and is expected to be representative of the PNH population in England. The probability of BTH among patients receiving pegcetacoplan after 17 weeks was informed by the open-label period of the PEGASUS trial, which represents the best source of data on the probability of BTH with pegcetacoplan. The proportion of patients discontinuing pegcetacoplan 17 weeks onwards was obtained from the PEGASUS trial and is anticipated to accurately reflect pegcetacoplan discontinuation in clinical practice. The remaining parameters presented in the tornado diagram did not result in a significant change in the NHB, therefore demonstrating that the base case results are robust to uncertainties in the model inputs and assumptions.

Figure 17: DSA tornado diagram for danicopan as an add-on to eculizumab or ravulizumab vs pegcetacoplan

Abbreviations: BTH: breakthrough haemolysis; C5i: C5 inhibitor; DANI: danicopan; DSA: deterministic sensitivity analysis; NHB: net health benefit; PEG: pegcetacoplan.

B.3.11.3 Scenario analysis

As described in Section B.3.11, scenario analyses were conducted to explore the impact of structural assumptions and alternative inputs on the results of the cost-effectiveness model. The results of the scenario analyses are presented below.

Overall, the results of the scenario analyses were consistent with the results of the base case analysis, demonstrating the results to be robust to uncertainties in the model inputs and assumptions. The ICER and NHB were most sensitive to the exclusion of treatment discontinuation of danicopan and pegcetacoplan beyond Year 1, the application of a 10- or 20-year time horizon, and the inclusion of a proportion of patients who discontinue or dose escalate pegcetacoplan following BTH, as per data from the PEGASUS trial. However, the base case inputs or settings for these parameters are considered to provide a conservative assumption or reflect clinical practice accurately. No discontinuation beyond Year 1 is in line with NICE TA778.[5] The 'lifetime' time horizon in the base case is reasonable given that EVH is a chronic condition, and is consistent with TA778.[5] Patients on pegcetacoplan were not modelled to discontinue treatment as a result of BTH based on UK clinical expert opinion.[50] Therefore, the base case inputs for these parameters represent the most suitable inputs for this analysis.

Table 68: Scenario analysis results for danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan (probabilistic)

Scenario		Danicopan + C5i[a] vs pegcetacoplan			
		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB
Base case		[redacted]	0.418	Dominant	[redacted]
1	Time horizon: 10 Years	[redacted]	0.194	Dominant	[redacted]
2	Time horizon: 20 Years	[redacted]	0.320	Dominant	[redacted]
3	Dose escalation: All danicopan patients escalate to 200 mg for Week 53+	[redacted]	0.416	Dominant	[redacted]
4	C5i distribution: Based on ALPHA trial	[redacted]	0.315	Dominant	[redacted]
5	Discontinuation: Sustained discontinuation in Year 1+	[redacted]	0.161	Dominant	[redacted]
6	BTH management: Pegcetacoplan discontinuation/escalation from PEGASUS trial	[redacted]	0.492	Dominant	[redacted]
7	Iron overload: C5i monotherapy patients receive phlebotomies	[redacted]	0.419	Dominant	[redacted]
8	Utilities: Values derived from arithmetic means	[redacted]	0.445	Dominant	[redacted]
9	Health states based on 10.5 Hb cut-off (Transitions informed by MAIC)	[redacted]	0.314	Dominant	[redacted]
10	Health states based on 10.5 Hb cut-off (Transitions informed by MAIC, Max ESS weights)	[redacted]	-0.893	SW Quadrant	[redacted]

11	Health states based on 10.5 Hb cut-off (Transitions informed by MAIC, Utilities from Hakimi 2022)	[redacted]	0.313	Dominant	[redacted]
12	Utilities: Apply transfusion utility value from TA778	[redacted]	0.418	Dominant	[redacted]
13	Utilities: No disutility applied for iron overload	[redacted]	0.420	Dominant	[redacted]
14	Utilities: Eculizumab and pegcetacoplan disutility aligned with TA698	[redacted]	0.850	Dominant	[redacted]
15	Utilities: EORTC from ALPHA mapped to EQ-5D-3L	[redacted]	0.451	Dominant	[redacted]

[a] Eculizumab or ravulizumab.
Abbreviations: BTH: breakthrough haemolysis; C5i: complement component 5 inhibitor; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: Euro-QoL 5 Dimensions 3 Level; Hb: haemoglobin; HSUV: health state utility value; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; INHB: incremental net health benefit; QALY: quality-adjusted life year; TA: technology appraisal.

B.3.12 *Subgroup analysis*

No subgroups were considered relevant to this appraisal and as such no subgroup analyses were included in the cost-effectiveness analysis.

B.3.13 *Benefits not captured in the QALY calculation*

The main benefit of danicopan as add-on treatment to eculizumab or ravulizumab, as expressed by clinical experts consulted at a UK advisory board, is the reassurance that IVH will be well-controlled alongside the treatment of csEVH.[4] For patients receiving pegcetacoplan, they must discontinue treatment with eculizumab or ravulizumab after the co-administration of pegcetacoplan with eculizumab or ravulizumab for the first 4 weeks of treatment. The discontinuation of eculizumab or ravulizumab may result in the potential for suboptimal control of IVH due to an incomplete terminal inhibition. The complete and sustained inhibition of both the terminal and proximal components of the complement system with danicopan thus provides reassurance of controlled BTH, which is not explicitly captured in the QALY calculations.

Additionally, another key benefit of danicopan add-on treatment to eculizumab or ravulizumab is the convenient methods of administration. Danicopan is administered orally, and eculizumab and ravulizumab are administered intravenously at home by trained healthcare professionals. The costs of administration of eculizumab and ravulizumab are paid for by their manufacturers. As described in Section B.1.3.3, pegcetacoplan has a higher dosing frequency (i.e., twice a week) and is self-administered as a SC injection. However, clinical experts indicated that a proportion of patients have difficulties with self-administering SC injections due to reasons such as dexterity issues and sight-related issues. Furthermore, patients with minimal SC tissues, mental health issues and other sight-related issues, may be unable to self-administer pegcetacoplan. Danicopan add-on treatment to eculizumab or ravulizumab thus provides a more convenient method of administration for patients, which is not captured in the QALY calculations.

Lastly, COVID-19 has enhanced the general population's understanding of fatigue and the severity of its impact on people, which are not fully captured in current questionnaires assessing

fatigue and people's HRQoL. Fatigue is a key symptom and area of unmet need for people with csEVH, and the full extent of danicopan's benefit in lowering levels of fatigue therefore may not be captured in the economic model.

B.3.14 *Validation*

B.3.14.1 Validation of cost-effectiveness analysis

The cost-effectiveness model was designed and built in line with NICE's preferred methods and reference case.[153] The economic analysis was conducted from a NHS and PSS perspective, costs and benefits were discounted at an annual rate of 3.5%, and a lifetime time horizon was used to capture all costs and benefits associated with each treatment.

Economic model validation

Quality-control procedures of the model were performed by health economists who were not involved in the development of the model, to ensure that the programming and physical implementation of the conceptual model was completed correctly. These procedures involved the verification of all model inputs against the data sources, and a programming validation of the model's calculations and results, data references, interface, and Visual Basic for Applications code. Any discrepancies were identified, discussed, and corrected as required.

Validation of economic model outputs against clinical expert opinion

Clinical feedback was sought to validate the cost and resource use inputs utilised in the model, as well as key modelling assumptions. Where possible, UK source were used for model inputs and similar inputs and approaches to those used in prior appraisal were adopted.[5]

B.3.15 *Interpretation and conclusions of economic evidence*

Summary of the cost-effectiveness evidence

In order to assess the cost-effectiveness of danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan in PNH patients with csEVH, a *de novo* cost-effectiveness analysis was conducted from the perspective of the NHS and PSS in England.

In the deterministic base case analysis, danicopan as an add-on to eculizumab or ravulizumab dominated pegcetacoplan, being cost-saving and more effective than pegcetacoplan. Additionally, danicopan as an add-on to eculizumab or ravulizumab resulted in a NHB of [redacted] and [redacted] in the deterministic and probabilistic analyses, respectively. Therefore, at a WTP of £30,000/QALY gained, danicopan as an add-on to eculizumab or ravulizumab can be considered a cost-effective use of NHS resources in adults with PNH experiencing csEVH on eculizumab or ravulizumab.

The PSA found the probability of danicopan as an add-on to eculizumab or ravulizumab being cost-effective to be 100% and 100% at a WTP threshold of £20,000 and £30,000 per QALY gained, respectively. The DSA results identified a small number of key influential parameters including patient age, the probability of BTH among patients receiving pegcetacoplan in Weeks 17+ and the proportions of patients discontinuing pegcetacoplan to eculizumab or ravulizumab

monotherapy between 17 weeks and a year. However, overall the base case results were found to be robust to uncertainty in the majority of model parameters. Scenario analyses conducted to address sources of uncertainty in modelling assumptions found cost-effectiveness conclusions remained largely the same, with danicopan as an add-on to eculizumab or ravulizumab remaining cost-effective at a WTP of £30,000 per QALY gained across the majority of scenarios.

Strengths

A robust clinical validation exercise was conducted by Alexion with 9 clinical experts and 2 health economic experts in the UK in order to validate key inputs and assumptions, including cycle length, transition probabilities and HSUVs.[4] Additionally, the clinical experts reviewed the baseline characteristics of patients enrolled in the ALPHA and PEGASUS trials both of which were deemed to be representative of UK clinical practice. The results of the economic analysis are therefore considered highly relevant to decision-making on the introduction of danicopan as an add-on to eculizumab or ravulizumab into NHS clinical practice.

The cost-effectiveness analysis is associated with several strengths, the first being that previous therapies in PNH have been appraised by NICE. A review of relevant NICE evaluations was conducted during model design and development, and thus it was possible to take into account a number of learnings from previously developed models for PNH, in addition to prior external assessment group (EAG) and Committee preferences for methodological approaches in this area, such as cost and resource use and the selection of HSUVs. In particular, key learnings were taken from a recent appraisal of pegcetacoplan in a similar indication [TA778], the committee papers were reviewed to ensure, where possible, this evaluation was conducted in alignment with previous committee preferences in this area.[5]

The model further closely aligns to the NICE reference case, adopting an NHS and PSS perspective as well as utilising a lifetime time horizon to ensure all costs and QALY gains associated with the interventions are fully capture and discounting costs and benefits at a rate of 3.5% per annum.[173]

Limitations

As with many clinical trials in a rare disease, a key limitation of the evidence base was the lack of a direct comparison versus the relevant comparator to this appraisal, pegcetacoplan monotherapy. To address this limitation, the feasibility of a MAIC, as discussed in Section B.2.10, was investigated to obtain relative efficacy estimates of danicopan as an add-on to eculizumab or ravulizumab treatment versus pegcetacoplan.[111]

However, owing to the identification of significant heterogeneity in the feasibility assessment between the ALPHA and PEGASUS trials that could not be adjusted for, including prior transfusion history and baseline bilirubin levels, the results of the MAIC were associated with significant uncertainty and were not deemed suitable for inclusion in the economic analysis.[111] Therefore, naïve results from the ALPHA and PEGASUS trials were used to inform the base case transition probabilities in the model. In order to explore uncertainty around this point, a scenario analysis whereby transition probabilities generated from the MAIC outputs was conducted, which showed a similar IHNB to the base case.

Furthermore, clinical data informing the economic model were informed by small patient numbers. Clinical data were derived from the ALPHA trial (86 patients, with 63 patients forming

the IAS) and the PEGASUS trial (80 patients) for danicopan add-on treatment and pegcetacoplan, respectively. As such, any extreme clinical values observed in these small patient sets may introduce bias to the clinical measures driving the economic analysis. However, in prior NICE appraisal TA778, the economic model for pegcetacoplan was considered suitable for decision-making by the committee despite the small patient numbers in the PEGASUS trial informing clinical measures.

Uncertainty in the clinical outcomes included in the economic model were exacerbated by limited follow-up data available from the ALPHA and PEGASUS trials. Transition probabilities for patients receiving danicopan add-on treatment to eculizumab or ravulizumab were derived from all treatment periods available in the ALPHA trial; TP1 (Week 0–12), TP2 (Week 13–24) and the open-label extension period (Week 25–52), whilst data from the PEGASUS trial were available from the randomised controlled period (Week 4–16) and the open-label period (Week 17–48). Furthermore, AE data for the PEGASUS trial were available for the randomised controlled period (Week 0–12) necessitating the assumption that probabilities of SAEs beyond Week 12 were consistent after this timepoint.

Conclusion

There remains a considerably high unmet need amongst adult patients with PNH experiencing csEVH for a treatment that effectively manages both IVH and csEVH. As danicopan is an add-on treatment that effectively manages EVH, whilst also allowing patients to continue ongoing treatment with eculizumab or ravulizumab, proven treatments in the control of IVH, danicopan represents a valuable new treatment option that addresses the current unmet need associated with csEVH.[105, 106] In particular, a substantial proportion of patients with csEVH require blood transfusions which are time-consuming (1.5–4 hours per transfusion) and involve visits to the hospital or an outpatient clinic.[78, 79, 97, 98] Danicopan add-on treatment to eculizumab or ravulizumab results in a reduction in the proportion of patients who require blood transfusions, and would thus lead to a lower impact on the HRQoL of patients and carers. Furthermore, as danicopan as an add-on to eculizumab or ravulizumab dominated pegcetacoplan and resulted in a deterministic NHB of [redacted], danicopan as an add-on to eculizumab or ravulizumab can be considered a cost-effective use of NHS resources at a WTP threshold of £30,000/QALY gained.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria

ID5088

Summary of Information for Patients (SIP)

12th January 2024

File name	Version	Contains confidential information	Date
ID5088_Danicopan_NICE_SIP_FINAL_12Dec23 [noCON]	2.0	No	12th January 2024

Summary of Information for Patients (SIP): The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Terms highlighted in **bold** throughout this Summary of Information for Patients have been defined in the **Glossary (Section 4b)**. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

1a. Name of the medicine (generic and brand name):

Generic name: Danicopan **Brand name:** Voydeya™

1b. Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

This medicine is under consideration for the treatment of clinically significant ***extravascular haemolysis (csEVH)*** (see **Section 2a**) in adults with a disease called **paroxysmal nocturnal haemoglobinuria (PNH)** during treatment with another type of PNH medicine called a complement component 5 inhibitor (C5 inhibitor) [eculizumab or ravulizumab] (see **Section 2c**). Symptoms of EVH include **anaemia** (low levels of a **protein** called **haemoglobin**, which transports oxygen around the body), and related symptoms such as tiredness, weakness, and shortness of breath (1, 2).

1c. Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The **Medicines and Healthcare products Regulatory Agency** (**MHRA**) is currently reviewing whether danicopan as an add-on to eculizumab or ravulizumab should receive marketing authorisation in the United Kingdom (UK). More information about this can be found in **Document B** in **Section B.1.2**.

1d. Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The table below shows support from Alexion to relevant patient advocacy groups in the UK, and how the company engages or supports these charities and/or people who use them. Financial support varies from annual support of core services to support people with csEVH and/or staff to attend meetings or events.

Patient group:	**Engagement/activity with each group:**	**Financial support provided:**
PNH Support	Participation in two Advisory Board meetings	EUR 700
	Speaking engagement in Zurich, Switzerland	EUR 500
	Input into clinical study design	GBP 190
Aplastic Anaemia Trust	Winter Webinar series sponsorship	USD 13,429
Aplastic Anaemia Trust	PNH Support and Aplastic Anaemia Trust organised and led the National Community Survey which was sponsored by Alexion	Phase I: USD 24,772 Phase II: USD 24,807

SECTION 2: Current landscape

2a. The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is paroxysmal nocturnal haemoglobinuria?

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, long-term, and serious blood disorder, where healthy blood cells are attacked and ultimately destroyed by the body's **immune system** (3-6). The destruction of **red blood cells** (cells which transport oxygen and carbon dioxide in the blood) by the body's immune system is known as **haemolysis**. Two forms of haemolysis can occur in PNH:

- **Intravascular haemolysis (IVH):** When healthy red blood cells within blood vessels are destroyed.
- **Extravascular haemolysis (EVH):** When healthy red blood cells outside blood vessels (i.e., in the liver, **spleen**, **bone marrow** and **lymph nodes**) are destroyed (7).

IVH is treated with medicines known as complement component 5 inhibitors (C5 inhibitors). Complement component 5 is a **protein** in the **immune system** that helps defend against diseases (8). Eculizumab and ravulizumab are two types of C5 inhibitors currently available in the UK. Following treatment with eculizumab or ravulizumab, some people may still experience low levels of **haemoglobin** due to EVH and continue to experience symptoms such as tiredness. In these cases, people with PNH may discontinue their C5 inhibitor treatment and receive treatment with a complement component 3 inhibitor (C3 inhibitor), pegcetacoplan, instead. In the UK, only pegcetacoplan is available for the treatment of EVH.

The form of **haemolysis** being considered in this NICE evaluation is EVH.

How common is paroxysmal nocturnal haemoglobinuria and extravascular haemolysis?

PNH is a rare disease. The predicted prevalence of PNH in the UK is approximately 1 in 62,500 people (9). Between 2022 and 2023, the National PNH Service in the UK reported 926 people in England living with this condition (10).

There is no significant difference in the incidence of PNH between males and females (5, 11-13). All people with PNH receiving eculizumab or ravulizumab experience EVH to a varying degree. However, a proportion of people display symptoms which require treatment; these people are defined as having "clinically significant" EVH (csEVH). Published literature estimate that 10–20% of people who are treated with eculizumab or ravulizumab experience csEVH (14, 15).

What causes paroxysmal nocturnal haemoglobinuria and extravascular haemolysis?

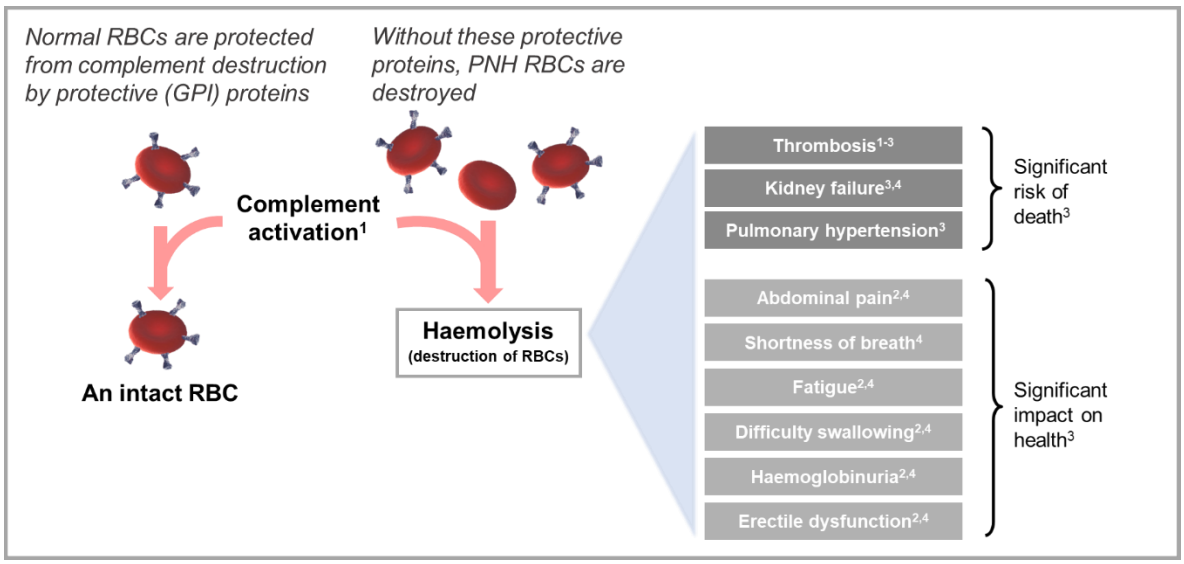
PNH is caused by **mutations** (changes) in the **gene** that controls the development of blood **stem cells** (cells that give rise to other types of blood cells). These changes result in the production of abnormal blood cells which have a reduced number of protective

proteins, known as **glycosylphosphatidylinositol (GPI)** proteins, on their cell surface. These protective proteins ensure that the body's **immune system** recognises the cells as healthy, and so it does not destroy them (7).

Specifically in abnormal **red blood cells**, the reduced number of **GPI** proteins increases the likelihood of them being destroyed by a part of the **immune system** known as the **complement system** (7, 16). The complement system is a group of over 30 proteins which is involved in the recognition and removal of bacteria, viruses, and damaged cells from the body (16-18).

In PNH, **red blood cells** that have a reduced number of **GPI** proteins are mistaken for damaged cells, and are subsequently destroyed by the **complement system**, resulting in **haemolysis** as shown by Figure 1 (7, 16).

Figure 1: Cause of PNH



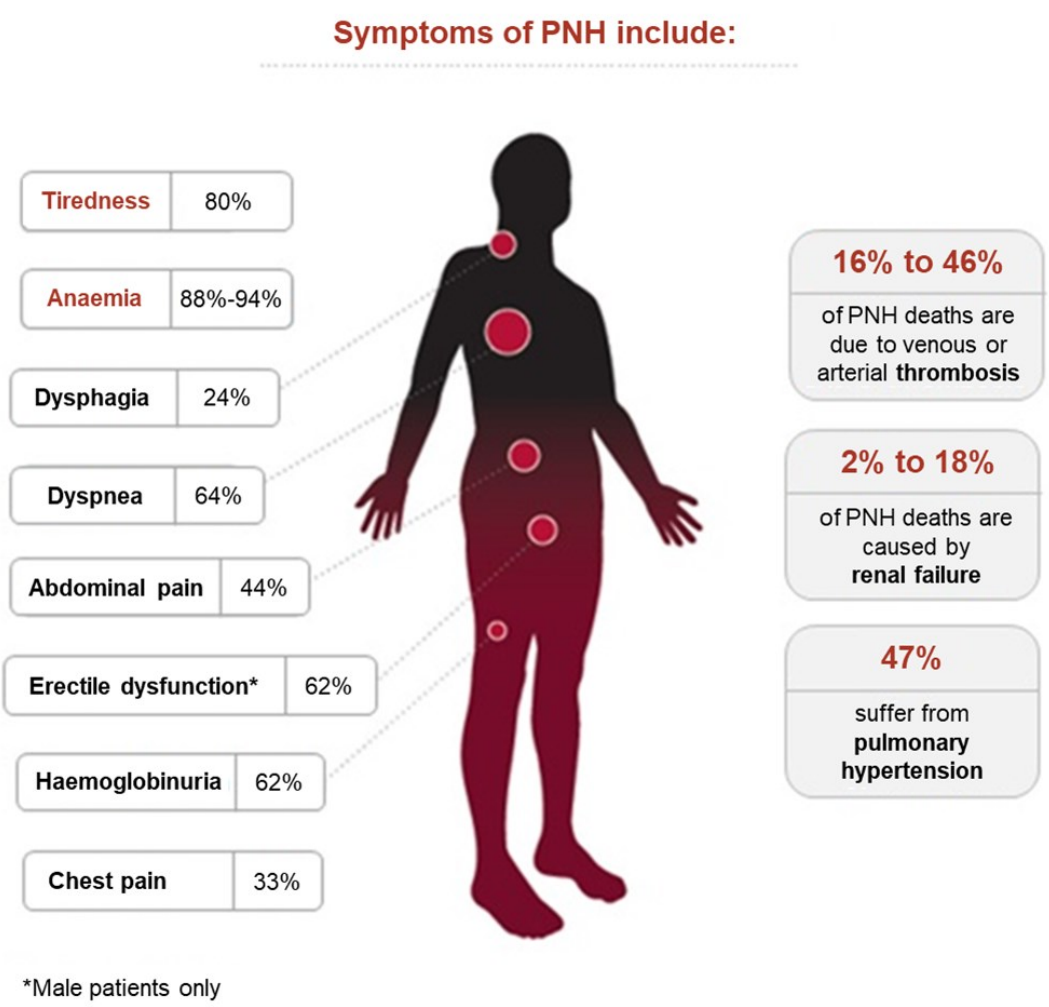
Abbreviations: GPI: glycosylphosphatidylinositol; PNH: paroxysmal nocturnal haemoglobinuria; RBC: **red blood cell.**
Source: 1. Brodsky, et al. (2018) (19); 2. Rother, et al. (2005) (20); 3. Weitz, et al. (2013) (21); 4. Lee, et al. (2013) (22).

C5 inhibitors reduce the destruction of these PNH **red blood cells**. However, red blood cells that survive **haemolysis** due to a patient's C5 inhibitor treatment may then go on to be destroyed via a separate part of the complement pathway instead (23, 24). This type of haemolysis is called EVH. It occurs outside of blood vessels and leads to a decrease in the number of red blood cells in the blood (7, 23).

What are the symptoms of paroxysmal nocturnal haemoglobinuria (intravascular haemolysis and extravascular haemolysis)?

PNH results in a range of symptoms which can affect multiple areas of the body, as shown in Figure 2. IVH and EVH are each associated with different types and severities of symptoms. People are typically diagnosed with PNH due to the display of symptoms of IVH. While all people treated for PNH with eculizumab or ravulizumab experience EVH to varying extents, a small proportion of people have symptoms which require treatment and are defined to have csEVH (described further in the 'Extravascular haemolysis' section below). An overview of the symptoms associated with both IVH and EVH is provided below.

Figure 2: Symptoms of PNH



Notes: **Anaemia** is defined by a low level of **red blood cells**; **dysphagia** is also known as swallowing difficulties; **dyspnea** refers to a shortness in breath.
Abbreviation: PNH: paroxysmal nocturnal haemoglobinuria.
Source: Alexion Data on File. Danicopan PNH EVH GVD. 2023 (25).

Intravascular haemolysis

The majority of symptoms associated with PNH are caused by IVH, including tiredness (~80%), low **haemoglobin** levels (known as **anaemia**) (88–94%), shortness of breath (64%) and abdominal pain (44%) (26-30). Serious and potentially life-threatening consequences of IVH include **blood clots** (when blood cells clump together; also known as **thrombosis**), long-term kidney disease, kidney and liver failure, infection/**blood poisoning** and cancer (29, 31-34). Thrombosis is a serious complication of IVH and is the leading cause of death in PNH if left untreated (7).

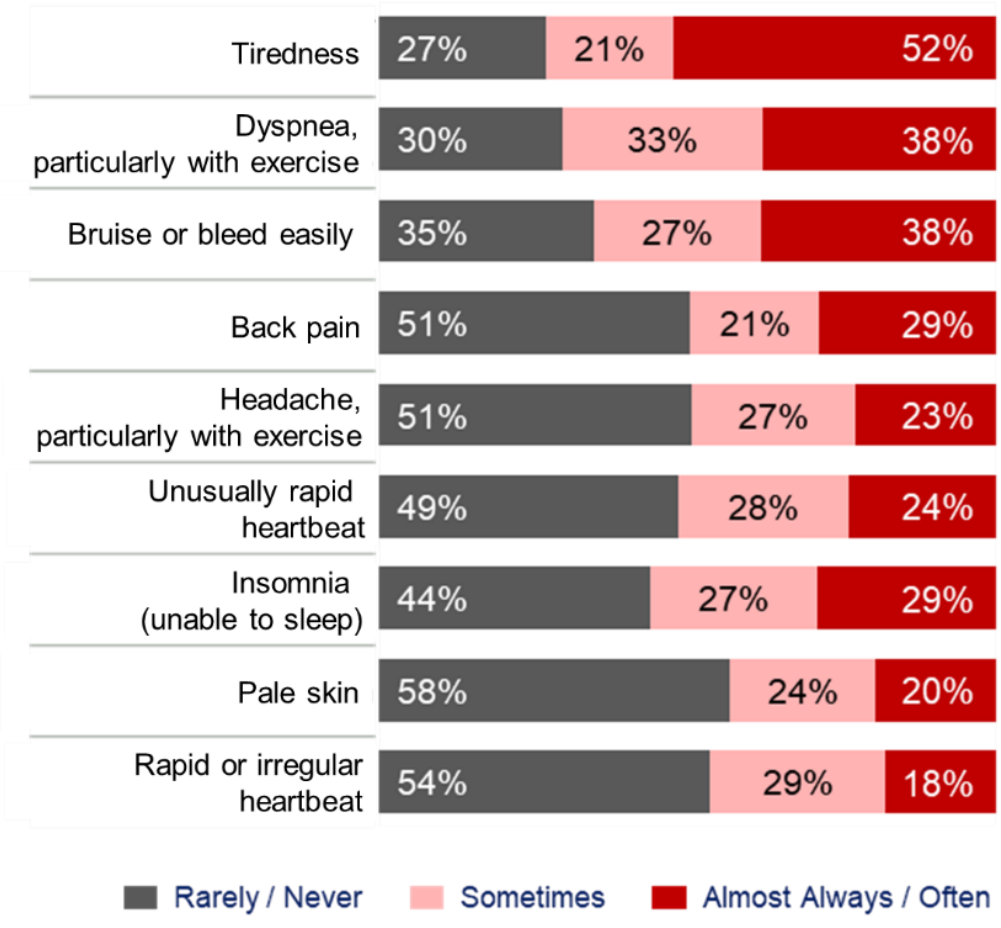
The symptoms and severity of IVH vary widely across people and as such not all people with PNH require treatment with C5 inhibitors (35, 36). According to the annual report published by the PNH National Service in the UK, only 36.6% of people with PNH receive treatment with eculizumab or ravulizumab (10). People with severe IVH are at an increased risk of severe complications. Among people who require treatment with a C5 inhibitor, if an insufficient inhibition of IVH occurs, **breakthrough haemolysis (BTH)** may

arise (37). BTH is defined by a new or worsening sign or symptom of IVH, along with a higher than normal level of an **enzyme** called lactate dehydrogenase (LDH) (37, 38).

Extravascular haemolysis

All people with PNH treated with either eculizumab or ravulizumab will experience EVH to a varying degree. However, 10–20% of people with PNH treated with eculizumab or ravulizumab display symptoms which require treatment, and are defined as having csEVH (14, 15). As a result of low **haemoglobin**, approximately 20% of people with symptoms of EVH require a regular receipt of donated blood (**blood transfusion**) to replenish their **red blood cell** levels (39). The process of receiving a blood transfusion is time-consuming (ranging from 1.5 to 4 hours for each transfusion) and requires a trip to the hospital or outpatient clinic (40-43). Additionally, loss of energy and tiredness are the most frequently reported physical symptoms of EVH (73%), with 52% of people experiencing them almost always or often, as presented in Figure 3 (44, 45). UK clinical experts have also emphasised that ongoing tiredness is a key symptom of EVH, and remains a significant need among people with EVH which has yet to be addressed (36). While symptoms of EVH can have a substantial impact on the quality of life of people with EVH, studies have shown that EVH does not result in an increased risk of death for people who are treated with C5 inhibitors (32).

Figure 3: Symptoms of EVH



Abbreviation: EVH: extravascular **haemolysis**.
Source: Alexion Data on File. Danicopan PNH EVH GVD. 2023 (25).

What is the impact of paroxysmal nocturnal haemoglobinuria and extravascular haemolysis on patients' quality of life?

For some people with PNH, EVH symptoms have an impact on their physical and mental health (46). In medicine, the physical and mental health of people are referred to as **health-related quality of life** (**HRQoL**). The HRQoL of people are typically measured through patient questionnaires, and their scores are compared to those of the general population to assess the impact of disease. In general, a higher HRQoL is beneficial and reflects a better quality of life in terms of physical and mental health, and vice versa. Although eculizumab and ravulizumab have improved symptom control and HRQoL among people with IVH, people receiving them have reported significantly higher levels of tiredness (tiredness score: 35.6–33.8 vs 43.5, respectively) and lower HRQoL (HRQoL score: 62.9–68.7 vs 75.0, respectively) compared with the general population (47). A lower HRQoL is similarly reported among people with csEVH. From a small study of 25 people with PNH, a smaller proportion of people with csEVH (56%) reported a good to excellent HRQoL compared with people without csEVH (79%) (15).

People with tiredness may experience the need to sleep for prolonged hours during the day, experience **brain fog** (thinking more slowly than usual) and have difficulties walking, climbing stairs, leaving the house and participation and performance in school or working (47-50). As such, people with tiredness may have to rely on carers to help them perform daily activities such as climbing the stairs, impacting their independence. If caregiving takes the form of informal assistance through family and friends, this may strain patient relationships with their immediate family network (51).

Inconveniences relating to the regular administration of treatments also leads to a negative impact on the **HRQoL** of people with PNH and their carers. Eculizumab and ravulizumab are infusions received through the vein, which require administration by a trained healthcare professional (via homecare; most people in the UK receive their treatment at home) once every 2 weeks and 8 weeks, respectively (52-54). The treatment administration-related burden of eculizumab and ravulizumab is worsened when considering that people may need to make trips to the hospital in order to receive **blood transfusions** due to low **haemoglobin** levels (36, 42, 55). Although pegcetacoplan can be self-administered, training is required and each administration involves a 10-step process lasting 30–60 minutes (36, 56). Moreover, people who have issues related to eyesight or **dexterity** (the ability to perform tasks, especially using their hands), may not be capable of administering pegcetacoplan themselves (36). Compared with eculizumab and ravulizumab, pegcetacoplan also has a higher dosing frequency of twice weekly, which may be increased to once every three days.

What is the economic impact of paroxysmal nocturnal haemoglobinuria and extravascular haemolysis?

PNH is costly to the healthcare system due to high rates of **hospitalisations, blood transfusions and management of PNH-related complications** (40, 41, 57, 58). Uncontrolled IVH leads to severe and life-threatening symptoms, and thus results in additional costs to the healthcare system. For example, **BTH** events require urgent hospital treatment, incurring high costs, in complement inhibitor treated people. Furthermore, 20% of people with PNH who develop csEVH may require regular **blood transfusions** (39). Direct medical costs have been reported to increase 8.3 times among people with PNH who require **blood transfusions** compared to those who do not,

demonstrating the substantial costs incurred by the healthcare system owing to the need for **blood transfusions** (57).

PNH is further associated with a loss of income due to unemployment. A study conducted in 71 people with PNH treated with eculizumab or ravulizumab in the UK, France and Germany, revealed 42.3% of people were unemployed. Additionally, people with PNH who were employed reported reduced levels of work efficiency (productivity losses; 97.6%) from working while unwell (physically, mentally, or emotionally; 70.3%) (47).

2b. Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

PNH is typically diagnosed using a specialist blood test known as **flow cytometry** to detect abnormal **red blood cells** that have low levels of a specific **protein** known as **GPI** (see **Section 2a**) (59). **Flow cytometry** is a technique using lasers and detectors that measure light passing through cells in a sample to identify the abnormal **red blood cells** (60).

People who have **red blood cells** with low levels of **GPI** proteins subsequently undergo further tests to determine if they have PNH, which mainly include blood tests, tissue samples, and a **Coombs test** (a blood test to detect proteins that attack **red blood cells**) (61-65).

In order to determine if a patient is exhibiting csEVH whilst on treatment with a **complement system** inhibitor, UK clinicians will consider tiredness levels and the impact of PNH on **HRQoL** as reported by people during **clinical trials**, in addition to the results of blood tests (such as for **haemoglobin** levels) (36).

2c. Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Eculizumab and ravulizumab

The goal of treatment of PNH is to eliminate IVH (29, 31, 34, 66). People who are diagnosed with PNH typically receive either eculizumab or ravulizumab to manage the symptoms of IVH. Eculizumab and ravulizumab both work by binding to and inhibiting C5, a **protein** in the **complement system** which causes inflammation, thereby preventing the body's **immune system** from attacking and destroying the vulnerable PNH blood cells (52, 53). However, as described in **Section 2a**, PNH blood cells that survive following treatment with eculizumab or ravulizumab may subsequently be destroyed via a separate part of the complement pathway, leading to the occurrence of EVH (23, 24).

Pegcetacoplan

People who have been treated with eculizumab or ravulizumab for a specified period of time (3–6 months) may continue to have low **haemoglobin** levels (**anaemia**) as a result of EVH. Pegcetacoplan is an alternative treatment option for these people, and they are required to stop treatment with eculizumab or ravulizumab after an initial four-week overlap in order to receive it. Pegcetacoplan binds to and blocks C3, a different **protein** in the **complement system**, and thus prevents the destruction of PNH blood cells by the **immune system** (56). Through C3 inhibition, pegcetacoplan treats anaemia caused by EVH whilst also managing IVH. However, pegcetacoplan may not control IVH sufficiently in some people, with 24% of people on pegcetacoplan treatment still experiencing **BTH** (defined in **Section 2a**) (67-69). Cases of BTH have also been reported to be more severe with pegcetacoplan than eculizumab or ravulizumab (70).

2d. Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

PBE among people with EVH are rare, however, the impact of the common symptoms associated with EVH are reported in studies conducted in people with PNH.

Health-related quality of life of patients with paroxysmal nocturnal haemoglobinuria and extravascular haemolysis

A burden of illness study was conducted in 71 people with PNH treated with eculizumab or ravulizumab in the UK, France and Germany (47). Tiredness was the most common

symptom reported (eculizumab: 61.2%; ravulizumab: 68.2%). Furthermore, tiredness scores (ranked on a scale of 0–52, whereby lower scores indicate increased tiredness) were lower among people with PNH treated with eculizumab or ravulizumab (35.6 and 33.8, respectively) than that of the general population (43.5). Similarly, the patients reported a significantly lower level of **HRQoL** (eculizumab: 68.7; ravulizumab: 62.9) than the general population (75.0).

A preliminary research study among 25 people who were stable on C5 inhibitor treatment and with csEVH similarly reported a lower **HRQoL** than people without csEVH (15). A smaller proportion of people with csEVH (56%) reported a good to excellent HRQoL compared with people without csEVH (79%).

Paroxysmal nocturnal haemoglobinuria from the patient's perspective

As described above, the symptoms of PNH have led to a significant reduction in the **HRQoL** of people with this condition. These effects were similarly reported by people with PNH in patient interviews, where a person said, prior to diagnosis, "I suffered extreme fatigue, breathlessness, bone and muscle pain, extreme **brain fog**, struggled to speak or even open my eyes, inability to stand or walk for long", which left her unable to work (48). Another person further described his experience with tiredness prior to receiving treatment for PNH: "I was sleeping a lot – through the night, back to bed for an hour or so in the morning, up for lunch, another sleep in the afternoon, a snooze in the evening, then back to bed" (49).

A person with EVH who participated in the ALPHA trial reported an improvement in symptoms with danicopan as an add-on to ongoing C5 inhibitor treatment: "I had adjusted to living with a low **haemoglobin** on both eculizumab and ravulizumab but the tablet has transformed my health and I feel amazing and have so much more energy" (71).

SECTION 3: The treatment

3a. How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

What is danicopan?

Danicopan is a tablet that is swallowed for people with PNH experiencing csEVH. It is taken as an add-on to eculizumab or ravulizumab infusions. Danicopan has been designed to block a **protein** called **complement factor D**, which is a part of the **complement system** (see **Section 2c**) (56). Danicopan therefore stops the **immune system** from destroying **red blood cells** outside of blood vessels (EVH) and is the first of its kind, offering a new and effective way of preventing the complement system from damaging red blood cells (72). Furthermore, as an oral treatment, patients with problems that may hinder self-injection of pegcetacoplan (such as **dexterity** or eyesight problems) will have an alternative treatment option available to them.

How is danicopan different from pegcetacoplan?

As described in **Section 2c**, pegcetacoplan is the only available treatment for **anaemia** in people receiving eculizumab or ravulizumab. However, these people must stop treatment with eculizumab and ravulizumab after an initial four-week overlap in order to receive pegcetacoplan. **BTH** has been reported to be more severe among people treated with pegcetacoplan compared with eculizumab or ravulizumab (70).

One of the key benefits of danicopan as an add-on therapy includes the ability of people to continue treatment with eculizumab or ravulizumab whilst receiving danicopan. As eculizumab and ravulizumab control IVH and danicopan targets EVH, this ensures that the symptoms of both IVH and EVH are both addressed at the same time. UK clinical experts have highlighted that danicopan as an add-on to eculizumab or ravulizumab provides reassurance to people with PNH that their IVH continues to be well-managed, whilst also treating csEVH (36).

3b. Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

Yes

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Danicopan is used as an add-on to ongoing treatment with eculizumab (Soliris®) or ravulizumab (Ultomiris®). Danicopan specifically addresses EVH while eculizumab or ravulizumab controls IVH. Danicopan as an add-on to ongoing treatment with eculizumab or ravulizumab will effectively address both EVH and IVH in people with PNH.

Eculizumab and ravulizumab

The mechanisms of action of eculizumab and ravulizumab are further described in **Section 2c**. The dosing and administration of eculizumab and ravulizumab are further discussed in **Section 3c**. Very common **side effects** (affecting more than 1 in 10 people) of eculizumab and ravulizumab include headache (both treatments), diarrhoea, upper respiratory tract infections and the common cold (ravulizumab only). Common side effects (affecting up to 1 in 10 people) of eculizumab and ravulizumab include urinary tract infection, dizziness, nausea, abdominal pain, and rash. Further details on the side effects of eculizumab and ravulizumab are available in the respective **Patient Information Leaflets** (52, 53).

3c. Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How much medicine do patients take and when?

Danicopan

Danicopan is taken as an **oral tablet** which can be taken with or without food. The recommended starting **dose** of danicopan is 150 mg three times a day, approximately 8 hours apart (however, it is acceptable for these doses to be between 6–10 hours apart).

Doctors may increase the **dose** to 200 mg three times a day depending on the patient's response to treatment. If a dose is missed, the dose should be taken as soon as possible. If it is almost time to take the next dose, the missed dose should be skipped. A double dose should not be taken to make up for the missed dose.

PNH is a lifelong condition and therefore it is expected that patients will receive danicopan for the rest of their life. Treatment with danicopan should not be stopped unless advised by a doctor. If a patient has to stop taking danicopan, the **dose** will be reduced gradually by the doctor.

Danicopan should be given alongside the maintenance dosing regimens of either eculizumab or ravulizumab. Maintenance doses refer to the doses that patients receive after the first two or four weeks of treatment with ravulizumab or eculizumab, respectively. Further information on the administration and dosing of danicopan will be available in the **Patient Information Leaflet** when published.

Eculizumab

In the maintenance phase, eculizumab is administered as an **intravenous infusion** at a **dose** of 900 mg (3 vials of 30 ml) over a 25–45-minute period every 2 weeks (plus or minus 2 days) in adults. Patients should receive eculizumab continuously, unless advised

by a doctor to stop treatment. Further information on the administration of eculizumab is available in the **Patient Information Leaflet** (52).

Ravulizumab

The **dose** of ravulizumab administered is dependent on the patient's body weight, as presented in Table 1. The maintenance dose of ravulizumab is administered as an **intravenous infusion** once every 8 weeks (plus or minus 7 days, except for the first maintenance dose) in adults. Patients should receive ravulizumab continuously, unless advised by a doctor to stop treatment. Further information on the administration of ravulizumab is available in the **Patient Information Leaflet** (53).

Table 1: Weight-based maintenance dosing regimen for ravulizumab

Body weight range (kg)	Dose (mg)
≥40 to <60	3,000
≥60 to <100	3,300
≥100	3,600

3d. Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The ALPHA trial (NCT04469465) has studied danicopan as an add-on treatment to eculizumab or ravulizumab for the treatment of people with PNH who have csEVH. It is an ongoing **Phase 3 trial.** The ALPHA trial is randomised (patients are assigned a treatment at random) and double-blinded (the assigned treatment is not known by either patients or study investigators). The trial is also **placebo**-controlled, meaning the comparator includes a placebo. A placebo is a treatment that appears the same as the active treatment but does not have any treatment effect, serving as a comparator to study the treatment effects of danicopan as an add-on to treatment with eculizumab or ravulizumab. A total of 80 study sites across the world have been included in the study, with three study sites in England and Scotland (London, Airdrie, and Leeds). As a Phase 3 clinical trial, the ALPHA trial looks at how well danicopan as an add-on to eculizumab and ravulizumab works to treat the csEVH (its **efficacy**), how **safe** it is, as well as the impact on quality of life among people with csEVH. This study is expected to be completed in December 2023 (73).

Comparator

Danicopan as an add-on to eculizumab or ravulizumab is compared with **placebo** as an add-on to eculizumab or ravulizumab (73).

Key inclusion criteria

Inclusion criteria define a set of characteristics which people must meet in order to be able to participate in the study. The ALPHA trial includes adults diagnosed with PNH who have csEVH, and had been receiving eculizumab or ravulizumab for at least 6 months before the start of the study (73).

Key exclusion criteria

Exclusion criteria define a set of characteristics whereby people having these characteristics would not be able to participate in the study. People with a history of a major organ transplant or blood **stem cell** transplantation (a surgery to receive donated organs or blood stem cells), **bone marrow** failure, or a lack of **complement system** proteins were excluded from the ALPHA trial (73).

Further information on the ALPHA trial can be found on ClinicalTrials.gov.

3e. Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

How is the ALPHA trial being carried out?

The ALPHA trial consists of three parts. In the first part (treatment period 1), people in the trial were randomly assigned to receive either of the two treatments below for 12 weeks (73):

1. Danicopan as an add-on to either eculizumab or ravulizumab OR
2. **Placebo** as an add-on to either eculizumab or ravulizumab

In the second part of the ALPHA trial (treatment period 2), people who received **placebo** in combination with either eculizumab or ravulizumab were switched to receive danicopan with either eculizumab or ravulizumab, such that all people received danicopan for another 12 weeks (74).

Upon completion of treatment period 2, all people in the trial continued on the treatment for a year (long-term extension Year 1). Following this, each person could choose to stop participating in the trial or continue for one more year (long-term extension Year 2). This long-term extension is still ongoing (74).

Trial results

The goal of the ALPHA trial was to assess the improvement in **haemoglobin** levels (a **protein** found in **red blood cells** that transports oxygen) from the start of the study in people receiving danicopan as an add-on to either eculizumab or ravulizumab, versus people receiving **placebo** as an add-on to either eculizumab or ravulizumab (38, 75). A greater increase in haemoglobin levels was achieved with danicopan as an add-on to eculizumab or ravulizumab compared with placebo as an add-on to eculizumab or ravulizumab (74). An increase in haemoglobin is anticipated to reduce tiredness, a key symptom of EVH and contributor to reduced **HRQoL** in PNH.

Other outcomes evaluated in the trial found that compared with **placebo** as an add-on to eculizumab or ravulizumab, danicopan as an add-on to eculizumab or ravulizumab led to:

- Fewer people requiring **blood transfusions** (74)
- Lower levels of **tiredness**, signifying higher levels of energy to conduct normal daily activities (74)
- A greater reduction in the levels of undeveloped **red blood cells**, an important indicator of EVH, demonstrating an improved control of EVH (76)
- Greater improvements in **HRQoL**, in terms of reduced tiredness, and improvements in physical (the ability to perform basic activities of daily living) and social functioning (the ability to interact with others) (38)
- A greater proportion of **red blood cells** which are affected by PNH (38)

Overall, the trial demonstrated that danicopan is more effective than **placebo** as an add-on to eculizumab and ravulizumab after 12 weeks of treatment (treatment period 1). These treatment benefits were maintained over another 12 weeks in people continuing danicopan as an add-on therapy in treatment period 2. Similar improvements were also reported among people who switched to receive danicopan as an add-on to eculizumab or ravulizumab from receiving placebo as an add-on to eculizumab or ravulizumab in treatment period 1. More **efficacy** results can be found in **Document B, Section B.2.7**.

Indirect treatment comparison

When there is no data directly comparing two drugs, an **indirect treatment comparison** is typically performed. It is a form of analysis where differences between the **clinical trials** evaluating each of the two drugs are adjusted for, allowing their outcomes to be compared. This analysis was attempted for danicopan as an add-on to eculizumab or ravulizumab (ALPHA trial) and pegcetacoplan (PEGASUS trial). Outcomes that were investigated in the indirect treatment comparison were:

- The increase in **haemoglobin** level, from the start of the trials
- The increase in LDH level, from the start of the trials
- The increase in tiredness scores (ranked from 0–52, with higher scores indicating less tiredness), from the start of the trials

- The increase in reticulocytes (a type of immature blood cell, that can be used to measure EVH), from the start of the trials (76)

- The increase in the number of people who do not require **blood transfusions** while being treated with either drug

However, due to significant differences between the trials which could not be adjusted for, the **indirect treatment comparison** was not feasible. The unadjusted results from the ALPHA and PEGASUS trials showed that danicopan as an add-on to eculizumab or ravulizumab is more effective than pegcetacoplan.

3f. Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used, does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

During the ALPHA trial, people were asked to answer questions about their **HRQoL**, using various questionnaires (38). Data were collected at the start of the trial, and regularly throughout all three parts of the trial (treatment period 1, treatment period 2, and long-term extension period).

- **Three-level EuroQoL 5 dimensions (EQ-5D-3L)**: A questionnaire assessing the **HRQoL** of people in terms of (1) mobility, (2) self-care, (3) usual activities, (4) pain or discomfort, and (5) anxiety or depression

- **European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale (QLQ-C30):** A questionnaire assessing the physical, **psychological** (a person's mental or emotional state), and social functions in cancer patients specifically

- **Work Productivity and Activity Impairment Questionnaire: Anaemic Symptoms (WPAI:ANS)**: A questionnaire assessing the impact of anaemic (low level of **red blood cells**) symptoms on the work efficiency and activities of people

In general, people receiving danicopan as an add-on to eculizumab or ravulizumab and people receiving **placebo** as an add-on to eculizumab or ravulizumab had similar overall levels of **HRQoL** and work efficiency in the first 12 weeks of the trial. However, in specific domains such as tiredness, physical and social functioning, larger improvements were reported in the people receiving danicopan as an add-on to eculizumab or ravulizumab compared with the people receiving placebo as an add-on to eculizumab or ravulizumab. These reflect important improvements in the HRQoL of people with csEVH, as tiredness is a key symptom of EVH. Improvements in physical and social functioning also indicate that

these people are more independent and rely less on carers, signifying an improvement in carers' HRQoL as well. These treatment benefits relating to HRQoL were maintained in treatment period 2.

3g. Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, danicopan can cause **side effects**, although not everybody gets them. The Summary of Product Characteristics typically categorises side effects as (77):

- Very common: affecting more than 1 in 10 people
- Common: affecting more than 1 in 100 people and less than 1 in 10 people
- Uncommon: affecting more than 1 in 1,000 people and less than 1 in 100 people

Very common side effects of danicopan

Very common **side effects** of danicopan include headache and blood tests showing increased levels of liver **enzymes**, both of which are temporary and can be managed (77). UK clinical experts use headache as an indication that the medication is working and do not view it as a significant concern (36).

Safety results from the ALPHA trial

The **safety** of danicopan as an add-on to eculizumab or ravulizumab was assessed in comparison with **placebo** as an add-on to eculizumab or ravulizumab in the ALPHA trial (38). In general, side effects were infrequent among all patients in the ALPHA trial. A slightly higher proportion of people receiving danicopan as an add-on to eculizumab or ravulizumab experienced severe and/or life-threatening or disabling **side effects** compared with people receiving placebo as an add-on to eculizumab or ravulizumab, such as an increased level of liver **enzymes**. No deaths were reported, serious side effects were infrequent in both groups in the trial, and a minority of side effects were considered to be caused by the treatment received. Furthermore, only one person receiving danicopan as an add-on to eculizumab or ravulizumab had to stop treatment due to **side effects**, indicating that most people could continue to receive danicopan as an add-on to

eculizumab or ravulizumab for a longer duration and benefit from treatment without experiencing significant side effects (38).

Overall, danicopan as an add-on to eculizumab or ravulizumab is generally well-**tolerated** and its common **side effects** can be managed. Information on other potential side effects will be available in the **Patient Information Leaflet** when published, and further details on the **safety** results of the ALPHA trials are reported in **Document B**, **Section B.2.11**.

3h. Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety, and mode of administration

The key benefits of danicopan as an add-on to eculizumab or ravulizumab for people with PNH who experience csEVH include:

First treatment specifically targeting EVH: Danicopan as an add-on to eculizumab or ravulizumab is the first treatment for PNH with a **mechanism of action** to specifically address csEVH. In particular, danicopan as an add-on to eculizumab or ravulizumab addresses tiredness, which is a key area of unmet need highlighted by UK clinical experts (36).

Improved patients' and carers' HRQoL: Danicopan as an add-on to eculizumab or ravulizumab improves the HRQoL and tiredness levels of people with PNH experiencing csEVH (38). Danicopan as an add-on to eculizumab or ravulizumab improved the physical and social functioning of people with csEVH (38). This may allow people with PNH to be more independent in performing daily activities and rely less on their carers.

Tolerable safety profile: Danicopan as an add-on therapy is well-**tolerated** with manageable **side effects** (38).

Alternative method of administration: Danicopan is the only oral treatment available for the csEVH. People with PNH who have **dexterity** issues or who have problems with their eyesight may be unable to administer pegcetacoplan by themselves. Danicopan as an add-on to eculizumab or ravulizumab therefore offers people with PNH an alternative treatment option which may improve their treatment burden (36).

Sustained control of IVH: As an add-on therapy, danicopan allows people with PNH to continue treatment with eculizumab or ravulizumab to manage IVH, whilst EVH is addressed by danicopan. A smaller proportion of people receiving danicopan as an add-on to eculizumab or ravulizumab experienced **BTH**, compared with people receiving pegcetacoplan (78, 79). UK clinical experts have indicated that this provides reassurance to physicians and patients that IVH continues to be controlled (36).

3i. Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Danicopan as an add-on to eculizumab or ravulizumab is generally well-**tolerated** and effective in managing csEVH in people with PNH. Key **side effects** include headache and increased levels of liver **enzymes**, however, these only occur temporarily and can be managed (38).

As PNH is a lifelong condition, danicopan needs to be taken in the long term, three times a day. Some people with PNH may find the frequent dosing to be inconvenient or may forget to take the medication. Danicopan is an oral tablet, which is a convenient method of administration. Comparatively, pegcetacoplan is a **subcutaneous injection** which people with **dexterity** issues or visual difficulties may not be capable of administering on their own (36).

Additionally, danicopan is administered together with eculizumab or ravulizumab, which are given once every 2 weeks or 8 weeks respectively. Therefore, as a whole, danicopan as an add-on to eculizumab or ravulizumab is associated with a burden from the frequent administration of medications, when compared to treatment with only eculizumab or ravulizumab.

Overall, danicopan as an add-on therapy does not have any important disadvantages compared with other treatment options that are currently available for people with PNH.

3j. Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the

costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested, or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Introduction for patient groups

Health services need to get the most value from their limited budgets, and therefore they are interested in knowing whether a new medicine provides 'good value for money' compared to other medicines. In order to assess this, they compare the cost of the new medicine to the health improvements the new medicine is likely to bring to people with PNH. The pharmaceutical company that develops the medicines uses a health economic model to allow the comparison of the costs of the medicine versus its health benefits.

How the model reflects the condition

- The health economic model is used to capture the experience of having csEVH over time. The model is further designed to show how EVH is managed in UK clinical practice
- The model comprises of 4 health states which represent specific states of well-being associated with EVH. Each health state is associated with its own set of costs and utility values (which measure the health benefits gained)
- The economic model assigns people with PNH to different treatments (danicopan as an add-on to either eculizumab or ravulizumab OR pegcetacoplan) and sums up the costs and quality of life over the patients' lifetimes
- The goal of the model is to compare the costs and quality of life of people with PNH treated with danicopan as an add-on to eculizumab or ravulizumab compared to pegcetacoplan
- If danicopan as an add-on to eculizumab or ravulizumab maximises survival and quality of life for the amount of money it costs, danicopan as an add-on to eculizumab or ravulizumab is considered a "good use of National Health System (NHS) resources"

Modelling how a treatment reduces extravascular haemolysis

- The results of the ALPHA and PEGASUS trials are used to inform the economic model. The main result from the trials that is used in the model is the change in **haemoglobin** levels of people and their requirement for a **blood transfusion**
- The model also considers the frequency of **BTH** with each treatment, as well as the occurrence of **iron overload** (when there is too much iron in the body resulting from frequent blood transfusions)
- The results of the ALPHA and PEGASUS trials cover a total of 12 weeks and 16 weeks, respectively. However, the economic model simulates people with PNH for the rest of their lifetime, a much longer period of time than the length of the trials

Modelling how much a treatment improves quality of life

- As described in **Section 3f**, people from the ALPHA trial were asked about their quality of life at the start of the trial and were regularly asked again throughout all three parts of the trial
- People's responses were collected using questionnaires. These responses are used to inform the quality of life of people with PNH experiencing csEVH in each **haemoglobin** and **transfusion**-based health state of the economic model

Modelling how the costs of treatment differ with the new treatment

- The model accounts for costs associated with treatment including the following:
    - The cost of the medicines and the cost of administering the medicines
    - The cost of monitoring the patient throughout the treatment duration and routine healthcare treatment
    - The cost of treatment for **BTH**
    - The cost of **blood transfusions** and treatment of **iron overload**
    - The cost of managing **side effects** that occur during treatment

Uncertainty

- The ALPHA trial had a small number of people with csEVH (86 people) which potentially introduced bias to the trial's results used to inform the economic modelling. However, this is a well-known limitation associated with rare conditions such as PNH and csEVH
- The results of the **indirect treatment comparison** were subject to significant uncertainty due to the substantial differences between the ALPHA (danicopan) and PEGASUS (pegcetacoplan) trials. The unadjusted results from the ALPHA and

PEGASUS trials were used in the model to inform the relative effects of danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan

- Data for specific costs or outcomes to use in the model are sometimes unavailable. In such cases, assumptions on the input values are used in the model. To assess the sensitivity of the model's results (how much the results change) to the assumptions on the model inputs, these inputs are varied and their impact on the results of the model are recorded

What is the value of danicopan as an add-on to eculizumab or ravulizumab for patients, carers, and the health service?

As EVH has a negative impact on people with PNH, their carers and the healthcare system, there is a demand for new and effective treatment options that can reduce the impact associated with EVH. Danicopan as an add-on to eculizumab or ravulizumab is the first treatment that is effective in treating csEVH, whilst enabling the continued receipt of eculizumab or ravulizumab to control IVH (36). Danicopan as an add-on to eculizumab or ravulizumab also improves the **HRQoL** and tiredness levels of people with PNH experiencing csEVH, particularly in terms of their physical and social functioning, enabling people to be less reliant on their carers.

Economic analysis

All these considerations affect whether danicopan as an add-on to eculizumab or ravulizumab represents good value for money and a good use of NHS resources. Based on the evidence that is available and the economic analysis results, danicopan as an add-on to eculizumab or ravulizumab is associated with lower costs, but also higher benefits (measured in 'quality-adjusted life years' [QALYs]) than pegcetacoplan.

Benefits of danicopan as an add-on to eculizumab or ravulizumab not captured in the model

Several benefits of danicopan add-on treatment not captured in the model include:

1. The level of reassurance that danicopan offers in terms of a continued control of IVH. As previously discussed, IVH leads to life-threatening symptoms in PNH (7).
2. Danicopan is an oral treatment, and eculizumab and ravulizumab are administered intravenously by trained healthcare professionals at home. The cost of eculizumab or ravulizumab administration is covered by the pharmaceutical company that makes these medicines. Danicopan add-on treatment therefore also provides a convenient method of administration for the proportion of people with **dexterity** issues, problems with their eyesight, difficulty injecting themselves and mental health issues, who are unable to self-administer subcutaneous treatments as highlighted by UK clinical experts. This is relevant to pegcetacoplan, the only other treatment available for EVH in the UK, which is delivered via **subcutaneous injection**.
3. Lastly, COVID-19 has enhanced the general population's understanding of tiredness and the severity of its impact on people, which are not fully captured in current methods of assessing tiredness and people's **HRQoL**. Tiredness is a key symptom and area of unmet need for people with csEVH, and the full extent of

danicopan's benefit in lowering levels of tiredness may not be captured in the economic model.

3k. Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative, please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Danicopan as an add-on to eculizumab or ravulizumab is a new and innovative treatment for extravascular haemolysis

PNH is a serious and lifelong condition that can have a significant effect on a patient's mental and emotional wellbeing and quality of life. Although the availability of eculizumab and ravulizumab has helped to control the life-threatening aspect of PNH (IVH), some people subsequently experience csEVH, for which there are currently no specific treatment options available. Danicopan as an add-on to eculizumab or ravulizumab is the first treatment to specifically target csEVH. Danicopan has an innovative **mechanism of action** as it targets a different **protein** in the **complement system**. By targeting different proteins, danicopan offers a new and effective way of controlling csEVH and the associated symptoms. There is also some evidence available to suggest that danicopan add-on treatment may reduce the likelihood of patients developing serious infections, when compared to treatment with eculizumab or ravulizumab alone (80).

As an add-on treatment, people with PNH are able to receive danicopan and continue treatment with eculizumab or ravulizumab. This provides reassurance to patients and their physician that both EVH and IVH remain controlled.

In summary, danicopan as an add-on to eculizumab or ravulizumab is an innovative medicine, being a treatment with a novel **mechanism of action** that specifically addresses the csEVH, whilst effectively managing IVH. Furthermore, danicopan is the only treatment for EVH that can be taken orally, offering people with **dexterity** issues, problems with their eyesight or difficulties with self-injection an alternative to pegcetacoplan. Alongside the strong evidence of its **efficacy** and **safety** in the ALPHA trial, danicopan as an add-on to eculizumab or ravulizumab represents a valuable new treatment for people with PNH experiencing the csEVH.

3l. Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No potential equality issues are anticipated for danicopan in the treatment of people with PNH showing csEVH as no specifically disadvantaged groups have been identified.

SECTION 4: Further information, glossary, and references

4a. Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on PNH: • https://pnhserviceuk.co.uk/patient-information/what-is-pnh/ • https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6142517/ Further information on danicopan: • Summary of Product Characteristics (SmPC) • Patient Information Leaflet (**PIL**) Further information on the ALPHA trial: • https://clinicaltrials.gov/study/NCT04469465 Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • European Patients' Academy guidance on patient involvement in NICE: https://toolbox.eupati.eu/resources/patient-toolbox/guidance-for-patient-involvement-in-hta/

- European Federation of Pharmaceutical Industries and Associations – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative: https://nationalhealthcouncil.org/issue/value/
- International Network of Agencies for Health Technology Assessment: https://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: https://iris.who.int/handle/10665/332207

4b. Glossary of terms

This glossary explains terms highlighted in **bold** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms. These terms have been **bolded** within the definitions.

Term	**Definition**
Anaemia	A condition that occurs when the body has fewer healthy **red blood cells**, and therefore lower levels of **haemoglobin,** than normal.
Blood clot	A clump that forms in the blood vessels when blood cells stick together, blocking the flow of blood through blood vessels.
Blood poisoning	An infection that occurs when germs (bacteria, viruses, or fungi) are present in the blood.
Blood transfusion	A procedure in which donated blood is transferred to a recipient.
Bone marrow	A soft, spongy tissue inside most bones where blood cells (red blood cells, white blood cells and platelets) are made.
Brain fog	Confusion, forgetfulness, and a lack of focus and mental clarity.
Breakthrough haemolysis (BTH)	The return of **IVH** and symptoms associated with **PNH**.
Clinical trial/study	A type of research study that tests how well new medical approaches work in people. These studies test

	new methods of screening, prevention, diagnosis, or treatment of a disease.
Complement factor D	An **enzyme** responsible for the production of **proteins** involved in the activation of the **complement system**.
Complement system	A group of proteins in the **immune system** which help to protect against infections.
Coombs test	A laboratory procedure to detect the presence of abnormal **red blood cells**, carrying **proteins** that facilitate their destruction by the **immune system**.
Clinically significant extravascular haemolysis (csEVH)	The destruction of **red blood cells** by the **immune system** outside blood vessels (i.e., in the liver, **spleen**, **bone marrow** and **lymph nodes**).
Dexterity	The ability to perform tasks, especially using the hands.
Dose	The measured amount of a medicine that is taken at a particular time.
Dysphagia	Difficulty in swallowing.
Dyspnea	Difficulty in breathing or shortness of breath.
Efficacy	The ability of a medicine to produce a desired positive effect on your disease or illness in a **clinical trial**.
Enzyme	A **protein** that helps speed up chemical reactions in the human body.
Flow cytometry	A test that can be used to measure the properties of single cells in the body.
Gene	An inherited part of a cell in a living thing that controls physical characteristics, growth, and development.
Glycosylphosphatidylinositol (GPI)	A **protein** present on the surface of healthy **red blood cells** which serves as an anchor for other proteins to attach themselves to the red blood cell.
Haemoglobin	A **protein** found in **red blood cells** that transports oxygen in the body.
Haemolysis	The rupture or destruction of **red blood cells**.

Health-related quality of life (HRQoL)	The overall enjoyment of life. Many **clinical trials** assess the effects of a disease and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being (e.g., mental or emotional state) and their ability to carry out activities of daily living (e.g., mobility, self-care, work efficiency)
Indirect treatment comparison	An analysis that compares medicines that have not been compared directly in a head-to-head, randomised trial.
Immune system	A complex network of cells, tissues, organs, and the substances they make that helps the body fight infections and other diseases.
Intravenous infusion	A type of injection in which a short needle is used to inject a drug into one of your veins.
Intravascular haemolysis (IVH)	The destruction of **red blood cells** by the **immune system** within blood vessels.
Iron overload	When there is too much iron in the body resulting from frequent **blood transfusions**.
Lymph nodes	Small structures in the body that trap germs and abnormal cells. Found in the neck, armpit, and groin. Lymph nodes are part of the **immune system**.
Mechanism of action	The biochemical process in which a medication acts on the body to produce a treatment effect.
Medicines and Healthcare products Regulatory Agency (MHRA)	The regulatory body that evaluates, approves, and supervises medicines in the UK.
Mutation	Our **genes** pick up changes that happen when cells divide. These changes are called genetic mutations.
Paroxysmal nocturnal haemoglobinuria (PNH)	A rare, serious blood disorder involving the destruction of **red blood cells** by the **immune system**.
Patient information leaflet (PIL)	A document included in the package of a medication that provides information about that drug and its use.
Phase 3 clinical trial	A type of **clinical trial** that tests the **safety** and how well a new treatment works compared with a standard

	treatment. For example, it evaluates which group of patients has better survival rates or fewer **side effects**.
Placebo	A treatment that appears real, but that does not treat the disease. It is used in **clinical trials** to compare treatments.
Protein	Proteins are needed for the body to function properly. They are the basis of body structures, such as skin and hair.
Psychological	Matters that relate to a person's mental or emotional state, rather than physical.
Red blood cell	A type of blood cell that is made in the **bone marrow** and found in the blood. It has a range of functions in the body, including the transport of oxygen.
Safety	The number and severity of **side effects**.
Side effect	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate, or severe.
Spleen	An organ behind the rib cage that helps filter blood and helps fight infection.
Stem cell	A cell from which other types of cells develop. For example, blood cells develop from blood-forming stem cells.
Subcutaneous injection	A type of injection in which a short needle is used to inject a drug into tissue layer between the skin and the muscle.
Thrombosis	The formation of **blood clots** which blocks the flow of blood within blood vessels.
Tolerated	The ability of a patient to handle the **side effects** of treatment.

4c. References

Please provide a list of all references in the Vancouver style, numbered, and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

Clarification questions

February 2024

File name	Version	Contains confidential information	Date
ID5088 danicopan clarification questions to PM for company [CON]_23Feb24	3.0	Yes	23rd February 2024

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

A1. Please provide details on how many people stayed on their original C5 inhibitor, and how many people started or switched to a new C5 inhibitor, by arm and C5 inhibitor of the ALPHA trial.

After further clarification on question A1, Alexion would like to confirm that no patients, at entry to the ALPHA trial, switched complement component 5 (C5) inhibitor treatment. This is due to the protocol-specified eligibility criteria: *"(Patients) receiving an approved C5 inhibitor for at least 6 months prior to Day 1 in this study at an approved dose (or higher) and with no change in the prescribed dose or interval for at least 24 weeks preceding Day 1. For those patients who recently switched from eculizumab to ravulizumab, they must have received at least the loading dose and 3 maintenance doses (minimum of 24 weeks) of ravulizumab preceding Day 1."* (ALPHA trial protocol, Section 5.1).[1] Therefore, patients were not permitted to switch C5 inhibitor at entry to the trial, as they were required to be stable on treatment.

A2. Please provide details on patients in the ALPHA trial, by arm, who had a diagnosis of aplastic anaemia at baseline or during the trial. (i.e. removing resolved/controlled cases). We are aware that there are data in confidential CSR that report history of aplastic anaemia but the rates differ. Please also provide an

explanation of the difference between the data reported in Table 14.1.3.1.9 and Table 14.1.3.2.2?

Paroxysmal nocturnal haemoglobinuria (PNH) and aplastic anaemia are closely related, with PNH often arising from aplastic anaemia (>10% of patients with aplastic anaemia).[2, 3] Hence, patients with PNH with a history of aplastic anaemia are common. Based on the exclusion criteria of the ALPHA trial (Protocol; Section 5.2),[4] patients were excluded from the trial if they had "*known aplastic anaemia or other bone marrow failure that requires haematopoietic stem cell transplantation (HSCT) or other therapies including anti-thymocyte globulin and/or immunosuppressants, unless the dosage regimen of immunosuppressant had been stable for at least 12 weeks before Day 1 and the patient was expected to remain on stable doses through to Week 24*".

Furthermore, patients with aplastic anaemia do not have adequate bone marrow function, and as such, severe aplastic anaemia is defined by a low absolute reticulocyte count (ARC) of $<60 \times 10^9$/L.[5] As reticulocyte counts are indicative of bone marrow function, and patients enrolled into the ALPHA trial must have had an elevated ARC at baseline of $\geq 120 \times 10^9$/L,[4] patients entering the ALPHA trial had adequate bone marrow function.[6] Therefore, whilst some patients enrolled in the trial had a history of aplastic anaemia, all cases were either resolved or controlled prior to study entry. As no adverse events of aplastic anaemia were recorded during the ALPHA trial, the number of patients with aplastic anaemia during the ALPHA trial is assumed to be the same as the number of patients with aplastic anaemia at baseline.[7]

Regarding the discrepancies between Table 14.1.3.1.9 and Table 14.1.3.2.2, Table 14.1.3.1.9 presents the diagnosed conditions specifically associated with PNH at any time prior to informed consent, whilst Table 14.1.3.2.2 presents relevant general medical and surgical history of patients (including conditions which are not associated with PNH) prior to the ALPHA trial.[7] The data presented in both tables were based on separate Case Report Forms (CRFs), a Medical History CRF and PNH Medical History CRF, completed by the trials investigators. In some instances, a prior history of aplastic anaemia may not be considered relevant for inclusion in the

Medical History CRF; this decision was made by the investigators of the ALPHA trial on a per-patient basis.

A3. Please confirm what is meant by the term “Background C5 inhibitor” in the subgroup analysis. If this does not refer to the C5 inhibitor received during the ALPHA trial, please perform this analysis based on the C5 inhibitor received in the ALPHA trial.

The term “background C5 inhibitor” used in the subgroup analysis, provided in Section B.2.7 of the Company submission, refers to the C5 inhibitor treatment (eculizumab or ravulizumab) received by patients at the time of study enrolment and during TP1 and TP2 of the ALPHA trial. As such, no re-analysis is required.

A4. Please reproduce relevant sections of results (e.g. condensed form of B.2.7) but including scores of people who received a transfusion in week 8 or beyond where they were previously excluded.

Approach to censoring of transfusion events

For the primary efficacy endpoint of change from baseline in haemoglobin level at Week 12, haemoglobin values collected within four weeks of the timepoint of assessment were censored. This approach was taken because the receipt of a transfusion is an intercurrent event that can impact haemoglobin levels. The results of a sensitivity analysis, which included the scores of patients who had received a transfusion within four weeks of the timepoint of assessment, are provided in the ALPHA trial CSR (Table 14.2.1.3.1) and are reproduced in Table 1 below for convenience.[7] Similarly, the analysis of change from baseline in haemoglobin at Week 24 excluded scores collected within four weeks of a transfusion (i.e., patients’ scores were excluded if a transfusion occurred at Week 20 or beyond).[7] A sensitivity analysis of change from baseline in haemoglobin values at Week 24, including scores for people who received a transfusion four weeks prior to the timepoint of assessment, is therefore presented in Table 2.

Key secondary endpoints relating to haemoglobin included transfusion avoidance and the proportion of patients achieving haemoglobin increase of 2 g/dL in the absence of transfusion. Since the occurrence or not of a transfusion informs the binary definition of these two endpoints, it is not applicable to censor the scores of

people who received a transfusion within four weeks of the timepoint of assessment, and therefore these re-analyses have not been performed for questions A4–A6. For key secondary endpoints unrelated to haemoglobin (change from baseline in FACIT-F scores and ARC) and patient reported outcomes (PROs) (EQ-5D-3L UK index values), no censoring due to transfusion was performed in the trial analysis as transfusion is not considered an intercurrent event for these endpoints. Additionally, no censoring for transfusion for change from baseline in PNH RBC clone sizes and lactate dehydrogenase (LDH) levels were performed in the trial analysis. For clarity, the relevance of LDH as an endpoint is discussed in clarification question A7. Thus, the results for these endpoints, presented in Table 1 and Table 2, are the same as the results presented in Section B.2.7 of the Company submission.

Results

Results for all efficacy and HRQoL endpoint results, at Week 12 and Week 24, which include scores for patients receiving transfusion within four weeks of the timepoint of assessment are presented in Table 1 and Table 2, respectively.

Table 1: Efficacy and HRQoL endpoint results at Week 12 (including scores from patients receiving transfusion within four weeks of the timepoint of assessment) (IAS)

	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=21	Difference (Danicopan - Placebo)	p-value
Change from baseline in haemoglobin at Week 12				
LS mean (SE), g/dL	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
Proportion of patients with a haemoglobin increase of ≥2 g/dL at Week 12 in the absence of transfusion[b]				
Number of participants (n)	25	0	N/A	p<0.0001
Percentage (%)	59.5	0	46.9	
95% CI	43.3, 74.4	0.0, 16.1	29.2, 64.7	
Proportion of patients with transfusion avoidance at Week 12[b]				
Number of participants (n)	35	8	N/A	p=0.0004
Percentage	83.3	38.1	41.7	
95% CI	68.6, 93.0	18.1, 61.6	22.7, 60.8	
Change from baseline in FACIT-F scores at Week 12				
LS mean (SE)	7.97 (1.13)	1.85 (1.58)	6.12 (1.89)	p=0.0021

95% CI for LS mean	5.72, 10.23	−1.31, 5.02	2.33, 9.91	
Change from baseline in ARC at Week 12				
LS mean (SE), 10^9/L	−83.8 (8.93)	3.5 (12.7)	−87.2 (15.3)	p<0.0001
95% CI for LS mean	−101.6, −65.9	−21.9, 28.8	−117.7, −56.7	
Change from baseline in LDH at Week 12				
LS mean (SE), U/L	−23.5 (8.3)	−2.9 (11.9)	−20.6 (14.3)	p=0.1569
95% CI for LS mean	−40.1, −6.9	−26.8, 20.9	−49.3, 8.2	
Total PNH RBC Clone Size (Type II + Type III) at Week 12, (%)				
Number of participants (n)	[redacted]	[redacted]	[redacted]	
LS mean (SE)	24.60 (4.18)	−3.04 (5.86)	27.63 (6.91)	p=0.0010
95% CI for LS mean	15.78, 33.42	−15.32, 9.25	13.03, 42.24	
PNH RBC Type III Clone Size at Week 12, (%)				
Number of participants (n)	[redacted]	[redacted]	[redacted]	
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
PNH RBC Type II Clone Size at Week 12, (%)				
Number of participants (n)	[redacted]	[redacted]	[redacted]	
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
Change from baseline in EQ-5D-3L UK health state index scores by treatment visit through Week 12				
Week 2: LS mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 4: LS mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 8: LS mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 12: LS mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Eculizumab or ravulizumab.
[b] As the occurrence or not of transfusion is informed by the binary definition of this endpoint, censoring of patients who received a transfusion in Week 8 or beyond is not applicable.
Abbreviations: ARC: absolute reticulocyte count; C5i: complement component 5 inhibitor; CI: confidence interval; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; HRQoL: health-related quality of life; IAS: interim efficacy analysis set; LDH: lactate dehydrogenase; LS: least squares; N: number of patients; RBC: red blood cell; SD: standard deviation; SE: standard error.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[7] Table 14.2.1.3.1, Table 14.2.2.1.1, Table 14.2.2.2.1, Table 14.2.2.3.1, Table 14.2.2.4.1, Table 14.2.3.3.1, Table 14.2.3.4.1,Table 14.2.5.1.1; Lee, *et al.* (2023).[8]

Table 2: Efficacy and HRQoL endpoint results at Week 24 (including scores from patients receiving transfusion within four weeks of the timepoint of assessment) (IAS)

	DAN/DAN + C5i[a] N=41	PBO/DAN + C5i[a] N=20
Change from baseline in haemoglobin at Week 24		
Number of participants (n)	[redacted]	[redacted]
LS mean (SE), g/dL	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Proportion of patients with a haemoglobin increase of ≥2 g/dL at Week 24 in the absence of transfusion[b]		
Number of participants (n)	19	7
Percentage (%)	46.3	35.0
95% CI	30.7, 62.6	15.4, 59.2
Proportion of patients with transfusion avoidance from Week 12 to Week 24[b]		
Number of participants (n)	32	18
Percentage	78.0	90.0
95% CI	62.4, 89.4	68.3, 98.8
Change from baseline in FACIT-F scores at Week 24		
Number of participants (n)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Change from baseline in ARC at Week 24		
Number of participants (n)	37	19
LS mean (SE), 10^{12}/L	−0.0802 (0.0088)	−0.0652 (0.0127)
95% CI for LS mean	−0.0977, -0.0627	−0.0909, -0.0395
Change from baseline in LDH at Week 24		
LS mean (SE), U/L	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Total PNH RBC Clone Size (Type II + Type III) at Week 24, (%)		
Number of participants (n)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
PNH RBC Type III Clone Size at Week 24, (%)		
Number of participants (n)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]

95% CI for LS mean	[redacted]	[redacted]
PNH RBC Type II Clone Size at Week 24, (%)		
Number of participants (n)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Change from baseline in EQ-5D-3L UK health state index scores by treatment visit through Week 24[c]		
Week 14: Mean (SD)	[redacted]	[redacted]
Week 16: Mean (SD)	[redacted]	[redacted]
Week 20: Mean (SD)	[redacted]	[redacted]
Week 24: Mean (SD)	[redacted]	[redacted]

[a] Eculizumab or ravulizumab.
[b] As the occurrence or not of transfusion is informed by the binary definition of this endpoint, censoring of patients who received a transfusion in Week 8 or beyond is not applicable.
[c] In line with the Company submission, EQ-5D-3L UK index values presented at and prior to Week 12 are presented as least squares (LS) mean values derived from the MMRM model, whereas EQ-5D-3L UK index values from Week 12 onwards are presented as arithmetic means.
Abbreviations: ARC: absolute reticulocyte count; C5i: complement component 5 inhibitor; CI: confidence interval; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; HRQoL: health-related quality of life; IAS: interim efficacy analysis set; LDH: lactate dehydrogenase; LS: least squares; MMRM: mixed model repeated measures; N: number of patients; RBC: red blood cell; SD: standard deviation; SE: standard error.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[7] Table 14.2.4.1.2, Table 14.2.4.2.1, Table 14.2.4.3.1, Table 14.2.4.5.1, Table 14.2.4.7.1, Table 14.2.4.9.1, Table 14.2.6.1.1, Table 14.2.4.6.1, Table 14.2.5.3.1; Lee, *et al.* (2023).[8]

Interpretation

Regarding the change from baseline in haemoglobin at Week 12 and Week 24, the results are consistent with respect to the primary analysis which excluded scores of patients who received a transfusion within four weeks of the timepoint of assessment. When including scores for patients who received a transfusion in these sensitivity analyses, danicopan as an add-to eculizumab or ravulizumab results in a statistically significant increase in haemoglobin from baseline compared to placebo as an add-on to eculizumab or ravulizumab. As expected, change from baseline in haemoglobin at both timepoints was higher than the primary analyses, as these results included patients whose haemoglobin had been increased by transfusion, reiterating the appropriateness of censoring transfusions as an intercurrent event. As described above, results presented below for all other endpoints remain the same with respect to the Company submission.

A5. Priority Question: Please reproduce a section of results (e.g. condensed form of B.2.7) but excluding scores for all outcomes that were measured after

a transfusion was received at any point in the trial follow-up, matching the approach taken in the PEGASUS primary analysis, including LDH. Please also reperform all of the MAIC analyses using this dataset. If these MAIC weights produce a different set of transition probabilities, then please also provide this.

PEGASUS primary analysis

The censoring approach taken in the PEGASUS trial has been sourced from the Hillmen *et al.* 2021 publication.[1] Specifically, excluding scores for all outcomes that were measured after transfusion (at any point in the trial) is aligned with the approach described in Section 6 of the statistical analysis plan (version 2.0) located in the PEGASUS trial protocol, stating *"For transfusion and withdrawal from the study: all measurements after the intercurrent event will be set to missing (while on-treatment strategy)"*.[1]

Therefore, all key efficacy and HRQoL results presented in the Company submission have been re-performed, where applicable, by setting all values collected after transfusion to missing, aligned with the approach detailed in the PEGASUS protocol.

Results of the re-analysis (setting scores collected after transfusion to missing)

As previously noted, it is not applicable to censor transfusion avoidance and the proportion of patients achieving haemoglobin increase of 2 g/dL in the absence of transfusion, due to the binary definitions of the endpoints. Therefore, the results for the haemoglobin-related key secondary endpoints presented in Section B.2.7.1 in the Company submission fulfil the requirements of the question and are reproduced, for Week 12 and Week 24, in At Week 24, change from baseline in haemoglobin was consistent in the danicopan arm with respect to the primary analysis.[7] Change in baseline in ARC and EQ-5D-3L UK index value scores (in the danicopan treatment arm) were broadly consistent at Week 24 with respect to the primary analysis. However, the increase in LDH level observed at Week 24 in both treatment arms differed from the primary analysis; the large 95% CIs (which cross zero), as illustrated by Table 4, indicate that this result should be interpreted with caution. FACIT-F scores, EQ-5D-3L UK index scores (in the placebo arm) and change from baseline in PNH RBC clone sizes at Week 24 varied with respect to the primary

analysis, however, in the case of PNH RBC clone sizes (Table 14.2.4.6.1 of the ALPHA trial CSR) this is expected to be due to the exceedingly small patient numbers associated with these results.[7]

Interpretation of reperformed results

The reanalysis supports the statistically significant superiority (p< [redacted]) of danicopan versus placebo for the primary endpoint of the ALPHA trial: change from baseline in haemoglobin at Week 12. Many of the secondary endpoints were also consistent with respect to the primary analyses presented in the Company submission. However, given that transfusions are not intercurrent events for the reperformed secondary endpoints, and given censoring all measurements after a transfusion to missing values reduces the patient sample size for each result, the approach used for the primary analysis is still considered the most appropriate method. Additionally, it should be noted that excluding patients who required transfusion from the analysis increases the weight of the scores of patients who did not require transfusion, and therefore those who are performing better. As the placebo arm in the ALPHA trial was anticipated to have an increased number of patients requiring transfusions, this re-analysis may bias results in favour of the placebo arm.

Table 3 and Table 4 below for completeness.[7]

The remaining endpoints presented in Section B.2.7 of the Company submission did not censor patients' scores for transfusion. The re-analysis for these endpoints, which sets all values collected after transfusion to missing, are presented in At Week 24, change from baseline in haemoglobin was consistent in the danicopan arm with respect to the primary analysis.[7] Change in baseline in ARC and EQ-5D-3L UK index value scores (in the danicopan treatment arm) were broadly consistent at Week 24 with respect to the primary analysis. However, the increase in LDH level observed at Week 24 in both treatment arms differed from the primary analysis; the large 95% CIs (which cross zero), as illustrated by Table 4, indicate that this result should be interpreted with caution. FACIT-F scores, EQ-5D-3L UK index scores (in the placebo arm) and change from baseline in PNH RBC clone sizes at Week 24 varied with respect to the primary analysis, however, in the case of PNH RBC clone sizes (Table 14.2.4.6.1 of the ALPHA trial CSR) this is expected to be due to the exceedingly small patient numbers associated with these results.[7]

Interpretation of reperformed results

The reanalysis supports the statistically significant superiority (p<[redacted]) of danicopan versus placebo for the primary endpoint of the ALPHA trial: change from baseline in haemoglobin at Week 12. Many of the secondary endpoints were also consistent with respect to the primary analyses presented in the Company submission. However, given that transfusions are not intercurrent events for the reperformed secondary endpoints, and given censoring all measurements after a transfusion to missing values reduces the patient sample size for each result, the approach used for the primary analysis is still considered the most appropriate method. Additionally, it should be noted that excluding patients who required transfusion from the analysis increases the weight of the scores of patients who did not require transfusion, and therefore those who are performing better. As the placebo arm in the ALPHA trial was anticipated to have an increased number of patients requiring transfusions, this re-analysis may bias results in favour of the placebo arm.

Table 3 and Table 4 for Week 12 and Week 24 results, respectively.

At Week 12, change from baseline in haemoglobin for the danicopan arm was highly consistent with respect to the primary analysis, i.e., the original result presented in the Company submission, with the treatment arm difference between danicopan and placebo remaining statistically significant (p<[redacted]).[7] Change from baseline in ARC, LDH level and PNH RBC clone sizes at Week 12, and EQ-5D-3L UK index values to Week 12, remained consistent with respect to the primary analysis. The placebo arm did, however, perform slightly poorer for these endpoints when compared to the primary analysis. Change from baseline in FACIT-F scores varied from the primary analysis; however, the mean change from baseline in FACIT-F score at Week 12 remained greater for patients in the danicopan arm compared to the placebo arm.

Given that transfusions are not intercurrent events for these endpoints, and censoring reduces the patient sample size, the approach used in the primary analysis is considered appropriate. As shown by Table 3, the sample size of the placebo arm was substantially decreased in these reanalyses, due to the increased

number of patients in the placebo arm (versus the danicopan arm) receiving transfusion during TP1. As such, the scores informing the results in the placebo arm are informed by the small number of patients in the placebo arm who did not require transfusion during this trial period. Therefore, this analysis may introduce a bias against the efficacy results for danicopan.

At Week 24, change from baseline in haemoglobin was consistent in the danicopan arm with respect to the primary analysis.[7] Change in baseline in ARC and EQ-5D-3L UK index value scores (in the danicopan treatment arm) were broadly consistent at Week 24 with respect to the primary analysis. However, the increase in LDH level observed at Week 24 in both treatment arms differed from the primary analysis; the large 95% CIs (which cross zero), as illustrated by Table 4, indicate that this result should be interpreted with caution. FACIT-F scores, EQ-5D-3L UK index scores (in the placebo arm) and change from baseline in PNH RBC clone sizes at Week 24 varied with respect to the primary analysis, however, in the case of PNH RBC clone sizes (Table 14.2.4.6.1 of the ALPHA trial CSR) this is expected to be due to the exceedingly small patient numbers associated with these results.[7]

Interpretation of reperformed results

The reanalysis supports the statistically significant superiority (p<[redacted]) of danicopan versus placebo for the primary endpoint of the ALPHA trial: change from baseline in haemoglobin at Week 12. Many of the secondary endpoints were also consistent with respect to the primary analyses presented in the Company submission. However, given that transfusions are not intercurrent events for the reperformed secondary endpoints, and given censoring all measurements after a transfusion to missing values reduces the patient sample size for each result, the approach used for the primary analysis is still considered the most appropriate method. Additionally, it should be noted that excluding patients who required transfusion from the analysis increases the weight of the scores of patients who did not require transfusion, and therefore those who are performing better. As the placebo arm in the ALPHA trial was anticipated to have an increased number of patients requiring transfusions, this re-analysis may bias results in favour of the placebo arm.

Table 3: Efficacy and HRQoL endpoint results at Week 12 (setting scores collected after transfusion to missing) (IAS)

	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=21	Difference (Danicopan - Placebo)	p-value
Change from baseline in haemoglobin at Week 12				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE), g/dL	[redacted]	[redacted]	[redacted]	
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
Proportion of patients with a haemoglobin increase of ≥2 g/dL at Week 12 in the absence of transfusion[b]				
Number of participants (n)	25	0	N/A	p<0.0001
Percentage (%)	59.5	0	46.9	
95% CI	43.3, 74.4	0.0, 16.1	29.2, 64.7	
Proportion of patients with transfusion avoidance at Week 12[b]				
Number of participants (n)	35	8	N/A	p=0.0004
Percentage	83.3	38.1	41.7	
95% CI	68.6, 93.0	18.1, 61.6	22.7, 60.8	
Change from baseline in FACIT-F scores at Week 12				
Number of participants (n)	[redacted]	[redacted]	[redacted]	
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
Change from baseline in ARC at Week 12				
Number of participants (n)	[redacted]	[redacted]	[redacted]	
LS mean (SE), 10^9/L	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
Change from baseline in LDH at Week 12				
Number of participants (n)	[redacted]	[redacted]	[redacted]	
LS mean (SE), U/L	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
Change from baseline in total PNH RBC Clone Size (Type II + Type III) at Week 12, %				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]

LS mean (SE)	[redacted]	[redacted]	[redacted]	
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
Change from baseline in PNH RBC Type III Clone Size at Week 12, %				
Number of participants (n)	[redacted]	[redacted]	[redacted]	
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
Change from baseline in PNH RBC Type II Clone Size at Week 12, %				
Number of participants (n)	[redacted]	[redacted]	[redacted]	
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
Change from baseline in EQ-5D-3L UK health state index scores by treatment visit through Week 12				
Week 2: LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Week 4: LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Week 8: LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Week 12: LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Eculizumab or ravulizumab.
[b] As the occurrence or not of transfusion is informed by the binary definition of this endpoint, censoring of patients who received a transfusion in Week 8 or beyond is not applicable.
Abbreviations: ARC: absolute reticulocyte count; C5i: complement component 5 inhibitor; CI: confidence interval; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; HRQoL: health-related quality of life; IAS: interim efficacy analysis set; LS: least squares; N: number of patients; SD: standard deviation; SE: standard error.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[7] Table 14.2.2.1.1, Table 14.2.2.2.1, Table 14.2.2.3.1.2, Table 14.2.2.3.3, Table 14.2.2.4.3, Table 14.2.3.3.2, Table 14.2.3.4.2, Table 14.2.5.1.2; Lee *et al.* (2023).[8]

Table 4: Efficacy and HRQoL endpoint results at Week 24 (setting scores collected after transfusion to missing) (IAS)

	DAN/DAN + C5i[a] N=41	PBO/DAN + C5i[a] N=20
Change from baseline in haemoglobin at Week 24		
Number of participants	[redacted]	[redacted]
LS mean (SE), g/dL	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Proportion of patients with a haemoglobin increase of ≥2 g/dL at Week 24 in the absence of transfusion[b]		
Number of participants (n)	19	7
Percentage (%)	46.3	35.0
95% CI	30.7, 62.6	15.4, 59.2
Proportion of patients with transfusion avoidance from Week 12 to Week 24[b]		

Number of participants (n)	32	18
Percentage	78.0	90.0
95% CI	62.4, 89.4	68.3, 98.8
Change from baseline in FACIT-F scores at Week 24		
Number of patients (n)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Change from baseline in ARC at Week 24		
Number of participants	[redacted]	[redacted]
LS mean (SE), 10^9/L	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Change from baseline in LDH at Week 24		
Number of participants	[redacted]	[redacted]
LS mean (SE), U/L	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Change from baseline in Total PNH RBC Clone Size (Type II + Type III) at Week 24, %		
Number of participants (n)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Change from baseline in PNH RBC Type III Clone Size at Week 24, %		
Number of participants (n)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Change from baseline in PNH RBC Type II Clone Size at Week 24, %		
Number of participants (n)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Change from baseline in EQ-5D-3L UK health state index scores by treatment visit through Week 24[c]		
Week 14: Mean (SD)	[redacted]	[redacted]
Week 16: Mean (SD)	[redacted]	[redacted]
Week 20: Mean (SD)	[redacted]	[redacted]
Week 24: Mean (SD)	[redacted]	[redacted]

[a] Eculizumab or ravulizumab.
[b] As the occurrence or not of transfusion is informed by the binary definition of this endpoint, censoring of patients who received a transfusion in Week 8 or beyond is not applicable.
[c] In line with the Company submission, EQ-5D-3L UK index values presented at and prior to Week 12 are presented as least squares (LS) mean values derived from the MMRM model, whereas EQ-5D-3L UK index values from Week 12 onwards are presented as arithmetic means.
Abbreviations: ARC: absolute reticulocyte count; C5i: complement component 5 inhibitor; CI: confidence interval; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; HRQoL: health-related quality of life; IAS: interim efficacy analysis set; LDH: lactate dehydrogenase; LS: least squares; MMRM: mixed model repeated measures; N: number of patients; RBC: red blood cell; SD: standard deviation; SE: standard error.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[7] Table 14.2.4.2.2, Table 14.2.4.3.2, Table 14.2.4.5.2, Table 14.2.4.6.2, Table 14.2.4.7.1, Table 14.2.4.9.1, Table 14.2.5.3.2.

Reperformed MAIC analyses

The anchored and unanchored MAIC analyses were re-performed using the ALPHA trial endpoint results, at Week 12, setting scores to missing if patients had received a transfusion at any point during the trial follow up (Table 5).

Interpretation of re-performed MAIC results

Re-performing the anchored and unanchored MAIC analyses, by setting scores collected after transfusion to missing, resulted in broadly consistent MAIC results with respect to the primary analyses (presented in Appendix D.3.3. of the Company submission). The broad confidence intervals displayed in Table 5 support the conclusions presented in the Company submission; the anchored and the unanchored MAIC results are associated with substantial uncertainty.

Table 5: Reperformed anchored and unanchored MAIC analyses (setting scores collected after transfusion to missing)

Outcome	Danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan	
	Anchored analyses	Unanchored analyses
Mean increase in haemoglobin level from baseline (g/dL) (95% CI)		
Naïve	[redacted]	[redacted]
Adjusted (Signorovitch *et al*.)	[redacted]	[redacted]
Adjusted (Jackson *et al*.)	[redacted]	[redacted]
Mean increase in absolute reticulocyte count from baseline (10^9/L) (95% CI)		
Naïve	[redacted]	[redacted]
Adjusted (Signorovitch *et al*.)	[redacted]	[redacted]
Adjusted (Jackson *et al*.)	[redacted]	[redacted]
Mean increase in LDH level from baseline (U/L) (95% CI)		
Naïve	[redacted]	[redacted]
Adjusted (Signorovitch *et al*.)	[redacted]	[redacted]
Adjusted (Jackson *et al*.)	[redacted]	[redacted]
Mean increase in FACIT-F score level from baseline (95% CI)		
Naïve	[redacted]	[redacted]
Adjusted (Signorovitch *et al*.)	[redacted]	[redacted]
Adjusted (Jackson *et al*.)	[redacted]	[redacted]
Mean increase in log-odds of patients with transfusion avoidance[a] (%) (95% CI)		
Naïve	[redacted]	[redacted]
Adjusted (Signorovitch *et al*.)	[redacted]	[redacted]
Adjusted (Jackson *et al*.)	[redacted]	[redacted]

[a] Up to 12 weeks in the ALPHA trial.
Abbreviations: ARC: absolute reticulocyte count; CI: confidence interval; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; MAIC: matching-adjusted indirect comparison.

Transition probabilities

As described in Section B.3 of the Company submission, the cost-effectiveness model for danicopan add-on therapy comprises three states: Low Hb' and 'Moderate Hb') and 'blood transfusion'. To calculate the transition probabilities for each health state, it is necessary for the corresponding clinical outcome (in this case, occurrence of transfusion) to be included in the analysis set, rather than censored. Alternative transition probabilities have therefore not been generated.

A6. It is unclear which outcomes had measurements excluded from their respective analyses due to transfusions. Please reproduce all sections of results (e.g. condensed form of B.2.7) but excluding scores of people who received a transfusion in week 8 or beyond.

The re-analysis of efficacy and HRQoL endpoints presented in response to clarification question A5 also satisfy the requirements of clarification question A6. Therefore, these results are reproduced in Table 6 and Table 7 below, for clarity.

As discussed in response to clarification question A5, the re-analyses of these secondary endpoints, with the same rule of censoring due to transfusions, produced consistent results with respect to the corresponding analyses for the principle trial analyses.

Table 6: Efficacy and HRQoL endpoint results at Week 12 (excluding scores from patients receiving transfusion within four weeks of the timepoint of assessment) (IAS)

	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=21	Difference (Danicopan - Placebo)	p-value
Change from baseline in haemoglobin at Week 12				
Number of patients (n)	42	21	NR	p<0.0001
LS mean (SE), g/dL	2.94 (0.21)	0.50 (0.31)	2.44 (0.38)	
95% CI for LS mean	2.52, 3.36	-0.13, 1.12	1.69, 3.20	
Proportion of patients with a haemoglobin increase of ≥2 g/dL at Week 12 in the absence of transfusion[b]				
Number of participants (n)	25	0	N/A	p<0.0001
Percentage (%)	59.5	0	46.9	
95% CI	43.3, 74.4	0.0, 16.1	29.2, 64.7	
Proportion of patients with transfusion avoidance at Week 12[b]				
Number of participants (n)	35	8	N/A	p=0.0004
Percentage	83.3	38.1	41.7	
95% CI	68.6, 93.0	18.1, 61.6	22.7, 60.8	
Change from baseline in FACIT-F scores at Week 12				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	[redacted]	
95% CI for LS mean	[redacted]	[redacted]	[redacted]	

Change from baseline in ARC at Week 12				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE), 10^9/L	[redacted]	[redacted]	[redacted]	
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
Change from baseline in LDH at Week 12				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE), U/L	[redacted]	[redacted]	[redacted]	
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
Total PNH RBC Clone Size (Type II + Type III) at Week 12, %				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	[redacted]	
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
PNH RBC Type III Clone Size at Week 12, %				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	[redacted]	
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
PNH RBC Type II Clone Size at Week 12, %				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	[redacted]	
95% CI for LS mean	[redacted]	[redacted]	[redacted]	
Change from baseline in EQ-5D-3L UK health state index scores by treatment visit through Week 12				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]
Week 2: LS mean (SE)	[redacted]	[redacted]	[redacted]	
Week 4: LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Week 8: LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Week 12: LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Eculizumab or ravulizumab.

[b] As the occurrence or not of transfusion is informed by the binary definition of this endpoint, censoring of patients who received a transfusion in Week 8 or beyond is not applicable.

Abbreviations: ARC: absolute reticulocyte count; C5i: complement component 5 inhibitor; CI: confidence interval; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; HRQoL: health-related quality of life; IAS: interim efficacy analysis set; LS: least squares; N: number of patients; SD: standard deviation; SE: standard error.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[7] Table 14.2.2.1.1, Table 14.2.2.2.1, Table 14.2.2.3.1.2, Table 14.2.2.3.3, Table 14.2.2.4.3, Table 14.2.3.3.2, Table 14.2.3.4.2, Table 14.2.5.1.2; Lee *et al.* (2023).[8]

Table 7: Efficacy and HRQoL endpoint results at Week 24 (excluding scores from patients receiving transfusion within four weeks of the timepoint of assessment) (IAS)

	DAN/DAN + C5i[a] N=41	PBO/DAN + C5i[a] N=20
Change from baseline in haemoglobin at Week 24		
Number of participants	37	20
LS mean (SE), g/dL	31.7 (3.0)	22.6 (3.4)
95% CI for LS mean	25.6, 37.7	15.7, 29.4
Proportion of patients with a haemoglobin increase of ≥2 g/dL at Week 24 in the absence of transfusion[b]		
Number of participants (n)	19	7
Percentage (%)	46.3	35.0
95% CI	30.7, 62.6	15.4, 59.2
Proportion of patients with transfusion avoidance from Week 12 to Week 24[b]		
Number of participants (n)	32	18
Percentage	78.0	90.0
95% CI	62.4, 89.4	68.3, 98.8
Change from baseline in FACIT-F scores at Week 24		
Number of patients (n)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Change from baseline in ARC at Week 24		
Number of participants	[redacted]	[redacted]
LS mean (SE), 10^9/L	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Change from baseline in LDH at Week 24		
Number of participants	[redacted]	[redacted]
LS mean (SE), U/L	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Total PNH RBC Clone Size (Type II + Type III) at Week 24, %		
Number of participants (n)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
PNH RBC Type III Clone Size at Week 24, %		
Number of participants (n)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]

PNH RBC Type II Clone Size at Week 24, %		
Number of participants (n)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]
Change from baseline in EQ-5D-3L UK health state index scores by treatment visit through Week 24[c]		
Week 14: Mean (SD)	[redacted]	[redacted]
Number of participants for Week 14 (n)	[redacted]	[redacted]
Week 16: Mean (SD)	[redacted]	[redacted]
Number of participants for Week 16 (n)	[redacted]	[redacted]
Week 20: Mean (SD)	[redacted]	[redacted]
Number of participants for Week 20 (n)	[redacted]	[redacted]
Week 24: Mean (SD)	[redacted]	[redacted]
Number of participants for Week 24 (n)	[redacted]	[redacted]

[a] Eculizumab or ravulizumab.
[b] As the occurrence or not of transfusion is informed by the binary definition of this endpoint, censoring of patients who received a transfusion in Week 8 or beyond is not applicable.
[c] In line with the Company submission, EQ-5D-3L UK index values presented at and prior to Week 12 are presented as least squares (LS) mean values derived from the MMRM model, whereas EQ-5D-3L UK index values from Week 12 onwards are presented as arithmetic means.
Abbreviations: ARC: absolute reticulocyte count; C5i: complement component 5 inhibitor; CI: confidence interval; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; HRQoL: health-related quality of life; IAS: interim efficacy analysis set; LDH: lactate dehydrogenase; LS: least squares; MMRM: mixed model repeated measures; N: number of patients; RBC: red blood cell; SD: standard deviation; SE: standard error.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[7] Table 14.2.4.2.2, Table 14.2.4.3.2, Table 14.2.4.5.2, Table 14.2.4.6.2, Table 14.2.4.7.1, Table 14.2.4.9.1, Table 14.2.5.3.2.

A7. CS decision problem, p12, states that the development of C5 inhibitors has led to the control of IVH and that as such IVH is not considered a key outcome. IVH is largely measured by lactate dehydrogenase (LDH) and the CS states that data on LDH levels are presented for completion. However, the CS does not provide these data.

Please provide change from baseline scores for LDH levels at the analysis time points where measured in ALPHA.

As described in the decision problem table of the Company submission (Document B; Table 1), intravascular haemolysis (IVH) is a key contributor to mortality and morbidity associated with PNH. However, the introduction of C5 inhibitors in UK clinical practice has led to the successful management of patients' IVH. The efficacy of C5 inhibitors in the control of IVH through normalisation of LDH levels has been demonstrated and proven in the SHEPHERD (eculizumab) and Study 301 (ravulizumab) trials.[9, 10] Danicopan aims to address clinically significant extravascular haemolysis (csEVH) rather than IVH. As described in Section B.1.3.1 of the Company submission, EVH is a mechanistic consequence of effective C5 inhibition. Accordingly, the inclusion criteria of the ALPHA trial state that patients "must be receiving an approved C5 inhibitor for at least 6 months prior to Day 1 in this study".[4] Additionally, the mean baseline LDH level across both treatment arms in the ALPHA trial was 292.1 U/L, which falls within the normal reference range (135–330 U/L) and indicates the control of IVH with C5 inhibitor treatment.[7, 11] Therefore, IVH, and hence LDH levels, are not relevant efficacy outcomes for this evaluation. However, for completeness, the change from baseline in LDH levels at Week 12 (TP1) and Week 24 (TP2) during the ALPHA trial are presented in Table 8 and Table 9, respectively.

Table 8: Change from baseline in LDH at Week 12 (IAS)

	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=20	Difference (Danicopan – Placebo)	p-value
LS mean (SE), U/L	−23.5 (8.3)	−2.9 (11.9)	−20.6 (14.3)	0.1569
95% CI for LS mean	−40.1, −6.9	−26.8, 20.9	−49.3, 8.2	

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; CI: confidence interval; IAS: interim efficacy analysis set; LDH: lactate dehydrogenase; LS: least squares; SE: standard error.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[7] Table 14.2.3.3.1.

Table 9: Change from baseline in LDH at Week 24 (IAS)

	DAN/DAN + C5i[a] N=41	PBO/DAN + C5i[a] N=19
LS mean (SE), U/L	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; CI: confidence interval; DAN/DAN: patients received danicopan in TP1 and continued with danicopan in TP2; IAS: interim efficacy analysis set; LDH: lactate dehydrogenase; LS: least squares; NR: not reported; PBO/DAN: patients received placebo in TP1 and switched to receive danicopan in TP2; SE: standard error.
Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[7] Table 14.2.4.5.1.

A8. As C3 inhibition affects C5 please provide further justification as to why no additional benefit to IVH is anticipated with the use of danicopan as an add-on treatment. The EAG notes that in the exploratory single-arm phase II study of danicopan as monotherapy in treatment naïve populations (CS reference 38) there was an observed effect on IVH and EVH. Please outline why IVH does not appear to be considered important in the current CS.

As noted in Section B.1.1 of Document B, the population of interest for this submission is patients with PNH who have csEVH whilst on treatment with a C5 inhibitor (eculizumab or ravulizumab), which is consistent with the anticipated licensed indication.[12] EVH manifests as residual anaemia following the treatment of IVH with a C5 inhibitor, hence danicopan is expected to be used in patients whose IVH is controlled.

This is supported by the ALPHA trial; as mentioned in response to question A7, the inclusion criteria dictate that patients must have received either eculizumab or ravulizumab, with no changes in the prescribed dose or interval permitted within 24 weeks prior to the trial.[4] Additionally, the mean baseline LDH level across both treatment arms was within the normal reference range.[4, 7] Furthermore, given the risk of mortality and morbidity associated with IVH, IVH would be treated as a priority among patients with uncontrolled IVH prior to consideration of treatment with danicopan. Therefore, in the ALPHA trial where IVH is already well-controlled, no additional clinical benefit in terms of IVH is anticipated with danicopan, and it was therefore not considered relevant to assess the impact of danicopan on IVH in ALPHA.

Furthermore, the exploratory single-arm Phase II trial published by Risitano et al. 2021 noted that danicopan monotherapy did not consistently achieve complete inhibition of the alternative pathway across all patients, with residual IVH reported in some patients.[13] This trial evaluated a different patient population from the ALPHA trial,[13] specifically, patients with untreated PNH with LDH ≥1.5×ULN, whereas ALPHA considered patients already receiving stable C5 inhibitor treatment, as described above.[4] Since patients in the Phase II trial were not receiving any prior complement inhibition and had elevated LDH at baseline, danicopan demonstrated some impact on IVH. However, the impact of danicopan add-on treatment on IVH levels, for patients receiving complement inhibition, is anticipated to be negligible. This conclusion is supported by the non-statistically significant (p<[redacted]) difference in LDH levels from baseline to Week 12 observed in the ALPHA trial, which are provided in response to clarification question A7.

A9. The CS decision problem is focused on those with clinically significant EVH. The company confirm that there is no standard definition for csEVH but the definition used in ALPHA is haemoglobin (Hb) ≤9.5 g/dL and absolute reticulocyte count (ARC) ≥120 × 10^9 /L. Does the company anticipate that in UK clinical practice these thresholds will be used to confirm eligibility for danicopan treatment as an add on to C5 therapies? Will this incur any additional investigations over those typically used to assess 'any' EVH after treatment with C5 inhibitors?

As noted in Section B.1.3.1 of Document B, feedback obtained from UK clinical experts in an advisory board meeting indicated that there is no standardised definition of csEVH in UK clinical practice.[14] CsEVH is instead assessed on an individual basis using a range of parameters and clinical opinion. These parameters include the levels of biomarkers such as haemoglobin, bilirubin, reticulocyte counts, and the deposition of C3 fragments on RBCs, the need for transfusions, as well as patient-reported factors including fatigue levels and the condition's impact on the patient's quality of life.[14, 15]

In the ALPHA trial, clear eligibility criteria were required for the recruitment of trial participants. Hence, specific thresholds for haemoglobin and ARC levels were defined. These specific haemoglobin and ARC level thresholds are not anticipated to be used in UK clinical practice to determine patients' eligibility to receive danicopan. UK clinical

experts in the advisory board noted that the eligibility criteria of the ALPHA trial were stricter than those typically used to determine patients with csEVH (who would be eligible to receive danicopan) in UK clinical practice, an approach that is commonplace for clinical trials.[14] The clinical experts noted that patient-reported factors, such as fatigue levels and patient HRQoL, are often used during diagnosis of csEVH in clinical practice. However, it was highlighted that patient reported outcome measures, using fatigue as an example, are difficult to quantify and are therefore not typically used as recruitment criteria in clinical trials. The clinical experts emphasised that in clinical practice, csEVH should be determined through an assessment of the full clinical picture rather than specific threshold values for parameters such as haemoglobin levels.[16] As such, it is not anticipated that specific thresholds will be used to confirm eligibility for treatment with danicopan in UK clinical practice.

Finally, the UK clinical experts in PNH confirmed that no further tests or consultations, over and above those already used to determine EVH in current clinical practice, would be required to determine patients' eligibility for danicopan in UK clinical practice.

A10. Is the presence or history of aplastic anaemia a potential prognostic or treatment-effect modifier in PNH? If so, please show how this was considered in the indirect treatment comparison.

Aplastic anaemia and PNH are closely related, and as such, aplastic anaemia is common in the PNH population. As discussed in the NICE appraisal for pegcetacoplan (TA778), around 50% of patients with PNH have some form of underlying bone marrow failure (such as aplastic anaemia).[17] Uncontrolled, or active aplastic anaemia may be considered a prognostic factor and treatment effect modifier in PNH, as patients with ongoing bone marrow failure are unable to produce an adequate treatment response resulting in improved haemoglobin levels. As noted in response to question A2, patients were excluded from the ALPHA trial if they had "*known aplastic anaemia or other bone marrow failure that requires HSCT or other therapies including anti-thymocyte globulin and/or immunosuppressants, unless the dosage regimen of immunosuppressant had been stable for at least 12 weeks before Day 1 and patient was expected to remain on stable doses through Week 24*". Additionally, patients in the ALPHA trial were required to have an ARC of ≥ 120 x 10^9/L; low reticulocyte counts are indicative of aplastic anaemia.[18] The ALPHA trial

therefore only included patients with no presence of, or resolved or controlled, aplastic anaemia, as evidenced by the inclusion criteria for ARC.

As patients enrolled in the PEGASUS trial for pegcetacoplan had the same requirements for reticulocyte counts (≥ 120 x 10^9/L), both populations considered in the ITC had controlled or resolved aplastic anaemia. As aplastic anaemia was therefore controlled for in both trials, it is expected that that this factor would not have impacted ITC results. Additionally, as reticulocyte counts, which are indicative of aplastic anaemia, were adjusted for in the adjusted MAICs, aplastic anaemia was indirectly addressed in these analyses.

A11. In the ALPHA protocol, section 9.5 says that the purpose of any interim analysis was to evaluate the study for stopping early for efficacy. The study was not stopped early at the interim analysis, does that mean it was considered not to meet the efficacy criteria?

Section 9.5 of the ALPHA trial protocol states that “the purpose of the interim analysis is to evaluate the study for stopping early for efficacy”. Alexion would like to clarify that this statement refers to stopping the study enrolment (if enrolment is still ongoing at the time of the interim analysis readout) and stopping the randomised primary evaluation period early (i.e., TP1 for the interim analysis set [IAS]), rather than stopping the entire ALPHA trial. The pre-specified interim analysis did indeed meet all the pre-defined efficacy criteria,[4] and therefore upon positive results from the interim analysis, the study was unblinded per the recommendation from the independent data monitoring committee (DMC). Patients on placebo treatment during TP1 were then switched to treatment with danicopan, and all patients receiving danicopan in TP1 continued to receive danicopan, as specified in Section 9.5 of the study protocol. These patients continued with danicopan treatment in TP2 (i.e., Weeks 12–24) in order to assess the long term efficacy and safety of danicopan add-on treatment.

A12. In the CS it states that enrolment was completed in September 2022. TP1 is only 12 weeks so the last enrolled patient should have completed TP1 by December 2022 at the very latest. Please confirm when the next interim and/or final results will

be available, and why no more recent follow-up has been provided in the current submission.

The first interim analysis for the ALPHA trial, interim analysis 1 (IA1), took place on the 28th June 2022 and provided efficacy data for the 63 patients who had reached 12 weeks of treatment, in addition to 73 patients in the safety analysis set. These data were provided for the purposes of the [redacted] marketing authorisation submission. An updated data-cut (20th September 2022) (IA2) was used to inform the [redacted] marketing authorisation submission and was presented in the danicopan NICE submission. It included all 24-week (TP1 and TP2) efficacy data for the pre-specified interim analysis set of 63 patients. An additional data-cut (31st March 2023) formed IA3 of the ALPHA trial, with all randomised patients reaching the end of TP2. This data cut was not prespecified in the trial protocol, rather, it was conducted for supplemental analyses in order to address specific requests from the regulatory agencies as an addendum. A CSR for the 31st March 2023 DCO (IA3) is not available. The 20th September 2022 DCO (IA2) was presented in the submission as more complete data were available for this data cut within the NICE submission timelines.

The final database lock for the ALPHA trial is planned for [redacted]. However, the accompanying CSR is not anticipated to become available until [redacted].

A13. Please provide details of the number with transfusions, the volume and mean number of transfusions in ALPHA by trial arm. We are aware that data in the CSR reports change in RBC units transfused and number of transfusion instances but not absolute values.

Absolute values for RBC units transfused, and transfusion instances, 12 weeks prior and 12 weeks post treatment initiation are provided in Tables 14.1.3.1.5 and 14.2.6.5.1 of the ALPHA trial CSR. This document was provided as part of the reference pack (file name: 'alxn2040-pnh-301-ia-17-mar-2023-tables-and-figures') for the Company submission.[7] For clarity, these values are presented in Table 10 below.

The numbers of patients in each treatment arm receiving a transfusion during Weeks 1–12 of the trial are not reported in the ALPHA trial CSR. Instead, the proportion of patients achieving 'transfusion avoidance' at Week 12 was evaluated, defined as the

proportion of patients remaining transfusion-free and who do not require a transfusion as per protocol-specified guidelines through Week 12 (Section 1.1, Table 1 of the protocol).[4] Table 10 presents the number of patients who did not achieve this protocol defined transfusion avoidance criteria at Week 12, calculated as the number of patients in each treatment arm minus the number of patients who achieved transfusion avoidance in Week 12. Importantly, these numbers include patients who did not achieve transfusion avoidance as per the pre-specified criteria, but may not have received a transfusion from Weeks 1 to 12 (due to meeting the per-protocol specified guidelines for transfusion, but not ultimately receiving a transfusion). Transfusion data from Week 1−12 are currently being generated and will be available shortly after submission of the clarification question responses.

Patients' transfusion history, including the proportion of patients who did not achieve transfusion avoidance (including patients who were eligible to receive a transfusion as well as those who actually received a transfusion), transfusion instances and units transfused 12 weeks prior to treatment initiation were consistent across treatment arms in the ALPHA trial (Table 10). Following treatment initiation, danicopan add-on treatment improved transfusion requirements of patients across all three endpoints listed in Table 10 versus placebo at Week 12. Danicopan therefore reduces the need for transfusion, evidenced by the number of transfusion instances post-12 weeks treatment initiation, by approximately 58% versus placebo, demonstrating that danicopan add-on treatment rapidly addresses EVH requirements.

Table 10: Transfusions received 12 weeks prior and 12 weeks post treatment initiation in the ALPHA trial (IAS)

	Danicopan + C5i[a] N=42	Placebo + C5i[a] n=21	Difference
Proportion of patients who were not transfusion avoidant at Week 12			
Number of participants who did not achieve transfusion avoidance (n)	7	13	−6
Percentage	16.7	61.9	−45.2
Number of RBC units transferred, mean (SD)			
12 weeks prior to treatment initiation	[redacted]	[redacted]	[redacted]
Post 12 weeks of treatment initiation	[redacted]	[redacted]	[redacted]
Number of transfusion instances, mean (SD)			
12 weeks prior to treatment initiation	[redacted]	[redacted]	[redacted]
Post 12 weeks of treatment initiation	[redacted]	[redacted]	[redacted]

[a] Eculizumab or ravulizumab.

Abbreviations: C5: complement component 5; CS: company submission; CSR: clinical study report; IAS: interim analysis set; NR: not reported; RBC: red blood cell.
Source: ALPHA trial CSR (20th September 2022 DCO).[7] Tables 14.1.3.1.5, 14.2.6.5.1 and 14.2.2.2.1.

A14. In ALPHA a protocol amendment was made to allow patients with no prior transfusion on to the study, [redacted]. Could you provide an explanation for this?

The protocol amendment, implemented on the 25th February 2022, removed the inclusion criterion requiring patients to have received at least 1 packed RBC or whole blood transfusion within six months prior to the start of the study.[7] At the 20th September 2022 DCO (IA2) [redacted] in the safety analysis without receipt of a RBC transfusion in the previous 6 months had been enrolled into the trial. However, neither of these patients were included in the pre-specified IAS, by definition of the analysis set (defined as the first 63 randomised patients in ALPHA trial; ALPHA trial CSR Section 3.7.2, Table 6).[7] As noted in Section B.1.3.1 of the Company submission, a continued need for blood transfusions despite C5 inhibitor monotherapy is a common manifestation of csEVH.[19] Therefore, this result is not unexpected due to the known dependency of this patient population on regular transfusions; as highlighted by clinical experts during a UK advisory board, the McKinley, et al. 2017 publication demonstrates that 36% of 141 treated patients with PNH experiencing csEVH had received at least one blood transfusion in a 12-month period.[15]

A15. For people eligible for both Danicopan + C5 inhibitor under this indication, and pegcetacoplan, what factors will influence a clinician's and patient's decision to select a preferred treatment in real-world use?

A key factor resulting in danicopan add-on treatment being used preferentially over pegcetacoplan is the presence of the C5 inhibitor backbone. By continuing treatment with a C5 inhibitor, patients and clinicians may be reassured that life-threatening IVH, the underlying cause of morbidity and mortality in PNH, and thrombosis, are controlled by complete and sustained disease inhibition. This reassurance was highlighted by clinical experts in PNH consulted as part of a UK advisory board.[14, 20]

Conversely, patients on C5 inhibitors who develop csEVH must discontinue C5 inhibition in order to receive pegcetacoplan monotherapy, which is indicated in the treatment of adult patients with PNH who are anaemic after treatment with a C5

inhibitor for at least 3 months.[21] The transition to proximal complement inhibition monotherapy risks a lapse in control of IVH in the absence of complete terminal complement inhibition, and subsequently, manifestations such as severe breakthrough haemolysis (BTH) may occur due to rapid haemolysis in patients.[22-24] In the PEGASUS trial, after 16 weeks of treatment with pegcetacoplan, four patients (10%) experienced BTH.[1] Additionally, relative to C5 inhibitors, pegcetacoplan is associated with more severe episodes of BTH, with reported LDH levels up to 10–15 times the ULN.[25] Comparatively, LDH level increases of more than five times the ULN are rare amongst patients treated with a C5 inhibitor.[25] This may lead to danicopan add-on treatment being preferentially prescribed by clinicians over pegcetacoplan.

Patient preference may also be a key determinant in treatment choice; patients may prefer to continue treatment with a C5 inhibitor providing reassurance of controlled IVH, with the addition of danicopan add-on treatment, rather than switch to an entirely new treatment. Alternatively, a clinician more experienced using pegcetacoplan as a treatment following C5 inhibition may be more inclined to prescribe this treatment based on experience, rather than prescribing a new treatment such as danicopan.

The administration requirements of the two treatments will also likely be a key differentiating factor between danicopan add-on treatment and pegcetacoplan. Danicopan add-on treatment is available as an oral tablet to be taken three times daily (TID), approximately eight hours apart, in addition to intravenous infusions of eculizumab (once every two weeks) or ravulizumab (once every eight weeks).[12, 26, 27] Pegcetacoplan is a subcutaneous (SC) injection self-administered by patients twice weekly, or up to once every three days.[21] As such, if a clinician views that a patient may struggle to effectively adhere to the frequent TID dosing of danicopan, pegcetacoplan may be the preferable treatment choice. Conversely, the requirement for patients to self-administer SC pegcetacoplan may mean that a subset of patients is unable or unwilling to receive this treatment. In particular, patients with visual difficulties, dexterity issues, mental health issues or minimal subcutaneous fat may struggle to administer a SC treatment, as highlighted by clinicians as part of a UK advisory board.[14] Therefore, if a clinician determines that a patient is unlikely to be

willing or able to effectively self-administer a SC injection twice weekly, danicopan add-on treatment is likely to be the preferred treatment. During the advisory board, clinicians also highlighted the general burden of subcutaneous injections; administration is required twice weekly and typically takes 30–60 minutes, depending on the number of injection sites.[14] The infusion volume, of 20 ml, is also fairly large, and the entire infusion process, as outlined in the patient information leaflet (PIL) for pegcetacoplan, may be burdensome to patients.[21] As such, patients may select an oral treatment with infrequent intravenous infusions over twice weekly subcutaneous injections based on personal preference. Danicopan add-on treatment therefore facilitates patient choice in addition to providing continued reassurance of control of IVH.

Finally, the logistical implications associated with the differing modes of administrations of the two treatments may also constitute a differentiating factor between the two treatment options. As noted previously, danicopan requires TID dosing in addition to infrequent infusions of eculizumab or ravulizumab, however, the tablets are easily transportable with no requirement for refrigeration. In contrast, pegcetacoplan must be kept refrigerated and maintained at a constant temperature between 2–8°C, this, combined with the requirement for an infusion pump and associated consumables, presents a major restriction to patients, especially when travelling.[21] For this reason, patients may preferentially select danicopan add-on treatment over pegcetacoplan monotherapy.

In summary, selection of danicopan add-on treatment over pegcetacoplan is anticipated to be decided on a per-patient basis, taking into account patient's symptoms, overall health, logistical requirements in addition to personal preferences.

Section B: Clarification on cost-effectiveness data

B1. Please provide justification to support the implicit assumption in the company's base case where a lower proportion of people receiving danicopan + C5 inhibitor

remain on treatment compared to people receiving pegcetacoplan throughout the model time horizon.

As explained in detail in B.3.3.6 and B.3.3.3 of the Company Submission, patients are modelled to discontinue treatment in either arm due to non BTH-related events such as adverse events.

Neither patients on pegcetacoplan or danicopan as an add-on to a C5 inhibitor discontinue treatment due to a BTH-related event in the model. The management of patients who experience BTH in both arms is informed by consulted UK clinical experts, who advised that patients receiving pegcetacoplan would have a dose-escalation and patients on danicopan + C5 inhibitor would receive dosing of their C5 inhibitor treatment earlier than scheduled in order to address the BTH.

Discontinuation due to non-BTH related events was informed by the ALPHA trial (TP1 [Week 1-12] and TP2 [Week 13–24] and the long-term extension period [Week 25–52]) and PEGASUS trial (randomised, controlled period [Week 4–16] and open-label period [Week 17-48]), for danicopan as an add-on to a C5 inhibitor and pegcetacoplan, respectively.[7] Observed non-BTH related treatment discontinuation was higher in the ALPHA trial than the PEGASUS trial, and model inputs were accordingly aligned with the trial data. Due to the lack of long-term data, it is assumed for both treatment arms there is no discontinuation after Year 1, in line with the assumption accepted in NICE TA778.[17] A scenario was presented which removed this assumption and instead assumed that the discontinuation observed in the long-term extension period (Week 25–52) and open-label period (Week 17–48) for danicopan as an add-on to a C5 inhibitor and pegcetacoplan, respectively, is maintained, with similar discontinuation rates for both treatments (1.24% and 1.36%, respectively). The scenario had no impact on the conclusions of the cost-effectiveness analysis, i.e., danicopan as an add-on to a C5 inhibitor dominated pegcetacoplan.

B2. Please provide a table of transition probabilities for both arms of the ALPHA trial, as per Table 37 and 38, but for the MAIC trimmed population ([redacted])

Please see below, in Table 11 and Table 12, the transition probabilities for both arms of the ALPHA trial for the MAIC trimmed population. A multinomial regression model was used to calculate these transition probabilities with the inclusion of a random

intercept for Subject ID. Low Hb health state was defined as a patient without a transfusion and with a haemoglobin level of <10.5 g/dL; Moderate Hb health state was defined as a patient without a transfusion and with a haemoglobin level of ≥10.5 g/dL; Transfusion was defined as a patient who underwent a transfusion. Changing the transition probabilities in the model (i.e., using the transition probabilities from the MAIC trimmed population) does not change the conclusions of the cost effectiveness analysis.

Table 11. Transition probabilities for the danicopan add-on to eculizumab or ravulizumab arm of the ALPHA trial for the MAIC trimmed population

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; Tr.: transfusion.

Table 12. Transition probabilities for the placebo (eculizumab or ravulizumab monotherapy) arm of the ALPHA trial for the MAIC trimmed population

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; Tr.: transfusion.

B3. Please provide a table of transition probabilities for both arms of the ALPHA trial, as per Table 37 and 38, but for the anchored MAIC weighted population.

Please see below, in Table 13 and Table 14, the transition probabilities for both arms of the ALPHA trial for the anchored MAIC weighted population. A multinomial regression model was used to calculate these transition probabilities with the inclusion of a random intercept for Subject ID. Low Hb health state was defined as a patient without a transfusion and with a haemoglobin level of <10.5 g/dL; Moderate

Hb health state was defined as a patient without a transfusion and with a haemoglobin level of ≥10.5 g/dL; Transfusion was defined as a patient who underwent a transfusion. Changing the transition probabilities in the model (i.e., using the transition probabilities from the anchored MAIC weighted population) does not change the conclusions of the cost effectiveness analysis.

Table 13. Transition probabilities for the danicopan add-on to eculizumab or ravulizumab arm of the ALPHA trial for the anchored MAIC weighted population

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; Tr.: transfusion.

Table 14. Transition probabilities for the placebo (eculizumab or ravulizumab monotherapy) arm of the ALPHA trial for the anchored MAIC weighted population

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; Tr.: transfusion.

B4. Please provide a table of transition probabilities for both arms of the ALPHA trial, as per Table 37 and 38, but for the unanchored MAIC weighted population.

Please see below, in Table 15 and Table 16, the transition probabilities for both arms of the ALPHA trial for the unanchored MAIC weighted population. A multinomial regression model was used to calculate these transition probabilities with the inclusion of a random intercept for Subject ID. Low Hb health state was defined as a patient without a transfusion and with a haemoglobin level of <10.5 g/dL; Moderate Hb health state was defined as a patient without a transfusion and with a haemoglobin level of ≥10.5 g/dL; Transfusion was defined as a patient who

underwent a transfusion. Changing the transition probabilities in the model (i.e., using the transition probabilities from the unanchored MAIC weighted population) does not change the conclusions of the cost effectiveness analysis.

Table 15. Transition probabilities for the danicopan add-on to eculizumab or ravulizumab arm of the ALPHA trial for the unanchored MAIC weighted population

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; Tr.: transfusion.

Table 16. Transition probabilities for the placebo (eculizumab or ravulizumab monotherapy) arm of the ALPHA trial for the unanchored MAIC weighted population

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; Tr.: transfusion.

B5. Please provide a table of transition probabilities for both arms of the ALPHA trial, as per Table 37 and 38, but for the anchored maximised ESS weighted population.

Please see below, in Table 17 and Table 18, the transition probabilities for both arms of the ALPHA trial for the anchored maximised ESS weighted population. A multinomial regression model was used to calculate these transition probabilities with the inclusion of a random intercept for Subject ID. Low Hb health state was defined as a patient without a transfusion and with a haemoglobin level of <10.5 g/dL; Moderate Hb health state was defined as a patient without a transfusion and with a haemoglobin level of ≥10.5 g/dL; Transfusion was defined as a patient who underwent a transfusion. Changing the transition probabilities in the model (i.e.,

using the transition probabilities from the anchored maximised ESS weighted population) does not change the conclusions of the cost effectiveness analysis.

Table 17. Transition probabilities for the danicopan add-on to eculizumab or ravulizumab arm of the ALPHA trial for the anchored maximised ESS weighted population

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; Tr.: transfusion.

Table 18. Transition probabilities for the placebo (eculizumab or ravulizumab monotherapy) arm of the ALPHA trial for the anchored maximised ESS weighted population

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; Tr.: transfusion.

B6. Please provide a table of transition probabilities for both arms of the ALPHA trial, as per Table 37 and 38, but for the unanchored maximised ESS weighted population.

Please see below, in Table 19 and Table 20, the transition probabilities for both arms of the ALPHA trial for the unanchored maximised ESS weighted population. A multinomial regression model was used to calculate these transition probabilities with the inclusion of a random intercept for Subject ID. Low Hb health state was defined as a patient without a transfusion and with a haemoglobin level of <10.5 g/dL; Moderate Hb health state was defined as a patient without a transfusion and with a haemoglobin level of ≥10.5 g/dL; Transfusion was defined as a patient who underwent a transfusion. Changing the transition probabilities in the model (i.e.,

using the transition probabilities from the unanchored maximised ESS weighted population) does not change the conclusions of the cost effectiveness analysis.

Table 19. Transition probabilities for the danicopan add-on to eculizumab or ravulizumab arm of the ALPHA trial for the unanchored maximised ESS weighted population

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; Tr.: transfusion.

Table 20. Transition probabilities for the placebo (eculizumab or ravulizumab monotherapy) arm of the ALPHA trial for the unanchored maximised ESS weighted population

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; Tr.: transfusion.

B7. Please confirm if the multinomial regression model included a patient-level random intercept, as per Hakimi et al. 2022. If not, please provide all previously presented transition probabilities, including those requested in this question list, using a model which includes this random intercept in addition to the other covariates already included and implement this within the economic model.

Originally, the multinomial regression model used to calculate the transition probabilities did not include a patient-level random intercept. All transition probabilities have now been recalculated to include a random effect for Subject**.** Please see below, in Table 21 and Table 22, the transition probabilities for both arms of the ALPHA trial based on a threshold of 9.5 mg/dL. As summarised in Table 23,

the impact on the cost-effectiveness results are very minimal (change to base case INHB of ~0.02 versus pegcetacoplan).

Table 21. Transition probabilities for the danicopan add-on to eculizumab or ravulizumab arm of the ALPHA trial including patient-level random intercept

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; Tr.: transfusion.

Table 22. Transition probabilities for the placebo (eculizumab or ravulizumab monotherapy) arm of the ALPHA trial including patient-level random intercept

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; Tr.: transfusion.

Table 23. Deterministic base case results with transition probabilities including patient-level random intercept

Scenario		Danicopan + C5i[a] vs pegcetacoplan			
		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB
Base case		[redacted]	0.429	Dominant	[redacted]
1	Inclusion of patient-level random intercept in multinomial regression	[redacted]	0.446	Dominant	[redacted]

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; QALY: quality-adjusted life year.

B8. Please provide details on the variable “Treatment Period” included in the calculation of transition probabilities, and why this could be considered equivalent to the “Visit Category” parameter included by Hakimi et al.

The variable “Treatment Period” was not included in the calculation of transition probabilities. The only variables included in the calculation of transition probabilities were start state, age and treatment status (if the patient was on danicopan or placebo for the first twelve weeks of the trial). Additionally, in response to question B7, Subject ID is now included in the model as well as a random effect.

B9. Under the rationale that IVH is not a key outcome, could you provide your rationale as to why it is appropriate to include costs of BTH (clinical sign of IVH) in the economic model?

As outlined in response to question A8, as danicopan is an add-on to eculizumab or ravulizumab, danicopan is expected to be used in an IVH-controlled patient population and therefore IVH is not a key efficacy outcome of the ALPHA trial. However, as detailed in Section B.1.3.2 of the Company submission, whilst IVH is typically well-controlled in patients receiving treatment with a C5 inhibitor, episodes of BTH can still occur, although infrequently. This may be due to either the occurrence of an infection (known as pharmacodynamic BTH), whereby the body’s immune system triggers complement amplification in response to the infection, thereby also inducing IVH.[28] Alternatively, BTH may occur due to insufficient levels of complement inhibitors in the plasma (known as pharmacokinetic BTH), such as through insufficient dosing levels.[28] BTH events pose a significant risk to patients’ health as well as significant costs to the healthcare system due to the management of these adverse events.[25, 29] BTH is therefore considered a key safety endpoint in the patient population with csEVH and is hence included in the economic model.

As noted in Section B.3.3.3 of the Company submission, patients receiving danicopan add-on treatment are subject to a different likelihood of BTH to patients receiving pegcetacoplan monotherapy, given the presence of a C5 inhibitor backbone as part of patients’ treatment regimen. As confirmed by UK clinical experts in PNH, patients receiving ravulizumab, the predominant C5 inhibitor used in England, very rarely experience pharmacokinetic BTH in clinical practice.[16, 30] The clinical experts noted that patients receiving pegcetacoplan however may experience

pharmacokinetic BTH, leading to dose escalations (to three times weekly dosing).[16, 30] As described in clarification question A15, patients who receive pegcetacoplan must discontinue treatment with C5 inhibitors and are at risk of severe BTH due to rapid haemolysis. Therefore, the inclusion of BTH events in the economic model ensures the key clinical consequences that may occur in a csEVH patient population are captured, alongside the comparative benefits and costs associated with danicopan add-on treatment versus pegcetacoplan monotherapy. The importance of the inclusion of BTH in this setting is supported by the inclusion of BTH events in the economic model for pegcetacoplan (TA778), which similarly investigated an IVH-controlled patient population.[17]

B10. The definitions used for BTH in the ALPHA and PEGASUS trials differ. Please could you clarify how rates for BTH were calculated for Danicopan and Pegcetacoplan for use in the model?

Only BTH events requiring clinical intervention were included in the economic model, as these are the ones that are expected to change patient management and/or impact a patient's quality of life.

BTH events requiring clinical intervention were defined in Section B.3.3.3 of the Company submission as: "*at least one new or worsening sign or symptom of IVH (fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia, major adverse vascular events [thrombosis], dysphagia or erectile dysfunction) in the presence of LDH levels >2 the ULN following a prior reduction of LDH levels to <1.5 times ULN.*" This definition was used in the pivotal clinical studies for ravulizumab in PNH and validated by UK clinical experts.[10, 16, 31]

Incidences of clinically actionable BTH were identified from the ALPHA trial based on the above definition, which included one patient. In the PEGASUS trial protocol it is specified that dose escalation of pegcetacoplan is carried out for patients with an LDH value at least twice the upper limit of normal.[23] As all BTH events observed in the PEGASUS trial resulted in dose escalation, all BTH events recorded in the PEGASUS trial are assumed to meet the above definition and be considered 'clinically actionable'.

B11. Noting the dosing regime for eculizumab presented in Table 34 of document B states 900mg every 14 days, could you clarify why 3.46% and 0.58% of patients receiving a C5 inhibitor are on 1200mg and 1500mg respectively in the CEM (Table 35)?

Table 34 of Document B outlines the licensed dose for eculizumab as reported in the SmPC (900 mg every 14 days).[26] However, a proportion of patients on eculizumab were on higher than licensed dosing in both the ALPHA and PEGASUS trials. As such, the proportion of patients across each dose of eculizumab and ravulizumab in the economic model was based on the administered doses observed in the ALPHA trial in alignment with the approach accepted in the NICE submission for pegcetacoplan (TA778), where dosing was modelled as per the administered doses in the PEGASUS trial.[17]

For completeness, a scenario analysis exploring the impact of aligning with the licensed dose for eculizumab was conducted, the results of which are provided in Table 24 below. The impact on the cost-effectiveness results was found to be minimal, resulting in a small increase in the net health benefit of danicopan.

Table 24: Scenario analysis results for danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan (deterministic)

Scenario		Danicopan + C5i[a] vs pegcetacoplan			
		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB
Base case		[redacted]	0.429	Dominant	[redacted]
1	C5i distribution for eculizumab: Based on licensed dosing	[redacted]	0.429	Dominant	[redacted]

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; QALY: quality-adjusted life year.

Section C: Textual clarification and additional points

C1. Please provide the following references:

4 “Alexion Data on File. UK advisory board meeting report: Danicopan in paroxysmal nocturnal haemoglobinuria (PNH), 2023.”

49 “Alexion Data on File. UK consultancy meeting with Dr Griffin: Danicopan in paroxysmal nocturnal haemoglobinuria (PNH), 2023.”

50 “Alexion Data on File. UK consultancy meeting with Dr Kulasekararaj:

Danicopan in paroxysmal nocturnal haemoglobinuria (PNH), 2023."

93 "Alexion Pharmaceuticals Inc. Data on File, 2022."

112 "Alexion Data on File"

122 "Alexion Data on File"

The UK advisory board meeting report (reference 4), in addition to reports for both of the UK consultancy meetings with clinical experts in PNH (reference 49 and 50), have been provided along with this clarification questions responses document.

Reference 112 refers to the clinical, humanistic and economic systematic literature review (SLR) report for EVH in PNH. This document was provided in the reference pack supplied alongside the original company submission (file name: 'SLR on EVH in PNH for Danicopan - Final Report').

Reference 122 relates to the LDH reference range (135–330 U/L) reflecting control of IVH provided in Document B, Section B.2.5. This reference range was taken from the central laboratory used to process results in the ALPHA trial, as such, a physical reference for this range cannot be supplied.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	PNH Support
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	PNH Support (www.pnhuk.org) is a Charitable Incorporated Organisation registered with the Charities Commission of England and Wales (no.1161518). The 4 patient trustees operate within PNH Support's constitution dated 30 April 2015 amended on 16 May 2021. The Constitution is an 'Association' model and has 152 voting members. The objects of PNH Support (as set out in its Constitution) are as follows: 1) To promote, protect and preserve the physical and mental health of those diagnosed with PNH who reside in England, Wales and Northern Ireland (either permanently or temporarily) through the provision of support, education, advocacy and practical advice; 2) To advance the education of patients with PNH who reside in England, Wales and Northern Ireland, in particular but not exclusively, by the provision of advice and a point of contact for newly diagnosed PNH patients, in England, Wales and Northern Ireland. We moderate a closed Facebook group, send email updates to members, hold regional face-to-face and online patient and family meetings and a biennial patient and family conference. PNH Support is funded by donations, honoraria and consultancy fees (for the provision of advice relating to the lived experience of PNH). PNH Support has received small grants from pharmaceutical companies in the past.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	**Alexion AstraZeneca Rare Diseases (danicopan eculizumab, ravulizumab)** 01.09.23 - £190 - providing a patient advocate perspective on trial design **Swedish Orphan Biovitrum (pegcetacoplan)** 30.09.22 - £948.75 - providing patient advocate perspective on: developing symptom app; ethnographic research into PNH burden of illness; and patient survey **Alexion AstraZeneca Rare Diseases, Roche (crovalimab)** and **Swedish Orphan Biovitrum** (pegcetacoplan) contributed to funding for a National Community Survey project which surveyed 7 rare disease communities including PNH Support. The report of this survey called 'Rare Voices" can be found here **Novartis (iptacopan)** 14.11.23 - £501.50 - advice provided regarding market research study, patient advisory board content

amount, and purpose of funding.	15.08.23 - £619.50 - providing patient advocate perspective as part of the Novartis Global Oncology Patient Involvement Panel (GOPIP) on awareness raising campaign, preparation for a September 2023 patient advisory board, working together 06.06.23 - £737.50 - providing patient advocate perspective re discussing awareness raising campaign; proposed patient engagement plans 30.06.23 - £236.00 - providing patient advocate perspective re advice on sharing trial results and patient engagement strategy 30.01.23 - £236.00 - discussion of patient engagement strategy **Roche Products (crovalimab)** 25.05.23 - £1,125.00 - preparation, attendance and follow up for 2 day patient advisory board 09.11.23 - £750.00 - attending patient advisory board meeting
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	On 23 October 2023 PNH Support made a patient/carer submission for appraisal ID 6176 which provided responses to these questions in relation to 75 patients and 19 carers. Due to survey fatigue we chose not to survey the wider population again so soon after the last survey and therefore only requested those patients and carers treated with danicopan or crovalimab (as the NICE crovalimab appraisal is also soon approaching) to complete another survey. We refer you to the responses provided in our submission for ID 6176 in relation to living with PNH, unmet needs and views on current treatment and care (see **attached)**. This online survey (comprising primarily multi-choice questions) of PNH patients and carers across England and Wales who had been treated with danicopan or crovalimab was disseminated via: email to PNH Support members; posts on our closed Facebook group; email by the PNH National Service (Kings College Hospital, London) to patients for which they held email addresses; and email by the PNH National Service (St James's Hospital, Leeds) to patients treated with these drugs. Five respondents were patients treated with danicopan and one was from carer of a patient treated with danicopan. All are living in England. **Ethnicity:** 100% of danicopan respondents identified as **"**English / Welsh / Scottish / Northern Irish / British"

	Gender: All 4 patients treated with danicopan are female and the one carer is also female. **Age:** The average age of patients treated with danicopan who completed the survey was 52. The age of the carer who completed the survey was 64.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Respondents were asked to describe what life is like for them to currently live with PNH where they could choose more than one multi-choice answer. **Patients (n=4)** • 3/4 chose "Travelling is difficult due to treatment restrictions"; • 3/4 chose "My (or their) veins are damaged because of repeated cannulation from infusions"; • 2/4 chose "I need to restrict my everyday activities because of PNH"; • 2/4 chose "There is a lack of understanding of PNH by non-PNH specialists which impacts me negatively"; • 2/4 chose "PNH has a negative impact on my family and social life"; • 1/4 chose "Living with (or caring for someone with) PNH has a minimal impact on my life"; • 1/4 chose "My (or the person I care for's) PNH is managed well"; • 1/4 chose "I have a fear of getting infections (or the person I care for getting them) which will make PNH worse"; • 1/4 chose "I consider myself to have a normal quality of life"; **In terms of symptoms**, patients were asked if they experienced any PNH symptoms and to select as many which were listed as they wished and/or to provide their own. • 2/4 experience "fatigue (e.g. exhaustion, limited energy, heaviness in limbs)". All patients were then asked to rate their fatigue with 1 being not fatigued at all and 10 being severely fatigued (to which 3/4 patients provided ratings) with the average rating being 7. • 2/4 experience "yellow pigmenting in eyes due to jaundice"; • 2/4 experience "anaemia requiring blood red blood cell transfusions"; • 1/4 experience "shortness of breath (difficulty breathing or breathlessness)" • 1/4 experience "cognitive problems (e.g. memory problems, brain fog, problems concentrating, difficulty focusing on tasks)". The patient was then asked to choose what cognitive problems they experience or to provide their own to which they chose "problems concentrating" and "Word finding difficulties" • 1/4 experience "hair loss"; • 1/4 experience "blood clot/s"; • 1/4 experience "dark urine (haemoglobinuria)"; **Carer (n=1)** In response to being asked to describe what life is like to care for someone with PNH where they could choose more than one multi-choice answer, the one carer respondent chose: "My (or the person I care for's) PNH is managed well;" and "Living with (or caring for someone with) PNH has a minimal impact on my life"; and "I have a fear of getting infections (or the person I care for getting them) which will make PNH worse"; and they included the following comment "*I constantly worry about my daughter's health and what might happen in the future.*" The carer also commented *"I am constantly concerned for my daughter's health and wellbeing and would like more reassurance that she will be ok - I'm sure she will but as a parent you can't help but worry. And I would like her not to have*

	to rely on infusions but at least it is a treatment and we are eternally grateful to the NHS for funding her treatment. Thank the lord for the NHS - where would we be if we had to pay for this treatment?"

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**Current Treatments – Patients (n=4)** When patients were asked what they thought of the current PNH treatments available on the NHS (where they could choose more than one answer and/or provide their own): • 4/4 chose "The opportunity to take part in clinical trials is an advantage"; • 3/4 chose "I would like there to be more treatment options with different delivery methods e.g. injections, tablets etc". • 2/4 patients chose "I am satisfied with the currently available treatments". However, 1/2 patients who chose this response also chose they would like there to be treatment options with different delivery methods and treatments which provide better quality of life • 1/4 chose "I would like there to be more treatment options which provide me with better quality of life (less symptoms etc)"; • 1/4 chose "I am neither satisfied nor dissatisfied with the current treatment options"**;** **Current Treatments – Carer (n=1)** When the one carer respondent was asked what they thought of the current PNH treatments available on the NHS (where they could choose more than one answer and/or provide their own) they chose the following: • "I would like there to be more treatment options with different delivery methods e.g. injections, tablets etc"; and "I would like there to be more treatment options which provide me with better quality of life (less symptoms etc)"; and "The opportunity to take part in clinical trials is an advantage". **Current Care - Patients (n=4)** Care provided by the PNH National Service and care provided by the NHS (outside the PNH National Service) was asked about separately. When patients were asked to choose what they thought of the current care available for PNH **from the PNH National Service** from a Likert scale with 5 options, all 4 chose "Very satisfactory"; When patients were asked to choose what they thought of the current care available from the NHS for PNH **outside the PNH National Service** e.g. GPs, local haematologists (not part of the PNH National Service), other healthcare professionals: • 1/4 chose "Somewhat Satisfactory"; • 1/4 chose "Neither satisfactory nor unsatisfactory"; • 1/4 chose "Somewhat unsatisfactory" • 1/4 chose "Very unsatisfactory"; **Current Care – Carer (n=1)** When the carer respondent was asked to choose what they thought of the current care available for PNH **from the PNH National Service** from a Likert scale with 5 options, they chose "Very satisfactory";

	When the carer was asked to choose what they thought of the current care available from the NHS for PNH **outside the PNH National Service** e.g. GPs, local haematologists (not part of the PNH National Service), other healthcare professionals they chose “Somewhat satisfactory”.
8. Is there an unmet need for patients with this condition?	When patients were asked to choose what they thought their unmet needs were (where an "unmet need" was described as something that is not addressed by current NHS care or available treatments) and to choose all responses that applied and were relevant to them: • 4/4 chose “Lack of education of healthcare professionals about PNH”. When asked what other support respondents would like to be able to live well with PNH or better care for someone with PNH, one patient commented “*More local awareness and understanding, with trained staff*” and another commented “*More local understanding.*” We note that “local” refers to regional care provided to patients outside the two PNH National Services centres at St James’s Hospital, Leeds and Kings College Hospital, London. • 4/4 chose “The impact of repeated cannulation (vein access) for treatment with infusions”; • 3/4 chose “There is a need for more treatment choices”. When asked what other support respondents would like to be able to live well with PNH or better care for someone with PNH, one patient commented “*The new drugs being trialled and hopefully approved will change the life's of PNH patients*.” • 3/4 chose “The burden of treatments with infusions”; • 1/4 chose “Negative side effects from treatment”;

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The 4 patient respondents treated with danicopan were asked what they thought the advantages of the treatment were (where they could choose more than one answer and/or provide their own): • 4/4 chose "The delivery method of this treatment (i.e. tablet)". One commented "*Tablets instead of infusions is life changing."* • 2/4 chose "It has improved my PNH symptoms". One patient commented: "*No longer transfusion dependent*". • 2/4 chose "The ability to travel with the medication"; • 2/4 chose "It has a positive impact on my ability to work or undertake education". Two patients were able to return to full time work and two were retired. • 1/4 chose "It has a positive impact on my family and social life"; • 1/4 chose "It has a positive impact on my mental health"; One patient commented "*Overall the experience has been pretty positive. It has been a long process but has become second nature.*" The one carer chose the following response as an advantage: "The delivery method of this treatment (i.e. tablet)*."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The 4 patients respondents treated with danicopan were asked what they thought the **disadvantages of the treatment** were (where they could choose more than one answer and/or provide their own): • 3/4 chose "There are no disadvantages"; • 1/4 chose "The number of times the danicopan tablets need to be taken per day is a disadvantage" Carer - The one carer respondent said a disadvantage was *"The rigidity of the timing of taking the tablets"* and *"It dominates her life in as much as the time for taking the tablet is strict - this would improve greatly if it could be taken only twice a day. If it could be taken without infusion it would be fantastic for her".*

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who experience clinically significant extravascular haemolysis and associated symptoms (including anaemia requiring blood transfusions) whilst being treated with a C5 inhibitor will benefit from danicopan as an add-on therapy to address their extravascular haemolysis, especially those who don't wish to be treated with the available sub-cutaneous C3 inhibitor treatment pegcetacoplan.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are not aware of any equality issues.

Other issues

13. Are there any other issues that you would like the committee to consider?	**Employment status** When asked about whether their employment status was affected by having PNH (or by caring for someone with PNH), all 4 patients said their work status was not affected by having PNH (2/4 were retired and 2/4 work full time). The carer commented they "*take time off to accompany my daughter to her appointments*". When asked if since they (or the person they cared for) started treatment with danicopan ,whether statements about working, studying or providing care for dependants were true for them: • 2/4 patients chose "I can now work full time"; • 2/4 said "Not applicable e.g. I am retired" (it is noted that 2 patients are retired) We are aware that the EQ 5D-5L questionnaire asks patients about their ability to undertake "usual activities (e.g. work, study, housework, family or leisure activities)". The way this question is worded won't necessarily capture patients who have not been working or studying or caring for dependants as these activities would not be considered usual for them. This therapy will present a cost saving to the: • public purse for patients who (as a result of the impact of this treatment which addresses clinically significant extravascular haemolysis as well as intravascular haemolysis) are now able to work, work more, study or care for dependants. • NHS by reducing the time and costs needed to manage, care for and treat patients whose symptoms resulting from clinically significant extravascular haemolysis (not addressed by a C5 inhibitor alone) have improved as a result of this therapy (including those who no longer need blood transfusions).

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• **Despite available treatments, living with PNH involves restricting everyday activities including travelling, damaged veins and negative impacts on family and social life. Fatigue is a symptom which most patients still live with:** 50% (n=2/4) of patients from this survey still experience fatigue with an average fatigue rating of 7/10 (with 1 being not fatigued at all and 10 being severely fatigued). Our previous survey for appraisal ID 6176 showed that 83% (n=62/75) patients still experience fatigue with an average fatigue rating of 6/10. • **100% (n=4/4) of patients said their unmet needs were: lack of education of healthcare professionals about PNH; the impact of repeated cannulation (vein access) for treatment with C5 inhibitor infusions; and the need for more treatment choices**. 75% (n=3/4) patients said their unmet need was the burden of treatments with infusions. 75% (n= 3/4) of patients and the carer respondent also said they wanted **more treatment options with**

	different delivery methods e.g. injections, tablets etc. Although this sample size is small, our survey for appraisal ID6176 identified that 61% (n=46/75) of patients and 63% (n=12/19) of carers said they would like more treatment options with different delivery methods. That survey also showed that 45% (n=34/75) of patients and 47% (n=9/19) of carers said they would like there to be more treatment options which provide patients with better quality of li**fe** (less symptoms etc). **Licencing of danicopan as an add-on tablet therapy to C5 inhibitor infusions will not address the unmet needs caused by the burden and impact of infusions however** it could provide those with clinically significant extravascular haemolysis (following treatment with a C5 inhibitor) with improved quality of life (as a result of less symptoms) via a convenient delivery method i.e. tablet. Danicopan's possible use as a monotherapy in future would address the burden of infusions and the need for more treatments with different delivery methods or which provide better quality of life. • **All patient respondents treated with danicopan (n=4/4) identified its main advantage to be the delivery method i.e. tablet**. 50% (n=2/4) said: it had improved their PNH symptoms; that the ability to travel with the medication was an advantage; and it had a positive impact on their ability to work or undertake education. 75% (n= 3/4) said there were no **disadvantages** with 25% (n= 1/4) saying the number of times the tablets had to be taken per day (i.e. 3 times) was a disadvantage. • **50% (n=2/4) of patient respondents treated with danicopan are now able to work full time** (2/4 patient respondents are retired). Employment means patients can contribute more fully to society and can rely less on the State and their families leading to increased independence and quality of life. • Although the burden of PNH has been mitigated significantly in many patients by intravenous treatments with C5 inhibitors, some patients still remain affected by clinically significant extravascular haemolysis including anaemia requiring blood transfusions (n=2/4 patient respondents in this survey still need blood transfusions). These patients have the potential to benefit from danicopan in order for them, and their families, to experience an improved quality of life with an add-on therapy to **address their extravascular haemolysis via a less invasive delivery method** (i.e. tablet). **The NHS will also benefit from reduced costs in treating those with clinically significant extravascular haemolysis** and the ability for patients to work as a result of this treatment allows them to be contributing members of society, including as taxpayers.

Thank you for your time.
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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Danicopan with a C5 inhibitor for treating paroxysmal nocturnal haemoglobinuria with extravascular haemolysis [ID5088]

NHS organisation submission

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and Social Care and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Social Care and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name	[redacted]
Name of your organisation	National PNH Service
Please indicate your position in the organisation	Department of Health and Social Care or Welsh Government in general? • A specialist in the treatment of people with the condition for which NICE is considering this technology: I am [redacted] at the Leeds PNH centre which is one of the 2 commissioned centres for treating patients with PNH.
Do you have any links with, or funding from, the tobacco industry? Please declare any direct or indirect links to, and receipt of funding from the tobacco industry	No.

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the	The current standard of care is to treat patients with PNH with the complement inhibitors ravulizumab or eculizumab. These therapies have been shown to reduce morbidity and mortality in the disease. However the majority of patients remain anaemic on these treatment (~80%) and a proportion of patients (~25%) continue to require blood transfusions to help with the fatigue they are experiencing. The addition of danicopan to either eculizumab or ravulizumab has been shown to improve anaemia and reduce the requirement for transfusions. There is no geographical variation in current practice. All patients are managed by a small number of specialists at one of 2 centres and the treatment of patients is the

current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?	same at these centres. The current alternative to this proposed treatment is pegcetacoplan. Patients who remain anaemic on a stable dose of eculizumab or ravulizumab are eligible to switch therapy to pegcetacoplan which is given as a twice a week subcutaneous infusion and has been shown to improve anaemia in this patient group. Both danicopan and pegcetacoplan have shown efficacy and a reasonable safety profile in clinical trials. Patients have to be trained to self administer pegcetacoplan at home. For Danicopan and eculizumab or ravulizumab, patients would need to take danicopan three times a day (orally) as well as continuing their intravenous eculizumab (every 2 weeks) or intravenous ravulizumab (every 8 weeks). Another therapy being considered by NICE is iptacopan. This is an oral monotherapy and if approved would be an alternative to using danicopan and a C5 inhibitor.
To what extent and in which population(s) is the technology being used in your local health economy? **Is there variation in how it is being used in your local health economy?** **Is it always used within its licensed indications? If not, under what circumstances does this occur?** **What is the impact of the current use of the technology on resources?** **What is the outcome of any evaluations or audits of the use of the technology?** **What is your opinion on the appropriate use of the technology?**	We are currently only using danicopan in a trial setting. If approved it would only be used in its licensed indications.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?	
In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?	If approved danicopan should only be available for use from the PNH specialist centres. There would not be a requirement for additional resources.
Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).	No. Issues to consider: As danicopan is not a monotherapy the main issue is that of cost. The cost of the therapy would be in addition to that of eculizumab or ravulizumab. The phase 3 ALPHA study (NCT04469465) presented at the European Hematology Association meeting in 2023 showed an improvement in haemoglobin with the addition of danicopan after 12 weeks of therapy of 2.94g/dl. 83.3% of patients treated with danicopan remained transfusion independent compared to 38.1% who received placebo. This would reduce the need for patients to receive transfusions as well as increasing their quality of life due to the improvement in their haemoglobin.
Would implementing this technology have resource implications for other services (for example, the	No.

trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?	
Would there be any need for education and training of NHS staff?	No.

Equality

Please let us know if you think that this appraisal: **Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licenced** **Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology** **Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.**	No.
Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.	You need to review the clinical trial data on danicopan.

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Other issues

Please include here any other issues you would like the appraisal committee to consider when appraising this technology	

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NICE National Institute for Health and Care Excellence

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes

	Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England is funded by the DHSC
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There is existing NICE Guidance for the use of ravulizumab and pegcetacoplan. Eculizumab is commissioned by NHS England to treat PNH. Crovalimab and Iptacopan are both subject to NICE ongoing appraisal.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined. There are two centres commissioned to provide treatment for this cohort of patients who work collaboratively. There are no differences of opinion relating to the care pathway.
8. What impact would the technology have on the current pathway of care?	It would provide an alternative for pegcetacoplan, for both existing and new patients. As this technology is an oral therapy and the other treatments are infusions, this technology would be a major improvement in the patient experience.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	There are some patients who have been in a clinical trial relating to this intervention, but it is not currently commissioned by NHS England
10. Will the technology be used (or is it already used) in the same way	The technology would be used in the treatment pathway for PNH as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia". It would be positioned in-line with pegcetacoplan.

as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	The technology is an oral treatment so uses less health care resources to administer than the current infusion pathway.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology would only be available through the two commissioned tertiary services.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No new investment is required.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Patients would need to meet the service treatment thresholds and treatment commencement is confirmed by the MDT. No additional testing is required. The clinicians are best placed to provide the detail.
11. What is the outcome of any evaluations or audits of the use of the technology?	This drug is not routinely commissioned, there are no NHS audits as far as the commissioners are aware.

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	This is an oral therapy which means it would be easier for patients with needle phobias and who have compromised venous access to comply with treatment.
12b. Consider whether these issues are different from issues with current care and why.	The current treatment options are infusions which are invasive and time consuming for patients.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with paroxysmal nocturnal haemoglobinuria or caring for a patient with paroxysmal nocturnal haemoglobinuria. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Patient expert statement

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Patient expert statement

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with paroxysmal nocturnal haemoglobinuria

Table 1 About you, paroxysmal nocturnal haemoglobinuria, current treatments and equality

1. Your name	Kate Monan
2. Are you (please tick all that apply)	☒ A patient with paroxysmal nocturnal haemoglobinuria? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with paroxysmal nocturnal haemoglobinuria? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	PNH Support
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with paroxysmal nocturnal haemoglobinuria? **If you are a carer (for someone with paroxysmal nocturnal haemoglobinuria please share your experience of caring for them**	I was diagnosed in 2017 after a weeklong stay in hospital. It left me quite jaundice and tired, but as I was a University student at the time didn't take my notice of my symptoms. I often suffer with tiredness but don't often experience pain and am able to work full time and have an active social life.
7a. What do you think of the current treatments and care available for paroxysmal nocturnal haemoglobinuria on the NHS? If you are able to, please also comment specifically on current treatments and care available on the NHS for people with paroxysmal nocturnal haemoglobinuria with residual haemolytic anaemia/extravascular haemolysis. **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I think we are fortunate to have the treatments that are available given the rare nature of the disease and very much prefer being able to have the 8 weekly Ravulizumab alongside the opportunity to be part of the trial. The tablets have really given me to ability to live comfortably and have a life very similar to someone without the condition. The care from the teams I have seen has been fantastic and I really appreciate having people to speak to who have knowledge on the disease. I am unsure of comparative views as I haven't spoken to many patients who are on different treatments directly. But do believe that many people enjoy being able to have treatment to achieve a good quality of life.
8. If there are disadvantages for patients of current NHS treatments for paroxysmal nocturnal haemoglobinuria (for example, how they are given or taken, side effects of treatment, and any others)	I believe one disadvantage is the time involved in having infusions. I like the fact that tablets allow me to continue my day with less intrusion, without having to put too much thought into my condition compared to having an infusion. I am fully grateful for the infusions ability to let me live a comfortable life but believe the

please describe these. If you are able to please also comment specifically on the disadvantages for patients of current NHS treatments for paroxysmal nocturnal with residual haemolytic anaemia/extravascular haemolysis.	tablets do give me a more continuous level of good health without the drops in levels of energy that come with the infusions. I personally don't seem to suffer major side effects to my treatments, other than the occasional haemolysis (along with headaches and joint aches) but am able to manage this myself fairly easily with paracetamol.
9a. If there are advantages of danicopan as an add-on to a C5 inhibitor over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does danicopan as an add-on to a C5 inhibitor help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	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. I feel I have answered 9c in question 8.
10. If there are disadvantages of danicopan as an add-on to a C5 inhibitor over current treatments on the NHS please describe these. For example, are there any risks with danicopan? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I find the rigidity of taking the tablets a slight disadvantage as I find with the later dose, I can often feel unwell if I take them too long after the designated time. As mentioned in question 8, I find I can suffer headaches and joint aches but am able to manage this with paracetamol quite easily. Personally, I also find it tricky to keep to the times if I feel tired or have social plans where I have to consider being able to take them.
11. Are there any groups of patients who might benefit more from danicopan as an add-on to a C5 inhibitor or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility,	I am not sure I am able to answer this question.

dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering paroxysmal nocturnal haemoglobinuria and danicopan? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I am not sure I am able to answer this question.
13. Are there any other issues that you would like the committee to consider?	I believe tablets as a form of treatment gives much greater freedom as it reduces the need for patients to rely on healthcare services to provide intravenous care, allowing us to live a good quality of life and not feel controlled by the disease.

Patient expert statement

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I believe the tablets alongside the infusion give me a better quality of life.
- The advancements in treatments available to PNH patients has been fantastic.
- I can work full time and have an active social life whilst on both infusions and danicopan.
- Even though I occasionally find I suffer with headaches and joint pains the benefits of the tablets out way the negatives.
- I feel the advancement in tablet forms of medication will provide greater freedoms to PNH patients giving them more independence.

Thank you for your time.

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Single Technology Appraisal

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

Patient expert statement

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Patient expert statement

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Patient expert statement

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with paroxysmal nocturnal haemoglobinuria

Table 1 About you, paroxysmal nocturnal haemoglobinuria, current treatments and equality

1. Your name	Maria Piggin
2. Are you (please tick all that apply)	☒ A patient with paroxysmal nocturnal haemoglobinuria? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with paroxysmal nocturnal haemoglobinuria? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	PNH Support
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) **x**☐ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with paroxysmal nocturnal haemoglobinuria? **If you are a carer (for someone with paroxysmal nocturnal haemoglobinuria please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for paroxysmal nocturnal haemoglobinuria on the NHS? If you are able to, please also comment specifically on current treatments and care available on the NHS for people with paroxysmal nocturnal haemoglobinuria with residual haemolytic anaemia/extravascular haemolysis. **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for paroxysmal nocturnal haemoglobinuria (for example, how they are given or taken, side effects of treatment, and any others) please describe these. If you are able to please also comment specifically on the disadvantages for patients of current NHS treatments for paroxysmal	

nocturnal with residual haemolytic anaemia/extravascular haemolysis.	
9a. If there are advantages of danicopan as an add-on to a C5 inhibitor over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does danicopan as an add-on to a C5 inhibitor help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of danicopan as an add-on to a C5 inhibitor over current treatments on the NHS please describe these. For example, are there any risks with danicopan? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from danicopan as an add-on to a C5 inhibitor or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering paroxysmal	

nocturnal haemoglobinuria and danicopan? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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Single Technology Appraisal

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

Clinical expert statement

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NICE National Institute for Health and Care Excellence

Part 1: Treating PNH and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Talha Munir
2. Name of organisation	St James's Hospital, Leeds, UK
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with PNH? ☒ A specialist in the clinical evidence base for PNH or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No
8. What is the main aim of treatment for PNH? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To control intravascular haemolysis, prevent thrombotic complications and end organ damage such as renal impairment, pulmonary hypertension in PNH patients. For patients on C5 inhibitor such as Ravulizumab or Eculizumab, an

	important consideration is control of clinically significant extravascular haemolysis
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduction in red cell transfusion, improved quality of life, improvement in laboratory parameters suggestive of extravascular haemolysis
10. In your view, is there an unmet need for patients and healthcare professionals in PNH?	Whilst C5 inhibitors benefit most PNH patients, there is a significant proportion of patient with extravascular haemolysis on C5 inhibitors. For this group of patients, this is clearly an unmet need
11. How is PNH currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	As PNH is a nationally commissioned service, there are national PNH service guidelines which are followed stringently. The pathway is very clear and there is a total of 8 UK and 1 Scottish consultant discussing all cases in the national MDT. There is mostly a consensus amongst national PNH experts as all patients starting PNH directed therapy will be discussed in the national MDT. Current technology appraisal will add to the current pathway of care, but this pathway is robust in my view.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	There is not a lot of difference in the healthcare resource. As C5 inhibitors are already used, the main addition would be incorporation of Danicopan as an add on therapy which can be delivered by home care team. This still has to be a specialist clinic generated prescription.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I believe that it will improve quality of life for the patients. However, it is not possible to comment on the length of life more than current care. PNH patients have now got a normal life expectancy apart from patients with concurrent bone marrow failure hence it would be difficult to expect the length of life extending further.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The only issue would be compliance with oral tablets as Danicopan needs to be taken three time a day. However, the benefit of the add on therapy is that C5 inhibitors will always be in the background.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	All PNH patient exhibiting extravascular haemolysis have routine tests done which are already well established. All cases are discussed in the national MDT. I don't think that any additional testing is needed.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	As this is an add on oral therapy without change in C5 inhibitor therapy, I don't believe that there was any major change in technology appraisal is needed.

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, I believe that there will be improvement in health-related benefits. There is potential reduction in transfusion requirement, reduced need for iron chelation, reduced hospital visits for transfusion.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, they do. As PNH is a rare disease, the patients participating in the clinical trials reflect the real-world experience.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	TA11132 In process at present

23. How do data on real-world experience compare with the trial data?	It is comparable to real world experience
Add any topic-specific questions here and renumber	N/A
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	N/A, I believe there is equity build in the delivery of PNH directed therapy

Find more general information about the Equality Act and equalities issues here.	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Danicopan as an add on therapy to C5 inhibitors is valuable to control extravascular haemolysis.

The add on therapy is likely improve quality of life for PNH patients.

The add on therapy is unlikely to have impact on survival.

It would be a useful additional therapy for PNH patients.

All PNH cases are discussed on national MDT so equity of care is likely to be maintained.

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Single Technology Appraisal

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

Clinical expert statement

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NICE National Institute for Health and Care Excellence

Part 1: Treating residual haemolytic anaemia in adults with paroxysmal nocturnal haemoglobinuria and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	
2. Name of organisation	
3. Job title or position	
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with paroxysmal nocturnal haemoglobinuria? ☐ A specialist in the clinical evidence base for paroxysmal nocturnal haemoglobinuria or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

8. What is the main aim of treatment for adults with paroxysmal nocturnal haemoglobinuria who have residual haemolytic anaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in the treatment of adults with paroxysmal nocturnal haemoglobinuria who have residual haemolytic anaemia?	
11. How is paroxysmal nocturnal haemoglobinuria currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 778 [TA778]?	No however there is another comparator treatment (Iptacopan) being assessed by NICE. GID-TA11132. There was longer Pegcetacoplan data presented at American society of hematology meeting 2023.
23. How do data on real-world experience compare with the trial data?	The real-world experience is like the trial data.
24. Can the populations "patients with PNH who have residual haemolytic anaemia" and "patients with PNH who have signs and symptoms of extravascular haemolysis" be considered the same from a clinical standpoint?	Yes, if the word residual haemolytic anaemia is used after ensuring that intravascular haemolysis is well controlled on C5 inhibitor
25. NICE has heard from the company that there is no established definition of clinically significant extravascular haemolysis in NHS clinical practice. **In your opinion, how would a patient's eligibility to receive danicopan for clinically significant extravascular haemolysis be determined in NHS clinical practice?** **In the Alpha trial, inclusion criteria includes haemoglobin ≤9.5 g/dL with ARC ≥120 × 10^9/L. How representative are the Alpha trial patient population of patients that you expect would expect to receive danicopan in NHS clinical practice?**	The definition differs and very much depends on individual PNH patient. In clinical context, the definition used in clinical trials have varied. For example, in PEGASYS trial the cut-off of 10.5 g/dl was used but reticulocytes count needed to be >1.0 times upper limit normal. It is hard to define as different trial use different cut offs. Symptomatic patients with EVH would have symptomatic anaemia (regardless of Hb level) with raised reticulocyte count and mildly raised bilirubin. In my opinion, Alpha trial patients did represent this group of patients.

26. For people with residual anaemia following treatment with a C5 inhibitor (C5i), what are the potential treatment options? **Would remaining on C5i monotherapy be an option?**	Yes, C5 inhibitor is reasonable but the patients will have poor QOL with different needs for transfusion support. Potential treatment options would be Pegcetacoplan, Iptacopan (Compassionate access programme) and proximal inhibitor clinical trials,
27. In NHS clinical practice, for patients who discontinue danicopan + C5i (due to reasons such as AEs), what proportion of patients do you expect will switch to • **C5i monotherapy** • **Pegcetacoplan** • **Other (please state)?**	**C5i monotherapy- 30%** • **Pegcetacoplan -50%** • Other (please state)?- Clinical trials or compassionate access iptacopan if available (20%)
28. Do you expect there to be any difference in the rate of breakthrough haemolysis between patients receiving danicopan and a C5i compared with patients receiving with pegcetacoplan? **For patients who experience breakthrough haemolysis whilst receiving pegcetacoplan, would the dosage change from twice weekly? If so, what would be the dosage escalation regime?**	As Pegcetacoplan is single therapy, the breakthrough haemolysis with it is mainly intravascular haemolysis which is usually severe. If BTH was related to inciting factor such as infection or immune stimulated event (For e.g. vaccination), then dose is not increased forever but may be increased short term to cover the event. If there was no inciting factor, then dose would be increased to every 3 days as per SPC guidance.
29. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	No, I think that we provide good cover to all patients in UK.

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

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Part 1: Treating residual haemolytic anaemia in adults with paroxysmal nocturnal haemoglobinuria and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Richard Kelly
2. Name of organisation	NHSE commissioned National PNH service (Leeds and London)
3. Job title or position	Consultant Haematologist, PNH Joint Service Lead
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with paroxysmal nocturnal haemoglobinuria? ☒ A specialist in the clinical evidence base for paroxysmal nocturnal haemoglobinuria or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A.

8. What is the main aim of treatment for adults with paroxysmal nocturnal haemoglobinuria who have residual haemolytic anaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	PNH is a rare haemolytic and thrombotic condition. The main aim of treatment for PNH is disease control, to reduce life threatening complications, improve patient quality of life, and normalise life expectancy. Treatment with eculizumab (approved in 2007) and latterly ravulizumab has enabled the service to treat patients, achieving the majority of the above aims, however patients develop extravascular haemolysis, which can affect quality of life and productivity. Both the above treatments are administered intravenously.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	PNH disease control, with cessation of intravascular haemolysis and prevention of thrombosis. This is assessed clinically, and with a lactate dehydrogenase and haemoglobin response as well as patient symptoms. For proximal complement inhibition, clinically significant response including the above, but also include an improvement in haemoglobin of >2g/dl, and a reduction in blood transfusion requirement.
10. In your view, is there an unmet need for patients and healthcare professionals in the treatment of adults with paroxysmal nocturnal haemoglobinuria who have residual haemolytic anaemia?	If patients develop extravascular haemolysis with anaemia +/- a transfusion requirement, this significantly affects patient quality of life, and they have the option of pegcetacoplan, a subcutaneous twice a week infusion treatment. However, some patients have needle aversion, or do not response to pegcetacoplan. It also makes travel more complicated due to transportation needles, infusion device and drug. The unmet needs are: Extravascular haemolysis causing anaemia, ongoing transfusion requirement and fatigue. This is a significant issue for patients with PNH, leading to a reduction in work productivity and affecting family life.
11. How is paroxysmal nocturnal haemoglobinuria currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	Clinical guidelines are nationally agreed treatment indications which are reflected also in centres worldwide https://pnhserviceuk.co.uk/healthcare-professionals/indications-for-treatment-with-eculizumab-ravulizumab-and-pegcetacoplan/

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The pathway is well defined and does not vary from the 2 centres (Leeds and London). All patients with significant PNH are also discussed at a monthly MDT. Depending on approval indications, the PNH service would use in complement inhibitor treated patients with anaemia as an additional therapy to their C5 inhibitor. The option of pegcetacoplan therapy would also be discussed with the patient.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Healthcare resource will remain unchanged: Homecare nursing would still be required as danicopan is an oral therapy used in conjunction with C5 inhibitors which are administered intravenously. Clinical setting - Specialist clinics: PNH is an ultrarare condition, all patients should continue to be managed by the National PNH service, who have the expertise and experience in treating patients, advising about medication, and managing complications/infections if they arise. Investment: No investment should be required from the NHS, the PNH service is well established. Patients already attend clinic and treatment options are discussed regularly as part of a clinic consultation.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Current treatment with eculizumab or ravulizumab has been shown to increase length of life. The addition of danicopan to C5 inhibition is not likely to increase length of life further but will significantly increase health-related quality of life when compared to current care. ALPHA trial findings (Lee et al., Lancet Haematol. 2023 Dec;10(12):e955-e965.): Danicopan as add-on treatment to ravulizumab or eculizumab significantly improved haemoglobin concentrations at week 12 with no new safety concerns,

	suggesting an improved benefit-risk profile in patients with PNH and clinically significant extravascular haemolysis. 73 patients with PNH were enrolled in the study between Dec 16, 2020, and Aug 29, 2022. At week 12, danicopan plus ravulizumab or eculizumab increased haemoglobin versus placebo plus ravulizumab or eculizumab change from baseline: danicopan, 2·94 g/dL [95% CI 2·52 to 3·36]; placebo, 0·50 g/dL [-0·13 to 1·12]; LSM difference, 2·44 g/dL [1·69 to 3·20]; p<0·0001). As well as the improvement in haemoglobin there was a significant reduction in transfusion requirements and a significant reduction in fatigue as assessed by the FACIT-fatigue score.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It will be the same. Danicopan is an additional oral medication. Patients will still require the same homecare management for administration of their C5 inhibitor. Standard monitoring of bloods when starting a new treatment will be undertake: A FBC and LDH 2-3 weeks after treatment.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting treatment will depend on approved indications. Stopping treatment: If patients have remitted their PNH clone to <10% treatment will be stopped (5% of patents over several years). Other situations would be a change of treatment rather than stopping complement inhibition and would include side effects, or non-compliance

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	PNH is an ultra-rare disorder, with patients treated by an NHSE commissioned service. Pegcetacoplan, the only other approved proximal complement inhibitor is a subcutaneous infusion twice a week. When on holiday patients are required to take drug, infusion equipment with them, as well as requiring a fridge for storage which is quite inconvenient. Fatigue is experienced by a large proportion of patients with PNH secondary to anaemia due to extravascular haemolysis. This is often difficult to quantify in the current quality of life measures. Fatigue also reduce productivity of patients.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, it is innovative and will significantly improve the health of patients. Proximal complement inhibition in PNH is a step change in treatment and addresses an unmet need. Unmet need: Danicopan is a proximal complement inhibitor and prevents extravascular haemolysis which is a phenomenon of treatment with C5 inhibition. With the addition of danicopan to C5 inhibition haemoglobin increases to near normal/normal enables patients to improve their quality of life and productivity.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Danicopan side effects from the ALPHA trial: Deranged liver function tests (4), leukopenia (2%), neutropenia (4%), cholecystitis (2%), COVID-19 (2%), and increased blood pressure (2%). There were no serious adverse events related to study drug or deaths reported in the study.

	Breakthrough haemolysis (BTH): this is when patients have a loss of complement inhibition and a recurrence of PNH symptoms. One benefit of being treated with a C5 inhibitor as well as danicopan is that if a patient is non-compliant with danicopan or unable to take an oral medication (such as during surgery) they will not experience intravascular haemolysis as they are still receiving a C5 inhibitor. Patients have 24 hour access to an on-call consultant within the PNH service, for advice in the event of becoming unwell/having BTH If patients develop BTH, a sudden haemoglobin drop and LDH rise may occur, causing patients to feel unwell. This is manageable by experienced clinicians and occurs with all complement inhibitors.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The PNH service (Leeds and Kings) have participated in danicopan clinical trials, with patients experiencing good responses. The general population of treated and untreated patients is reflected similar to trial entry criteria, and thus responses would be similar. The most valuable outcomes are control of intravascular haemolysis (LDH controlled) and improvement in haemoglobin and subsequent fatigue scores (FACIT-fatigue). These were measured in the ALPHA trial. There are no adverse effects that were not apparent in clinical trials but have come to light subsequently.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 778 [TA778]?	No.

23. How do data on real-world experience compare with the trial data?	In the UK we have no experience of real-world data on danicopan yet. All patients receiving danicopan within the service have so far been treated within clinical trials. However, we expect the same benefit to be observed in a real-world setting.
24. Can the populations "patients with PNH who have residual haemolytic anaemia" and "patients with PNH who have signs and symptoms of extravascular haemolysis" be considered the same from a clinical standpoint?	It depends on what you mean by "residual haemolytic anaemia" as intravascular haemolysis and extravascular haemolysis are different. If breakthrough haemolysis occurs this is intravascular haemolysis and needs immediate treatment and this would be different. I expect what is meant is extravascular haemolysis , so yes it can be considered to be the same.
25. NICE has heard from the company that there is no established definition of clinically significant extravascular haemolysis in NHS clinical practice. **In your opinion, how would a patient's eligibility to receive danicopan for clinically significant extravascular haemolysis be determined in NHS clinical practice?** **In the Alpha trial, inclusion criteria includes haemoglobin ≤9.5 g/dL with ARC ≥120 × 10^9/L. How representative are the Alpha trial patient population of patients that you expect would expect to receive danicopan in NHS clinical practice?**	There is no single test for extravascular haemolysis. We rely on the expert view of the PNH teams in London and Leeds to assess the cause of anaemia. Evaluation would include assessment of bone marrow function (including the blood count, reticulocyte count, bone marrow biopsy) as well as excluding non-haematological causes, assessing for intravascular haemolysis and checking for C3 loading on PNH red blood cells. The eligibility to receive danicopan for clinically significant extravascular haemolysis would be evaluated by a PNH expert from the National Service using the assessment parameters above. All clinical trials in PNH have cut off values relating to bone marrow failure. There will be individuals with PNH with significant extravascular haemolysis who are not as anaemic as those in the APLHA trial. I would hope/expect clinicians from the National Service to be allowed after assessing the patient as above to be able to prescribe danicopan as an add on treatment for patients with PNH with anaemia where extravascular haemolysis was felt to be causative.

26. For people with residual anaemia following treatment with a C5 inhibitor (C5i), what are the potential treatment options? **Would remaining on C5i monotherapy be an option?**	Not all patients with residual anaemia on C5 inhibition are symptomatic due to anaemia. If not symptomatic we would continue the patient on their C5 inhibitor as a monotherapy. If they are symptomatic especially if requiring transfusions and it appears to be due to extravascular haemolysis rather than bone marrow failure current treatment options are: Clinical trials of new proximal inhibitors. Pegcetacoplan monotherapy. Remaining on C5 inhibition with anaemia and it's symptoms (not ideal).
27. In NHS clinical practice, for patients who discontinue danicopan + C5i (due to reasons such as AEs), what proportion of patients do you expect will switch to • **C5i monotherapy** • **Pegcetacoplan** • **Other (please state)?**	We would not want to switch to C5i monotherapy as these patients were commenced on danicopan due to extravascular haemolysis. C5i monotherapy 20% Pegcetacoplan 30% Other (clinical trial) 10% Other (compassionate use iptacopan) 40%
28. Do you expect there to be any difference in the rate of breakthrough haemolysis between patients receiving danicopan and a C5i compared with patients receiving with pegcetacoplan? **For patients who experience breakthrough haemolysis whilst receiving pegcetacoplan, would the dosage change from twice weekly? If so, what would be the dosage escalation regime?**	The majority of patients on C5i in the UK are on ravulizumab. There appears to be less breakthrough haemolysis with ravulizumab than with eculizumab. There are no direct comparisons of rates of breakthrough haemolysis between C5i and danicopan vs pegcetacoplan but we expect there would be less breakthrough haemolysis with C5i and danicopan (especially with ravulizumab) given it is a combination of 2 complement inhibitors used. For breakthrough haemolysis on pegcetacoplan the dose of pegcetacoplan would be increased from twice a week to three times a week.
29. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	No. All patients with PNH are treated within the NSHE commissioned service equally. Danicopan clinical trials are for patient over the age of 18 and thus the paediatric cohort is not served by the current evidence. Approximately 14% of patients

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	with PNH are below the age of 18, and are currently treated with ravulizumab or within a clinical trial for pegcetacoplan. Pregnancy: Patients who are pregnant are currently not advised to take danicopan, due to limited toxicology data. Patients are currently and will continue to be managed with eculizumab.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

PNH is now a chronic disease once diagnosed in the UK, as C5 inhibition has near normalised life expectancy.

Unmet needs in PNH remain, in particular with extravascular haemolysis with fatigue. Whilst addressed with pegcetacoplan it is not suitable for all patients.

Danicopan has been shown to be effective in improving haemoglobin levels as an add on therapy to C5 inhibition in patients with PNH who are anaemic on C5 inhibition.

Danicopan is well tolerated with minimal side effects experienced.

Increasing treatment options empowers patients in their disease ownership and management.

Thank you for your time.

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

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Contributions of authors
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Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

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Executive summary

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

Section 0.1 provides an overview of the key issues. Section 0.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 0.3 to 0.6 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 EAG report (section 1 onwards).

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

0.1 *Overview of the EAG's key issues*

Table 1 contains a summary of the key issues identified by the EAG in their critique of the company submission.

Table 1: Summary of key issues

ID5088	Summary of issue	Report sections
1	Unclear definition for defining target population and implementation into NHS use	1.3
2	ALPHA trial: Data from interim analysis of incomplete trial population and potential lack of generalisability.	2.2
3	Insufficient information for meaningful comparison of danicopan + C5i to pegcetacoplan.	2.4
4	Use of differing transition probabilities for danicopan + C5i and pegcetacoplan	3.2.6.1
5	Subsequent therapy received after discontinuing danicopan + C5i	3.2.8.1
6	Uncertainty over long term discontinuation probabilities for danicopan and pegcetacoplan	3.2.8.1
7	Economic modelling corrections	3.2.8.6 and 3.2.8.7
8	Differing probability of BTH for danicopan + C5i and pegcetacoplan	3.2.8.7
9	Inconsistent pegcetacoplan dosing for breakthrough haemolysis.	3.2.8.7

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the company's preference to proceed with a naïve

comparison of the danicopan + C5i, whilst the EAG concludes it is not possible for a meaningful comparison to be performed and carried forward into the economic analysis.

0.2 *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 modelled to affect QALYs by:

- Having a lower rate of BTH events
- Having a means of administration that is not associated with a disutility

Overall, the technology is modelled to affect costs by:

- Having a different price and method of administration versus the comparator
- Having a lower rate of BTH events and different associated management costs

The modelling assumptions that have the greatest effect on the ICER are:

- The rate and management of BTH events
- The rate of treatment discontinuation

0.3 *The decision problem: summary of the EAG's key issues*

Issue 1: Unclear definition for defining target population and implementation into NHS use

Report section	Section 1.3
Description of issue and why the EAG has identified it as important	There is no established definition of clinically significant extravascular haemolysis. This means there is subjectivity in the eligibility for danicopan + C5i treatment in routine NHS use, and the ALPHA trial may not provide representative estimates of the real-world efficacy.
What alternative approach has the EAG suggested?	There are no alternative approaches available at present.
What is the expected effect on the cost-effectiveness estimates?	Unclear
What additional evidence or analyses might help to resolve this key issue?	If national guidelines and thresholds were established, then the data could be reanalysed accordingly.

0.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

Issue 2: ALPHA trial: Data from interim analysis of incomplete trial population and potential lack of generalisability.

Report section	Section 2.2
Description of issue and why the EAG has identified it as important	The majority of results provided come from the second interim analysis of the ALPHA trial, which consists of short-term follow-up for approximately 75% of the target sample size. Full results may reduce the uncertainty associated with key parameters of long-term efficacy in the economic model.
What alternative approach has the EAG suggested?	The EAG enquired about the availability of updated analyses for TP1 to include the full trial sample, which the final patient should have completed by December 2022 company. The company responded to say that a third interim analysis had been performed which included TP1 and TP2 for all trial participants, but this would not be made available as it was only conducted to address specific requests from regulatory agencies.
What is the expected effect on the cost-effectiveness estimates?	Potentially very large, as it could vary treatment efficacy and other model parameters.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends the company releasing additional analyses as mentioned above.

Issue 3: Insufficient information for a meaningful comparison of danicopan + C5i to pegcetacoplan.

Report section	Section 2.4
Description of issue and why the EAG has identified it as important	There is insufficient information for a meaningful comparison of danicopan + C5i to pegcetacoplan as the two trials have clearly different populations and the indirect comparisons performed do not offer any improvement.
What alternative approach has the EAG suggested?	The EAG is unable to obtain any reliable estimate of relative efficacy as the trial populations are too different. A comparison of danicopan + C5i to C5i avoids this issue and therefore could be considered be more appropriate
What is the expected effect on the cost-effectiveness estimates?	Potentially very large, as it could affect which treatment is associated with more QALYs. The ICER in comparison to C5i is very different to the company's comparison to pegcetacoplan.
What additional evidence or analyses might help to resolve this key issue?	A new randomised controlled trial comparing danicopan + C5i to pegcetacoplan would be required to generate the required evidence. The company could also try a simulated treatment comparison.

0.5 *The cost-effectiveness evidence: summary of the EAG's key issues*

Issue 4: Transition probabilities

Report section	Section 3.2.6.1
Description of issue and why the EAG has identified it as important	The transition probabilities used by the company come from short term follow-up with limited sample sizes and are based on a naïve comparison.
What alternative approach has the EAG suggested?	As no reliable estimate of relative benefit can be obtained, the EAG does not present a base case analysis for the comparison to pegcetacoplan. However it presents analyses assuming equal efficacy believing these may be of interest to the committee.
What is the expected effect on the cost-effectiveness estimates?	Currently this has a relatively small impact on the cost-effectiveness, however this could be changed based on other model assumptions which affect the estimated cost and QALYs
What additional evidence or analyses might help to resolve this key issue?	Estimation of transition probabilities from longer follow-up from ALPHA would reduce some of the uncertainty. The company could provide transition probabilities from original or trimmed ALPHA population using 10.5g/dL cut-off. A new randomised controlled trial comparing danicopan + C5i to pegcetacoplan would be the ideal way to generate the required evidence.

Issue 5: Subsequent therapy received after discontinuing danicopan + C5i

Report section	Section 3.2.8.1
Description of issue and why the EAG has identified it as important	The company assume that people who discontinue danicopan + C5i will switch to C5i monotherapy. The EAG understands that it is more likely that these people would instead switch to pegcetacoplan.
What alternative approach has the EAG suggested?	The EAG has presented a case where 80% of people who discontinue danicopan + C5i incur the costs associated with 2 x weekly dose of pegcetacoplan. However the EAG was not able to adjust the transition probabilities for those who have discontinued or their treatment related disutility.
What is the expected effect on the cost-effectiveness estimates?	This has a large impact on the incremental costs, which could be more influential depending on other preferred assumptions
What additional evidence or analyses might help to resolve this key issue?	Long term follow-up from real world evidence would inform what is done in practice.

Issue 6: Uncertainty over long term discontinuation probabilities for danicopan and pegcetacoplan

Report section	Section 3.2.8.1
Description of issue and why the EAG has identified it as important	The company assume that no one will discontinue either pegcetacoplan or danicopan after week 52. Whilst there is minimal evidence on this, the company's own scenario analysis shows this to be extremely influential on the cost-effectiveness.
What alternative approach has the EAG suggested?	The EAG has presented a scenario on top of its other changes to the model, where a 1% discontinuation probability is applied in week 53 and beyond for both treatments.
What is the expected effect on the cost-effectiveness estimates?	This has a very large impact on the incremental costs.
What additional evidence or analyses might help to resolve this key issue?	Long term follow-up from real world evidence would inform more accurate estimation of this probability.

Issue 7: Economic modelling corrections

Report section	Sections 3.2.8.6 and 3.2.8.7
Description of issue and why the EAG has identified it as important	The company model contained the following three features which the EAG understand to be mistakes. - Duration of alanine aminotransferase for danicopan + C5i applied for 12 cycles rather than 12 weeks. - Probability of alanine aminotransferase for danicopan + C5i based on 3 people rather than 4 events. - Costs of C5i dose escalation associated with breakthrough haemolysis events on pegcetacoplan were applied for all BTH events rather than just for those associated with C5i therapy.
What alternative approach has the EAG suggested?	The EAG has corrected the errors associated with alanine aminotransferase duration and probability, and ensured that C5i accelerated dosing costs are only applied for BTH events for people who have discontinued pegcetacoplan and are receiving C5i.
What is the expected effect on the cost-effectiveness estimates?	The alanine aminotransferase corrections have a negligible impact. The other correction has a meaningful impact on the incremental costs, however this appears relatively small compared with some of the other key issues.
What additional evidence or analyses might help to resolve this key issue?	None, the EAG considers these resolved. Additional evidence on accelerated C5i dosing for people receiving pegcetacoplan may affect the final EAG correction.

Issue 8: Modelling of breakthrough haemolysis probabilities

Report section	Section 3.2.8.7
Description of issue and why the EAG has identified it as important	The probabilities used by the company come from a naïve comparison, despite clear differences in the underlying populations. These result in a much higher rate of breakthrough haemolysis (BTH).
What alternative approach has the EAG suggested?	The EAG present analyses assuming equal rate of BTH believing these may be of interest to the committee.
What is the expected effect on the cost-effectiveness estimates?	This has a large impact on the incremental costs, and is linked to the next key issue.
What additional evidence or analyses might help to resolve this key issue?	A new randomised controlled trial comparing danicopan + C5i to pegcetacoplan would be required to generate the required evidence of relative effect. Long term follow-up from real world evidence would inform what the future transition probabilities.

Issue 9: Modelling of costs associated with breakthrough haemolysis

Report section	Section 3.2.8.7
Description of issue and why the EAG has identified it as important	The company assume that over time the majority of people receiving pegcetacoplan will experience breakthrough haemolysis and be escalated to receiving 3 doses per week. This appears inconsistent with the approach taken in the appraisal for pegcetacoplan (TA778) which assumed dosing would be fixed at 2 per week.
What alternative approach has the EAG suggested?	The EAG has presented a scenario where BTH is assumed to be zero for danicopan and pegcetacoplan, removing this dose-escalation.
What is the expected effect on the cost-effectiveness estimates?	Very large. This also has implications for the cost-effectiveness of pegcetacoplan, as its costs are varying significantly.
What additional evidence or analyses might help to resolve this key issue?	Long term follow-up from real world evidence would inform what the true resource use is associated with BTH events for each intervention.

0.6 *Other key issues: summary of the EAG's view*

The EAG identified no further key issues.

0.7 *Summary of EAG's preferred assumptions and resulting ICER*

The EAG concludes that there is insufficient evidence to support any form of comparison of danicopan + C5i to pegcetacoplan, and do not present a base case. The EAG instead presents analyses correcting and extending the company's base case analysis (Table 2).

Table 2: Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's corrected base case (issue 7)	[redacted]	0.429	Dominant
EAG analysis with equal transition probabilities, subsequent pegcetacoplan and equal BTH long probability (issues 4, 5 and 8)	[redacted]	0.320	Dominant
EAG analysis with zero BTH events after week 16/24 (issue 9)	[redacted]	0.320	Dominant
EAG analysis with 1% long term discontinuation probability (issue 6)	[redacted]	0.151	[redacted]
EAG's preferred analysis (danicopan vs C5i; issue 3)	[redacted]	0.912	[redacted]

Modelling errors identified and corrected by the EAG are described in sections 3.2.8.6 and 3.2.8.7. For further details of the exploratory and sensitivity analyses done by the EAG, see sections 5.1 and 5.2.

Table 3: Acronyms and Abbreviations

AE	Adverse events
ALT	Alanine aminotransferase
BMI	Body mass index
BSA	Body surface area
BTH	Breakthrough haemolysis
C3i	C3 inhibitor
C5i	C5 inhibitor
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CS	Company Submission
csEVH	Clinically significant extravascular haemolysis
CSR	Clinical study report
EAG	External Assessment Group
EQ-5D	EuroQol five dimension
ESS	Effective sample size
EVH	Extravascular haemolysis
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
HSUV	Health State Utility value
HTA	Health Technology Assessments
IAS	Interim analysis set
ICER	Incremental Cost-Effectiveness Ratios
IPI	International Prognostic Index
IQR	Interquartile range
ITC	Indirect treatment comparisons
IVH	Intravascular haemolysis
KM	Kaplan-Meier
MAIC	Matching- adjusted indirect comparison
LDH	Lactate dehydrogenase
LY	Life Year
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OR	Odds ratio
PAS	Patient Access Scheme
PD	Pharmacodynamic
PF	Progression-free
PICOS	Population, intervention, comparators, outcomes, and study design
PK	Pharmacokinetic
PNH	Paroxysmal nocturnal haemoglobinuria
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services

QALY	Quality-adjusted life year
QoL	Quality of life
RBC	Red blood cell
RCTs	Randomised controlled trials
RWE	Real-world evidence
SCT	Stem cell transplantation
SD	Standard deviation
SLR	Systematic literature review
STA	Single technology appraisal
SWB	Social/family well-being
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TID	Three times a day
TP	Treatment period
TSD	Technical Support Document
UK	United Kingdom
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WHO	World Health Organization
WTP	Willingness-to-pay

External Assessment Group Report

1 INTRODUCTION AND BACKGROUND

1.1 *Introduction*

Remit of the appraisal

To appraise the clinical and cost effectiveness of danicopan as an add on to a C5 inhibitor (C5i) within its marketing authorisation for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria (PNH).

Condition, symptoms and economic burden

PNH is an extremely rare, chronic, life threatening blood disorder characterised by uncontrolled activation of the complement system (an arm of the immune system), resulting in impairment of blood cells and components such as red blood cells (RBCs), white blood cells, and platelets. The disease prevalence is around 1/62500 in Great Britain,[1] and between April 2022-April 2023, there were 1025 patients in the UK PNH service.[2] As a result of an acquired genetic mutation, destruction of RBCs (haemolysis) occurs in PNH leading to anaemia, and other significant consequences of PNH including thrombosis (clot formation), which has the potential to be fatal. Patients present with fatigue, difficulty breathing abdominal pain, erectile dysfunction among other symptoms,[3] and generally have lower quality of life scores as compared to the general public.[4]. In addition, the economic burden of disease includes costs associated with hospital admissions due to BTH, and transfusion costs.[5, 6] There are two types of haemolysis experienced in PNH; intravascular haemolysis (IVH), occurs inside blood vessels and constitutes the major disease burden as it is associated with life threatening conditions such as thrombosis. Due to the mortality and morbidity associated with it, control of IVH is a primary treatment goal for PNH; this is currently achieved using inhibitors of the C5 protein of the complement cascade (C5i) eculizumab and ravulizumab.[7] The second type of haemolysis is extravascular haemolysis (EVH), referring to haemolysis which occurs in organs such as the liver and spleen and not inside the blood vessels; EVH does not occur in all patients, and is unmasked after treatment with C5i.[7], (See section 1.2.1 for pathogenesis).

1.2 *Background*

1.2.1 Treatment pathway

The current treatment pathway for PNH is discussed in section B.1.3.3 of the company submission (CS). PNH is a consequence of a loss-of-function mutation in bone marrow stem cells, leading to defective blood cells such as platelets, RBCs, and other immune cells.[8] In particular a deficiency of the surface proteins CD55 and CD59 on RBCs leave them susceptible to attack and destruction by the complement system. The complement system consists of several proteins which are part of the body's innate immune system, and is an important part of infection control. However, with genetic mutations such as those in PNH, the complement system is stimulated by healthy cells.[7] Two important targets in the pathway are C3 and C5; the former first amplifies the complement cascade, while the latter then aids the formation of 'membrane complexes' which destroy cells. C3's action is mitigated by CD55 and C5 via the action of CD59; a lack of these proteins leave the RBCs vulnerable to destruction by the complement system, leading to haemolysis.[7] Hence, C5 inhibition through ravulizumab or eculizumab compensates for the lack of CD59, and stops haemolysis. However, once C5 inhibition occurs, the RBC survives for longer and high concentrations of C3 fragments build up on the surface (as the action of C3 is still not inhibited); these fragments tag the cells (opsonisation) for destruction by the body's immune cells in organs, leading to EVH.[7]

The current treatment pathway for PNH involves first starting on a C5i, either ravulizumab or eculizumab if certain clinical criteria are met; the indications include symptomatic haemolytic anaemia and complications and thrombosis related to PNH, but there is also scope for starting treatment on a case-by-case basis if patients do not fit the indication[9]. Eculizumab and ravulizumab are considered to be equal in efficacy,[10] and are both intravenous infusions; eculizumab is initially given at 600mg once weekly for four weeks, then increased to 900mg once weekly for a week, and maintained with 900mg every 12-16 days hereafter.[11] The dose of ravulizumab is weight based, and starts with an initial loading dose of 2.4g-3g, a break of two weeks, followed by maintenance dosing between 3g-3.6g every eight weeks. As ravulizumab presents a lower burden of treatment administration, it is the preferred option for PNH patients;[9] the CS states that [redacted] of patients on C5i treatment are on eculizumab, and [redacted] are on ravulizumab. If a patient is asymptomatic or mildly

symptomatic, treatment may not be initiated and a 'watch and wait' approach might be taken.[12] Other supportive treatments include blood transfusions, steroids, folic acid to aid production of blood cells in the bone marrow, iron supplements or removal depending on need, and anticoagulation (to mitigate risk of thrombosis by inhibiting clotting)[13]. As shown in Figure 2 in the CS, the second line treatment is the C3i pegcetacoplan, for use if established on a C5i for three months and persisting anaemia is a problem.[9, 12] Treatment with pegcetacoplan is given as a subcutaneous infusion at 1080mg twice weekly; the C5i is continued for the first four weeks of pegcetacoplan treatment, then stopped.[11]

Danicopan is presented as an oral add on to C5i to address EVH; as per the CS, it is an oral tablet at a starting dose of 150mg taken three times a day (TID), with potential for escalation to 200mg TID. The CS places danicopan in the treatment pathway as an alternative to pegcetacoplan in patients with clinically significant EVH (csEVH). As danicopan would be in addition to the C5i instead of requiring discontinuation, the treatment combination would directly target EVH by inhibiting factor D, a component of the complement system that also works at the amplification stage, while retaining control of IVH. While proximal inhibition of the complement pathway with danicopan could theoretically control IVH as well as EVH (As C3 works before C5 in the complement cascade sequence), the company's clarifications draw attention to a small exploratory trial investigating danicopan monotherapy,[14] which showed low levels of residual IVH. Furthermore, the CS clarification states that the population investigated in the ALPHA trial and of interest in the CS are patients who are stable on a C5i, and that the effect of danicopan on IVH in this population is anticipated to be negligible. The EAG discusses this in more detail in the decision problem (section 1.3).

The EAG's clinical expert informed that PNH correlates with conditions such as aplastic anaemia, and it is possible that treatments have an interactive effect; a possible example is someone receiving a stem cell transplant for aplastic anaemia which, if successful, would also cure PNH.

1.2.2 PNH Complications

Two significant complications of PNH are breakthrough haemolysis (BTH) and thrombosis.[7] BTH refers to inadequate control of IVH, and is associated with an

increase in lactate dehydrogenase (LDH), a chemical secreted by RBCs upon haemolysis; the seminal trials for ravulizumab and pegcetacoplan define this as 'one new or worsening sign or symptom of IVH (fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia, major adverse vascular events [thrombosis], dysphagia or erectile dysfunction) in the presence of LDH levels twice the upper limit of normal (ULN) following a prior reduction of LDH levels to <1.5 times ULN'.[10, 15, 16] There are two types of BTH; pharmacokinetic (PK) and pharmacodynamic (PD). PK BTH occurs when there is an insufficient concentration of C5i circulating e.g. due to the wrong dosage, and PD BTH occurs when a change in body state, for example response to infection, causes an increase in complement activation and BTH occurs regardless of C5i concentrations.[17] While the mechanism is not yet not fully understood,[7] one of the life threatening consequences of IVH is thrombosis; the literature states that eculizumab C5i reduced the treatment significantly reduced the rate of thromboembolic events to 1.07 events/100 patient-years from 7.37 events/100 patient-years.[18] There is evidence that pegcetacoplan increases the rate and severity of BTH, with 15% of patients discontinuing the treatment at 48 weeks during the PEGASUS trial.[6] Hence, there is a need to ensure adequate control of IVH while treating for EVH.

1.2.3 Unmet clinical need

The company states that there is an unmet need for a treatment solution to reliably address the consequences of csEVH, namely reduced quality of life and fatigue; while EVH does not increase mortality and is not symptomatic in many patients, some patients experience csEVH. As per the CS, there is no unifying definition for csEVH and blood markers such as raised bilirubin and high reticulocyte levels along with persisting anaemia are markers, along with patient factors such as fatigue. The CS highlights fatigue as a key symptom of EVH leading to reduced quality of life; recent studies and reviews have also highlighted that a proportion of patients with controlled IVH on C5i continue to experience signs and symptoms of anaemia including a reliance on blood transfusions, leading to hypotheses that the cause is csEVH.[19, 20] As per clinical advice to the EAG, fatigue and ongoing anaemia are the main problems associated with csEVH, and the advice agrees with the general literature consensus that this constitutes an unmet need to address EVH.[17, 21]

The literature states that only csEVH requires treatment, and that up to 20%[21, 22] of patients on C5i experience csEVH, although the CS's clinical expert group puts this number at around 30%; The clinical advice to the EAG puts this number at closer to 20%, but suggests that given there is no unifying definition of csEVH, variations might arise due to differing local definitions.

Pegcetacoplan is a C3 inhibitor approved for use in PNH[6] and is termed a 'proximal complement inhibitor' as C3 works before C5 in the complement cascade. Pegcetacoplan presents a solution to both IVH and EVH, and is an option on the current treatment pathway if a patient experiences persisting anaemia after three months of C5i treatment.[9] However, treatment with pegcetacoplan requires discontinuation of the C5i,[11] which the CS states may result in loss of established IVH control and breakthrough haemolysis (BTH), leading to dose adjustments or treatment cessation of pegcetacoplan; patients on pegcetacoplan have also been shown to have increased severity of BTH episodes.[6] Furthermore, pegcetacoplan is a twice weekly subcutaneous infusion (which may be self-administered after appropriate training), which the CS indicates may result in a high treatment burden and barriers to access may include lack of dexterity, mental health conditions and visual difficulties. Hence, the company also emphasises that there is an unmet need to provide an alternative to pegcetacoplan to both control IVH and EVH reliably, and reduce the burden of administration.

The EAG has created a simplified diagram which illustrates the disease pathway, treatment actions and potential effects (Appendix 3).

1.3 *Critique of company's definition of decision problem*

The EAG's critique of the company's definitions of the decision problem is presented in Table 4.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with paroxysmal nocturnal haemoglobinuria who have signs and symptoms of extravascular haemolysis while on treatment with a C5 inhibitor (eculizumab or ravulizumab).	Adult patients with PNH who have csEVH while on treatment with a C5 inhibitor (eculizumab or ravulizumab).	The population is in line with the final NICE scope, however, further detail is provided as follows. Some patients with PNH treated with C5 inhibitors will experience EVH to a varying degree. A subgroup of these patients will require treatment for their symptoms; these patients are defined as having csEVH. Published literature indicates that around 10–20% of patients develop csEVH.[21, 22] Clinical experts in the United Kingdom (UK) consulted at an advisory board estimated the prevalence of csEVH to be approximately 30%.[2] Clinical experts noted that csEVH has no standardised definition and is evaluated based on a range of parameters in clinical practice, including anaemia, need for blood transfusions, bilirubin and reticulocyte levels, as well as patient-reported fatigue and impact on HRQoL.[2]	The EAG considers that the population is generally in line with the NICE scope. However, the NICE scope states 'signs and symptoms of EVH', whereas the CS decision problem specifies 'clinically significant EVH'. As noted by the company, there is no standardised definition of clinically significant EVH. Specific thresholds for haemoglobin and ARC levels were defined for recruitment to the ALPHA trial, but the company does not anticipate these to be used in UK clinical practice to determine eligibility for danicopan (Clarification A9). The company's clinical experts considered that the eligibility criteria of ALPHA were stricter than those typically used to determine patients with csEVH who would be eligible to receive danicopan in UK clinical practice and the EAG clinical adviser agrees.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				The EAG also has some other concerns regarding the generalisability of the submitted clinical evidence to the patient population in England and Wales eligible for treatment.
Intervention	Danicopan as an add-on treatment to a C5 inhibitor (eculizumab or ravulizumab).	Danicopan as an add-on to a C5 inhibitor (eculizumab or ravulizumab)	N/A	The EAG agrees that the intervention is in line with the NICE scope.
Comparators	• Pegcetacoplan • Eculizumab • Ravulizumab • Iptacopan (subject to NICE ongoing appraisal)	Pegcetacoplan	At present, pegcetacoplan is the only therapy recommended by NICE for the treatment of PNH patients with uncontrolled anaemia after treatment with a C5 inhibitor.[23] CsEVH is characterised by persistent residual anaemia and its accompanying symptoms following C5 inhibitor treatment.[17, 24-26] As such, pegcetacoplan is a relevant comparator in the indication under consideration in this evaluation. Eculizumab and ravulizumab are licensed for the treatment of PNH in patients who experience haemolysis with clinical symptoms indicative of high disease activity.[27,28] They are administered to address intravascular haemolysis (IVH), the lysis of red blood cells (RBCs) within blood vessels, which	The EAG agrees that pegcetacoplan is the only therapy recommended by NICE for the treatment of PNH patients with uncontrolled anaemia after treatment with a C5 inhibitor. The EAG agrees with the company's statements regarding eculizumab and ravulizumab, but notes that the key trial, ALPHA, submitted for the clinical evidence for danicopan add on therapy to eculizumab or ravulizumab, compares danicopan + eculizumab/ravulizumab vs placebo +

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			is the underlying cause of morbidity and mortality in PNH; uncontrolled IVH results in thrombosis which is the leading cause of death in PNH.[7] Eculizumab and ravulizumab reduce IVH by inhibiting C5 and consequently the terminal complement pathway.[27,28] By reducing IVH, eculizumab and ravulizumab therefore reduce the risk of thromboembolic events and death. The manifestation of EVH, the destruction of RBCs in the liver and spleen, subsequently only becomes apparent upon terminal complement inhibition by C5 inhibitors.[29] In the setting of treatment with C5 inhibitors, PNH RBCs are no longer subject to IVH, but instead may become opsonised (marked for destruction) with C3 fragments, making them susceptible to destruction in the liver or spleen (EVH).[17, 30] Accordingly, eculizumab and ravulizumab do not address EVH and are not licensed nor recommended in UK clinical practice for the treatment of csEVH, and therefore are not considered as relevant comparators for the evaluation of danicopan. Further details of the pathogenesis of PNH, including the different complement pathways, are	eculizumab/ravulizumab and therefore these are comparator technologies in the ALPHA trial. As current standard of care for patients with csEVH includes remaining on C5 inhibitor the EAG considers these cannot be excluded as a comparators. The EAG agrees that iptacopan is subject to NICE ongoing appraisal with expected publication June 2024 (one month prior to danicopan expected publication).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			provided in section B.1.3.1 of Document B. Iptacopan has not been included as a comparator as it has not received a positive recommendation from NICE at the time of submission, and final publication of NICE guidance is not expected until mid-2024.[31] Accordingly, iptacopan is not considered established practice for the treatment of csEVH in the NHS.	
Outcomes	• Overall survival (OS) • Intravascular haemolysis • EVH • Breakthrough haemolysis (BTH) • Transfusion avoidance • Haemoglobin • Thrombotic events • Adverse effects (AEs) of treatment • HRQoL	• IVH • EVH • BTH • Transfusion avoidance • Haemoglobin • Thrombotic events • AEs of treatment • HRQoL	As described above, when haemolysis of RBCs occurs inside blood vessels, it is known as IVH.[32] Complement-mediated IVH is the main contributor to morbidity and mortality associated with PNH, and leads to symptoms such as fatigue, anaemia, and haemoglobinuria, and can be life-threatening.[3, 7, 33-37] However, the development of C5 inhibitors has led to the control of IVH, and thus control of the occurrence of life-threatening events.[37] The indication of focus for this evaluation is patients with csEVH following treatment with a C5 inhibitor. Accordingly, IVH is not considered a key outcome of interest for this decision problem. The effectiveness of C5 inhibitors in managing IVH has been	The EAG acknowledge IVH is largely controlled by the use of C5 inhibitors but believes the outcome of IVH remains a relevant outcome. IVH was a pre-defined outcome in the ALPHA trial and there was some potential effect on IVH seen with danicopan in earlier phase II trials (See clarification A8). Although the CS says IVH is controlled in the csEVH population of focus here, the EAG note that BTH still occurs, particularly when there is infection or if insufficient levels of C5-inhibitors (clarification B9)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			established in prior clinical trials.[10, 38] Nevertheless, data on lactate dehydrogenase (LDH) levels, which are indicative of RBC destruction and IVH, are presented for completion.[39] Similarly, OS is not considered a key outcome for this decision problem since life-threatening symptoms of IVH are controlled by C5 inhibitors[37] Furthermore, EVH is not life-threatening to patients and does not impact survival outcomes of patients.[39, 40] The incidence of death is therefore only reported as safety data for danicopan in the ALPHA trial.[41] The occurrence of csEVH is captured through haemoglobin levels and the requirement for blood transfusions in the ALPHA trial.[32] Finally, data on BTH and thrombotic events are available in the AE reporting of the ALPHA trial. BTH was determined by the investigator's clinical judgement.[41] As discussed in Section B.1.3.1 of Document B, BTH is the phenomenon whereby sustained control of IVH is suboptimal; the maintenance of IVH control alongside treatment of EVH as	and this was an included outcome in the company decision problem. As such the EAG has reported IVH outcomes provided at clarification (A7). In addition, the EAG considers that OS is a potentially relevant outcome as the comparator pegcetacoplan requires removing C5 inhibitors which is considered a 'risk'.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			part of PNH patients' care is extremely important.[23]	
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 (QALY) • 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 a National Health Service (NHS) and Personal Social Services (PSS) perspective • The availability of any commercial	As per the NICE final scope	N/A	The EAG are satisfied the company's economic analysis adheres to the NICE reference case.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account			

2 CLINICAL EFFECTIVENESS

2.1 *Critique of the methods of review(s)*

The methods used in the CS for their systematic literature review (SLR) to identify and synthesise evidence of danicopan plus C5-inhibitor (danicopan + C5i) was reviewed by the EAG. The SLR undertaken by the company was designed to capture studies of clinical evidence, burden of disease evidence (referred to in the CS as humanistic studies) and economic evidence. The steps taken in the SLR to search for, assess eligibility, extract data, assess the risk of bias and synthesise evidence were assessed using a modification of the ROBIS tool.[42] Overall the EAG found the SLR to be of high concern.

Table 5 provides a summary of the EAG critique for each methodological step of the SLR and cross-references to the relevant section in the CS where more detail can be found. An overview of the key points of interest from the critique of the SLR follow and the full EAG assessment using the modified ROBIS can be found in Appendix 1.

A sufficient and appropriate range of sources were searched to identify clinical studies, including bibliographic databases as well as websites of HTA agencies, Google, reference lists, and conference proceedings (CS Appendix D 1.1). The search strategies for each database, Medline, Embase and the Cochrane Library (Ovid) and numbers for each line are provided (CS Appendix D1.1, Tables 1, 2 and 3). The search strategy does not state which version of Medline or Embase was used (CS Appendix D 1.1, Table 1).

An overall search strategy for Medline, Embase and the Cochrane Library was carried out simultaneously (CS Appendix D 1.1, Table 1 and Table 2). The search strategy addressed the condition/ population only, that is adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who experience csEVH on a C5 inhibitor (eculizumab or ravulizumab) (CS B.1.1 Decision problem). It is reported that the search only included terms for the population, as it was anticipated that the amount of search results would be low, as ‘EVH is a recently described clinical manifestation’ (CS Appendix D.1.1.) The search therefore incorporates the searches for the clinical, economic and humanistic evidence.

The searches were carried out on the 1st November 2022 (SLR1) and updated on the 12th June 2023. The EAG consider this search to not be sufficiently up to date. The EAG replicated the search in Medline, Embase and the Cochrane Library on the 4th Jan 2023 and found that there was a difference of 139 results (after the removal of duplicate records via Ovid).

The search strategies for Embase, MEDLINE and the Cochrane Library reported in the CS Appendix D.1.1 Table 1 are not sufficiently comprehensive, as the terms for the condition was searched for in the title and abstract only and keywords were not included. This means that records with key population terms in the keyword field terms would have been missed. The search could have also included search terms for C5 inhibitors (eculizumab or ravulizumab) to capture studies reporting that patients were on C5 inhibitors as well as terms for inadequate response (and

combined this using the Boolean operator Or) to increase the sensitivity. The search also didn't include the Emtree indexing term paroxysmal nocturnal hemoglobinuria/ which could exclude potentially relevant results. Search line 4 combines phrases searches for terms related to suboptimal response. The search would be more comprehensive if it searched for those terms using a Boolean operator or adjacency searching in-between words. Search line 5 searches for terms related to suboptimal or inadequate response but combines these using a single adjacency operator. This would be more sensitive if it searched for terms with a numerical character attributed to the adjacency operator as searching using adj searches for terms separated by a single space. Indexing terms for this concept are also not included, for example Hemolysis/.

The update search reported in Table 2 includes an additional search line: ((remain or persisten* or continu*) adj an?emia).ti,ab. This additional search line means that the later searches are not a true update of the 2022 searches (CS Appendix D.1.1. Search strategy, Table 2).

Appropriate grey literature resources were searched, and the search terms and results were provided. Clinical trials registers such as Clinical Trials.gov were not searched.

Inclusion of studies

The CS reports 63 articles were included in the overall SLR but it is not clear what numbers were relevant to each section of the SLR. Full details of SLR are in a data on file document[43] and in this document there is a distinction between clinical and humanistic articles combined (n=58) and cost-utility articles (n=5), but not between the clinical and humanistic articles. Of these 58 papers there were 32 unique clinical and humanistic studies and five cost-utility studies. Open label extension (OLE) studies and post hoc analyses were considered as separate trials. Across all of the included articles 50 were published only as conference abstracts.

In the clinical effectiveness review seven studies were in mixed treatment experienced and treatment naïve populations and 10 were in treatment naïve populations but the CS does not summarise these 17 studies.

Eligibility criteria was specific to populations with EVH (CS Appendix Table 4), however the company does not state how EVH should be defined. In the 'data on file' manuscript[43] summary characteristics from the included studies were provided in tables. The definition of EVH / suboptimal response was tabulated for many of the studies, however, for a number of studies (particularly conference abstracts) this was not reported. It is therefore unclear if the populations in all studies had EVH or whether this was similar between studies.

There was a second selection process for the NMA which restricted studies by intervention to assess danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan.

CS Appendix Table 7 lists the excluded studies. The EAG has checked through the titles and reasons for exclusion and largely agrees with the CS exclusions. One study, De Castro et al., 2020[44] was excluded for study design as it was a phase 1b trial. However, the eligibility criteria for the SLR included any prospective or retrospective study design and as such this study may have been eligible on this basis.

Table 5: Summary of the EAG's critique of the company SLR

Method step	Section(s) of CS of relevance	EAG overall assessment
Eligibility criteria	CS Appendix D, Table 4	Unclear concern
Searches and selection of studies	CS Appendix D, Section D.1.1-D1.2 and D.2	Unclear concern
Data extraction and risk of bias assessment	CS Appendix D, Section D.1.3	Low concern
Evidence synthesis	CS section B.2.3 and B.2.9; Appendix D, Section D.3	High concern

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

The source of evidence for the assessment of clinical evidence of danicopan as an add-on treatment to a C5 inhibitor comes from a single RCT, the ALPHA trial. ALPHA is an ongoing study (NCT04469465), with the first interim results published[45] and later (post hoc) interim results from the 20th September 2022 data cut presented in the CS and CSR. Clarification A12 states that an additional (post hoc) data cut (31st March 2023) was conducted for supplemental analyses to address specific requests from regulatory agencies, however results have not been provided with this submission. The CSR for the final database lock planned for [redacted] is anticipated in [redacted]

ALPHA is a Phase III multinational study consisting of a 12-week double-blind randomised period (TP1) comparing danicopan as an add-on to eculizumab or ravulizumab versus placebo as an add-on to eculizumab or ravulizumab. This is followed by open label extension periods of 12 weeks (TP2), one year (LTE Year 1) and two years (LTE Year 2), in which all participants received danicopan as an add-on treatment. A summary of the ALPHA trial methodology with cross-reference in the relevant sections in the CS where more detail can be found is presented in Table 6.

At least one transfusion was required within the previous 6 months, although this requirement was removed in a protocol update (February 2022).

Table 6: Summary of ALPHA methodology

Method step	Summary details	Section(s) of CS of relevance or other source
Method of randomisation	Stochastic dynamic allocation in a 2:1 ratio, stratified by transfusion history (> 2 or ≤ 2 transfusions within 6 months of screening), Hgb (< 8.5 g/dL and ≥ 8.5 g/dL), and Japanese patients (defined as patients enrolled from Japan)/non-Japanese patients. Interactive response technology.	B.2.3.1, Table 4 B.2.3.2 Lee 2023[45]
Eligibility criteria	• Diagnosis of PNH • CsEVH, defined by anaemia (haemoglobin ≤9.5 g/dL) with ARC ≥120 × 10^9/L • Receiving an approved C5 inhibitor for ≥ 6 months prior at an approved dose (or higher), with no change for ≥ 24 weeks • Age ≥18 years • Platelet count ≥30,000/μL without the need for platelet transfusions • ANC ≥500/μL • Documentation of vaccination for Neisseria meningitidis	B.2.3.2, Table 5
Trial drugs by period of study	Danicopan or placebo as an add-on to eculizumab or ravulizumab	B.2.3.2
Primary endpoints of relevance to the decision problem	Change from baseline haemoglobin at week 12	B.2.3.1, Table 4
Key secondary endpoints of relevance to	Proportion of patients with haemoglobin increase of ≥ 2 g/dL at week 12 in the absence of transfusion	B.2.3.1, Table 4

the decision problem	Proportion of patients with transfusion avoidance at week 12 Change from baseline FACIT-Fatigue at week 12	
Statistical analysis	Data from the interim analysis set (IAS, discussed in section 2.2.2) was used to analyse efficacy outcomes and data from the interim safety analysis set was used to analyse safety. Primary outcome analysed using a two-sided Cochran-Mantel-Haenszel test. Longitudinal changes from baseline in haemoglobin were analysed using a mixed model for repeated measures. Key secondary endpoints were assessed using a hierarchical fixed sequence test procedure.	B.2.4

Eligibility criteria

The ALPHA trial included people aged at least 18 years with a diagnosis of PNH and csEVH (defined as haemoglobin ≤9.5 g/dL with ARC ≥120 × 10^9/L). The EAG clinical expert agrees that there is no standard definition of csEVH, and considers the definition used in the trial to be reasonable. However, the company notes in Clarification A9 that the specific haemoglobin and ARC level thresholds are not anticipated to be used in UK clinical practice to determine patients' eligibility to receive danicopan. Participants were required to have been receiving an approved C5 inhibitor (eculizumab or ravulizumab) for at least 6 months, with no change in the prescribed dose or interval for at least 24 weeks. A platelet count ≥30,000/μL without the need for platelet transfusions and an ANC ≥500/μL were also required, and participants must have received a meningococcal vaccine. Patients with known aplastic anaemia or other bone marrow failure requiring haematopoietic stem cell transplantation (HSCT) or other therapies including anti-thymocyte globulin and/or immunosuppressants, were excluded, unless the dose of immunosuppressant had been stable for at least 12 weeks and was expected to remain stable.

Interventions

In TP1, danicopan 150 mg was administered orally TID, with dose escalations to 200 mg TID permitted after a minimum of 4 weeks, based on:

- haemoglobin response (escalated if the response had not increased by ≥2 g/dL from baseline value), and
- transfusion requirements (escalated if the patient required a transfusion during the previous four weeks of treatment).

Eculizumab or ravulizumab were administered in each group as an IV infusion once every two or once every eight weeks, respectively.

In TP2, dose escalations were permitted at week 12 and week 18 if, at week 10 and week 16, respectively:

- haemoglobin had not normalised from the patient's baseline level to at least the midpoint of the normal range relevant to the patient's sex;
- patient had received a transfusion in the last four weeks of treatment.

In LTE Year 1 and LTE Year 2, dose escalations to 200 mg TID were permitted if the patient had been on their previous dose for a minimum of four weeks.

Baseline characteristics

Participant flow is described in CS B.2.3.3 and a CONSORT diagram is presented in CS Figure 5. A total of 86 participants were randomised; 57 to danicopan and 29 to placebo.

A number of different analysis sets were defined (section 2.2.2).

Baseline characteristics are presented in CS Table 9 for the IAS, which is the analysis set informing the efficacy results for the submission, N=63 (danicopan n=42, placebo n=21). Baselines for all randomised participants (n=86, safety analysis set) were available in the CSR. These have been examined by the EAG but not reproduced here. The EAG notes that the Lee 2023 publication[45] presents baselines for 73 participants who had been randomised by the June 2022 data-cut, at the time

of the protocol-prespecified first interim analysis. These are not reproduced in this report.

There were some imbalances between the two groups, and these appeared to be slightly more pronounced in the smaller IAS (Table 7) than in the full randomised population (CSR Table 11). Compared with the danicopan group, the placebo group had a higher proportion of females (66.7% vs 54.8%) and people aged less than 65 years (81.0% vs 71.4%), and fewer Asian patients (33.3% vs 42.9%) and those with Hispanic or Latino ethnicity (0% vs 9.5%), although as the CS notes they may be attributable to unreported data. Clinical advice to the EAG is that these differences would have minimal impact on efficacy. There was also a [redacted] proportion of participants in the danicopan group with a history of PNH-associated aplastic anaemia ([redacted]), however all cases were either resolved or controlled prior to study entry (Clarification A2).

In terms of disease characteristics, LDH levels were higher in the danicopan group compared with placebo (298.73 U/L vs 278.25 U/L), although both groups fall within the normal reference range (135–330 U/L) indicating control of IVH with C5 inhibitor treatment (Alexion data on file, no reference provided). The CS also notes that PHN RBC clone sizes varied slightly between the treatment arms, but states that these differences were not consistent across the PNH RBC clone sizes. Clinical advice to the EAG is that these imbalances are not different enough to be clinically meaningful. The proportion of patients with reported clone size data was relatively low (danicopan n=14 to n=24, placebo n=8 to n=10); the footnote of CS Table 18 states that some samples could not be analysed due to quality issues, however the CS does not comment on this and it is not clear what impact this may have.

The current C5 inhibitor was not balanced between the groups (Table 8), with a higher proportion of the danicopan group taking ravulizumab compared with placebo (64.3% vs 47.6%), and the remaining participants taking eculizumab (danicopan 35.7%, placebo 52.4%). A higher proportion of participants in the danicopan group had received packed red blood cell transfusions during the 24 weeks prior to the first study dose. The EAG clinical adviser did not consider these imbalances would have any important impact on the trial results.

Table 7: Key baseline demographics and disease characteristics from the IAS of ALPHA

	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=21
Female	23 (54.8)	14 (66.7)
Mean age, years (SD)	55.0 (15.6)	53.1 (14.3)
Age group (years) at informed consent, n (%)		
< 65	30 (71.4)	17 (81.0)
≥ 65 to < 85	12 (28.6)	4 (19.0)
Race, n (%)		
American Indian or Alaska Native	1 (2.4)	0 (0.0)
Asian	18 (42.9)	7 (33.3)
Black or African American	1 (2.4)	0 (0.0)
White	19 (45.2)	9 (42.9)
Other	1 (2.4)	0 (0.0)
NR	2 (4.8)	4 (19.0)
Unknown	0 (0.0)	1 (4.8)
Ethnicity, n (%)		
Hispanic or Latino	4 (9.5)	0 (0.0)
Not Hispanic or Latino	34 (81.0)	17 (81.0)
NR	4 (9.5)	4 (19.0)
Mean BMI (SD)	26.7 (5.4)	24.8 (4.9)
Japanese ancestry, n (%)	5 (11.9)	2 (9.5)
Age (years) at PNH diagnosis, mean (SD)	44.2 (16.6)	40.8 (16.3)
Years from diagnosis to informed consent, mean (SD)	11.3 (10.6)	12.8 (10.4)
Haemoglobin at Baseline (g/dL), mean (SD)	7.66 (0.94)	7.74 (1.04)
History of PNH-associated aplastic anaemia	[redacted]	[redacted]
FACIT-Fatigue scores at Baseline Mean (SD)	33.5 (11.1)	33.9 (10.8)
ARC at Baseline (1012/L), mean (SD)	0.2 (0.1)	0.2 (0.1)
Total PNH RBC Clone Size (Type II + Type III) (%), mean (SD)	n=14 51.6 (25.4)	n=9 65.5 (29.6)

	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=21
PNH RBC Type III Clone Size (%), mean (SD)	n=24 47.5 (22.2)	n=10 51.7 (29.0)
PNH RBC Type II Clone Size (%), mean (SD)	n=14 6.9 (12.6)	n=8 6.1 (5.3)
LDH at Baseline (U/L), mean (SD)	298.7 (105.7)	278.3 (68.4)

[a] Eculizumab or ravulizumab.
BMI: body mass index; C5i: complement component 5 inhibitor; IAS: interim efficacy analysis set NR: not reported; pRBC: packed red blood cell; SD: standard deviation.
Source: Adapted from CS Tables 9 and 10, CSR Tables.

Table 8: Prior treatments (IAS)

	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=21
Current C5i: Ravulizumab, n (%)	27 (64.3)	10 (47.6)
Current C5i: Eculizumab, n (%)	15 (35.7)	11 (52.4)
Age (years) at first C5i infusion, mean (SD)	50.1 (15.3)	47.1 (14.6)
Duration (years) from initial C5i to first dose of study intervention, mean (SD)	5.5 (3.9)	6.7 (4.6)
Duration (years) from start of current C5i to first dose of study intervention, mean (SD)	3.9 (3.3)	4.5 (4.0)
Number of RBC units transferred 12 weeks prior to treatment, mean (SD)	[redacted]	[redacted]
Number of transfusion instances 12 weeks prior to treatment, mean (SD)	[redacted]	[redacted]
Number of patients with pRBC transfusions during the 24 weeks prior to first dose, n (%)	38 (90.5)	17 (81.0)
Number of transfusion instances within 24 weeks prior to receiving study intervention, mean (SD)	2.5 (2.2)	2.6 (2.1)
Number of units transfused within 24 weeks prior to	4.3 (4.7)	4.4 (3.8)

receiving study intervention, mean (SD)		

[a] Eculizumab or ravulizumab.
C5i: complement component 5 inhibitor; IAS: interim efficacy analysis set; SD: standard deviation.
Source: Adapted from CS Table 11 and Clarification A13.

2.2.1 ALPHA Risk of Bias

TP1: 12 week double-blind randomised period

The company assessed the risk of bias in the ALPHA trial in CS Table 12, B.2.6 using the minimum criteria recommended by NICE, and also in CS Appendix Table 17 using Cochrane RoB version 2. CS Appendix Table 17 only presents domains 1 and 2 of Cochrane RoB2, however assessments for the remaining domains were provided by the company in their full SLR report.[43] The EAG considers that the risk of bias assessments using these tools apply only to the 12-week randomised period of ALPHA and not to the open label periods.

The EAG has checked the company's assessment in CS Table 12 and has no concerns with the company's judgements. The EAG also completed an independent assessment of ALPHA using RoB2 (see Appendix 1). There were some minor differences to the company's assessments. For example, the company stated 'no information' and 'probably yes' to questions 2.6 and 2.7 respectively (bias due to deviations from intended interventions), suggesting that there was potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised. But this doesn't tie in with the company's response in CS Table 12 (appropriate analysis). The EAG agrees with the company's judgement of low risk of bias for this domain.

Overall, the company's SLR[43] judged ALPHA to have high risk of bias due to the absence of a published CONSORT diagram, which lead to an assessment of a high risk of bias due to missing outcome data. The CSR was not available to the reviewers undertaking the company SLR. In light of the information provided in the CS, the EAG found some concerns regarding the overall risk of bias in ALPHA, due to potential bias from missing outcome data. This was due to concerns regarding unreported data for 23/86 (27%) of randomised participants. Enrolment was completed in August 2022, and the CS and CSR report results from a second interim analysis (data-cut off September 2022), comprising the first 75% of patients (n=63) of the target enrolment of 84 patients when they had the opportunity to complete

Treatment Period 1. The first interim analysis of this group is described in the protocol and was to be conducted at the discretion of the sponsor. The purpose was to evaluate the study for stopping early for efficacy. The second interim analysis was repeated when the 63 participants completed Treatment period 2; this was not prespecified in the study protocol. At this cut-off, 71 patients had completed TP1, but results were not reported.

TP 2: week 12 to 24 open label extension, and long-term extension periods
During TP2, patients randomised to danicopan remained on danicopan treatment for another 12 weeks (DAN/DAN), and patients randomised to placebo were switched to danicopan (PBO/DAN). All patients were made aware that they were receiving danicopan and patients and investigators made aware of the treatment received in the previous period. Outcomes during this period are therefore at risk of bias arising from knowledge of the intervention; this may be more likely in the subjective outcome measures.

CS B.2.7.3 presents data for efficacy endpoints at week 24 for both the DAN/DAN group and the PBO/DAN group, however it should be noted that the PBO/DAN group have only had 12 weeks of treatment at this point, and that the groups are not comparable. Only the DAN/DAN group provides data at 24 weeks. This has a small number of participants, with just n=40 having completed TP2 at the September data-cut. At this point, [redacted] patients in the DAN/DAN group had completed the 1-year long-term extension, and [redacted] in the PBO/DAN group had completed this (i.e. 9 months of danicopan). None had completed the 2 year long-term extension. It is unclear whether the sample size and length of follow-up is sufficient to adequately capture long-term effects and adverse events.

2.2.2 ALPHA trial results overview

Outcomes from the ALPHA trial of relevance to the DP were presented in Section B.2.7.1 to Section B.2.7.3 for EVH (surrogate endpoints of haemoglobin, transfusion avoidance and absolute reticulocyte count) and in Section B.2.11 (adverse events) for BTH and thrombotic events. IVH surrogate outcomes were not presented from ALPHA in the CS as it was not considered a key outcome of interest (despite being

specified on the NICE scope), however changes in LDH were provided in response to Clarification A7. Results are summarised here for the 12 week randomised placebo comparison period and for the 24 week period for the DAN/DAN and PBO/DAN groups. For discussion of health-related quality of life (HRQoL) measures and AE see sections 2.2.2 and 2.2.3.

As per the CS, data presented here are based on the interim data cut of 20th September 2022 using the interim analysis set (75% of randomised patients 63 participants).

TP1 (randomised placebo comparison), 12 weeks

In the interim analysis, a statistically significant improvement was found for danicopan + C5i compared with placebo + C5i for all key outcome measures (Table 9). For change from baseline haemoglobin, the baseline value used was the lowest value observed between and including screening and day 1. For change from baseline absolute reticulocyte count, the baseline value was the [redacted]. The mean number of RBC units transferred and the mean number of transfusion instances was [redacted], but statistical analyses were not conducted (Table 10, Clarification A13). There was no statistically significant difference between groups for change from baseline LDH (Table 8, Clarification A7), although baseline values for both groups fell within the normal range. Caution should be taken when interpreting these results from an interim analysis.

Table 9: Interim ALPHA trial outcomes at 12 weeks

	Danicopan + C5i, n=42	**Placebo + C5i, n=21**
IVH surrogate endpoints		
LDH cfb, LS mean (95% CI) U/L	−23.5 (−40.1, −6.9)	−2.9 (−26.8, 20.9)
Difference (95% CI) between groups	−20.6 (−49.3, 8.2) p=0.1569	
EVH surrogate endpoints		
Haemoglobin cfb, LS mean (95% CI) g/dL	2.94 (2.52, 3.36)	0.50 (-0.13, 1.12)
Difference (95% CI) between groups adjusted for stratification factors	2.44, (1.69, 3.20) p<0.0001	

% participants with haemoglobin increase ≥2 (95% CI) g/dL in the absence of transfusion	59.5 (43.3, 74.4)	0 (0.0, 16.1)
Difference (95% CI) between groups adjusted for stratification factors	46.9, (29.2, 64.7) p<0.0001	
% participants avoiding transfusion (95% CI)	83.3 (68.6, 93.0)	38.1 (18.1, 61.6)
Difference (95% CI) between groups adjusted for stratification factors	41.7, (22.7, 60.8) p=0.0004	
Number of RBC units transferred 12 weeks post treatment initiation, mean (SD)	[redacted]	[redacted]
Number of transfusion instances 12 weeks post treatment initiation, mean (SD)	[redacted]	[redacted]
Absolute reticulocyte count cfb, LS mean (95% CI)	-83.8 (-101.6, -65.9)	3.5 (-21.9, 28.8)
Difference (95% CI) between groups adjusted for stratification factors	-87.2 (-117.7, -56.7), p<0.0001	
Non-scoped endpoints		
PNH RBC clone size, cfb, LS mean (95% CI) Total (Type II + Type III)	24.60 (15.78, 33.42), [redacted]	-3.04 (-15.32, 9.25), [redacted]
Difference (95% CI) between groups	27.63 (13.03, 42.24) p=0.001	
PNH RBC clone size type III	[redacted]	[redacted]
Difference (95% CI) between groups	[redacted]	
PNH RBC RBC clone size type II	[redacted]	[redacted]
Difference (95% CI) between groups	[redacted]	

Table adapted from CS Tables 13-15, 17-18, and Clarifications A7 and A13.
Abbreviations: cfb: Change from baseline; CI: confidence interval; LS: least squares

TP2 (DAN/DAN and PBO/DAN at 24 weeks)

Results of key outcomes in treatment period two are from a non-randomised period and need to be considered as two single arm before and after comparisons. The outcomes after 24 weeks for those continuing to receive danicopan appear to be improved from baseline, and those who switched to danicopan at the end of the 12-

week placebo period also appear to have positive outcomes at 24 weeks compared with baseline (Table 10). Although some of the 24 week results for the PBO/DAN arm appear to be lower than the 12 week results seen in the DAN/DAN arm which the EAG would have anticipated should have been comparable. This may be due to the differences in sample size. No statistical comparisons with baseline were undertaken on these interim results and caution is required in their interpretation.

Table 10: Interim ALPHA trial outcomes at 24 weeks

	DAN/DAN + C5i, n=41	**PBO/DAN + C5i, n=20**
IVH surrogate endpoints		
LDH cfb, LS mean (95% CI) U/L	[redacted]	[redacted]
EVH surrogate endpoints		
Haemoglobin cfb, mean (SD) g/dL	[redacted]	[redacted]
% participants with haemoglobin increase ≥2 g/dL without transfusion (95% CI)	46.3 (30.7, 62.6), n=19	35.0 (15.4, 59.2), n=7
% participants avoiding transfusion week 12-24 (95% CI)	78.0 (62.4, 89.4), n=32	90.0 (68.3, 98.8), n=18
Absolute reticulocyte count cfb, LS mean (95% CI) 10^{12}/L	-0.08 (-0.1, -0.06), n=37	-0.07 (0.09, -0.04), n=19

Adapted from CS Table 19 and clarification A7.
[a]LS mean change 3.17 (SE 3.02) for the DAN/DAN group and 2.26 (SE 3.40) for the PBO/DAN group (CS B.2.7.3).

Long-term extension period, interim analysis

The CS reports minimal outcome data from the long term extension period of ALPHA. In the CSR data are presented in Figures and Tables for actual values of haemoglobin and mean change in haemoglobin up to 48 weeks and 72 weeks. It appears that mean change in haemoglobin in those in DAN/DAN [redacted]; for those in PBO/DAN the change from baseline [redacted] across the long-term period, however, participant numbers are small [redacted]. The CSR also reports data in tables for the change in absolute reticulocyte counts over time; which appear to be [redacted]. These data are not least square means and there are no before-and-after statistical comparisons at this interim data cut.

Patient reported outcomes

Change from baseline in FACIT-Fatigue score at week 12 was a key secondary endpoint in ALPHA. There are no formal rigid clinically meaningful differences for the FACIT scales (https://www.facit.org/faq), however a recent study[46] has supported the use of 5 points as the clinically important difference in PNH patients. A clinically important improvement from baseline in FACIT-Fatigue score was found with danicopan (7.97) but not placebo (1.85, difference 6.12, p=0.0021) at 12 weeks (Table 11). The CS also reports the proportion of patients with an improvement of at least 5 points in FACIT-Fatigue score at 12 weeks. This was [redacted] in the danicopan group compared with the placebo group[redacted].[41]

There was [redacted] in EQ-5D-3L UK health state index score at week 12 (Table 11).

Although not presented in the CS, EORTC QLQ-C30 scores were available in the CSR. The EAG has not reproduced results for all domains here, but has focused on the overall score (Global health status) and the fatigue score, since fatigue is considered important in the CS. [redacted](Table 11), and the proportion of patients with a clinically important improvement of at least 10 points[47] was [redacted]. The difference in mean change from baseline in the EORTC QLQ-C30 Fatigue score for danicopan [redacted]

Patient reported outcomes during the non-randomised TP2 and LTE, where all participants received danicopan, are summarised in Table 12. Both the DAN/DAN and PBO/DAN groups had a [redacted] from baseline in FACIT-Fatigue and EORTC QLQ-C30 Fatigue scores at 24 weeks. [redacted] in EORTC QLQ-C30 Global health status and EORTC QLQ-C30 Fatigue scores at 24 weeks (Table 12). Changes from baseline EQ-5D-3L UK health state index scores at 24 weeks were [redacted]. [redacted] numbers were available for the 72-week LTE (DAN/DAN: [redacted], PBO/DAN: [redacted]), and other than for FACIT-F score these data are not least square means therefore results should be viewed with caution.

Table 11: Key patient reported outcomes (IAS) during 12 week randomised period

	Danicopan + C5i[a] N=42	**Placebo + C5i[a] N=21**
FACIT-Fatigue score		
Change from baseline, LS mean (95% CI)	7.97 (5.72, 10.23)	1.85 (−1.31, 5.02)
Difference between groups (95% CI)	6.12 (2.33, 9.91), p=0.0021	
Patients with improvement of ≥ 5 points, n (%) (95I CI)	[redacted]	[redacted]
Difference between groups (95% CI)	[redacted]	
EQ-5D-3L UK health state index score		
Change from baseline, LS mean (SD)[b]	[redacted]	[redacted]
Difference between groups (95% CI)	[redacted]	
EORTC QLQ-C30 Scores: Global health status		
Change from baseline, LS mean (95% CI)	[redacted]	[redacted]
Difference between groups (95% CI)	[redacted]	
Proportion with improvement of ≥ 10 points, n (%)	[redacted]	[redacted]
Difference between groups (95% CI)	[redacted]	

EORTC QLQ-C30 Scores: Fatigue		
Change from baseline, LS mean (95% CI)	[redacted]	[redacted]
Difference between groups (95% CI)	[redacted]	
Proportion with improvement of ≥ 10 points, n (%)	[redacted]	[redacted]
Difference between groups (95% CI)	[redacted]	

[a] Eculizumab or ravulizumab. [b] Estimates based on MMRM; the SDs reported here (from CS Table 20) appear to be SEMs as reported in CSR Table.
Abbreviations: C5i: complement component 5 inhibitor; CI: confidence interval; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; IAS: interim efficacy analysis set; LS: least squares; N: number of patients in treatment group; SE: standard error.
Source: CS Table 16 and 20, CSR

Table 12: Key patient reported outcomes (IAS) during non-randomised TP2 and LTE

	DAN / DAN N=42	PBO / DAN N=21
FACIT-Fatigue score		
Change from baseline at Week 24, LS mean 95% CI for LS mean	[redacted]	[redacted]
Change from baseline at week 72, mean (SD)	[redacted]	[redacted]
EQ-5D-3L UK health state index score		
Change from baseline at week 24, mean (SD)	[redacted]	[redacted]
Change from baseline at week 72, mean (SD)	[redacted]	[redacted]
EORTC QLQ-C30 Scores: Global health status		
Change from baseline at week 24, mean (SD)	[redacted]	[redacted]
Change from baseline at week 72, mean (SD)	[redacted]	[redacted]
Proportion with an improvement of ≥ 10 points at 24 weeks, n (%)	[redacted]	[redacted]
EORTC QLQ-C30 Scores: Fatigue		
Change from baseline at week 24, mean (SD)	[redacted]	[redacted]

Change from baseline at week 72, mean (SD)	[redacted]	[redacted]
Proportion with an improvement of ≥ 10 points at 24 weeks, n (%)	[redacted]	[redacted]

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; CI: confidence interval; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; IAS: interim efficacy analysis set; LS: least squares; N: number of patients in treatment group; SE: standard error.
Source: CS Table 19 and 20, CSR

Subgroups

The NICE scope did not identify any subgroups of interest. CS Section B.2.8 reports the following subgroup analyses from ALPHA on the primary endpoint of change from baseline in haemoglobin at week 12:

- Stratification factors (prespecified subgroups): Haemoglobin at screening (<8.5 g/dL, ≥8.5 g/dL), transfusion history (>2, ≤2 transfusions) and Japanese and non-Japanese participants, CS Table 22.
- Sex, race, region, age and background C5 inhibitor treatment (eculizumab or ravulizumab), CS Table 23

The CS reports that results were broadly consistent with respect to the primary analyses, although this was based on observation of the data only as no statistical analysis was reported.

The CS narratively reports that subgroup analyses undertaken on the key secondary outcomes were [redacted] at week 12 for key subgroups such as sex and age. FACIT-F scores to week 24 'varied'. These subgroup analyses results are reported in CS Appendix E.

As all of the subgroup analyses were conducted on an interim analysis set, many had small participant numbers, and no statistical analysis was undertaken, therefore the meaning of these results is limited.

2.2.3 ALPHA trial adverse events overview

The CS presents treatment-emergent adverse events (TEAEs, i.e. started during or after the first dose) for the safety analysis set (N=86) during TP1, and for N=71 and

N=60 in TP2 and LTE, respectively. An overview of TEAEs is presented in Table 13. During TP2 and the LTE all patients received danicopan, therefore for simplicity the EAG has presented data for the total group during each period and the cumulative incidence in the [redacted] participants exposed to danicopan to the September 2022 data cut-off (CSR Table 34). Separate data for the DAN/DAN and PBO/DAN groups can be viewed in CS Table 28; there appears to be some variability between the groups, although these are likely due to the small numbers. It is possible that additional AEs emerge from future follow-up of people receiving danicopan, as the current trial follow-up is short.

During TP1, slightly more participants in the danicopan group experienced an AE compared with placebo (73.7% vs 62.1%), however the proportions with a SAE (5.3% vs 6.9%), an AE leading to withdrawal of intervention (5.3% vs 3.4%) an SAE leading to withdrawal of study intervention (1.8% vs 0%) and Grade 3 (17.5% vs 13.8%) or Grade 4 (1.8% vs 0%) AEs were similar.

Of [redacted] participants exposed to danicopan through to the September 2022 data-cut, [redacted] experienced an AE and [redacted] experienced an SAE. One participant experienced SAEs (TP1, blood bilirubin increased and pancreatitis) considered by the investigator as related to the study intervention and led to study discontinuation. Two participants also discontinued danicopan during TP1 due to nonserious AEs (abnormal liver enzyme values, hepatic enzyme increased), and one discontinued during the LTE (due to nonserious TEAE of abnormal liver enzyme laboratory values). No deaths or meningococcal infections (an AE of special interest) occurred throughout the study. Liver abnormalities were experienced by [redacted] of participants.

Table 13: Overview of TEAEs during each study period and cumulatively

	TP1		**TP2**	**LTE**	**Exposed to DAN to data-cut**
	DAN + C5i[a] [redacted]	**PBO + C5i[a]** [redacted]	**Total** [redacted]	**Total** [redacted]	[redacted]
	n (%)	**n (%)**	**n (%)**	**n (%)**	
Any AE	42 (73.7)	18 (62.1)	44 (62.0)	41 (68.3)	[redacted]
Any SAE	3 (5.3)	2 (6.9)	6 (8.5)	7 (11.7)	[redacted]

Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
AE leading to withdrawal of study intervention	3 (5.3)	1 (3.4)	0 (0.0)	1 (1.7)	[redacted]
SAE leading to withdrawal of study intervention	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]
AE by relationship					
Related	12 (21.1)	8 (27.6)	8 (11.3)	3 (5.0)	[redacted]
Not related	35 (61.4)	18 (62.1)	43 (60.6)	41 (68.3)	[redacted]
SAE by relationship					
Related	1 (1.8)	0 (0.0)	1 (1.4)	0 (0.0)	[redacted]
Not related	2 (3.5)	2 (6.9)	5 (7.0)	7 (11.7)	[redacted]
AE by toxicity					
Grade 1	33 (57.9)	16 (55.2)	39 (54.9)	34 (56.7)	[redacted]
Grade 2	23 (40.4)	15 (51.7)	19 (26.8)	22 (36.7)	[redacted]
Grade 3	10 (17.5)	4 (13.8)	9 (12.7)	6 (10.0)	[redacted]
Grade 4	1 (1.8)	0 (0.0)	1 (1.4)	2 (3.3)	[redacted]
AE of Special Interest					
Meningococcal infections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
Liver enzyme elevations[d]	8 (14.0)	3 (10.3)	6 (8.5)	2 (3.3)	[redacted]

[a] Eculizumab or ravulizumab.
b One patient in the DAN/DAN arm discontinued treatment in TP2 as a result of an AE that began in TP1. For this reason, the discontinuation is listed under TP1, as the time the AE was first recorded.
Abbreviations: AE: adverse event; AESI: adverse event of special interest; C5i: complement component 5 inhibitor; DAN/DAN: patients received danicopan as an add-on to ongoing C5 inhibitor treatment in TP1, and continued with treatment in TP2; LTE: long-term extension; N: number of patients in treatment group; n: number of patients; PBO/DAN: patients received placebo as an add-on to ongoing C5 inhibitor treatment in TP1 and switched to danicopan as an add-on to ongoing C5 inhibitor treatment in TP2.
Source: Adapted from CS Table 28 and CSR Table 34.

Grade 3 and 4 TEAEs

Grade 3 and 4 TEAEs are summarised in CS Table 30. In TP1 there appears to be a discrepancy between the values for any Grade 3 TEAE in the danicopan arm between CS Tables 28 (17.5%) and Table 30 (15.8%); the same two different values

are also reported in the CSR and the reason for the difference is unclear. The most common Grade 3 events (occurring in more than one participant) were alanine amino transferase (ALT) increased (n=3, 5.3%) in the danicopan arm, and anaemia (n=2, 6.9%) in the placebo arm. One participant in the danicopan arm experienced a Grade 4 event (pancreatitis, 1.8%)

Among the [redacted] participants exposed to danicopan through to the September 2022 data-cut, [redacted] participants had [redacted] Grade 4 TEAEs [redacted]

Adverse events of special interest

Meningococcal infections and liver enzymes elevation were adverse events of special interest (AESIs) in the ALPHA trial. No occurrences of meningococcal infections occurred during the study. Liver enzyme elevations during TP1 and TP2 are reported in CS Table 31. The most common event during TP1 in the danicopan arm was ALT increased (5.3%), followed by blood bilirubin increased (3.5%) and AST increased (3.5%). No events of ALT increased occurred in TP2.

Common TEAEs

TEAEs occurring in ≥5% of participants are reported in CS Table 29. These were generally balanced between treatment groups in TP1, with the most common events in the danicopan group being headache (10.5%), nausea (8.8%) diarrhoea (7.0%) and arthralgia (7.0%). The most comment events in the placebo group were anaemia (13.8%) and asthenia (13.8%), with nausea, diarrhoea, confusion, AST increased, headache and insomnia each occurring in 10.3%.

Among the [redacted] participants exposed to danicopan through to the September 2022 data-cut, the most frequent TEAEs were COVID-19, diarrhoea, headache, pyrexia, nausea and fatigue, occurring in [redacted], respectively.

Adverse events specified in the decision problem

BTH and thrombotic events were scoped outcomes and included in the company decision problem. BTH events that occurred during each stage of the study are summarised in

Table 14 below; a total of [redacted] participants exposed to danicopan experienced BTH, the CS reports that one patient reported a LDH level >2 times ULN in the trial, which is the definition of BTH used in other clinical trials. The EAG searched the CSR for thrombotic events and did not identify any.

Table 14: Summary of BTH events

	TP1		TP2	LTE	Exposed to DAN to data-cut
	DAN + C5i N=57	**PBO + C5i N=29**	**Total N=71**	**Total N=60**	[redacted]
Grade 1	0 (0.0)	0 (0.0)	[redacted]	[redacted]	
Grade 2	0 (0.0)	0 (0.0)	[redacted]	[redacted]	
Grade 3	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	
Totals (any grade)	0 (0.0)	0 (0.0)	[redacted]	[redacted]	[redacted]

Source: CS Table 30, CSR Tables

Danicopan phase II studies

The company's SLR identified two phase II studies of danicopan[14, 48] (CS Appendix D.3). These were excluded from the company's ITC and not summarised in the CS (although Kulasekararaj 2021[48] is presented in CS Appendix Table 25 of HRQoL studies). The studies were conducted concurrently; Kulasekararaj 2021 was a dose-finding study of danicopan as an add-on to eculizumab (n=12), whereas Risitano 2021 was a dose-finding study of danicopan monotherapy in patients who had not received complement inhibitor treatment (n=10). A summary of the studies is presented in

Table 15.

Serious adverse effects occurring in the Phase 2 studies are presented in Table 16.

Table 15: Study characteristics of Phase 2 studies of danicopan

Study	Key inclusion criteria	Intervention
Kulasekararaj 2021[48] NCT03472885 N=12 Phase 2, open-label study of danicopan in patients with an inadequate response to eculizumab Multicentre (international) 24 weeks plus long term extension period (not defined)	- PNH and RBC transfusion- dependent anaemia (≥1 RBC during 12 weeks prior) - Stable dose of eculizumab - Hb < 10 g/dL (and adequate reticulocytosis), platelets ≥ 40,000 per µl	Danicopan 100-200 mg TID Starting dose 100mg TID, N=10 150mg TID, N=2 50 mg escalations at 4 week intervals based on safety and Hgb levels Background eculizumab, IV 900mg every 2 weeks (Q2W), N=8 1200mg Q2W, N=2 1500mg Q2W, N=1
Risitano 2021[14] NCT03053102 N=10 Phase 2, open label study of danicopan in patients without complement inhibitor treatment Multicentre (international) 84 days	- Hb <12 g/dL - Adequate reticulocytosis according to investigator - LDH ≥1.5 x ULN - Platelet counts ≥50x10^9/L	Danicopan 100-200 mg TID Starting dose 100 - 150mg TID Escalations based on haemolysis control, assessed by LDH, for first 28 days. Thereafter based on haemoglobin response; absolute reticulocyte count, LDH, and indirect bilirubin.

Table 16: Serious adverse events in Phase 2 studies of danicopan

Kulasekararaj 2021[48] **N=12**	**Risitano 2021**[14] **N=10**
Discontinued due to SAE: 1/12 (8.3%)	Discontinued due to SAE: 1/10 (10%)
SAE: 2 (16.7%) Pneumonia Pulmonary hypertension / oedema	SAE: 1/10 (10%) Haemolysis Alanine aminotransferase increased Aspartate aminotransferase increased
Long-term extension period SAE: 7/11 (63.6%) Febrile neutropenia Haemolysis	

Pancreatitis Influenza like illness Pyrexia Device related infection Pyelonephritis Tracheobronchitis viral Schwannoma Haemoglobinuria	

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

The CS included one RCT from their SLR to compare danicopan with pegcetacoplan via a match adjusted indirect comparison (MAIC).

PEGASUS[15] (NCT03500549) was a phase 3 multicentre international open-label RCT to assess the efficacy and safety of pegcetacoplan compared with eculizumab in adults with PNH and a haemoglobin level of less than 10.5 g/dl despite treatment with eculizumab. It was the key trial in the NICE appraisal of pegcetacoplan (TA778).[23]

The trial consisted of three parts:

- 4-week run-in: all patients continued to receive current dose of eculizumab with the addition of pegcetacoplan 1080 mg subcutaneously twice weekly
- 16-week randomised controlled period: patients randomised (1:1 ratio) to pegcetacoplan monotherapy or eculizumab monotherapy
- 32-week period: all patients received pegcetacoplan

PEGASUS Risk of Bias

The company's SLR[43] judged PEGASUS to have an overall high risk of bias, with a high risk of bias arising from the randomisation process. However, the EAG notes that this judgment is due to 'No Information' responses regarding the methods of randomisation. The company also had some concerns regarding bias due to deviations from the intended interventions (effect of assignment to intervention), missing outcome data and measurement of the outcome.

The EAG examined the quality assessment of PEGASUS undertaken in the NICE appraisal of pegcetacoplan (TA778).[23] The evidence review group in TA778 considered that the PEGASUS trial was well-designed and well conducted, with appropriate randomisation and concealment of treatment allocation. The current EAG notes that PEGASUS was an open-label study and has some concerns regarding the risk of bias resulting from this.

Comparison of trial design and eligibility criteria: ALPHA and PEGASUS

As discussed in CS section B.2.10.3, there were a number of key differences in trial design and eligibility criteria between the two studies, these are summarised in Table 17. The company considered that some of these differences would cause biases in an indirect treatment comparison (ITC). The EAG agrees and discusses this further in section 2.4.

Table 17: Key differences between ALPHA and PEGASUS design

	ALPHA	PEGASUS
Study design		
Comparator arm	Eculizumab (52.4%) or ravulizumab (47.6%)	Eculizumab only
Blinding	Double blind (randomised period)	Open label
Run-in period	None	4 weeks: all patients received eculizumab + pegcetacoplan
Time-point of assessment	12 weeks	16 weeks (following the 4 week run-in with treatment)
Eligibility criteria		
Diagnosis	Documented diagnosis of PNH	Documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry
Diagnosis	CsEVH (haemoglobin level ≤ 9.5 g/dL and ARC ≥ 120 × 10^9/L)	Haemoglobin level <10.5 g/dL (despite stable treatment with eculizumab)
Transfusion history	≥1 transfusion within previous 6 month (protocol amendment made so no prior history of transfusion required)	-

Prior treatment	Received eculizumab or ravulizumab for ≥6 months at approved dose before study entry	Received eculizumab treatment for ≥3 months prior to screening
Labs	Platelet count ≥ 30 x10^9/L ANC ≥ 0.5 x10^9/L Haemoglobin level ≤9.5 g/dL - *Exclusions:* ALT >2 x ULN eGFR <30 mL/min/1.73 m^2	Platelet count >50 x10^9/L ANC > 0.5 x10^9/L Haemoglobin level <10.5 g/dL BMI <35.0 kg/m^2 [a] - -
Medical history	*Exclusions:* History of major organ transplant or HSCT History of aplastic anaemia or bone marrow failure requiring HSCT Received another investigational product with specified timeframe Complement deficiency Bleeding disorders Human immunodeficiency virus (HIV), hepatitis B or active hepatitis C History of *N meningitidis* infection	*Exclusions:* History of bone marrow transplantation Active bacterial infection Hereditary complement deficiency Certain cardiac conduction abnormalities, including QTcF prolongation >470ms and PR interval >280ms Personal or family history of long QT syndrome, torsade de pointes, or unexplained syncope

[a] CS Table 24 states BMI < 40 kg/m^2, however it is stated as <35.0 in the PEGASUS protocol and Clinical Trials register; the EAG notes that a protocol amendment was made on 8th Feb 2019 (Amendment 3, Version 1.0) to exclude participants with BMI ≥35.0.[15]

Abbreviations: ALT: alanine transaminase; ARC: absolute reticulocyte count; BMI: body mass index; C5: complement component 5; csEVH: clinically significant EVH; eGFR: estimated glomerular filtration rate; EVH: extravascular haemolysis; HIV: human immunodeficiency virus; HSCT: haematopoietic stem cell transplantation; PNH: paroxysmal nocturnal haemoglobinuria; pRBC: packed red blood cell; ULN: upper limit of normal

Baseline characteristics of trials in the MAIC: ALPHA and PEGASUS

Important differences in baseline characteristics were identified between ALPHA and PEGASUS. The company therefore created a subset of ALPHA that more closely aligned with that of PEGASUS by excluding participants with a BMI ≥ 40 or a platelet count ≤50,000/µL. The EAG notes that an amendment to the PEGASUS protocol

amendment was made on 8th Feb 2019 (Amendment 3, Version 1.0) to exclude participants with BMI ≥35.0.[15] The number of patients with BMI ≥35.0 in either study is not reported.

A summary of baseline characteristics in the ALPHA subset (N=[redacted]) and PEGASUS is presented in Table 19. A number of differences between the two trials remained, but no further exclusions were made in order to keep an adequate sample size:

- Participants in the ALPHA subset were slightly older than in PEGASUS, and there were a higher proportion of Asian participants and fewer with race not reported in the ALPHA subset. There was also an imbalance in the proportion of females in the respective intervention arms and comparator arms across the trials.
- [redacted] participants in the ALPHA subset had received a transfusion within the previous 12 months, compared with 75% in PEGASUS. However, fewer participants in ALPHA had received four or more transfusions in the previous 12 months.
- Platelet counts, bilirubin levels and haemoglobin levels were lower in the ALPHA subset compared with PEGASUS, while reticulocyte count was higher in the ALPHA subset. Elevated bilirubin levels are correlated with haemolysis. Low reticulocyte counts are indicative of aplastic anaemia, however as both ALPHA and PEGASUS had the same eligibility requirements (≥ 120 x 10^9/L), the company considered that both populations had controlled or resolved aplastic anaemia (Clarification A10). Reticulocyte counts and haemoglobin levels were adjusted for in the adjusted MAICs (see section 2.4.1).
- The CS states that FACIT-Fatigue scores were ‘marginally higher’ in the ALPHA subset compared with PEGASUS, but the EAG notes that the difference is not clinically important.

2.4 *Critique of the indirect comparison and/or multiple treatment comparison*

2.4.1 Indirect comparison methods

The company performed a series of MAICs to compare the efficacy of danicopan in the ALPHA trial to the efficacy of pegcetacoplan in the PEGASUS trial. A MAIC analysis attempts to adjust for some of the baseline differences between the trials which may otherwise introduce bias into a naïve comparison of their outcomes, and is most suited when there is summary data available for one trial and patient level data available for the other. The company applied two different weighting algorithms: the Signorovitch et al. approach[49] (referred to onwards as the MAIC) and the Jackson et al. approach[50] (referred to as the maximised effective sample size [ESS]).

The company performed anchored and unanchored analyses of both weighting approaches, where the anchored comparisons compare the relative effects of danicopan and pegcetacoplan against their respective placebo arms, whilst the unanchored comparisons compare the absolute effects of the danicopan and pegcetacoplan arms. Typically, an anchored comparison is favoured as it has slightly softer assumptions, requiring only the matching of effect-modifying characteristics rather than also requiring prognostic variables. (NICE TSD 18)[51]

In their analyses, the company assumed equivalence between ravulizumab and eculizumab due to them both being used in ALPHA, but only eculizumab being used in PEGASUS. This preserved the starting sample size, which reduced slightly from the ALPHA analysis population due a small number of people in the ALPHA trial not meeting the inclusion criteria for the PEGASUS trial based on either a BMI ≥ 40kg/m^2 or a platelet count ≤ 50,000/μL.

The analyses could not account for differences between the trials run-in period, as noted by the company, or the differences in trial eligibility discussed in section 2.3.

The EAG noted an additional difference between the trials in how they censored patients who received a transfusion during the trial period. This led the EAG to request additional analyses where a consistent censoring rule was applied across the two trials. For the analysis of the primary outcome in ALPHA (haemoglobin level) patients who received a transfusion at week 8 or later had their week 12 haemoglobin level excluded from the analysis. Meanwhile, in PEGASUS if a patient

received a transfusion at any point in the trial follow-up, then all their subsequent haemoglobin levels were censored. The EAG requested the company perform analyses where the rule applied in the ALPHA study reflected what was done in the PEGASUS trial.

Across all the indirect comparison analyses performed, the company only included two covariates for adjustment (mean baseline haemoglobin level and mean baseline reticulocyte count). The company states that this was the only feasible analysis due to limitations over initial and resulting sample sizes. The EAG's clinical expert confirmed that these were the two most important variables to consider when adjusting. Whilst the EAG accepts the rationale for the company's choice of variables, there are a number of other important prognostic and effect-modifying variables that are not included meaning that these indirect comparison analyses are at an extremely high risk of bias. Ideally, the sample size would permit the inclusion of a wider number of these baseline factors such as LDH, FACIT-F, age, sex, transfusion history, platelet counts, bilirubin levels and history of aplastic anaemia, which would in turn provide a more robust estimate of relative efficacy.

Initially it appeared as if the company used the same weightings for the anchored and unanchored indirect comparison analyses as only one set of weights was provided without appropriate description. In the FAC stage, the company clarified that different weightings were used, based on anchoring status.

Table 18 shows how the effective sample sizes of the indirect comparisons contain roughly a third of the information compared to the original ALPHA analysis population. These small numbers mean there is considerable uncertainty over the relative efficacy estimates, which would only increase by the further reduced sample size if additional variables were to be added.

The outcomes compared by the company are from the randomised period of each trial (ALPHA – 12 weeks; PEGASUS – 16 weeks). The company state that this is because one outcome (transfusion avoidance) was only reported at this point, however it is not clear why the company have not sought to compare other outcomes based on longer follow-up.

Table 18: Resulting sample sizes from indirect comparisons

	Danicopan	Placebo
ALPHA Trial	42	21
ALPHA Trimmed Population to match PEGASUS eligibility	[redacted]	[redacted]
MAIC Effective Sample Size	13.908	6.599
Maximised ESS Effective Sample size	15.271	7.395

2.4.2 Indirect comparison results

The company is aware of the many limitations of the MAIC and maximised ESS analyses, and so presented the results in their submission appendix. They do not consider the results suitable for drawing conclusions over relative efficacy and do not carry them into the economic analysis. Instead they prefer to use information from a naïve comparison.

The EAG agrees that the indirect comparisons have severe limitations, however almost all the same limitations apply to a naïve comparison, with only the sample size increasing for inputs from the ALPHA trial. To demonstrate this, the EAG presents in Table 19 the baseline characteristics of the original ALPHA analysis set, the ALPHA MAIC weighted population and the PEGASUS trial. It is clear that both the MAIC and original ALPHA populations have a number of differences to the PEGASUS population. Looking at the baseline variables within the ALPHA trial, the EAG notes that some variables that are higher for one arm in the subset ALPHA population are now lower in that arm after the MAIC weights are applied (e.g. time since PNH diagnosis, ≥ 4 transfusions in previous 12 months), and for others it introduces or enlarges differences between the arms (e.g. FACIT-F, total and indirect bilirubin). Hence, all of the comparisons have severe limitations and the EAG is unable to recommend a preferred option.

Table 19: Comparison of baseline characteristics across ALPHA, ALPHA MAIC and PEGASUS populations, adapted from CS Doc B Table 25 and CS Appendices Table 15

Characteristic		ALPHA – subset population		ALPHA – Maximised ESS		PEGASUS	
		Danicopan + C5i[a] (n=[redacted])	Placebo + C5i[a] (n=[redacted])	Danicopan (n=15.271)	Placebo (n=7.395)	Pegcetacoplan (n=41)	Eculizumab (n=39)
Age (years) - mean (range)		[redacted]	[redacted]	[redacted]	[redacted]	50.2 (19–81)	47.3 (23–78)
Age >65 (years) - %		[redacted]	[redacted]	[redacted]	[redacted]	24%	18%
Sex (female) - %		[redacted]	[redacted]	[redacted]	[redacted]	66%	56%
Race - %	Asian	[redacted]	[redacted]	[redacted]	[redacted]	12%	18%
	Black	[redacted]	[redacted]	[redacted]	[redacted]	5%	0%
	White	[redacted]	[redacted]	[redacted]	[redacted]	59%	64%
	Other	[redacted]	[redacted]	[redacted]	[redacted]	0%	3%
	NR	[redacted]	[redacted]	[redacted]	[redacted]	24%	15%
BMI - mean ± SD		[redacted]	[redacted]	[redacted]	[redacted]	26.7±4.3	25.9±4.3
No transfusions within previous 12 months - %		[redacted]	[redacted]	[redacted]	[redacted]	24%	26%
Time since PNH diagnosis (years) – median (range)		[redacted]	[redacted]	[redacted]	[redacted]	6.0 (1–31)	9.7 (1–38)
Duration of prior treatment with eculizumab/C5 inhibitor (years) – median (range)		[redacted]	[redacted]	[redacted]	[redacted]	4.4 (0.4–17.1)	3.4 (0.3–13.8)
Platelets (x10^9/litre) – mean ± SD		[redacted]	[redacted]	[redacted]	[redacted]	166.6±98.3	146.9±68.8
≥4 transfusions in previous 12 months %		[redacted]	[redacted]	[redacted]	[redacted]	51%	59%
Haemoglobin (g/dl) – mean ± SD		[redacted]	[redacted]	[redacted]	[redacted]	8.69±1.08	8.68±0.89
Reticulocyte count (×10^{-9}/L) – mean ± SD		[redacted]	[redacted]	[redacted]	[redacted]	217.5±75.0	216.2±69.1
LDH (U/L) - mean ± SD		[redacted]	[redacted]	[redacted]	[redacted]	257.5±97.6	308.6±284.8
Total bilirubin (µmol/L) - mean ± SD		[redacted]	[redacted]	[redacted]	[redacted]	42.5±31.5	40.5±26.6
Indirect bilirubin (µmol/L) - mean ± SD		[redacted]	[redacted]	[redacted]	[redacted]	34.7±28.5	32.9±23.0
FACIT-F score - mean ± SD		[redacted]	[redacted]	[redacted]	[redacted]	32.2±11.4	31.6±12.5

***indicates a difference of 10% or greater in mean or proportion from the relevant arm of the PEGASUS trial.**

[a] Eculizumab or ravulizumab. [b] Normal reference range.

Abbreviations: BMI: body mass index; C5i: complement component 5 inhibitor; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; LDH: lactate dehydrogenase; N: total number of patients in treatment arm; n: number of patients; NR: not reported; SD: standard deviation.
Source: Adapted from CS Table 25

The results of the company indirect comparison are show in Table 20. Across all the analyses, only a small minority of the analyses suggest there might be a benefit of danicopan over pegcetacoplan. Most that suggest a benefit for danicopan are unanchored analyses and are for outcomes where the placebo arms of each trial performed noticeably differently to each other, suggesting an unanchored comparison is not appropriate.

Table 20: Results from indirect comparisons, adapted from Company Submission Appendices Table 16

Outcome	Danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan	
	Anchored analyses	Unanchored analyses
Mean difference in haemoglobin level from baseline (g/dL) (95% CI)		
Naïve	[redacted]	[redacted]
Adjusted (Signorovitch *et al.*)	[redacted]	[redacted]
Adjusted (Jackson *et al.*)	[redacted]	[redacted]
Mean difference in absolute reticulocyte count from baseline (10^9/L) (95% CI)		
Naïve	[redacted]	[redacted]
Adjusted (Signorovitch *et al.*)	[redacted]	[redacted]
Adjusted (Jackson *et al.*)	[redacted]	[redacted]
Mean difference in LDH level from baseline (U/L) (95% CI)		
Naïve	[redacted]	[redacted]
Adjusted (Signorovitch *et al.*)	[redacted]	[redacted]
Adjusted (Jackson *et al.*)	[redacted]	[redacted]
Mean difference in FACIT-F score level from baseline (95% CI)		
Naïve	[redacted]	[redacted]
Adjusted (Signorovitch *et al.*)	[redacted]	[redacted]
Adjusted (Jackson *et al.*)	[redacted]	[redacted]
Mean difference in proportion of patients with transfusion avoidance (%) (95% CI)		
Naïve	[redacted]	[redacted]
Adjusted (Signorovitch *et al.*)	[redacted]	[redacted]
Adjusted (Jackson *et al.*)	[redacted]	[redacted]

*indicates that mean effect size estimate suggests benefit in favour of danicopan

The EAG assumes the company has used the trimmed data set of ALPHA for the naïve comparison, as the EAG performed their own naïve comparison of the

reported trial outcomes which shows minor inconsistency regarding relative effect size estimates (Table 21). Overall, the majority of estimates are not associated with a potential benefit in favour of danicopan. Outcomes for the trimmed dataset were not provided.

Table 21: Comparison of results from PEGASUS and ALPHA trials

	ALPHA		PEGASUS	
	Danicopan	Placebo	Pegcetacoplan	Placebo
Mean change in haemoglobin level from baseline (g/dL) (vs placebo)#				
Unanchored (Anchored)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in absolute reticulocyte count from baseline (10^9/L)				
Unanchored (Anchored)	[redacted]	[redacted]	-136* [redacted]	[redacted]
Mean change in LDH level from baseline (U/L) (vs placebo)				
Unanchored (Anchored)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in FACIT-F score level from baseline (vs placebo)				
Unanchored (Anchored)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in proportion of patients with transfusion avoidance (%) (vs placebo)				
Unanchored (Anchored)	[redacted]	[redacted]	[redacted]	[redacted]

*indicates anticipated benefit for either danicopan or pegcetacoplan in the naïve comparison in unanchored or (anchored) analysis. # note the trials used different censoring rules related to transfusions.

The analyses provided by the company have severe weaknesses and uncertainties, and hence the EAG conclude that it would not be appropriate to conclude that danicopan offers benefit over pegcetacoplan. The analyses provided suggest that danicopan is more likely to be inferior.

The EAG requested that the company perform a number of sensitivity analyses on the data from the ALPHA trial to explore the impact of the censoring rule for transfusions.

The EAG has compiled the key outcomes provided for Week 12 in Table 22. As more transfusions were received in the placebo arm of ALPHA, it is anticipated that the benefit of danicopan would increase as the censoring rule becomes more severe due to the beneficial effects of transfusions being removed. The most

severe censoring rule of censoring after any transfusion is consistent with approach taken in the analysis of the primary outcome of change in Hb in the PEGASUS trial.

When this rule is applied to the ALPHA trial data, a mean difference of [redacted]g/dL ([redacted]) is estimated, compared to a difference of 3.8g/dL (2.3, 5.3) in PEGASUS. The effect estimates do not all increase as expected as the censoring rule becomes stronger. The EAG notes that when the same rule is applied for ALPHA as was done in PEGASUS, that the mean difference in FACIT-F score [redacted] compared to the difference estimated for pegcetacoplan from PEGASUS of 11.9 (5.5, 18.3).

Table 22: Week 12 outcomes from ALPHA varying censoring rule.

All results are: Dan – Plac (95% CI)	No censoring	Censored if transfusion at 8 weeks or later.	Censored after any transfusion
Change in Hb	[redacted]	2.44 (1.69, 3.20)	[redacted]
Change in FACIT Fatigue score	6.12 (2.33, 9.91)	[redacted]	[redacted]
Change in ARC	-87.2 (-117.7, -56.7)	[redacted]	[redacted]
Change in LDH	-20.60 (49.30, 8.20)	[redacted]	[redacted]
Total PNH RBC Clone Size	27.63 (13.03, 42.24)	[redacted]	[redacted]
PNH RBC Type III Clone Size	[redacted]	[redacted]	[redacted]
PNH RBC Type II Clone Size	[redacted]	[redacted]	[redacted]
Change in EQ-5D-3L	[redacted]	[redacted]	[redacted]
Note that 13/21 (62%) placebo+C5i patients received a transfusion compared to 7/42 (17%) danicopan + C5i.			
ARC: absolute reticulocyte count, CI: confidence interval, dan: danicopan, Hb: haemoglobin, plac: placebo, PNH: paroxysmal nocturnal haemoglobinuria, RBC: red blood cell.			

2.5 *Additional work on clinical effectiveness undertaken by the EAG*

As the company's SLRs did not consider the comparators iptacopan, and because the EAG wanted to check for any additional evidence on the effectiveness and/or real-world use of pegcetacoplan the EAG ran brief, targeted Medline and Embase searches for iptacopan and pegcetacoplan. The EAG Additional searches run by the EAG can be found in Appendix 4.

The EAG screened the additional references identified in their update searches using the same PICO as the company submission (CS Appendix Table 4). No new studies of pegcetacoplan were identified for the SLR of clinical effectiveness studies although secondary publications from the PEGASUS trial were identified. The searches identified six studies relating to RWE of pegcetacoplan. The most relevant study (NCT05776472) is ongoing and due to publish results in 2028.

EAG searches for evidence of iptacopan identified two phase III trials and a proof of concept phase II study. Iptacopan is a NICE scoped comparator to danicopan add-on treatment (and vice versa) and is undergoing appraisal by NICE (ID6176, expected publication June 2024). It is a Factor B inhibitor which is taken orally twice daily. The EAG has summarised the two key iptacopan trials for context. The trial results are presented on ClinicalTrials.gov but the full publications are not yet available:

- APPOINT-PNH (NCT04820530): 24-week single-arm study of 40 treatment-naïve patients
- APPLY-PNH (NCT04558918): an open-label 24-week RCT of 97 treatment-experienced patients with csEVH comparing iptacopan monotherapy versus continued treatment with eculizumab or ravulizumab

The eligibility criteria for the APPLY-PNH RCT differed slightly to those for ALPHA: clone size ≥10% was required for a diagnosis of PNH; and csEVH was defined by Hb <10 g/dL and reticulocyte count ≥100 × 109 cells/L. Key baseline characteristics were broadly similar between the two RCTs, although only 58% of APPLY-PNH had received a red blood cell transfusion in the 6 months to randomisation compared to 87.3% within 24 weeks of the first study dose in the IAS of the ALPHA trial, and eculizumab was taken by 65% of participants in APPLY-PNH, compared with 41% in ALPHA. A significant difference in the co-primary outcomes was found in favour of iptacopan compared with a C5i (NCT04558918):

- The proportion of participants with sustained increase of haemoglobin levels ≥ 2 g/dL from baseline in the absence of transfusions: 82.3% vs 2.0%

- The proportion of participants with a sustained haemoglobin level ≥ 12 g/dL in the absence of transfusions: 68.8% vs 1.8%

Breakthrough haemolysis was experienced by 3.2% (compared with 17% of C5i group). One participant had a thrombotic event, myocardial infarction, not assessed as being related to iptacopan.

Generalisability of ALPHA population

The CS states in Section B.2.5 that the ALPHA trial population is broadly representative to the global PNH population. In the absence of UK data the company compared the participant characteristics in ALPHA with those in the International PNH Registry. The EAG has compared key participant characteristics from ALPHA (those included in the first interim analysis n=63) with two analyses of the PNH database[3, 52] and also the small UK based study referenced in CS Section B.2.13.2.[53] (See Appendix 2).

The IAS group in the ALPHA trial had a higher proportion of Asians, and a lower percentage of white participants compared to the other trials analysed. In addition, the age at baseline was higher in the ALPHA trial than in the PNH registry analyses. There were also differences in disease characteristics between the participants in the ALPHA trial and comparators; the median haemoglobin at baseline of the IAS population was 78.0 g/L, which was lower than any of the other studies, including the 2020 analysis of patients from the PNH registry not on treatment at baseline[3]; of note is that a key inclusion criteria for the ALPHA trial was haemoglobin <9.5g/dl (<95 g/L) The percentage of patients with a history of PNH-associated aplastic anaemia was lower in the ALPHA trial ([redacted])(clarification A6) compared to other analyses of PNH populations; although in ALPHA all cases were either resolved or controlled prior to study entry (Clarification A2), whereas this was not known for the other studies. The EAG clinical expert indicated that when aplastic anaemia is controlled, this would not be a significant factor. CS Section B.2.13.2 states that [redacted] of centres in ALPHA were from the UK, and CSR Table 14.1.1.4.2 reports that there were [redacted] UK participants randomised ([redacted]). The EAG considers that together with the small proportion of UK participants in ALPHA, the

differences in characteristics identified lead to concerns over the generalisability of the ALPHA population to the PNH population in the UK.

2.6 *Conclusions of the clinical effectiveness section*

The CS presents evidence from the ALPHA trial, a phase III multinational double-blind RCT comparing danicopan as an add-on to eculizumab or ravulizumab versus placebo as an add-on to eculizumab or ravulizumab. ALPHA is ongoing and interim analyses were reported. The trial consists of a 12-week randomised period, followed by open label extension periods of 12 weeks, one year and two years, in which all participants received danicopan as an add-on treatment.

Interim-analyses (20th September 2022 data-cut) of ALPHA found a statistically significant improvement for danicopan compared with placebo (both as an add-on to eculizumab or ravulizumab) for all key outcome measures after 12 weeks of treatment, including surrogate endpoints for EVH (change in haemoglobin, proportion of participants with haemoglobin increase ≥2 g/dL in the absence of transfusion, proportion of participants avoiding transfusion, absolute reticulocyte count) and change in FACIT-Fatigue score. There were no differences between the groups in overall HRQoL as measured by the EQ-5D-3L UK health state index score or EORTC QLQ-C30 Global Health Status. Serious adverse events, adverse events leading to withdrawal of intervention, and grade 3 and 4 adverse events were similar between groups. Of [redacted] participants exposed to danicopan through to the September 2022 data-cut, including non-randomised phases of the trial, [redacted] experienced a serious adverse event.

The EAG has some concerns regarding the evidence provided. There are concerns with the overall risk of bias in ALPHA, due to potential bias regarding unreported data for 23/86 (27%) of randomised participants. There are also uncertainties regarding the generalisability of the population in ALPHA to the patient population in England and Wales eligible for treatment.

The data available did not allow for a meaningful comparison to pegcetacoplan to be performed. Indirect comparisons that were performed showed unclear and inconsistent estimates of relative effect.

3 COST EFFECTIVENESS

3.1 *EAG comment on company's review of cost-effectiveness evidence*

3.1.1 Search strategies

An appropriate range of sources were searched to identify economic and HRQoL studies, including bibliographic databases as well as websites of HTA agencies, Google, reference lists, publications from independent research institutions, patient groups, and conference proceedings (CS Appendix D 1.1).

The search strategies for Embase, MEDLINE and the Cochrane Library for the original November 2022 SLR and update search carried out on the 12th June 2023 reported in CS Appendix D 1.1. Table 1 and Table 2 are not sufficiently comprehensive. Phrase searching is used to search for the terms for extravascular haemolysis (EVH), whereas use of Boolean AND or proximity operators to link terms would have been more sensitive. Indexing terms, for example Hemolysis/ are not included. The search could have also included search terms for C5 inhibitors (eculizumab or ravulizumab) to capture studies reporting that patients were on C5 inhibitors as well as terms for inadequate response (and combined this using the Boolean operator Or) to increase the sensitivity. The used in the original SLR didn't include the Emtree indexing term paroxysmal nocturnal hemoglobinuria/. However, this term was included in the SLR update (12th June 2023, search number #1, Table 2, Appendix D.1.1) The free text search lines searched for title and abstract only and did not included keywords. This means that records with key population terms in the keyword field terms would have been missed. Search line 4 combines phrases for terms related to suboptimal response. The search would be more comprehensive if it searched for those terms using a Boolean operator or adjacency searching in-between words. Search line 5 searches for terms related to suboptimal or inadequate response but combines these using a single adjacency operator. This would be more sensitive if it searched for terms with a numerical character attributed to the adjacency operator as searching using adj searches for terms separated by a single space. Indexing terms for this concept are not included, for example Hemolysis/ are not included.

The update search reported in Table 2 includes an additional search line: ((remain or persisten* or continu*) adj an?emia).ti,ab. This additional search line means that the later searches are not a true update of the 2022 searches (CS Appendix D.1.1. Search strategy, Table 2). The EAG ran brief, targeted Medline and Embase searches for PNH and pegcetacoplan to see if we could identify any additional evidence reporting on the real-world use. The EAG also ran additional targeted searches for danicopan or iptacopan, pegcetacoplan, eculizumab or ravulizumab and cost-effectiveness or quality of life and was unable to find any additional cost-effectiveness studies relating to PNH and cost-effectiveness or quality of life. The EAG additional searches run can be found in the Appendix 4, and the studies looked at in full-text detail

The EAG has some concerns about the reporting of the numbers of results in the PRISMA flow diagram (CS Appendix D.2 Figure 1) and the write up in Appendix D.2 The company combined the results of the original and update SLR searches and report the number of included studies only of the original SLR (n=35). A more transparent approach would have been to present two PRISMA flow-diagrams, one for the original SLR and one for the update. The PRISMA flow-diagram does not present an accurate picture of how many results were assessed for eligibility in the original SLR.

3.2 *Summary and critique of the company's submitted economic evaluation by the EAG*

The following sections summarise components of the economic evaluation submitted by the company and provide EAG critique.

3.2.1 NICE reference case checklist

The EAG's comments on the adherence of the company submission to the NICE reference case are provided in

Table 23: NICE reference case checklist

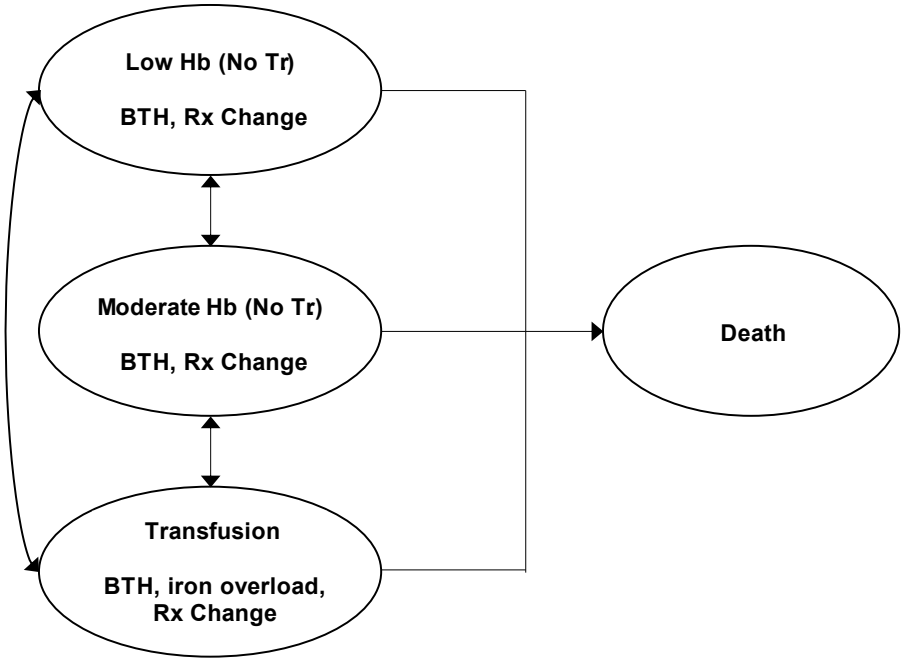
Table 23.

Table 23: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

3.2.2 Model structure

The company produced a *de novo* Markov cohort model for this submission. This comprised four health states defined by haemoglobin levels ('Low Hb' and 'Moderate Hb'), blood transfusion status, and death (see Figure 1).



Footnotes: Rx change refers to the changes in PNH treatment dosing regimens patients receive upon experiencing a BTH event.
Abbreviations: BTH: breakthrough haemolysis; Rx: treatment; SAE: serious adverse event; Tr: transfusion.

Figure 1: Company model structure (Fig.14 CS doc B)

Health states are mutually exclusive and mutually exhaustive with a cut-off Hb level of 9.5 g/dL set by the company in line with the inclusion criteria of the ALPHA trial:

- Low Hb (No Tr.): Haemoglobin level <9.5 g/dL and not currently receiving a transfusion
- Moderate Hb (No Tr.): Haemoglobin level ≥9.5 g/dL and not currently receiving a transfusion
- Transfusion: Currently receiving a transfusion
- Death

All patients enter the model in the 'Low Hb (No Tr.)' state and progress through the model in 4-week cycles. Patients may remain in their current health state or move to

a different health state or ‘death’. ‘Death’ is an absorbing health state where patients stay for the remaining time horizon of the model. Movement of patients is informed by health-state transition probabilities applied at the start of each cycle. The health states and transition probabilities used do not correspond to specific clinical effectiveness outcome presented by the company, which represents an inconsistency between the clinical and cost effectiveness sections.

Each health state has a utility value assigned. Costs apportioned in the model included drug acquisition and administration costs, monitoring costs, transfusion costs, BTH management costs, costs of iron overload, and AE management costs.

In each cycle, the number of costs and utilities are multiplied by the proportion of patients in each health state to calculate weighted costs and QALYs. The weighted costs and QALYs per cycle were then summed for each treatment arm across the entire time horizon of the model. Incremental costs and QALYs by treatment arm were subsequently calculated. Half-cycle correction was applied to both costs and health benefits to account for transition across health states which may occur at any point within a model cycle. Parameters for the model are generally divided into three stages to reflect the different trial treatment periods of ALPHA and PEGASUS (TP1, TP2, LTE). Whilst this allows for variability between short-term and long-term probabilities, it also splits the data into smaller groups, meaning the uncertainty associated with each parameter is increased. For example, rare events that may have occurred in only one period by chance might wrongly be represented with zero probabilities in other periods. It is the long-term parameters which apply for the majority of the model time horizon. Limited follow-up and small patient numbers, particularly in the long-term follow-up means there is high uncertainty around all input parameters.

3.2.3 Population

The population considered within the model are adult patients with PNH who have clinically significant EVH while on treatment with a C5 inhibitor (eculizumab or ravulizumab). As noted in the decision problem (see Table 4), the EAG considers that the population is generally in line with the NICE scope. However, the NICE scope states ‘signs and symptoms of EVH’, whereas the CS decision problem

specifies ‘clinically significant EVH’. Both the company and EAG clinical expert confirm there is no standardised definition of clinically significant EVH.

Baseline characteristics at model entry were patients’ age (mean 54.30 years) and sex (41.27% male), with all population characteristics informed by data from the ALPHA trial (see CS doc B, Section B.3.3).

3.2.4 Interventions and comparators

The intervention considered within this appraisal is danicopan as an add-on treatment to eculizumab or ravulizumab. A single comparator, pegcetacoplan, is presented by the company in their cost-effectiveness analysis. This excludes eculizumab or ravulizumab alone as standard of care for PNH patients, and iptacopan (which had not received a positive recommendation from NICE at the time of submission), which are listed in the NICE final scope.[54]

3.2.5 Perspective, time horizon and discounting

The perspective is as per the NICE reference case,[55] with benefits from a patient perspective and costs from an NHS and personal social services (PSS) perspective. In the base case, costs and benefits were discounted at an annual rate of 3.5% in line with NICE reference case. The 45.7-year time horizon is sufficient to capture all important differences in costs and outcomes between technologies compared given the model cohort age.

3.2.6 Treatment effectiveness and extrapolation

3.2.6.1 Transition probabilities

The company modelled the movement of people through their Markov model using transition probabilities from different sources.

For the company’s base case modelling of the danicopan + C5i group, the transition probabilities were estimated from a multinomial model fitted to data from the ALPHA trial. In response to the clarification questions, the company confirmed that the model included terms for initial state, age, treatment group. This appears to be a minor contradiction to the company submission which states that the model included terms for age, initial state, treatment period, and treatment group.

For the company's modelling of pegcetacoplan, they use transition probabilities reported by Hakimi et al.[56] in their published cost-effectiveness comparison of pegcetacoplan and ravulizumab based on the PEGASUS trial. Hakimi et al. reports that they were estimated from a multinomial model which included terms for previous health state, treatment, visit category and age, alongside a patient level random intercept term.

The company's choice of transition probabilities is effectively implementing a naïve comparison of the relevant arms of the ALPHA and PEGASUS trials, and does not account for underlying differences in population baseline characteristics or the differences in the models used to estimate the transition probabilities. Note that the transition probabilities reported by Hakimi et al. also used a slightly different cut-off for Hb when defining their health states, and based them on a threshold of 10.5g/dL rather than 9.5g/dL as was used in this appraisal. The threshold of 10.5g/dL was also used in the transition probabilities from the indirect comparisons.

The transition probabilities used by the company for danicopan + C5i and pegcetacoplan are shown in Table 24, where small differences can be observed. From the starting low Hb health state, people receiving danicopan have a higher probability of moving to the moderate Hb health state, though people receiving pegcetacoplan have a higher probability of remaining in the moderate Hb health state. Pegcetacoplan is associated with a higher transition probability to the transfusion health state from the low Hb health state, and a higher probability of remaining in the transfusion health state.

Table 24: Transition probabilities used in company base case for danicopan and pegcetacoplan

	Danicopan + C5i		
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]
	Pegcetacoplan		

Beginning health state	Ending health state		
	Low Hb (No Tr.)	Moderate Hb (No Tr.)	Transfusion
Low Hb (No Tr.)	0.437	0.490	0.073*
Moderate Hb (No Tr.)	0.031	0.966	0.003
Transfusion	0.266	0.612	0.122

*Note that the company increased the reported value of 0.072 from Hakimi et al. to 0.073 so that the sum of probabilities was equal to 1.

The EAG's principal concern with the company's approach is that it ignores the differences in the underlying populations and is at high risk of bias. This is supported by a comparison of the transition probabilities estimated for the comparator arms of the ALPHA and PEGASUS trials, as shown in

Table 25. Furthermore, these transition probabilities are estimated from limited follow-up of a small sample size, and are applied for the full model time horizon.

Comparing these two groups, which are considered equivalent under the company's analysis, there are much larger differences than when comparing the transition probabilities of danicopan and pegcetacoplan. The C5i arm of PEGASUS shows a higher probability of moving to the transfusion health state from the low Hb state, and a higher probability of remaining in the transfusion health state. There is also a much lower probability of remaining in the moderate Hb health state. These differences suggest firstly that a naïve comparison is not appropriate, but also do not support that any benefit apparent from a naïve comparison can be attributed to the danicopan treatment rather than the underlying differences. A visual comparison of the relative difference in the transition probabilities of the intervention arms of the ALPHA and PEGASUS trials suggests that pegcetacoplan is more likely to provide greater benefit. This would also be more consistent with the naïve and indirect comparisons of clinical outcomes presented in section 2.4.

The company uses the transition probabilities from the C5i arm of ALPHA to model the transitions for people who discontinue their initial treatment in either arm. The company does not use the transition probabilities for C5i from the PEGASUS trial.

Table 25: Transition probabilities for C5i arms of ALPHA and PEGASUS trials.

	C5i from ALPHA		
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]
	C5i from PEGASUS		
Beginning health state	**Ending health state**		
	Low Hb (No Tr.)	**Moderate Hb (No Tr.)**	**Transfusion**
Low Hb (No Tr.)	0.652	0.001	0.347
Moderate Hb (No Tr.)	0.742	0.030	0.2280
Transfusion	0.404	0.001	0.595

Ultimately, the EAG considers the data are not sufficient to support any meaningful comparison of danicopan and pegcetacoplan. However it performs an analysis which assumes equal efficacy of danicopan and pegcetacoplan in terms of transition probabilities, and events such as BTH and iron overload. The only difference in efficacy is the treatment related disutility for administration and adverse events.

The EAG also presents an economic analysis comparing danicopan to C5i, as there are less concerns about the comparability of the two arms within the ALPHA trial. This was achieved by utilising the company's model and setting all people in the pegcetacoplan arm as having switched to C5i monotherapy from the first cycle.

The company performed some alternative analyses which explored the impact of estimating the transition probabilities based on a cut-off of 10.5g/dL for danicopan + C5i from the MAIC and maximised ESS indirect comparisons. Additionally, in response to clarification questions, the company fitted a model to the ALPHA data which included a patient level random effect, to improve the consistency with the model used by Hakimi et al.[56] The effect of this on the outcomes was minimal.

The EAG presents in Table 26 the transition probabilities for danicopan across the various analyses the company has performed. It is not possible to ascertain whether the variation is attributed mostly to the change in cut-offs, or the weightings. From the volatility of estimates across the analyses, the EAG is unable to conclude whether any analysis can be deemed reliable. A similar degree of variation is seen across the transition probabilities for the C5i arm, which the company also provided for each analysis.

Table 26: Comparison of transition probabilities for danicopan across multiple approaches

	Danicopan – ALPHA trimmed (company preferred)		
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]
	Danicopan – MAIC Weighted Anchored		
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]
	Danicopan – MAIC weighted Unanchored		
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]
	Danicopan – Maximised ESS Anchored		
	Ending health state		

Beginning 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]
	Danicopan – Maximised ESS Unanchored		
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]
	Danicopan – ALPHA trimmed with random patient effect		
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]

3.2.6.1 Mortality

The company assumed the probability of mortality to be equal between treatments and used estimates based on age and sex-matched general population mortality for England. Their rationale was that current treatments such as eculizumab and ravulizumab are effective in managing IVH with life-threatening complications of IVH such as thrombosis well-controlled, and that EVH is not life-threatening and does not impact patients' survival (CS doc B, section B.3.3.7). The EAG considers this largely appropriate, however cannot rule out the possibility of a slight increased mortality rate for patients who do not respond well to danicopan or pegcetacoplan and revert to C5i therapy when this has previously proven unsatisfactory.

3.2.7 Health related quality of life

HRQoL data for use in the model was retrieved through a SLR as detailed in Appendix H of the company submission and discussed by the EAG (section 3.1). 13 unique studies were identified that reported on HRQoL data in patients with PNH experiencing EVH.

Health state utility values (HSUVs) and utility decrements used in the cost-effectiveness analysis are summarised below in

Table 27.

Table 27: Summary of utility values for cost-effectiveness analysis (CS doc B, Table 51)

Parameter	Utility value	Reference in company submission (section and page number)	Justification
Low Hb	0.8181	Section B.3.4.1, page 114	EQ-5D-3L data were obtained directly from patients during the ALPHA trial.
Moderate Hb	0.8644		
Transfusion	0.7018		
Death	0.000		
ALT increased	−0.050	Section B.3.4.4, page 116	Assumption based on TA171
Eculizumab	−0.025	Section B.3.4.5, page 116	Assumption based on TA778
Pegcetacoplan	−0.025		
BTH	−0.400	Section B.3.4.6, page 116	O'Connell et al. 2020; the disutility of BTH was not captured in EQ-5D-3L data from the ALPHA trial
Iron overload	−0.030		Assumption based on TA778

- [a] The utility decrements listed are on an annual basis, except for iron overload which is the utility decrement incurred over 3 months.
- **Abbreviations**: ALT: alanine aminotransferase; BTH: breakthrough haemolysis; CI: confidence interval; Hb: haemoglobin; N/A: not applicable.

HSUVs for each health state are derived from the ALPHA trial. The ALPHA trial assessed HRQoL via the EQ-5D health utilities instrument. EQ-5D-3L scores which were collected across several treatment visits during TP1 (Weeks 0–12), TP2 and LTE (Weeks 13–52). Since EQ-5D-3L outcomes were collected in the ALPHA trial, no mapping was required, but appropriate multiplicative age adjustment was performed to produce HSUVs for use in the company base case.

The EAG find the methodologies employed by the company transparent, and reasonable justification provided for all chosen utility value inputs.

A comprehensive range of HSUVs were also explored by the company in the following scenario analyses:

- Values derived from arithmetic means from ALPHA
- Values based on a 10.5 g/dL haemoglobin level threshold from ALPHA with transition probabilities informed by the MAIC
- Values based on a 10.5 g/dL haemoglobin level threshold from ALPHA with transition probabilities informed by the MAIC, using the maximised effective sample size weights
- Values based on a 10.5 g/dL haemoglobin level threshold with transition probabilities informed by the MAIC, using utilities from Hakimi et al. 2022[56]
- Values based on EORTC scores from the ALPHA trial mapped to the EQ-5D using the algorithm published by Longworth et al. 2014.

The EAG are satisfied with the company approach to HRQoL within the model.

3.2.8 Resources and costs

The company included the following cost categories within the economic model:

- Drug acquisition costs,
- Administration costs.
- Monitoring costs,
- Transfusion costs,

- Iron overload management costs,
- AE management costs,
- BTH management costs.

The company performed a SLR to identify relevant cost or resource use studies for incorporation in the model, retrieving 2 unique studies[57, 58] reporting on cost or healthcare resource use in patients with PNH. However, all costs and resources use estimates (except those taken directly from the ALPHA trial for Danicopan), were referenced by the company as 'informed by' those used in TA778.[23]

3.2.8.1 Drug Acquisition costs

Drug acquisition costs for treatment regimens were calculated based on the cost per pack and dosing regimens reported in the ALPHA and PEGASUS trial, with list prices of danicopan, eculizumab and pegcetacoplan used in the model. PAS pricing was applied to ravulizumab (See CS doc B, Table 53).

Resource use was modelled assuming [redacted] of patients were treated with ravulizumab and [redacted] of patients with eculizumab which the company cite as supported by to Alexion sales their clinical expert opinion. Dosing regimens and distribution of patients receiving each dose of eculizumab, ravulizumab and danicopan were taken from the ALPHA trial, with dosing regimen for pegcetacoplan was taken from the PEGASUS trial. These distributions/regimes for C5i were applied to patients taking danicopan and C5i and for the 4-week run-in period during which pegcetacoplan patients remained on their C5i treatment (CS doc B, Section B.3.5.1).

Per cycle acquisition costs were calculated using the number of treatment administrations occurring within a given cycle. Treatment was assumed across a lifetime horizon, with both treatment discontinuation and treatment dose escalation applied on the following basis:

Patients receiving danicopan as an add-on to eculizumab or ravulizumab were modelled to discontinue treatment with danicopan but continue to receive the same regimen of eculizumab or ravulizumab monotherapy. Treatment discontinuation of danicopan was for reasons such as AEs and was not applied beyond Year 1. Dose

escalation with danicopan was modelled to gradually increase to 200 mg (from 150mg), in line with the proportion of patients who receive an increased dose of 200 mg of danicopan over time in the ALPHA trial (CS doc B, Table 52). The company also presented a scenario analysis where all patients in the danicopan add-on cohort are dose escalated to 200 mg after Week 52.

The EAG does not believe this to be representative of UK clinical practice if danicopan were to be approved as an add-on to eculizumab or ravulizumab for patients with csEVH. Pegcetacoplan is currently in use in this indication therefore the EAG believe a large proportion of those who discontinue danicopan would go on to receive pegcetacoplan. Whilst this proportion is unknown, the EAG has assumed that 80% of those discontinuing danicopan would commence pegcetacoplan, with the remaining 20% continuing with C5i monotherapy.

Patients receiving pegcetacoplan treatment were modelled to discontinue pegcetacoplan and receive eculizumab or ravulizumab monotherapy based on the observed distribution of patients across eculizumab and ravulizumab doses in the ALPHA trial. Discontinuation rates are based on the proportion of patients in the PEGASUS trial experiencing severe TEAEs from Weeks 17–48. Discontinuation of pegcetacoplan observed within-trial during weeks 1–16 were due to BTH events which the company did not model. They rely on feedback from a clinical expert to justify this approach, suggesting that in real-world practice treatment dose adjustments of pegcetacoplan may be implemented (unlike in the PEGASUS trial where this was not allowed). See CS doc B, section B.3.3.3 for full rationale. Treatment discontinuation of pegcetacoplan does not occur beyond Year 1.

The assumption of no discontinuation beyond one year for either danicopan or pegcetacoplan is not supported by evidence due to the limited trial follow-up available, and it is plausible that there will be a small long-term discontinuation rate for both arms. However, the company's approach is at least generally consistent across the two arms. The company performed a scenario analysis maintaining the discontinuation rates for the duration of the economic model, which had a large impact on the incremental costs (CS doc B, Table 68). The EAG performed a

similar scenario on top of their changes where a 1% discontinuation rate is applied for both danicopan and pegcetacoplan in week 53 and beyond.

Table 28: Treatment discontinuation rates (Weeks 1–52) (CS doc B, Table 43)

Treatment	Value (%)	Source	Value (%)	Source	Value (%)	Source
Danicopan + C5i[a]	**Weeks 1–12**		**Weeks 13–24**		**Weeks 25–52**	
	1.58	ALPHA trial: TP1 (Weeks 0–12)	0.47	ALPHA trial: TP2 (Weeks 13–24)	1.24	ALPHA: LTE (Weeks 25–52)
Pegcetacoplan	**Weeks 1–16**		**Weeks 17–52**			
	0.00	PEGASUS: Randomised controlled period (Week 4–16)	1.36	PEGASUS: Open-label period (Week 17–48)		

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; LTE: long-term extension; TP: treatment period.
Sources: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[59] Table 14.3.1.1.1, Table 14.3.1.1.2 and Table 14.3.1.1.3; Hillmen et al. 2021;[15] de Latour et al. 2022[16]

The EAG accept the discontinuation rates used by the company in the model in the absence of any further evidence. The drug costs associated with application of increased dosing schedules in the event of BTH are discussed in section 3.2.8.7.

3.2.8.2 Administration costs

Administration costs were applied for pegcetacoplan only, as a one-off cost of training to self-administer this as a subcutaneous (SC) injection. The unit cost for SC administration training was estimated to be £17.67 (assuming 20 minutes of specialist nurse time, band 6).

No administration costs were associated with danicopan as it is administered orally. No administration costs were included for either eculizumab or ravulizumab as costs for these are borne by the manufacturer and are therefore not incurred by the NHS.

The EAG agree with the company approach to administration costs which are appropriate given the NHS/PSS payer perspective of the model.

3.2.8.3 Monitoring costs

Monitoring costs for each health state were calculated by multiplying the unit costs for each resource by the number of visits/tests required per health state per cycle.

Resource use frequencies were sourced from TA778[23] and applied as per cycle rates (Table 29).

Table 29: Number of physician visits/tests per cycle (CS doc B, Table 56)

	Number of physician visits/tests per cycle			Source
	Low Hb (No Tr.)	Moderate Hb (No Tr.)	Transfusion	
GP visit	0.00	0.00	0.00	NICE TA778
Haematologist	0.15	0.15	2.00	
Blood test	0.31	0.31	2.00	
Cost per cycle, £	**36.14**	**36.14**	**411.29**	**-**

Abbreviations: GP: general practitioner; Hb: haemoglobin; NICE: National Institute for Health and Care Excellence; TA: technology appraisal.

The EAG finds the rates and cost estimates presented by the company appropriate for use in this appraisal.

3.2.8.4 Transfusion costs

Blood transfusion costs were estimated based on the unit cost per transfusion and transfusion frequency per cycle. This was applied to those in the transfusion health state only. Unit cost per transfusion was taken from TA778 (£532.46 derived from 2020 NHS reference cost[23]) and inflated by the company to 2022 prices.

The EAG are satisfied with the company approach to transfusion costs.

3.2.8.5 Iron overload management costs

Transfusion-related iron overload is a treatment-dependent per-cycle probability applied to those in the transfusion health state only. Probabilities were derived from the ALPHA trial and Hakimi et al.[56] for patients receiving danicopan as an add-on to eculizumab or ravulizumab and pegcetacoplan, respectively (Table 30).

Table 30: Per model cycle probability of transfusion-related iron overload (CS doc B, Table 42)

Treatment	Probability (%)	Source
Danicopan + C5i[a]	0.47	ALPHA CSR
Pegcetacoplan	0.65	Hakimi et al. 2022
C5i[a]	0.47	Assumed same as danicopan + C5i[a]

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor.
Sources: Source: Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[59] Table 14.3.1.3.2.2.2; Hakimi et al. 2022[56]

Iron overload is associated with a utility decrement and treatment specific management costs. Both danicopan as an add-on to C5i and pegcetacoplan are assumed to be managed by phlebotomy, to remove excess iron, an average of 3 times per year. Patients on C5i monotherapy as a result of discontinuation of either treatment are managed by chelation therapy. See Table 31 and Table 32 below.

Table 31: Cost of phlebotomies (CS doc B, Table 58)

Procedure	Unit cost	Average number in a year	Average number in a 4-week cycle	Cost per 4-week cycle	Source
Phlebotomy	£4.70	3	0.23	£1.08	NHS Reference Costs 2021/22 (DAPS08)

Abbreviations: NICE: National Institute for Health and Care Excellence; TA: technology appraisal.

Table 32: Cost of chelation therapy (CS doc B, Table 59)

Drug	Pack size	Dosage (mg)	Pack cost	Dosage (mg/kg)	Frequency	Cost per four-week cycle	Source
Deferasirox	30	360	£165.45	21	Once daily	£645.05	BNF 2023
Deferoxamine mesilate	10	500	£40.54	35	Once daily	£681.07	BNF 2023
Total average weighted cost per four-week cycle			**£661.35**				

The EAG are satisfied with the management approaches and costings for iron overload modelled in the company submission. The EAG caution the use of probabilities extracted from ALPHA and PEGASUS trials applied naively to inform model-cycle probabilities due to significant differences in trial populations. The EAG prefers to assume equal probabilities for all treatment arms within the model and use a probability of 0.47% in its scenario analysis.

3.2.8.6 AE management costs

The only AE included in the model is increased alanine aminotransferase (ALT) for patients receiving danicopan as an add-on to eculizumab or ravulizumab. The per-cycle cost of managing ALT increase was estimated as £388.08 based on weighted average of the total day case costs of liver failure disorders without interventions from the NHS Reference Costs 2021/22.[60]

The EAG agree with the management cost estimates and support the rationale used by the company to apply ALT costs to patients receiving danicopan add-on treatment in weeks 1-12. These are based on outcomes of the ALPHA trial with full explanation and justification detailed in section B.3.3.5 in the company submission. However, the EAG noted 2 errors in the application of ALT adverse events within the model:

1. AE duration

The company applied the probability of ALT events occurring up to 12 model cycles, rather than 12 weeks (4 cycles). The relevant equation was corrected by the EAG to reduce duration to the 12 weeks as intended.

2. AE frequency

The company calculated the probability of ALT events ignoring the fact that multiple events occurred for the same individual within their trial. The EAG have corrected calculating the probability based on four events occurring across the 12 week period. This changes the probability used in the model from 1.79% to 2.31%.

The EAG found neither correction had meaningful impact on the ICER.

It is possible that new AEs emerge from additional follow-up and real-world use of all treatments modelled, however this information is not currently available.

3.2.8.7 Breakthrough haemolysis

The company model included a probability of experiencing a BTH event in each cycle. The probabilities used for danicopan + C5i came from the ALPHA trial based on BTH events which required intervention, with different probabilities used for the different treatment periods. A similar approach was taken for pegcetacoplan, using information from the PEGASUS study, but where all BTH events required intervention. It is not clear whether the thresholds for BTH intervention were the same across the trials, nor whether the degree of any potential intervention was comparable. The probabilities from both trials for both of their respective arms is shown in

Table 33.

Table 33: Details of data and probability calculation for BTH events requiring intervention.

	ALPHA – Danicopan + C5i	ALPHA – C5i	PEGASUS – C5i	PEGASUS - Pegcetacoplan
ALPHA: Week 1-24 PEGASUS: Week 1-16	0 events out of 49 people in 24 weeks of follow-up 0.00%	No events. Assumed same as danicopan 0.00%	9 events out of 39 people in 16 weeks of follow-up 6.35%	4 events out of 41 people in 16 weeks of follow-up 2.53%
ALPHA: Week 25+ PEGASUS: Week 17+	1 event out of 60 people in 28 weeks of follow-up 0.24%	Assumed same as danicopan 0.24%	N/A	15 events out of 77 people in 32 weeks of follow-up 2.67%

The EAG does not consider this reliable evidence to carry these probabilities from a naïve comparison into the model, particularly given that the difference in BTH between the C5i (control) arms of each trial is greater than the BTH between the danicopan + C5i and pegcetacoplan arms. The EAG preference is to assume an equal rate of BTH across these two treatments.

The company then applies their preferred probabilities to model associated costs for interventions to resolve BTH events. Interventions vary by treatment although the primary approach is through dose escalation (see Table 34 for standard dose escalations).

Table 34: Progression of treatment regimens per BTH event (CS doc B, Table 41)

Starting treatment	Treatment escalation	
	First dose escalation	Second dose escalation
Pegcetacoplan 1,080 mg twice per week	Pegcetacoplan 1,080 mg daily for three consecutive days,[a] followed by once every three days	Pegcetacoplan 1,080 mg daily for three consecutive days,[a] followed by three times per week
Danicopan 150 mg three times a day + ravulizumab once every eight weeks	Ravulizumab once every seven weeks during the course of the BTH event. Following resolution of BTH, patients will revert to ravulizumab once every eight weeks.	
Danicopan 150 mg + eculizumab 900 mg once every two weeks	Eculizumab once every eleven days during the course of the BTH event. Following resolution of BTH, patients will revert to eculizumab once every two weeks.	

[a] Pegcetacoplan is administered as 1,080 mg daily for three consecutive days for the immediate treatment of BTH.
Abbreviation: BTH: breakthrough haemolysis.

For danicopan + C5i, the company applies costs for dose escalation of the relevant C5i, which is consistent with current practice for BTH intervention in people receiving C5i. This is modelled as a one-off advanced dose cost within the relevant cycle (assuming the BTH event resolves within that cycle). Patients remain on the same dose of danicopan throughout and do not occur any other management costs.

For patients on C5i monotherapy, following discontinuation of either danicopan or pegcetacoplan, the same approach is used with one-off advanced dosing of their substantive C5i and no additional management costs incurred.

For pegcetacoplan, the company models a permanent dose escalation of pegcetacoplan in the event of BTH. This is calculated based on the dose they are receiving at the time a BTH event occurs. Those on second dose escalation remain at that maximum dose regime even if further BTH events occur.

Under the company's assumptions for pegcetacoplan, the dose escalation is rapid and soon results in the majority of people receiving the maximum treatment regime of three doses per week (Figure 2). The EAG notes that this appears to be inconsistent with the approach taken in the appraisal of pegcetacoplan, where the publicly available documents from TA778 suggest that two doses per week were used with no dose escalation. The EAG's clinical expert confirmed that they had observed temporary increased frequency of pegcetacoplan dosing that returned to twice weekly once within roughly one month. This has a substantial impact on the cost-effectiveness of danicopan and also of pegcetacoplan.

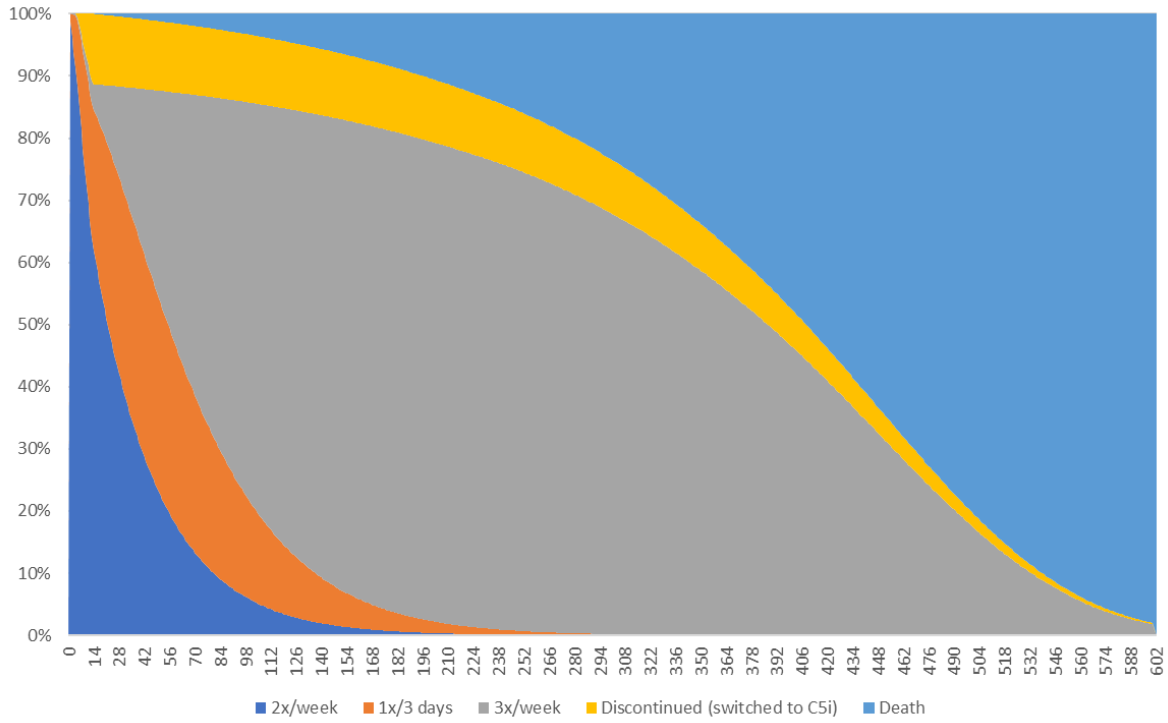


Figure 2: Pegcetacoplan dosing-states per model cycle under company preferred assumptions

When the EAG sets the long-term probability of BTH for pegcetacoplan to be equal to the value for danicopan, then this results in a much smaller proportion of the population receiving three doses of pegcetacoplan per week (Figure 3).

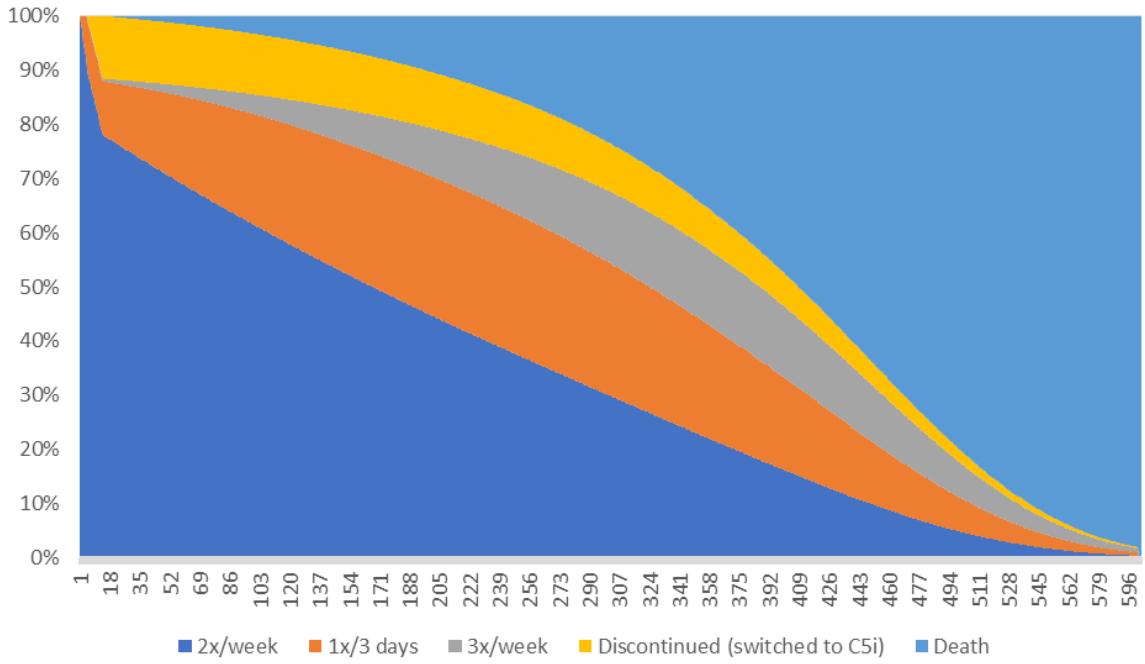


Figure 3: Pegcetacoplan dosing-states under when setting long-term BTH probability to be equal to danicopan

The EAG also explores a scenario where the long term BTH is set to zero, reducing further the pegcetacoplan and C5i dose escalation. This was a step closer towards what the EAG understands was the approach taken in TA778, but still includes some dose escalation (Figure 4).

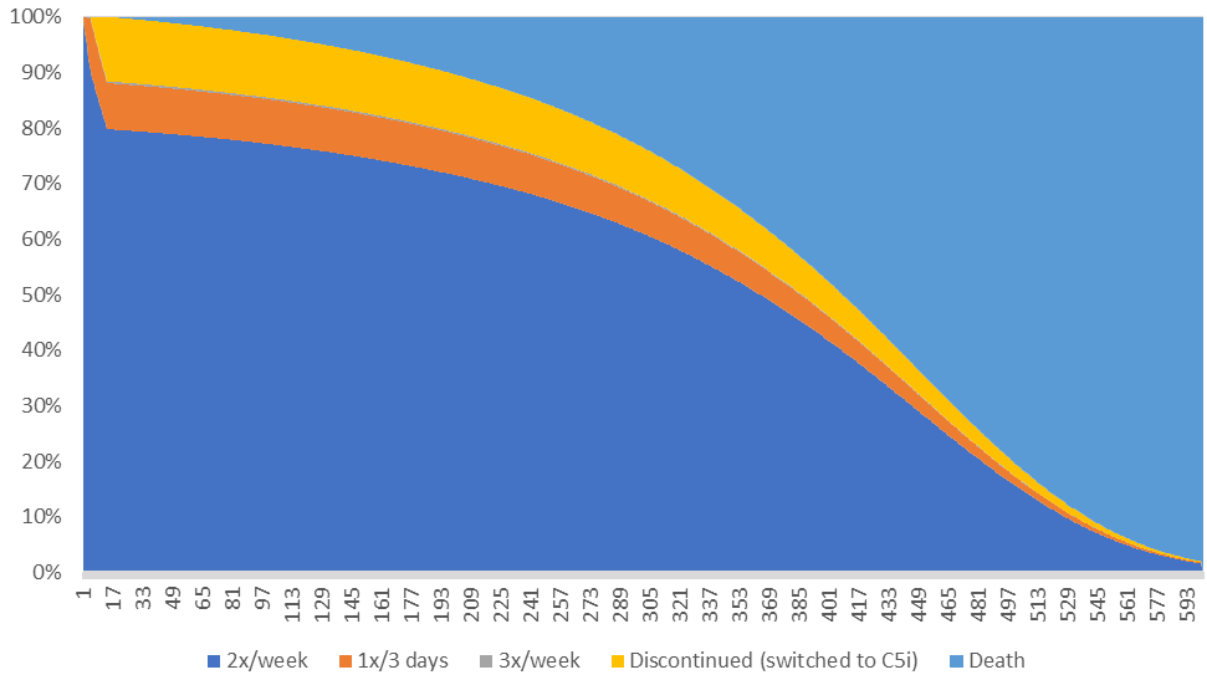


Figure 4: Pegcetacoplan dosing-states when setting long-term BTH probability set to zero.

The EAG notes that the company also applies a cost for the accelerated dose of the C5i therapy for the pegcetacoplan population. The EAG considers the company's approach to overestimate this cost, as it is applied for all the modelled BTH events, and does not distinguish between BTH for C5i therapies. The EAG have corrected this.

The company also calculated a separate BTH management cost, following the approach used in TA778, to derive a cost per event (see

Table 35). This BTH management cost is applied to all BTH events experienced by all patients across treatments.

Table 35: Derivation of BTH event cost (CS doc B, Table 57)

	% patients/ n days	Source	Cost (£)
General ward	15%/ 1 day	NHS Reference Costs 2021/2022 SA03G-H	103.25
Intensive care	1%/ 1 day	NHS Reference Costs 2021/2022 XC01Z-7Z	21.44
Dialysis	4%/ 7 days	NHS Reference Costs 2021/2022 LE01A, LE02A	101.09
Total			**£225.78**

Abbreviations: BTH: breakthrough haemolysis; NHS: National Health Service.
Sources: NICE. Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria committee papers [ID3746]. 2021.[61]

The EAG are satisfied with the methodology used to derive BTH management cost but remain uncertain that the proportions used to inform their application in the model in any of the treatment strategies are appropriate.

The EAG note that in TA778, BTH management costs were applied only to patients discontinuing pegcetacoplan due to BTH, and with dose escalation alone used for those who remained on pegcetacoplan. BTH management costs were also incurred by all on C5i when a BTH event occurred. Incidentally, dose escalation for patients treated with pegcetacoplan in TA778 modelling was advanced dosing of eculizumab whilst remaining at pre-event dose of pegcetacoplan, in contrast to the escalating pegcetacoplan regime assumed by the company in this appraisal.

The EAG find the modelling assumptions regarding dose escalation and BTH management used in the pegcetacoplan appraisal (TA778) and the current appraisal vastly different and suspect BTH event real world clinical practices are not reflected suitably in either. Whilst these represent important model inputs, and BTH event costs are a key driver of the model, the EAG preferred assumption that BTH event probabilities are the same across treatment strategies (0.24%) long-term (Table 40, scenario 7) goes some way to reduce the impact of these other company assumptions and should be considered a conservative adjustment by the EAG. The EAG also provides a scenario analysis with no long term BTH events (Table 41), for completeness.

3.2.9 Severity

The company did not submit a case for a 'severity modifier' to be applied as the QALY shortfall analysis they conducted resulted in a QALY weight of 1. Therefore, no severity modifier was applied to the base case economic analysis.

The EAG concurs with the company's calculations (see CS doc B, Table 63) and the conclusion that no severity modification is appropriate in this case.

4 COST EFFECTIVENESS RESULTS

4.1 *Company's cost effectiveness results*

The company presented base case deterministic and probabilistic cost-effectiveness results for danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan, using the list prices of danicopan, eculizumab and pegcetacoplan, and PAS price of ravulizumab.

Danicopan as an add-on to eculizumab or ravulizumab dominated pegcetacoplan in both deterministic and probabilistic analyses, and resulted in a positive net health benefit (NHB) at a WTP threshold of £30,000/QALY of [redacted] in the deterministic analysis, and [redacted] in the probabilistic analysis. Deterministic and probabilistic results for the company's preferred analysis are summarised in Table 36 and Table 37 respectively.

Table 36: Company deterministic base-case results (prices as per company submission; cPAS applied to danicopan and ravulizumab only, all other drug costs sourced from BNF 2023 and eMIT 2022)

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

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 37: Company probabilistic base-case results

Intervention	Total Costs	Total LY	Total QALY	Inc' Costs	Inc' QALY	ICER	Inc' NHB
Danicopan + C5i[a]	[redacted]	17.90	14.37				
Pegcetacoplan	£7,722,911	17.90	13.95	[redacted]	0.418	Dominant	[redacted]

[a] Eculizumab or ravulizumab.
Abbreviations: C5i: complement component 5 inhibitor; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Probabilistic sensitivity analysis (PSA) was performed using Monte-Carlo simulation with 1,000 iterations, where model inputs were randomly sampled from pre-specified probability distributions. Results are plotted in

Figure 5: Probabilistic cost-effectiveness plane for danicopan as an add-on to eculizumab or ravulizumab vs pegcetacoplan (CS doc B, fig. 16)

4.2 *Company's sensitivity analyses*

The company conducted extensive sensitivity analyses. Deterministic sensitivity analyses (DSAs) were performed by varying the input for each parameter in the model, whilst keeping all other inputs the same. These inputs used are detailed in the CS, section B.3.9.1. with a tornado diagram (CS Doc B Figure 17) showing the top 10 most influential parameters on the NHB. The NHB was most sensitive to the

age of patients, the probability of pegcetacoplan patients experiencing a BTH event from 17 weeks onwards, and the probability of patients discontinuing pegcetacoplan to eculizumab or ravulizumab monotherapy between 17 weeks and a year.

The company also undertook scenario analyses to explore the impact of structural assumptions and alternative inputs on the results of the cost-effectiveness model. The results of the scenario analyses are presented in Table 38.

Table 38: Scenario analysis results for danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan (probabilistic) (CS doc B, Table 68)

Scenario		Danicopan + C5i[a] vs pegcetacoplan			
		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB
Base case		[redacted]	0.418	Dominant	[redacted]
1	Time horizon: 10 Years	[redacted]	0.194	Dominant	[redacted]
2	Time horizon: 20 Years	[redacted]	0.320	Dominant	[redacted]
3	Dose escalation: All danicopan patients escalate to 200 mg for Week 53+	[redacted]	0.416	Dominant	[redacted]
4	C5i distribution: Based on ALPHA trial	[redacted]	0.315	Dominant	[redacted]
5	Discontinuation: Sustained discontinuation in Year 1+	[redacted]	0.161	Dominant	[redacted]
6	BTH management: Pegcetacoplan discontinuation/escalation from PEGASUS trial	[redacted]	0.492	Dominant	[redacted]
7	Iron overload: C5i monotherapy patients receive phlebotomies	[redacted]	0.419	Dominant	[redacted]
8	Utilities: Values derived from arithmetic means	[redacted]	0.445	Dominant	[redacted]
9	Health states based on 10.5 Hb cut-off (Transitions informed by MAIC)	[redacted]	0.314	Dominant	[redacted]
10	Health states based on 10.5 Hb cut-off (Transitions informed by MAIC, Max ESS weights)	[redacted]	-0.893	SW Quadrant	[redacted]
11	Health states based on 10.5 Hb cut-off (Transitions informed by MAIC, Utilities from Hakimi 2022)	[redacted]	0.313	Dominant	[redacted]
12	Utilities: Apply transfusion utility value from TA778	[redacted]	0.418	Dominant	[redacted]
13	Utilities: No disutility applied for iron overload	[redacted]	0.420	Dominant	[redacted]
14	Utilities: Eculizumab and pegcetacoplan disutility aligned with TA698	[redacted]	0.850	Dominant	[redacted]

15	Utilities: EORTC from ALPHA mapped to EQ-5D-3L	[redacted]	0.451	Dominant	[redacted]

[a] Eculizumab or ravulizumab.
Abbreviations: BTH: breakthrough haemolysis; C5i: complement component 5 inhibitor; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: Euro-QoL 5 Dimensions 3 Level; Hb: haemoglobin; HSUV: health state utility value; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; INHB: incremental net health benefit; QALY: quality-adjusted life year; TA: technology appraisal.

The incremental NHB and ICER were most sensitive to treatment discontinuation of danicopan and pegcetacoplan being excluded beyond Year 1, reduced time horizon of 10- or 20-years, and inclusion of a proportion of patients who discontinue or dose escalate pegcetacoplan following BTH.

4.3 *Model validation and face validity check*

The EAG performed validation checks on the company model and identified a number of minor errors which were corrected by the EAG. Three errors (further discussed in section 5.1) are amended individually in Table 39 with the cumulative changes presented as the revised company base case. Changes have negligible impact with an increase in incremental cost from [redacted] to [redacted], and decrease in incremental NHB from [redacted] to [redacted].

Table 39: EAG corrections applied to company submitted base case

EAG correction	Intervention	Total costs	Total QALYs	Inc' Cost	Inc' QALY	ICER	Inc' NHB
Company submitted base case	Dan + C5i	[redacted]	14.207				
	Peg	£7,711,022	13.778	[redacted]	0.43	Dominant	[redacted]
1. AE duration change	Dan + C5i	[redacted]	14.207				
	Peg	£7,711,022	13.778	[redacted]	0.43	Dominant	[redacted]
2. AE freq change	Dan + C5i	[redacted]	14.207				
	Peg	£7,711,022	13.778	[redacted]	0.43	Dominant	[redacted]
3. Peg C5i BTH	Dan + C5i	[redacted]	14.207				
	Peg	£7,698,711	13.778	[redacted]	0.43	Dominant	[redacted]
4. Combined corrections 1-3: Corrected company base case	Dan + C5i	[redacted]	14.207				
	Peg	£7,698,711	13.778	[redacted]	0.43	Dominant	[redacted]

Whilst overall model structure is appropriate for this appraisal and supports its face validity, the EAG find insufficient clinical evidence to support cost-effectiveness

modelling of danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan, thereby undermining its predictive validity.

5 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

5.1 *Exploratory and sensitivity analyses undertaken by the EAG*

The EAG identified 3 separate errors in the company economic model (CEM) and considered changes to 4 additional assumptions made by the company in its base case. The combination of these 7 changes is presented in a scenario which represents the EAG's 'preferred company base case' and sensitivity analysis is performed on this. The EAG undertook additional analyses to establish the cost effectiveness of danicopan + C5i when compared to C5i alone, and further exploratory analysis to compare pegcetacoplan to C5i monotherapy.

5.1.1 Exploratory analyses

The exploratory analyses performed are summarised below, with results presented in section 5.2.

1. AE duration for ALT applied to patients on danicopan + C5i applied to weeks 1-12 only

The company intended to model to week 12 but was applied to cycle 12 in CS.

2. AE frequency for ALT changed from 1.79% to 2.31% for weeks 1-12

The company modelled the probability of ALT using number of people experiencing the event, rather than using the actual number of events. The EAG calculated the probability using the number of ALT events observed and applied this in the model.

3. Pegcetacoplan C5i BTH

The company applied a single advanced dose of either eculizumab or ravulizumab to all patients in pegcetacoplan cohort who experienced a BTH event. The EAG amended this so that the advanced dose was only applied to those who had discontinued pegcetacoplan and were on C5i monotherapy. The EAG understands that it is plausible that some patients on pegcetacoplan would receive a one-off dose of eculizumab if they have a BTH event, but the company has not described

trying to capture this. Even if this were the case, the company's approach would likely overestimate this.

4. Subsequent pegcetacoplan after danicopan

The company modelled all PNH patients who discontinue danicopan to receive C5i monotherapy for the remaining model lifetime. The EAG assumed that 80% of those discontinuing danicopan would receive pegcetacoplan. This is in line with real world treatment options for PNH patients with EVH. The EAG has only modelled the costs of subsequent pegcetacoplan and associated BTH probability, and not altered any other probabilities or disutilities for those who have discontinued danicopan.

5. Equal transition probabilities pegcetacoplan vs danicopan

The company used health state transition probabilities from ALPHA for danicopan, and from PEGASUS for pegcetacoplan. The EAG assume equal transition probabilities for both danicopan and pegcetacoplan using probabilities from ALPHA.

6. Equal probabilities of Iron overload (0.47%)

The company used probabilities of iron overload in the transfusion health state from ALPHA for danicopan, and from PEGASUS for pegcetacoplan. The EAG assume equal iron overload probabilities for danicopan and pegcetacoplan using those from ALPHA.

7. Equal probabilities of long term BTH events for all treatments (0.24%)

The company used probabilities of BTH events from ALPHA for danicopan (assuming equal for those continuing on C5i alone), and from PEGASUS for pegcetacoplan. The EAG maintain the BTH event probability for weeks 1-16 for those receiving pegcetacoplan, then assume equal BTH events for all treatments from week 17/25 for pegcetacoplan/danicopan and beyond (using long term ALPHA estimates). When contextualised within real world data and additional trial literature, naïve comparison of event rates cannot be justified by the EAG.

8. Combination of corrections and changes (1-7)

The EAG apply the corrections in scenarios 1-3 and further preferred changes in scenarios 4-7, cumulatively, to produce an EAG preferred company base case.

5.1.2 Sensitivity analysis

The EAG undertook sensitivity analysis on their preferred company base case to explore the impact of BTH event management costs (see section 5.2) and discontinuation.

1. Equal probabilities of long term BTH events for all treatments (0%)

Changes 1-6 (above) are applied and EAG maintain the BTH event probability for weeks 1-16 for those receiving pegcetacoplan, then assume equal long term BTH events of 0% for all treatments. This removes BTH management costs from the analysis as well as reducing the impact of maximum pegcetacoplan dosing escalation.

2. Long-term discontinuation set to 1% for both arms.

Changes 1-7 (above) are applied and EAG maintain the discontinuation probabilities for the first 52 weeks of the model, but additionally set the non-BTH related discontinuation probability for the rest of the model time horizon to be 1% per cycle for both danicopan and pegcetacoplan.

5.1.3 Additional cost effectiveness analyses

The EAG considered the clinical evidence was more appropriate and justifiable in the cost effectiveness modelling of danicopan + C5i against C5i monotherapy. This within trial comparison avoids many of the issues of the comparison to pegcetacoplan. Additional analyses were carried out:

1. Danicopan + C5i compared to C5i monotherapy with EAG corrections 1-3 applied

2. Danicopan + C5i compared to C5i monotherapy with EAG corrections 1-3 applied plus subsequent pegcetacoplan after danicopan

The EAG also explored the cost effectiveness of pegcetacoplan against C5i monotherapy to establish the input parameters and assumptions required to yield pegcetacoplan cost effective at a WTP threshold accepted in the UK, in an attempt to find consistency with publicly available results from TA778.

1. Pegcetacoplan compared to C5i monotherapy using PEGASUS baseline characteristics with EAG corrections 1-3 applied

2. Pegcetacoplan compared to C5i monotherapy using PEGASUS baseline characteristics and transition probabilities with EAG corrections 1-3 applied and no BTH events

5.2 *Impact on the ICER of additional clinical and economic analyses undertaken by the EAG*

Results of the EAG analyses described in sections 5.1.1, 5.1.2 and 5.1.3 can be found in Table 40,

Table 41 and Table 42 respectively.

Table 40: EAG changes to company base case

EAG change to company base case	Intervention	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	Incremental NHB
Original Company Base Case	Danicopan + C5i[a]	[redacted]	14.207				
	Pegcetacoplan	£7,711,022	13.778	[redacted]	0.429	Dominant	[redacted]
1-3 Corrected Company Base Case	Danicopan + C5i	[redacted]	14.207				
	C5i	£7,698,711	13.778	[redacted]	0.43	Dominant	[redacted]
4. Subsequent pegcetacoplan after danicopan	Danicopan + C5i	[redacted]	14.195				
	Pegcetacoplan	£7,711,022	13.778	[redacted]	0.418	Dominant	[redacted]
5. Equal transition probabilities peg vs dan	Danicopan + C5i	[redacted]	14.207				
	Pegcetacoplan	£7,711,799	13.745	[redacted]	0.462	Dominant	[redacted]
6. Equal probabilities of Iron overload (0.47%)	Danicopan + C5i	[redacted]	14.207				
	Pegcetacoplan	£7,711,022	13.778	[redacted]	0.429	Dominant	[redacted]
7. Equal probabilities of long term BTH events for all treatments (0.24%)	Danicopan + C5i	[redacted]	14.207				
	Pegcetacoplan	[redacted]	13.928	[redacted]	0.279	Dominant	[redacted]
8. Combination of corrections and changes (1-7)	Danicopan + C5i	[redacted]	14.215				
	Pegcetacoplan	£6,159,094	13.895	[redacted]	0.320	Dominant	[redacted]

Table 41: EAG sensitivity analysis to remove treatment management costs for BTH

EAG scenario analysis	Intervention	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	Inc' NHB
1. Combined changes 1-6 with no BTH events long term for all treatments	Danicopan + C5i	[redacted]	14.231				
	Pegcetacoplan	£5,760,221	13.912	[redacted]	0.320	Dominant	[redacted]
2. Combined changes 1-7 with 1% discontinuation 53+ weeks for all treatments	Danicopan + C5i	[redacted]	13.691				
	Pegcetacoplan	£5,012,817	13.540	[redacted]	0.151	[redacted]	[redacted]

Table 42: EAG analyses comparing to danicopan and pegcetacoplan to C5i

	Intervention	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	Incremental NHB
EAG analyses comparing danicopan + C5i to C5i monotherapy							
1. EAG corrections 1-3 applied	Danicopan + C5i	[redacted]	14.207				
	C5i	£4,481,326	13.295	[redacted]	0.912	[redacted]	[redacted]
2. EAG corrections 1-3 applied plus subsequent pegcetacoplan after danicopan	Danicopan + C5i	[redacted]	14.196				
	C5i	£4,481,326	13.295	[redacted]	0.901	[redacted]	[redacted]
EAG analyses using PEGASUS baseline comparing pegcetacoplan to C5i monotherapy							
1. EAG corrections 1-3 applied	Pegcetacoplan	[redacted]	15.173				
	C5i	£4,958,813	14.238	[redacted]	0.935	[redacted]	[redacted]
2. EAG corrections 1-3 applied and no BTH events	Pegcetacoplan	[redacted]	15.357				
	C5i	£4,957,323	14.257	[redacted]	1.100	[redacted]	[redacted]

5.3 *EAG's preferred assumptions*

The EAG presents corrections and preferred modelling assumptions for the company base case in sections 5.1 and 5.2. However, these do not represent an EAG base case as the EAG maintains that there is insufficient evidence to support a relative comparison of danicopan + C5i and pegcetacoplan. The EAG preference is for a robust comparison of danicopan as an add-on to eculizumab or ravulizumab compared to eculizumab or ravulizumab alone (see section 5.1.3).

Deterministic cost-effectiveness analysis of danicopan + C5i compared to C5i monotherapy produces an ICER of [redacted]/QALY and a [redacted]_NHB of [redacted] at a WTP threshold of £30,000. The ICER then increases to [redacted]/QALY when subsequent pegcetacoplan treatment is applied after discontinuation of danicopan, with a resultant_[redacted] in NHB to_[redacted] at the £30,000 WTP threshold.

5.4 *Conclusions of the cost effectiveness section*

The EAG find the clinical evidence for this appraisal insufficient to support full cost-effectiveness modelling of danicopan as an add-on to eculizumab or ravulizumab compared to pegcetacoplan.

The company cost effectiveness results rely on naïve comparisons between ALPHA and PEGASUS trials with bold assumptions regarding BTH event management and subsequent lifetime dosing regimens. The EAG notes apparent inconsistency with the modelling of pegcetacoplan compared with TA778.

The exploratory analyses conducted by the EAG demonstrated that probability of BTH events from 17 weeks, and probability of discontinuation are major drivers of cost effectiveness within the model.

The EAG are unable to substantiate these assumptions with additional real-world evidence or clinical expert opinion. The uncertainty in these key parameters remains too great for the EAG to advocate decision analytic modelling for danicopan + C5i compared with pegcetacoplan.

The EAG attempts to eliminate the uncertainty introduced by naïve comparison across trials and model the direct comparison of danicopan + C5i compared with C5i monotherapy from the ALPHA trial. The EAG find this the most robust use of the

limited evidence on which to gauge the cost effectiveness of danicopan as an add-on treatment for the PNH population currently on C5i monotherapy but who experience csEVH. The relevance of this comparison is further supported when considering the eligible cohort for treatment. Without a clinically accepted standard definition of csEVH, characteristics and treatment preferences of the eligible population may vary considerably, to the effect that C5i monotherapy is a valid comparator in this appraisal.

The EAG conclude the most appropriate use of current evidence in this appraisal is economic modelling of danicopan + C5i compared to C5i. This results in cost effectiveness estimates between [redacted] and [redacted] per QALY, which [redacted] the WTP threshold of £30,000/QALY.

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7 APPENDICES

7.1 *Appendix 1*

Table 43: Risk of bias assessment of ALPHA by EAG

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Stochastic dynamic allocation in a 2:1 ratio, stratified by transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening), Hgb (< 8.5 g/dL and ≥ 8.5 g/dL) at Screening, and Japanese patients (defined as patients enrolled from Japan)/non-Japanese patients. Interactive response technology.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Some imbalances between the groups, and these were slightly more pronounced in the smaller interim efficacy set. However, these may be due to chance rather than a problem with the randomisation process.
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	The study is described as double-blind, but the protocol does not specify who is blinded or how blinding was maintained; however, the publication states 'treatment group assignments were concealed from all participants, investigative sites, and the sponsor study team'.[45]
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations	NA	

	from intended intervention balanced between groups?		
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Intent-to-treat analysis used, this analysed data by the allocated group even if the patient does not take the assigned treatment, does not receive the correct treatment, or does not comply with the protocol.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	The CS and CSR report a second interim analysis, comprising the first 75% of patients (n=63) of the target enrolment of 84 patients (N=86 were actually randomised) when they had the opportunity to complete Treatment Period 1. The first interim analysis of this group is described at the protocol and was to be conducted at the discretion of the sponsor. The purpose was to evaluate the study for stopping early for efficacy. The second interim analysis (datacut of September 2022) was repeated when the 63 participants completed Treatment period 2; this was not prespecified in the study protocol. At this cut-off, 71 patients had completed TP1, but results were not reported.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	There is no evidence that the result was not biased by missing outcome data.
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI	It is unlikely that missingness in the outcome depends on its true value
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in	PN	

	the outcome depended on its true value?		
	Risk of bias judgement	**Some concerns**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Methods were appropriate
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	The study is described as double-blind, but the protocol does not specify who is blinded or how blinding was maintained; however, the publication states 'treatment group assignments were concealed from all participants, investigative sites, and the sponsor study team'.[45]
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	The second interim analysis was not prespecified in the protocol, however results from the prespecified June 2022 interim analysis were published in Lee 2023[45] and were comparable. The company has not provided the most recently available data-cut.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	Some of the patient outcome measures were not presented in the CS but are available in the CSR
	5.3 ... multiple eligible analyses of the data?	N	

	Risk of bias judgement	Low	
Overall bias	**Risk of bias judgement**	**Some concerns**	**Some concerns regarding unreported data for 23/86 (27%) of randomised participants**

Table 44: EAG assessment of risks of bias of the CS systematic review in relation to the scope of the appraisal (modified ROBIS).

ROBIS domain, and signalling questions	EAG's rating	Reasoning
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	**Probably no**	Eligibility criteria are reported in CS Appendix D (Table 4) and an additional 'data on file' manuscript provides further detail of the apriori criteria. However, studies were included with mixed populations which was not defined in the eligibility criteria and it was unclear if the population in all studies had EVH. Additional steps to assess studies for the NMA were also taken but these criteria do not appear to have been pre-defined
1.2 Were the eligibility criteria appropriate for the review question?	**Yes**	The pre-stated criteria appear appropriate for the review question and aligned with the NICE scope.
1.3 Were eligibility criteria unambiguous?	**Probably yes**	Eligibility criteria were clear although it was unclear if all included studies met the full criteria
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	**Yes**	Restrictions on study design were appropriate, any study design was included with the exception of reviews
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	**Probably yes**	Non-English language studies were excluded and conference abstracts were excluded if older than 2 years. These exclusions are likely to be reasonable.
Concerns regarding specification of study eligibility criteria	**Unclear concern**	Not all eligibility criteria were specified a priori.
2: Identification and selection of studies		

2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	**Yes**	A sufficient and appropriate range of sources were searched to identify clinical studies
2.2 Were methods additional to database searching used to identify relevant reports?	**Probably yes**	Appropriate grey literature resources were searched, and the search terms and results were provided. Clinical trials registers such as Clinical Trials.gov were not searched.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	**Probably no**	The search strategies for Embase, MEDLINE and the Cochrane Library are not sufficiently comprehensive.
2.4 Were restrictions based on date, publication format, or language appropriate?	**Probably no**	Language was restricted to English therefore there is a potential for publication bias. Conference abstracts were restricted to those published in the last 2 years which appears appropriate.
2.5 Were efforts made to minimise errors in selection of studies?	**Probably yes**	Titles and abstracts and full text articles were screened independently by two reviewers with discrepancies resolved by a third reviewer for the primary selection of studies. No details provided as to how the subsequent stage of selection was made.
Concerns regarding methods used to identify and/or select studies	**Unclear concern**	Some concerns noted in the methods used to identify studies
3: Data collection and study appraisal		
3.1 Were efforts made to minimise error in data collection?	**Yes**	Data from the included studies were extracted by two independent reviewers and any discrepancies were resolved through discussion.
3.2 Were sufficient study characteristics	**Probably Yes**	Summary study characteristics were presented in the CS and Appendix D for

available for both review authors and readers to be able to interpret the results?		the studies considered for the NMA. Although summary study characteristics were not provided in the CS or Appendices for the other included studies a 'data on file' manuscript was presented which had summary tables.
3.3 Were all relevant study results collected for use in the synthesis?	**Yes**	Results from ALPHA were summarised in the CS, the EAG requested additional outcome data which was provided in clarification
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	**Yes**	Risk of bias was performed using questions recommended by NICE (presented in the CS) and the Cochrane ROB 2 tool in CS Appendix Table 17. However only domains 1 and 2 were presented. The full ROB assessments were available in the 'data on file' manuscript however.
3.5 Were efforts made to minimise error in risk of bias assessment?	**Probably Yes**	ROB was assessed by a single reviewer and checked by a second reviewer. Any discrepancies were resolved through discussion.
Concerns regarding methods used to collect data and appraise studies	**Low concern**	Data collection methods and processes appear appropriate
4: Synthesis and findings		
4.1 Did the synthesis include all studies that it should?	**Probably yes**	Only one comparison was include. No comparison to other comparators was attempted as the company consider these to be inappropriate (see decision problem critique)
4.2 Were all predefined analyses followed or departures explained?	**No information**	No discussion of predefined analyses reported
4.3 Was the synthesis appropriate given the	**No**	There were a number of differences in the two studies compared in the synthesis. As

nature and similarity in the research questions, study designs and outcomes across included studies?		such a series of MAICs were used. The EAG has concerns with the naïve and adjusted comparisons presented by the company.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	**No**	Only two covariates were considered for adjustment owing to the available data, however, this excludes other potentially important variables. However a naïve approach was utilised in the economic modelling.
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	**No**	The effective sample sizes were very low suggesting the analyses may not be reliable.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	**No**	Bias was not explicitly incorporated into the findings/ conclusions of the SLR
Concerns regarding the synthesis and findings	**High concern**	More than one question has no or probably no response
Summary of concerns identified (Overall risk of bias) in the review		
Risk of bias	**High concern**	Only one aspect of risk of bias considered to be low concern

7.2 *Appendix 2*

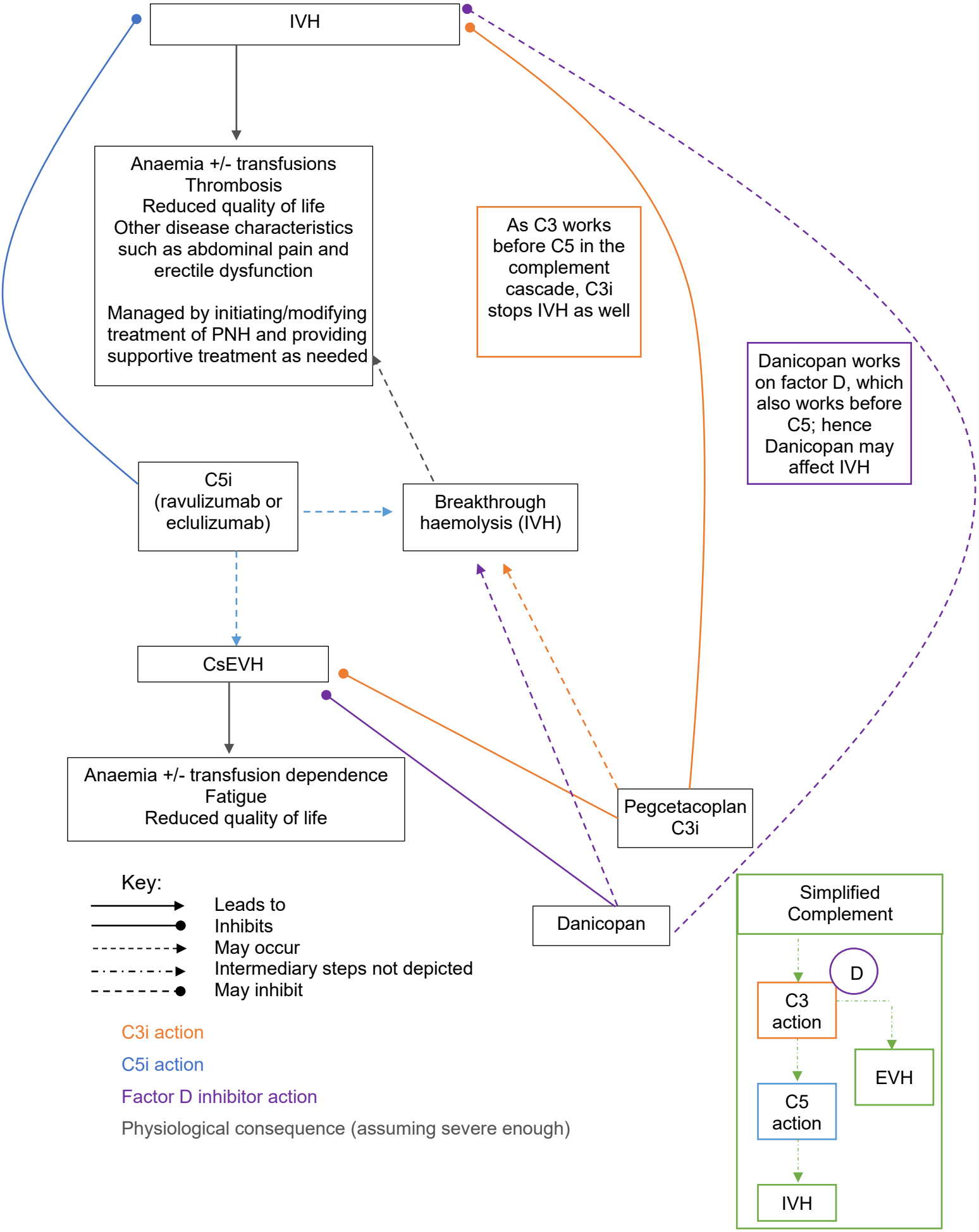
Table 45: Comparing key baseline characteristics of ALPHA with real world evidence sources

Characteristic	**Alpha Trial (overall population, n=63)**	**Updated analysis of PNH registry (population n=4439), Hubert Schrezenmeier et al, 2020**[52d]	**PNH registry preliminary analysis (population analysis n=1610), Hubert Schrezenmeier, Petra Muus, et al, 2014**[3]	**UK study (n=509)**[53]

Asian	39.7 %	16.3 %	5.0%[l]	NR
White	44.4 %	78.4 %	87.5 %	NR
Black	1.6 %[a]	3 %	3.5 %[f]	NR
Other	14.3 %[b]	2.3 %	4.1 %[m]	NR
Japanese	11.1 %	NR	NR	NR
Female	58.70 %	53 %	53.20 %	53.40 %
Age at onset of disease, mean	43.1	39.3	32[g]	43.92
Age at baseline, mean	54.3	45.1	42[h]	NR
Aplastic anaemia	[redacted][c]	53[e] %	43.5 %[i]	42.2 %[j]
Haemoglobin at baseline (median)	78.0	98.0 (n=3581)	106 (n=1425)	107.7[k]

a: Black or African American origin
b: American Indian or Alaska native, other, unknown, not reported
c: [redacted]
d: Study did not look at patients who were on treatment at baseline, although the time point for the baseline varied
e: History of aplastic or hypoplastic anaemia at baseline
f: African Descent
g: Median value
h: Median value
i: Ever diagnosed with aplastic anaemia
j: Documented history of Aplastic Anaemia, resolution/time point unspecified
k: Mean Hb 12 months after starting C5i
l: Asian or pacific islander
m: Native/Aboriginal or of other/unknown ethnicity/race

7.3 *Appendix 3*



7.4 *Appendix 4*

Additional literature searches undertaken by the EAG

Searches for Pegcetacoplan Date: 04/01/2023

Ovid MEDLINE(R) ALL 1946 to February 23, 2024

1	pegcetacoplan/	0
2	Pegcetacoplan.ti,ab.	114
3	(Aspaveli or EMPAVELI).ti,ab.	7
4	1 or 2 or 3	115
5	add-on.ti,ab,kf.	12937
6	(ravulizumab or ultomiris).ti,ab.	182
7	(eculizumab or soliris).ti,ab.	2430
8	5 or 6 or 7	15410
9	4 and 8	49
10	Hemoglobinuria, Paroxysmal/	3878
11	Marchiafava-Micheli syndrome*.ti,ab,kf.	37
12	paroxysmal nocturnal haemoglobinuria*.ti,ab.	696
13	paroxysmal nocturnal hemoglobinuria*.ti,ab.	2776
14	10 or 11 or 12 or 13	4709
15	9 and 14	46
16	limit 15 to english language	45

Embase Classic+Embase 1947 to 2024 February 23

1	pegcetacoplan/	461
2	Pegcetacoplan.ti,ab.	285
3	(Aspaveli or EMPAVELI).ti,ab.	10
4	1 or 2 or 3	480
5	add-on.ti,ab,kf.	22071
6	ravulizumab/	782
7	(ravulizumab or ultomiris).ti,ab.	503
8	eculizumab/	9788
9	(eculizumab or soliris).ti,ab.	5624
10	5 or 6 or 7 or 8 or 9	32309
11	4 and 10	273
12	exp Hemoglobinuria, Paroxysmal/	7473
13	Marchiafava-Micheli syndrome*.ti,ab,kf.	41
14	paroxysmal nocturnal haemoglobinuria*.ti,ab.	1109
15	paroxysmal nocturnal hemoglobinuria*.ti,ab.	4598
16	12 or 13 or 14 or 15	8050
17	11 and 16	195
18	limit 17 to english language	192

Paroxysmal nocturnal hemoglobinuria and danicopan or iptacoplan, pegcetacoplan, eculizumab or ravulizumab and costs, quality of life, clinical effectiveness
Ovid MEDLINE(R) ALL 1946 to January 18, 2024

1	exp hemoglobinuria, paroxysmal/ or paroxysmal nocturnal h?emoglobinuria.ti,ab.	4693
2	Marchiafava-Micheli syndrome.ti,ab.	35
3	1 or 2	4693

4 (extravascular h?emolysis or EVH or persistent an?emia or transfusion dependen* or transfusion-dependen*).ti,ab. 4241
5 ((sub?optimal or inadequate) adj (response or responder)).ti,ab. 4574
6 4 or 5 8799
7 3 and 6 119
8 limit 7 to yr="1860 - 2022" 95
9 Hemoglobinuria, Paroxysmal/3868
10 (Paroxysmal Hemoglobinuria or paroxysmal haemoglobinuria or paroxysmal nocturnal hemoglobinuria or Paroxysmal Nocturnal Haemoglobinuria).ti,ab,kf. 3605
11 Marchiafava-Micheli syndrome*.ti,ab,kf. 37
12 PNH.ti,ab. 2344
13 9 or 10 or 11 or 12 5133
14 Danicopan.af. 15
15 (ACH-0144471 or ALXN2040 or ach 144471 or ach 4471 or ach0144471 or ach144471 or ach4471 or alxn 2040 or alxn2040).ti,ab. 4
16 Alexion.af. 3172
17 pegcetacoplan/ 0
18 (Pegcetacoplan or Aspaveli or EMPAVELI).ti,ab. 108
19 (apl 2 or apl2 or syfovre).ti,ab. 54
20 (eculizumab or soliris).ti,ab. 2404
21 (abp 959 or abp959 or amt 904 or amt904 or bcd 148 or bcd148 or bekemv or "bow 080" or bow080 or elizaria or epysqli or isu 305 or isu305 or monoclonal antibody 5G1*).ti,ab. 14
22 (Ravulizumab or Ultomiris or ALXN1210).ti,ab. 177
23 (alxn1210 or alxn 1810 or alxn1810 or bnj 441 or bnj441).ti,ab. 18
24 Iptacopan/ 0
25 (Iptacopan or Fabhalta).ti,ab,kf. 21
26 ("lnp 023" or "lnp 023 aab" or lnp023 or lnp023 aab or lnp023aab or "nvp lnp 023" or "nvp lnp 023 aab" or "nvp lnp 023 nx" or nvp lnp023 or nvp lnp023 aab or nvp lnp023 nx or nvplnp023 or nvplnp023aab or nvplnp023nx).ti,ab. 8
27 (Crovalimab or ch 7092230 ch 7092230 or ch7092230 or rg 6107 or rg6107 or ro 7092230 or ro 7112689 or ro7092230 or ro7112689 or sky 59 or sky59).ti,ab. 20
28 Complement C5/ 2750
29 Complement C3/ 13384
30 ((C3 or C5) adj3 (Complement or inhibit*)).ti,ab,kf. 10882
31 (beta 1 f globulin or beta1 f globulin).ti,ab,kf. 0
32 Complement Activation/ 11340
33 Complement Inactivating Agents/ 982
34 (Complement adj1 (activat* or inactivat* or inhibitor*)).ti,ab. 16604
35 Treatment Outcome/ 1172931
36 ((Clinical* or treatment) adj1 (effective* or efficac* or outcome*)).ti,ab. 502323
37 Hemolysis/de [Drug Effects] 8768
38 budgets/ or exp "costs and cost analysis"/ or economics, hospital/ or economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or economics/ or "fees and charges"/ or financial management, hospital/ or financial management/ or health care rationing/ or health priorities/ or health resources/ or "health services needs and demand"/ or models, econometric/ or models, economic/ or resource allocation/428175
39 (cost$ or financ$ or fiscal$ or funding or price or prices or pricing or resource$).ti. 246938
40 (economic$ or pharmacoeconomic$).ti,ab. 382429
41 (budget$ or expenditure$).ti,ab. 104344
42 (cost adj2 (effectiv$ or reduc$ or saving$)).ti,ab. 219908
43 (value adj2 money).ti,ab. 2244
44 quality-adjusted life years/ 16076
45 (qaly$ or lifeyear$ or life year$).ti,ab. 28962

46 (cost* or economic* or pharmacoeconomic* or pharmaco economic*).ti. or (cost* adj2 (effective* or utilit* or benefit* or minimi*)).ab. or economic model*.tw. or (budget* or fee or fees or financ* or price or prices or pricing or resource* allocat* or (value adj2 (monetary or money))).ti,ab. 578352
47 decision theory/ or decision tree/ or monte carlo method/ or *nonbiological model/ or (statistical model/ and exp economic aspect/) or stochastic model/ or *theoretical model/ 109144
48 exp decision theory/ or markov chains/ or exp models, economic/ or *models, organizational/ or *models, theoretical/ or monte carlo method/ 142444
49 exp decision theory/ or exp stochastic modeling/ 13541
50 ((decision adj (analy* or model* or tree*)) or economic model* or markov or monte carlo).ti,ab. 110609
51 quality adjusted life year/ or "quality of life index"/ or short form 12/ or short form 20/ or short form 36/ or short form 8/ or sickness impact profile.tw. 17157
52 quality-adjusted life years/ or sickness impact profile/ 23237
53 "*quality of life"/ 0
54 (((disability or quality) adj adjusted) or (adjusted adj2 life)).ti,ab. 25153
55 (disutili* or (utilit* adj1 (health or score* or value* or weigh*))).ti,ab. 7083
56 (health year equivalent or hye or hyes).ti,ab. 76
57 (daly or qal or qald or qale or qaly or qtime* or qwb*).ti,ab. 15420
58 discrete choice.ti,ab. 3380
59 (euroqol* or euro qol* or eq5d* or eq 5d*).ti,ab. 17539
60 (hui or hui1 or hui2 or hui3).ti,ab. 2028
61 ((quality adj2 (wellbeing or well being)) or quality adjusted life or qwb or (value adj2 (money or monetary))).ti,ab. 23434
62 (qol or hql* or hqol*or h qol* or hrqol or hr qol or hr ql or hrql).ti,ab. 79615
63 sickness impact profile.ti,ab. 1086
64 (standard gamble or time trade* or tto or willingness to pay or wtp).ti,ab. 12243
65 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw. 14925
66 (time trade off or time tradeoff or tto).ti,ab,kw. 2398
67 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw. 23760
68 duke health profile.ti,ab,kw. 94
69 functional status questionnaire.ti,ab,kw. 133
70 dartmouth coop functional health assessment*.ti,ab,kw. 14
71 or/14-70 2976064
72 13 and 71 1207
73 72 not 8 1129
74 from 73 keep 1001-1129 129

Embase Classic+Embase 1947 to 2024 February 23

1 pegcetacoplan/ 461
2 Pegcetacoplan.ti,ab. 285
3 (Aspaveli or EMPAVELI).ti,ab. 10
4 1 or 2 or 3 480
5 add-on.ti,ab,kf. 22071
6 ravulizumab/ 782
7 (ravulizumab or ultomiris).ti,ab. 503
8 eculizumab/ 9788
9 (eculizumab or soliris).ti,ab. 5624
10 5 or 6 or 7 or 8 or 9 32309
11 4 and 10 273
12 exp Hemoglobinuria, Paroxysmal/ 7473
13 Marchiafava-Micheli syndrome*.ti,ab,kf. 41

14 paroxysmal nocturnal haemoglobinuria*.ti,ab. 1109
15 paroxysmal nocturnal hemoglobinuria*.ti,ab. 4598
16 12 or 13 or 14 or 15 8050
17 11 and 16 195
18 limit 17 to english language 192
19 exp hemoglobinuria, paroxysmal/ or paroxysmal nocturnal h?emoglobinuria.ti,ab. 8045
20 Marchiafava-Micheli syndrome.ti,ab. 39
21 19 or 20 8047
22 (extravascular h?emolysis or EVH or persistent an?emia or transfusion dependen* or transfusion-dependen*).ti,ab. 9893
23 ((sub?optimal or inadequate) adj (response or responder)).ti,ab. 11397
24 22 or 23 21227
25 21 and 24 458
26 limit 25 to yr="1860 - 2022" 394
27 paroxysmal nocturnal hemoglobinuria/ 7473
28 (Paroxysmal Hemoglobinuria or paroxysmal haemoglobinuria or paroxysmal nocturnal hemoglobinuria or Paroxysmal Nocturnal Haemoglobinuria).ti,ab,kf. 5807
29 Marchiafava-Micheli syndrome*.ti,ab,kf. 41
30 PNH.ti,ab. 4687
31 27 or 28 or 29 or 30 8846
32 danicopan/ 89
33 Danicopan.af. 93
34 (ACH-0144471 or ALXN2040).ti,ab. 12
35 Alexion.af. 5237
36 pegcetacoplan/ 461
37 (Pegcetacoplan or Aspaveli or EMPAVELI).ti,ab. 285
38 eculizumab/ 9788
39 (eculizumab or soliris).ti,ab. 5624
40 (abp 959 or abp959 or amt 904 or amt904 or bcd 148 or bcd148 or bekemv or "bow 080" or bow080 or elizaria or epysqli or isu 305 or isu305 or monoclonal antibody 5G1*).ti,ab. 29
41 ravulizumab/ 782
42 (Ravulizumab or Ultomiris or ALXN1210).ti,ab. 512
43 (alxn1210 or alxn 1810 or alxn1810 or bnj 441 or bnj441).ti,ab. 57
44 Iptacopan/ 160
45 (Iptacopan or Fabhalta).ti,ab,kf,tn. 88
46 ("lnp 023" or "lnp 023 aab" or lnp023 or lnp023 aab or lnp023aab or "nvp lnp 023" or "nvp lnp 023 aab" or "nvp lnp 023 nx" or nvp lnp023 or nvp lnp023 aab or nvp lnp023 nx or nvplnp023 or nvplnp023aab or nvplnp023nx).ti,ab,tn. 87
47 crovalimab/ 117
48 Crovalimab.ti,ab. 64
49 (ch 7092230 ch 7092230 or ch7092230 or rg 6107 or rg6107 or ro 7092230 or ro 7112689 or ro7092230 or ro7112689 or sky 59 or sky59).ti,ab. 14
50 *complement component C5/ 1040
51 *Complement C3/ 6462
52 ((C3 or C5) adj3 (Complement or inhibit*)).ti,ab,kf. 16253
53 *complement activation/ 8150
54 *complement inhibitor/ 1066
55 (Complement adj1 (activat* or inactivat*)).ti,ab. 21712
56 *budget/ 8138
57 *"cost benefit analysis"/ 13616
58 *economics/ 28652
59 *pharmacoeconomics/ 6196
60 *financial management/ 47712

61 (cost$ or financ$ or fiscal$ or funding or price or prices or pricing or resource$).ti. 321228
62 (economic$ or pharmacoeconomic$).ti,ab. 486997
63 (budget$ or expenditure$).ti,ab. 140783
64 (cost adj2 (effectiv$ or reduc$ or saving$)).ti,ab. 305761
65 (value adj2 money).ti,ab. 3120
66 *quality adjusted life year/ 1944
67 (qaly$ or lifeyear$ or life year$).ti,ab. 46029
68 (cost* or economic* or pharmacoeconomic* or pharmaco economic*).ti. or (cost* adj2 (effective* or utilit* or benefit* or minimi*)).ab. or economic model*.tw. or (budget* or fee or fees or financ* or price or prices or pricing or resource* allocat* or (value adj2 (monetary or money))).ti,ab. 782534
69 *decision theory/ 578
70 *Monte Carlo method/ 8516
71 *nonbiological model/ 5181
72 statistical model/ and economic aspect/ 560
73 *statistical model/ 25981
74 *economic model/ 1017
75 ((decision adj (analy* or model* or tree*)) or economic model* or markov or monte carlo).ti,ab. 133026
76 quality adjusted life year/ 36718
77 "Quality of Life Index"/ 3253
78 *Short Form 12/ 703
79 *Short Form 20/ 8
80 *Short Form 36/ 2878
81 sickness impact profile.ti,ab. 1250
82 *quality adjusted life year/ 1944
83 *Sickness Impact Profile/ 736
84 *"quality of life"/ 142673
85 (((disability or quality) adj adjusted) or (adjusted adj2 life)).ti,ab. 36704
86 (disutili* or (utilit* adj1 (health or score* or value* or weigh*))).ti,ab. 12555
87 (health year equivalent or hye or hyes).ti,ab. 187
88 (daly or qal or qald or qale or qaly or qtime* or qwb*).ti,ab. 26899
89 discrete choice.ti,ab. 4908
90 (euroqol* or euro qol* or eq5d* or eq 5d*).ti,ab. 31991
91 (hui or hui1 or hui2 or hui3).ti,ab. 3261
92 ((quality adj2 (wellbeing or well being)) or quality adjusted life or qwb or (value adj2 (money or monetary))).ti,ab. 34946
93 (qol or hql* or hqol*or h qol* or hrqol or hr qol or hr ql or hrql).ti,ab. 142448
94 sickness impact profile.ti,ab. 1250
95 (standard gamble or time trade* or tto or willingness to pay or wtp).ti,ab. 18524
96 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw. 19983
97 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw. 40317
98 duke health profile.ti,ab,kw. 121
99 functional status questionnaire.ti,ab,kw. 180
100 dartmouth coop functional health assessment*.ti,ab,kw. 14
101 *treatment outcome/ 39592
102 ((Clinical* or treatment) adj1 (effective* or efficac* or outcome*)).ti,ab. 785799
103 or/32-102 2504675
104 31 and 103 2949
105 104 not 26 2610

7.5 *Appendix 5*

Full text studies assessed from targeted searches

Fishman. Analysis of Costs per Responder in US Adults with Paroxysmal Nocturnal Hemoglobinuria with a Suboptimal Response to Prior Eculizumab Treatment. Hematology Reports 2023. http://dx.doi.org/10.3390/hematolrep15040060

Menosi Gualandro. Characteristics of paroxysmal nocturnal hemoglobinuria patients in Brazil: A retrospective administrative claims database analysis of PNH patients in Brazilian public healthcare system. PLoS One 2023;18(7):e0288708. http://dx.doi.org/10.1371/journal.pone.0288708

Fishman. The cost-effectiveness of pegcetacoplan in complement treatment-naïve adults with paroxysmal nocturnal hemoglobinuria in the USA. J Comp Eff Res 2023;12(10):e230055. http://dx.doi.org/10.57264/cer-2023-0055

Quist. Cost-effectiveness of ravulizumab compared with eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria in the Netherlands. Eur J Health Econ 2023;24(9):1455-72. http://dx.doi.org/10.1007/s10198-022-01556-5

Broderick. Descriptive, real-world treatment patterns, resource use, and total cost of care among eculizumab- and ravulizumab-treated members with paroxysmal nocturnal hemoglobinuria. J Manag Care Spec Pharm 2023;29(8):941-51. http://dx.doi.org/10.18553/jmcp.2023.29.8.941

Rich. The disease burden of paroxysmal nocturnal hemoglobinuria in Denmark: Epidemiology, survival, healthcare resource utilization, costs, treatment gaps, and labor market attachment. Eur J Haematol 2024;112(3):412-23. http://dx.doi.org/10.1111/ejh.14128

Cheng. Dosing Patterns of Patients with Paroxysmal Nocturnal Hemoglobinuria Treated with Ravulizumab in the United States: A Retrospective Claims-Based Analysis. Advances in Therapy 2024;41(1):413-30. http://dx.doi.org/10.1007/s12325-023-02725-5

Dou. Economic Burden of Patients with Paroxysmal Nocturnal Hemoglobinuria in China. Value in Health 2023;26(12 Supplement):S69. http://dx.doi.org/https://dx.doi.org/10.1016/j.jval.2023.09.369

Fishman. MDS-355 Work Productivity and Activity Impairment (WPAI), and Hemoglobin Levels During OPERA: a Real-World Study of Pegcetacoplan Treatment in US Adults With Paroxysmal Nocturnal Hemoglobinuria (PNH). Clinical Lymphoma Myeloma and Leukemia 2023;23:S363. http://dx.doi.org/https://doi.org/10.1016/S2152-2650(23)01182-5

Clayton. Treatment Patterns and Healthcare Resource Utilization of Patients With Paroxysmal Nocturnal Hemoglobinuria: A Retrospective Claims Data Analysis. Clin Appl Thromb Hemost 2024;30:10760296231213073. http://dx.doi.org/10.1177/10760296231213073

Single Technology Appraisal

Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]

EAG Response to company factual accuracy check and confidential information check on the EAG Report

1. Introduction and Background

Issue 1 Update to the anticipated licence for danicopan as an add-on to eculizumab or ravulizumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 16, Section 1.1 of the EAG report states that the remit of the appraisal is "to appraise the clinical and cost effectiveness of danicopan as an add on to a C5 inhibitor (C5i) within its marketing authorisation for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria (PNH)."	Please can this statement be amended as follows: "to appraise the clinical and cost effectiveness of danicopan as an add on to **eculizumab or ravulizumab. This falls within** its anticipated marketing authorisation for the treatment of [redacted]. **In patients treated with C5 inhibitors, residual haemolytic anaemia is caused by EVH, as IVH remains well-controlled due to the C5 inhibitor backbone.[1]**	This statement should be amended to reflect that the anticipated licence wording for danicopan refers specifically to eculizumab and ravulizumab. Since submission, the anticipated licence wording for danicopan as an add-on to eculizumab or ravulizumab has been updated to adult patients with PNH who have residual haemolytic anaemia. As such, wording for the licence for danicopan should be updated throughout, and marked as commercial in confidence. In patients treated with C5 inhibitors, residual haemolytic anaemia is caused by EVH, as IVH remains well-controlled due to the C5 inhibitor backbone.[1] In around 30% of patients, this EVH	Not a factual error, this is the remit of the appraisal as stated in the NICE scope.

		is clinically significant and requires medical treatment, as supported by a UK advisory board.[2] As such, the updated licence wording for danicopan add on treatment directly aligns with the population considered in the NICE submission: 'adult patients with PNH who experience clinically significant extravascular haemolysis (csEVH) on a C5 inhibitor (eculizumab or ravulizumab)'.	

Issue 2 Patients registered in the PNH National Service

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 16, Section 1.1 of the EAG report states that "The disease prevalence is around 1/62500 in Great Britain,[1] and between April 2022-April 2023, there were 1025 patients in the PNH service.[2]"	Please may this text be amended as follows: "The disease prevalence is around 1/62500 in Great Britain,[1] and between April 2022-April 2023, there were 1025 patients in the PNH service**, including patients enrolled in Northern Ireland and territories other than England, Scotland and Wales**.[2]"	This sentence implies that 1,025 patients are registered in the PNH National Service in Great Britain and should be revised for clarity.	Thank you, we have changed the sentence ending to say 'there were 1025 patients in the **UK** PNH service"

Issue 3 Indications for eculizumab and ravulizumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 17, Section 1.2.1 of the EAG report states that (for eculizumab and ravulizumab): "the indications include symptomatic haemolytic anaemia and complications, but there is also scope for starting treatment on a case-by-case basis if patients do not fit the indication[9]."	Please may this text be amended as follows: "the indications include symptomatic haemolytic anaemia and complications **and thrombosis related to PNH.** There is also scope for starting treatment on a case-by-case basis if patients do not fit the indication[9]."	This text should be amended to provide a complete overview of the indications for treatment with eculizumab or ravulizumab, as recommended by the PNH National Service.[3]	Thank you, we have added the text as suggested

Issue 4 Up-dosing of eculizumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 17, Section 1.2.1 of the EAG report states "eculizumab is initially given at 600mg once weekly for four weeks, then increased to 900mg once weekly for a week, and maintained with 900mg every 12-16 days hereafter.[11]"	Please may this statement be amended as follows: "eculizumab is initially given at 600mg once weekly for four weeks, then increased to 900mg once weekly for a week, and maintained with 900mg every 12-16 days hereafter.[11] **In clinical practice, patients may escalate to off-label doses of 1,200**	It should be noted that off-label dosing of eculizumab is frequently observed in patients with PNH,[4] as these doses are relevant to the cost-effectiveness model.	Not a factual error, no response required.

	mg or 1,500 mg every two weeks to achieve sufficient disease control."		

Issue 5 Clinically significant EVH

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 19, Section 1.2.3 of the EAG report states that "the company states that there is an unmet need for a treatment solution to reliably address the consequences of EVH."	Please may this statement be amended to: "The company states that there is an unmet need for a treatment solution to reliably address the consequences of **csEVH**."	Many patients who experience EVH have no symptoms, and as such, the unmet need exists in symptomatic patients who are experiencing csEVH, which is associated with symptoms such as anaemia, transfusion dependence and fatigue.[2] These statements should be amended throughout to avoid implying danicopan will be used to treat every patient experiencing residual haemolytic anaemia due to EVH, as many patients will not require treatment; only those exhibiting clinically significant symptoms.	Thank you, we have amended the text as suggested.

Issue 6 Standard of care for csEVH

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Table 4, page 23, Section 1.3 of the EAG report states that "As current standard of care for patients with csEVH includes remaining on C5 inhibitor the EAG considers these cannot be excluded as comparators."	Please remove this statement.	As described in the decision problem (Section B.1.1 of the CS, Table 1), eculizumab and ravulizumab are licensed for the treatment of PNH in patients who experience haemolysis with clinical symptoms indicative of high disease activity.[5, 6] Eculizumab and ravulizumab are the standard of care first-line treatments for IVH specifically; they do not address csEVH. For patients who go on to develop csEVH, pegcetacoplan is the only treatment option recommended by NICE.[7] As such, unless a patient with csEVH is unable to receive pegcetacoplan for any reason (e.g. due to eyesight or dexterity problems), they would be treated with pegcetacoplan, in order to address the clinical symptoms the patient is experiencing. Therefore, the	Not a factual error, no change required.

		standard of care for csEVH in the UK is pegcetacoplan.	

Issue 7 BTH in C5 inhibitor treated patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Table 4, Page 24, Section 1.3 of the EAG report states that "although the CS says IVH is controlled in the csEVH population of focus here, the EAG note that BTH still occurs, particularly when there is infection or if insufficient levels of C5-inhibitors (clarification B9)"	Please may this statement be amended to: "although the CS says IVH is controlled in the csEVH population of focus here, the EAG note that BTH **may still occur infrequently**, **if** there is infection or if insufficient levels of C5-inhibitors (clarification B9)"	The current statement implies that BTH is frequent in C5 inhibitor treated patients, which is not supported by observations from the ALPHA trial or clinical opinion. In the ALPHA trial, only one BTH event featuring LDH level >2 x ULN was observed. This event occurred in the LTE alongside a COVID-19 infection, and resolved without intervention.[8] Furthermore, UK clinical experts in PNH stated that patients on ravulizumab very rarely experience pharmacokinetic BTH (insufficient dosing levels) in clinical practice.[9, 10] This statement should therefore be	Not a factual error, no change required.

		amended to reflect the infrequency of these events.	

2. Clinical Effectiveness

Issue 1 Criticism of the search date of the Company SLR

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 29, Section 2.1 of the EAG report states that, in the context of the clinical, economic and humanistic SLR: "the searches were carried out on the 1st November 2022 (SLR1) and updated on the 12th June 2023. The EAG consider this search to not be sufficiently up to date. The EAG replicated the search in Medline, Embase and the Cochrane Library on the 4th Jan 2023 and found that there was a difference of 139 results (after the removal of duplicate records via Ovid)."	The EAG report should indicate that SLR searches were conducted within 6 months of submission. The EAG report should specify how many of the 139 results were considered relevant to the clinical, economic and humanistic SLR.	The Company SLR was performed within 6 months of submission (12th December 2023). It may not therefore be appropriate to state that these searches were not appropriately up to date when no strict date limit is available. Furthermore, as the EAG have not specified how many of the 139 new results, if any, were relevant hits for the clinical, economic or humanistic SLRs; this statement is potentially misleading and therefore should be clarified.	Not a factual error. The role of the EAG is to review and critique the available evidence for each technology. It is not the role of the EAG to carry out the searches and screening; therefore updating the systematic literature review.

Issue 2 Search terms used in the SLR

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 29, Section 2.1 of the EAG report states that: "The search also didn't include the Emtree indexing term paroxysmal nocturnal hemoglobinuria/ which could exclude potentially relevant results"	Please may this statement be amended as follows: "The search **used in the original SLR** didn't include the Emtree indexing term paroxysmal nocturnal hemoglobinuria/ which could exclude potentially relevant results. **However, this term was included in the SLR update (12th June 2023, search number #1, Table 2, Appendix D.1.1)**"	This statement should be amended; the term was included in the SLR update, and as such, these additional results are anticipated to have been picked up in the search (search number #1, Table 2, Appendix D.1.1).	Thank you, we have amended the text as suggested.

Issue 3 Included articles in the Company SLR

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 30, Section 2.1 of the EAG report states that: "The CS reports 63 articles were included in the overall SLR but it is not clear what numbers were relevant to each section of the SLR."	Please amend this statement as follows: "The CS reports 63 articles were included in the overall SLR. **As stated in the Appendices (G.2.1.) of the Company submission, five cost-effectiveness studies were included in the SLR.**"	While the distinction between clinical and humanistic studies is not provided in the Company submission, the number of published cost-effectiveness studies is stated in the Appendices.	Not a factual error.

Issue 4 Availability of data from the 31st March 2023 DCO

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 31, Section 2.2 of the EAG report states that: "Clarification A12 states that an additional (post hoc) data cut (31st March 2023) was conducted for supplemental analyses to address specific requests from regulatory agencies, however results have not been provided with this submission."	Please amend this statement as follows: "Clarification A12 states that an additional (post hoc) data cut (31st March 2023) was conducted for supplemental analyses to address specific requests from regulatory agencies. **As these results were provided as a brief addendum, and no CSR is currently available for this data cut, results were not provided within the submission."**	Data for the 31st March 2023 DCO were not supplied in the submission due to the absence of a CSR or detailed summary of results for this data cut. This should be disclosed when discussing the availability of these data, for clarity.	Not a factual error. The EAG is not able to provide any description of the results that have not been provided.

Issue 5 Eligibility criteria of the ALPHA trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Table 6, Page 32, Section 2.2 of the EAG report lists key eligibility criteria for the ALPHA trial; one criterion is missing when compared to Table 5, Section B.2.3.2 of the Company submission.	Please may the following eligibility criterion be added to the table: **"Patients who are on iron, folic acid, and vitamin B12 supplementation are eligible for the study if on a stable dose for at least 30 days prior to Day 1."**	To align with Table 5 of the Company submission, please may the full key eligibility criteria be listed in the EAG report.	Not a factual error, no response required

Issue 6 Primary and key secondary endpoints in the ALPHA trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Table 6, Page 32 and 33, Section 2.2 of the EAG report states that the primary endpoint of the ALPHA trial is: "Change in haemoglobin" Table 6 also states that key secondary endpoints of relevance to the decision problem are: "Proportion of patients with haemoglobin increase of ≥ 2 g/dL in the absence of transfusion Proportion of patients with transfusion avoidance Change in FACIT-Fatigue"	Please may the primary endpoint of the ALPHA trial be amended to: "Change **from baseline** in haemoglobin at **Week 12**" Please may the key second endpoints of relevance to the decision problem be amended to: " Proportion of patients with haemoglobin increase of ≥ 2 g/dL **at Week 12** in the absence of transfusion" "Proportion of patients with transfusion avoidance **at Week 12**" "Change **from baseline** in FACIT-Fatigue scores **at Week 12**" It may also be useful to note that all results are also reported at Week 24.	The timepoints of assessment, and defining change from baseline for several results, are required to define the primary and key secondary endpoints of relevance to the decision problem.	We have amended this table to improve the clarity.

Issue 7 Risk of bias in the ALPHA trial (1/2)

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 38, Section 2.2.1 of the EAG report states: "For example, the company stated 'no information' and 'probably yes' to questions 2.6 and 2.7 respectively (bias due to deviations from intended interventions), suggesting that there was potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised. But this doesn't tie in with the company's response in CS Table 12 (appropriate analysis) and there is no explanation as to why they considered there was potential for an impact on the result."	Please may this text be amended to: "For example, the company stated 'no information' and 'probably yes' to questions 2.6 and 2.7 respectively (bias due to deviations from intended interventions), suggesting that there was potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised **when the trial was assessed using the Lee et al. 2023 publication.[11] This differed to the response in CS Table 12 (appropriate analysis) as the ALPHA trial CSR, which contained further information on the intention-to-treat analysis used in the trial, was also taken into account during this quality assessment."**	As stated on Page 53, Section B.2.6 of Document B, the quality assessment presented in Table 12 utilised information from the ALPHA trial CSR in addition to the Lee, et a. 2023 publication.[11] As stated in Page 53 of Appendix D.5, the quality assessment presented in Table 17 is based on the Lee 2023 publication only. Using the additional information provided in the trial CSR, the ALPHA trial was considered at low risk of bias, and this is why the responses differed between sections B.2.6 and Appendix D.5.	Thank you, we have amended the text to remove: "and there is no explanation as to why they considered there was potential for an impact on the result".

Issue 8 Risk of bias in the ALPHA trial (2/2)

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 38, Section 2.2.1 of the EAG report states: "Overall, the company's SLR[12] judged ALPHA to have high risk of bias due to the absence of a published CONSORT diagram, which lead to an assessment of a high risk of bias due to missing outcome data."	Please may this text be amended as follows: **"The company SLR[12] considered that the ALPHA trial had high risk of bias when assessing the trial based on the published study protocol and conference abstract. However, when assessing the trial for bias based on the published protocol, the conference abstract and the ALPHA trial CSR, which provides a CONSORT diagram for the trial, the risk of bias can be considered sufficiently low as per Table 12, Section B.2.6. of the Company submission."**	It should be clarified that the Alexion data on file SLR report[13] stated that the ALPHA trial was at high risk of bias when assessed using the published protocol and conference abstract, due to a lack of details of the trial reported. When assessing the trial using the ALPHA trial CSR, the trial may be considered at sufficiently low risk of bias due to the additional information available.	Thank you, we have amended the text to say: "Overall, the company's SLR judged ALPHA to have high risk of bias due to the absence of a published CONSORT diagram, which lead to an assessment of a high risk of bias due to missing outcome data. The CSR was not available to the reviewers undertaking the company CS".

Issue 9 Long-term extension data for the ALPHA trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 42, Section 2.2.2 of the EAG report states that:	Please may this text be amended as follows: **"The CS reports a summary of HRQoL (Section B.2.7.4, CS) and safety (B.2.11, CS) outcome data for the long term**	It is inaccurate to state that no outcome data for the LTE are reported in the Company submission; Figure 7, Section B.2.7.1 illustrates haemoglobin	Thank you, we have replaced the text to say: "The CS reports minimal outcome data from the long

"The CS does not report outcome data from the long term extension period of ALPHA."	**extension period of the ALPHA trial. Furthermore, mean haemoglobin values through to Week 48 of the ALPHA trial are presented in Figure 7, Section B.2.7.1 of the CS. No other outcome data for the long term extension period are presented in the CS"**	levels in the first 24 weeks of the LTE while summary HRQoL and safety data are presented for the LTE in their respective sections.	term extension period of ALPHA."

Issue 10 EORTC-QLQ-C30 results in the ALPHA trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 43, Section 2.2.2 of the EAG report states: "There was no statistically significant difference between groups in change from baseline in Global health status at week 12 (Table 11)."	Please may this text be amended as follows: "**While numerical benefits were observed for danicopan (******) versus placebo (****),** there was no statistically significant difference between groups in change from baseline in Global health status at week 12 (Table 11)."	For clarity, the numerical benefits of danicopan add-on treatment on EORTC-QLQ-C30 global health status scores should be acknowledged, though this difference is not clinically significant.	Not a factual error, no response required

Issue 11 Weighting used in the anchored and unanchored MAICs

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 57, Section 2.4.1 of the EAG report states: "Unusually, the company appear to have used the same weightings for the anchored and unanchored indirect comparison analyses. This may mean that the unanchored indirect comparisons are sub-optimal, as they still account for the placebo arm characteristics and do not focus solely on the unanchored danicopan – pegcetacoplan comparison."	Please remove this statement.	Different weightings were used for the anchored and unanchored MAIC analyses. The results from the unanchored MAIC analysis and the anchored MAIC analysis yielded different results, indicating that different weights were used in these analyses. For completeness, a summary of the weights used in the unanchored MAIC analyses are provided in the Addendum (Section 8 of this form). A summary of the weights used in the anchored MAIC analyses are provided in Table 14, Appendix D.3.2 of the Company submission.	Not a factual error. This statement was accurate at the time of writing as the company only provided information on one set of weights without any reference to anchoring status. The EAG statement is not incorrect as it allows for the possibility of separate weightings to be used. However new information provided at the FAC stage does now suggest separate weightings were used across the analyses and the EAG has amended the text to this effect.

Issue 12 Naïve comparison of results between the ALPHA and PEGASUS trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 61, Section 2.4.2 states that, with respect to Table 21: "The analyses provided suggest that danicopan is more likely to be inferior."	Please amend this statement as follows: "**In the analyses provided, pegcetacoplan is observed to have numerical benefits versus danicopan add-on treatment for several endpoints. However, due to the naïve comparison selected and the substantial heterogeneity in trial designs and populations highlighted in the Company submission and in this report, these results are associated with uncertainty and should be interpreted with caution.**"	Throughout the EAG report, limitations of naïve comparisons are highlighted (for example, Page 58, Section 2.4.1 of the EAG report). It is therefore inappropriate to conclude that results from a naïve comparison, which are associated with uncertainty, indicate the inferiority of danicopan, considering that the results of the adjusted comparisons were not considered appropriate to determine the comparative treatment effect of danicopan add-on treatment and pegcetacoplan.	Not a factual error, no response required

Issue 13 Bias introduced by censoring approaches

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 61, Section 2.4.2 of the EAG report states:	Please add further clarification to this statement regarding:	It is currently unclear why the EAG believe censoring would introduce bias in favour of	The EAG has amended the text as follows:

“As more transfusions were received in the placebo arm of ALPHA, it is anticipated that the benefit of danicopan would increase as the censoring rule becomes more severe.”	1. Why the EAG anticipate a bias in favour of danicopan upon censoring for transfusion 2. A description regarding the size of the bias expected to be introduced by censoring 3. Clarify the meaning behind the censoring rule ‘becoming more severe’ Additionally, please disclose that the censoring approach used in response to clarification question A5 aligns with the approach taken for the primary analysis of the PEGASUS trial.	danicopan add-on treatment, therefore, further clarification on this statement would be useful. The EAG have not disclosed the anticipated size of the bias introduced by censoring, and therefore it is currently unclear whether this is a key concern. It is also currently unclear what is meant by the severity of censoring, i.e., whether this severity is defined by the timepoint at which censoring is applied, or, the specific methodology used to censor results. Finally, for clarity, it should be noted that these analyses were conducted by the request of the EAG and align with the approach taken in the PEGASUS primary analysis, which was accepted for decision making by NICE in TA778.[7, 14]	“As more transfusions were received in the placebo arm of ALPHA, it is anticipated that the benefit of danicopan would increase as the censoring rule becomes more severe due to the beneficial effects of transfusions being removed”

Issue 14 UK participants in the ALPHA trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 64, Section 2.5 of the EAG report states: "CSR Table 14.1.1.4.2 reports that there were ** UK participants randomised (******)."	Please clarify what the ***** percentage represents.	It is currently unclear how this percentage was calculated, and it does not correspond to the IAS (N=63), FAS (N=86) or total screened participants (N=111) of the ALPHA trial, so clarity should be added.	Thank you, we believe this is a transcription error and the amount should be *** text amended to say: CSR Table 14.1.1.4.2 reports that there were 10 UK participants randomised ******

3. Cost Effectiveness

Issue 1 Inclusion of INAHTA HTA database in SLR

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 66, Section 3.1.1 of the EAG report states "As the CRD HTA and NHS EED databases are no longer updated, the EAG recommends also searching the	This statement should be removed.	The International HTA Database by INAHTA was included in the SLR under grey literature (Appendix D.1.1), with the grey literature search strategy summarised in Table 3.	Thank you. We have removed this comment.

INAHTA HTA database to ensure completeness."			

Issue 2 Inconsistency between the clinical and cost effectiveness sections

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 70, Section 3.2.2 of the EAG report states "The health states and transition probabilities used do not correspond to specific clinical effectiveness outcome presented by the company, which represents an inconsistency between the clinical and cost effectiveness sections."	Please can this statement be amended as follows: "The health states and transition probabilities used do not correspond to specific clinical effectiveness outcome presented by the company, which **is in line with the accepted approach used in NICE's evaluation of pegcetacoplan [TA778]**."	As described in B.3.2.2 of the CS, the model structure adopted for this submission is similar to the model accepted by the NICE committee in TA778. In the submitted model for TA778, transition probabilities were similarly calculated by classifying patients in the PEGASUS trial into the appropriate haemoglobin level and transfusion-based health states, instead of corresponding to the specific clinical effectiveness outcomes. This was not raised as an issue during the committee meeting.	Not a factual error, no response required

Issue 3 Intervention and comparators

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 71, Section 3.2.4 of the EAG report states: "This excludes eculizumab or ravulizumab alone as standard of care for PNH patients, and iptacopan, which are listed in the NICE final scope."	Please can this statement be amended as follows: "This excludes eculizumab or ravulizumab alone, **which the company consider to be first-line** standard of care for PNH patients, and iptacopan **(which had not received a positive recommendation from NICE at the time of submission)**, which are listed in the NICE final scope."	Additional context for the exclusion of C5 inhibitor monotherapy and iptacopan as comparators is required. As mentioned in Section 1 Issue 6, eculizumab and ravulizumab are first-line treatments which address IVH, and EVH manifests following treatment of IVH. Therefore, eculizumab and ravulizumab do not address EVH and are not considered relevant comparators. Additionally, given that iptacopan had not received a positive recommendation from NICE at the time of submission (publication of NICE guidance expected in mid-2024), iptacopan is not an established treatment for PNH patients with residual haemolytic anaemia in the NHS. Hence, iptacopan is not a relevant comparator.	The EAG has amended the latter part of the sentence as suggested.

Issue 4 Naïve comparison of transition probabilities

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 72, Section 3.2.6 of the EAG report states: "The company's choice of transition probabilities is effectively implementing a naïve comparison of the relevant arms of the ALPHA and PEGASUS trials, and does not account for underlying differences in population baseline characteristics or the differences in the models used to estimate the transition probabilities."	Please can this statement be amended as follows: "The company's choice of transition probabilities is effectively implementing a naïve comparison of the relevant arms of the ALPHA and PEGASUS trials. **However, the un-adjustable heterogeneity between patient characteristics and trial designs is noted**."	In Section B.2.10 of the CS, there are no studies which report on the relative efficacy of danicopan as an add-on to eculizumab or ravulizumab compared to pegcetacoplan, hence a MAIC was explored. It was then discussed that the ALPHA and PEGASUS trials had significant differences in terms of patient baseline characteristics and trial designs which could not be adjusted for. As such, the results of the MAIC were associated with considerable uncertainty and were not suitable to inform the economic analysis and the naïve trial results were used.	Not a factual error, no response required
Page 9, Section 0.4 of the EAG report outlines key issue 4, stating as a suggestion for additional analyses:	Please adapt the text to make it clear that the company provided a MAIC scenario analysis within the CS (Section B.3.11.3) whereby alternative transition probabilities from the trimmed ALPHA population using a	As noted on Page 72, Section 3.2.6 of the EAG report, a MAIC scenario analysis was presented in the submission whereby alternative transition probabilities from the trimmed ALPHA	Not a factual error. Whilst this analysis was performed using the original company assumptions, the probabilities were not

“The company could provide transition probabilities from original or trimmed ALPHA population using 10.5g/dL cut-off.”	10.5 g/dL haemoglobin level cut off were used to inform the cost-effectiveness model.	population using a 10.5 g/dL haemoglobin level cut off were provided. Therefore, this approach has previously been explored by the company.	provided in the company submission.

Issue 5 Equal probabilities of iron overload for all treatment arms

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 83, Section 3.2.8 of the EAG report states: “The EAG prefers to assume equal probabilities for all treatment arms within the model and use a probability of 0.47% in its scenario analysis.”	Justification should be added for the rationale for assuming equal probabilities between treatment arms.	It is expected that the application of transition probabilities from treatment-specific data obtained in their respective clinical trials would provide more certainty than a simplifying assumption of equal probability, which may over- or underestimate the clinical benefit, and thus economic benefits of danicopan.	Not a factual error, no response required.

Issue 6 BTH rates for danicopan as an add-on to eculizumab or ravulizumab and pegcetacoplan

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 85, Section 3.2.8.7 of the EAG report states: "The EAG does not consider this reliable evidence to carry these probabilities from a naïve comparison into the model, particularly given that the difference in BTH between the C5i (control) arms of each trial is greater than the BTH between the danicopan + C5i and pegcetacoplan arms. The EAG preference is to assume an equal rate of BTH across these two treatments."	Please can this statement be amended to quantify the difference in BTH rate observed between the C5 inhibitor arms for the ALPHA and the PEGASUS trial. Furthermore, please may the EAG acknowledge the lack of alternative evidence to inform rates of BTH, for example: "**Nonetheless, no published evidence on the comparative efficacy of danicopan as an add-on to eculizumab or ravulizumab versus pegcetacoplan monotherapy in preventing BTH is available, and the MAIC results were associated with considerable uncertainty.** The EAG preference is **therefore** to assume an equal rate of BTH across these two treatments."	The EAG should clarify the difference observed in BTH between the C5 inhibitor arms of the ALPHA and the PEGASUS trials. Using available data, and as per the definition of breakthrough haemolysis included in the supplement of the Hillmen, *et al.* PEGASUS publication:[14] *"At least one new or worsening symptom or sign of intravascular haemolysis (fatigue; haemoglobinuria; abdominal pain; shortness of breath [dyspnea];anaemia [haemoglobin <10 g/dl]; major adverse vascular events, including thrombosis; dysphagia; or erectile dysfunction) in the presence of elevated LDH ≥2 × ULN after prior LDH reduction to <1.5 × ULN on therapy."*	Not a factual error, no response required

		Only 2 of the 9 eculizumab treated patients reporting a BTH event met the pre-specified BTH definition with elevated LDH levels ≥2x ULN in the PEGASUS trial. Therefore, in total, 4 pegcetacoplan (3 discontinuations) and 2 eculizumab (no discontinuations) treated patients experienced BTH during the 16-week treatment period based on this definition. The C5 inhibitor treatment arm in the PEGASUS trial was formed of patients receiving eculizumab only; as discussed in TA698, the rate of BTH observed in eculizumab treated patients is higher than those treated with ravulizumab, which may explain this discrepancy.[15] Furthermore, clinicians consulted as part of a UK advisory board supported that BTH on C5 inhibitors, particularly ravulizumab, is particularly infrequent, and as such, an assumption of an equal rate of BTH for pegcetacoplan and	

		danicopan add-on treatment is not considered appropriate. As described in Issue 4 above, no published studies directly comparing danicopan as an add-on and pegcetacoplan are available. While MAIC analyses were explored, substantial un-adjustable heterogeneity between the ALPHA and PEGASUS trials rendered the MAIC's results unsuitable for informing the cost-effectiveness model due to the results being associated with substantial uncertainty. Given the lack of suitable data, a naïve comparison is used. Whilst the EAG do not consider the naïve comparison of BTH between danicopan add-on treatment and pegcetacoplan to be reliable evidence to inform BTH inputs in the model, it is important to acknowledge that no alternative data are available.	

Issue 7 Dose escalation of pegcetacoplan following BTH

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 86, Section 3.2.8.7 of the EAG report states: "Under the company's assumptions for pegcetacoplan, the dose escalation is rapid and soon results in the majority of people receiving the maximum treatment regime of three doses per week (Figure 2)."	Please can this statement be amended as follows: "Under the company's assumptions for pegcetacoplan, **which is based on the open label extension study of pegcetacoplan and consultation with UK clinical experts,** the dose escalation is rapid and soon results in the majority of people receiving the maximum treatment regime of three doses per week (Figure 2)."	Additional context for the dose escalation of pegcetacoplan is required. The dose escalation regimen of pegcetacoplan is in line with the SmPC for this intervention, and is also aligned with the approach adopted in an open-label extension study of pegcetacoplan.[16] Management of BTH on pegcetacoplan has evolved since the appraisal of TA778; use of the dose escalation regimen described in the CS has been confirmed by UK clinical experts to reflect the management of BTH in clinical practice, and a 2024 real world study conducted by Griffin et al. supports the use of dose escalations of pegcetacoplan to three times a week to achieve sufficient disease control.[9, 10] In summary, there is sufficient evidence to support the	Not a factual error, no response required.

		assumptions made in the submission.	

Issue 8 Accelerated dose of C5i therapy

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 88, Section 3.2.8.7 of the EAG report states "The EAG notes that the company also applies a cost for the accelerated dose of the C5i therapy for the pegcetacoplan population. The EAG considers the company's approach to overestimate this cost, as it is applied for all the modelled BTH events, and does not distinguish between BTH for C5i therapies."	Please can this statement be amended as follows: "The EAG notes that the company also applies a cost for the accelerated dose of the C5i therapy for the **danicopan as an add-on to eculizumab or ravulizumab** population." The last sentence of the statement should be removed.	As described in Section B.3.3.3 and B.3.5.1 of the CS, patients in the pegcetacoplan arm receive an escalated dosing frequency regimen of pegcetacoplan in response to BTH (Table 41), not eculizumab or ravulizumab. On the other hand, patients receiving danicopan as an add-on to eculizumab or ravulizumab receive an escalated dose of the relevant C5 inhibitor. The escalated dosing regimens are differentiated between eculizumab and ravulizumab as presented in Table 41 of the CS.	In the model provided by the company, for the modelling of the pegcetacoplan population, the probability of a BTH event is multiplied by the cost of accelerated C5i dosing, regardless of which treatment is associated with the BTH event. The EAG identified this as an error in the company base case. Not a factual error.

Issue 9 BTH management costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 88, Section 3.2.8.7 of the EAG report states "This BTH management cost is applied to all BTH events experienced by patients on pegcetacoplan in addition to dose escalation costs. They are not applied to BTH events for those on danicopan + C5i or C5i alone."	Please can this statement be amended as follows: "This BTH management cost is applied to all BTH events experienced by **all** patients **across treatment arms**."	As described in Section B.3.5.2 of the CS, the one-off cost of managing BTH was applied to all BTH events occurring in any given model cycle.	The EAG has made this amendment.

4. External Assessment Group's Additional Analyses

Issue 1 AE frequency for ALT

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 94, Section 5.1.1 of the EAG report states "The company modelled the probability of ALT using number of people experiencing the event, rather than the probability based on the rate of	Please can this statement be amended as follows: **"The company modelled the probability of ALT by converting the trial-informed probability of experiencing ALT to a per-**	In the economic model, the probability of ALT was calculated as follows: First, the probability of ALT in treatment period 1 (12 weeks) was informed by the number of	The EAG has clarified this point in the text. The EAG undertook a similar approach to the company in calculating their preferred figure. In the reported follow-

events. The EAG calculated the probability from the ALT event rate and applied this in the model"	**cycle probability via an instantaneous rate."** The phrase "rather than the probability based on the rate of events" should be removed.	people experiencing the event in the ALPHA trial, i.e., $^{3}/_{57}$ Secondly, this probability was converted to an instantaneous rate to calculate to account for the different time frame. $r = -\frac{1}{t}\ln(1-p)$ $= -\frac{4}{12}\ln\left(1 - \frac{3}{57}\right) \approx 0.018$ Finally, this rate was converted back to a per-cycle probability. $p = 1 - e^{-rt} = 1 - e^{-0.018*1}$ $\approx 1.78\%$ This approach has been employed to convert other event probabilities in the model that are informed by the ALPHA trial, such as BTH events and discontinuation events, and appropriately captures AE frequency for ALT.	up there were 4 events observed in the 57 people followed for 12 weeks. This gives a rate of 4/(57*12) = 0.005848 events per person week. This is multiplied by 4 to estimate the rate for every 4 person-weeks (matching the model cycle length) and is then converted to a probability using the formula provided by the company.

		Additional context for the EAG's calculation of the ALT event rate is required, as the Company were not able to replicate the 2.31% percentage provided by the EAG.	

Issue 2 Equal transition probabilities, and probabilities of iron overload, for pegcetacoplan vs danicopan

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 95, Section 5.1.1 of the EAG report states "The EAG assume equal transition probabilities for both danicopan and pegcetacoplan using probabilities from ALPHA. This negates additional uncertainty from naïve comparison."	The final statement in this paragraph ("This negates additional uncertainty from naïve comparison") should be removed.	The assumptions of equal transition probabilities, as well as probabilities of iron overload and BTH for danicopan and pegcetacoplan do not negate additional uncertainty from a naïve comparison. As mentioned in Section 3 Issue 5, these are simplifying assumptions which may over- or underestimate the clinical and economic benefits of danicopan. It is expected that the application of treatment-specific inputs from their respective clinical trials would provide more certainty than a broad assumption of equal probabilities.	The EAG has removed the text as requested.
Page 95, Section 5.1.1 of the EAG report states "The EAG assume equal iron overload probabilities for danicopan and pegcetacoplan using those from ALPHA. This reduces uncertainty from naïve comparison between the two trials."	The final statement in this paragraph ("This negates additional uncertainty from naïve comparison") should be removed.		The EAG has removed the text as requested.

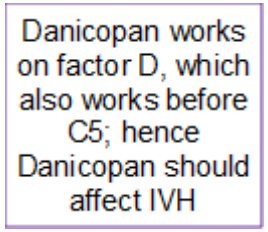
Issue 3 Long-term discontinuation rates in both arms

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 96, Section 5.1.2 of the EAG report states "Changes 1-7 (above) are applied and EAG maintain the discontinuation probabilities for the first 52 weeks of the model, but additionally set the discontinuation probability for the rest of the model time horizon to be 1% per cycle for both danicopan and pegcetacoplan." "	Please can this statement be amended as follows: "Changes 1-7 (above) are applied and EAG maintain the discontinuation probabilities for the first 52 weeks of the model, but additionally set the **non-BTH related** discontinuation probability for the rest of the model time horizon to be 1% per cycle for both danicopan and pegcetacoplan."	It is currently unclear whether the discontinuation probability amended for the EAG's sensitivity analysis refers to non-BTH related discontinuation, BTH-related discontinuation or both. As per the results provided in Table 41, it appears that a 1% per cycle discontinuation probability has only been applied to non-BTH related discontinuation for both treatment arms.	The EAG has removed the text as requested.
Page 96, Section 5.1.2 of the EAG report outlines the sensitivity analysis, wherein the EAG "set the discontinuation probability for the rest of the model time horizon to be 1% per cycle for both danicopan and pegcetacoplan.	Please clarify where the 1% long-term discontinuation rate has been sourced from. Please also disclose that this approach is not in line with the discontinuation approach used in TA778.[7]	It is currently unclear where this percentage was derived from. This assumption would imply that the majority of patients will have discontinued treatment within 6 years; this assumption is not clinically valid, given that EVH is a chronic condition and treatment with danicopan is recommended to continue for a patient's lifetime, unless the discontinuation of	Not a factual error. As the company states, there is no evidence on long-term discontinuation rates, and this scenario was selected to explore the impact of discontinuation when applied equally to both treatment arms.

		danicopan is clinically indicated.[17] There is also currently no established evidence on discontinuation rates after week 52 for both danicopan and pegcetacoplan, so clarity should be added. It is important to add context that this approach is not in line with that taken in the appraisal for pegcetacoplan, TA778.[7] In the base case analysis; discontinuation of pegcetacoplan was modelled as a 'one-off' discontinuation at Week 16, while discontinuation from eculizumab or ravulizumab was not considered. An EAG scenario analysis also considered an increased discontinuation rate of pegcetacoplan in year 1 only.	

5. Appendices

Issue 1 Long-term discontinuation rates in both arms

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 115, Appendix 3 of the EAG report illustrates the following: 	Please remove the statement “hence danicopan should affect IVH” or alternatively, please add a footnote to the diagram to acknowledge the available evidence base regarding danicopan’s expected impact on IVH.	Danicopan is positioned for adults with PNH who are experiencing csEVH whilst on treatment with eculizumab or ravulizumab. As such, IVH is expected to be controlled in this patient population, thus, danicopan add-on treatment is anticipated to have a negligible effect on IVH. This is supported by the non-statistically significant (p[redacted]) difference in LDH levels, a proxy for IVH, from baseline to Week 12 observed in the ALPHA trial.[8] Furthermore, this is supported by the exploratory single-arm Phase II trial published by Risitano et al. 2021, which notes that danicopan monotherapy did not consistently achieve complete inhibition of the alternative pathway across all	The EAG has amended the wording to say “Danicopan may affect IVH”.

		patients, with residual IVH reported in some patients.[18] As such, for clarity, the lack of evidence for danicopan impacting IVH should be acknowledged in this diagram.	

6. Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 29, Section 2.1 of the EAG report states: "The update search reported in Table 2 includes an additional search line: ((remain or persisten* or continu*) adj an?emia).ti,ab."	Please can this statement be amended as follows: "The update search reported in Table 2 includes an additional search line: ((remain or persisten[a] or continu[a]) adj an?emi[a]).ti,ab.**; where a denotes the following: EconLit was accessed via EBSCOhost (June 12, 2023) and a search for "paroxysmal nocturnal hemoglobinuria" yielded no results.**"	Typographical error. As presented in Appendix D.1.1 of the CS, of the CS, this is the correct search term.	The EAG upholds this statement. There appears to be a formatting, typographical or syntax error in the search line as reported in the Ovid search strategy CS Appendix D 1.1. Tables 1 and 2 and in the proposed amendment. The EAG has consulted

			the Ovid guide and can confirm that ‘a’ is not an operator that is compatible with the Ovid platform. The unlimited truncation symbols are * and $, which the EAG had assumed had been used in the search strategy, with the ‘a’ being a later formatting error. It is not possible to replicate the company’s search to check the impact this may have had on the search results, as it is not reported which versions of Medline, Embase and the Cochrane Library were searched. The EAG believe that the separate note

			under Table 2 is related to the overall search strategy that indicates that the company attempted to search EconLit via EbscoHOST, which is not connected to the root terms in search lines 4 and 6 of the Ovid searches. To maximise transparency and reproducibility the EAG would recommend reporting the search strategy utilised on EconLit via EBSCOHost, even if it yielded 0 results.
Page 32, Table 6, Section 2.2 of the EAG report states: “CsEVH, defined by anaemia (haemoglobin ≤9.5 g/dL) with ARC ≥120 × 109/L”	Please can this statement be amended as follows: “CsEVH, defined by anaemia (haemoglobin ≤9.5 g/dL) with ARC ≥120 × 10^9/L”	Typographical error. The correct definition is reported in Table 5,	This has been amended

		Page 50, Section B.2.3.2	
Page 33, Section 2.2 of the EAG report states: "The ALPHA trial included people aged at least 18 years with a diagnosis of PNH and csEVH (defined as haemoglobin ≤9.5 g/dL with ARC ≥120 × 109/L)."	Please can this statement be amended as follows: "The ALPHA trial included people aged at least 18 years with a diagnosis of PNH and csEVH (defined as haemoglobin ≤9.5 g/dL with ARC ≥120 × 10^{9}/L)."	Typographical error. The correct definition is reported in Table 5, Page 50, Section B.2.3.2	This has been amended
Page 40, Section 2.2.2 of the EAG report states: "As per the CS, data presented here are based on the post hoc data cut of 20th September 2022 using the interim analysis set (75% of randomised patients 63 participants)."	Please may this text be amended as follows: "As per the CS, data presented here are based on the **interim** data cut of 20th September 2022 using the interim analysis set (75% of randomised patients 63 participants)."	Typographical error. At the 20th September 2022 DCO, the ALPHA trial was ongoing, therefore, it is more appropriate to describe this data cut as an interim cut.	This has been amended
Page 40, Section 2.2.2 of the EAG report states: "The mean number of RBC units transferred and the mean number of transfusion instances was lower with danicopan compared with placebo, but statistical analyses were not conducted (Table 9, Clarification A13)."	Please can this statement be amended as follows: "The mean number of RBC units transferred and the mean number of transfusion instances was lower with danicopan compared with placebo, but statistical analyses were not conducted (Table **10**, Clarification A13)."	Typographical error. Table 10, rather than Table 9, is presented in support of the company's response to Clarification Question A.13	This has been amended

Page 40, Section 2.2.2 of the EAG report states: "There was no statistically significant difference between groups for change from baseline LDH (Table 7, Clarification A7), although baseline values for both groups fell within the normal range."	Please can this statement be amended as follows: "There was no statistically significant difference between groups for change from baseline LDH (Table **8**, Clarification A7), although baseline values for both groups fell within the normal range."	Typographical error. Table 8, rather than Table 7, is presented in support of the company's response to Clarification Question A.7	This has been amended
The footnote of Table 9 Page 41, Section 2.2.2 of the EAG report states: "Table adapted from CS Tables 13-18, and Clarifications A7 and A13."	Please can this statement be amended as follows: "Table adapted from CS Tables 13-**15 and 17-18**, and Clarifications A7 and A13."	Typographical error. Table 16, Section B.2.7.1 of the CS presents "Change from baseline in FACIT-F scores at Week 12", these data are not presented in Table 9 of the EAG report.	This has been amended
The footnote of Table 10 Page 42, Section 2.2.2 of the EAG report states: "Table adapted from CS Table 19"	Please can this statement be amended as follows: "Table adapted from CS Table 19**, and Clarifications A7.**"	Typographical error. The data for change from baseline in LDH at Week 24 are presented in Clarification Question A.7.	This has been amended

<table>
<tr>
<td>Page 43, Section 2.2.2 of the EAG report states:

“The proportion of patients with a clinically important improvement of at least 10 points[19] was [redacted]</td>
<td>Please can this statement be amended as follows:

“The proportion of patients with a clinically important improvement of at least 10 points[19] was [redacted].”</td>
<td>Typographical error.

The correct data for the proportion of patients in the placebo arm with a clinically important improvement of at least 10 points (for the EORTC-QLQ-C30 global health status) is provided in Table 14.2.5.7.1 of the ALPHA trial CSR.</td>
<td>This has been amended</td>
</tr>
<tr>
<td>Table 11, Page 44, Section 2.2.2 of the EAG report states:

<table>
<tr><td>Patients with improvement of ≥ 5 points, n (%) (95I CI)</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>Please may this table be amended as follows:

<table>
<tr><td>Patients with improvement of ≥ 5 points, n (%) (95I CI)</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>Typographical error.

The correct patient n number in the danicopan treatment for an improvement of 5 points (FACIT-Fatigue score) is provided in Table 14.2.3.6.2 of the ALPHA trial CSR.</td>
<td>This has been amended</td>
</tr>
<tr>
<td>The footnote of Table 11 Page 44, Section 2.2.2 of the EAG report states: “Source: CS Table 16 and 19, CSR”</td>
<td>Please can this statement be amended as follows: “Source: CS Table 16 and 20, CSR”</td>
<td>Typographical error.

Table 11 of the EAG report includes no data from Table 19 of the CS,</td>
<td>This has been amended</td>
</tr>
</table>

		instead the EQ-5D-3L UK health state index score data presented in the EAG report can be found in Table 20, Section B.2.7.4 of the CS.	
The footnote of Table 12 Page 44, Section 2.2.2 of the EAG report states: "**Source:** CS Table 19, CSR"	Please can this statement be amended as follows: "**Source:** CS Table 19 **and 20**, CSR"	Typographical error. The EQ-5D-3L UK health state index score data presented in Table 12 of the EAG report are taken from Table 20, Section B.2.7.4 of the CS.	This has been amended
Table 12, Page 45, Section 2.2.2 of the EAG report states: Change from baseline at week 24, mean (SD) [redacted]	Please may this table be amended as follows: Change from baseline at week 24, mean (SD) [redacted]	Typographical error. The correct patient n number for the change from baseline in EORTC-QLQ-C30 Fatigue score at Week 24 in the DAN/PBO arm is provided in Table 14.2.5.4.1 of the ALPHA trial CSR.	This has been amended

<table>
<tr>
<td>Page 46, Section 2.2.2 of the EAG report states:

“Stratification factors (prespecified subgroups): Haemoglobin at screening (<8.5 g/dL, ≤8 .5 g/dL), transfusion history (>2, ≤2 transfusions) and Japanese and non-Japanese participants, CS Table 22.”</td>
<td>Please may this text be amended as follows:

“Stratification factors (prespecified subgroups): Haemoglobin at screening (<8.5 g/dL, ≥8 .5 g/dL), transfusion history (>2, ≤2 transfusions) and Japanese and non-Japanese participants, CS Table 22.”</td>
<td>Typographical error.

Please align the stratification factors as presented on Page 38, Section B.2.3.2 of the Company submission.</td>
<td>This has been amended</td>
</tr>
<tr>
<td>Table 19, Page 59, Section 2.4.2 of the EAG report provides patient numbers for the trimmed ALPHA trial population:

<table>
<tr><th colspan="2">ALPHA – subset population</th></tr>
<tr><th>Danicopan + C5i[a] (n=42)</th><th>Placebo + C5i[a] (n=21)</th></tr>
</table>
</td>
<td>Please may this table be amended as follows:

<table>
<tr><th colspan="2">ALPHA – subset population</th></tr>
<tr><th>Danicopan + C5i[a] (n=38)</th><th>Placebo + C5i[a] (n=19)</th></tr>
</table>
</td>
<td>The patient n numbers listed in Table 19 of the EAG report correspond to the full rather than the trimmed IAS of the ALPHA trial. The correct patient n numbers may be found in Table 25, Section B.2.10.3 of the Company submission.</td>
<td>This has been amended. The EAG has marked these numbers as CIC as they appear in the CS.</td>
</tr>
<tr>
<td>Table 19, Page 59, Section 2.4.2 of the EAG report presents the Race of patients in the ALPHA – Maximised ESS population:

<table>
<tr><th colspan="2" rowspan="2"></th><th colspan="2">ALPHA - MAIC</th></tr>
<tr><th>Danicopan (n=15.271)</th><th>Placebo (n=7.395)</th></tr>
<tr><td rowspan="2">Race (%)</td><td>Asian</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Black</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>Please may the table be amended as follows:

<table>
<tr><th colspan="2" rowspan="2"></th><th colspan="2">ALPHA – maximised ESS (n=22.610)</th></tr>
<tr><th>Danicopan (n=15.271)</th><th>Placebo (n=7.395)</th></tr>
<tr><td rowspan="4">Race (%)</td><td>Asian</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Black</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>White</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Other</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>These percentages should be amended to align with those presented in Table 15, Appendix D.3.2. Additionally, please specify that the patient n numbers refer to the maximised ESS population.</td>
<td>This has been amended</td>
</tr>
</table>

	White	[redacted]	[redacted]
	Other	[redacted]	[redacted]
	NR	[redacted]	[redacted]

	NR	[redacted]	[redacted]

Table 19, Page 59, Section 2.4.2 of the EAG report presents the mean haemoglobin values for the trimmed ALPHA population: Haemoglobin (g/dl) – mean ± SD [redacted] [redacted]	Please may this table be amended as follows: Haemoglobin (g/dl) – mean ± SD [redacted] [redacted]	Typographical error. The correct SD for this value is presented in Table 25, Section B.2.10.3 of the Company submission.	This has been amended
Table 22, Section 2.4.2 of the EAG report presents change from baseline in EQ-5D-3L UK index scores at Week 12 for varying censoring approaches: Change in EQ-5D-3L [redacted] [redacted] [redacted]	Please may the table be amended as follows: Change in EQ-5D-3L [redacted] [redacted] [redacted]	Please align the values with the standard errors presented in response to clarification question A4, A5 and A6 (Tables 1, Table 3 and Tabl2 6).	The EAG prefers to convert the SE to a 95% confidence interval for consistency. No change made.
Page 63, Section 2.5 of the EAG report states: “although only 58% of APPLY-PNH had received an RBC, compared with 100% of ALPHA”	Please amend this statement as follows: “although only 58% of APPLY-PNH had received an red **blood cell transfusion (RBCT)**, **in the prior 6 months to randomisation**, **compared to 87.3% of patients within 24 weeks of the first study dose, in the IAS of the ALPHA trial**”	Typographical error. Please clarify that 87.3% of patients in the APPLY-PNH trial had received a prior transfusion, adding the timepoint for this result for context, using the de Latour, 2022 abstract.[20]	We have made the following amendment: “… although only 58% of APPLY-PNH had received "a red blood cell transfusion in the 6 months to

		Furthermore, it is more appropriate to compare to prior transfusions in the 24 weeks prior to first study dose in the ALPHA trial (Table 11, B.2.5 of the Company submission), as the current value corresponds to the prior 12 months, which may be misleading.	randomisation compared to 87.3% within 24 weeks of the first study dose in the IAS of the ALPHA trial"
Table 24, Page 73, Section 3.2.6 of the EAG report states: A low Hb/Transfusion value of 0.072 in the table	Please can the value be changed to **0.073** and additionally a footnote be added underneath the table stating **'The probability of transitioning from the 'Low Hb' state to the 'transfusion' state was 0.072 as reported by Hakimi et al. 2022, and was adjusted in the model such that all transition probabilities for the 'Low Hb' state summed up to 1'.**	Typographical error. The correct value is reported in Table 39, Page 110, Section B.3.3.2 of NICE Document B	This has been amended, and a footnote added to the table.
Page 100, Section 5.3 of the EAG report states: "However, these to not represent an EAG base case as the EAG maintains that there is insufficient evidence to support a relative	Please amend this statement as follows: "However, these **do** not represent an EAG base case as the EAG maintains that there is insufficient evidence to support a relative	Typographical error.	This has been amended

comparison of danicopan + C5i and pegcetacoplan”	comparison of danicopan + C5i and pegcetacoplan”		
Page 114, Table 45, Appendix 2 of the EAG report presents a comparison of the key baseline characteristics of the ALPHA trial with real world evidence sources. It states the following values from the PNH registry preliminary analysis: • Asian: NR • Other: 9.10%	Please can the values be changed as follows • Asian: **5.0%** • Other: **4.1%** Additionally, please can the following footnotes be added: • Asian: **“Asian/Pacific Islanders”** • Others: **“Native/Aboriginal, or of other/unknown ethnicity/race”**	Typographical error. Schrezenmeier et al. 2014 reports the proportion of patients who are Asian/Pacific Islanders, which were mistakenly grouped under ‘Other’ in the EAG report. Additional context on the ethnicities included is required.	This has been amended
Page 114, Table 45, Appendix 2 of the EAG report presents a comparison of the key baseline characteristics of the ALPHA trial with real world evidence sources. Footnote e states the following: “e: History of aplastic anaemia at baseline”.	Please can the footnote be changed as follows: “e: History of aplastic **or hypoplastic** anaemia at baseline”.	Typographical error. Schrezenmeier et al. 2020 reports that the 53% of patients refer to patients with a history of aplastic or hypoplastic anaemia at baseline.	This has been amended

7. Inaccuracies in confidentiality highlighting

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
Page 20, Section 1.2.3 of the EAG report states "The literature states that only csEVH requires treatment, and that up to 20% of patients on C5i experience csEVH, although the CS's clinical expert group puts this [redacted]	Please can the confidentiality highlighting be removed from this statement as follows: "The literature states that only csEVH requires treatment, and that up to 20%21, 22 of patients on C5i experience csEVH, although the CS's clinical expert group puts this **number at around 30%**;"	As presented in Section B.1.3.1 of the CS, there is no confidentiality highlighting included for this statement.	This has been amended
Page 20, Table 4 Section 1.3 of the EAG report states "Clinical experts in the United Kingdom (UK) consulted at an advisory board estimated the prevalence of csEVH to be [redacted]"	Please can the confidentiality highlighting be removed from this statement as follows: "Clinical experts in the United Kingdom (UK) consulted at an advisory board estimated the prevalence of csEVH to be **approximately 30%**."	As presented in Section B.1.1 Table 1 of the CS, there is no confidentiality highlighting included for this statement.	This has been amended
Page 35, Section 2.2 of the EAG report states: "Compared with the danicopan group, the placebo group had a higher	Please can the confidentiality highlighting be removed from this statement as follows: "Compared with the danicopan group, the placebo group had a higher proportion of females **(66.7% vs 54.8%)** and people	As presented in Section B.2.5 Table 9 and Table 10 of the CS, there is no confidentiality highlighting included for these data.	This has been amended

proportion of females [redacted] and people aged less than 65 years [redacted] and fewer Asian patients (33.3% vs 42.9%) and those with Hispanic or Latino ethnicity [redacted] although as the CS notes they may be attributable to unreported data."	aged less than 65 years **(81.0% vs 71.4%)**, and fewer Asian patients (33.3% vs 42.9%) and those with Hispanic or Latino ethnicity (**0% vs 9.5%)**, although as the CS notes they may be attributable to unreported data."		
Page 36, Table 7 Section 2.2 of the EAG report presents "Key baseline demographics and disease characteristics from the IAS of ALPHA".	Please can the confidentiality highlighting be removed from the entire table, apart from the number and proportion of patients with a "History of PNH-associated aplastic anaemia".	As presented in Section B.2.5 Table 9 and Table 10 of the CS, there is no confidentiality highlighting included for these data.	This has been amended
Page 37, Table 8 Section 2.2 of the EAG report presents "Prior treatments (IAS)".	Please can the confidentiality highlighting be removed from the entire table, apart from "Number of RBC units transferred 12 weeks prior to treatment, mean (SD)" and "Number of transfusion instances 12 weeks prior to treatment, mean (SD)"	As presented in Section B.2.5 Table 11 of the CS, there is no confidentiality highlighting included for these data. Confidentiality highlighting are included for "Number of RBC units transferred 12 weeks prior to treatment, mean (SD)" and "Number of transfusion instances 12 weeks prior to treatment, mean (SD)" as presented in Clarification Question A.13.	This has been amended

Page 46, Section 2.2.3 of the EAG report states: "The CS presents treatment-emergent adverse events (TEAEs, i.e. started during or after the first dose) for the safety analysis set (N=86) during TP1, and for [redacted] and [redacted] in TP2 and LTE, respectively."	Please can the confidentiality highlighting be removed from this statement as follows: "The CS presents treatment-emergent adverse events (TEAEs, i.e. started during or after the first dose) for the safety analysis set (N=86) during TP1, and for **N=71** and **N=60** in TP2 and LTE, respectively."	As presented in B.2.11, there is no confidentiality highlighting for these data.	This has been amended
Page 47, Section 2.2.3 of the EAG report states: "During TP1, slightly more participants in the danicopan group experienced an AE compared with placebo ([redacted]), however the proportions with a SAE ([redacted]), an AE leading to withdrawal of intervention ([redacted]) an SAE leading to withdrawal of study intervention ([redacted]) and Grade 3 ([redacted] or Grade 4 ([redacted]) AEs were similar."	Please can the confidentiality highlighting be removed from this statement as follows: "During TP1, slightly more participants in the danicopan group experienced an AE compared with placebo **(73.7% vs 62.1%**), however the proportions with a SAE **(5.3% vs 6.9%),** an AE leading to withdrawal of intervention **(5.3% vs 3.4%)** an SAE leading to withdrawal of study intervention **(1.8% vs 0%)** and Grade 3 **(17.5% vs 13.8%)** or Grade 4 **(1.8% vs 0%)** AEs were similar."	As presented in Table 28, B.2.11.2, there is no confidentiality highlighting for these data.	This has been amended

Page 47, Table 13, Section 2.2.3 of the EAG report presents “Overview of TEAEs during each study period and cumulatively”.	Please may the confidentiality highlighting be removed from the data with respect to TP1, TP2 and the LTE. Confidentiality highlighting for the total patients exposed to danicopan at the data cut should be retained.	As presented in Table 28, B.2.11.2, there is no confidentiality highlighting for these data.	This has been amended
Page 48, Section 2.2.3 of the EAG report states: “In TP1 there appears to be a discrepancy between the values for any Grade 3 TEAE in the danicopan arm between CS Tables 28 ([redacted]) and Table 30 ([redacted]);”	Please can the confidentiality highlighting be removed from this statement as follows: “In TP1 there appears to be a discrepancy between the values for any Grade 3 TEAE in the danicopan arm between CS Tables 28 (**17.5%**) and Table 30 (**15.8%**);”	As presented in Table 28, B.2.11.2, and Table 30, B.2.11.4 there is no confidentiality highlighting for these data.	This has been amended
Page 48, Section 2.2.3 of the EAG report states: “The most common Grade 3 events (occurring in more than one participant) were [redacted] in the danicopan arm, and [redacted] in the placebo arm.”	Please can the confidentiality highlighting be removed from this statement as follows: “The most common Grade 3 events (occurring in more than one participant) were **alanine amino transferase (ALT) increased (n=3, 5.3%)** in the danicopan arm, and **anaemia (n=2, 6.9%)** in the placebo arm.”	As presented in Table 30, B.2.11.4 there is no confidentiality highlighting for these data.	This has been amended

Page 49, Section 2.2.3 of the EAG report states: "The most common event during TP1 in the danicopan arm was [redacted]"	Please can the confidentiality highlighting be removed from this statement as follows: "The most common event during TP1 in the danicopan arm was **ALT increased (5.3%), followed by blood bilirubin increased (3.5%) and AST increased (3.5%)**."	As presented in Table 31, B.2.11.5 there is no confidentiality highlighting for these data.	This has been amended
Page 49, Section 2.2.3 of the EAG report states: "These were generally balanced between treatment groups in TP1, with the most common events in the danicopan group being headache ([redacted]), nausea ([redacted]) diarrhoea ([redacted]) and arthralgia ([redacted]). The most comment events in the placebo group were [redacted]"	Please can the confidentiality highlighting be removed from this statement as follows, as well as making the indicated amendment: "These were generally balanced between treatment groups in TP1, with the most common events in the danicopan group being headache (**10.5%**), nausea (**8.8%**) diarrhoea (**7.0%**) and arthralgia (7.0%). The most comment events in the placebo group were **anaemia (13.8%) and** asthenia **(13.8%), with** nausea, diarrhoea, **contusion, AST increased,** headache and **insomnia each occurring in 10.3%**."	As presented in Table 29, B.2.11.3 there is no confidentiality highlighting for these data. Additionally, there is a typographical error. Table 29, Section B.2.11.3 presents data for contusion, not confusion as indicated in the EAG report.	This has been amended

<table>
<tr>
<td>Page 49, Section 2.2.3 of the EAG report states: “the CS reports that **** ****** reported a LDH level >2 times ULN in the trial,”</td>
<td>Please can the confidentiality highlighting be removed from this statement as follows: “the CS reports that one patient reported a LDH level >2 times ULN in the trial,”</td>
<td>As presented in B.2.11.4 there is no confidentiality highlighting for these data.</td>
<td>This has been amended</td>
</tr>
<tr>
<td>Page 50, Table 14, Section 2.2.3 of the EAG report presents a summary of BTH events for patients exposed to danicopan at the 20th September 2022.</td>
<td>Confidentiality highlighting may be removed from several of these values as they are not confidential and are presented in Section B.2.11 of the Company submission.</td>
<td>Please may this table be amended as follows:
<table>
<tr><th></th><th colspan="2">TP1</th><th>TP2</th><th>LTE</th><th>Exposed to DAN to data-cut</th></tr>
<tr><th></th><th>DAN + C5i[a] N=57</th><th>PBO + C5i[a] N=29</th><th>Total N=71</th><th>Total N=60</th><th>****
*******</th></tr>
<tr><td>Grade 1</td><td>0 (0.0)</td><td>0 (0.0)</td><td>*
***</td><td>*
***</td><td></td></tr>
<tr><td>Grade 2</td><td>0 (0.0)</td><td>0 (0.0)</td><td>*
***</td><td>*
***</td><td></td></tr>
<tr><td>Grade 3</td><td>0 (0.0)</td><td>0 (0.0)</td><td>1 (1.4)</td><td>0 (0.0)</td><td></td></tr>
<tr><td>Totals (any grade)</td><td>0 (0.0)</td><td>0 (0.0)</td><td>*
***</td><td>*
</td><td>***</td></tr>
</table>
</td>
<td>This has been amended</td>
</tr>
<tr>
<td>Page 77, Section 3.2.7 of the EAG report states the utility values in Table 27 for low Hb, moderate Hb and</td>
<td>Please can the confidentiality highlighting be removed from these 3 values in Table 27 of the EAG report.</td>
<td>As presented in Section B.3.4.7, Page 117, Table 51 of Document B, there is no confidentiality highlighting for these values in the table.</td>
<td>This has been amended</td>
</tr>
</table>

<table>
<tr>
<td>transfusion as [redacted] respectively</td>
<td>This will leave the utility values in the table for low Hb, moderate Hb and transfusion as follows:

0.8181, 0.8644, 0.7018</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Page 114, Table 45, Appendix 2 of the EAG report presents a comparison of the key baseline characteristics of the ALPHA trial with real world evidence sources.</td>
<td>Confidentiality highlighting may be removed from several of these values as they are not confidential and are presented in Section B.2.5 of the Company submission.</td>
<td>Please may this column be amended as follows:
<table>
<tr><th>Characteristic</th><th>ALPHA trial (overall population, n=63)</th></tr>
<tr><td>Asian</td><td>39.7 %</td></tr>
<tr><td>White</td><td>44.4 %</td></tr>
<tr><td>Black</td><td>1.6 %[a]</td></tr>
<tr><td>Other</td><td>14.3 %[b]</td></tr>
<tr><td>Japanese</td><td>11.1 %</td></tr>
<tr><td>Female</td><td>58.70 %</td></tr>
<tr><td>Age at onset of disease, mean</td><td>43.1</td></tr>
<tr><td>Age at baseline, mean</td><td>54.3</td></tr>
<tr><td>Aplastic anaemia</td><td>[redacted][c]</td></tr>
<tr><td>Haemoglobin at baseline (median)</td><td>78.0</td></tr>
</table>
</td>
<td>This has been amended</td>
</tr>
</table>

8. Company Addendum

Table 1 presents weights used for the unanchored MAIC and the unanchored, maximised ESS MAIC. Equivalent weights for the anchored MAIC are presented in Table 14, Appendix D.3.2 of the Company submission.

Table 1: Summary statistics for calculated weights (unanchored MAIC)

Abbreviations: ESS: effective sample size; MAIC: matching adjusted indirect comparison; Q: quartile; SD: standard deviation.

	MAIC weights			Maximized ESS weights		
	Danicopan	Placebo	Overall	Danicopan	Placebo	Overall
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range Lower	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range Upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]: addendum to EAG report factual accuracy check

The Company have submitted this addendum with the aim of resolving several key issues, as highlighted in the EAG report, for the danicopan NICE submission ahead of the appraisal committee meeting scheduled for 7th May 2024. This addendum provides several pieces of additional evidence that the Company hope will aid the NICE team, both in preparation for the Committee meeting, and during the Committee's decision-making process.

Key Issue 2 – ALPHA trial: Data from interim analysis of incomplete trial population and potential lack of generalisability

Page 8 of the EAG report states that "the Company responded to say that a third interim analysis had been performed which included TP1 and TP2 for all trial participants, but this would not be made available as it was only conducted to address specific requests from regulatory agencies". With the aim of resolving remaining uncertainty, a summary of the available data from interim analysis 3 (IA3) is provided in Appendix A.

IA3 provides efficacy data for all patients randomised to treatment in the ALPHA trial, providing additional data on n=[redacted] patients randomised to the danicopan arm and n=[redacted] patients randomised to the placebo arm, when compared to the interim analysis set (N=63 patients) for IA2. Specifically, Appendix A provides results for treatment period 1 (TP1) and treatment period 2 (TP2) for the modified randomised set (N=[redacted] patients) at the 31st March 2023 data cut.

As shown by Table 1, results for IA3 are [redacted] with IA2 at Week 12. In IA3, treatment with danicopan as an add-on to eculizumab or ravulizumab resulted in a [redacted] increase in haemoglobin at Week 12 ([redacted] g/dL) versus placebo ([redacted] g/dL) as an add-on to eculizumab or ravulizumab (treatment group difference: [redacted]; <[redacted]). In IA2, treatment with danicopan as an add-on to eculizumab or ravulizumab resulted in a statistically significant increase in haemoglobin (2.94 g/dL) versus placebo (0.50 g/dL) as an add-on to eculizumab or ravulizumab (treatment group difference: 2.44 g/dL; p<0.0001) at Week 12 in IA2. Additionally, danicopan treatment resulted in a [redacted] increase in FACIT-F score versus placebo at Week 12 in IA3.[1] Efficacy results at Week 24 were [redacted] between IA2 and IA3 (Table 2) supporting the robustness of the ALPHA trial results.

Key Issue 6 – Uncertainty over long term discontinuation probabilities for danicopan and pegcetacoplan

Page 10 of the EAG report states that "the EAG has presented a scenario on top of its other changes to the model, where a 1% discontinuation probability is applied in week 53 and beyond for both treatments".

The Company would like to reiterate the lack of clinical plausibility associated with this assumption by referring to the EAG model; under this assumption, 56% of patients considered in the model had discontinued treatment after 6 years. This rate of discontinuation is not clinically valid: EVH is a chronic condition and treatment with danicopan is recommended to continue for a patient's lifetime, unless the discontinuation of danicopan is clinically indicated.[2]

The Company would also like to reference Pages 36, 164, 165 and 448 of the committee papers for TA778, the NICE appraisal for pegcetacoplan.[3] In the Company base case, discontinuation of pegcetacoplan was modelled as a 'one-off' discontinuation at Week 16, while discontinuation from eculizumab or ravulizumab was not considered. These assumptions were based on clinical opinion.[3] While the EAG scenario analyses for the TA778 appraisal considered an increased discontinuation rate with pegcetacoplan when compared to the submitting Company's assumptions, this was only applied in Year 1.[3] Furthermore, the Committee's preferred assumption for this appraisal was to accept the one-off discontinuation rate at Week 16 proposed by the submitting Company, thus, the Company's approach in the present appraisal for danicopan, extending treatment discontinuation to 1 year, is a conservative assumption.

In summary, the 1% assumption rate applied at Week 53 and beyond is both clinically implausible and contradictory to the approach accepted by the NICE Committee for the rate of pegcetacoplan discontinuation in TA778. Given that the Company model pegcetacoplan discontinuation with a similar approach to that of TA778, namely, basing discontinuation rates on observed clinical trial data and assuming no discontinuation after Year 1, the Company's approach is more appropriate than that suggested by the EAG.

Key Issue 8 – Modelling of breakthrough haemolysis probabilities

Page 11 of the EAG report states: "the EAG present analyses assuming equal rate of breakthrough haemolysis (BTH) (for patients receiving danicopan as an add-on to eculizumab or ravulizumab and patients receiving pegcetacoplan) believing these may be of interest to the committee".

This assumption is not supported by data from the pivotal clinical trials for danicopan add-on treatment and pegcetacoplan. In the open-label extension (OLE) of the PEGASUS trial for pegcetacoplan, 18% of patients in the pegcetacoplan-to-pegcetacoplan treatment group experienced a haemolysis treatment-emergent adverse event (TEAE). In the long-term extension of the ALPHA trial (IA2), [redacted] ([redacted]%) of patients in the danicopan-to-danicopan treatment arm of the safety analysis set experienced a BTH TEAE.[4, 5]

As suggested by the EAG, the Company has also presented available long-term follow-up from real world evidence (RWE) studies on the rates of BTH observed on ravulizumab treatment, the predominant C5 inhibitor used in UK clinical practice, and pegcetacoplan. Evidence on the long-term rate of BTH associated with pegcetacoplan treatment is available from the Griffin, et al. 2024 study, which provides real world data on 48 patients with PNH receiving pegcetacoplan in the UK and France. At the time of study publication, patients had received treatment with pegcetacoplan for a mean duration of 20.2 months. A total of 32 BTH events had occurred in 13/48 patients, equating to a BTH rate of ~27.1%. As this study was not published at the time of submission, it was not included as part of the reference pack shared alongside the danicopan NICE submission documents. Therefore, the publication has been shared alongside this addendum.[6]

Long-term evidence on the rate of BTH associated with ravulizumab is available from the Kulasekararaj, et al. 2023 presentation at the European Hematology Association 2023 Hybrid Congress presenting long-term outcomes of Study 302 (NCT03056040), a Phase III study investigating ravulizumab versus eculizumab in C5 inhibitor treated patients. As reported by this presentation, rates of BTH during ravulizumab treatment were low, with 6.8% of patients reported to experience BTH with up to 4 years of study follow up. This poster was not provided as part of

the reference pack for the danicopan NICE submission, therefore, this poster has been shared alongside the addendum.[7]

The RWE presented above demonstrates a clear disparity in BTH rates between the two treatments; while comparison of the two studies is naïve, a difference in rate of over 20% indicates the greater treatment effect of ravulizumab in preventing BTH events. This RWE is also supplemented by comprehensive clinical expert validation obtained by the Company to support the ongoing appraisal for danicopan, indicating that patients receiving ravulizumab very rarely, if ever, experience pharmacokinetic BTH in clinical practice.[8] As such, the assumption of equal rates of BTH between pegcetacoplan and danicopan add-on treatment by the EAG is inappropriate, disregarding the available evidence on BTH rates on ravulizumab, the most commonly used C5 inhibitor backbone in UK clinical practice, and pegcetacoplan.

Key Issue 9 – Modelling of costs associated with breakthrough haemolysis

Page 12 of the EAG report states: "the company assume that over time the majority of people receiving pegcetacoplan will experience breakthrough haemolysis and be escalated to receiving 3 doses per week. This appears inconsistent with the approach taken in the appraisal for pegcetacoplan (TA778) which assumed dosing would be fixed at 2 per week. The EAG has presented a scenario where BTH is assumed to be zero for danicopan and pegcetacoplan, removing this dose-escalation".

As above, the Company has presented available long-term follow-up from RWE studies, as suggested by the EAG. The available evidence regarding the management of BTH on pegcetacoplan in clinical practice indicates that the approach to treatment has evolved since the pegcetacoplan appraisal (TA778), published in 2022.[3]

The Company would first like to highlight additional evidence available through the Griffin, et al. 2024 real-word study, which supports the use of three times per week dosing of pegcetacoplan due to haemolysis. This publication summarises the management of BTH on pegcetacoplan in clinical practice as informed by real-word data from patients treated with pegcetacoplan in the UK and France; the management pathway is replicated in Figure 1, Appendix B of this addendum.[6] While the pegcetacoplan dosing regimen for all patients included in the study is not provided, narratives for six patients in the study reporting repeated BTH events or combination treatment with a C5 inhibitor indicated the use of once every three days or three times weekly pegcetacoplan dosing in all patients.

This treatment regimen is also supported by the Griffin, et al. 2024 publication based on a pegcetacoplan OLE study (NCT03531255) investigating intensive pegcetacoplan dosing in the management of acute BTH events.[9] Of the 13 patients who had experienced intensive pegcetacoplan dosing in the OLE study, 8 (62%) patients received pegcetacoplan twice weekly, 4 (31%) patients received pegcetacoplan every three days and 1 patient received pegcetacoplan 3 times weekly prior to this intensive dosing. Both Griffin et al. 2024 publications have been provided alongside this addendum.[6, 9]

The RWE is further supplemented by the SmPC for pegcetacoplan (Section 4.2), which states that "the dosing regimen may be changed to 1,080 mg every third day (e.g., Day 1, Day 4, Day 7, Day 10, Day 13, and so forth) if a subject has a lactate dehydrogenase (LDH) level greater than 2 x upper limit of normal". Therefore, dose escalation of pegcetacoplan beyond the 1,080 mg twice weekly dose is supported by the label for this medicine and is frequently observed in clinical practice.

In conclusion, modelling a proportion of patients with escalated pegcetacoplan dosing is therefore a reasonable assumption that is more clinically valid than an assumption of no BTH, nor dose escalation, for both pegcetacoplan and danicopan add-on treatment.[10]

Appendix A: Interim analysis 3 (31st March 2023 data cut)

Table 1: Efficacy and HRQoL endpoint results at Week 12 (Comparison of IA2 and IA3 results)

	IA2				IA3			
	Danicopan + C5i[a] N=42	Placebo + C5i[a] N=21	Difference (Danicopan - Placebo)	p-value	Danicopan + C5i[a] [redacted]	Placebo + C5i[a] [redacted]	Difference (Danicopan - Placebo)	p-value
Change from baseline in haemoglobin at Week 12[b]								
Number of participants (n)	42	21	N/A	p<0.0001	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE), g/dL	2.94 (0.21)	0.50 (0.31)	2.44 (0.38)		[redacted]	[redacted]	[redacted]	
95% CI for LS mean	2.52, 3.36	−0.13, 1.12	1.69, 3.20		[redacted]	[redacted]	[redacted]	
Proportion of patients with a haemoglobin increase of ≥2 g/dL at Week 12 in the absence of transfusion								
Number of participants (n)	25	0	N/A	p<0.0001	[redacted]	[redacted]	[redacted]	[redacted]
Percentage (%)	59.5	0	46.9		[redacted]	[redacted]	[redacted]	
95% CI	43.3, 74.4	0.0, 16.1	29.2, 64.7		[redacted]	[redacted]	[redacted]	
Proportion of patients with transfusion avoidance at Week 12								
Number of participants (n)	35	8	N/A	p=0.0004	[redacted]	[redacted]	[redacted]	[redacted]
Percentage	83.3	38.1	41.7		[redacted]	[redacted]	[redacted]	
95% CI	68.6, 93.0	18.1, 61.6	22.7, 60.8		[redacted]	[redacted]	[redacted]	
Change from baseline in FACIT-F scores at Week 12								
Number of participants (n)	42	21	N/A	p=0.0021	[redacted]	[redacted]	[redacted]	[redacted]

LS mean (SE)	7.97 (1.13)	1.85 (1.58)	6.12 (1.89)		[redacted]	[redacted]	[redacted]	
95% CI for LS mean	5.72, 10.23	−1.31, 5.02	2.33, 9.91		[redacted]	[redacted]	[redacted]	
Change from baseline in ARC at Week 12								
Number of participants (n)	42	20	N/A		[redacted]	[redacted]	[redacted]	
LS mean (SE), 10^9/L	−83.8 (8.93)	3.5 (12.7)	−87.2 (15.3)	p<0.0001	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	−101.6, −65.9	−21.9, 28.8	−117.7, −56.7		[redacted]	[redacted]	[redacted]	
Change from baseline in LDH at Week 12								
Number of participants	42	20	N/A		[redacted]	[redacted]	[redacted]	
LS mean (SE), U/L	−23.5 (8.3)	−2.9 (11.9)	−20.6 (14.3)	p=0.1569	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	−40.1, −6.9	−26.8, 20.9	−49.3, 8.2		[redacted]	[redacted]	[redacted]	
Total PNH RBC Clone Size (Type II + Type III) at Week 12, (%)								
Number of participants (n)	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
LS mean (SE)	24.60 (4.18)	−3.04 (5.86)	27.63 (6.91)	p=0.0010	[redacted]	[redacted]	[redacted]	
95% CI for LS mean	15.78, 33.42	−15.32, 9.25	13.03, 42.24		[redacted]	[redacted]	[redacted]	[redacted]
PNH RBC Type III Clone Size at Week 12, (%)								
Number of participants (n)	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

95% CI for LS mean	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
PNH RBC Type II Clone Size at Week 12, (%)								
Number of participants (n)	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Change from baseline in EQ-5D-3L UK health state index scores by treatment visit through Week 12								
Week 2: LS mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4: LS mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8: LS mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12: LS mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] IA3 reports efficacy data for the modified randomised set: this analysis set consists of all randomised patients in the ALPHA trial except those who were randomised to the placebo group with their 12-week treatment period 1 cut short due to early switching from placebo to danicopan following positive Interim Analysis readout and DMC recommendation.
[b] Haemoglobin values collected within 4 weeks after transfusion are not included in the analysis.
Abbreviations: ARC: absolute reticulocyte count; C5i: complement component 5; CI: confidence interval; DMC: data monitoring committee; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; HRQoL: health-related quality of life; IA: interim analysis; LDH: lactate dehydrogenase; LS: least squares; n: number of patients for endpoint; N: number of patients in treatment arm; RBC: red blood cell; SD: standard deviation; SE: standard error.
Source: 1. Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[5] 2. Alexion Data on File, 2024.

Table 2: Efficacy and HRQoL endpoint results at Week 24 (Comparison of IA2 and IA3 results)

	IA2		IA3	
	DAN/DAN + C5i[a] N=41	PBO/DAN + C5i[a] N=20	DAN/DAN + C5i[a] [redacted]	PBO/DAN + C5i[a] [redacted]
Change from baseline in haemoglobin at Week 24[b]				
Number of participants (n)	37	20	[redacted]	[redacted]
LS mean (SE), g/dL	3.17 (0.30)	2.26 (0.34)	[redacted]	[redacted]
95% CI for LS mean	2.56, 3.77	1.57, 2.94	[redacted]	[redacted]
Proportion of patients with a haemoglobin increase of ≥2 g/dL at Week 24 in the absence of transfusion				
Number of participants (n)	19	7	[redacted]	
Percentage (%)	46.3	35.0	[redacted]	[redacted]
95% CI	30.7, 62.6	15.4, 59.2	[redacted]	
Proportion of patients with transfusion avoidance from Week 12 to Week 24				
Number of participants (n)	32	18	[redacted]	[redacted]
Percentage	78.0	90.0	[redacted]	[redacted]
95% CI	62.4, 89.4	68.3, 98.8	[redacted]	[redacted]
Change from baseline in FACIT-F scores at Week 24				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in ARC at Week 24				
Number of participants (n)	37	19	[redacted]	[redacted]
LS mean (SE), 10^9/L	−80.2 (8.8)	−65.2 (12.7)	[redacted]	[redacted]

95% CI for LS mean	−97.7, −62.7	−90.9, −39.5	[redacted]	[redacted]
Change from baseline in LDH at Week 24				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE), U/L	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	[redacted]
Total PNH RBC Clone Size (Type II + Type III) at Week 24, (%)				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	[redacted]
PNH RBC Type III Clone Size at Week 24, (%)				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	[redacted]
PNH RBC Type II Clone Size at Week 24, (%)				
Number of participants (n)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for LS mean	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in EQ-5D-3L UK health state index scores by treatment visit through Week 24				
Week 14: Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

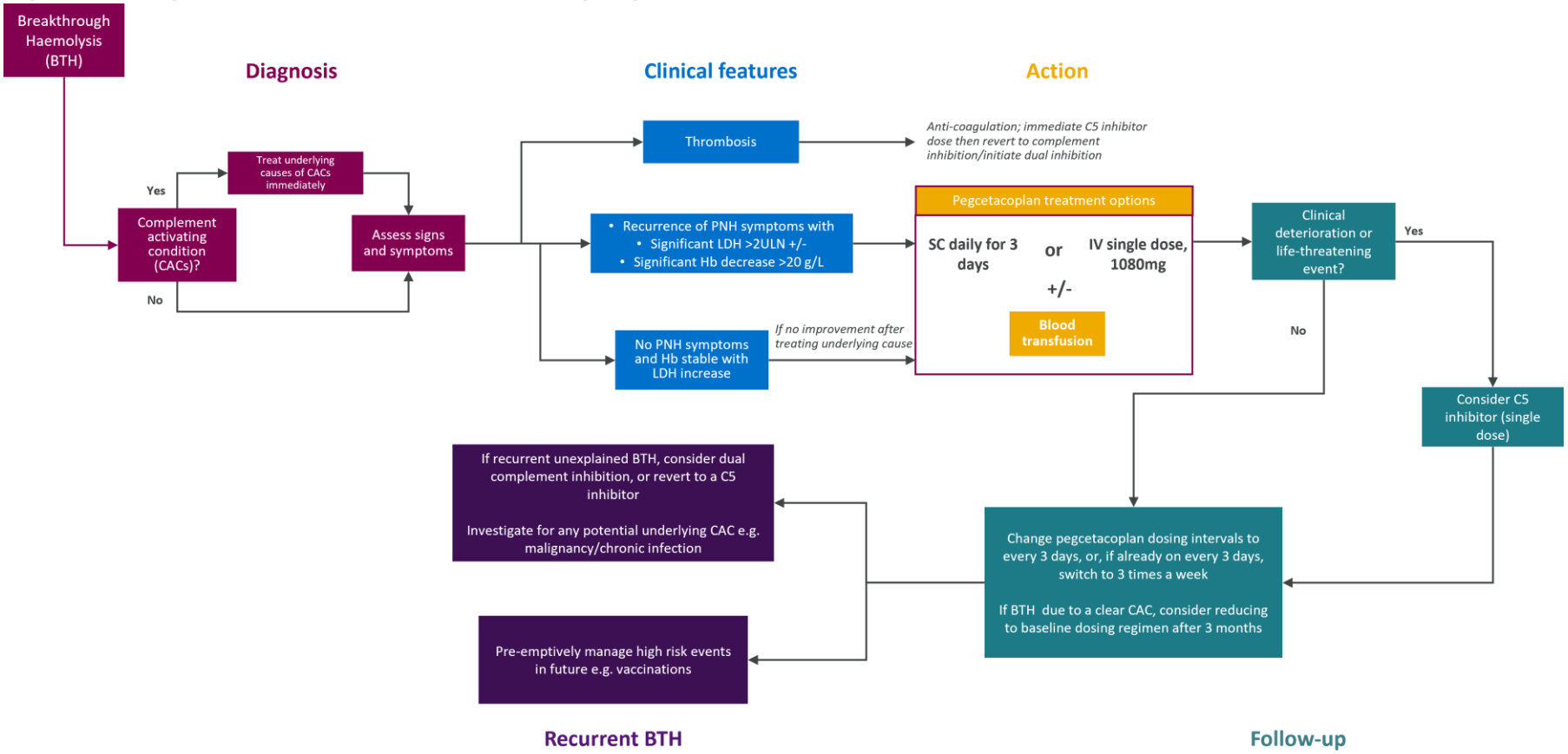
Week 16: Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 20: Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 24: Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

[a] IA3 reports efficacy data for the modified randomised set: this analysis set consists of all randomised patients in the ALPHA trial except those who were randomised to the placebo group with their 12-week treatment period 1 cut short due to early switching from placebo to danicopan following positive Interim Analysis readout and DMC recommendation.
[b] Haemoglobin values collected within 4 weeks after transfusion are not included in the analysis.
Abbreviations: ARC: absolute reticulocyte count; C5i: complement component 5; CI: confidence interval; DMC: data monitoring committee; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; HRQoL: health-related quality of life; IA: interim analysis; LDH: lactate dehydrogenase; LS: least squares; n: number of patients for endpoint; N: number of patients in treatment arm; RBC: red blood cell; SD: standard deviation; SE: standard error.
Source: 1. Alexion Data on File. ALPHA CSR (20th September 2022 data cut-off).[5] 2. Alexion Data on File, 2024.

Appendix B: Management of BTH

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

Figure 1 Management of BTH for patients receiving pegcetacoplan



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).[6]

References

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Patients with PNH. Blood Advances 2024;bloodadvances.2023011691.

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Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria [ID5088]: EAG Response to Company Addendum

Despite no technical engagement period being included in this technology appraisal, the company submitted an addendum of responses to some of the key issues raised in the EAG report.

Here the EAG provides brief comments on the addendum submission, as constrained by the limited time available for this critique.

Key Issue 2: ALPHA trial: Data from interim analysis of incomplete trial population and potential lack of generalisability

The EAG report highlighted concerns that the company had not provided data from interim analysis 3 (IA3) which had been performed to address requests from regulatory agencies. In their addendum the company provide some results for IA3 which includes follow-up for the randomised period (TP1) and the first non-randomised period (TP2) for the whole trial population (n=[redacted]) compared to the IA2 data used in the original company submission (n=63).

Looking at the relative efficacy between the two arms of the trial at week 12 (TP1), the EAG accepts that the data-cuts [redacted] However, the EAG notes that across several outcomes there are [redacted] of danicopan ([redacted]). This is potentially important because in their primary cost-effectiveness analyses, the company implement a naïve comparison with pegcetacoplan, which utilises the absolute efficacy of both treatments. The EAG assumes that IA2 data were used by the company to calculate the transition probabilities used in the economic model, presuming consistency with the clinical effectiveness section. If this is the case, then the EAG predicts that switching to IA3 data would [redacted]

Key Issue 6: Uncertainty over long term discontinuation probabilities for danicopan and pegcetacoplan

The EAG report presented a scenario analysis where it set a 1% probability of discontinuation unrelated to BTH per model cycle for both danicopan and pegcetacoplan, to which the company objects on grounds of implausibility.

Very limited information is available on the long-term follow-up of these treatments, hence the EAG explored this only as a scenario analysis. Whilst the absolute discontinuation in this scenario may be high as noted by the company, it is applied equally in this scenario for both danicopan and pegcetacoplan, and the EAG wanted to illustrate the severe impact of this parameter. The EAG notes that the 1% discontinuation rate is lower than the discontinuation rate unrelated to BTH for both danicopan and pegcetacoplan modelled for the period immediately preceding 52 weeks. The EAG maintains that this should be a scenario of interest to the committee.

Key Issue 8: Modelling of breakthrough haemolysis (BTH) probabilities

The EAG report noted a lack of evidence of direct comparison of danicopan and pegcetacoplan, and concerns over differences in the baseline populations of their respective clinical trials and their definitions of BTH. Hence, the EAG preferred equal long-term rates of BTH across treatments. The company claim that this is not supported by data from clinical trials.

The original concerns of the EAG about a lack of direct comparison between danicopan and pegcetacoplan, differences in both baseline populations and BTH definitions, and limited trial follow-up all still apply. The information submitted by the company does not affect these concerns, and the EAG maintains that this should be a scenario of interest to the committee.

Key Issue 9: Modelling of costs associated with breakthrough haemolysis

The EAG report noted that a consequence of the company's modelling was that the majority of people receiving pegcetacoplan end up receiving 3 doses per week, which has a large impact on the total costs associated with pegcetacoplan and is inconsistent with NICE appraisal of pegcetacoplan (TA778). The company has

provided two references to support its case for modelling patients to receive 3 doses of pegcetacoplan per week.

In the real-world study by Griffin et al. (1), 13 out of 48 participants experience BTH events. Out of these, the EAG can see that four (8.3%) were escalated to receive pegcetacoplan every 3 days, and two (4.2%) were escalated to receive three doses per week. The others may have experienced temporary dosing changes but did not appear to have their regular dose adjusted.

The open label extension of pegcetacoplan by Griffin et al. (2), focuses on dose escalation of pegcetacoplan in cases of acute BTH. As such, the population of this study is not representative of target population of this appraisal. At baseline four out of 13 people were receiving pegcetacoplan three days per week and one was receiving three times per week. However, only four of these higher dosing regimens were reported to be due to BTH events. It is unclear whether other dose increases within this study were sustained once the BTH event was under control.

Neither of these studies presents evidence of BTH occurrence or management for periods close to the 45-year duration of the company's economic model, and neither demonstrates dose-escalation to the magnitude as modelled by the company.

The EAG accepts that some dose-escalation of pegcetacoplan occurs in practice, however the prevalence and duration remains unknown. The EAG presented a scenario analysis removing dose-escalation for consistency with the approach taken in TA778, and to demonstrate the impact of this change. The EAG notes that whilst the company does model dose escalation for danicopan, this only occurs in the first 24 weeks of the model and could be considered a potential source of bias as no such constraint is applied to the escalation of pegcetacoplan. The escalation rates for danicopan are based on summary data from the CSR. The EAG considers this immature for informing long-term rates, and as it is summary data, it is not possible to tell whether there are late occurrences of escalation that are masked by others discontinuing.

The EAG still has concerns about the cost-effectiveness of pegcetacoplan, given the potential changes in practice since its review in TA778, which is now serving as the reference treatment in this appraisal.

References:

1. Griffin M, Kelly R, Brindel I, et al. Real-world experience of pegcetacoplan in paroxysmal nocturnal hemoglobinuria. Am J Hematol 2024.
2. Griffin M, Kelly RJ, Panse J, et al. Management of Acute Breakthrough Hemolysis with Intensive Pegcetacoplan Dosing in Patients with PNH. Blood Advances 2024