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

For public – redacted

Technology Appraisal Committee C [7 May 2024]

Chair: Stephen O'Brien

Lead team: Pedro Saramago Gonclaves, John Hampson, Ugochi Nwulu

External assessment group: Warwick Evidence

Technical team: Dilan Savani, Alexandra Filby, Jasdeep Hayre

Company: Alexion

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness

NICE National Institute for Health and Care Excellence

Background on paroxysmal nocturnal haemoglobinuria

PNH is rare chronic blood condition caused by:

- Acquired mutation of PIG-A gene within bone marrow stem cells
- Immune system ruptures blood cells within or outside blood vessels (IVH or EVH)

Epidemiology

- 1 in 770,000 annual incidence in Great Britian
- 1 in 62,500 prevalence in Great Britian
- Approximately 650 to 900 people living with PNH in England

Diagnosis and classification

- PNH can happen at any age, but most diagnosed between 30 and 40 years of age

Symptoms and prognosis

- Often anaemia – can result in transfusion dependence, symptoms of haemolysis and thrombosis
- Abdominal pain; kidney problems; fatigue; shortness of breath; bleeding; blood clots; dysphagia; organ damage; premature mortality
- Many of the common symptoms of PNH can be attributed to IVH but EVH may occur following treatment for IVH, potentially leading to residual anaemia and ongoing transfusion dependence

EVH, Extravascular haemolysis; IVH, Intravascular haemolysis; PIG-A, phosphatidylinositol glycan class A; PNH, Paroxysmal nocturnal haemoglobinuria

Patient perspectives

Submissions from PNH support and patient expert

Survey of people with PNH (n=75) and carers (n=19) in England and Wales, and a separate survey of people with PNH (n=4) and carers (n=1) of people with PNH, receiving danicopan in England

- Despite available treatments, living with PNH restricts independence, and negatively impacts family and social life
- Fatigue most common symptom in both surveys (83% and 50%, respectively)
- Unmet need for treatment options with different delivery methods. Due to regular infusions, people report:
  - damaged veins from repeated cannulations
  - Disruption to work, education and travel
- Danicopan offers benefit of oral dosage form, but people will still have to continue receiving C5 inhibitor infusions
- Unmet need for treatments that target EVH

"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…"

"PNH has many forms, and patients have very individual treatment needs. Currently, NHS covers only a small part of these needs, offering a service addressed mainly to the patients struggling with intra-vascular haemolysis…"

"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."

NICE

C5, Complement component 5; PNH, Paroxysmal nocturnal haemoglobinuria

Clinical perspectives

Submissions from National PNH service and clinical expert

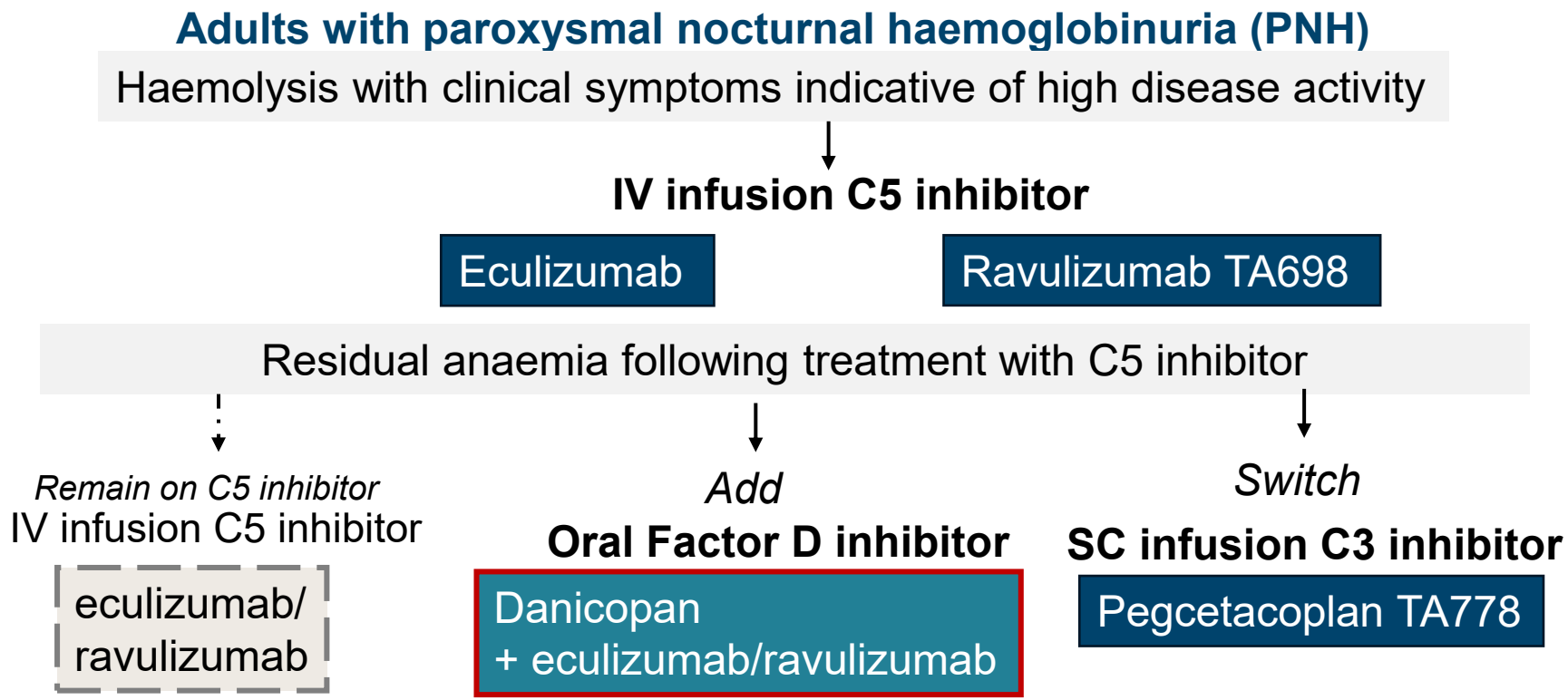
- ~80% of people with PNH who receive C5 inhibitors remain anaemic and ~25% continue to require blood transfusions
- Unmet need for significant proportion of people receiving C5i with EVH
- Reduction in red cell transfusion, improved QoL and improvement in parameters suggestive of extravascular haemolysis considered a clinically significant response in PNH
- Addition of danicopan to C5 inhibitor shown to improve anaemia and reduce requirement for transfusions
- Danicopan offers potential benefit of improved QoL, reduction in transfusion requirement (and reduced hospital visits) and reduced need for iron chelation
- Current alternative to danicopan is pegcetacoplan, which is given as a twice weekly subcutaneous infusion
- No additional resources required for implementation of danicopan
- Potential issue with compliance of danicopan, as danicopan needs to be taken 3 times a day. However, benefit of add-on therapy is that C5i will always be in background

C5, Complement component 5; PNH, Paroxysmal nocturnal haemoglobinuria; QoL, Quality of life

Treatment pathway

Danicopan as an add-on to a C5 inhibitor positioned at same place in pathway as pegcetacoplan

Figure: PNH treatment pathway



- TA698: Ravulizumab for PNH in adults with haemolysis with clinical symptoms or whose condition is clinically stable after eculizumab for ≥6 months
- TA778: Pegcetacoplan for PNH in adults with anaemia after ≥3 months treatment with C5 inhibitor

Supportive care as needed
Blood transfusion; Iron overload treatment; Anticoagulants; Supplements

EAG and company disagree whether C5i monotherapy is a relevant comparator- see key issue slide

Proposed positioning

Q for clinical experts: Does treatment pathway align with your experience of clinical practice?
Is C5i monotherapy a relevant comparator to danicopan?
If so, are eculizumab and ravulizumab both relevant comparators?

C3, Complement component 3; C5, Complement component 5; PNH, Paroxysmal nocturnal haemoglobinuria; SC, Subcutaneous; TA, Technology appraisal

Danicopan (Voydeya)

Table: Danicopan key information

Marketing authorisation	• CHMP opinion: indicated as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia • UK marketing authorisation expected: [redacted]

Mechanism of action	• 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
	• Inhibition of alternative complement pathway leads to:
	  • reduction in production of C3 fragments and C3-mediated EVH
	  • Impaired terminal (C5) complement activation (providing protection from BTH)

Administr-ation	• Danicopan is an oral treatment add on to C5 inhibitor (IV infusion) • Starting dose of 150mg three times daily, with potential for dose escalation to 200mg three times daily (depending on clinical response) • Discontinuation not recommended unless clinically indicated
Price	• List price: [redacted] for 90 x 50 mg tablet bottle; [redacted] for 90 x 100 mg tablet bottle • Annual cost of [redacted] (excluding cost of C5i*) assuming dosage of 150mg three times daily • Patient access scheme not applicable • Danicopan administered with intravenous eculizumab (every 2 weeks) or intravenous ravulizumab (every 8 weeks); confidential discounts applicable

BTH, Breakthrough haemolysis; C3, Complement component 3; C5, Complement component 5; EVH, Extravascular haemolysis; IV, Intravenous; IVH, Intravascular haemolysis; PNH, Paroxysmal nocturnal haemoglobinuria

Key issues for discussion

Table: Key issues

	Issue	ICER impact	Slide
Clinical	Unclear definition for defining target population and implementation into NHS use	Unknown	12
	ALPHA trial: Data from interim analysis of incomplete trial population and potential lack of generalisability	Unknown	13
	Insufficient information for meaningful comparison of danicopan + C5i to pegcetacoplan*	Unknown	14
Model	Use of differing transition probabilities for danicopan + C5i and pegcetacoplan	Small†	17
	Subsequent therapy after discontinuing danicopan + C5i	Moderate	18
	Uncertainty over long term discontinuation probabilities for danicopan and pegcetacoplan*	Large	19
	Differing probability of BTH for danicopan + C5i and pegcetacoplan*	Large	20
	Inconsistent pegcetacoplan dosing for BTH*	Large	22

* Key issues with largest potential impact on economic analyses

†small impact on the cost-effectiveness, however this could change based on other model assumptions

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

- ❑ Background and key issues
- ✓ **Clinical effectiveness**
- ❑ Modelling and cost effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trial

ALPHA trial comprised 3 distinct treatment periods: TP1, TP2 and LTE

See appendix for ALPHA trial design diagram

Table: ALPHA trial design

Alpha Trial	Treatment period 1 (TP1)	Treatment period 2 (TP2)	Long term extension (LTE)
Design	Phase 3 double-blind, placebo-controlled, multiple-region RCT	Non-randomised open-label	Non-randomised open-label
Population	Adults with PNH who have csEVH whilst receiving treatment with eculizumab or ravulizumab		
Intervention	Danicopan 150mg TID as oral tablet; dose escalations up to 200mg TID permitted + eculizumab or ravulizumab (as IV infusion once every 2 or once every 8 weeks, respectively		
Comparator	Placebo + C5i	None	None
Duration	12 weeks	12 weeks	2 distinct 1-year long treatment periods
Locations	80 centres across 18 countries in Europe (3 UK trial centres), Asia, North America and South America.		

- **Primary outcome:** Change in haemoglobin relative from baseline after 12 weeks of treatment with danicopan compared to placebo
- **Key secondary outcomes:** proportion with haemoglobin increase of ≥ 2 g/dL (≥ 2.0 g/dL) at Week 12 in absence of transfusion; proportion with transfusion avoidance though week 12; change from baseline in FACIT-Fatigue scores at Week 12; change from baseline in ARC at Week 12

ARC, Absolute reticulocyte count; C5i, Complement component 5 inhibitor; csEVH, Clinically significant extravascular haemolysis; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue LTE, Long term extension; IV, Intravenous; PNH, Paroxysmal nocturnal haemoglobinuria; RCT, Randomised controlled trial; TID, Three times daily; TP, Treatment period

Alpha Trial TP1 interim analysis results summary

See appendix for TP2 results summary

In the interim analysis, a statistically significant improvement was found for danicopan + C5i compared with placebo + C5i for all key outcome measures

Table: Alpha trial results summary from first interim analysis set (IA1;N=63)

	Danicopan + C5i, n=42	Placebo + C5i, n=21	Adj. difference (95% CI)
Primary endpoint, Interim trial outcomes at 12 weeks			
Hb change from baseline LS mean (95% CI) g/dL	2.94 (2.52, 3.36), n=42	0.50 (-0.13, 1.12), n=21	2.44 (1.69, 3.20); p<0.0001
Key secondary endpoints, Interim trial outcomes at 12 weeks			
% people with Hb increase ≥2 (95% CI) g/dL in absence of transfusion	59.5 (43.3, 74.4), n=25	0 (0.0, 16.1), n=0	46.9 (29.2, 64.7); p<0.0001
% participants avoiding transfusion (95% CI)	83.3 (68.6, 93.0), n=35	38.1 (18.1, 61.6), n=8	41.7,(22.7, 60.8); p=0.0004
FACIT-F scores change from baseline, LS mean (95% CI)	7.97 (5.72, 10.23), n=42	1.85 (-1.31, 5.02), n=21	6.12 (2.33, 9.91); P=0.0021
ARC change from baseline, LS mean (95% CI) 10^9/L	-83.8 (-101.6, -65.9), n=42	3.5 (-21.9, 28.8), n=20	-87.2 (-117.7, -56.7), p<0.0001

No direct evidence comparing danicopan add-on therapy (ALPHA trial) with pegcetacoplan (PEGASUS trial)→ company conducted ITC (series of MAICs)

Company and EAG agree MAIC results not sufficiently robust (key differences between populations could not be adjusted for and small effective sample size) – see appendix for further details

ARC, Absolute reticulocyte count; C5i, Complement component 5 inhibitor; CI, Confidence interval; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; Hb, Haemoglobin; LS, Least squared; TP, Treatment period

Key issue: Unclear definition for defining target population and implementation into NHS use

Background

- Population presented in company submission: Adult patients with PNH who have clinically significant EVH while on treatment with a C5i (eculizumab or ravulizumab)
- No standardised definition of clinically significant EVH in UK clinical practice

Company:

- Clear eligibility criteria required for ALPHA trial so specific thresholds for Hb and ARC levels defined (Hb ≤9.5 g/dL & ARC ≥120 × 10^9/L) but these thresholds not anticipated to be used to determine eligibility for danicopan
- Clinical experts noted that the ALPHA trial eligibility criteria stricter than those typically used to determine clinically significant EVH in UK clinical practice
- Clinically significant EVH assessed on individual basis using a range of parameters, patient-reported factors and clinical opinion –considering 'full clinical picture' rather than specific thresholds

EAG:

- Subjectivity in the eligibility for danicopan + C5i treatment for routine NHS use due to lack of established definition of clinically significant extravascular haemolysis in UK clinical practice
- ALPHA trial may not provide representative estimates of real-world efficacy

If danicopan were to be recommended, how would the eligible patient population be defined?
Are the results from the ALPHA trial generalisable to the eligible treatment population in the NHS?

ARC, Absolute reticulocyte count; C5i, Complement component 5 inhibitor; EVH, Extravascular haemolysis; Hb, Haemoglobin; PNH, Paroxysmal nocturnal haemoglobinuria

Key issue: Data from interim analysis of incomplete trial population and potential lack of generalisability

Background

- Efficacy results in submission based on the interim efficacy analysis set (IAS)→ IAS defined as first 75% of people out of the total planned enrolment of trial (N=84) who had completed TP1 (weeks 0 to 12)
- Second interim analysis was repeated when the 63 participants completed TP2 (weeks 12 to 24)
- At second interim analysis (IA2) cut-off, 71 patients had completed TP1, but results were not reported

Company:

- Third interim analysis (IA3) performed with randomised population reaching end of TP2 but this data cut was not prespecified in trial protocol and only conducted to address specific requests from regulatory agencies
- IA2 presented in submission as more complete data available within submission timelines. IA3 results (n=[redacted]) presented post EAG-report – see appendix → "results for IA3 are [redacted] with IA2 at Week 12"

EAG:

- Data-cuts [redacted] but across several outcomes [redacted]
- EAG assumes IA2 data used by company to calculate transition probabilities in model→ EAG predicts that switching to IA3 data would [redacted]

Is the efficacy data (sample size and length of follow-up) presented in the company submission sufficient for decision making? What is the committee's preferred ALPHA trial data cut for use in the economic model?

CSR, Clinical study report; EAG, External Assessment Group; IA2; Second interim analysis; IA3; Third interim analysis; IAS, Interim efficacy analysis set; TP, Treatment period

Key issue: Insufficient information for a meaningful comparison of danicopan + C5i to pegcetacoplan

Background

- Company and EAG agree that MAIC results not suitable for comparison of efficacy between danicopan + C5i and pegcetacoplan due to limitations with differences in trials and small ESS
- EAG suggest comparison of danicopan + C5i to C5i avoids this issue, so could be considered more appropriate

Company:

- Prefer using results from naïve comparison (directly using results from ALPHA and PEGASUS trials for estimates of relative efficacy between danicopan + C5i and pegcetacoplan)
- Pegcetacoplan is only treatment option recommended by NICE for clinically significant EVH
- C5is do not address clinically significant EVH. Unless patient with clinically significant EVH is unable to receive pegcetacoplan (e.g. due to eyesight or dexterity), they would receive pegcetacoplan→ SoC in UK

EAG:

- Almost all same limitations with MAICs also apply to naïve comparison → when comparing MAIC and original ALPHA populations, clear that both populations have a number of differences to PEGASUS population
- Neither MAIC or naïve comparison sufficiently robust for decision making
- Current SoC for clinically significant EVH includes remaining on C5i so these cannot be excluded as comparators→ provides scenario in economic analysis with C5is as comparators

Are results of the naïve comparison of danicopan + C5i and pegcetacoplan suitable for decision making?
Is a comparison of danicopan + C5i and C5i monotherapy more appropriate for decision making?

EAG, External Assessment Group; C5i, Complement component 5 inhibitor; ESS, Effective sample size; EVH, Extravascular haemolysis; MAIC, Matching-adjusted indirect comparison; SoC, Standard of care

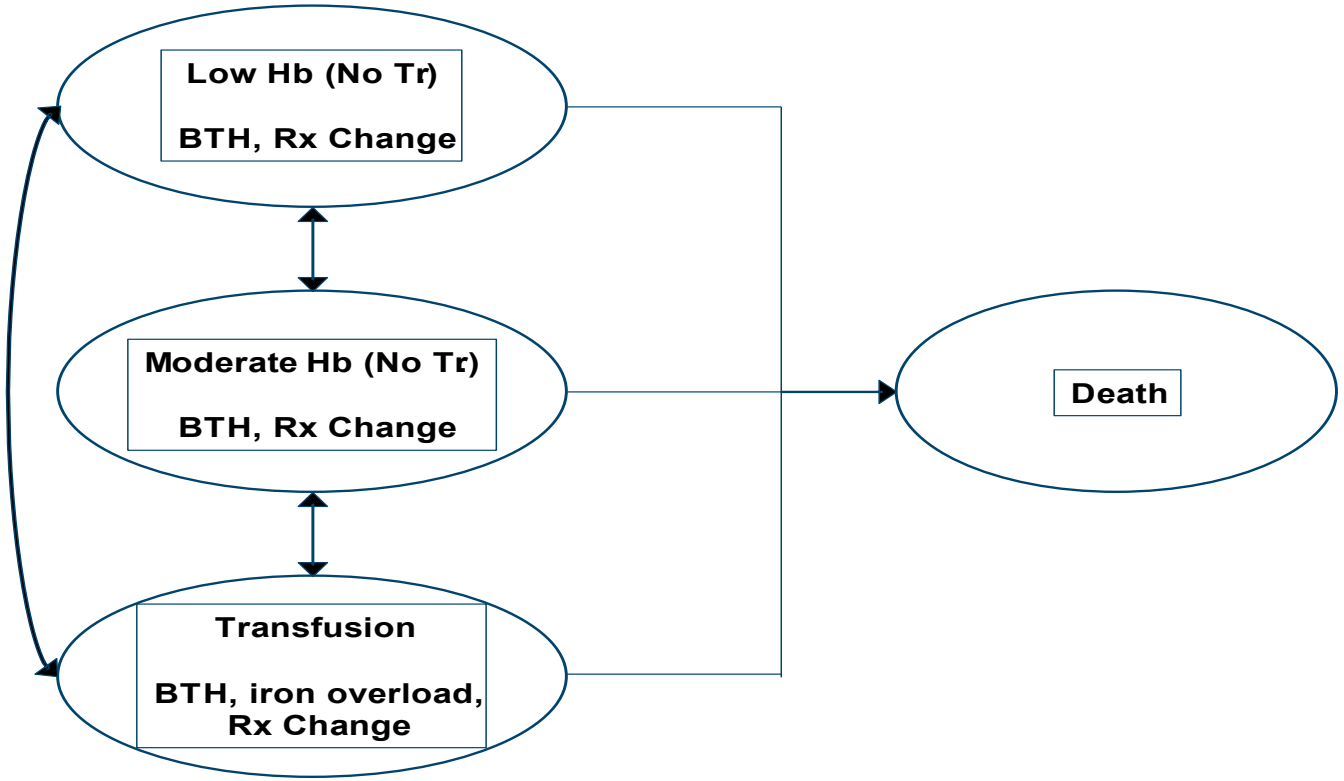
Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ✓ **Modelling and cost effectiveness**

NICE National Institute for Health and Care Excellence

Company's model overview

Figure: Company's model structure



Rx change refers to the changes in PNH treatment dosing regimens patients receive upon experiencing a BTH event

The company presented a **de novo Markov model** with a **cycle length of 4 weeks** and a **time horizon of 45.7 years**

Danicopan affects **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

Danicopan affects **QALYs** by:

- Having a lower rate of BTH events
- Having a means of administration that is not associated with a disutility (administration-related disutility modelled for pegcetacoplan and eculizumab)

Assumptions with greatest ICER effect:

- The rate and management of BTH events
- The rate of treatment discontinuation

EAG: Overall model structure appropriate for appraisal

BTH, Breakthrough haemolysis; EAG, External Assessment Group; Hb, Haemoglobin; ICER, Incremental cost-effectiveness ratio; PNH, Paroxysmal nocturnal haemoglobinuria; QALY, Quality-adjusted life year; RX, Treatment; Tr, Transfusion

Key issue: Transition probabilities

Background

- In company base case, transition probabilities for danicopan + C5i and pegcetacoplan derived from multinomial models fitted to data from ALPHA and PEGASUS trials, respectively (naïve comparison)
- Hb health states based on a threshold of 9.5 mg/dL and 10.5mg/dL for transition probabilities derived from ALPHA (danicopan + C5i) and PEGASUS trials, respectively (differing inclusion criteria for trials)

Company:

- Due to limitations with MAIC analyses, naïve comparison was considered most appropriate approach without introducing undue complexity into model
- Alternative transition probabilities for danicopan + C5i, informed by ALPHA trial data using a Hb level threshold of 10.5 mg/dL, were explored in a MAIC scenario analysis

EAG:

- Company's base case transition probabilities derived from short term follow up with limited sample size and based on naïve comparison→ not possible to obtain reliable estimate of relative effectiveness
- Relative effectiveness estimates too uncertain for EAG to provide base case. Instead, EAG presents analyses assuming equal efficacy (transition probabilities based on ALPHA trial) to aid decision-making

Are any of the presented transition probabilities acceptable for decision making?
If so, what are the most suitable transition probabilities for decision making?

EAG, External Assessment Group; C5i, Complement component 5 inhibitor; Hb, Haemoglobin; MAIC, Matching-adjusted indirect comparison

Key issue: Subsequent therapy received after discontinuing danicopan + C5i

Background

- In company base case, treatment discontinuation with danicopan + C5i was modelled in line with observations from the ALPHA trial. People receiving danicopan + C5i may discontinue danicopan due to AEs

Company:

- People who discontinue danicopan + C5i, assumed to switch to C5i monotherapy (continue receiving same regimen of eculizumab or ravulizumab monotherapy) for remaining model time horizon

EAG:

- Pegcetacoplan currently in use for this indication→ EAG believe a large proportion of those who discontinue danicopan would receive pegcetacoplan
- Proportion unknown but scenario provided assuming that 80% of those discontinuing danicopan would incur costs associated with 2 x weekly dose of pegcetacoplan, with remaining 20% continuing C5i monotherapy.

  Note EAG only modelled the costs of subsequent pegcetacoplan and associated BTH probability; did not adjust any other probabilities or disutilities for those who have discontinued danicopan

Is it expected that people will switch to C5i monotherapy or pegcetacoplan after discontinuing danicopan + C5i?
Is the EAG's scenario appropriate for decision making?

AE, Adverse event; BTH, Breakthrough Haemolysis; EAG, External Assessment Group; C5i, Complement component 5 inhibitor

Key issue: Uncertainty over long term discontinuation probabilities for danicopan and pegcetacoplan (wk 52+)

Background

- Company's base case assumes 0% discontinuation for danicopan + C5i and pegcetacoplan after week 52
- EAG Provided scenario exploring alternative rate of discontinuation beyond week 52, assuming 1% discontinuation per cycle from week 53 onwards for both danicopan and pegcetacoplan

Company:

- Currently no established evidence on discontinuation rates after week 52 for both danicopan and pegcetacoplan
- In EAG's scenario, 56% of people in model discontinued treatment after 6 years→ not clinically valid
- Extravascular haemolysis is a chronic condition and treatment with danicopan is recommended for a person's lifetime unless discontinuation is clinically indicated
- 0% discontinuation after week 52 assumption in line with NICE TA778 (Pegcetacoplan for treating PNH)

EAG:

- Company's assumption not supported by evidence due to limited trial follow-up but plausible that there will be a small long-term discontinuation rate for both arms
- Whilst absolute discontinuation in EAG scenario may be high, it is applied equally for both treatments. Notes 1% rate lower than rate (unrelated to BTH) for both treatments for period immediately before week 52

Is it more appropriate to assume no discontinuation after week 52 or to assume 1% discontinuation every 4 weeks after week 52?

EAG, External Assessment Group; C5i, Complement component 5 inhibitor; PNH, Paroxysmal nocturnal haemoglobinuria; TA, Technology appraisal

Key issue: Modelling of BTH probabilities

Background

- In company base case, modelled BTH probabilities for danicopan + C5i came from ALPHA trial based on classification of BTH events which required intervention
- Similar approach used for pegcetacoplan but in PEGASUS, all BTH events required intervention
- Resulting difference in BTH between C5i (control) arms of each trial greater than the difference in BTH between danicopan + C5i and pegcetacoplan arms

Company:

- Due to limitations with MAIC analyses, naïve comparison of BTH rates was considered most appropriate in absence of alternative data sources. Difference in rates of BTH also supported by data from OLEs for ALPHA and PEGASUS
- C5i arm in PEGASUS only included people receiving eculizumab → rate of BTH observed with eculizumab higher than with ravulizumab, which may explain discrepancy between BTH rates in control arms of both trials
- Lower likelihood of BTH events with danicopan + C5i than with pegcetacoplan due to C5i backbone
- Provided 2 studies showing disparity in long-term BTH rates between pegcetacoplan and ravulizumab

EAG:

- Unclear whether thresholds for BTH intervention were the same across trials, nor whether degree of any potential intervention was comparable
- Not appropriate to use naïve comparison results in modelling particularly given greater difference between BTH rates in C5i (control) arms of both trials→ preferred assuming equal long-term rate of BTH across both arms
- Studies provided by company do not affect EAG's concerns about limitations of naïve comparison of BTH rates

Is it more appropriate to use naïve comparison of BTH rates or assume long-term BTH rate is equal?

BTH, Breakthrough haemolysis; EAG, External Assessment Group; C5i, Complement component 5 inhibitor; MAIC, Matching-adjusted indirect comparison; OLE, Open-label extension

Breakthrough haemolysis events requiring intervention

Table: ALPHA trial BTH events and probability calculation for BTH events requiring intervention

	ALPHA – Danicopan + C5i	ALPHA – C5i
ALPHA: Week 1-24	0 events out of 49 people in 24 weeks of follow-up; 0.00%	No events. Assumed same as danicopan; 0.00%
ALPHA: Week 25+	1 event out of 60 people in 28 weeks of follow-up; 0.24%	Assumed same as danicopan 0.24%;

Table: PEGASUS trial BTH events and probability calculation for BTH events requiring intervention

	PEGASUS - Pegcetacoplan	PEGASUS – C5i
PEGASUS: Week 1-16	4 events out of 41 people in 16 weeks of follow-up; 2.53%	9 events out of 39 people in 16 weeks of follow-up; 6.35%*
PEGASUS: Week 17+	15 events out of 77 people in 32 weeks of follow-up; 2.67%	N/A

* based on classification of BTH events used in the model only 2 events met the definition of BTH events requiring intervention based on LDH levels (BTH rate of 1.31% requiring intervention).

BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor; LDH; Lactate dehydrogenase

Key issue: Modelling of costs associated with BTH

Background

- In company base case, assumed that people receiving pegcetacoplan who experience BTH will increase dosing frequency to once every 3 days for 1st dose escalation, and 3 times a week for 2nd escalation
- Results in majority of people receiving the maximum treatment regime of 3 doses per week

Company:

- Pegcetacoplan dose escalation regimen for BTH in line with the approach adopted in an OLE study of pegcetacoplan and has been confirmed by UK clinical experts to reflect UK clinical practice
- Provided 2 studies which support use of 3 times per week dosing of pegcetacoplan due to BTH – see appendix
- SmPC for pegcetacoplan supports escalation beyond the 1,080 mg twice weekly dose

EAG:

- Dose escalation approach appears inconsistent with TA778 which assumed dosing would be fixed at 2 per week
- EAG's clinical experts observed temporary increased pegcetacoplan dosing frequency for BTH that returned to twice weekly once within roughly 1 month
- Accepts some escalation occurs in practice but neither study present evidence of: BTH or BTH management close to modelled time horizon; nor dose escalation to magnitude modelled by company – see appendix
- Provided scenario with BTH event probability for weeks 1 -16 for pegcetacoplan as per company base case then assumed equal long term BTH events of 0% for all treatments, reducing impact of dose escalation assumption

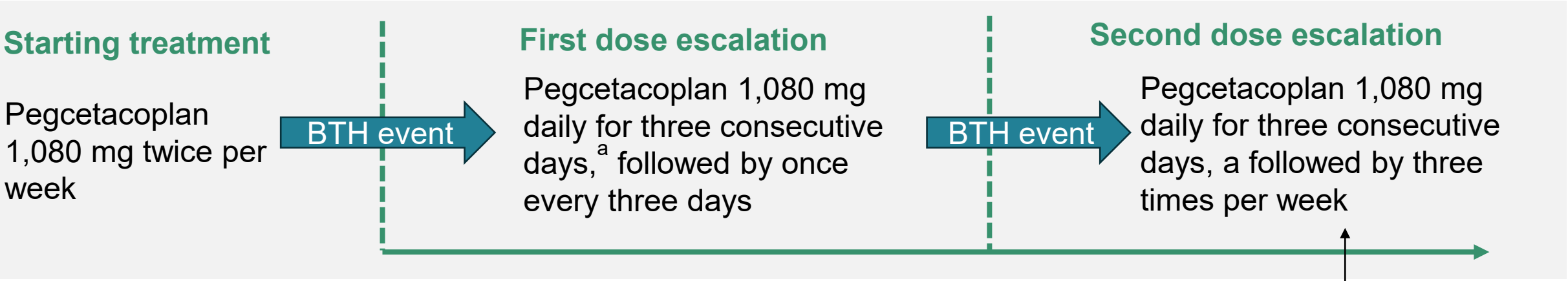
Is the company's pegcetacoplan dose escalation regimen for BTH reflective of NHS clinical practice?

BTH, Breakthrough haemolysis; EAG, External Assessment Group; C5i, Complement component 5 inhibitor; OLE, Open-label extension; SmPC, Summary of Product Characteristic; TA, Technology appraisal

Treatment regimens for breakthrough haemolysis

See appendix for danicopan + C5i treatment regime for BTH

Table: Progression of treatment regimens per BTH event



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

In company base case, majority of people eventually receive pegcetacoplan three times per week

BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor

Summary of differences in company base case; EAG preferred company base case and EAG's preferred analysis (1)

EAG views that there is insufficient evidence to support comparison of danicopan + C5i to pegcetacoplan, and do **not** present a base case. Instead EAG present:

- EAG preferred company base case (preferred assumptions in comparison against pegcetacoplan)
- EAG's preferred analysis (comparison against C5i monotherapy- within trial comparison)

Table: Summary of differences between analyses

Assumption	Company base case	EAG preferred company base case	EAG's preferred analysis
Comparator	Pegcetacoplan	Pegcetacoplan	C5i (monotherapy)
Subsequent therapy after discontinuing danicopan + C5i	100% C5i monotherapy	80% pegcetacoplan*; 20% C5i monotherapy	100% C5i monotherapy
Transition probabilities	Danicopan⁺: ALPHA; Pegcetacoplan: PEGASUS	Equal transition probabilities using probabilities from ALPHA	Danicopan⁺: ALPHA; C5i: ALPHA

⁺ Danicopan + C5i (resource use modelled assuming [redacted] of people treated with ravulizumab and [redacted] with eculizumab);
*EAG only modelled the costs of subsequent pegcetacoplan and associated BTH probability; did not adjust any other probabilities or disutilities for those who have discontinued danicopan
Note all analyses include corrections to 3 modelling errors identified by the EAG

BTH, Breakthrough haemolysis; EAG, External Assessment Group; C5i, Complement component 5 inhibitor

Summary of differences in company base case; EAG preferred company base case and EAG's preferred analysis (2)

Table: Summary of differences between analyses

Assumption	Company base case	EAG preferred company base case	EAG's preferred analysis
Transfusion-related iron overload probabilities	Danicopan[+]: ALPHA; Pegcetacoplan: PEGASUS	Equal iron overload probabilities using probabilities from ALPHA	Danicopan[+]: ALPHA; C5i: Assumed same as danicopan + C5i
BTH event probabilities	Danicopan[+]: ALPHA Pegcetacoplan: PEGASUS	Equal long term[‡] BTH event probabilities based on ALPHA long term estimates	Danicopan[+]: ALPHA; C5i: Assumed same as danicopan + C5i
Pegcetacoplan dosing for BTH	once every 3 days for 1st dose escalation; 3 times a week for 2nd escalation	As per company base case (separate scenario analysis[1])	N/A
Long term discontinuation rates (week 53+)	Danicopan[+]: 0% Pegcetacoplan: 0%	As per company base case (separate scenario analysis[2])	Danicopan[+]: 0% C5i: 0%

[+] Danicopan + C5i (resource use modelled assuming [redacted] of people treated with ravulizumab and [redacted] with eculizumab)
[‡] from week 17 and week 25 for pegcetacoplan and danicopan, respectively

BTH, Breakthrough haemolysis; EAG, External Assessment Group; C5i, Complement component 5 inhibitor

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator discounts

Results presented in part 2:

- Company base case – Dominant (lower costs and higher QALYs than pegcetacoplan)
- EAG preferred company base case– above the threshold usually considered an acceptable use of NHS resources versus pegcetacoplan
- EAG preferred analysis- above the threshold usually considered an acceptable use of NHS resources versus C5i monotherapy

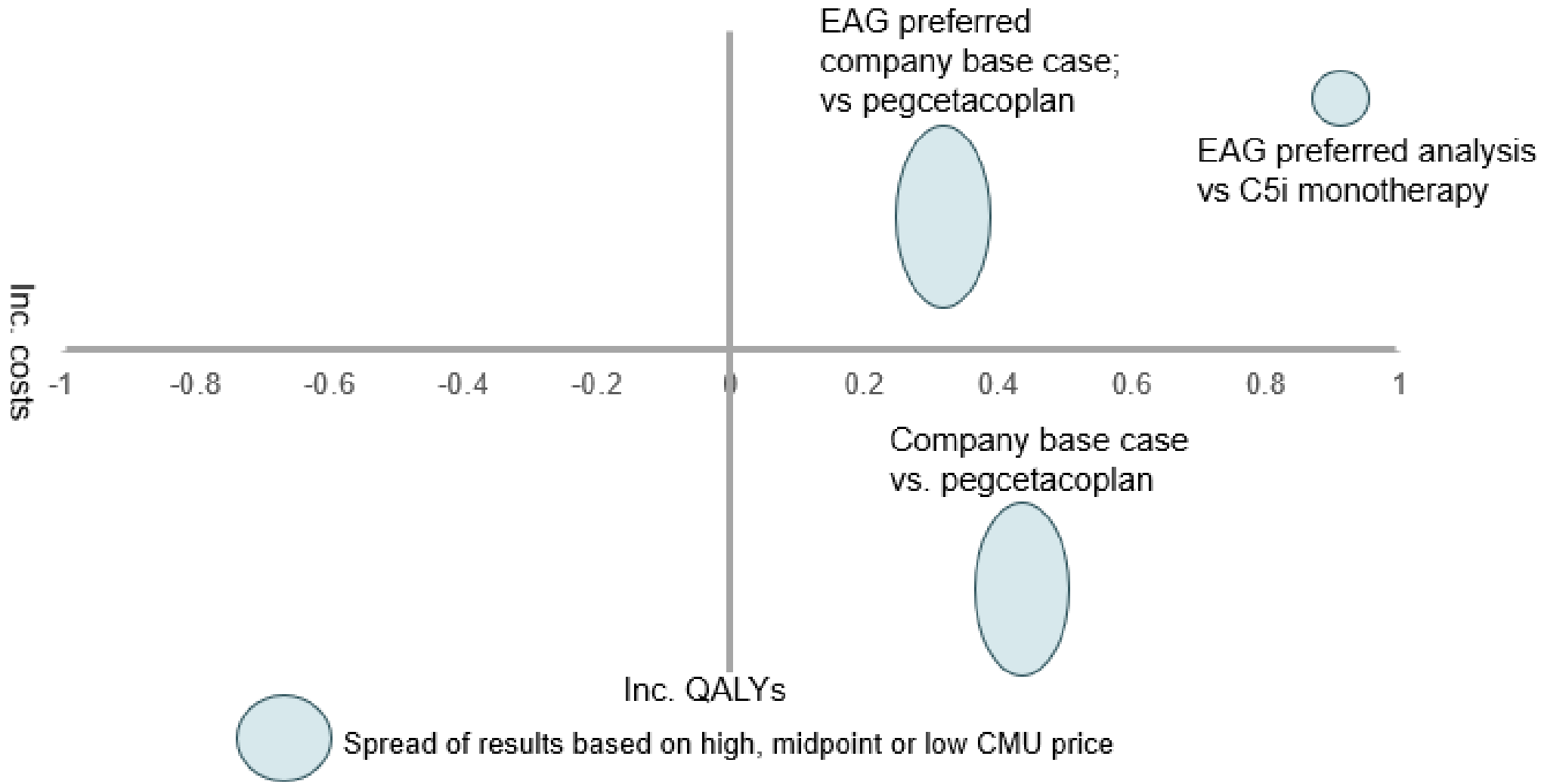
Scenarios presented in part 2:

- Scenarios in which each of the EAG preferred company base case assumptions (where different from company's preferred assumptions) are applied individually to company base case
- Scenario with no BTH events from week 17+ for all treatments
- Scenario with 1% per cycle discontinuation rate from week 53+ for danicopan + C5i and pegcetacoplan
- EAG's preferred analysis plus subsequent pegcetacoplan (for 80% of people) after danicopan + C5i

C5i, Complement component 5 inhibitor; BTH, Breakthrough haemolysis; EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; PAS, Patient access scheme; QALY, Quality-adjusted life year

Cost effectiveness plane

Cost effectiveness plane for danicopan + C5i; deterministic results



C5i, Complement component 5 inhibitor; CMU, Commercial Medicines Unit; EAG, External Assessment Group

Key committee questions (1)

Table: Key questions for committee

Parameter	Key Committee Questions
Comparators	Is C5i monotherapy a relevant comparator to danicopan? If so, are eculizumab and ravulizumab both relevant comparators?
Target population	If danicopan were to be recommended, how would the eligible patient population be defined? Are the results from ALPHA generalisable to the eligible treatment population in the NHS?
ALPHA trial data	Is the efficacy data (sample size and length of follow-up) presented in the company submission sufficient for decision making? What is the committee's preferred ALPHA trial data cut for use in the economic model?
Relative efficacy between danicopan and comparator (s)	Are results of the naïve comparison of danicopan + C5i and pegcetacoplan suitable for decision making? Is a comparison of danicopan + C5i and C5i monotherapy more appropriate for decision making?
Transition probabilities	Are any of the presented transition probabilities acceptable for decision making? If so, what are the most suitable transition probabilities for decision making?
Subsequent therapy after danicopan + C5i	Is it expected that people will switch to C5i monotherapy or pegcetacoplan after discontinuing danicopan + C5i? Is the EAG's scenario appropriate for decision making?

NICE

BTH, Breakthrough haemolysis; EAG, External Assessment Group; C5i, Complement component 5 inhibitor

Key committee questions (2)

Table: Key questions for committee

Parameter	Key Committee Questions
Long term discontinuation probabilities	Is it more appropriate to assume no discontinuation after week 52 or to assume 1% discontinuation every 4 weeks after week 52 for danicopan and pegcetacoplan?
BTH probabilities	Is it more appropriate to use naïve comparison of BTH rates or assume the long-term BTH rate is equal?
Costs associated with BTH	Is the company's pegcetacoplan dose escalation regimen for BTH reflective of NHS clinical practice?

Supplementary appendix

NICE National Institute for Health and Care Excellence

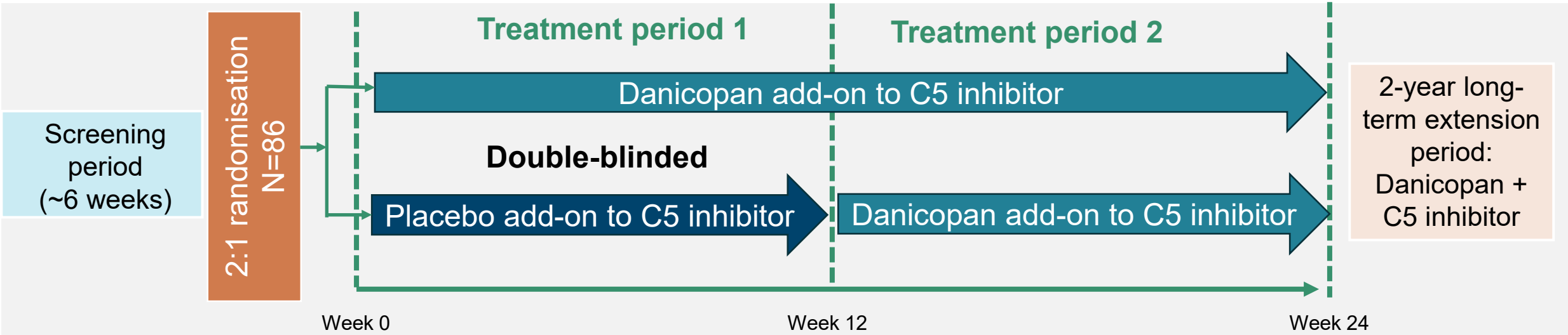
Equality considerations

No equality issues identified in submissions from company, PNH support and National PNH service

Alpha Trial design

For treatment period 1, 86 people were randomised in a 2:1 ratio to danicopan (N=57) or placebo (n=29) treatment arms

Figure: Alpha trial design



Alpha trial is ongoing; at data cut-off (20th September 2022) 71 and 60 people completed TP1 and TP2, respectively

Key Inclusion criteria:

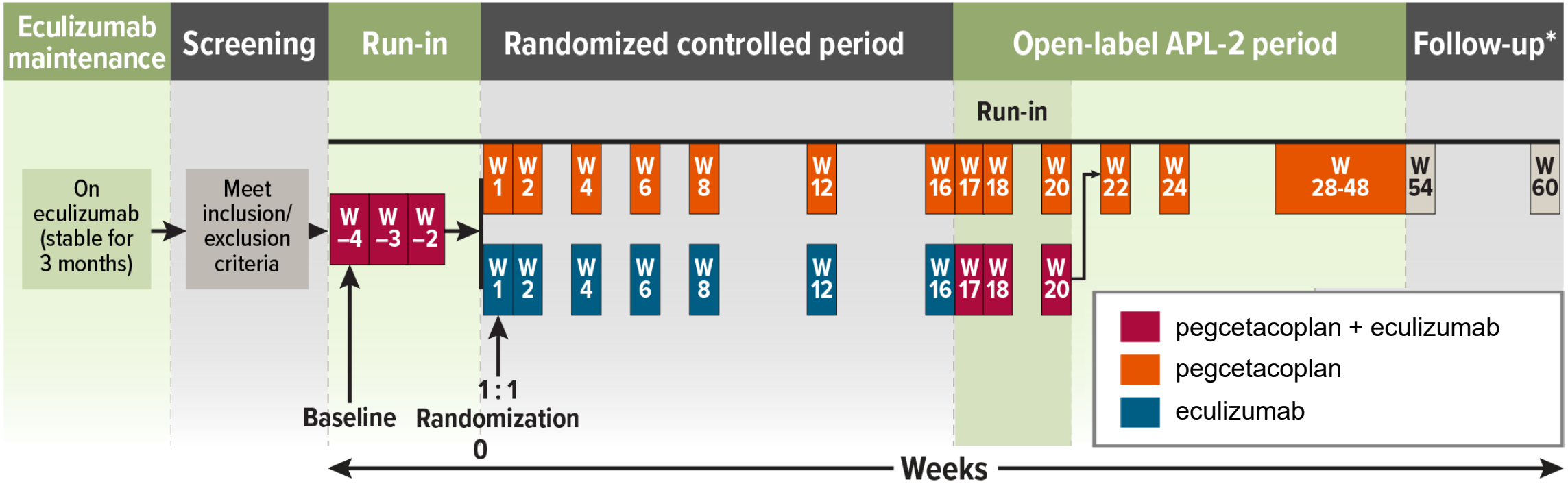
- Adult with diagnosis of PNH and CsEVH, defined by anaemia (haemoglobin ≤9.5 g/dL) with ARC ≥120 × 10^9/L
- Receiving approved C5 inhibitor for ≥6 months prior at approved dose (or higher), with no change for ≥24 weeks
- Platelet count ≥30,000/μL without the need for platelet transfusions
- ANC ≥500/μL
- Documentation of vaccination for Neisseria meningitidis

ANC, Absolute neutrophil count; ARC, Absolute reticulocyte count; C5, Complement component 5; CsEVH, Clinically significant extravascular haemolysis; PNH, Paroxysmal nocturnal haemoglobinuria; TP, Treatment period

PEGASUS Trial summary

PEGASUS trial: phase 3, multicentre, open-label, active-comparator, randomised controlled trial comparing pegcetacoplan (n=41) with eculizumab (n=39) in adults with PNH who had haemoglobin levels <10.5 g/L despite treatment with eculizumab

Figure: PEGASUS trial design



Primary outcome: change from baseline in haemoglobin level at week 16 was statistically significantly higher in the pegcetacoplan arm compared to the eculizumab arm.

NICE

PNH, Paroxysmal nocturnal haemoglobinuria

Alpha Trial TP2 interim analysis results summary

EAG:

- 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
- No statistical comparisons with baseline undertaken on interim results and caution required in interpretation

Table: Alpha trial results summary from second interim analysis set (N=61)

	DAN/DAN + C5i, n=41	PBO/DAN + C5i, n=20
Hb change from baseline at week 24 mean (SD) g/dL	[redacted]	[redacted]
% people with Hb increase ≥2 (95% CI) g/dL in absence of transfusion	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
FACIT-F scores change from baseline, LS mean (95% CI)	[redacted]	[redacted]
ARC change from baseline, LS mean (95% CI) 10^{12}/L	-0.08 (-0.1, -0.06), n=37	-0.07 (0.09, -0.04), n=19

* LS mean change 3.17 (SE 3.02) for the DAN/DAN group and 2.26 (SE 3.40) for the PBO/DAN group

ARC, Absolute reticulocyte count; C5i, Complement component 5 inhibitor; CI, Confidence interval; DAN, Danicopan; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; Hb, Haemoglobin; LS, Least squared; PBO, Placebo; TP, Treatment period

Alpha Trial Adverse events overview

Company submission presents treatment-emergent adverse events for the safety analysis set (N=86) during TP1, and for N=71 and N=60 in TP2 and LTE, respectively.

Table: Overview of TEAEs during each study period

	TP1		TP2	LTE
	DAN + C5i[a] N=57[b]	PBO + C5i[a] N=29	Total N=71	Total N=60
Any AE; n (%)	42 (73.7)	18 (62.1)	44 (62.0)	41 (68.3)
Any SAE; n (%)	3 (5.3)	2 (6.9)	6 (8.5)	7 (11.7)
Death; n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE leading to withdrawal of study intervention; n (%)	3 (5.3)	1 (3.4)	0 (0.0)	1 (1.7)
SAE leading to withdrawal of study intervention; n (%)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)

[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.

AE, Adverse event; C5i, Complement component 5 inhibitor; DAN, Danicopan; LTE, Long term extension; SAE, Serious adverse event; TEAE, Treatment-emergent adverse event; TP, Treatment period

Indirect treatment comparison overview

Company: MAIC results unsuitable for drawing conclusions on relative efficacy between danicopan add-on therapy and pegcetacoplan

Identification and selection of relevant studies

- No direct evidence comparing danicopan add-on therapy (ALPHA trial) with pegcetacoplan (PEGASUS trial)

Feasibility assessment

- Feasibility assessment identified key differences in trial designs, eligibility criteria and baseline characteristics→ company attempted series of MAICs in attempt to account for heterogeneity

MAIC methodology

- Prior to adjusting for treatment effect modifiers or prognostic factor variables, a trimmed population (N=[redacted]) of ALPHA trial was created to align more closely with PEGASUS population, based on BMI and platelet count
- Adjustment variables: 1) Mean baseline haemoglobin level and 2) mean baseline reticulocyte count → selected based on clinical opinion, data availability and resulting ESS
- Two methods used to balance covariates: Signorovitch et al. 2010 and Jackson et al. 2020, resulting in ESS of 13.9 patients and 15.3 patients, respectively
- Unanchored and anchored MAICs performed for selected key outcomes
- Compared danicopan and C5i at 12 weeks versus pegcetacoplan at 20 weeks (including 4-week run in period)

MAIC results

- Key differences between trial designs and populations could not be adjusted for. E.g. prior transfusion history and baseline bilirubin levels remained unbalanced between trial populations →both highly relevant to EVH
- Small ESS after adjustment introduced further uncertainty → company considered MAIC results unsuitable for drawing conclusions on relative efficacy between danicopan add-on therapy and pegcetacoplan

BMI, Body mass index; C5i, Complement component 5 inhibitor; ESS, Effective sample size; EVH, Extravascular haemolysis; MAIC, Matching-adjusted indirect comparison

Treatment regimens for breakthrough haemolysis

Table: 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.

How company incorporated evidence into base case model (1)

Table: Inputs, assumptions and evidence source for company base case model

Input	Assumption and evidence source
Baseline characteristics	Informed by data from ALPHA trial; all patients enter the model in the 'Low Hb (No Tr.)' state
Danicopan + C5i transition probabilities	Estimated from a multinomial model fitted to data from the ALPHA trial; based on a threshold of 9.5g/dL for Hb when defining health states
Pegcetacoplan transition probabilities	Estimated from a multinomial model fitted to data from the PEAGASUS trial (Hakimi et al.); based on a threshold of 10.5g/dL for Hb when defining health states
C5i treatment split	Resource use modelled assuming [redacted] of people treated with ravulizumab and [redacted] with eculizumab (based on Alexion sales clinical expert opinion)
BTH	Patients in transfusion health state: **Danicopan + C5i**: probability derived from ALPHA trial **Pegcetacoplan:** probability derived from PEGASUS trial **C5i monotherapy**: assumed same probability of BTH events as patients receiving danicopan as an add-on to C5i
Iron overload	**Danicopan + C5i**: probability derived from ALPHA trial **Pegcetacoplan:** probability derived from Hakimi et al. (PEGASUS trial) **C5i monotherapy**: assumed same probability of iron overload events as patients receiving danicopan as an add-on to C5i

BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor; Hb, Haemoglobin; Tr, Transfusion

How company incorporated evidence into base case model (2)

Table: Inputs, assumptions and evidence source for company base case model

Input	Assumption and evidence source
Adverse reactions	Included AEs grade ≥3, which occurred in >5% of patients in either treatment arm during the initial treatment period of the ALPHA or PEGASUS
Mortality	Assumed the probability of mortality to be equal between treatments and used estimates based on age and sex-matched general population mortality for England.
Discontinuation	**Danicopan + C5i**: discontinuation rates based on ALPHA trial for weeks 1 to 52 **Pegcetacoplan**: assumed no discontinuation for weeks 1 to 16 as discontinuations in PEGASUS during this time due to BTH; discontinuation rates based on PEGASUS trial for weeks 17 to 52 **In both arms assumed**: C5i monotherapy upon discontinuation; no discontinuation beyond year 1
Utilities	**Health state**: EQ-5D-3L data were obtained directly from ALPHA trial Increased ALT disutility, Iron overload disutility and administration-related disutility (eculizumab and pegcetacoplan) based on previous TAs and published literature
Costs	**Categories included**: Drug acquisition costs, administration costs, monitoring costs, transfusion costs, Iron overload management costs, AE management costs, BTH management costs **Unit prices based on**: NHS reference costs, BNF, eMIT, NCGC and PSSRU

AE, Adverse event; BNF, British National Formulary; BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor; eMIT, Drugs and pharmaceutical electronic market information tool; EQ-5D-3L, EuroQol 5-dimensions 3 levels; NCGC, National Clinical Guideline Centre; PSSRU, Personal Social Services Research Unit; TA, Technology appraisal

Alpha Trial TP1 IA3 results summary

Table: Alpha trial results summary from IA3

Primary endpoint, Interim trial outcomes at 12 weeks			
	Danicopan + C5i, n=	Placebo + C5i, n=	Adj. difference (95% CI)
Hb change from baseline LS mean (95% CI) g/dL			
Key secondary endpoints, Interim trial outcomes at 12 weeks			
% people with Hb increase ≥2 (95% CI) g/dL in absence of transfusion			
% participants avoiding transfusion (95% CI)			
FACIT-F scores change from baseline, LS mean (95% CI)			
ARC change from baseline, LS mean (95% CI) 10^9/L			

ARC, Absolute reticulocyte count; C5i, Complement component 5 inhibitor; CI, Confidence interval; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; Hb, Haemoglobin; LS, Least squared; TP, Treatment period

Alpha Trial TP2 IA3 results summary

Table: Alpha trial results summary from IA3

	DAN/DAN + C5i, n=[redacted]	PBO/DAN + C5i, n=[redacted]
Hb change from baseline at week 24 LS mean (95% CI) g/dL	[redacted]	[redacted]
% people with Hb increase ≥2 (95% CI) g/dL in absence of transfusion	[redacted]	[redacted]
% participants avoiding transfusion Week 12 – 24 (95% CI)	[redacted]	[redacted]
FACIT-F scores change from baseline, LS mean (95% CI)	[redacted]	[redacted]
ARC change from baseline, LS mean (95% CI) 10^9/L	[redacted]	[redacted]

ARC, Absolute reticulocyte count; C5i, Complement component 5 inhibitor; CI, Confidence interval; DAN, Danicopan; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; Hb, Haemoglobin; LS, Least squared; PBO, Placebo; TP, Treatment period

Key issue: Modelling of BTH probabilities (2)

Company:

- Provided 2 studies showing disparity in long-term BTH rates between pegcetacoplan and ravulizumab:
  - Griffin, et al. 2024 study, provides real world data on 48 people with PNH receiving pegcetacoplan in the UK and France. At time of study publication, people had received pegcetacoplan for a mean duration of 20.2 months. A total of 32 BTH events had occurred in 13/48 people, equating to a BTH rate of ~27.1%.
  - Kulasekararaj, et al. 2023 presentation shows long-term outcomes of a Phase 3 study investigating ravulizumab versus eculizumab in C5i- treated participants. 6.8% rate of BTH during ravulizumab treatment with up to 4 years of study follow up

BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor; PNH, Paroxysmal nocturnal haemoglobinuria

Key issue: Modelling of costs associated with BTH (2)

Company:

- Provided 2 studies which support use of 3 times per week dosing of pegcetacoplan due to BTH
  - Griffin, et al. 2024 real-word study summarises management of BTH for people receiving pegcetacoplan in in UK and France. Dosing regimen for all people included in study not provided but narratives for 6 people in study reporting repeated BTH events or combination treatment with a C5i, indicated use of once every 3 days or 3 times weekly pegcetacoplan dosing in all people
  - In additional Griffin, et al. 2024 publication based on a pegcetacoplan OLE study, of the 13 people who experienced intensive pegcetacoplan dosing, 8 (62%) people received pegcetacoplan twice weekly, 4 (31%) people received pegcetacoplan every 3 days and 1 person received pegcetacoplan 3 times weekly prior to this intensive dosing

EAG:

- In real-world study by Griffin et al. 13 out of 48 participants experience BTH events. Out of these, 4 (8.3%) were escalated to receive pegcetacoplan every 3 days, and 2 (4.2%) were escalated to receive 3 doses per week→ others may have experienced temporary dosing changes but did not appear to have their regular dose adjusted
- OLE of pegcetacoplan by Griffin et al. focuses on dose escalation of pegcetacoplan in cases of acute BTH→ population of this study is not representative of target population of this appraisal. At baseline 4 out of 13 people were receiving pegcetacoplan 3 days per week and 1 was receiving 3 times per week. Only 4 of these higher dosing regimens were reported to be due to BTH events → unclear whether other dose increases within this study were sustained once the BTH event was under control

BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor; OLE, Open-label extension; PNH, Paroxysmal nocturnal haemoglobinuria

EAG scenarios applied to company base case

Table: Impact of EAG scenarios applied to company base case

Scenario (to company base case)	Inc. NHB; Danicopan + C5i vs pegcetacoplan
1: Correction of 3 modelling errors	Decrease
2: Subsequent pegcetacoplan costs after danicopan (80% of people)	Decrease
3: Equal transition probabilities for danicopan + C5i and pegcetacoplan	Increase
4: Equal probabilities of Iron overload (0.47%) for danicopan + C5i and pegcetacoplan	Negligible
5: Equal probabilities of long term BTH events for danicopan + C5i and pegcetacoplan (0.24%)	Decrease
6: Combined changes 1 - 5 (EAG preferred company base case)	Decrease
7: Combined changes 1 - 4 with no BTH events from week 17+ for danicopan + C5i and pegcetacoplan	Decrease
8: Combined changes 1 - 5 with 1% discontinuation rate from week 53+ for danicopan + C5i and pegcetacoplan	Decrease

Large Moderate Small

BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor; EAG, External Assessment Group; Inc; Incremental; NHB, Net health benefit

Scenario applied to EAG preferred analysis

Table: Impact of scenario applied to EAG preferred analysis

Scenario (to EAG preferred analysis)	Inc. NHB; Danicopan +C5i vs C5i monotherapy
1: Subsequent pegcetacoplan costs after danicopan (80% of people)	Decrease

Large Moderate Small

NICE C5i, Complement component 5 inhibitor; EAG, External Assessment Group; Inc; Incremental; NHB, Net health benefit