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

For projector and zoom – redacted

Technology Appraisal Committee C [2 July 2024]

Chair: Stephen O'Brien

External assessment group: Warwick Evidence

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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

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Key issues and committee questions

Table: Key issues and questions for committee

Parameter	Key Committee Questions	ICER impact
Comparators	Has committee heard anything that would alter the appropriate comparators identified at ACM1?	Large
BTH probabilities	What are the most appropriate long term BTH event probabilities for danicopan + C5i and pegcetacoplan?	Large
Costs associated with BTH	Is the company's pegcetacoplan dose escalation regimen for BTH reflective of NHS clinical practice?	Large
Long term discontinuation probabilities	What is the most appropriate long term discontinuation rate for danicopan + C5i and pegcetacoplan?	Moderate
Pegcetacoplan disutility	Is it appropriate to apply an annual disutility of 0.025?	Small
Subsequent therapy after danicopan + C5i	What proportion of people will switch to pegcetacoplan after discontinuing danicopan + C5i?	Small
Transition probabilities	What are the most suitable transition probabilities for decision making?	Small

BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor; ICER, Incremental cost-effectiveness ratio

Danicopan (Voydeya) (1)

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

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

Danicopan (Voydeya) (2)

Table: Danicopan key information

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

C5i, Complement component 5 inhibitor

Key conclusions from ACM1 (1)

Recommendation after ACM 1: Danicopan is not recommended, within its anticipated marketing authorisation, as an add-on to ravulizumab or eculizumab for treating paroxysmal nocturnal haemoglobinuria (PNH) in adults with residual haemolytic anaemia

Table: Key issues

Issue	Resolved at consultation?	ACM conclusion
Comparators	Partially, to discuss	Pegcetacoplan is appropriate comparator
BTH probabilities for danicopan + C5i and pegcetacoplan	No, to discuss	Requested additional evidence
Pegcetacoplan dosing for BTH	No, to discuss	Requested additional evidence
Long term discontinuation probabilities for danicopan and pegcetacoplan	Partially, to discuss	Requested additional scenarios

ACM, Appraisal committee meeting; BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor; PNH, Paroxysmal nocturnal haemoglobinuria

Key conclusions from ACM1 (2)

Table: Key issues

Issue	Resolved at consultation?	ACM1 conclusion
Pegcetacoplan disutility	N/A	N/A - new key issue identified by EAG during its critique of company's response to draft guidance consultation
Subsequent therapy after discontinuing danicopan + C5i	No, to discuss	Requested additional evidence
Transition probabilities for danicopan + C5i and pegcetacoplan	No, to discuss	- Prefer transition probabilities for danicopan + C5i to be from IA3 data-cut - Uncertainty with both assuming equal efficacy or with using naïve comparison
ITC for comparison of danicopan + C5i to pegcetacoplan	No, unresolvable with available evidence	MAIC results not sufficiently robust to estimate relative efficacy

ACM, Appraisal committee meeting; C5i, Complement component 5 inhibitor; EAG, External Assessment Group; IA3, Third interim analysis; ITC, Indirect treatment comparison; MAIC, Matching-adjusted indirect comparison

Key conclusions from ACM1 (3)

Table: Key issues

Issue	Resolved at consultation?	ACM1 conclusion
Definition of target population and implementation into NHS	Yes	Positioning of danicopan + C5i for PNH in adults with csEVH is appropriate
ALPHA trial: Use of latest available data-cut	Yes	Requested latest data cut to be used in analyses

ACM, Appraisal committee meeting; C5i, Complement component 5 inhibitor; csEVH, Clinically significant extravascular haemolysis

Consultation responses to draft guidance summary (1)

- **Company (Alexion):**
- Unmet needs –
  - danicopan positioned to address symptoms of csEVH while maintaining sufficient control of IVH
  - Pegcetacoplan given as subcutaneous infusion→ unsuitable for some people
- Provided a response to areas of uncertainty and additional analyses requested by committee (further detail in key issue slides) and updated base case (slide 29)

Comparators

Novartis (manufacturer of iptacopan)

- Agrees that staying on a C5i alone would not address csEVH
- However, in UK clinical practice some people with residual anaemia on a C5i may not switch to pegcetacoplan, and instead remain on a C5i
- Conclusion in DG that only pegcetacoplan is appropriate comparator creates inconsistency between iptacopan appraisal (ID6176) and current appraisal for same population

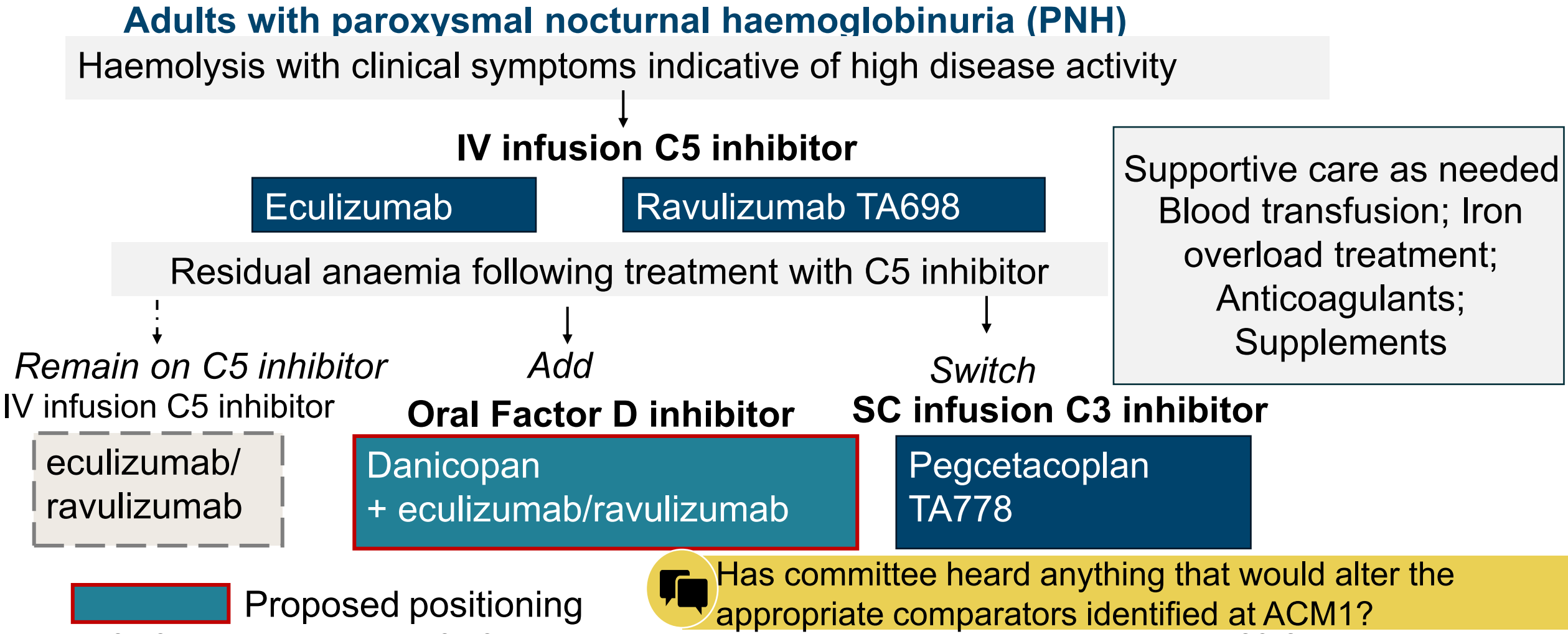
C5i, Complement component 5 inhibitor; csEVH, Clinically significant extravascular haemolysis; DG, Draft guidance; IVH, Intravascular haemolysis

RECAP

Treatment pathway

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

Figure: PNH treatment pathway



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

Defining target population

Background

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

Discussion at ACM1:

- Clinical experts: ~80% of people with PNH having C5i will remain anaemic. Of these, about 30% will have csEVH
- Clinical expert: to diagnose csEVH, haemoglobin levels and absolute reticulocyte count would be considered alongside other clinical parameters and symptoms as part of a wider clinical picture. Non-haematological causes would also be excluded, potential IVH would be assessed and C3 loading on PNH red blood cells would be checked
- Diagnosis of people with csEVH, and eligibility to have danicopan add-on therapy would be discussed at monthly multidisciplinary meetings

If danicopan were to be recommended in line with the company's proposed positioning, how should csEVH be defined in the guidance document?

C3, Complement component 3; C5i, Complement component 5 inhibitor; csEVH, Clinically significant extravascular haemolysis; IVH, Intravascular haemolysis; PNH, Paroxysmal nocturnal haemoglobinuria

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

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Alpha Trial TP1 IA3 results summary

See appendix for TP2 IA3 results summary

Table: Alpha trial results summary from IA3 (used in updated economic model)

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

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

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- issues with a large impact on cost effectiveness**

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Key issue: Modelling of BTH probabilities (1)

Table: Summary of differences between company base case and EAG preferred assumptions for long-term BTH rates

Assumption	Updated company base case	EAG preferred assumptions
Long term BTH annual rate: danicopan + C5i	3.07%	3.07%
Long term BTH annual rate: pegcetacoplan	23.47%	6.06%

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

Key issue: Modelling of BTH probabilities (2)

Background

- Company assumes higher probability of BTH events in pegcetacoplan arm compared with danicopan + C5i arm, based on a naïve comparison of BTH events in PEGASUS and ALPHA trials, respectively
- **ACM1 -** requested evidence to support company's assumptions about long term BTH-event rates including detail of criteria used to classify a BTH event and comparison to criteria in model

Company:

- Pegcetacoplan only been available for ~2 years in UK clinical practice→ lack of long term data on rate of BTH events ➔ unavoidable limitation

Definitions

- PEGASUS - Definition agreed on by UK clinical experts aligns with criteria used to classify BTH events (see appendix)
- ALPHA - BTH events in the ALPHA trial was investigator defined→ more broadly defined than UK clinical expert opinion and PEGASUS definition
- To align with UK clinical practice and also with the definition in PEGASUS, In model, the BTH event rate from the ALPHA calculated based on an LDH elevation ≥2 x ULN during these events → considered reasonable approach by UK clinical expert

BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor; LDH, Lactate dehydrogenase; OLE, Open-label extension; ULN, Upper limit of normal

Key issue: Modelling of BTH probabilities (3)

Company:

Event rates

- Scenario analysis done using Kulasekararaj et al. and Griffin et al. for long term BTH event rates for danicopan + C5i and pegcetacoplan, respectively – see appendix
- Clinical experts: annual long term BTH event rates for pegcetacoplan are likely to be between PEGASUS (29.68%) and the RWE study by Griffin et al (18.35%) – see appendix
- Clinical experts: PEGASUS is a more severely ill population than Griffin et al. → accounts for higher rate of BTH events observed in PEGASUS
- **Company's base case** updated to long term annual probability of BTH for pegcetacoplan of **23.47%** (previously 29.68%) based on Patriquin et al., a 48-week OLE study following PEGASUS → considered reflective of the BTH event rates expected in UK by clinical expert
- Long term BTH event rate derived from ALPHA (**3.07%** annually) maintained for danicopan + C5i in updated base case→ considered conservative as higher than BTH event rate from Kulasekararaj. et al (1.69% annually)

BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor; OLE, Open-label extension; RWE, Real world evidence

Key issue: Modelling of BTH probabilities (4)

EAG:

- Underlying differences in PEGASUS and ALPHA populations highlighted by differences in BTH events in randomised period of trials→ BTH events experienced by 9 (23%) and 0 (0%) people in the respective C5i arms → naive comparison not appropriate
- Patriquin et al. and Griffin et al. may underestimate pegcetacoplan BTH event rates as these generally report number of people rather than number of events
- Definitions and underlying risk of BTH are likely to vary further across these studies
- If dose escalation of pegcetacoplan is appropriate and accurately modelled, BTH rate for pegcetacoplan should reduce over time→ supported by reducing BTH rate between studies as length of follow up increases – see appendix. BTH rates may converge over time
- Also, if dose escalations not providing sufficient control, then returning to C5i may be preferred
- EAG prefers setting long term (Week 25+) BTH rate for pegcetacoplan to be twice the rate for danicopan + C5i used by company (EAG preferred rate of 6.06% annually) but considers this rate of convergence maybe slightly earlier than occurs in practice

What are the most appropriate long term BTH event probabilities for danicopan + C5i and pegcetacoplan?

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

Key issue: Modelling of costs associated with BTH (1)

Background

- **Pre-ACM1**, company assumed that people receiving pegcetacoplan who have BTH will increase dosing frequency to once every 3 days for 1st dose escalation, and 3 times a week for 2nd escalation (most people eventually escalate to 3 times a week dose)
- At **ACM1**, committee considered that evidence provided did not support a maintained dose increase→ preferred a base case in which pegcetacoplan dose increase maintained for up to 3 months and then reduced to a maintenance dose of twice weekly
- Committee also considered some people having pegcetacoplan may have a single dose of eculizumab to manage a BTH event, rather than a pegcetacoplan dose increase→ requested data on proportion of people treated with single dose of eculizumab

Company:

- 2 types of BTH event occur in practice
  - pharmacodynamic BTH - may occur due to temporary event such as infection. Clinical experts stated pegcetacoplan dose may escalate for ~3 months then return to previous dose
  - pharmacokinetic BTH - may occur due to insufficient level of complement inhibitor in plasma such as insufficient dosing levels. Clinical experts stated that if no identifiable cause, people will remain on escalated dose
- Supported by Griffin et al. – see appendix

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

Company:

- Clinical experts: ~50% of people having pegcetacoplan experiencing a BTH event will have temporary dose increase, with 50% permanently remaining on escalated dose
- Haemolysis events in PEGASUS - 9/19 people (47%) had a BTH event not associated with a complement amplifying condition (Latour et al.)
- **Company's updated base case**,
  - Assume 53% of people having pegcetacoplan who experience a BTH event have temporary dose escalation for 3 cycles (12 weeks)
  - C5 inhibition on pegcetacoplan reserved for use in rare cases of severe BTH, and does not represent typical UK clinical practice for people having pegcetacoplan→ one-off cost of eculizumab not included in economic modelling

EAG:

- Possibility of BTH events being observed without any dose escalation not considered by company but possible according to management plan and Griffin et al. study
- Latour et al. presented results of 26 BTH events from 19 people, with 19 events having LDH ≥ 2 x ULN. 13 people had dose escalated and 6 reported to demonstrate a benefit from escalated dose→ EAG is not clear how the company has obtained the percentage of 53%

BTH, Breakthrough haemolysis; C5, Complement component 5; EAG, External Assessment Group; LDH, Lactate dehydrogenase ULN, Upper limit of normal

Key issue: Modelling of costs associated with BTH (3)

EAG:

- Company's updated base case, majority of people having pegcetacoplan eventually escalate to maximum dose before [redacted]
- Combined modelling of dose-escalation and BTH event rates inconsistent → pegcetacoplan dosing increases over time but BTH event rate remains constant
- Griffin et al. reports management of 18 BTH events that were not managed within clinical trials, with 4 events resulting in permanent dose escalation (others resulting in either no dose escalation or temporary escalation
- Based on Griffin et al., EAG prefers applying 14/18 (78%) as temporary dose escalation but considers this could still substantially overestimate treatment costs for pegcetacoplan
- Diagrams showing dose escalation over time presented in appendix for: company's original base case, company's updated base case, EAG's preferred dose escalation scenario and EAG's preferred dose escalation scenario combined with EAG preferred BTH event rate and discontinuation rate

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

BTH, Breakthrough haemolysis; EAG, External Assessment Group

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- issues with a <u>small/moderate</u> impact on cost effectiveness**

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Key issue: Uncertainty over long term discontinuation probabilities for danicopan and pegcetacoplan (wk 52+) (1)

Background

- **ACM1 -** committee concluded that 4-weekly discontinuation rate beyond 1 year would likely be between 0% and 1%→ requested scenario analyses exploring the impact on cost effectiveness of this range

Company:

- Substantial concerns with modelling long term, non-BTH event associated discontinuation rates but provided scenarios in line with committee request
- Experts consulted reiterated that people are less likely to discontinue treatment for non-BTH event reasons beyond first year
- In Patriquin et al. OLE study, no discontinuation for non-BTH reasons during the 48-week follow-up period after completion of PEGASUS
- In ravulizumab studies (Study 301 and 302), 4-weekly ravulizumab discontinuation rates of 0.14% and 0.08%, respectively→ discontinuation over long period of time is negligible
- **Company's base case** maintains assumption of 0% discontinuation for danicopan + C5i and pegcetacoplan after Year 1

ACM, Appraisal committee meeting; BTH, Breakthrough Haemolysis; C5i, Complement component 5 inhibitor; OLE, Open-label extension

Key issue: Uncertainty over long term discontinuation probabilities for danicopan and pegcetacoplan (wk 52+) (2)

EAG:

- Follow-up from studies 301 and 302 suggest that 0% long term discontinuation rate is implausible and can be considered arbitrary
- EAG prefers to apply a 0.1% cycle (1.29% annual) discontinuation rate to both danicopan + C5i and pegcetacoplan, reflecting similarity to long-term follow-up from studies 301 and 302

What is the most appropriate long term discontinuation rate for danicopan +C5i and pegcetacoplan?

EAG, External Assessment Group; C5i, Complement component 5 inhibitor

Key issue: Pegcetacoplan disutility

Background

- EAG identified an additional issue about disutility applied to pegcetacoplan after consultation

Company:

- In line with TA778, an annual disutility of 0.025 associated with administration of eculizumab to account for the increased frequency of IV infusions versus ravulizumab was modelled
- As pegcetacoplan has a higher frequency of administration than ravulizumab, same annual disutility of 0.025 was assumed for pegcetacoplan

EAG:

- In TA778, disutility is only applied for eculizumab, with neither pegcetacoplan or ravulizumab incurring a disutility
- Major concerns about this inconsistency across appraisals and lack of supporting evidence
- EAG does not rule out possibility of disutility being relevant, however current approach appears flawed→ EAG prefers to remove disutility for pegcetacoplan

Is it appropriate to apply an annual disutility of 0.025? for pegcetacoplan?

EAG, External Assessment Group; IV, Intravenous; TA, Technology appraisal

Key issue: Subsequent therapy received after discontinuing danicopan + C5i (1)

Background

- **ACM1 –** committee: some people who stop danicopan + C5i would switch to pegcetacoplan→ requested an estimate of proportion of people who would be expected to switch, with supporting data or evidence

Company:

- Clinician stated that treatment choice after discontinuation of danicopan dependant on whether person was pegcetacoplan-naïve or experienced→ estimated ~50-60% of people discontinuing danicopan + C5i would receive pegcetacoplan
- Based on clinical expert statements provided in committee papers and reweighting proportions of subsequent treatments to only include treatments available within ALPHA and PEGASUS trials, ~60% of people are expected to switch to pegcetacoplan
- **Updated company base case** assumes 60% of people switch to pegcetacoplan
- Subsequent discontinuation to C5i monotherapy modelled in line with rate of non-BTH related discontinuation events

ACM, Appraisal committee meeting; BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor

Key issue: Subsequent therapy received after discontinuing danicopan + C5i (2)

EAG:

- Presumes that almost all pegcetacoplan-naïve people would switch to pegcetacoplan
- For those who have had pegcetacoplan and C5i, path is less clear. EAG unsure whether retreatment with pegcetacoplan would be permitted
- Considers company's estimate of 60% an improvement from original base case assumption of 0% but considers parameter highly uncertain
- Provided scenarios analyses exploring 50%, 70% and 80% of people switching to pegcetacoplan after discontinuing danicopan + C5i

What proportion of people will switch to pegcetacoplan after discontinuing danicopan + C5i?

EAG, External Assessment Group; C5i, Complement component 5 inhibitor

Key issue: Transition probabilities

Background

- In company's initial base case, transition probabilities for danicopan + C5i and pegcetacoplan derived using naïve comparison from ALPHA (IA2 data-cut) and PEGASUS trials, respectively
- EAG presented analyses assuming equal efficacy (probabilities based on ALPHA trial)
- **ACM1** - Committee considered both methods highly uncertain but requested transition probabilities for danicopan + C5i to be derived from ALPHA IA3 data-cut

Company:

- Updated transition probabilities and utilities with IA3 data-cut
- Updated the mean age of people in IA3 to [redacted] years

EAG:

- May be important differences between ALPHA and PEGASUS trial populations
- Updated inputs using IA3 data cut has a very minor impact on cost-effectiveness results
- EAG's preferred analysis updated with transition probabilities from IA3 data-cut

Is it more appropriate to use a naïve comparison or assume equal efficacy?

ACM, Appraisal committee meeting; C5i, Complement component 5 inhibitor; EAG, External Assessment Group; IA2, Second interim analysis; IA3, Third interim analysis

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

EAG view is 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 assumptions (preferred assumptions in comparison against pegcetacoplan)

Table: Summary of differences between analyses

Assumption	Initial company base case	Updated company base case	EAG preferred assumptions
Comparator	Pegcetacoplan	Pegcetacoplan	Pegcetacoplan
BTH event probabilities‡ (annual rates)	Danicopan⁺: ALPHA (3.07%)	Danicopan⁺: ALPHA (**3.07%**)	Danicopan⁺: ALPHA (**3.07%**)
	Pegcetacoplan: PEGASUS (29.68%)	Pegcetacoplan: PEGASUS OLE (Patriquin et al.; **23.47%**)	Pegcetacoplan: twice the rate for danicopan + C5i (**6.06%**)

⁺ 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; C5i, Complement component 5 inhibitor; EAG, External Assessment Group; OLE, Open-label extension

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	Initial company base case	Updated company base case	EAG preferred assumptions
% of people temporary pegcetacoplan dose escalation for BTH event	0%	53%	78%
Long term discontinuation rates (week 53+)	Danicopan+: 0% Pegcetacoplan: 0%	Danicopan+: 0% Pegcetacoplan: 0%	Danicopan+: 0.1% Pegcetacoplan: 0.1%
Pegcetacoplan annual disutility	0.025	0.025	0

+ Danicopan + C5i (resource use modelled assuming [redacted] of people treated with ravulizumab and [redacted] with eculizumab)

BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor; EAG, External Assessment Group; OLE, Open-label extension

Summary of differences in company base case; EAG preferred company base case and EAG's preferred analysis (3)

Table: Summary of differences between analyses

Assumption	Initial company base case	Updated company base case	EAG preferred assumptions
Subsequent therapy after discontinuing danicopan + C5i	100% C5i monotherapy	60% pegcetacoplan 40% C5i monotherapy	60% pegcetacoplan 40% C5i monotherapy
Transition probabilities	Danicopan[+]: ALPHA (IA2 data-cut); Pegcetacoplan: PEGASUS	Danicopan[+]: ALPHA (IA3 data-cut); Pegcetacoplan: PEGASUS	Danicopan[+]: ALPHA (IA3 data-cut); Pegcetacoplan: PEGASUS

[+] Danicopan + C5i (resource use modelled assuming [redacted] of people treated with ravulizumab and [redacted] with eculizumab)

C5i, Complement component 5 inhibitor; EAG, External Assessment Group; IA2, Second interim analysis; IA3, Third interim analysis

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 assumptions– above the threshold usually considered an acceptable use of NHS resources versus pegcetacoplan

Scenarios presented in part 2:

- Scenarios in which each of the EAG preferred assumptions (where different from company's preferred assumptions) are applied individually to company base case
- Scenarios exploring the impact of alternative long term BTH rates
- Scenarios exploring the impact of varying % temporary dose escalation
- Scenarios exploring impact of varying % discontinuation rate beyond week 52
- Scenarios exploring impact of varying % discontinuation to pegcetacoplan

BTH, Breakthrough haemolysis; EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

Key issues and committee questions

Table: Key issues and questions for committee

Parameter	Key Committee Questions	ICER impact
Comparators	Has committee heard anything that would alter the appropriate comparators identified at ACM1?	Large
BTH probabilities	What are the most appropriate long term BTH event probabilities for danicopan + C5i and pegcetacoplan?	Large
Costs associated with BTH	Is the company's pegcetacoplan dose escalation regimen for BTH reflective of NHS clinical practice?	Large
Long term discontinuation probabilities	What is the most appropriate long term discontinuation rate for danicopan + C5i and pegcetacoplan?	Moderate
Pegcetacoplan disutility	Is it appropriate to apply an annual disutility of 0.025?	Small
Subsequent therapy after danicopan + C5i	What proportion of people will switch to pegcetacoplan after discontinuing danicopan + C5i?	Small
Transition probabilities	What are the most suitable transition probabilities for decision making?	Small

BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor; ICER, Incremental cost-effectiveness ratio

Supplementary appendix

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Background on paroxysmal nocturnal haemoglobinuria

RECAP

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

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

Background on paroxysmal nocturnal haemoglobinuria

RECAP

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; PNH, Paroxysmal nocturnal haemoglobinuria

RECAP

Equality considerations

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

Model updates after ACM1 (1)

Company updated model functionality after ACM1, such that following scenarios can be run by user:

- Setting transition probabilities for pegcetacoplan equal to danicopan + C5i treatment
- Setting the long term probability for BTH events for pegcetacoplan equal to danicopan + C5i treatment
- Setting the probability for BTH events on C5i treatment from Week 25+ equal to danicopan + C5i treatment
- An alternative calculation for probability of alanine aminotransferase (Weeks 1–12) for people receiving danicopan + C5i treatment

ACM, Appraisal committee meeting; BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor

Model updates after ACM1 (2)

The company updated model functionality after ACM1, such that the following scenarios can be run by the user:

- Allowing differing proportions of patients discontinuing danicopan + C5i to receive pegcetacoplan or C5i monotherapy
  - updated to ensure that people who discontinue to pegcetacoplan are assigned correct treatment-related administration disutility, rates of BTH events and transition probabilities
  - updated with functionality to model subsequent discontinuation of treatment from pegcetacoplan to C5i monotherapy

Also updated EAG model to ensure that people who discontinue from danicopan + C5i to pegcetacoplan receive 3 doses of pegcetacoplan upon the event of BTH, which may have been unintentionally omitted from EAG model

ACM, Appraisal committee meeting; BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor; EAG, External Assessment Group

Key clinical trial

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

Table: ALPHA trial design

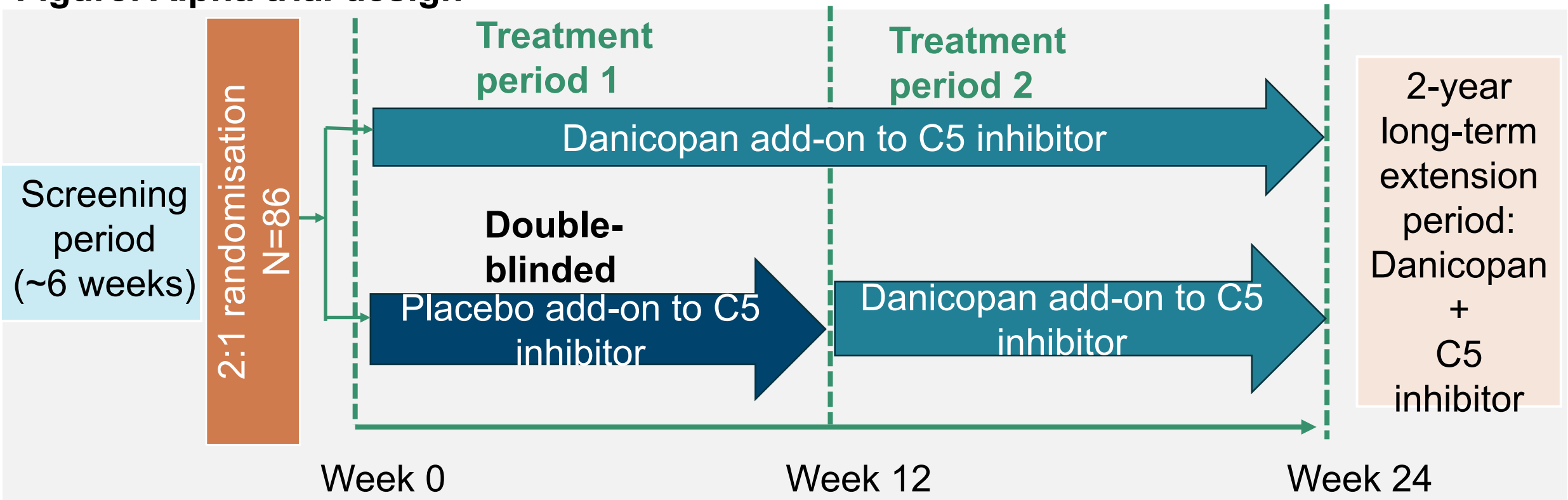
Alpha Trial	Treatment period 1 (TP1)	Treatment period 2 (TP2)	Long term extension (LTE)
Design	Phase 3 double-blind, placebo-controlled, multiple-region RCT	Non-randomised open-label	Non-randomised open-label
Population	Adults with PNH who have csEVH whilst receiving treatment with eculizumab or ravulizumab		
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 years
Locations	80 centres across 18 countries in Europe (3 UK trial centres), Asia, North America and South America.		

C5i, Complement component 5 inhibitor; csEVH, Clinically significant extravascular haemolysis; LTE, Long term extension; IV, Intravenous; PNH, Paroxysmal nocturnal haemoglobinuria; RCT, Randomised controlled trial; TID, Three times daily; TP, Treatment period

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



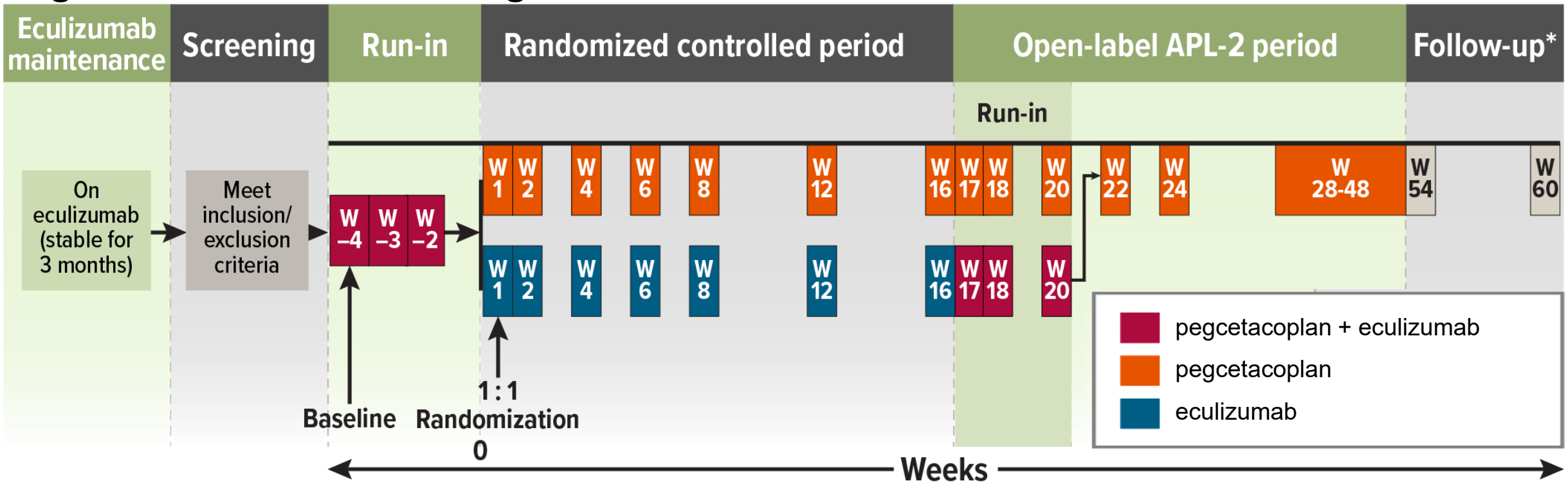
Alpha trial is ongoing; at data cut-off (20th September 2022) 71 and 60 people completed TP1 and TP2, respectively

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.

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PNH, Paroxysmal nocturnal haemoglobinuria

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

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Alpha Trial TP1 interim analysis results summary

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

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 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 BL 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 BL, LS mean (95% CI)	[redacted]	[redacted]
ARC change from BL, 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

Company's model overview

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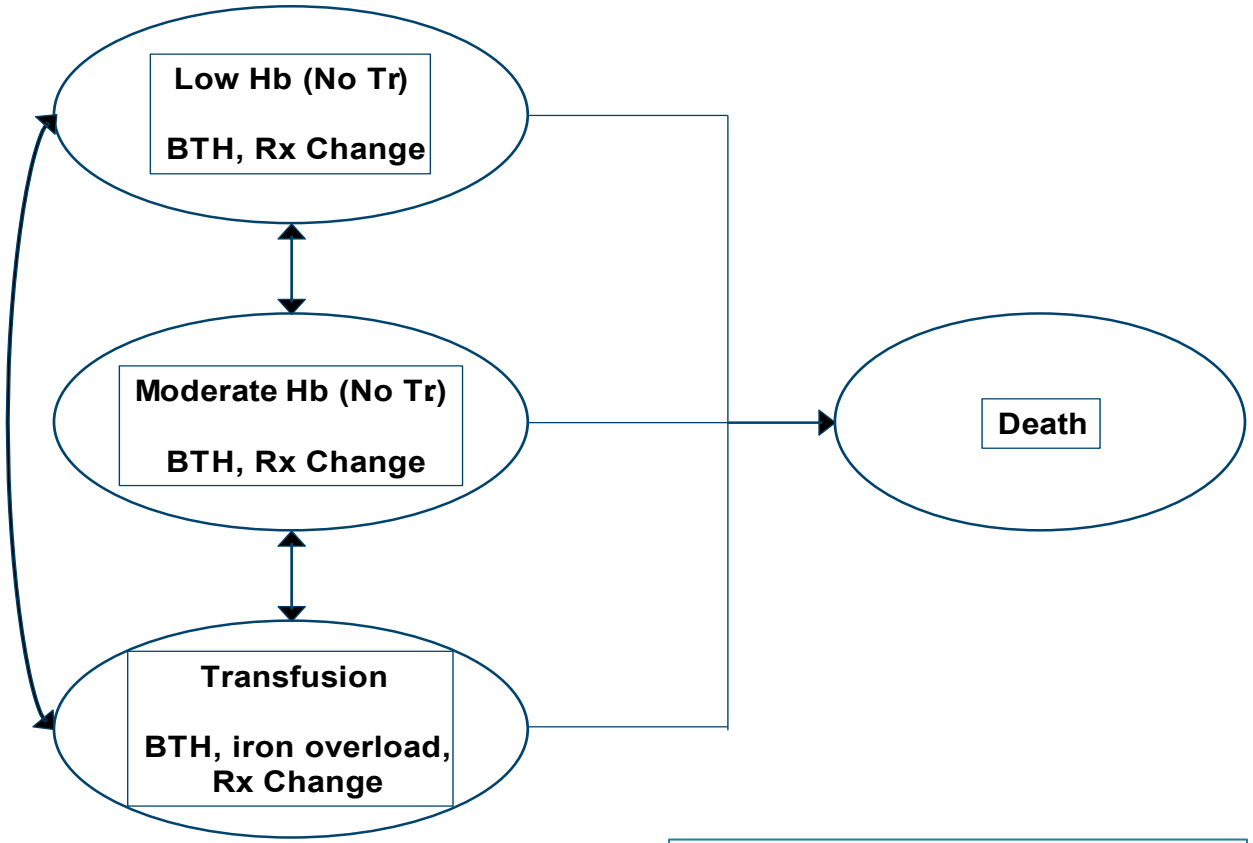
Figure: Company's model structure



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

EAG: Overall model structure appropriate for appraisal

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

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

Observed BTH event rates for pegcetacoplan and C5i

Table: Observed BTH event rates for pegcetacoplan

Publication	Trial	Length of follow-up	4-weekly probability	Annual probability
Latour et al. (2022)	PEGASUS trial (post-16 weeks)	32 weeks	2.67%	29.68%
Patriquin et al. (2024)	307 Open label extension study (PEGASUS)	48 weeks	2.04%	23.47%
Griffin et al. (2024)	Real-world evidence (France & UK)	20.2 months	1.55%	18.35%

Table: Observed BTH event rates for C5 inhibition

Publication	Trial	4-weekly probability	Annual probability
Data on File; danicopan + C5i	The ALPHA trial	0.24%	3.07%
Kulasekararaj. et al (2023); ravulizumab	Study 302	0.13%	1.69%

NICE

BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor

Definitions of BTH

The following definitions were used for BTH events in respective trials/studies:

- The ALPHA trial: *"BTH events were based on the clinical judgement of the Investigator".*
- 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".*
- Study 301 and 302: *"at least one new or worsening symptom or sign of intravascular haemolysis (fatigue; haemoglobinuria; abdominal pain; shortness of breath [dyspnoea]; anaemia; major adverse vascular events, including thrombosis; dysphagia; or erectile dysfunction) in the presence of elevated LDH ≥2 × ULN after prior LDH reduction to <1.5 × ULN on therapy*".
- Griffin et al. 2024 publication: *"an LDH rise above twice the upper limit of normal in patients with LDH predominantly controlled below 1.5 x ULN and a recurrence of PNH symptoms or a thrombotic event".*

BTH, Breakthrough haemolysis; IVH, Intravascular Haemolysis; LDH, Lactate dehydrogenase; PNH, Paroxysmal nocturnal haemoglobinuria; ULN, Upper limit of normal

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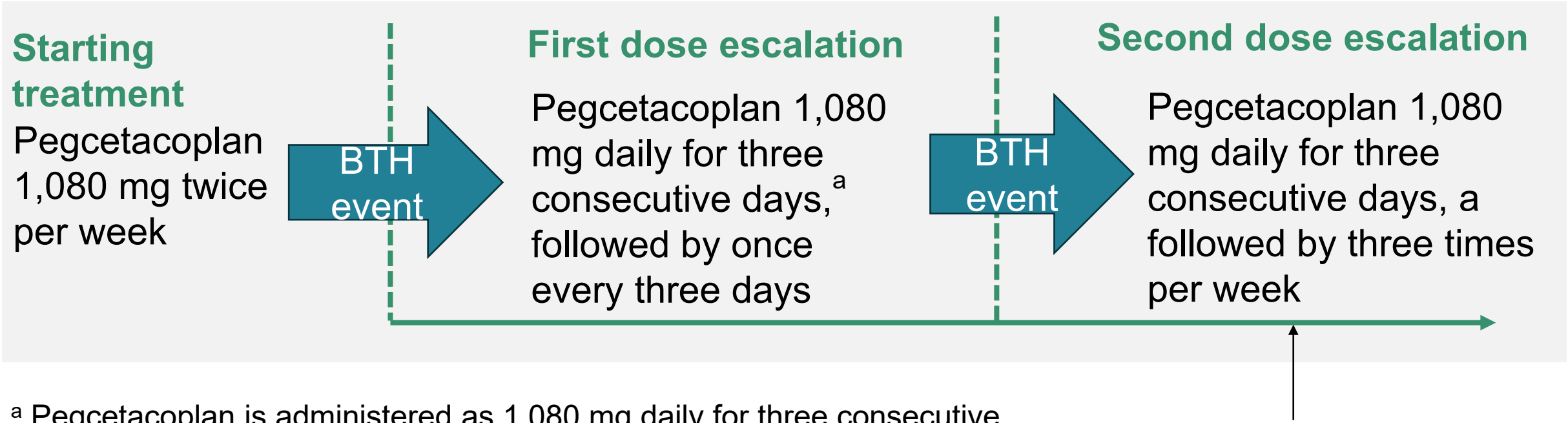
Treatment regimens for breakthrough haemolysis

Table: Progression of treatment regimens per pharmacokinetic BTH event



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

In company's original base case, majority of people eventually receive pegcetacoplan 3 times per week

BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor

Pegcetacoplan dose escalation assumption (1)

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

Pegcetacoplan dose escalation assumption (2)

Figure: Company dose escalation for pegcetacoplan from updated company base case

Pegcetacoplan dose escalation assumption (3)

Figure: EAG preferred dose escalation

Pegcetacoplan dose escalation assumption (4)

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

BTH, Breakthrough haemolysis; EAG, External Assessment Group

Breakthrough haemolysis events requiring intervention

Table: ALPHA trial BTH events and probability calculation for BTH events requiring intervention used in company's original base case

	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

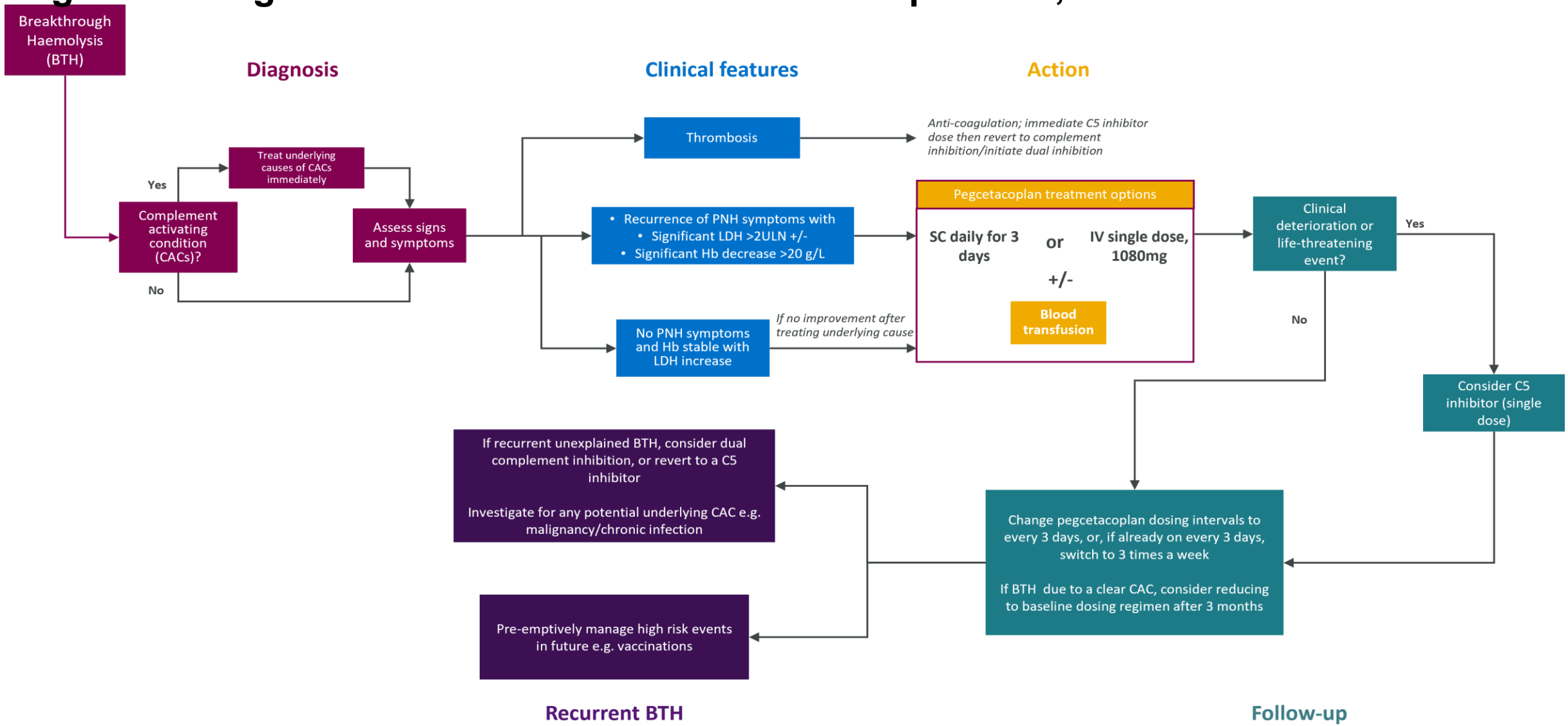
	PEGASUS - Pegcetacoplan	PEGASUS – C5i
PEGASUS: Week 1-16	4 events out of 41 people in 16 weeks of follow-up; 2.53%	9 events out of 39 people in 16 weeks of follow-up; 6.35%*
PEGASUS: Week 17+	15 events out of 77 people in 32 weeks of follow-up; 2.67%	N/A

* 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

Management of BTH events

Figure: Management flowchart for BTH in clinical practice; Griffin et al. 2024



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, 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
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
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.

AE, Adverse event; BTH, Breakthrough haemolysis; C5i, Complement component 5 inhibitor;

How company incorporated evidence into base case model (3)

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

Input	Assumption and evidence source
Discontinuation	**Danicopan + C5i**: discontinuation rates based on ALPHA 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

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

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
Set long term BTH rate for pegcetacoplan to double danicopan rate	Decrease
Set 78% of pegcetacoplan dose escalations to be temporary	Decrease
Apply 0.1%/cycle discontinuation rate for non-BTH events to both arms	Decrease
Remove disutility for pegcetacoplan	Decrease

Large Moderate Small

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

Scenarios applied to EAG preferred assumptions (1)

Table: Impact of scenarios applied to EAG preferred assumptions

Scenario (to EAG preferred assumptions)	Inc. NHB; Danicopan +C5i vs C5i monotherapy
Set long term BTH rate for pegcetacoplan equal to danicopan	Decrease
Set long term BTH rate for pegcetacoplan to triple danicopan rate	Increase
Set BTH dose escalation temporary to 70%	Increase
Set BTH dose escalation temporary to 90%	Decrease
Set BTH dose escalation temporary to 95%	Decrease
Change discontinuation rate on both arms to 0.05% per cycle	Decrease
Change discontinuation rate on both arms to 0.15% per cycle	Increase

Large Moderate Small

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

Scenarios applied to EAG preferred assumptions (2)

Table: Impact of scenarios applied to EAG preferred assumptions

Scenario (to EAG preferred assumptions)	Inc. NHB; Danicopan +C5i vs C5i monotherapy
Change danicopan discontinuation to 50% pegcetacoplan	Increase
Change danicopan discontinuation to 70% pegcetacoplan	Decrease
Change danicopan discontinuation to 80% pegcetacoplan	Decrease

Large Moderate Small

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