Iptacopan for treating paroxysmal nocturnal haemoglobinuria

HST committee [10 April 2024]

For screen – contains no confidential information

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Iptacopan for treating paroxysmal nocturnal haemoglobinuria

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

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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 (intra- or extravascular haemolysis)

Epidemiology

- 1 in 770,000 annual incidence in Great Britian
- 1 in 62,500 prevalence
- 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

Abbreviations: PNH: paroxysmal nocturnal haemoglobinuria

Patient perspectives

Submissions from PNH support

Survey of people with PNH (n=75) and carers (n=19) in England and Wales; n=6 having iptacopan

- Unmet need for treatment options – iptacopan has benefits as an oral tablet for people:
  - With damaged veins from repeated cannulations
  - Whose work or education are disrupted by infusions – allow more independence
  - Travelling more freely without being bound to infusion schedules
- Unmet need for treatments targeting extravascular haemolysis, associated with symptoms including anaemia, needing blood transfusions

"I was exhausted, struggled to swallow, was frequently breathless and suffered with chest and abdominal pain, plus severe headaches. I often had episodes of haemolysis with black urine and frequently jaundiced"

"Fortnightly treatment [with eculizumab] meant I often felt on a roller-coaster of symptoms as the positive impact of infusion would begin to wane relatively swiftly…"

"Sometimes a simple cold or sore throat was enough to trigger a severe haemolysis crisis"

"…[with iptacopan] I was in the normal range [blood count] for the first time in 17 years."

"[With iptacopan]…I no longer live in fear of haemolysis episodes and so my anxiety has greatly improved…I also have a long-term needle phobia and so daily tablets are a great improvement for me"

"[With iptacopan]…more independent, focused, active, dynamic, energetic, able to work, climb stairs, travelling longer distances, take longer walks. I can handle stress better. I do not have insomnia. My immunity has hugely improved"

"Iptacopan has given me options and opened some doors…options give us hope"

Abbreviations: PNH: paroxysmal nocturnal haemoglobinuria

Clinical perspectives

Submissions from Royal College of Pathologists, PNH UK national service, clinical experts on behalf of two NHSE commissioned services for PNH

- Treatment aim: PNH control, reduce complications, improve quality of life, normalise life expectancy
- Treatment response: Stop intravascular haemolysis, prevent thrombosis
    - For proximal complement inhibition, include Hb improvement >2 g/dL and fewer blood transfusion
- PNH pathway is well defined, and service is well established
- Unmet need:
    - Fatigue (from anaemia/extravascular haemolysis) – less productivity
    - Burden of existing treatments (administration – intravenous/subcutaneous)
- Iptacopan is a proximal complement inhibitor targeting intra- and extravascular haemolysis
    - Oral treatment – benefit people with poor venous access, needle aversion, limited dexterity, homecare nursing not needed
    - Subcutaneous pegcetacoplan (only other proximal inhibitor) is an option, but some have needle aversion or PNH does not respond to treatment, difficulties with travelling
- Stopping treatment: If PNH clone size remitted to <10% (5-10% people with PNH over several years)

Abbreviations: dL: decilitre; g: gram; Hb: haemoglobin; PNH: paroxysmal nocturnal haemoglobinuria

Equality considerations

No equality issues identified but company highlight:

- All current treatments for PNH administered via subcutaneous or IV infusion:
    - May disadvantage people with needle phobia
    - Some may find self-administering pegcetacoplan as subcutaneous infusion difficult or may not be able to – e.g. people with dexterity, visual, cognitive disabilities
    - Subcutaneous infusions may be unsuitable for people who are obese due to absorption issues

Abbreviations: PNH: paroxysmal nocturnal haemoglobinuria

Treatment pathway

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

Adults with paroxysmal nocturnal haemoglobinuria (PNH)

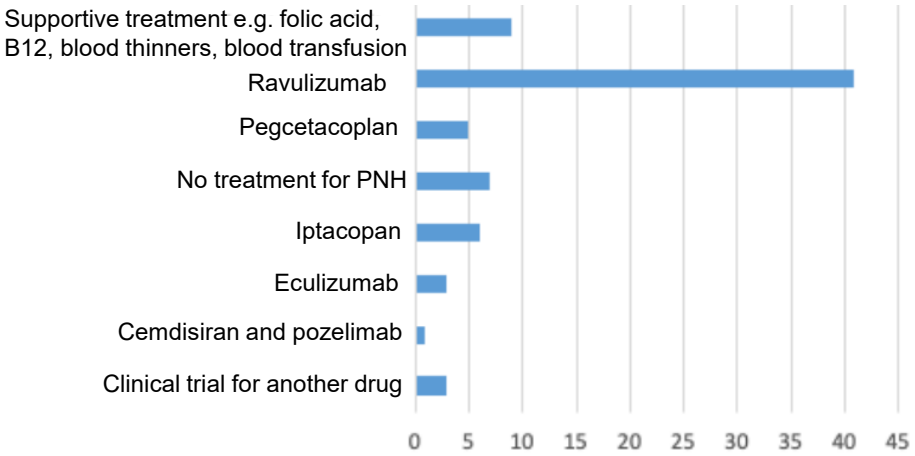
Complement inhibitor-naïve with haemolysis and clinical symptoms

- IV infusion C5 inhibitor: Eculizumab; TA698 Ravulizumab
- Oral FB inhibitor: Iptacopan

Complement inhibitor-experienced with residual anaemia

- *Remain on C5 inhibitor* — IV infusion C5 inhibitor: Eculizumab; TA698 Ravulizumab
- *Switch* — SC infusion C3 inhibitor: TA778 Pegcetacoplan
- *Switch* — Oral FB inhibitor: Iptacopan

Treatments used reported by people with PNH (PNH support)



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

EAG: ~35-40% have complement-inhibitor across UK in National PNH Service, most have ravulizumab initially

- Eculizumab considered useful particularly in emergency to avoid thrombosis in newly diagnosed people
- Renal failure or pregnancy – typically continue eculizumab (limited safety data for ravulizumab/pegcetacoplan)
- ~15% remaining anaemic after C5 inhibitor switch to pegcetacoplan (proportion is increasing)

Clinical experts: Ravulizumab is main initial treatment except for pregnancy indication (2022-23)

- Naïve: n=40 ravulizumab, n=1 eculizumab (pregnancy indication) (Leeds and Kings service)
- Experienced: ~n=271 ravulizumab, n=30-35 eculizumab; few switch for pregnancy or preference

Abbreviations: FB: factor B; PNH: paroxysmal nocturnal haemoglobinuria; SC: subcutaneous

*See appendix – Complement system overview

Technology (Fabhalta, Novartis)

Marketing authorisation	• Novartis anticipated indication: "Iptacopan is indicated for the treatment of adult patients with PNH who have haemolysis with clinical symptom(s) or who are anaemic after treatment with a complement inhibitor." • Positive CHMP opinion (March 2024): "Indicated as monotherapy in the treatment of adult patients with PNH who have haemolytic anaemia" • [redacted]
Mechanism of action	• Iptacopan is a proximal complement inhibitor and controls intra- and extravascular haemolysis mediated by the alternative pathway of the complement system • Iptacopan targets Factor B to selectively inhibit the alternative pathway of the complement system – which prevents the activity of C3 convertase and C5 convertase in the alternative pathway
Administration	• 200 mg capsules, twice daily, oral treatment • People switching from C5 inhibitors: Initiation no later than 1 week after last dose of eculizumab or no later than 6 weeks after last dose ravulizumab • Discontinuation not recommended unless clinically indicated
Price	• List price: [redacted] per 56 capsule pack • List price for 12 months of treatment: [redacted] • Patient access scheme is applicable

Abbreviations: CHMP: committee for medicinal products for human use; MHRA: medicines and healthcare products regulatory agency; PNH: paroxysmal nocturnal haemoglobinuria

Key issues

	Issue	ICER impact	Slide
Clinical	No direct comparative evidence for complement-inhibitor naïve population	Unknown	14
	Highly uncertain treatment effect of iptacopan vs pegcetacoplan for complement inhibitor-experienced with residual anaemia	Unknown	15
Model	No direct link between iptacopan trial endpoints and the transition probabilities used in the model	Unknown	18
	Modelled treatment sequences in the complement inhibitor-naïve population	Large	19
	Transition probabilities based on a lack of direct or indirect comparison of treatments	Unknown	20, 21
	Assessment time period from iptacopan trials	Large for complement inhibitor-experienced	22
	Annual discontinuation rates for iptacopan and pegcetacoplan	Large	23
	Treatment-specific health state utility values	Large	24, 25
	Concomitant eculizumab acquisition costs for people initiating pegcetacoplan	Small	26

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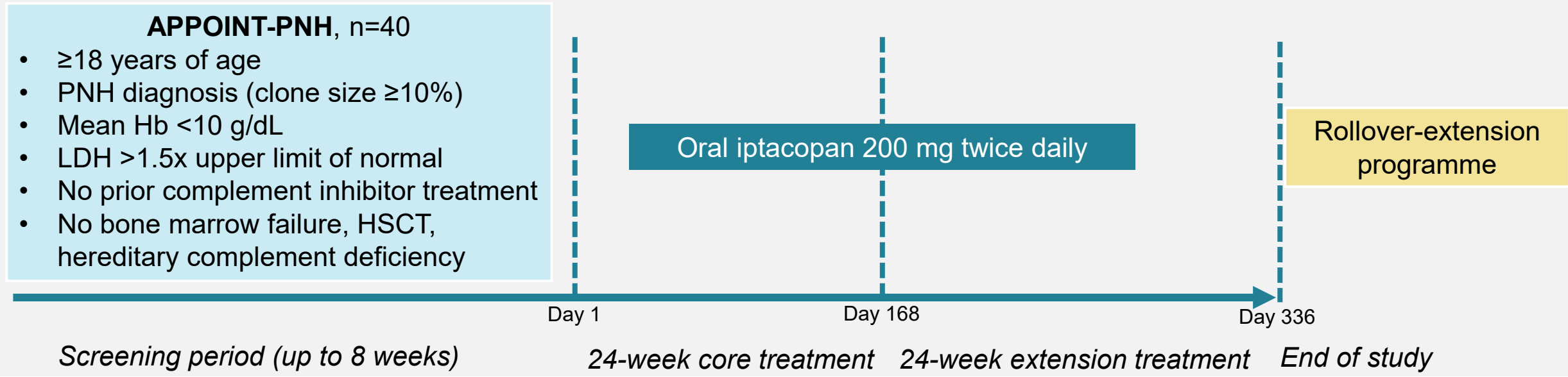
Key clinical trials – APPOINT-PNH

APPOINT-PNH: Phase 3, multi-centre, open-label, single-arm trial

- Evidence for complement inhibitor-naïve population with haemolysis with clinical symptoms



Locations: China, France, Germany, Italy, Republic of Korea, Malaysia, Singapore, UK (1 site in London, n=4)

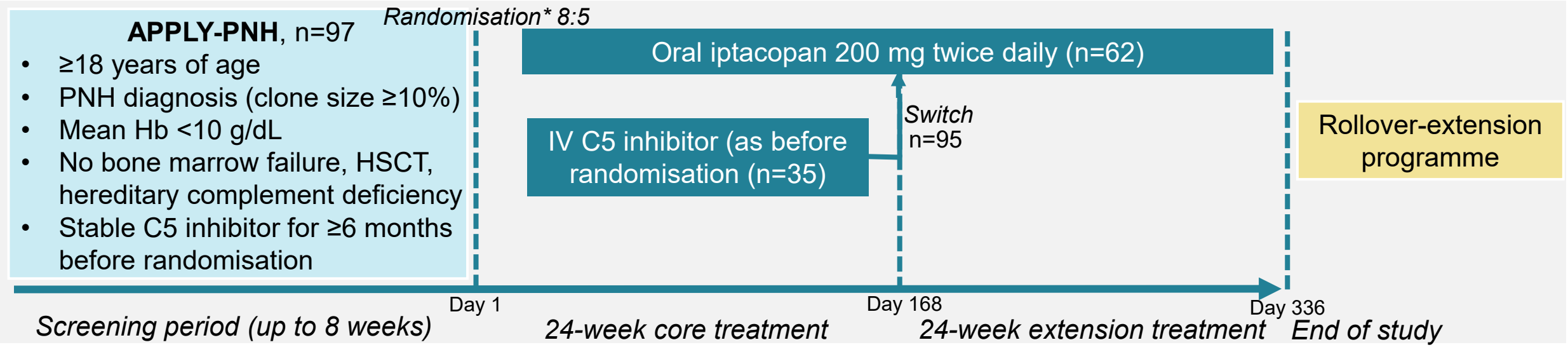
- **Primary outcome:** Haematological response (increase in Hb ≥2 g/dL from baseline in absence of pRBC transfusions)
- **Secondary outcomes:** Hb ≥12 g/dL; transfusion avoidance; change from baseline Hb levels factoring out effect of transfusion; LDH change from baseline; clinical BTH; absolute reticulocyte count change from baseline; FACIT-fatigue score change from baseline; MAVEs

Abbreviations: BTH: breakthrough haemolysis; dL: decilitre; g: gram; Hb: haemoglobin; HSCT: haematopoietic stem cell transplantation; LDH: lactate dehydrogenase; MAVE: major adverse vascular event; PNH: paroxysmal nocturnal haemoglobinuria; pRBC: packed red blood cells

Key clinical trials – APPLY-PNH

APPLY-PNH: Multi-centre, open-label, randomised controlled trial

- Evidence for complement inhibitor-experienced population with residual anaemia



*Randomisation stratified by prior C5 inhibitor treatment and RBC transfusions in preceding 6 months

Locations: Brazil, Czech Republic, France, Germany, Italy, Japan, Republic of Korea, Netherlands, Spain, Taiwan, UK (2 sites, n=11 in Leeds and London), USA

- **Co-primary outcomes: Haematological response (2 cut-offs):** Increase in Hb ≥2 g/dL from baseline; Hb ≥12 g/dL in absence of RBC transfusions at end of 24-week treatment period
- **Secondary outcomes:** Transfusion avoidance; change from baseline Hb levels; ratio to baseline in LDH; clinical BTH; absolute reticulocyte change from baseline; FACIT-fatigue score change from baseline; MAVEs

Abbreviations: BTH: breakthrough haemolysis; dL: decilitre; g: gram; Hb: haemoglobin; HSCT: haematopoietic stem cell transplantation; LDH: lactate dehydrogenase; MAVE: major adverse vascular event; PNH: paroxysmal nocturnal haemoglobinuria; RBC: red blood cell

APPOINT-PNH and APPLY-PNH primary results

APPOINT-PNH – Haematological response, n/N (marginal proportion)		
Primary endpoint	24-week*	48-week
≥2 g/dL increase from baseline Hb	31/33 (92.2)	38/39 (97.4)

Company: Pre-specified response threshold (15% lower bound of 95%CI in 24-week analysis) exceeded >5-fold
- Response maintained at 48 weeks

	APPLY-PNH – Haematological response, n/N (marginal proportion)				
	24-week*			48-week	
Co-primary endpoint	Iptacopan	C5 inhibitor	Adjusted treatment effect (95% CI)	Iptacopan	C5 inhibitor to iptacopan (at 24 weeks)
≥2 g/dL increase from baseline Hb	51/60 (82.3)	0/35 (2)	80.2 (71.2, 87.6)	51/62 (86.4%)	21/34 (72.4%)
≥12 g/dL Hb	42/60 (68.8)	0/35 (1.8)	67 (56.4, 76.9)	40/62 (67.8%)	17/34 (58.6%)

Company: Haematological response significantly greater for iptacopan than C5 inhibitors (24-week randomised period)
- 48-week data suggest haematological response maintained during 24-week extension in iptacopan arm and substantially increased among those switched from C5 inhibitors

*Primary analysis at 24-weeks required absence of transfusions as part of the endpoint; haematological endpoints in 48-week analysis include all Hb values irrespective of RBC transfusions

Abbreviations: CI: confidence interval; dL: decilitre; g: gram; Hb: haemoglobin; n: number

* See appendix – ITC overview and results

Key issues: No direct comparative evidence for complement inhibitor-naïve population

Background: APPOINT-PNH – Large statistically significant change from baseline to 24 weeks with iptacopan in reducing blood transfusions and increasing Hb, and some improvement in fatigue

Company: ITC for treatment effect vs C5 inhibitors (only use 24-week data and not used in economic model)

Unanchored MAIC
Study 301: RCT in complement-inhibitor-naïve PNH, comparing ravulizumab vs eculizumab

Favour iptacopan vs C5 inhibitors for all outcomes:
- Transfusion avoidance, % change from baseline LDH, change from baseline FACIT-Fatigue

EAG: Results highly uncertain – unanchored comparison and baseline Hb not adjusted
- Baseline Hb lower in APPOINT-PNH than Study 301 (bias against iptacopan)
- No data on relative effect of iptacopan on Hb response (primary outcome)

Augmented inverse probability weighting
APPEX (RWE) – weighted APPEX IPD to match APPOINT-PNH

Favour iptacopan vs C5 inhibitor for:
- Haematological response, change in LDH, change in reticulocyte count, absence of RBC transfusions, transfusion avoidance

EAG: Uncertain treatment effects – lack of control for potential selection bias/confounding in RWE
- Endpoints/eligibility aligned and includes IPD but uncertainty being unanchored comparison
- 1/85 from APPEX had ravulizumab – essentially iptacopan vs eculizumab not C5 inhibitor class

Abbreviations: Hb: haemoglobin; IPD: individual patient data; ITC: indirect treatment comparison; RBC: red blood cell; RCT: randomised controlled trial; RWE: real world evidence

* See appendix – ITC overview and results

Key issues: Uncertain treatment-effect of iptacopan vs pegcetacoplan in complement inhibitor-experienced population

Background: APPLY-PNH show significant greater treatment effects for iptacopan vs continued C5 inhibitor for Hb response and blood transfusion measures (24 weeks randomised period)

Company: Anchored ITC and unanchored MAIC using PEGASUS to estimate pegcetacoplan vs iptacopan

- PEGASUS: RCT pegcetacoplan vs eculizumab, 4-week run-in period with combined treatment then 16-week randomised period with monotherapy – ITC use 20-week timeframe out of 52-weeks (include randomised and run-in periods)
- Initially consider anchored comparison – clinicians advise eculizumab and ravulizumab sufficiently similar
- Prefer unanchored comparison because run-in period in PEGASUS involves those randomised to eculizumab also having pegcetacoplan – differences in control arms in APPLY-PNH and PEGASUS

EAG: Relative treatment effect not well established – results from 2 ITCs inconsistent in relative treatment effect estimates on Hb and transfusion avoidance outcomes

- Prefer to base conclusions on anchored comparison (as per TSD18)
- Small effective sample size for iptacopan group – uncertainty
- Discrepancies in C5 inhibitor comparator arms – PEGASUS includes a run-in period where pegcetacoplan and eculizumab are used

Are the ITCs robust for decision-making? Is the anchored or unanchored analysis more appropriate for decision-making?

Abbreviations: Hb: haemoglobin; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; TSD: technical support document

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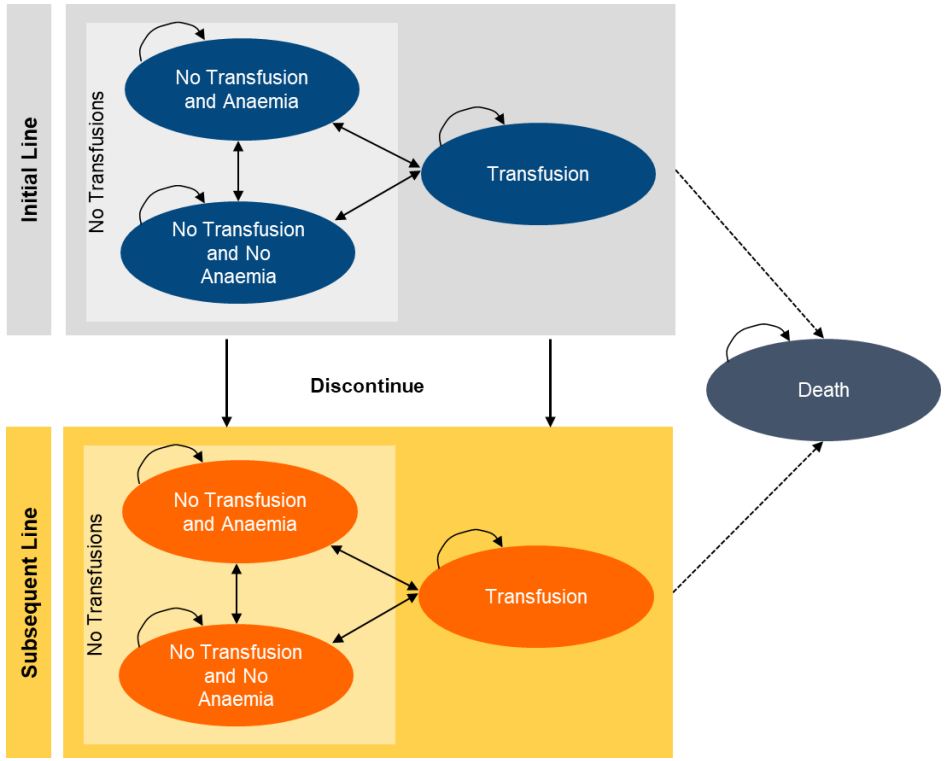
*See appendix – comparison of model with TA778 and TA698

Company's model overview

Cohort semi-Markov model – transition between mutually exclusive health states and at risk of all-cause mortality – consistent structure with TA778



Company: Inputs from clinical trial, published data, RWE

- ITC results do not inform model – health state definition need both Hb and transfusion outcome; transition probabilities derived independently
- Trial endpoints excluded – enable comparison with pegcetacoplan

Iptacopan affects **costs** by:

- No administration costs for iptacopan (oral tablet)
- Lower resource use (improved health states)
- Reducing incidence rate of BTH events

Iptacopan affects **QALYs** by:

- Increasing proportion of people not having transfusions and not having anaemia, and reducing proportion needing transfusions (improving HRQoL)
- Better HRQoL than C5 inhibitors

Assumptions with greatest ICER effect:

- Subsequent treatment line in complement inhibitor-naïve population
- Transition probabilities based on 48-week data vs 24-week data
- Transition probabilities for C5 inhibitors
- Annual treatment discontinuation for pegcetacoplan vs iptacopan
- Treatment-independent health state utility values

Abbreviations: BTH: breakthrough haemolysis; HRQoL; health-related quality of life; ICER; incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Key Issue: No direct link between iptacopan trial endpoints and transition probabilities in the model

Background: No direct link between statistical analysis of iptacopan trial endpoints and transition probabilities between health states in the model – unclear if model findings in line with outcomes in the trial

- Model includes same health states as in TA778 for pegcetacoplan model

Company: Direct comparisons of trial endpoints and modelled outcomes challenging

Transfusion outcomes:

- Trials focus on proportion transfusion-avoidant or –dependent, not considering transfusion frequency
- Model consider >1 transfusion possible – incorporate data on transfusions in 4-week time periods

Haematological response (defining anaemia):

- Trial: Hb ≥2 g/dL change from baseline; ≥12 g/dL, and no transfusion (24 weeks)
- Model defines health states on Hb threshold <10.5 g/dL
- Excluding trial endpoints from model allow comparison of iptacopan with pegcetacoplan – transition probabilities from TA778 use Hb <10.5 g/dL threshold anaemia definition (trials use Hb <10 g/dL inclusion criteria)

EAG: Uncertainty in treatment effectiveness evidence informing model without direct comparison of trial endpoints and modelled health state transitions

- Suggest alternative model structure/health states definition that more closely align with trial endpoints for comparison of iptacopan with C5 inhibitors – scenario where transition probabilities and utilities based on Hb<10 g/dL threshold for iptacopan and C5 inhibitors (small impact)

Are the modelled outcomes reflective of the clinical trial evidence?

Abbreviations: dL: decilitre; g: gram; Hb: haemoglobin

Key issue: Modelled treatment sequences in the complement inhibitor-naïve population

Background: Model allows 1-line subsequent treatment – naïve population with residual anaemia may have 2nd-line pegcetacoplan after ≥3 months C5 inhibitor (TA778) (considered complement-inhibitor experienced)

Treatment sequence		Discontinuation	Treatment switch
Complement inhibitor-naive	I → R	Continuous	Per model cycle
	E → P	One-time	24 weeks
	R → P	One-time	24 weeks
Complement inhibitor-experienced	I → R	Continuous	Per model cycle
	E	None	-
	R	None	-
	P → R	Continuous	Per model cycle

EAG: Likely to mask cost-effectiveness of iptacopan vs C5 inhibitors because these people considered complement inhibitor-experienced with residual anaemia while pegcetacoplan is not relevant comparator in naïve population (affects 30% who still have anaemia or have transfusions)

† Note ravulizumab and eculizumab assumed equal clinical effectiveness

EAG: Full range sequence possibilities not reflected – e.g. iptacopan → ravulizumab → pegcetacoplan

- Inconsistencies in naïve population: Use transition probabilities for 2nd-line ravulizumab from complement inhibitor-naïve population; use transition probabilities for 2nd-line pegcetacoplan from experienced population EAG base case: Iptacopan → ravulizumab vs ravulizumab/eculizumab† (no discontinuation) and using transition probabilities from naïve population for C5 inhibitors at 1st and 2nd line – consistent with approach used in experienced population (subsequent treatment not considered for C5 inhibitors)

Which modelled treatment sequence is appropriate for decision making?

Abbreviations: E: eculizumab; I: iptacopan; P: pegcetacoplan: R: ravulizumab

Key issue: Transition probabilities based on lack of direct or indirect comparison of treatments (1)

EAG: Large difference in outcomes of C5 inhibitor arms of APPLY-PNH and PEGASUS – concern comparison of iptacopan and pegcetacoplan is from 2 distinctively different trial populations

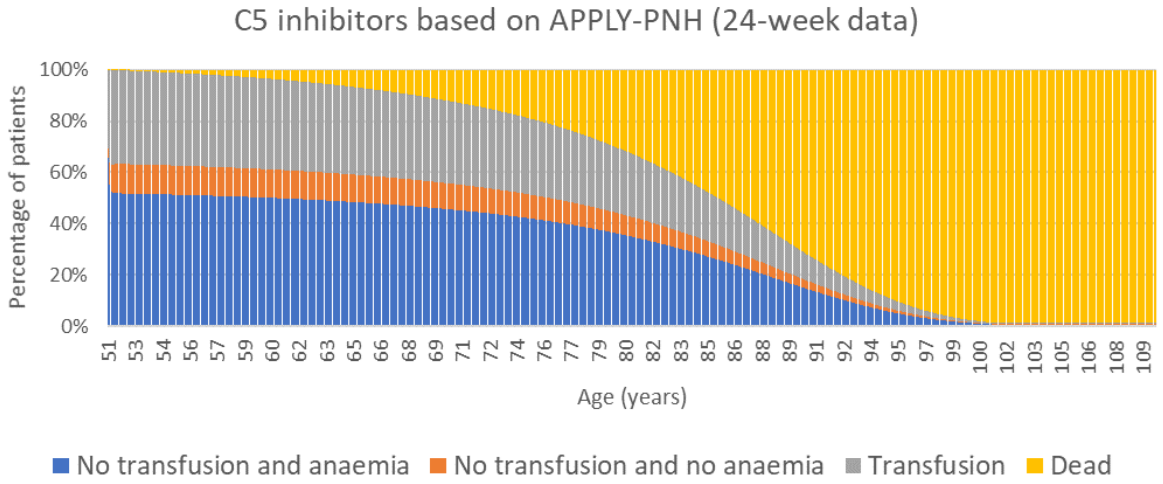
- Transition probabilities from PEGASUS based on week 4-16 period (exclude 4-week run-in with combination treatment) so unlikely reason for differences in C5 inhibitor outcomes seen

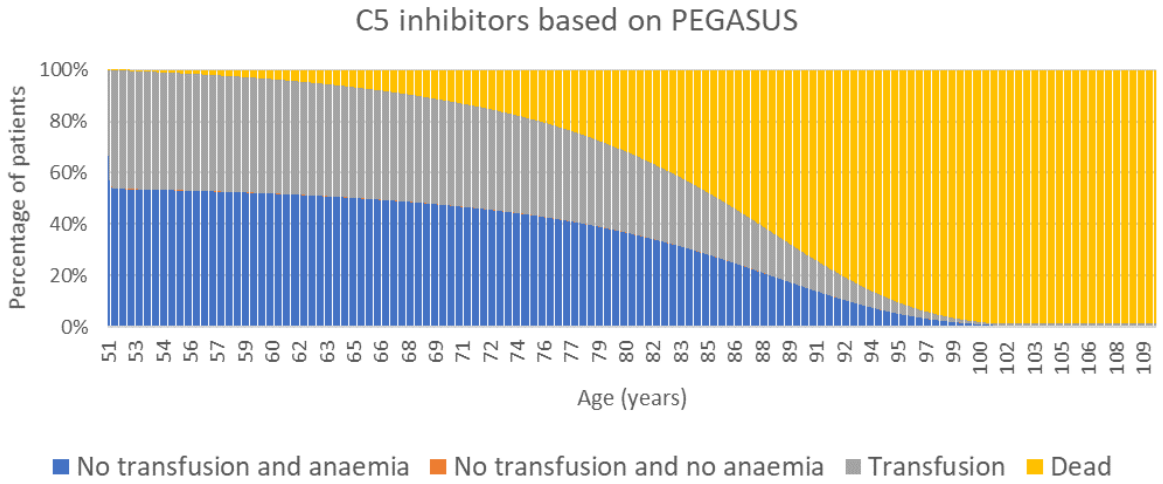
From:		To:		
Transition probabilities for C5 inhibitors (complement inhibitor-experienced)		No transfusion, no anaemia	No transfusion, anaemia	Transfusion
No transfusion, no anaemia	APPLY-PNH (24-week)	46%	48%	7%
	PEGASUS	3%	74%	23%
No transfusion, anaemia	APPLY-PNH (24-week)	8%	66%	27%
	PEGASUS	0.1%	65%	35%
Transfusion	APPLY-PNH (24-week)	6%	34%	60%
	PEGASUS	0.1%	40%	60%

In PEGASUS:

- Higher % need transfusions but % remaining transfusion dependent similar across trials
- Higher % in controlled anaemia state become uncontrolled but % uncontrolled anaemia similar across trials

Key issue: Transition probabilities based on lack of direct or indirect comparison of treatments (2)





EAG: Issue partially considered in scenario:

- Transition probabilities for C5 inhibitors based on PEGASUS rather than APPLY-PNH (as used in company base case for experienced population)

Should transition probabilities for C5 inhibitors come from APPLY-PNH or PEGASUS?

Key issue: Assessment time period from iptacopan trials

Background: Different assessment time periods used for inform transition probabilities, discontinuation and BTH rates for iptacopan and comparators

Transition probabilities used in company model (48-week data analysis)	
Iptacopan	• Transition probabilities, annual discontinuation, BTH rates updated • 24-week data used for utilities
C5 inhibitors	• 24-week data from APPLY-PNH used; same transition probabilities as 24-week • 24-week data used for utilities
Pegcetacoplan	• Same transition probabilities as 24-week • 24-week data used for utilities

EAG: Longer follow-up is best practice but concern 48-week analysis not making fair comparison of iptacopan, and comparator complement inhibitors

- Variation in assessment time for comparators and inconsistencies in data cut across modelled parameters
- EAG's cost-effectiveness results separated for 24-week and 48-week data to assess impact:
  - Complement inhibitor-naïve: No effect on conclusions except EAG scenario where modelled treatment sequence is iptacopan to ravulizumab vs C5 inhibitors (no discontinuation)
  - Complement inhibitor-experienced: Favour 48-week data than 24-week data – significant impact

Is the 24-week analysis or 48-week analysis more appropriate for decision making?

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Abbreviations: BTH: breakthrough haemolysis

*3.43% (24-week); 2.72% (48-week)

Key issue: Iptacopan and pegcetacoplan discontinuation rates

Background: Annual discontinuation informed by treatment-specific all-cause discontinuation rates in APPLY-PNH (iptacopan), PEGASUS (pegcetacoplan); discontinuation is independent of health state (equal rate)

Population	Treatment	Discontinuation type and probability
Complement inhibitor-naïve	I → R	Continuous; 3.43% per year (24-week)*
	E → P	One-time at 24 weeks; 30% people in transfusion or anaemia health states at 6 months
	R → P	
Complement inhibitor-experienced	I → R	Continuous; 3.43% per year (24-week)*
	E	N/A
	R	N/A
	P → R	Continuous; 16.13% per year

EAG: Concern large difference in discontinuation rates (16.13% vs 3.43%), may not reflect NHS

- 2nd-line ravulizumab in model associated with more uncontrolled anaemia and transfusion-dependence
- PEGASUS include non-treatment-specific reasons for discontinuing e.g. diffuse large B cell lymphoma
- Important driver of cost-effectiveness and uncertainty for iptacopan in experienced population
- Scenarios: 3.43% (2.72% 48-week), 5%, 10%

Clinical experts: Differences in discontinuation rates similar to clinical practice

- Reasons for discontinuation include intolerance from needle aversion or recurrent breakthrough events
- Anticipated to be less in iptacopan but less patient years usage to date compared with pegcetacoplan

Which annual discontinuation rate is appropriate?

Abbreviations: E: eculizumab; I: iptacopan; P: pegcetacoplan; R: ravulizumab

Key issue: Treatment-specific utility values (1)

Background: Model uses treatment-dependent health state utilities and predict better HRQoL with iptacopan

Company: EQ-5D-5L from trial mapped to 3L; utilities based on 24-week results (even for 48-week analysis)
- Scenario using treatment-independent pooled utilities with 0.025 disutility for eculizumab (as in TA778)
- Better HRQoL with iptacopan could be from oral administration, higher mean Hb, less fatigue (APPLY-PNH)

Health state	Treatment-dependent utility, mean (SE) [SD]		Pooled treatment-independent utility, mean (SE)	TA778
	Iptacopan	C5 inhibitors		
Baseline	0.79 (APPLY); 0.77 (APPOINT) [0.17]	0.69 [0.28]		-
No transfusion, no anaemia	0.879 (0.004)	0.775 (0.056)	0.878 (0.004)	0.809
No transfusion, anaemia	0.822 (0.008)	0.743 (0.015)	0.785 (0.009)	0.738
Transfusion	0.791 (0.015)	0.695 (0.021)	0.733 (0.015)	0.695

EAG: Unrealistic differences in treatment-dependent utility values between iptacopan and C5 inhibitors
- Observation size for Hb level and FACIT scores differ – e.g. 568 observations for iptacopan vs 8 for C5 inhibitors in 'no transfusion and no anaemia' health state – evidence of better scores for iptacopan is weak
- Baseline utility difference – may be due to small sample sizes and differences in population characteristics

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Abbreviations: Hb: haemoglobin; HRQoL: health-related quality of life; SD: standard deviation; SE: standard error

Key issue: Treatment-specific utility values (2)

Background: Model uses treatment-dependent health state utilities and predict better HRQoL with iptacopan

Method of administration of treatments	
Iptacopan	Oral tablet, twice daily
Eculizumab	2-weekly IV
Ravulizumab	8-weekly IV
Pegcetacoplan	Twice-weekly subcutaneous infusion

EAG: Greater utility for iptacopan modelled by higher probability of moving to improved health state and greater utility despite being in same health state as C5 inhibitor

- Only explanation seems to be method of administration – but size of difference is unrealistic
  - IV infusion every 8 weeks may be more convenient than twice-daily tablet
- Treatment-dependent utilities may lead to double-counting of treatment effect – benefits captured in health state transitions
- More appropriate to use treatment-independent health state utilities in line with TA778 and TA698 (scenario)
  - Reduces QALY gain by 50% in naïve population and 30% in experienced population

Are treatment-dependent or treatment-independent utilities appropriate?

Abbreviations: HRQoL: health-related quality of life; IV: intravenous

Key issue: Concomitant eculizumab acquisition costs for people starting pegcetacoplan in experienced population

Background: Model includes 4-week concomitant eculizumab acquisition cost for 12% starting pegcetacoplan in complement inhibitor-experienced population to reflect SmPC

Company:

- Pegcetacoplan SmPC recommend overlap transition period for people switching from C5 inhibitors
  - Continue C5 inhibitor at current dose for 4 weeks while starting pegcetacoplan
- Complement inhibitor-experienced base case: 12% switch from eculizumab; 88% from ravulizumab (based on clinical experts, UK medical advisory board)
- Weighted average cost C5 inhibitors calculated and added to pegcetacoplan cost in first cycle
- No additional cost for ravulizumab – administered every 8 weeks, assume all switch within 4 weeks of last dose

EAG: Concomitant eculizumab acquisition costs should be excluded

- Transition probabilities for pegcetacoplan based on randomised controlled period of PEGASUS from weeks 4-16 (people had either pegcetacoplan or eculizumab) not 4-week run-in where both treatments given
- Scenario excluding concomitant costs in complement inhibitor-experienced population (small impact on ICER)

Should concomitant acquisition costs for eculizumab be included or excluded? Are an overlap of treatments likely to happen in NHS practice?

Abbreviations: SmPC: summary of product characteristics

Summary of differences in company and EAG assumptions

Assumption		Company base case	EAG base case*
Complement inhibitor-naïve population	Modelled treatment sequence	Iptacopan to ravulizumab vs C5 inhibitor to pegcetacoplan	Iptacopan to ravulizumab vs C5 inhibitors (where C5 inhibitor considered current standard care)
	Utility values	Treatment-dependent	Treatment-independent
Complement inhibitor-experienced population	Discontinuation rate	16.13% per year (pegcetacoplan)	10% per year (pegcetacoplan)
	Utility values	Treatment-dependent	Treatment-independent
	Costs	Concomitant eculizumab acquisition costs for people starting pegcetacoplan	Excluding concomitant eculizumab acquisition costs

EAG scenarios not in base case

- Transition probabilities and utility based on Hb <10 g/dL for iptacopan and C5 inhibitors (Hb <10.5 g/dL for pegcetacoplan)
- Transition probabilities for C5 inhibitors based on PEGASUS rather than APPLY (experienced population)
- 1 treatment-line
- Discontinuation: Same discontinuation (3.43%) for iptacopan and pegcetacoplan (2.72% in 48-week); 5% for pegcetacoplan

*All EAG results presented separately for 24-week and 48-week data

Cost-effectiveness results

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

Iptacopan for treating paroxysmal nocturnal haemoglobinuria

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

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Key issues

	Issue	ICER impact	Slide
Clinical	No direct comparative evidence for complement-inhibitor naïve population	Unknown	14
	Highly uncertain treatment effect of iptacopan vs pegcetacoplan for complement inhibitor-experienced with residual anaemia	Unknown	15
Model	No direct link between iptacopan trial endpoints and the transition probabilities used in the model	Unknown	18
	Modelled treatment sequences in the complement inhibitor-naïve population	Large	19
	Transition probabilities based on a lack of direct or indirect comparison of treatments	Unknown	20, 21
	Assessment time period from iptacopan trials	Large for complement inhibitor-experienced	22
	Annual discontinuation rates for iptacopan and pegcetacoplan	Large	23
	Treatment-specific health state utility values	Large	24, 25
	Concomitant eculizumab acquisition costs for people initiating pegcetacoplan	Small	26

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Thank you.

Supplementary appendix

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Recent NICE appraisals for paroxysmal nocturnal haemoglobinuria

Recent NICE evaluations

Technology appraisal	Drug	Recommendation
NICE TA778 (2022)	Pegcetacoplan	Recommended within its marketing authorisation as an option for PNH in adults who have anaemia after at least 3 months of treatment with a C5 inhibitor
NICE TA698 (2021)	Ravulizumab	Recommended within its marketing authorisation as an option for PNH in adults with haemolysis with clinical symptoms suggesting high disease activity or whose condition is clinically stable after eculizumab for at least 6 months

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Abbreviations: PNH: paroxysmal nocturnal haemoglobinuria

Decision problem

	Final scope	Company
Population	Adults with PNH	Adults with PNH: • Complement inhibitor-naïve and haemolysis with clinical symptoms • Complement inhibitor-experienced with anaemia after complement inhibitor treatment
Comparators	Eculizumab; ravulizumab; pegcetacoplan; danicopan with C5 inhibitor (subject to ongoing NICE evaluation)	• Complement inhibitor-naïve: eculizumab; ravulizumab (Pegcetacoplan restricted to people with anaemia after ≥3 months C5 inhibitor) • Complement inhibitor-experienced with anaemia: eculizumab; ravulizumab; pegcetacoplan • Danicopan – no current license and not expected established NHS practice before ID6176
Outcomes	OS; intra- and extra-vascular haemolysis; breakthrough haemolysis; transfusion avoidance; haemoglobin; thrombotic events; adverse treatment effects; HRQoL	As per scope – intravascular haemolysis measured by lactate dehydrogenase; extravascular haemolysis measured by reticulocyte count

EAG: Real-world mortality may be higher (aplastic anaemia typically excluded from trials)

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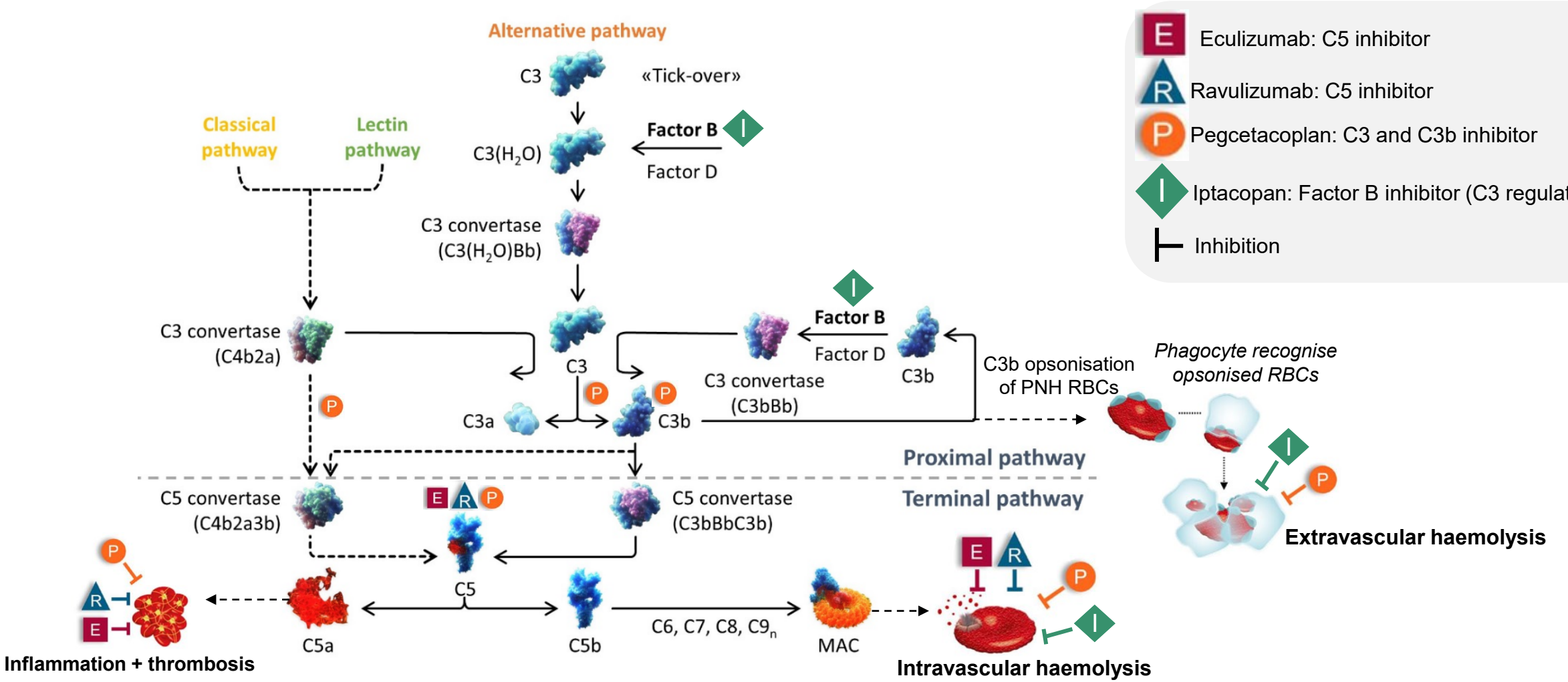
Abbreviations: HRQoL; health-related quality of life; PNH: paroxysmal nocturnal haemoglobinuria

Treatment pathway – complement system



Source: Company submission figure 1 and adapted using (Wong, 2022)

Wong RSM. Safety and efficacy of pegcetacoplan in paroxysmal nocturnal hemoglobinuria. Therapeutic Advances in Hematology. 2022;13.

Abbreviations: MAC: membrane attack complex; PNH: paroxysmal nocturnal haemoglobinuria; RBC: red blood cell

Key issues: Lack of evidence on rare events and longer-term effects of iptacopan

Background: Evidence limited to 2 small studies powered for haematological response changes – rare events and long-term effectiveness and safety not established (48 weeks treatment data)

Company: PNH is ultra-rare, evidence generation challenges – may affect reliability of clinical study results

- Sample size in APPOINT-PNH (n=40) and APPLY-PNH (n=62, iptacopan; n=35, C5 inhibitors) similar to PEGASUS in TA778 (n=41, pegcetacoplan; n=39, eculizumab)
- APPLY-PNH show statistically significant improvement in efficacy vs C5 inhibitors despite sample size

EAG: Limited comparative evidence, long-term evidence, small sample sizes – unknown longer-term risks of BTH and thrombosis and detecting rare but clinically significant events

- Results show 0 BTH in 24-weeks (APPOINT-PNH): Clinical advice – BTH more likely in real-world with compliance issues, so inappropriate to assume 0 long-term BTH
- No evidence on longer-term dose modifications or treatment compliance
- Extension study for long-term safety, tolerability and efficacy of iptacopan in PNH due completion June 2026*

*clinicaltrials.gov: estimated completion date Oct 2027

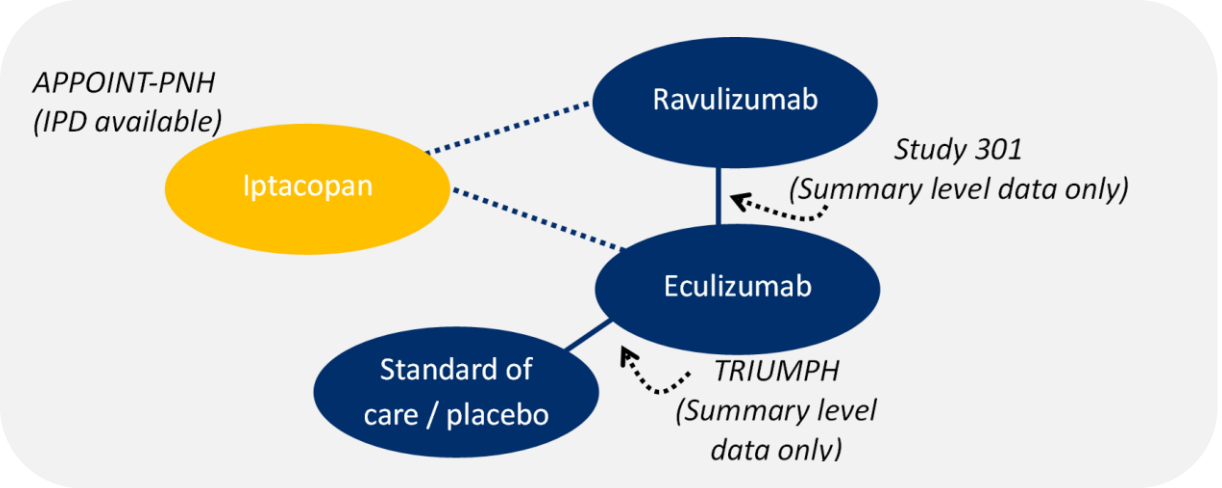
What is the committee's view on the limited evidence available?

Abbreviations: BTH: breakthrough haemolysis; PNH: paroxysmal nocturnal haemoglobinuria

Indirect treatment comparison for complement-inhibitor naïve population

Methods

- Population-adjusted unanchored ITC, with IPD for iptacopan from APPOINT-PNH and summary-level data for ravulizumab and eculizumab from Study 301
- No exclusions from APPOINT-PNH because high overlap in eligibility criteria
- Difference in Hb inclusion criteria not addressed, Study 301 had broader population
- Adjustment factors: Age, sex, % transfusion free in prior 12 months, baseline LDH, MAVE history – validated by UK clinicians
- Baseline Hb not included in re-weighting since analysis did not converge
- ITCs conducted for key endpoints in both trials – excluded haematological responder endpoints from APPOINT-PNH and change from baseline Hb (not reported in Study 301)



- *Study 301: RCT in complement-inhibitor-naïve PNH, comparing ravulizumab vs eculizumab*
- *TRIUMPH: Placebo-controlled eculizumab study – only including people with ≥4 transfusions during previous 12 months*
- Company prefer Study 301 over TRIUMPH – includes ravulizumab as most relevant comparator and larger sample size
- TRIUMPH eligibility criteria not representative of current UK population

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Abbreviations: Hb: haemoglobin; IPD: individual participant data; ITC: indirect treatment comparison; LDH: lactate dehydrogenase; MAVE: major adverse vascular event; PNH: paroxysmal nocturnal haemoglobinuria

Results for indirect treatment comparison for complement-inhibitor naïve population

Statistically significant

APPOINT-PNH vs Study 301	Transfusion avoidance (95%CI)	% change in baseline LDH (95%CI)	Change from baseline in FACIT-Fatigue score (95%CI)
Iptacopan (ESS=31)	78.6%	-85.1 (-87.8, -82.3)	10.9 (7.2, 14.5)
Ravulizumab (n=125)	73.5%	-76.8 (-80.0, -73.7)	7.1 (5.6, 8.6)
Eculizumab (n=121)	66.1%	-76.0 (-79.2, -72.8)	6.4 (4.9, 8.0)
Iptacopan vs ravulizumab	OR = 1.3 (0.5, 3.7)	MD = -8.2 (-13.3, -3.2)	MD = 3.8 (-1.4, 8.9)
Iptacopan vs eculizumab	OR = 1.9 (0.7, 5.3)	MD = -9.1 (-14.1, -4.0)	MD = 4.5 (-0.7, 9.6)

APPOINT-PNH vs APPEX	Iptacopan vs C5 inhibitors, average treatment effect (95%CI)
≥2 g/dL increase Hb from baseline, no RBC transfusions (% difference)	68.4 (41, 95.8)
Hb ≥12 g/dL, no RBC transfusions (% difference)	53.5 (31.6, 75.5)
Transfusion avoidance (% difference)	38.9 (15.1, 62.6)
% change from baseline in LDH (U/L) (ratio % levels to baseline)	0.52 (0.4, 0.7)
Change from baseline reticulocyte count ($x10^9$/L)	-75.8 (-107.2, -44.4)

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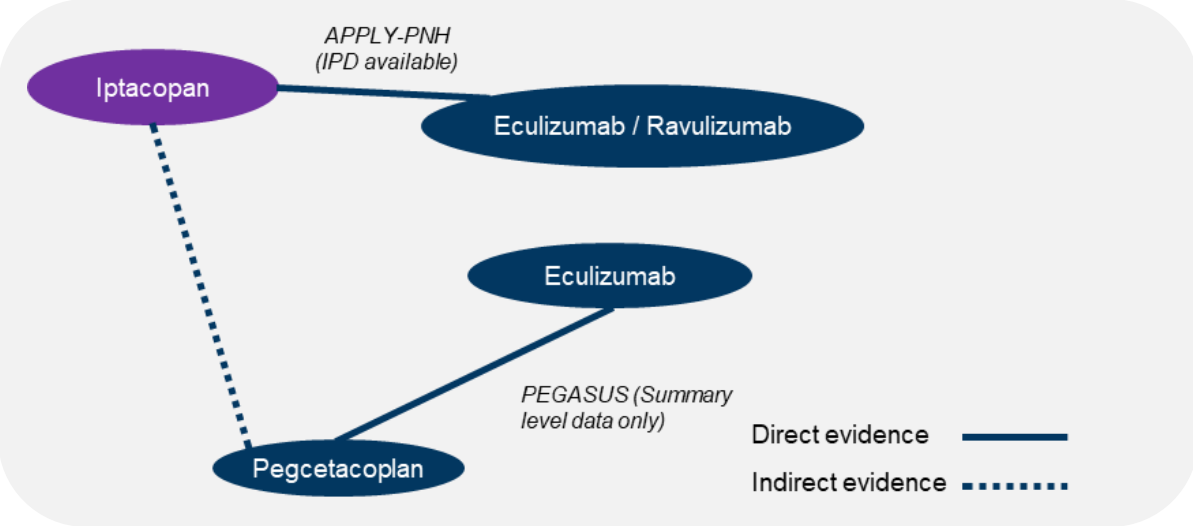
Abbreviations: dL: decilitre; g: gram; Hb: haemoglobin; LDH: lactate dehydrogenase; MD: mean difference; OR: odds ratio; PNH: paroxysmal nocturnal haemoglobinuria; RBC: red blood cell

Indirect treatment comparison for complement-inhibitor experienced population

Methods

Population-adjusted ITC – APPLY-PNH IPD and summary data from PEGASUS

- Exclude people from APPLY-PNH not eligible to enrol in PEGASUS
- Remaining re-weighted to balance pre-treatment characteristics with PEGASUS population
- Adjustment factors: Hb, LDH, age, reticulocytes, sex, % transfusion free in previous 12 months
- 20-week time-period used from APPLY-PNH to align with pegcetacoplan treatment time in PEGASUS



- *PEGASUS: Phase 3 RCT evaluating efficacy and safety of pegcetacoplan vs eculizumab in PNH with residual anaemia (Hb <10.5 g/dL) despite eculizumab for ≥3 months*
- *4-week run-in period where all continue eculizumab dose plus 2x weekly pegcetacoplan*
- *Randomisation to pegcetacoplan monotherapy or eculizumab monotherapy (16-week period)*

Abbreviations: dL: decilitre; g: grams; Hb: haemoglobin; IPD: individual participant data; ITC: indirect treatment comparison; LDH: lactate dehydrogenase; PNH: paroxysmal nocturnal haemoglobinuria; RCT: randomised controlled trial

Results for indirect treatment comparison for complement-inhibitor experienced population

		Change from baseline in Hb (95% CI)		Transfusion avoidance
		Excluding post-transfusion data	Including post-transfusion data	
Iptacopan (ESS=15)		3.4 (3.0, 3.8)	3.4 (3.0, 3.8)	98.7%
Pegcetacoplan (n=41)		2.4 (1.7, 3.1)	2.7 (2.2, 3.2)	85.4%
Eculizumab/ravulizumab APPLY-PNH (ESS=7)		[redacted]	[redacted]	[redacted]
Eculizumab PEGASUS (n=39)		-1.5 (-2.8, -0.2)	-0.03 (-0.5, 0.5)	15.4%
Iptacopan vs pegcetacoplan	Unanchored ITC	MD: 1.0 (95%CI: 0.2, 1.8)	MD: 0.76 (95%CI: 0.1, 1.4)	OR: 12.71 (95%CI: 1.9, 86.2)
	Anchored ITC	MD: [redacted] (95%CI: [redacted])	MD: [redacted] (95%CI: [redacted])	OR: [redacted] (95%CI: [redacted])

Statistically significant

Abbreviations: CI: confidence interval; ESS: effective sample size; Hb: haemoglobin; ITC: indirect treatment comparison; MD: mean difference; OR: odds ratio; PNH: paroxysmal nocturnal haemoglobinuria;

Comparison of assumptions with previous appraisals

Assumption	ID6176 iptacopan	TA778 pegcetacoplan	TA698 ravulizumab
Model structure	Semi-Markov	Semi-Markov	Semi-Markov
Health states	4 health states: No transfusion and no anaemia, no transfusion and anaemia, transfusion, death • Base case: no anaemia = Hb ≥10.5 g/dL; anaemia = Hb <10.5 g/dL	4 health states: No transfusion and Hb ≥10.5 g/dL, no transfusion and Hb <10.5 g/dL, transfusion, death	10 health states: 8 BTH health states, death, spontaneous remission (scenario only)
Discontinuation	Treatment-specific discontinuation rates	Some discontinuation for pegcetacoplan	No discontinuation
Subsequent treatments	1 subsequent treatment line based on same health state as initial treatment, continue subsequent for remainder time horizon	Subsequent line of treatment not considered	Subsequent line of treatment not considered
Cycle length	4 weeks (half-cycle correction)	4 weeks	2 weeks
Clinical efficacy and safety	APPOINT-PNH, APPLY-PNH, APPEX study (IPD), PEGASUS (published)	PEGASUS	Study 301, Study 302
Utilities	EQ-5D-5L from APPOINT-PNH and APPLY-PNH mapped to EQ-5D-3L; scenario mapping EORTC from trials • Treatment-specific utilities	EORTC QLQ-C30 mapped to EQ-5D-3L • Treatment-independent utilities	EORTC QLQ-C30 mapped to EQ-5D-3L • Treatment-independent utilities

Abbreviations: BTH: breakthrough haemolysis; dL; decilitre; g: gram; Hb: haemoglobin

How company incorporated evidence into model

Input	Complement inhibitor-naïve	Complement inhibitor-experienced
Mean age (SD)	42.1 (15.8)	51 (16.8)
Mean weight, kg (SD)	70.1 (12.7)	71.6 (18.8)
% male	57.5%	30.9%
Health state distribution baseline	75% anaemia; 25% transfusion; 0% no transfusion, no anaemia	74.2% anaemia; 25.8% transfusion; 0% no transfusion, no anaemia
Efficacy	Transition probabilities from APPOINT-PNH for iptacopan; IPD from APPEX for C5 inhibitors	Transition probabilities from APPLY-PNH IPD for iptacopan and C5 inhibitors; PEGASUS (Hakimi e al.) for pegcetacoplan

Abbreviations: IPD: individual participant data

Cost-effectiveness results for complement-inhibitor naïve population (24 weeks)

Scenario (to company base case)	ICER (£/QALY): iptacopan vs.	
	Eculizumab	Ravulizumab
• Hb threshold level 10 g/dL	[redacted]	[redacted]
• 1 treatment line (no discontinuation)	[redacted]	[redacted]
• Modelled treatment sequence	[redacted]	[redacted]
• Treatment-independent health state utilities	[redacted]	[redacted]

Large Moderate Small

Cost-effectiveness results for complement-inhibitor naïve population (48 weeks)

Scenario (to company base case)	ICER (£/QALY): iptacopan vs.	
	Eculizumab	Ravulizumab
• Hb threshold level 10 g/dL	[redacted]	[redacted]
• 1 treatment line (no discontinuation)	[redacted]	[redacted]
• Modelled treatment sequence	[redacted]	[redacted]
• Treatment-independent health state utilities	[redacted]	[redacted]

Large Moderate Small

Cost-effectiveness results for complement-inhibitor experienced population (24 weeks)

Scenario (applied to company base case)	ICER (£/QALY): iptacopan vs.		
	Eculizumab	Ravulizumab	Pegcetacoplan
• Hb threshold level 10 g/dL	[redacted]	[redacted]	[redacted]
• Transition probabilities from PEGASUS for C5 inhibitors	[redacted]	[redacted]	[redacted]
• 1 treatment line (no discontinuation)	[redacted]	[redacted]	[redacted]
• No concomitant eculizumab acquisition costs when starting pegcetacoplan	[redacted]	[redacted]	[redacted]
• Same annual discontinuation for iptacopan and pegcetacoplan (3.43%)	[redacted]	[redacted]	[redacted]
• Higher discontinuation rate for pegcetacoplan 5% per year	[redacted]	[redacted]	[redacted]
• Higher discontinuation rate for pegcetacoplan 10% per year	[redacted]	[redacted]	[redacted]
• Treatment-independent health state utility values	[redacted]	[redacted]	[redacted]

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Cost-effectiveness results for complement-inhibitor experienced population (48 weeks)

Scenario (applied to company base case)	ICER (£/QALY): iptacopan vs.		
	Eculizumab	Ravulizumab	Pegcetacoplan
• Hb threshold level 10 g/dL	[redacted]	[redacted]	[redacted]
• Transition probabilities from PEGASUS for C5 inhibitors	[redacted]	[redacted]	[redacted]
• 1 treatment line (no discontinuation)	[redacted]	[redacted]	[redacted]
• No concomitant eculizumab acquisition costs when starting pegcetacoplan	[redacted]	[redacted]	[redacted]
• Same annual discontinuation for iptacopan and pegcetacoplan (2.72%)	[redacted]	[redacted]	[redacted]
• Higher discontinuation rate for pegcetacoplan 5% per year	[redacted]	[redacted]	[redacted]
• Higher discontinuation rate for pegcetacoplan 10% per year	[redacted]	[redacted]	[redacted]
• Treatment-independent health state utility values	[redacted]	[redacted]	[redacted]

Large Moderate Small

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