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# Terminal Complement Blockade in Patients with PNH

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*Chair, Canadian PNH Network ([www.PNHnetwork.ca](http://www.PNHnetwork.ca))*

# Disclosures

## Speakers

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## Disclosures

**Employment:** University Health Network, Toronto, Canada

**Consultancy:** Alexion/AstraZeneca, Amgen, Apellis, BioCryst, Novartis, Ra Pharmaceuticals, Roche, Regeneron, Sobi, Sanofi, Takeda

**Speaking Honoraria:** Alexion/AstraZeneca, Amgen, Novartis, Sobi

**Membership on Trial/Board Advisory Committees:** Amgen, Novartis, IPIG PNH Registry

# Learning Objectives

- Describe the pathophysiology, epidemiology, and mortality risk of paroxysmal nocturnal hemoglobinuria (PNH)
- Review the long-term data and clinical implications of C5 inhibition with ravulizumab (Ultomiris<sup>®</sup>) in patients with PNH
- Explore the mechanisms and management of breakthrough hemolysis
- Discuss an approach to shared-decision making for PNH treatment



# Paroxysmal Nocturnal Hemoglobinuria<sup>1-3</sup>

Acquired non-malignant clonal abnormality (*PIGA*) of hematopoietic stem cells

- Ultra-rare (~2/million annually; 15/million population)
- Absent GPI-linked complement regulators CD55/59
- Triad of DAT-neg hemolysis, thrombosis, BMF

Common clinical features

- Fatigue, chest pain, dyspnea, abdominal pain, renal failure/nephropathy, impaired QoL
- Smooth muscle dystonia (ex. pHTN, dysphagia, ED)

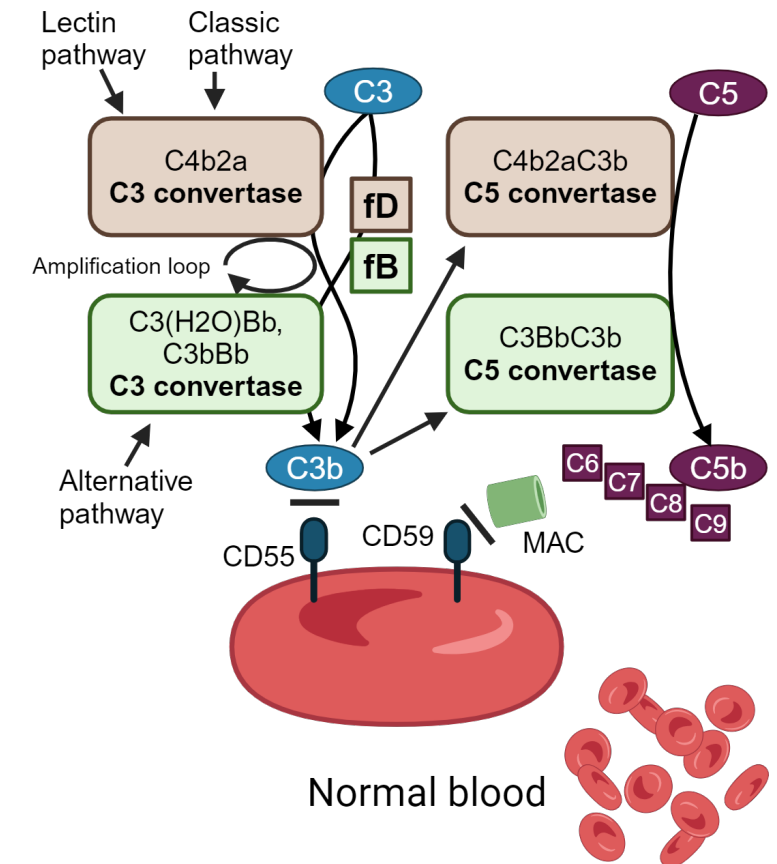


Figure generated by BioRender.com

C, complement component; CD, cluster of differentiation; fB, factor B; fD, factor D; GPI, glycosylphosphatidylinositol; MAC, membrane attack complex; pHTN, pulmonary hypertension Figure generated by BioRender.com



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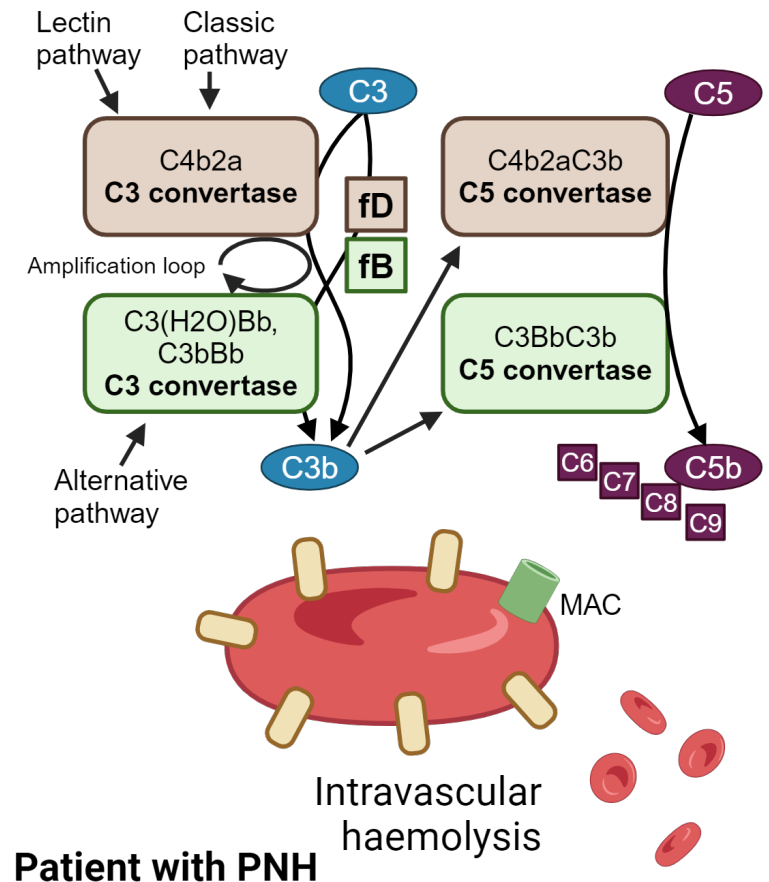
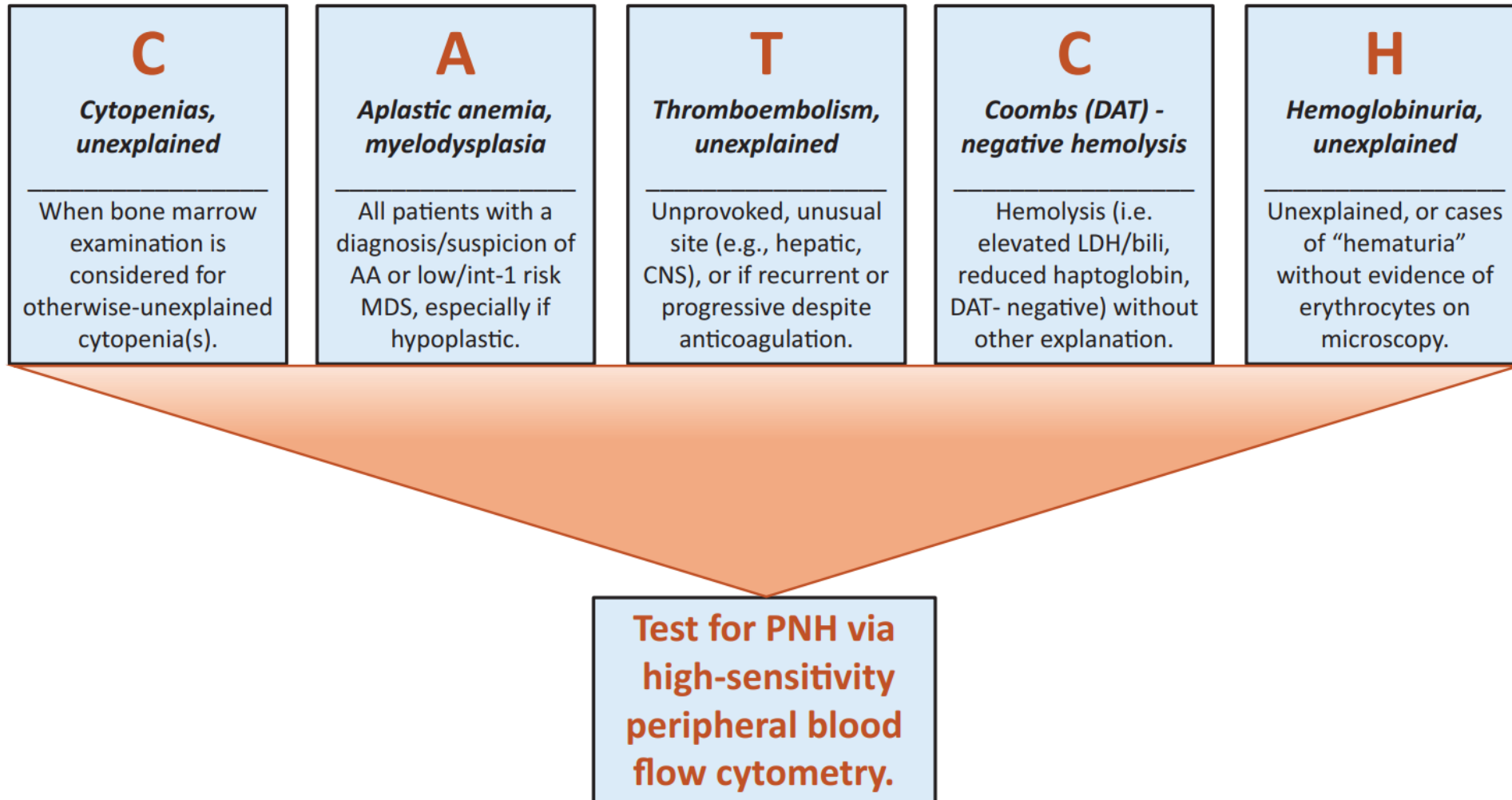


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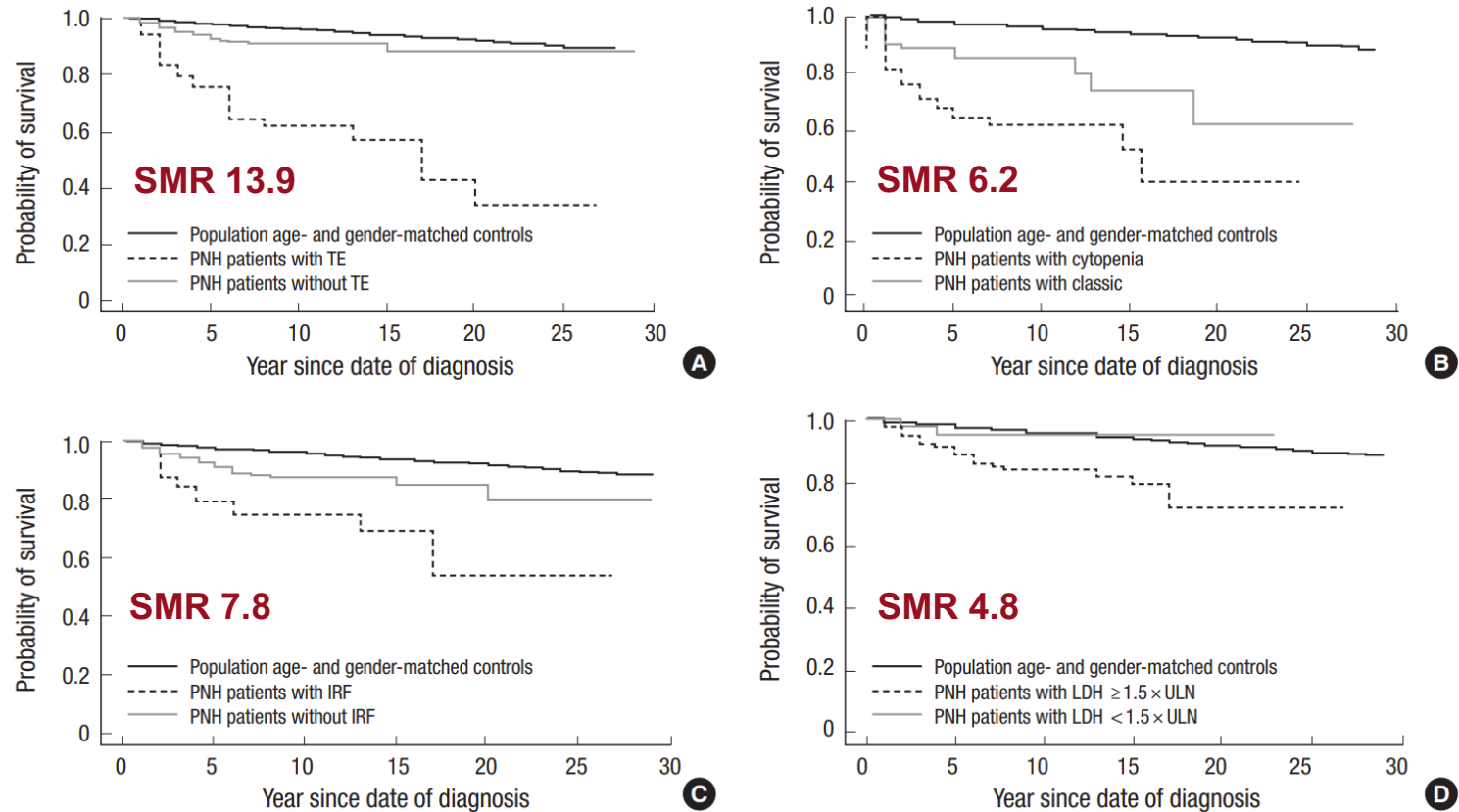
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# High-Yield Scenarios to “CATCH” PNH



# Increased Mortality Risk in Patients with PNH



**Fig. 2.** Kaplan-Meier survival of PNH patients compared with age- and gender-matched general population. **(A)** Patients with TE had a 14-fold higher mortality rate compared with the general population (standard mortality ratio [SMR] = 13.9; 95% confidence interval [CI], 8.2-19.6;  $P < 0.001$ ). **(B)** Patients with cytopenia had a mortality rate 6.2-fold greater than the age- and gender-matched general population (SMR = 6.2; 95% CI, 4.7-9.3;  $P < 0.001$ ). **(C)** Patients with impaired renal function (IRF) had a mortality rate 7.8-fold greater than the age- and gender-matched general population (SMR = 7.8; 95% CI, 3.9-11.8;  $P < 0.001$ ). **(D)** PNH patients with lactate dehydrogenase (LDH)  $\geq 1.5$  times the upper limit of normal (ULN) had a 5.0-fold greater risk for mortality compared with patients with LDH  $< 1.5 \times$  ULN (95% CI, 1.15-21.70;  $P = 0.009$ ). PNH patients with LDH  $\geq 1.5 \times$  ULN had a 4.8-fold higher mortality rate compared with the general population (SMR = 4.8; 95% CI, 3.0-6.6;  $P < 0.001$ ).

# Treatment Options for PNH

# Available Complement Inhibitors in PNH

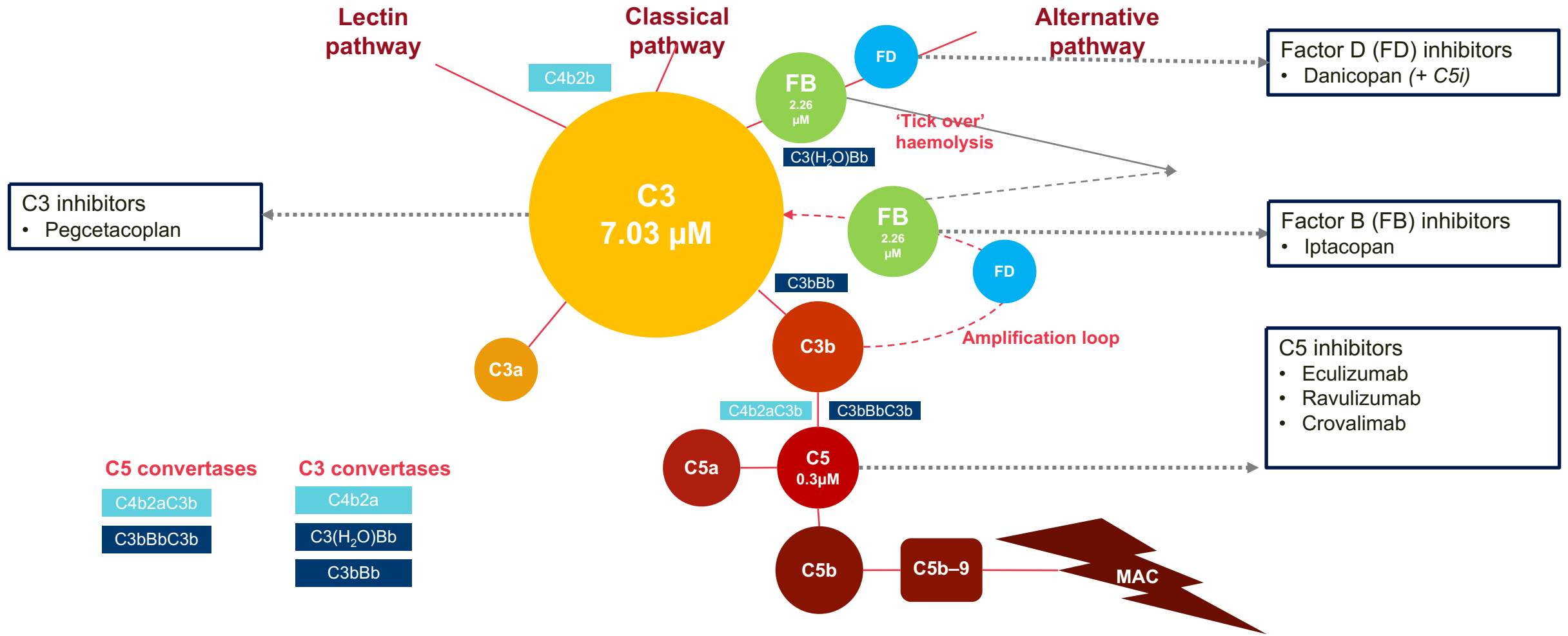


Figure adapted from Kulasekararaj AG, Lazana I. Paroxysmal nocturnal hemoglobinuria: Where are we going. Am J Hematol. 2023;98(S4):S33–S43.

# Available Complement Inhibitors in PNH

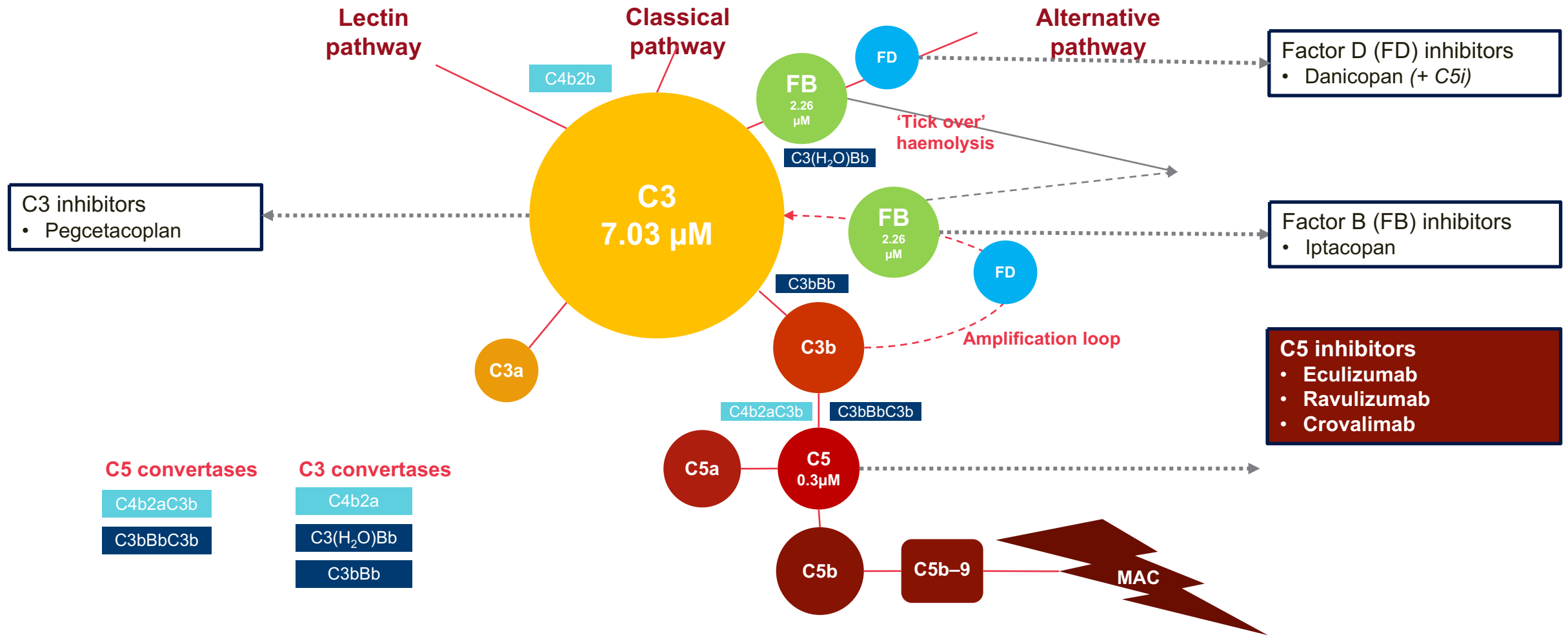
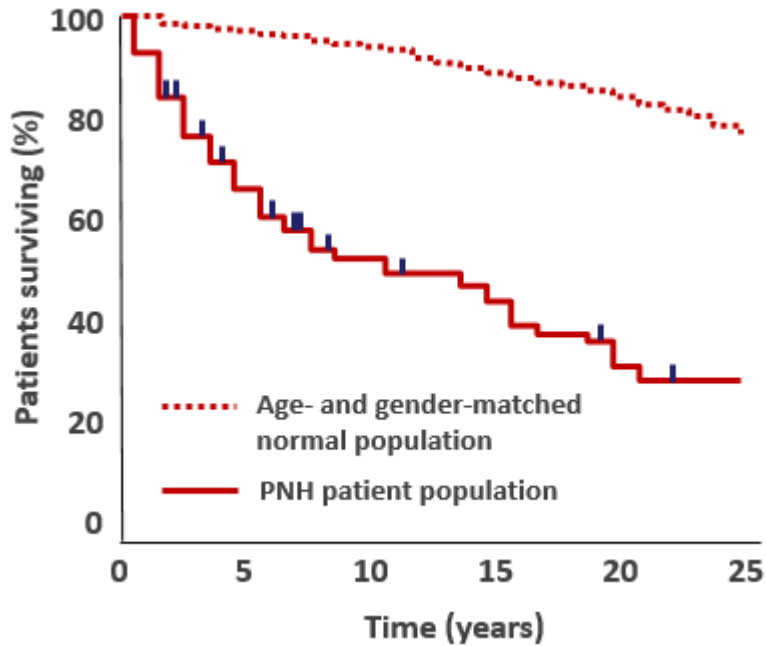


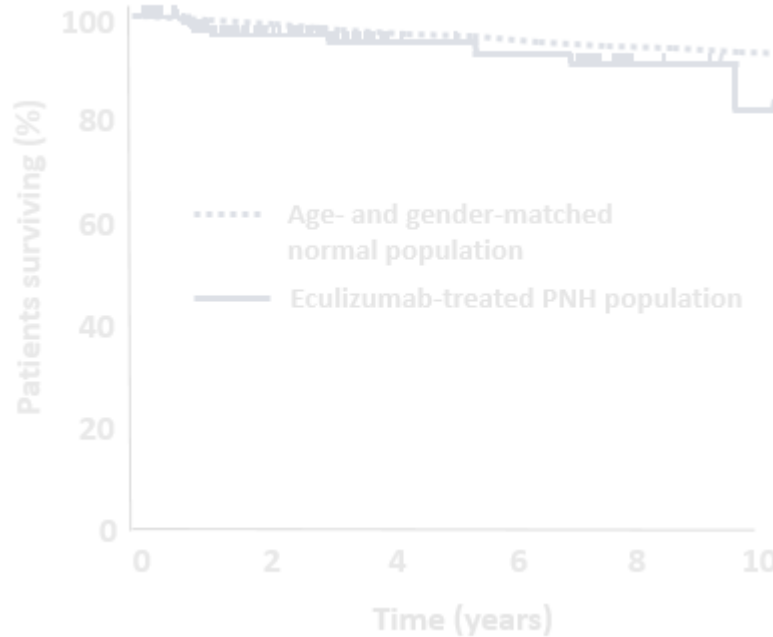
Figure adapted from Kulasekararaj AG, Lazana I. Paroxysmal nocturnal hemoglobinuria: Where are we going. Am J Hematol. 2023;98(S4):S33–S43.

# Evolution of PNH Patient Survival with C5i



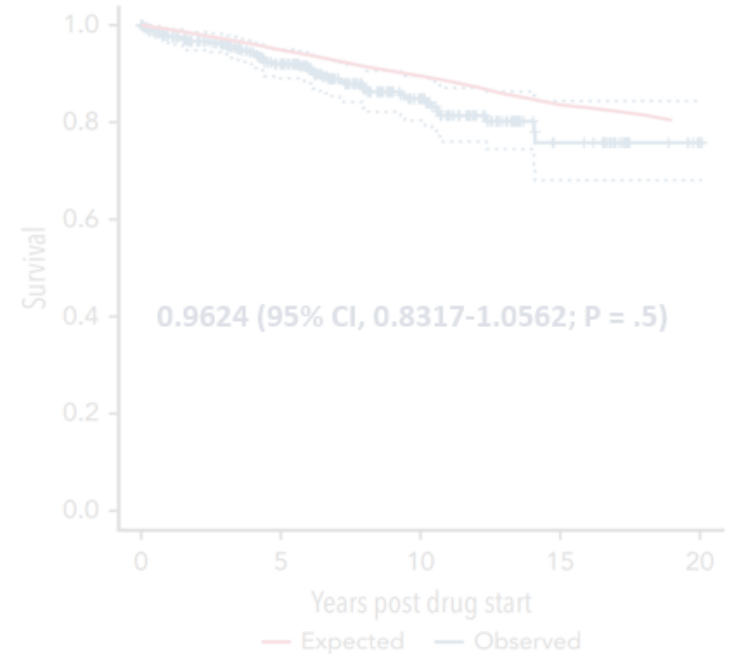
**Despite best supportive care, 5-year mortality rate was 35%**

Figure adapted from Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 1995 Nov 9;333(19):1253-8.



**Overall survival >90% over 10 years (deaths mostly due to**

Figure adapted from Kelly RJ, Hill A, Arnold LM, Gleeson SD, Granger DR, Richards SJ, et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. *Blood*. 2011 Jun 23;117(25):6786-92.



**Overall survival similar to overall population, excluding**

Figure adapted from Kelly RJ, Holt M, Vidler J, Arnold LM, Large J, Forrest B, et al. Treatment outcomes of complement protein C5 inhibition in 509 UK patients with paroxysmal nocturnal hemoglobinuria. *Blood*. 2014 Mar 21;143(12):1157-1166. Kelly RJ et al. *Blood*, 2024

# Approved PNH Therapies – C5 Inhibitors

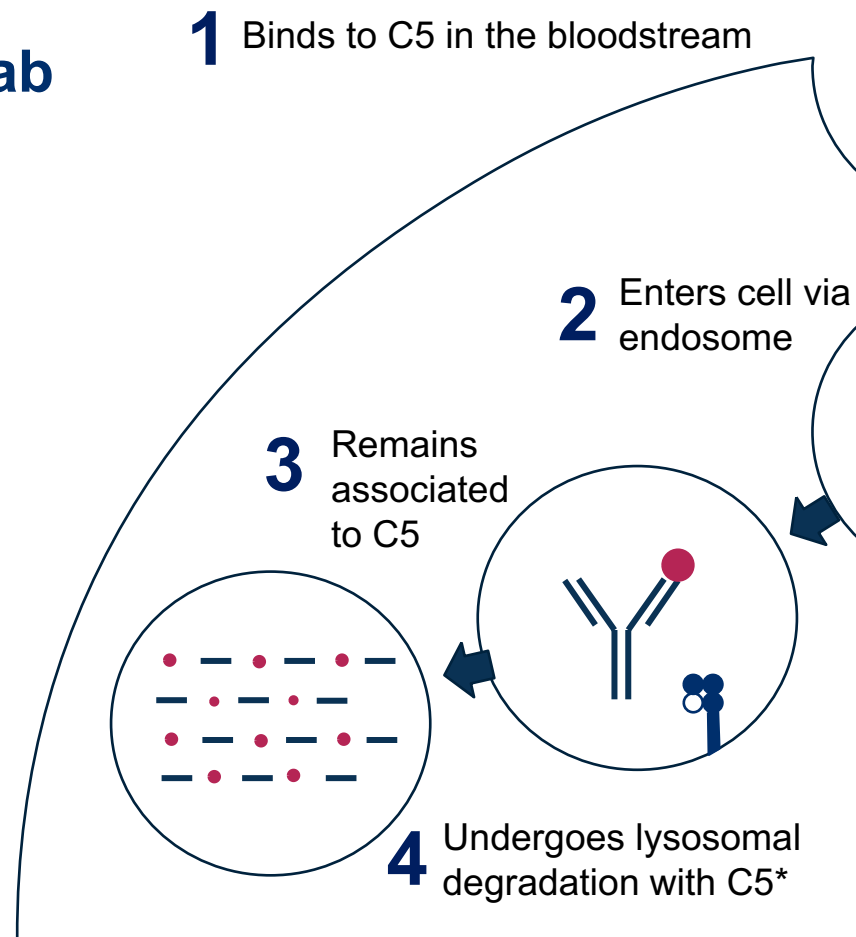
Drug	Molecular target	Drug class	Route and frequency <sup>a</sup>	Line of therapy <sup>b</sup>	Primary outcome(s)	Pregnancy data
Eculizumab	C5	Monoclonal antibody	900 mg IV every 2 weeks. Consider increased dosing to 1200 mg and/or shorter dosing interval if LDH >1.5×ULN.	First-line (TRIUMPH, SHEPHERD)	TRIUMPH: Hb stabilization in 49% (21/43) vs 0% receiving placebo. No packed red cell administered vs 10 units in the placebo group. SHEPHERD: LDH reduced by 87% with eculizumab.	Benefit outweighs risk based on large international series (no maternal deaths or antepartum thrombosis).
Ravulizumab	C5	Monoclonal antibody (modified eculizumab to permit pH-dependent C5 offloading and recirculation via FcRn)	IV every 8 weeks. 40 kg to <60 kg, 3000 mg; 60 kg to <100 kg, 3300 mg; ≥100 kg, 3600 mg.	First-line (301 Study) or transition from eculizumab (302 Study)	301 Study (C5i-naive): noninferior to eculizumab for percentage of patients remaining transfusion-free and LDH normalization. 302 Study (eculizumab-treated): noninferior to eculizumab for CFB LDH.	Limited information. Recent case series reported.
Crovalimab	C5	Monoclonal antibody (permits pH-dependent C5 offloading and recirculation via FcRn)	≥40 kg to <100kg: 680 mg SC every 4 weeks. ≥100 kg: 1020 mg every 4 weeks.	First-line (COMMODORE-2) or transition from other C5i (COMMODORE-1). Monitor for DTDC reaction for switch patients	COMMODORE-1 (switch cohort): Target recruitment not met; efficacy end points exploratory. COMMODORE-2 (C5i-naive): noninferior to eculizumab in the coprimary end points of hemolysis control and transfusion avoidance.	N/A

Figure adapted from Bienz M, Patriquin CJ. The varieties of therapeutic experience: navigating treatment options for patients with PNH. Hematology Am Soc Hematol Educ Program. 2025:154-163..

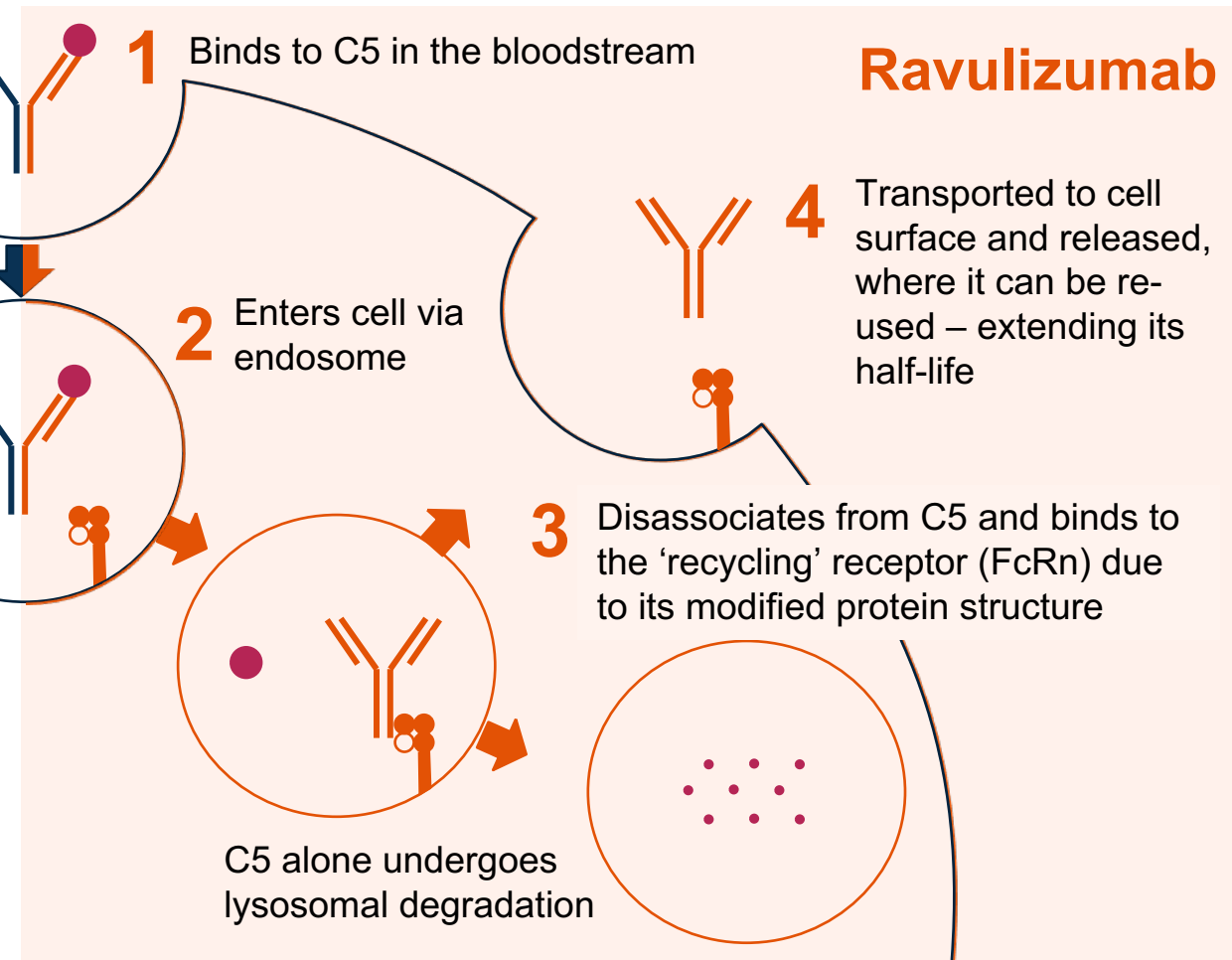


# Approved PNH Therapies – C5 Inhibitors

## Eculizumab

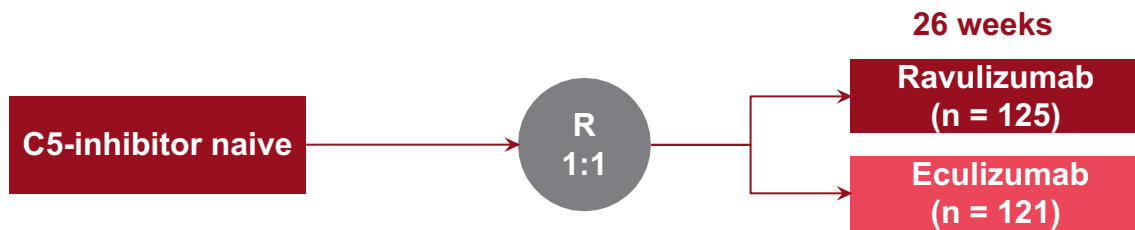


## Ravulizumab

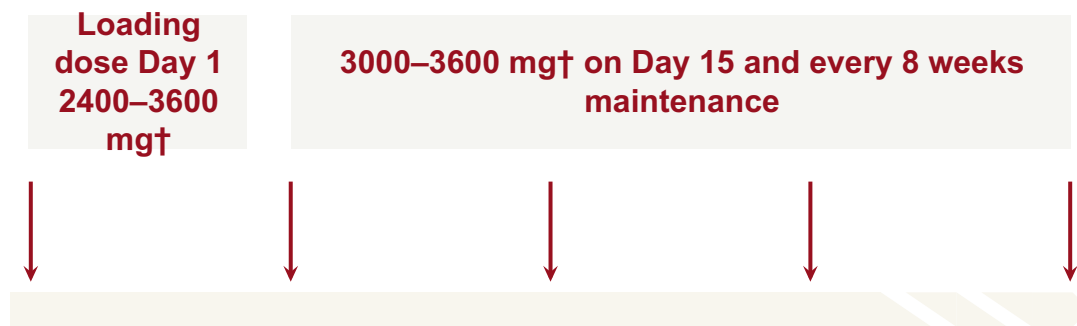


# Ravulizumab non-inferior in C5i-naïve patients

## Study design

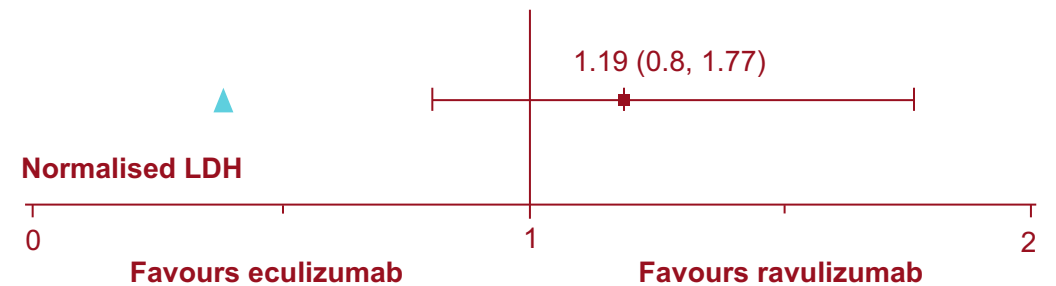
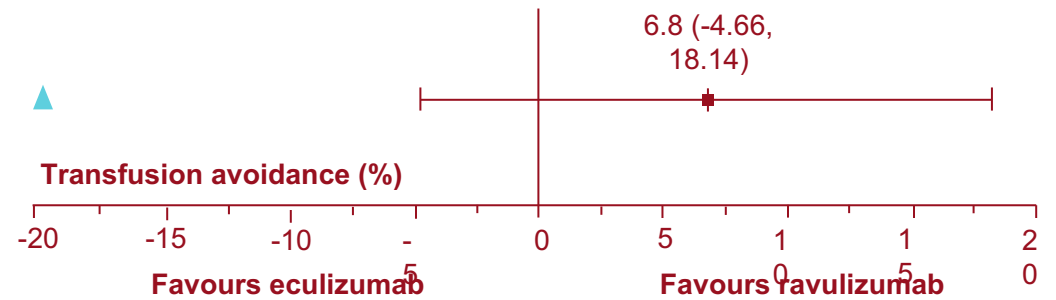


## Ravulizumab dosing schedule (IV administration)



C5i, C5 inhibitor; IV, intravenous; R, randomised; †Weight-based dosing.

## Difference (95% CI)

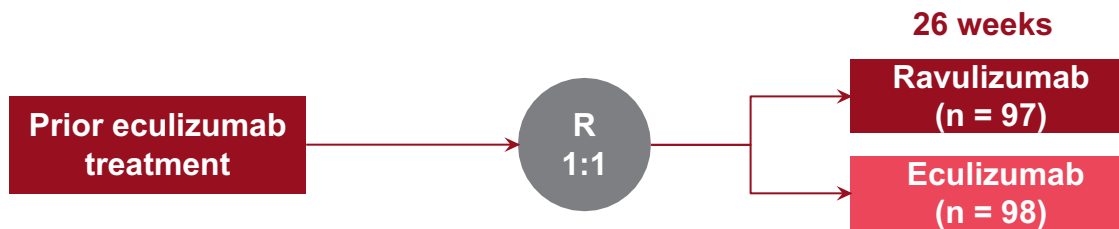


▲ Non-inferiority margin

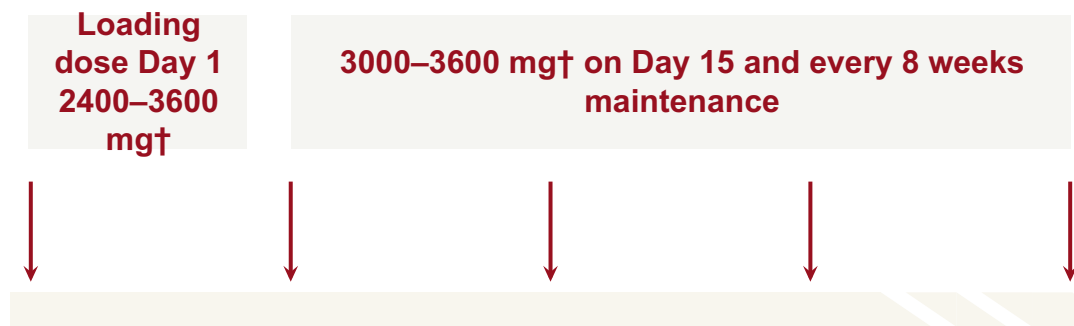


# Ravulizumab non-inferior in C5i-switch patients

## Study design

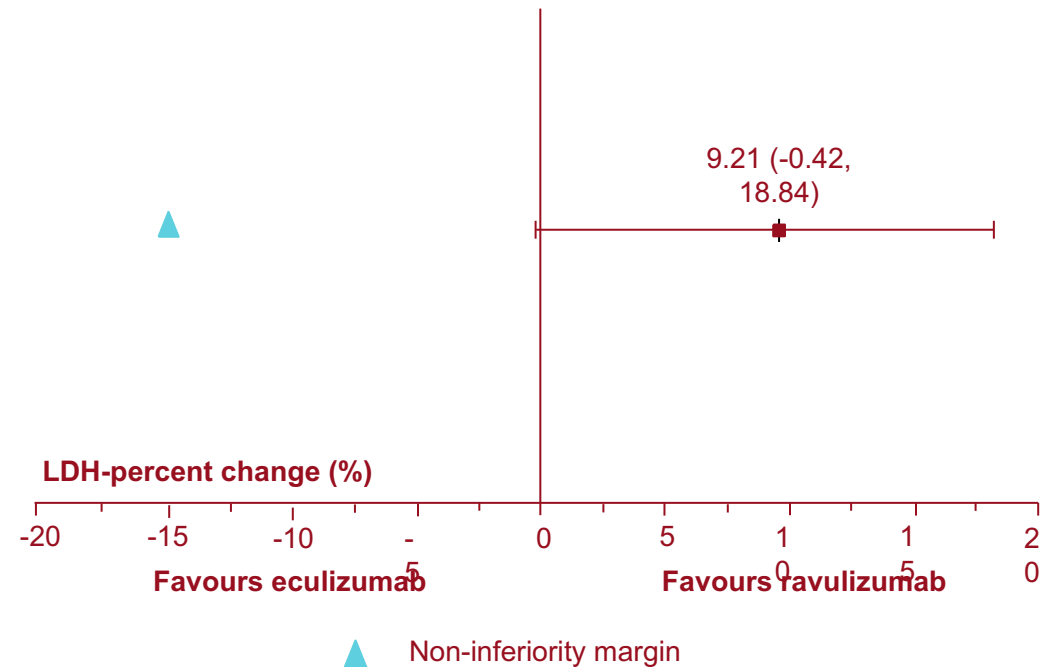


## Ravulizumab dosing schedule (IV administration)



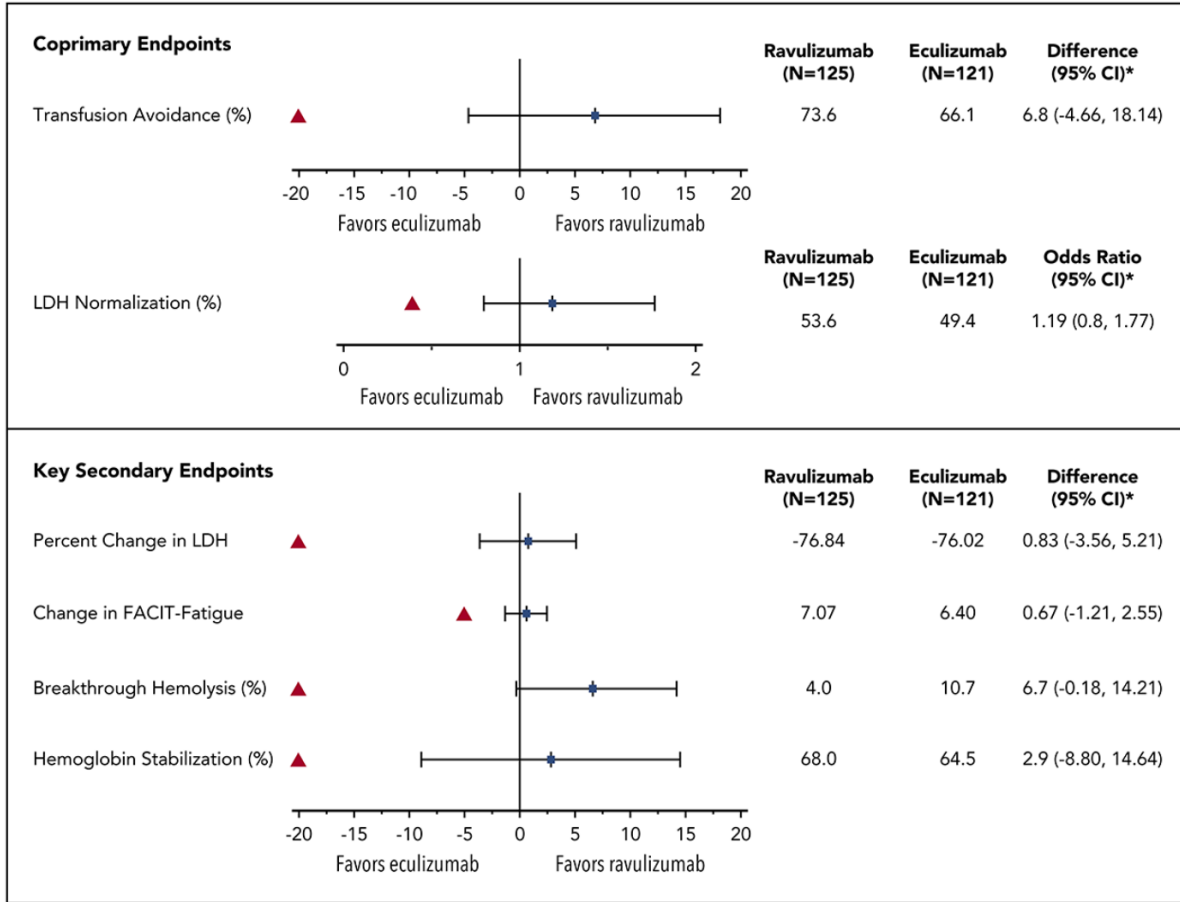
C5i, C5 inhibitor; IV, intravenous; R, randomised; †Weight-based dosing.

## Difference (95% CI)



# Ravulizumab is Non-Inferior to Eculizumab

Efficacy of Ravulizumab and Eculizumab in Complement Inhibitor–Naive PNH Patients



Efficacy of Ravulizumab and Eculizumab in PNH Patients Stable on Eculizumab

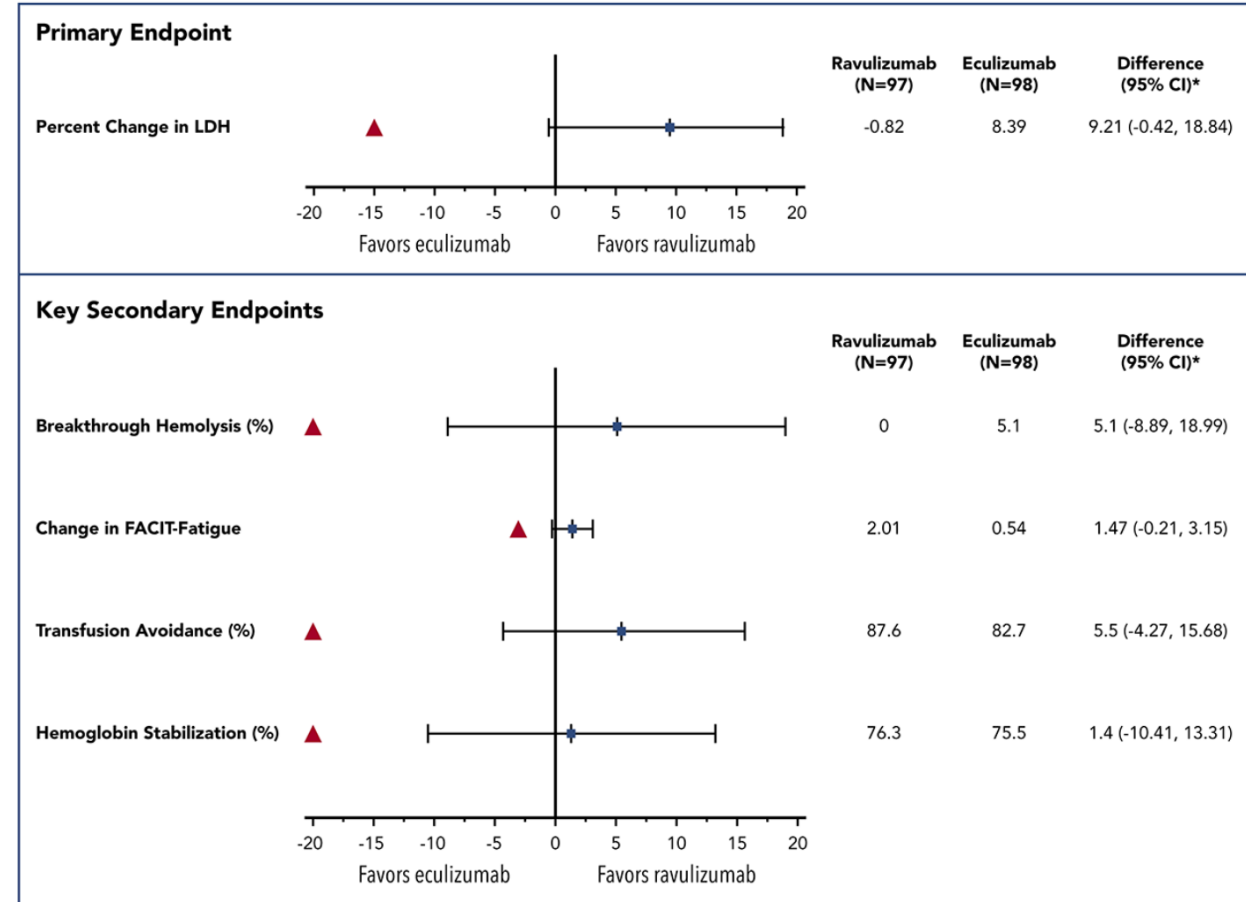


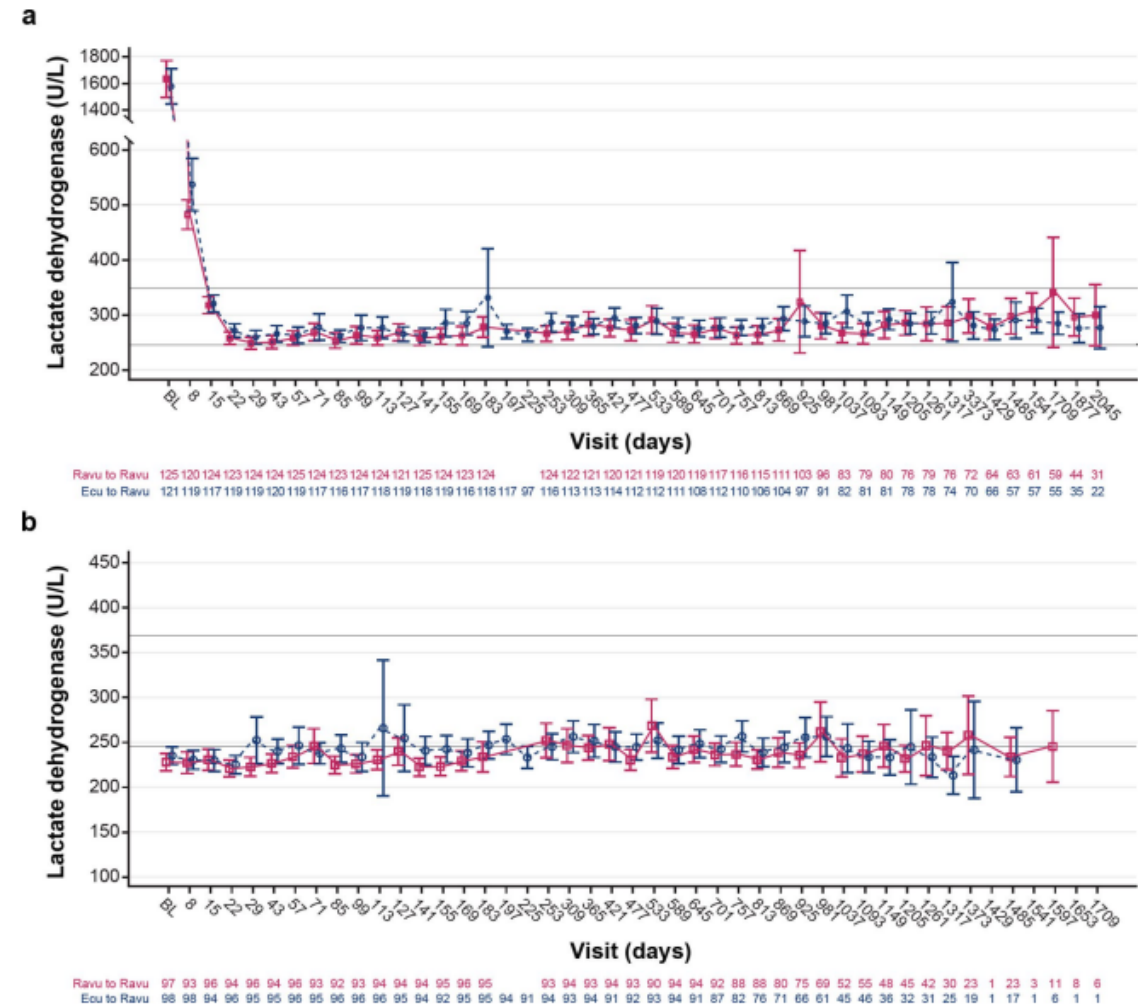
Figure adapted from Lee JW, Sicre de Fontbrune F, Lee LW, Pessoa V, Gualandro S, Füreder W, Ptushkin V, Rottinghaus ST, Volles L, Shafner L, Aguzzi R, Pradhan R, Schrezenmeier H, Hill A. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood*. 2019;133(6):530-9.

Figure adapted from Kulasekararaj AG, Hill A, Rottinghaus ST, Langemeijer S, Wells R, Gonzalez-Fernandez FA, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor–experienced adult patients with PNH: the 302 study. *Blood*. 2019 Feb 7;133(6):540-549.



# Long-term Experience with Ravulizumab<sup>1</sup>

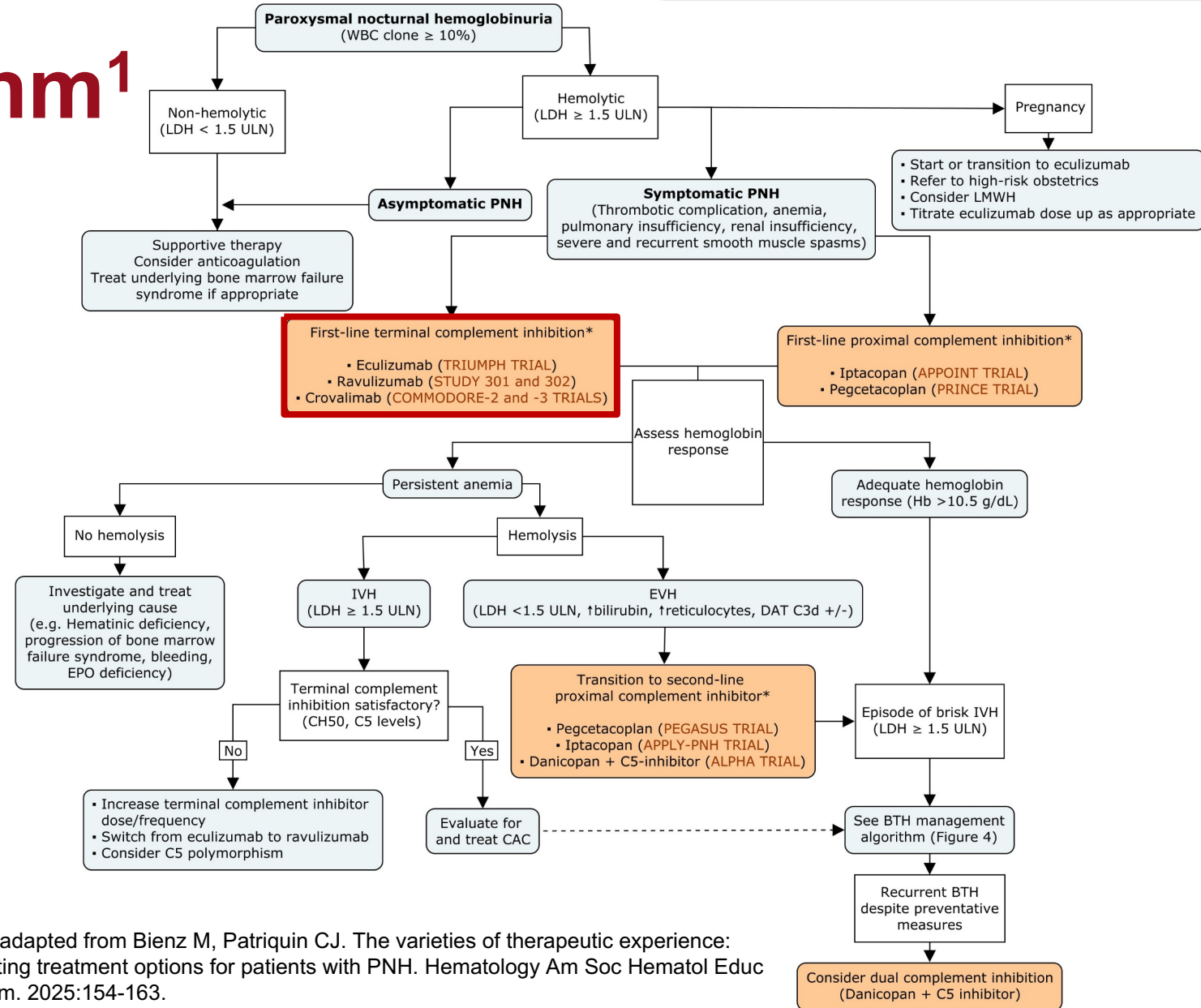
- Combined long-term data following completion of the 301 (N=244) and 302 (N=191) trials, with up to 6 years of follow-up (~1500 PYs of exposure)
  - Indirect comparison with untreated registry patients
- Tight control of terminal complement and IVH
- Low rate of MAVEs (0.7-1.4 per 100 PYs)
- Breakthrough hemolysis typically associated with infectious CACs; only ~2% from suboptimal PK
- Mortality rate reduced by 5-fold (vs. untreated)



**Fig. 4** Mean (95% CI) LDH level over time for patients with PNH in (a) the C5i-naive group and (b) eculizumab-experienced group, by treatment sequence. References: (a) Kulasekararaj et al. [41]. © American Society of Hematology (2024). Reused with permission. (b) Kulasekararaj et al. [40]. Note. On both charts, the lower horizontal line indicates the ULN (246 U/L) and the upper horizontal line indicates 1.5 × ULN (369 U/L). Data points with sample sizes were less than 10 were excluded. CI, confidence interval; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal



# Treatment Algorithm<sup>1</sup>



## Primary Goals

- Control IVH (LDH <1.5x)
- Protect from thromboembolism
- Improve HRQoL
- Normalise survival
- Improve pregnancy outcomes

## Secondary Goals

- Increase hemoglobin (?csEVH)
- Further improve HRQoL
- Reduce treatment burden

Figure adapted from Bienz M, Patriquin CJ. The varieties of therapeutic experience: navigating treatment options for patients with PNH. Hematology Am Soc Hematol Educ Program. 2025:154-163.

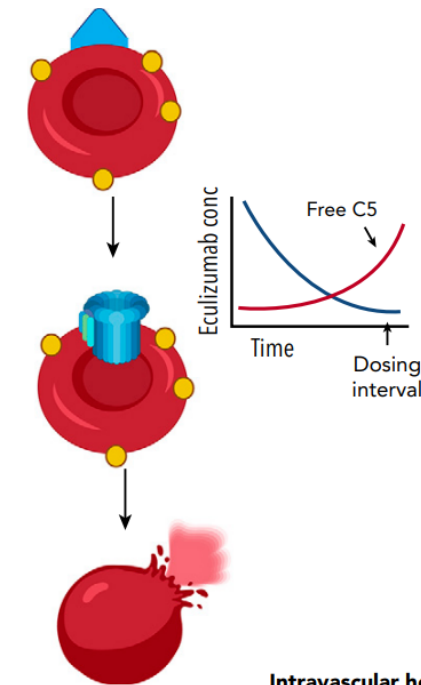


# Breakthrough Hemolysis in PNH

# Breakthrough Hemolysis Risk & Remediation<sup>1,2</sup>

- Breakthrough hemolysis (BTH) is a return of intravascular hemolysis (LDH >1.5x) and the associated potential risks
- Pharmacokinetic (PK) factors must be assessed and optimised
  - Dose, schedule of IV infusions
  - Adherence for self-administration
- Pharmacodynamic (PD) stressors may drive BTH alone/accompany PK factors

**Pharmacokinetic breakthrough hemolysis**



**D Pharmacodynamic breakthrough hemolysis**

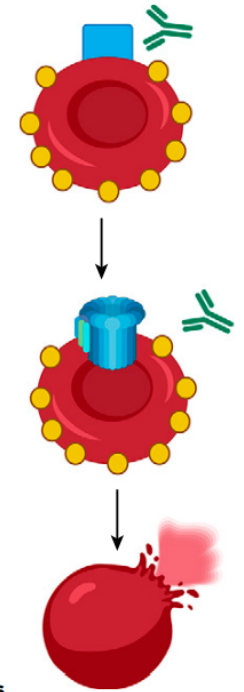
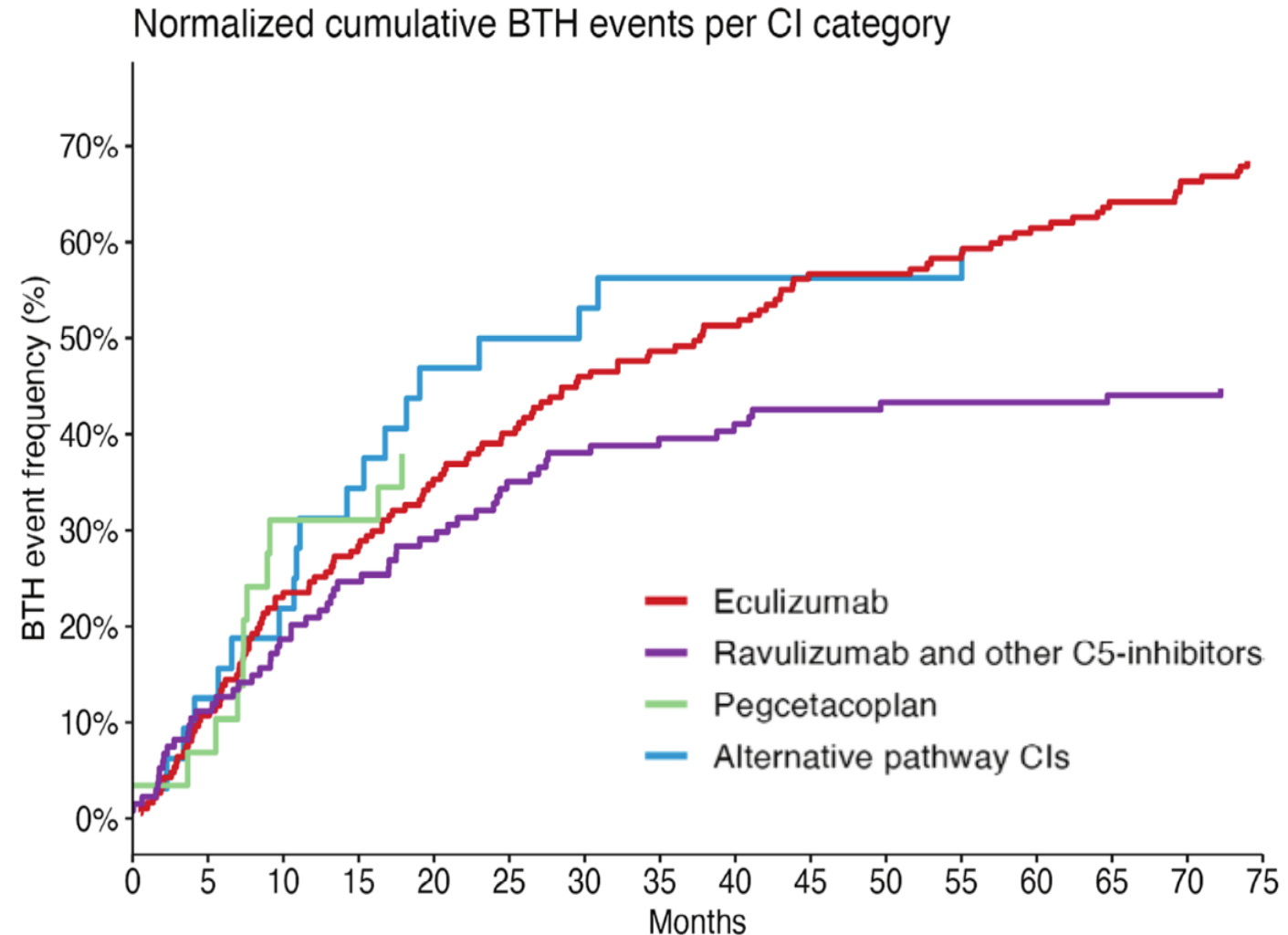


Figure adapted from Eisfeldt AK, Kohlschmidt J, Mrozek K, Blachly JS, Nicolet D, Orwick S, et al. Mutations in the CCNA2, CCNB1, and CCNB2 cell cycle genes are rare events in acute myeloid leukemia. *Blood*. 2020;135(4):361-365..

# Breakthrough Hemolysis Risk Across Drugs

- BTH events were collected between 2007 and February 2025:
  - Most common CI was eculizumab
  - 4/271 patients switched to proximal CI within a month before the BTH event
- Complications of BTH included anemia requiring transfusion support (46%) and thrombosis (2%)
- Clinical management of BTH included:
  - Transfusions (58%)
  - Anticoagulation (16%)
  - Extra or early CI dosing (17%)

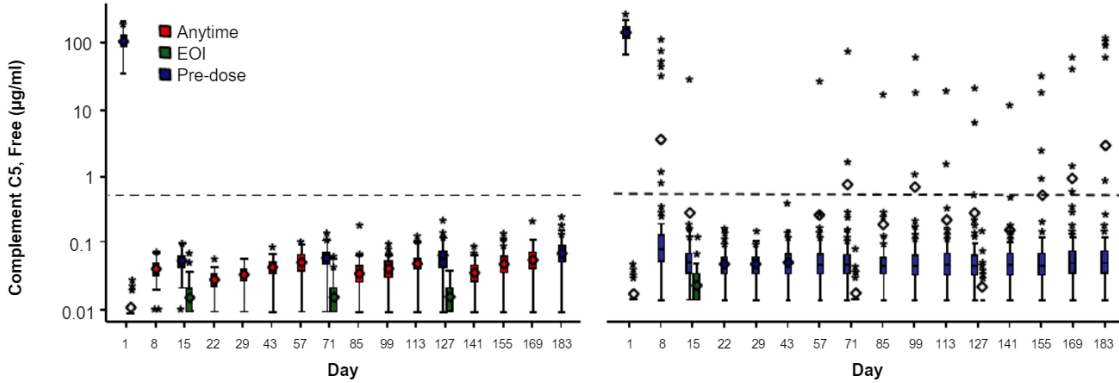


# PK-BTH is Reduced with Ravulizumab<sup>1-4</sup>

A Study 301

Ravulizumab

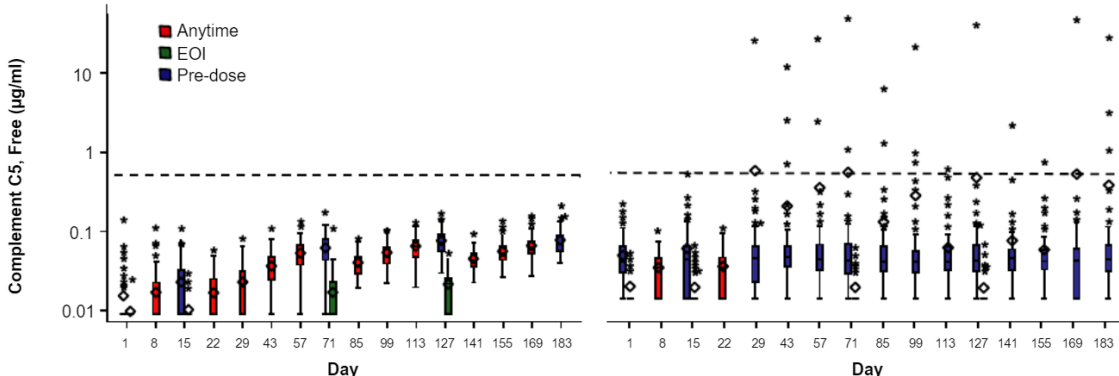
Eculizumab



B Study 302

Ravulizumab

Eculizumab



Study 301  
(C5i-naïve patients)

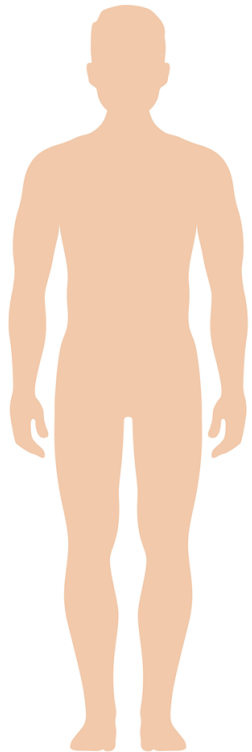
Study 302  
(Stable on eculizumab)

	Ravulizumab b n=125	Eculizumab n=121	Ravulizumab b n=97	Eculizumab n=98
Patients w/ BTH (%)	5 (4.0)	13 (10.7)	0 (0.0)	5 (5.1)
BTH events   pts	5   5	15   13	0	7   5
BTH events with free C5 ≥ 0.5 µg/mL	0	7	0	4
BTH events with infection (w/ no free C5 elevation)	4	4	0	2
BTH events unrelated to elevated free C5 or infection	1	4	0	1

1. Lee JW, Sicre de Fontbrune F, Lee LW, Pessoa V, Gualandro S, Füreder W, Ptushkin V, Rottinghaus ST, Volles L, Shafner L, Aguzzi R, Pradhan R, Schrezenmeier H, Hill A. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naïve to complement inhibitors: the 301 study. *Blood*. 2019 Feb 7;133(6):530-539. 2. Kulasekararaj AG, Hill A, Rottinghaus ST, Langemeijer S, Wells R, Gonzalez-Fernandez FA, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood*. 2019 Feb 7;133(6):540-9. 3. Apostolidou E, Georgoulis V, Leonardos D, Kapsali E, Hatzimichael E. Paroxysmal nocturnal hemoglobinuria: unraveling its molecular pathogenesis and advancing targeted therapeutic strategies. *Diseases*. 2025;13(9):298. 4. Brodsky RA, Peffault de Latour R, Rottinghaus ST, Röth A, Risitano AM, Weitz IC, Hillmen P, Maciejewski JP, Szer J, Lee JW, Kulasekararaj AG, Volles L, Damokosh AI, Ortiz S, Shafner L, Liu P, Hill A, Schrezenmeier H. Characterization of breakthrough hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. *Haematologica*. 2021;106(1):230-7.

# New Discussions, More Decisions...

# Initial Therapeutic Options for PNH Patients<sup>1,2</sup>



- Clinically significant IVH (*high disease activity or other regional approval criteria*)
- PNH-related thrombosis\*
- Pregnancy\*

(*high*)

**Initial Therapy  
(C5i)**

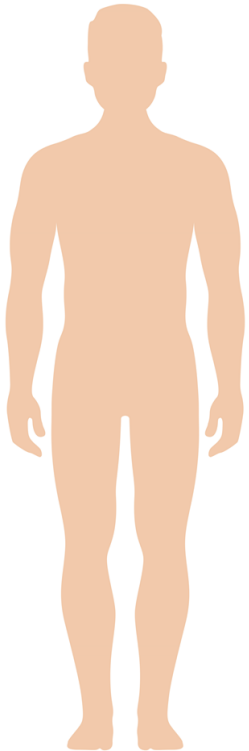
**Subsequent Therapy**

- Safe & effective alternatives
- Scrutinize reason(s) for change
- Consider patient preferences and jurisdictional availability

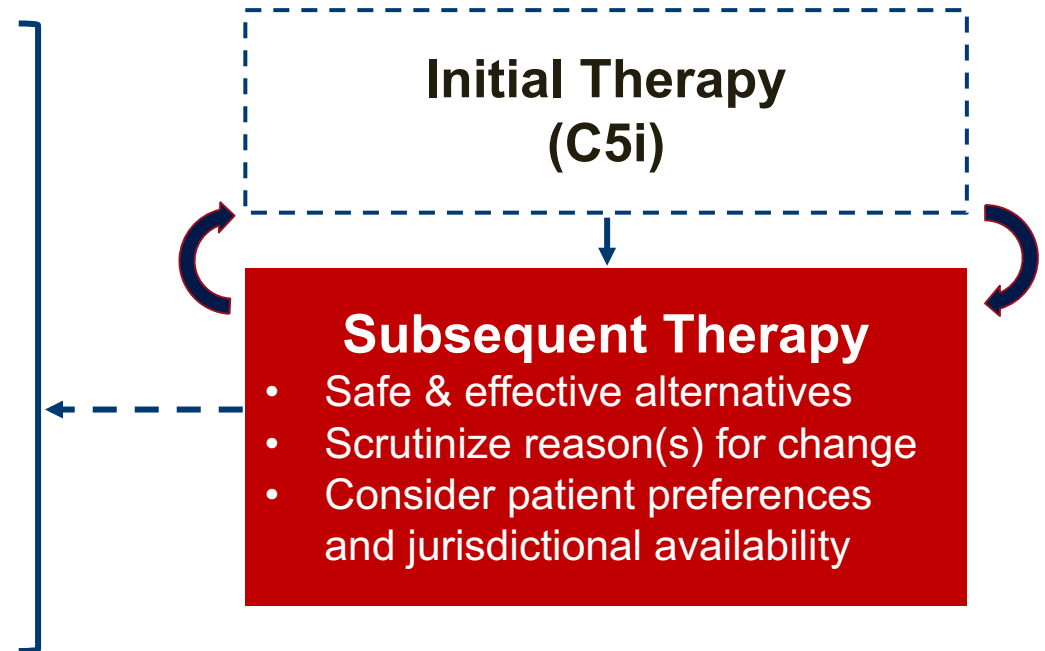
*\*Current data support initiation of C5 inhibitor for these indications.*



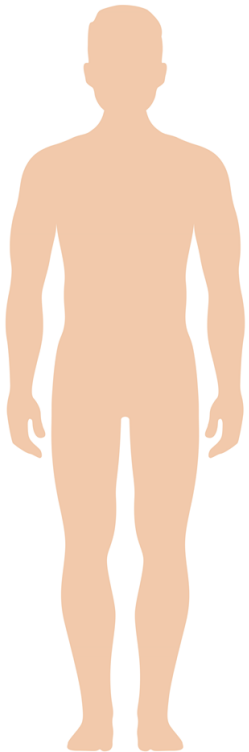
# Subsequent Options for PNH Patients



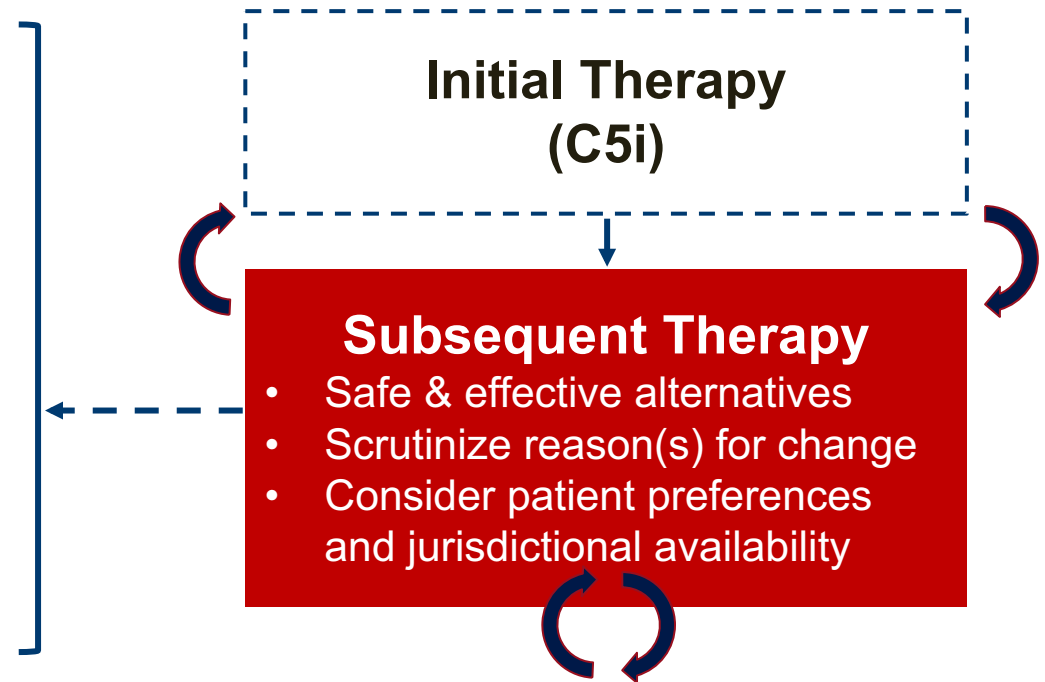
- Inadequate Hb with C5i?  
*Proximal/dual inhibition*
- Intolerance to C5 inhibition?  
*Alternate C5i or proximal CI*
- BTH risk, recurrence, severity?  
*Assess adherence/PK factors, CAC exposure, organ reserve*



# Subsequent Options for PNH Patients



- Inadequate Hb with C5i?  
*Proximal/dual inhibition*
- Intolerance to C5 inhibition?  
*Alternate C5i or proximal CI*
- BTH risk, recurrence, severity?  
*Assess adherence/PK factors, CAC exposure, organ reserve*



# Illustrative Patient Stories

# PNH Case Histories

Clinical Case Dr. Christopher J. Patriquin

**Case 1: SL, 31yo male**

**Case 2: LC, 63yo female**

**Case 3: MS, 32yo female**

# Navigating Therapeutic Options in PNH – Key takeaways

- PNH is ultrarare; we need to identify patients before we can treat them!
- Uncontrolled terminal complement predisposes patients to life-threatening complications from intravascular hemolysis, including thrombosis, kidney failure, pulmonary hypertension
- C5 inhibition with eculizumab and ravulizumab can block IVH (LDH <1.5x ULN), prevent thrombosis, reduce transfusions, improve HRQoL, and extend survival
- Shared decision-making is essential to maximize adherence, minimize complications, and fit life circumstances

# The end. Thank you!



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[www.PNHnetwork.ca](http://www.PNHnetwork.ca)

# Canais de informação e farmacovigilância



**Champion**

Para reportar uma queixa técnica, eventos adversos ou solicitar informações médicas referentes aos produtos AstraZeneca, utilize o formulário web Champion, acessível através do QR Code. A sua colaboração é fundamental para garantir a segurança e eficácia contínua de nossos produtos.

Material destinado a profissionais habilitados a prescrever e dispensar medicamentos. BR-50921. Maio/2026  
Esta atividade é promovida/ financiada/ apoiada pela AstraZeneca Brasil

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**Contraindicações:** Hipersensibilidade ao eculizumabe, às proteínas murinas ou a qualquer um dos excipientes da fórmula. A terapêutica com **Soliris®** (eculizumabe) não deve ser iniciada em pacientes: com infecção por *Neisseria meningitidis* não resolvida; que não estejam vacinados contra *Neisseria meningitidis* (a menos que recebam tratamento profilático com antibióticos apropriados até 2 semanas após a vacinação). **Interações medicamentosas:** Não foram realizados estudos de interação medicamentosa. A troca de plasma, plasmaférese e a infusão de plasma fresco congelado, demonstraram reduzir os níveis séricos de **Soliris®**. Uma dosagem suplementar de **Soliris®** é necessária nesses casos. Consulte a bula para orientação. O uso concomitante de **Soliris®** com bloqueadores dos receptores Fc neonatais (FcRn) pode diminuir as exposições sistêmicas e reduzir a eficácia de **Soliris®**. Monitore de perto a eficácia reduzida de **Soliris®**. O tratamento crônico intravenoso com imunoglobulina humana (IVIg) pode interferir com o mecanismo de reciclagem dos receptores monoclonais endossomal neonato Fc (FcRn), tal como o eculizumabe, dessa forma diminuindo assim as concentrações séricas de eculizumabe. Os estudos de interação medicamentosa não foram realizados com eculizumabe em pacientes tratados com IVIg. **Reações adversas:** A reação adversa mais frequente foi cefaleia (principalmente na fase inicial), e a reação adversa mais grave foi a infecção meningocócica.

Para mais informações consulte a bula  
do medicamento:



**SOLIRIS®**  
(e c u l i z u m a b e)

**Contraindicações:** Hipersensibilidade ao ravulizumabe ou a qualquer um dos excipientes da fórmula. A terapêutica com Ultomiris® não deve ser iniciada em pacientes: com infecção por Neisseria meningitidis não resolvida e em pacientes que não estão atualmente vacinados contra Neisseria meningitidis, a menos que recebam tratamento profilático com antibióticos apropriados até 2 semanas após a vacinação. **Interações Medicamentosas:** Não foram realizados estudos de interação medicamentosa. A utilização concomitante de Ultomiris® com bloqueadores do receptor Fc neonatal (FcRn) pode diminuir as concentrações sistêmicas e reduzir a eficácia de Ultomiris®. Monitore atentamente qualquer redução na eficácia de Ultomiris®. **Reações adversas:** Em todos os estudos clínicos, as reações adversas mais graves de Ultomiris® foram infecções meningocócicas. As reações medicamentosas adversas mais comuns ( $\geq 10\%$ ) em todos os ensaios clínicos foram cefaleia, infecção do trato respiratório superior, nasofaringite, diarreia, febre, náuseas, artralgia, dor nas costas, fadiga, dor abdominal, infecção do trato urinário e tontura.

Para mais  
informações consulte  
a bula do  
medicamento:



**ULTOMIRIS®**  
(ravulizumabe)  
Solução para Diluição para Infusão

**Contraindicações:** Pacientes com hipersensibilidade à danicopana ou a qualquer dos excipientes listados na composição. A terapia com Voydeya® não deve ser iniciada em pacientes com infecção por Neisseria meningite disnão resolvida e pacientes com histórico de vacinação desconhecido ou que não estão atualizados com suas vacinas meningocócicas. Os pacientes que iniciarão o tratamento com Voydeya® menos de 2 semanas após receberem uma vacina meningocócica devem receber o tratamento com antibióticos profiláticos adequados até 2 semanas a pós a vacinação. **Interações Medicamentosas:** Efeitos de outros medicamentos com danicopana - Dados não clínicos disponíveis mostraram que a via de depuração predominante para danicopana não depende do metabolismo no citocromo P450 (CYP). Efeitos da danicopana sobre outros medicamentos - Danicopana não é um inibidor de CYP1A2, CYP2C8 e CYP2D6. Substratos da glicoproteína-P (gp-P) - A coadministração de doses orais únicas de fexofenadina e tacrolimus, substratos da gp-P com a danicopana administrada até o estado estacionário resultou em aumentos da concentração sérica máxima (C<sub>max</sub>) e da área sob a curva de concentração plasmática tempo (AUC)<sub>0-inf</sub> dos substratos da gp-P, sugerindo que danicopana é uma inibidora da gp-P e pode ser necessária cautela na administração concomitante de medicamentos que são conhecidos por serem substratos da gp-P. Substratos de substrato da proteína de resistência ao câncer de mama (BCRP) - A coadministração de uma dose oral única de rosuvastatina, um substrato de BCRP, com danicopana administrada até o estado estacionário, resultou num aumento da C<sub>máx</sub> e da AUC<sub>0-inf</sub> da rosuvastatina, sugerindo que danicopana é uma inibidora de BCRP e pode ser necessária precaução na administração concomitante de fármacos que sejam conhecidos como substratos da BCRP. **Reações adversas:** As reações adversas à droga mais comuns (≥ 10%) em todos os estudos clínicos foram aumento de enzima hepática e cefaleia. Não foram observadas reações adversas graves à droga em pacientes com HPN em estudos clínicos.

Para mais informações consulte a bula  
do medicamento:

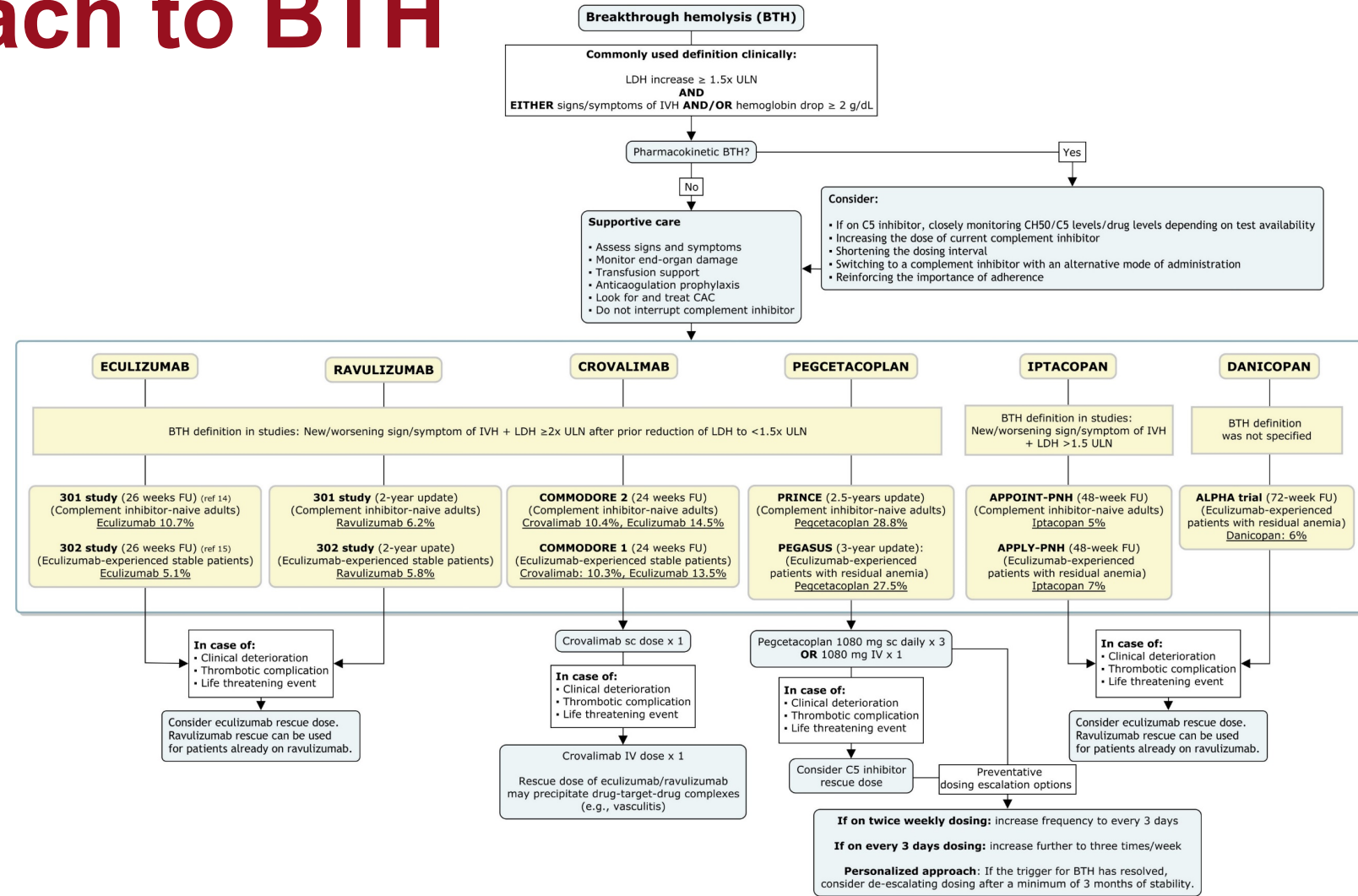


 **Voydeya**<sup>®</sup>  
(danicopana) 50mg · 100mg  
Comprimidos revestidos

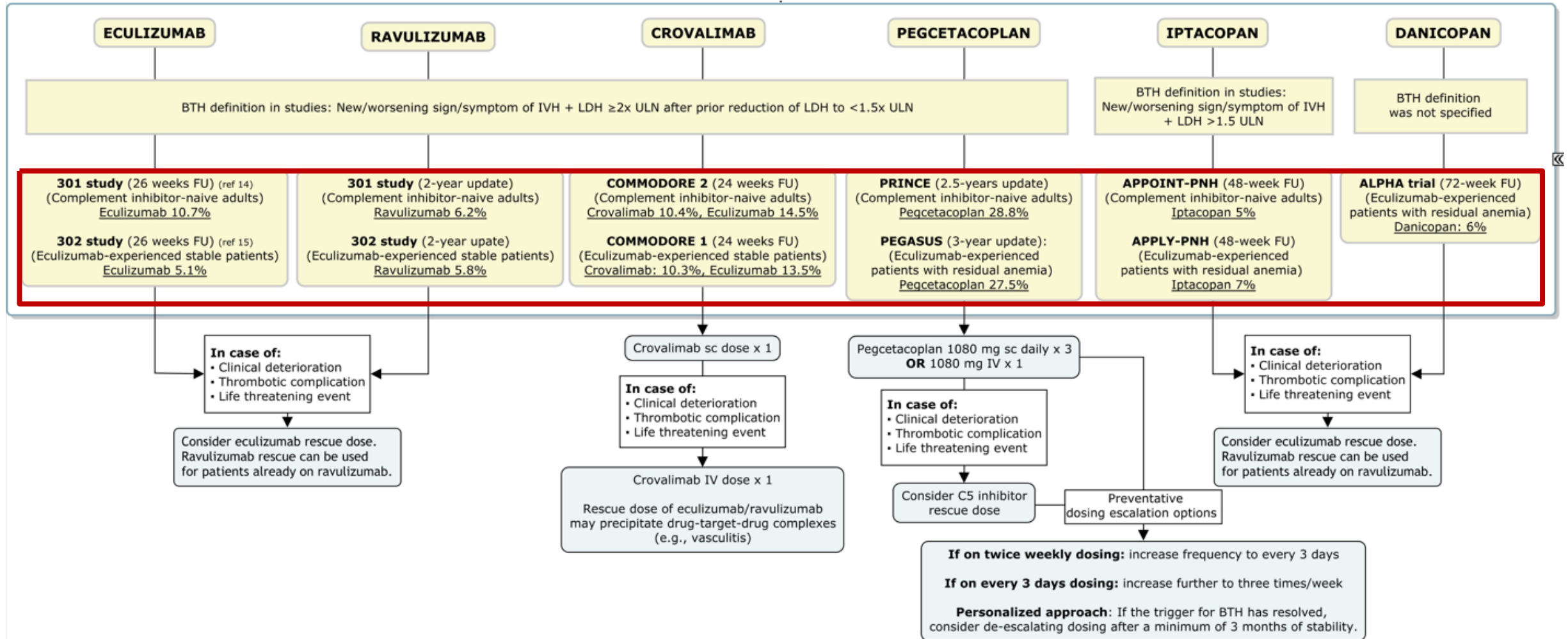
# Back-up Slides

# General Approach to BTH

- Education & prevention!
- Identify it early
  - Monitor closely and consider hospital admission
- Assess for pharmacokinetic insufficiency
- Supportive care may include:
  - Transfusions
  - Antimicrobials
  - Prophylactic anticoagulation



# Approach to BTH & Specific Therapies



# Breakthrough Hemolysis Risk & Remediation<sup>1,2</sup>

- Breakthrough hemolysis (BTH) is a return of intravascular hemolysis (LDH >1.5x) and the associated potential risks
- Pharmacokinetic (PK) factors must be assessed and optimised
  - Dose, schedule of IV infusions
  - Adherence for self-administration
- Pharmacodynamic (PD) stressors may drive BTH alone/accompany PK factors

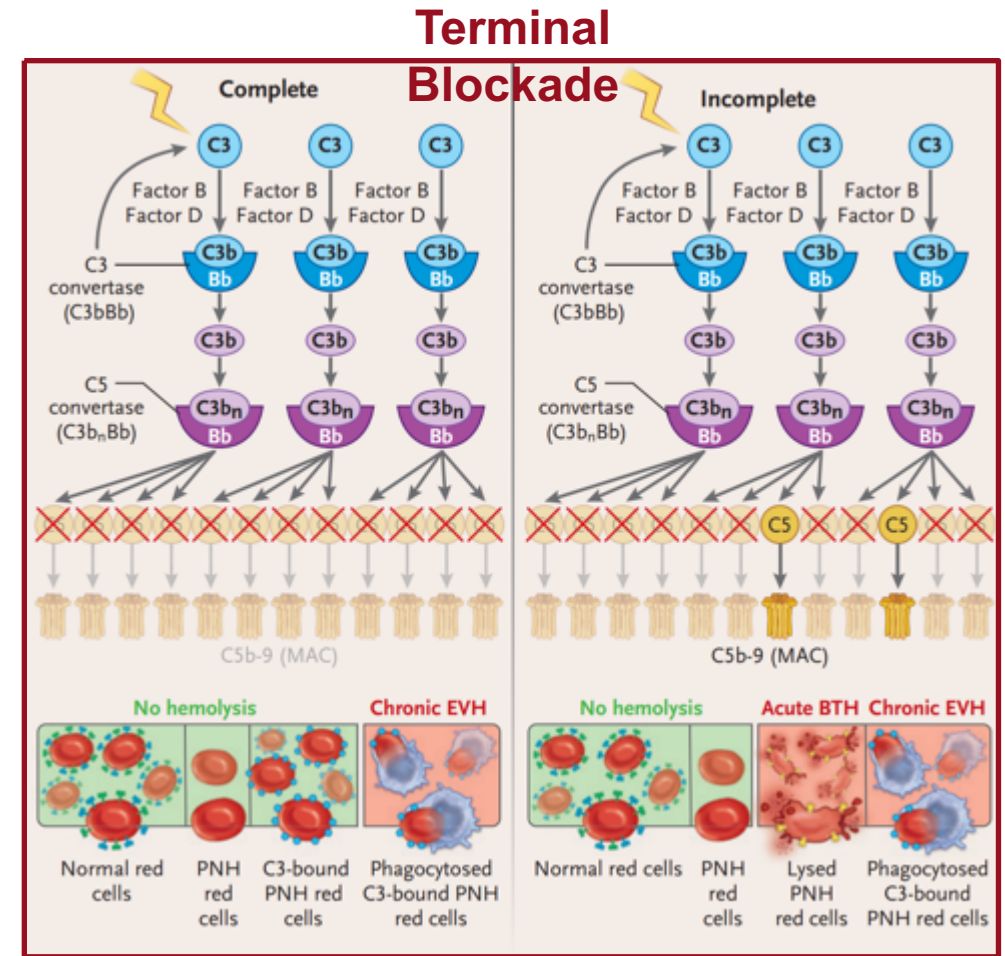


Figure adapted from Notaro R, Luzzatto L. Breakthrough hemolysis in PNH with proximal or terminal complement inhibition. N Engl J Med. 2022 Jul 14;387(2):160-166..

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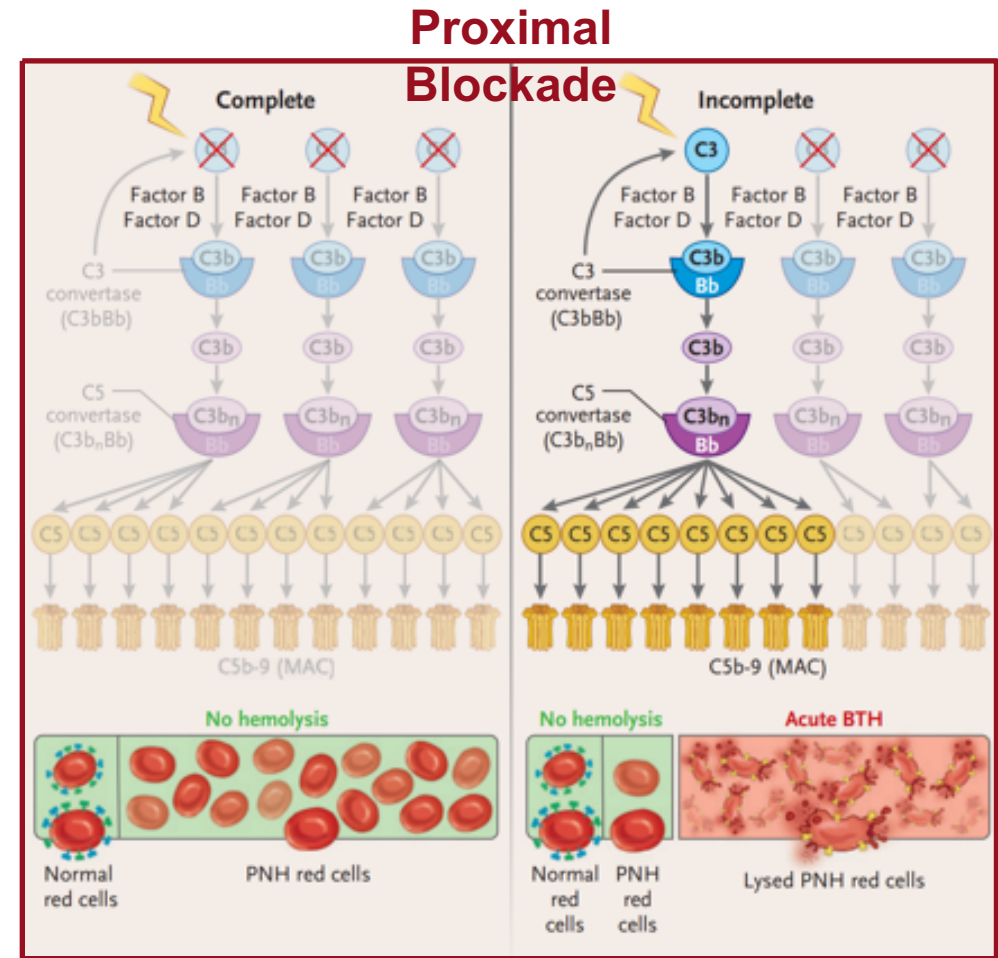


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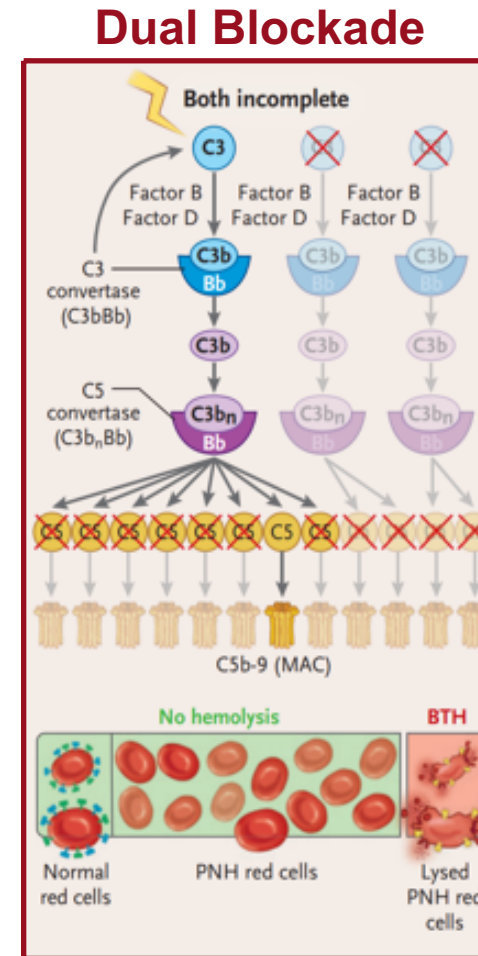


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