



SINTOMA²⁶

14 A 16 DE MAIO | HOTEL INTERCONTINENTAL | SÃO PAULO

PARCERIA **soho**
society of hematologic oncology

APOIO INSTITUCIONAL Faculdade **bp**

GERENCIAMENTO
E PRODUÇÃO

RV+
EVENTOS

Inibição do Complemento na Hemoglobinúria Paroxística Noturna da Inibição Terminal ao Alvo Proximal

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Hospital A Beneficência Portuguesa
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De acordo com a resolução do Conselho Federal de Medicina nº 1595/2000 e Resolução da Diretoria Colegiada da ANVISA nº 96/2008, eu declaro os potenciais conflitos de interesses:

Empresa	Palestrante	Material Educacional	Suporte Científico	Pesquisa Clínica	Advisory Board
Novartis	X		X	X	X
Alexion	X		X		X
Janssen	X				
Roche			X		X
Pfizer			X		X

Norma 1595/ 2000 - CFM

Resolução RDC nº 96/2008 - Anvisa

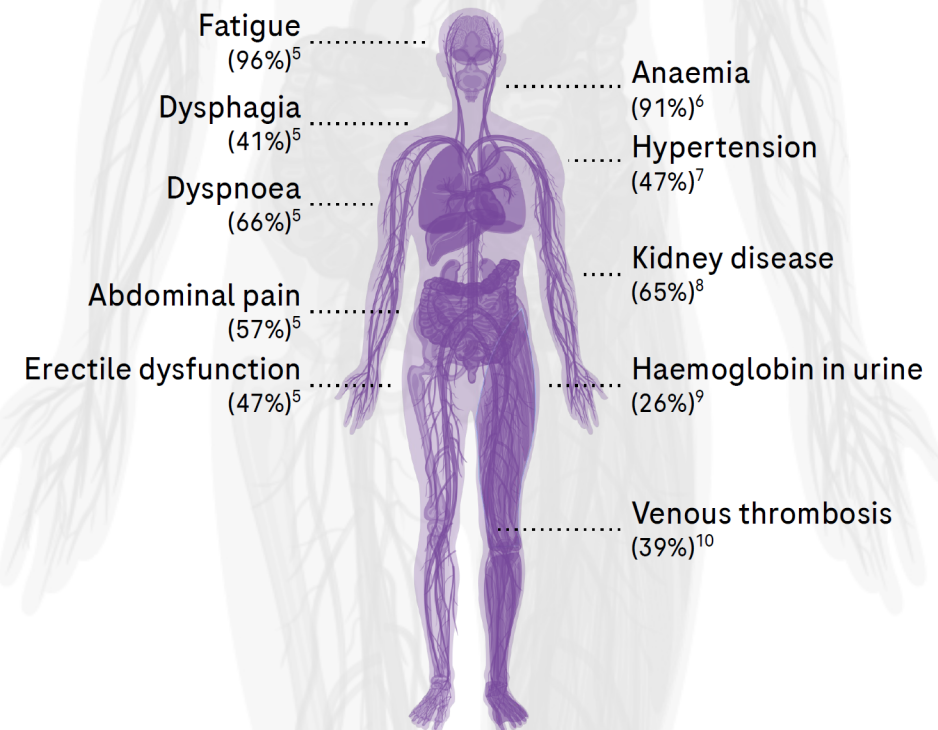
Declaro não ter ações em bolsa de valores das empresas supracitadas.

Meus pré-requisitos para participar destas atividades são o intercâmbio científico, a autonomia do pensamento científico, independência de opinião e liberdade de expressão, aspectos estes respeitados pela Novartis

PNH is a rare, life-threatening, complement-mediated haematologic disorder¹

- The incidence of clinically significant PNH is estimated to be at least 1 to 10 cases per million population¹
- Haemolysis is persistent in PNH²
 - Ongoing haemolysis leads to anaemia and other symptoms
 - Symptoms can have an adverse impact on quality of life and may be disabling
- PNH can be fatal if left untreated³
 - Mortality in untreated patients with severe PNH is ~35% at 5 years
 - Thrombosis is the most significant cause of morbidity and mortality
- Approximately 30–40% of people with PNH develop AA, MDS or AML within a 10-year follow-up period⁴

Common PNH symptoms



AA, aplastic anaemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal haemoglobinuria

1. Gulbis B et al. Adv Exp Med Biol 2010;686:375–96; 2. Hill A et al. Nat Rev Dis Primers 2017;3:17028; 3. Loschi M et al. Am J Hematol 2016;91:366–70; 4. Szlendak U et al. Pol Arch Intern Med 2022;132:16271;






5. Meyers G et al. Blood 2007;110:3683; 6. Nishimura J et al. Medicine 2004;83:193–207; 7. Hill A et al. Br J Haematol 2010;149:414–25; 8. Hillmen P et al. Am J Hematol 2010;85:553–9; 9. Parker C et al. Blood 2005;106:3699–709;

10. Hillmen P et al. N Engl J Med 1995;333:1253–8



Before C5 inhibitors were available, PNH treatment options were limited and often inadequate

Pre-C5 inhibitors/C5 inhibitors not available

Option	Description
 Blood transfusions	Used to alleviate anaemia. ¹ Painful and disruptive to patients' lives, with risk of infections and alloimmunisation
 Bone marrow transplant	Associated with morbidity and mortality risks, including GVHD; limited availability of compatible donors ^{2,3}
 Long-term anticoagulation	Necessary for patients with thrombosis who do not have access to eculizumab; despite treatment, risk of thrombosis and death remains ⁴
 Corticosteroids	May improve haemoglobin levels and reduce haemolytic episodes in some cases; associated with long-term toxicity and limited efficacy ²
 Clinical trials	If trials are available, they may offer patients an alternative to bone marrow transplant ⁵

For people with PNH who cannot access C5 inhibitors now, these less efficacious treatments are still prescribed to manage symptoms

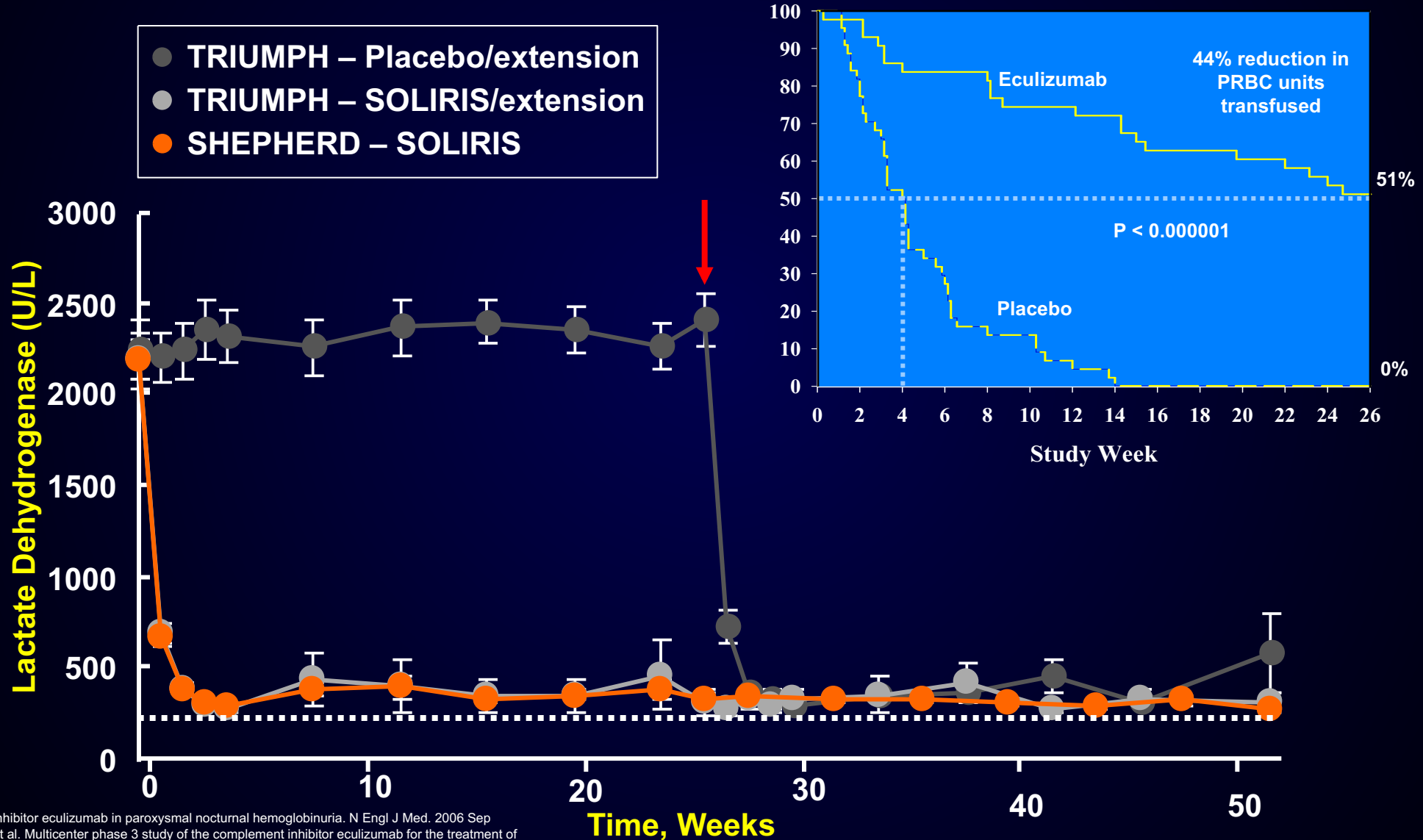


GVHD, graft-vs-host disease; PNH, paroxysmal nocturnal haemoglobinuria

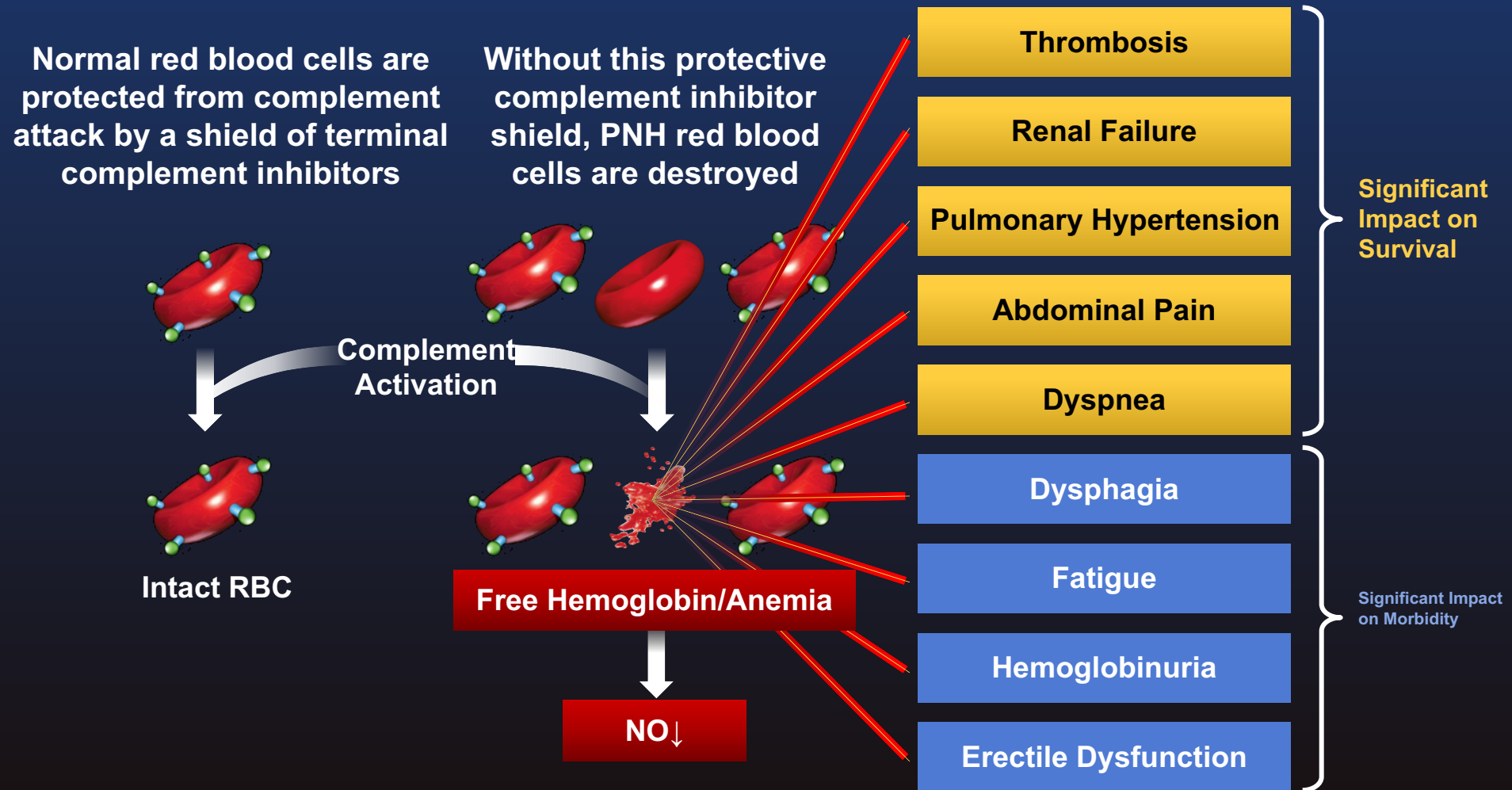
1. Olutogun T. Blood Transfus 2015;13:363-9; 2. Brodsky RA. Blood 2014;124:2804-11; 3. Risitano AM et al. Front Immunol 2019;10:1157; 4. Griffin M, Munir T. Ther Adv Haematol 2017;8:119-26; 5. Hill A et al. Nat Rev Dis Primers 2017;3:17028

EFFECT OF ECULIZUMAB ON HEMOLYSIS

Lactate dehydrogenase (LDH) and transfusion independency



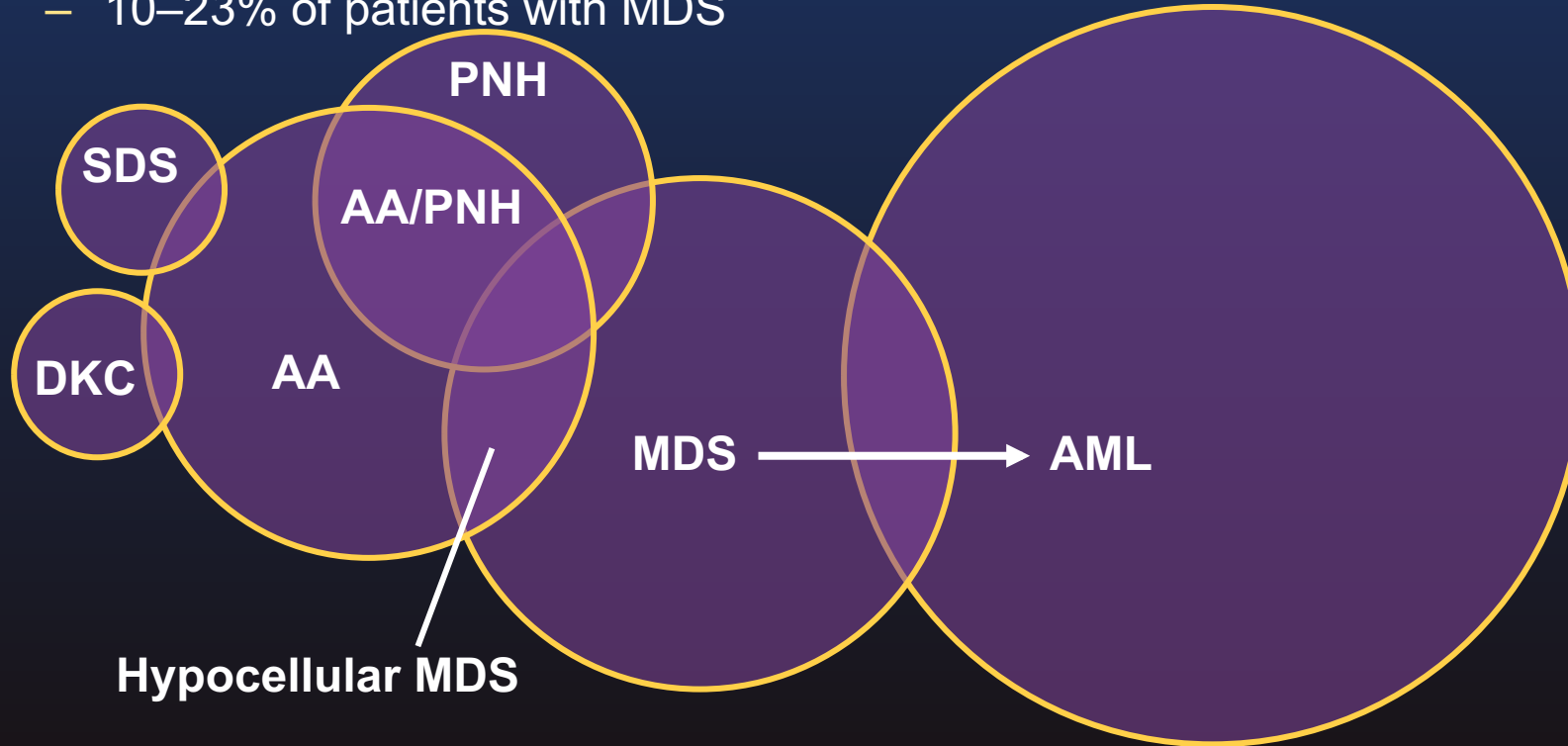
Chronic Uncontrolled Complement Activation Leads to Devastating Consequences ¹⁻⁸



1. International PNH Interest Group. *Blood*. 2005;106:3699-3709. 2. Brodsky R. Paroxysmal Nocturnal Hemoglobinuria. In: *Hematology - Basic Principles and Practices*. 4th ed. R Hoffman; EJ Benz; S Shattil et al, eds. Philadelphia, PA: Elsevier Churchill Livingstone; 2005;419-427. 3. Rother RP et al. *JAMA*. 2005;293:1653-1662. 4. Socie G et al. *Lancet*. 1996;348:573-577. 5. Hill A et al. *Br J Haematol*. 2007;137:181-192. 6. Lee JW et al. *Hematologica* 2010;95(s2): Abstract #505 and 506. 7. Hill A et al. *Br J Haematol*. 2010; May;149(3):414-425. 8. Hillmen P et al. *Am J Hematol*. 2010;85:553-559.

Expansion of PNH Clone¹

- PNH clone is more common in patients with bone marrow failure syndromes²⁻⁵
 - 25–45% of patients with aplastic anaemia
 - 10–23% of patients with MDS



AA, aplastic anaemia; AML, acute myelogenous leukaemia;
DKC, dyskeratosis congenita; SDS, Shwachman-Diamond syndrome;
MDS, myelodysplastic syndrome;
PNH, paroxysmal nocturnal haemoglobinuria

Young, NS *et al. Blood* 2006;108:2509-2519

1. Araten DJ *et al. Proc Natl Acad Sci USA* 1999;96:5209-14;
2. Johnson RJ, Hillmen P. *Mol Pathol* 2002;55:145-52;
3. Wang H *et al. Blood* 2002;100:3897-902;
4. Iwanga M *et al. Br J Haematol* 1998;102:465-74;
5. Maciejewski JP *et al. Br J Haematol* 2001;115:1015-22

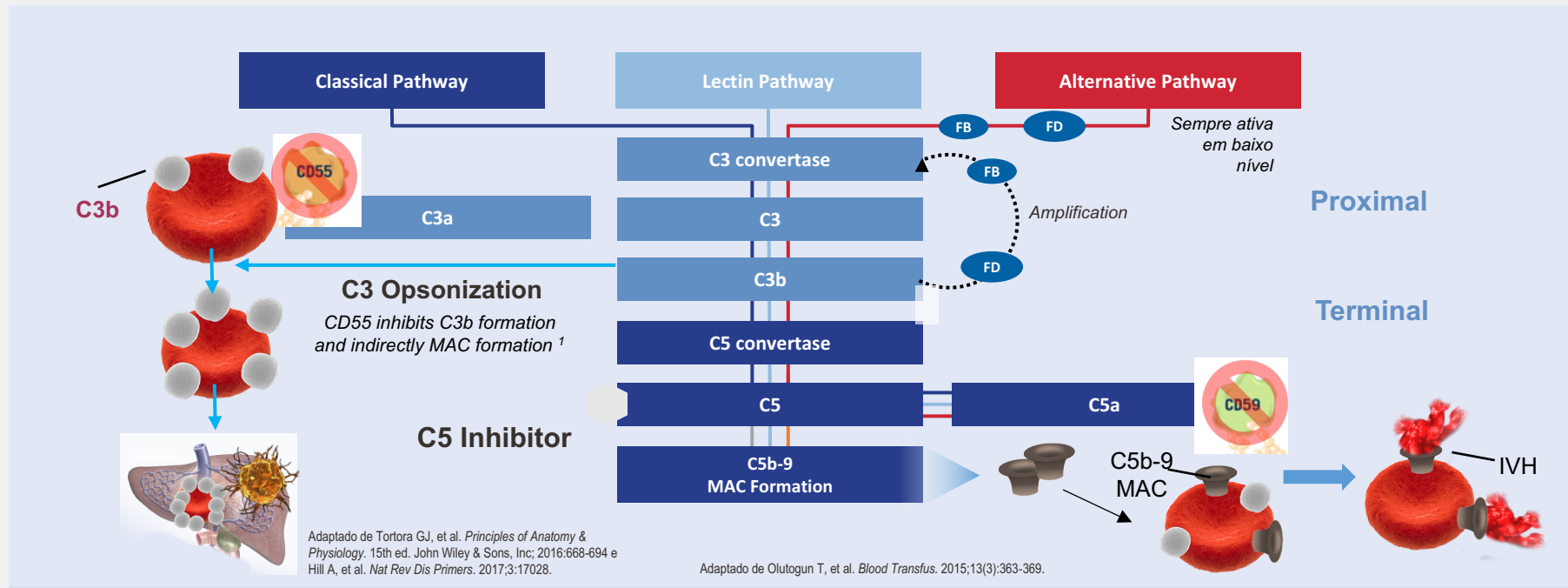
Unmet Medical Need Despite

Multicenter, real-life, retrospective study of 160 patients with PNH treated with eculizumab¹

	Response category	Response criteria	Main goal of new therapy
21.3%	Complete response 11% BTH, 17% EVH	Hb ≥ 12 g/dL, transfusion independent	Decrease hospital visits
40.2%	Good response 8% BTH, 43% EVH	Hb 10 – 12 g/dL, transfusion independent	Normalization of Hb
26.8%	Partial response 21% BTH, 55% EVH	Hb 8 – 10 g/dL, occasional transfusions	Transfusion independency
11.8%	Minor response 27% BTH, 66% EVH	Hb < 8 g/dL, regular transfusions	Transfusion independency, limit hemochromatosis

Hb, hemoglobin; RBCT, red blood cell transfusion; SoC, standard of care; BTH, breakthrough hemolysis; EVH, extravascular hemolysis

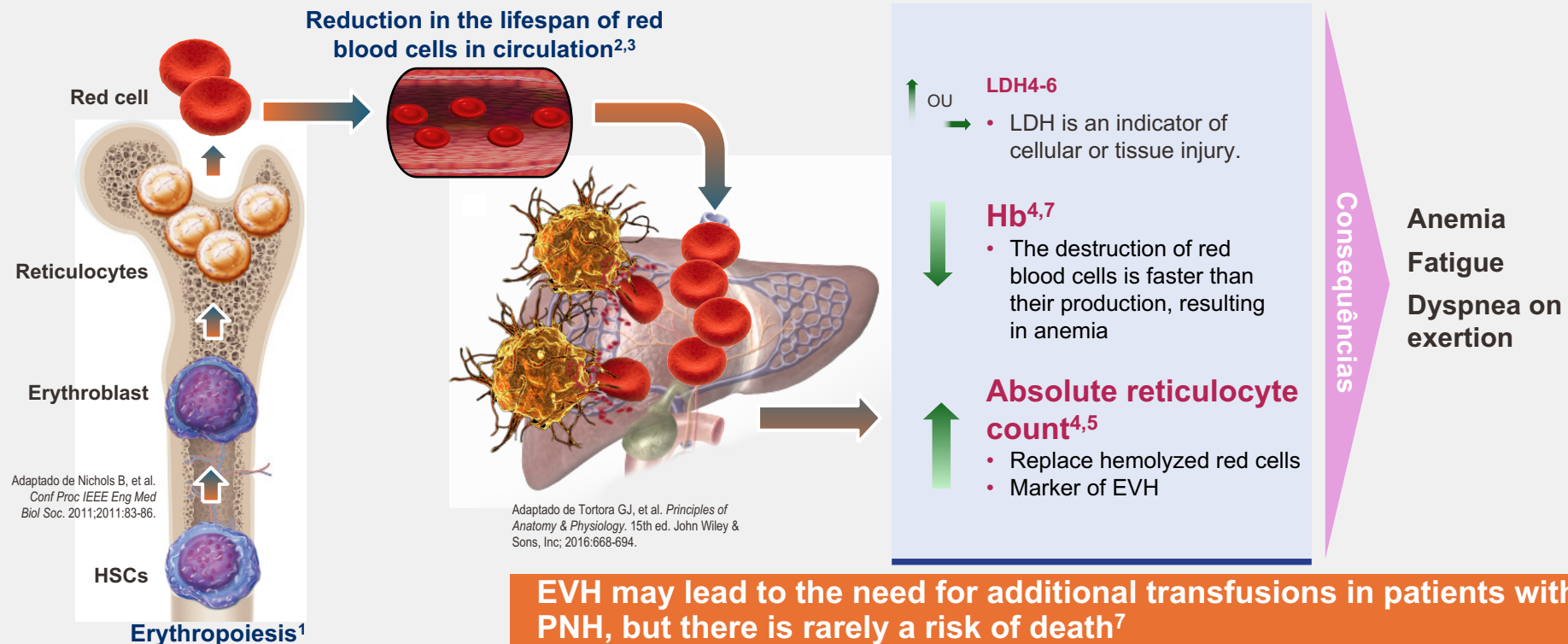
TERMINAL COMPLEMENT INHIBITION LEADS TO INCREASED C3 OPSONIZATION ON PNH RED BLOOD CELLS, POTENTIALLY RESULTING IN EVH ¹⁻⁵



C3 = componente 3 do complemento; C5 = componente 5 do complemento; CD = cluster de diferenciação; HEV= hemólise extravascular; FB = fator B do complemento; FD = fator D do complemento; MAC = complexo de ataque à membrana; HPN = hemoglobinúria paroxística noturna.

1. Hill A, et al. *Nat Rev Dis Primers*. 2017;3:17028. 2. Ricklin D, et al. [published online December 9, 2019]. *Nat Rev Drug Discov*. doi: 10.1038/s41573-019-0055-y. 3. Walport MJ. *N Engl J Med*. 2001;344(14):1058-1066. 4. Tortora GJ, et al. *Principles of Anatomy & Physiology*. 15th ed. John Wiley & Sons, Inc; 2016:668-694. 5. Olutogun T, et al. *Blood Transfus*. 2015;13(3):363-369.

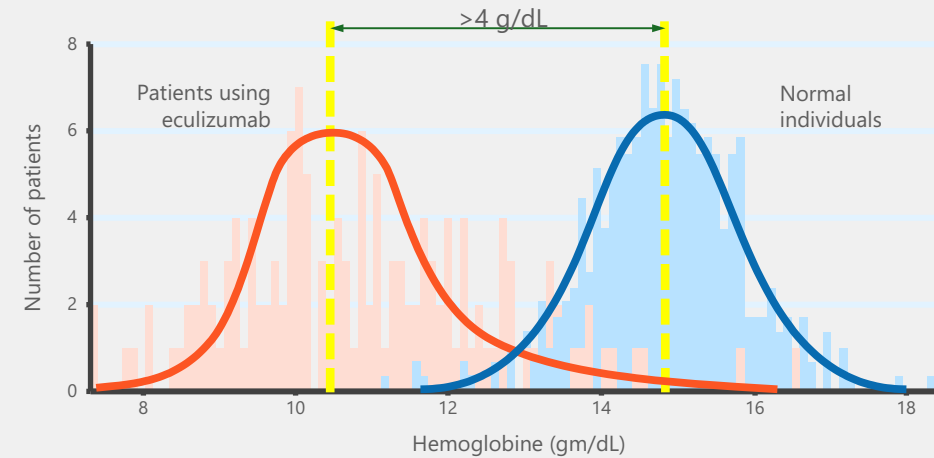
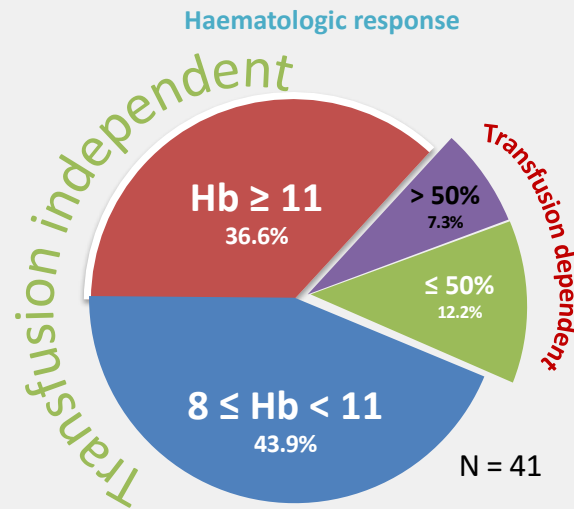
MAIN CONSEQUENCES AND LABORATORY FINDINGS OF EVH IN PNH



HEV = hemólise extravascular; Hb = hemoglobina; DHL = lactato desidrogenase; HPN = hemoglobinúria paroxística noturna.

1. Nichols B, et al. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:83-86. 2. Dhaliwal G, et al. *Am Fam Phys.* 2004;69(11):2599-2606. 3. Tortora GJ, et al. *Principles of Anatomy & Physiology.* 15th ed. John Wiley & Sons, Inc; 2016:668-694. 4. Brodsky RA. In: Hoffman R, et al, eds. *Hematology: Basic Principles and Practices.* 6th ed. Livingstone; 2013:373-382. 5. McKinley CE, et al. *Blood.* 2017;130 (suppl 1): 3471. 6. Noronha SA. *Pediatr Rev.* 2016;37(6):235-246. 7. Hill A, et al. *Nat Rev Dis Primers.* 2017;3:17028.

HEMOGLOBIN LEVELS IN ECULIZMAB TREATED PATIENTS



ARC normal or low	
Marrow Failure (AA, MDS)	Follow AA guidelines
Folate Deficiency	Foli acidid
Relaive Epo deficiency	SQ Epo
Iron overload	Iron replacement

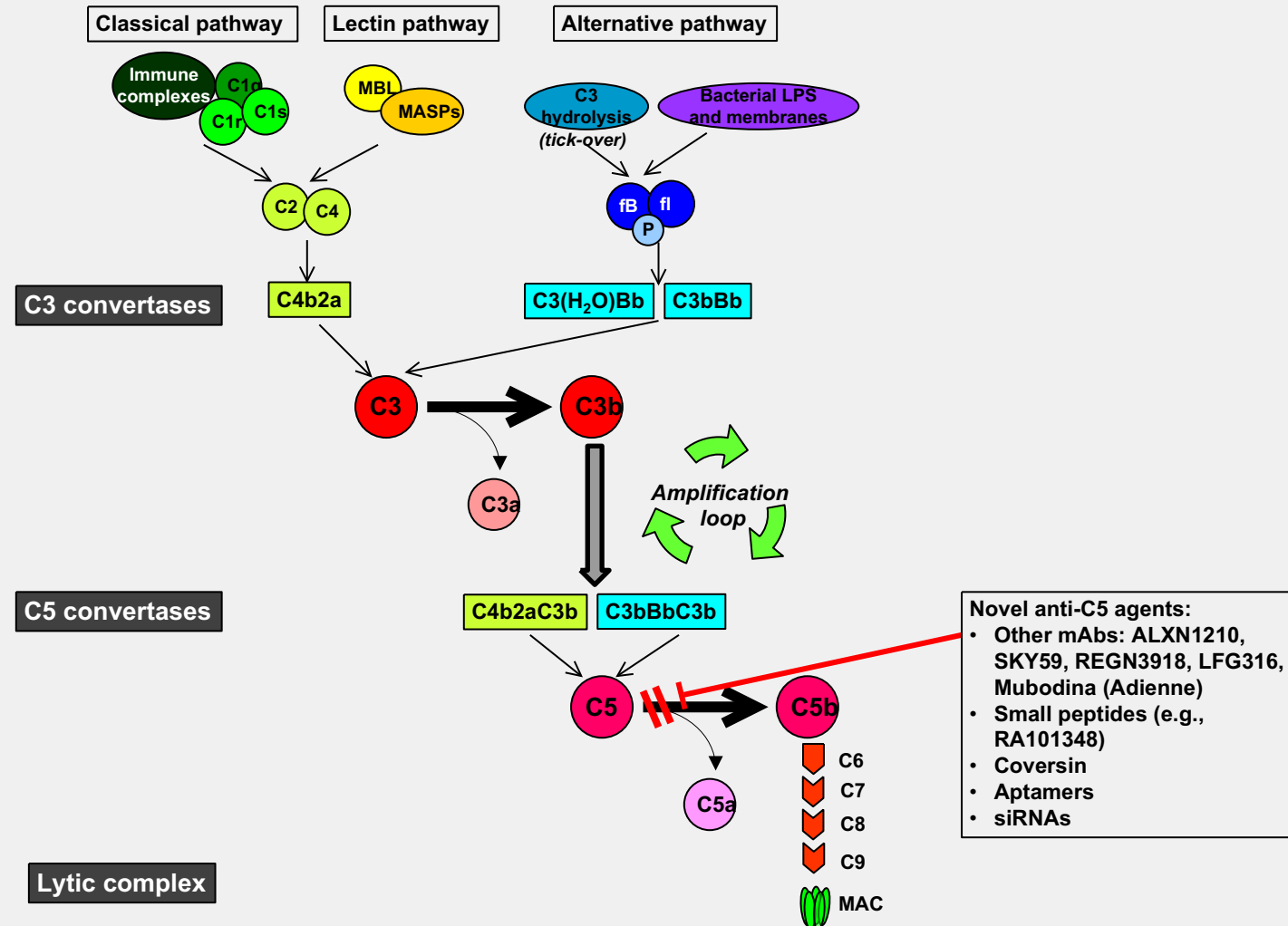
Risitano AM, et al. Blood. 2009;113:4094-100.

High ARC	
Persistent IVH	Pharmacokinetic breakthrough
Clinically significant EVH	Proximal inhibition
Hypersplenism	Splenic embolization
Bleeding	Direcionado para causar
Aloantibodies	Blood transfusion

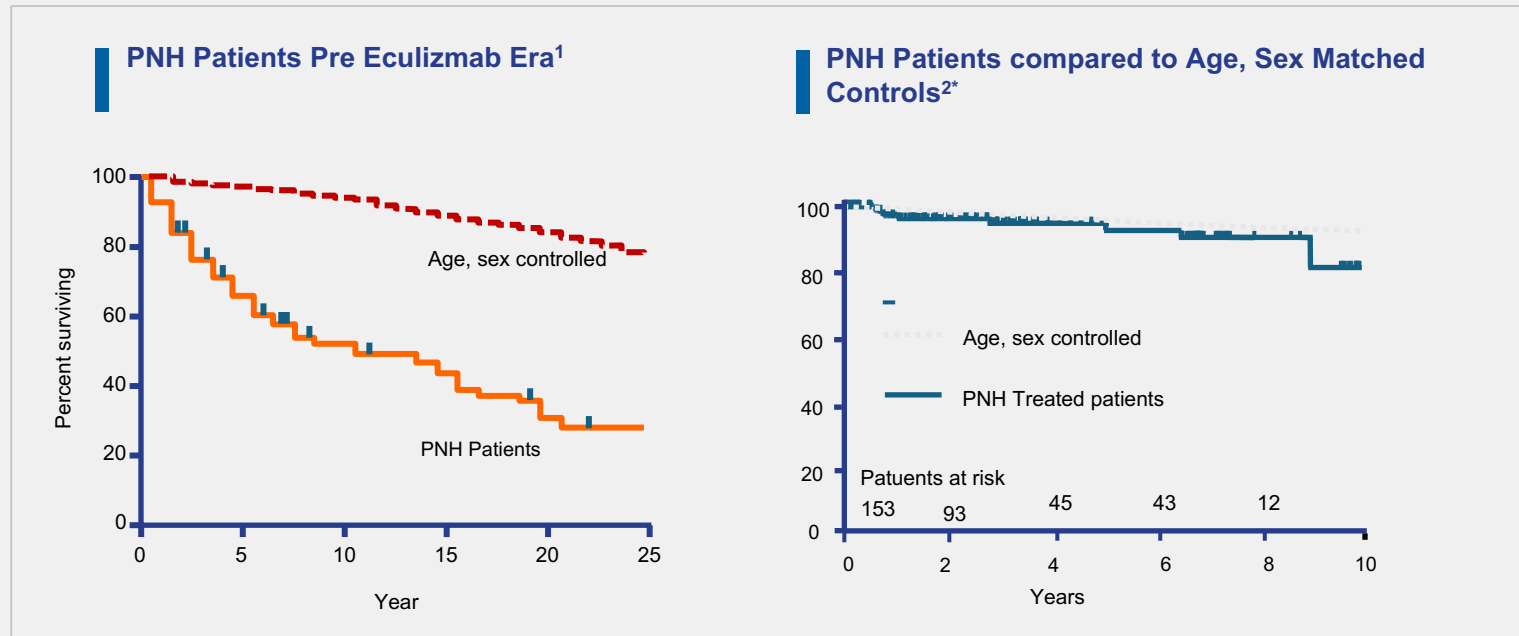
Source: Peter Hillmen, Professor of Experimental Haematology, University of Leeds

Improved strategies in the management of PNH

- **Administration route**
 - intravenous/ subcutaneous/ oral
- **Frequency of administration**
- **Prevention of breakthrough haemolysis**
 - 1/5th of patients require a higher than standard dose of eculizumab
- **Improvement in extravascular haemolysis**
- **Accessibility to therapy**
- **C5 mutation patients**
- **Management of the underlying bone marrow failure**



Overall Survival Pre and Post Eculizumab



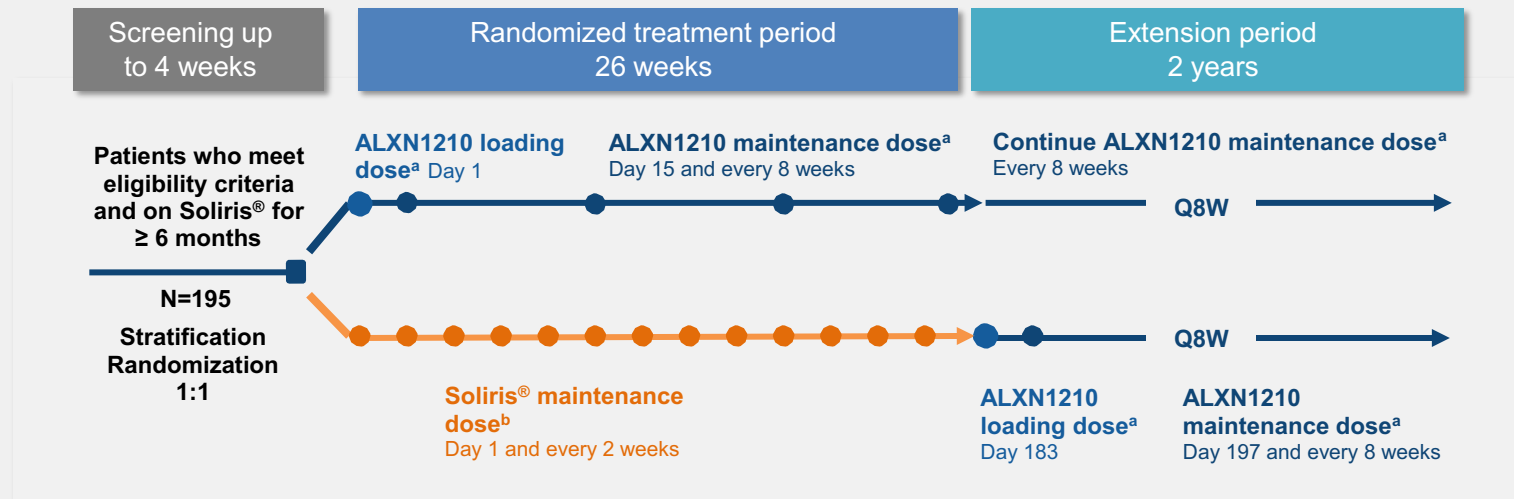
Mortality of 35% in 5 Years ¹

HR= 2.24 (P=0.013)

A sobrevida após 10 anos é ligeiramente inferior quando as causas de morte são relacionadas à falência da medula óssea, e não à hemólise ou trombose.

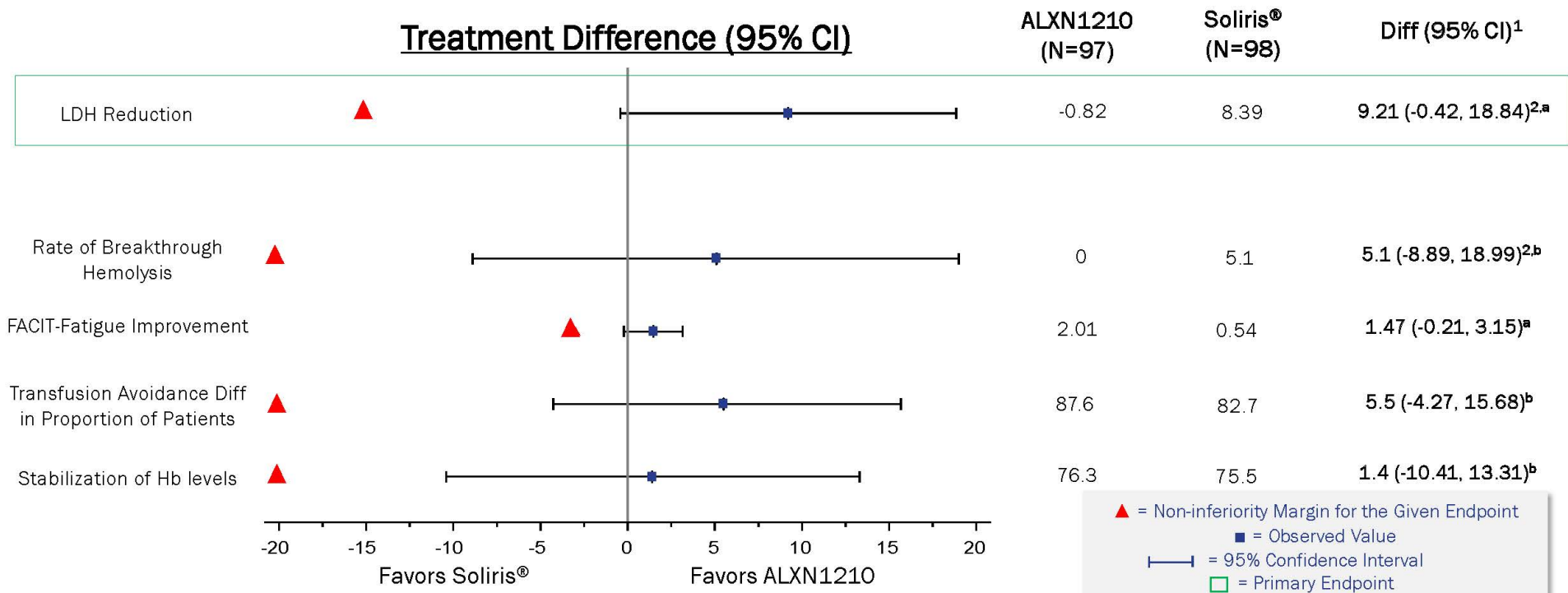
ALXN1210 Phase 3 PNH Switch Study: Trial Design (Ravulizumab)

- **Primary Objective:** Assess non-inferiority of ALXN1210 compared to Soliris® in patients with PNH who are clinically stable after having been treated with Soliris® for at least the past 6 months
- **Primary Endpoint:** Hemolysis as directly measured by percentage change in LDH levels from Baseline to Day 183.



^aALXN1210 dosage: loading dose = 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg; maintenance dose=3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg. ^bSoliris maintenance dose=900 mg. NCT03056040. Clinical Trial.gov website. <https://clinicaltrials.gov/ct2/show/NCT03056040>
Provided April 26, 2018, as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Alexion disclaims any duty to update.

ALXN1210 Phase 3 Switch Study: Non-Inferiority Achieved on All Endpoints



Statistically Significant Non-inferiority Achieved on All Primary & Key Secondary Endpoints. All Endpoints Numerically Favor ALXN1210

Note: CI=Confidence Interval; Diff=difference; TA=Transfusion Avoidance; LDH Reduction = LDH % change from baseline; BTH=Breakthrough Hemolysis; HGB-S=Stabilized Hemoglobin. The red triangle indicates the non-inferiority margin.

¹ For endpoints TA, LDH Reduction, BTH, and HGB-S, Diff (95% CI) are based on estimated differences in percent with 95% CI. For FACIT-Fatigue, Diff (95% CI) are based on estimated differences in change from baseline with 95% CI.

² Treatment difference is estimated for ALXN1210-Soliris® except for LDH Reduction and Rate of Breakthrough Hemolysis where treatment difference is based on Soliris-ALXN1210.

^aDifference in change from Baseline; ^bDifference in proportion of patients;

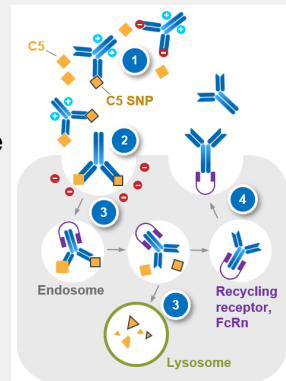
Provided April 26, 2018, as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Alexion disclaims any duty to update.



Crovalimab is a novel **anti-C5 recycling monoclonal antibody**^{1,2} with a long-half life, high solubility, and high bioavailability, which allows for **low-volume, Q4W SC injection**

Mechanism of action³

- 1 High-affinity binding
- 2 Preferential antibody uptake (proprietary innovative engineering)
- 3 Acid-sensitive binding and antigen degradation
- 4 Antibody recycling by FcRn engineering



Adapted from Igawa T, Biochim Biophys Acta 2014.

Phase III COMMODORE studies in PNH

COMMODORE 2 (NCT04434092)⁴

- Global **C5i-naive** patients (**N=204**) 🌍
- **Randomized** 2:1 to receive crovalimab or eculizumab
- Pediatric patients were enrolled in a descriptive arm to receive crovalimab

COMMODORE 3 (NCT04654468)^{5,6}

- Chinese **C5i-naive** patients (**N=51**) 🇨🇳
- **Single arm**

COMMODORE 1 (NCT04432584)⁷

- Global **C5i-experienced** patients (**N=89**) 🌍
- **Randomized** 1:1 to receive crovalimab or eculizumab
- Select patients^a were enrolled in a descriptive arm to receive crovalimab

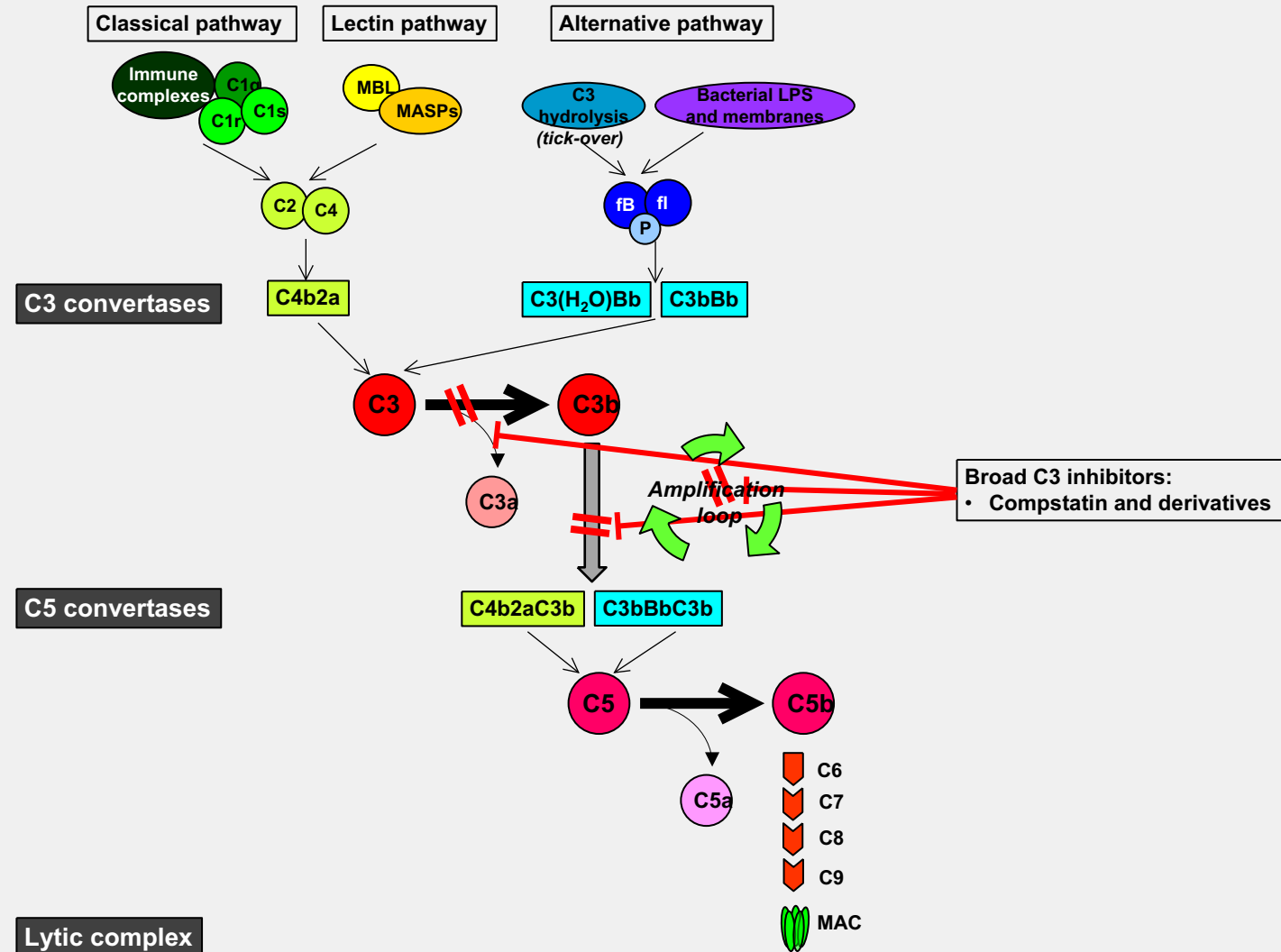


Here, we report **pooled safety data** for crovalimab and eculizumab from the 3 open-label, multicenter, **Phase III COMMODORE studies**

Efficacy across Phase III COMMODORE studies

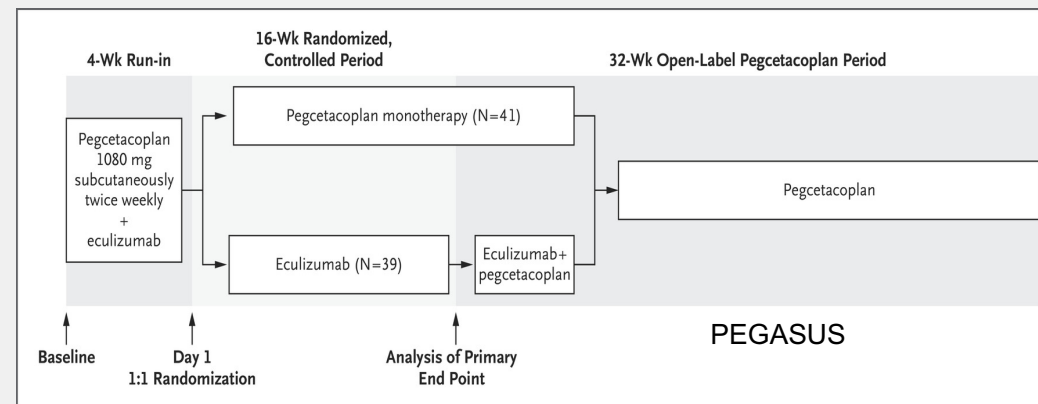
	C5i naive			Switched from a C5i to crovalimab	
	COMMODORE 2 ¹		COMMODORE 3 ²	COMMODORE 1 ³	
	Crovalimab (n=134)	Eculizumab (n=69)	Crovalimab (n=51)	Crovalimab (n=39)	Eculizumab (n=37)
Hemolysis control (central LDH $\leq 1.5 \times \text{ULN}$), mean	79.3%	79.0%	78.7%	92.9%	93.7%
Odds ratio ^a (95% CI)	1.0 (0.6, 1.8); non-inferior		NA	0.9 (0.3, 2.8)	
Transfusion avoidance	65.7%	68.1%	51.0%	79.5%	78.4%
Difference in proportion (95% CI)	-2.8 (-15.7, 11.1); non-inferior		51.0 (34.3, 65.1) ^b	1.8 (-16.7, 19.9)	
Patients with breakthrough hemolysis	10.4%	14.5%	3.9%	10.3%	13.5%
Difference in proportion (95% CI)	-3.9 (-14.8, 5.3); non-inferior		NA	-3.5 (-19.2, 11.7)	
Patients with hemoglobin stabilization	63.4%	60.9%	51.0%	59.0%	70.3%
Difference in proportion (95% CI)	2.2 (-11.4, 16.3); non-inferior		NA	-10.8 (-30.8, 10.4) ^c	
Mean change from baseline in FACIT-Fatigue	n=128 7.8 ^d	n=66 5.2 ^d	n=48 8.8 ^e	n=38 1.1 ^d	n=32 -2.6 ^d
Difference in adjusted means (95% CI)	2.6 (0.7, 4.6); descriptive		NA	3.7 (0.1, 7.4)	

^a Odds ratio >1 favors crovalimab. ^b Based on inpatient comparison of transfusion avoidance between pre-screening vs primary treatment period. ^c Driven by a difference of only 3 patients between arms. ^d From baseline through Week 25. ^e From baseline through Week 17; 95% CI: 6.0, 11.6.
1. Röth A, EHA 2023 [abs S181]; 2. Liu H, Am J Hematol 2023; 3. Scheinberg P, EHA 2023 [abs S183].



Pegcetacoplan

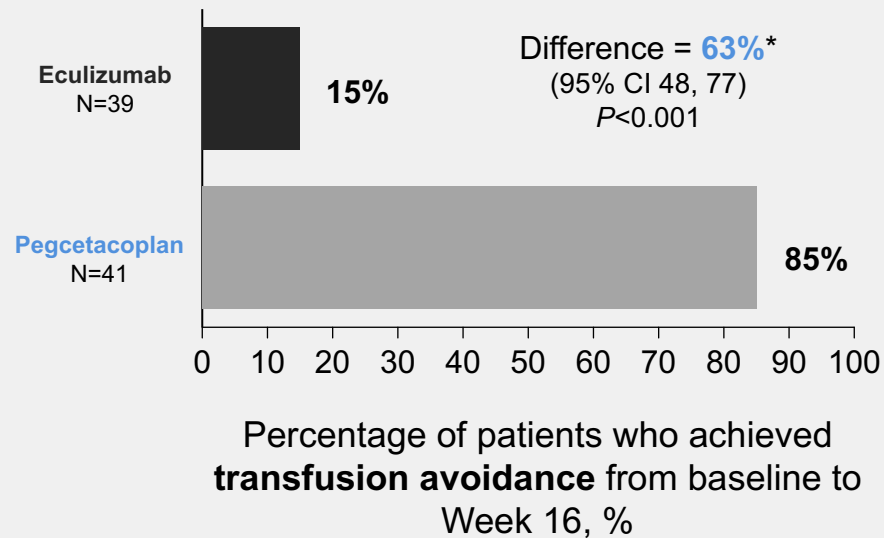
- Pegcetacoplan is a targeted C3 inhibitor.
- Pegcetacoplan targets the proximal complement pathway, binding to C3 and inhibiting its activation¹
- Pegcetacoplan is administered SC twice weekly¹⁻⁴



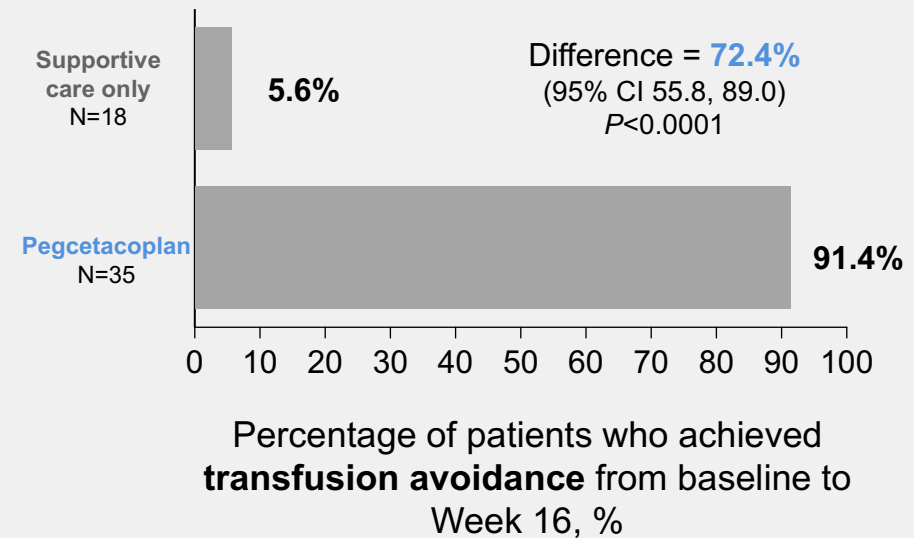
1. De Castro C *et al.* *Am J Hematol* 2020;95:1334–43; 2. Hillmen P *et al.* *N Engl J Med* 2021;384:1028–37; 3. Apellis Pharmaceuticals, Inc. EMPAVELI (pegcetacoplan) Prescribing Information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215014s000lbl.pdf (accessed March 2022); 4. Swedish Orphan Biovitrum AB (publ). ASPAVELI Summary of Product Characteristics. 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/aspaveli-epar-product-information_en.pdf (accessed March 2022);

Pegcetacoplan

Pegcetacoplan (Phase III; PEGASUS)¹
(80 patients who were anemic despite receiving eculizumab)

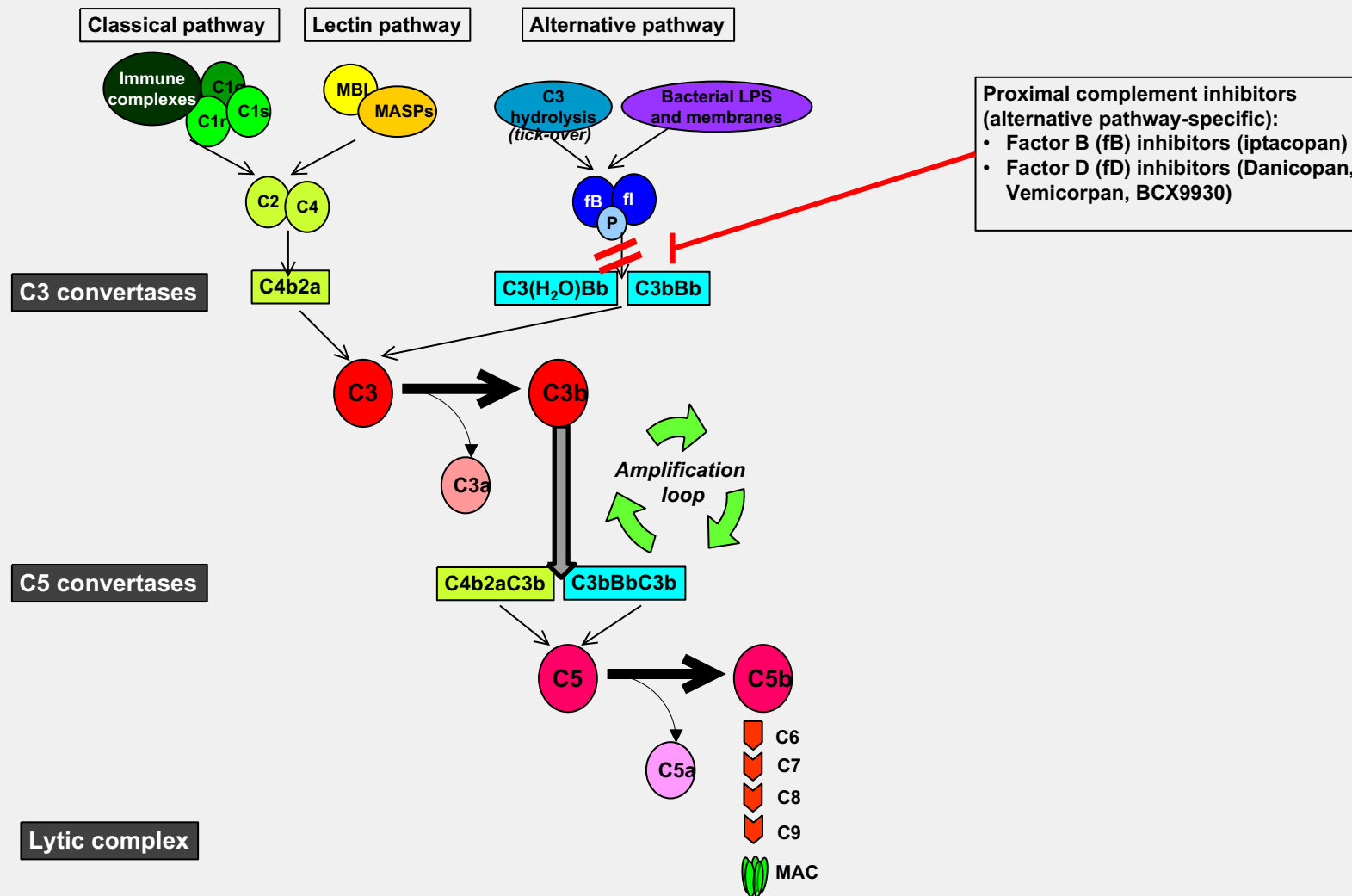


Pegcetacoplan (Phase III; PRINCE)²
(53 complement inhibitor-naïve patients)



*Pegcetacoplan was non-inferior to eculizumab. To control for a type 1 error, the proportion of patients who did not require a transfusion during the randomized controlled period were tested for non-inferiority if superiority was declared for the primary endpoint

1. Hillmen P et al. *N Engl J Med* 2021;384:1028–37; 2. Wong RS et al. *Blood Adv* 2023 doi: <https://doi.org/10.1182/bloodadvances.2022009129>

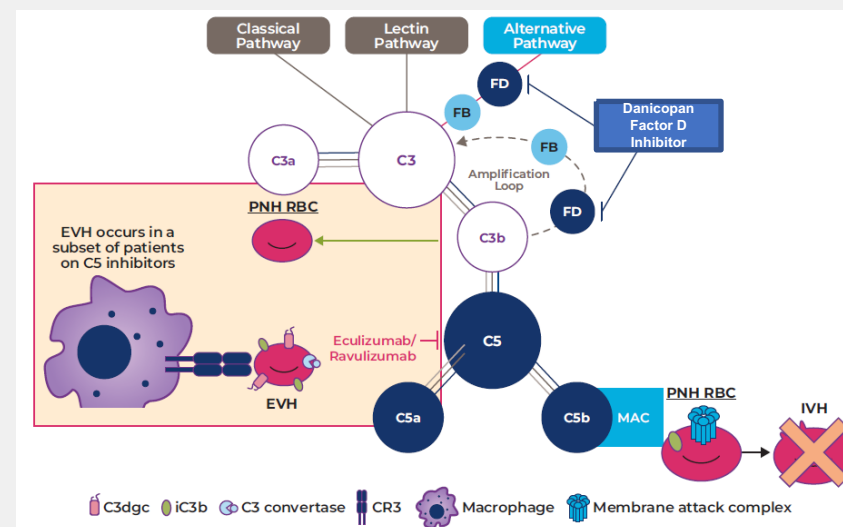


Danicopan

Introduction

- Danicopan (ALXN2040) is an investigational, first-in-class, oral factor D inhibitor targeting complement AP activity
 - The AP, unlike the classical and lectin pathways, turns over continuously at a low level in the blood via C3 hydrolysis¹
- Danicopan demonstrated predictable pharmacokinetics and a favorable benefit-risk profile in phase 2 trials in patients with PNH^{2,3}

IVH and EVH Associated Complement System in PNH

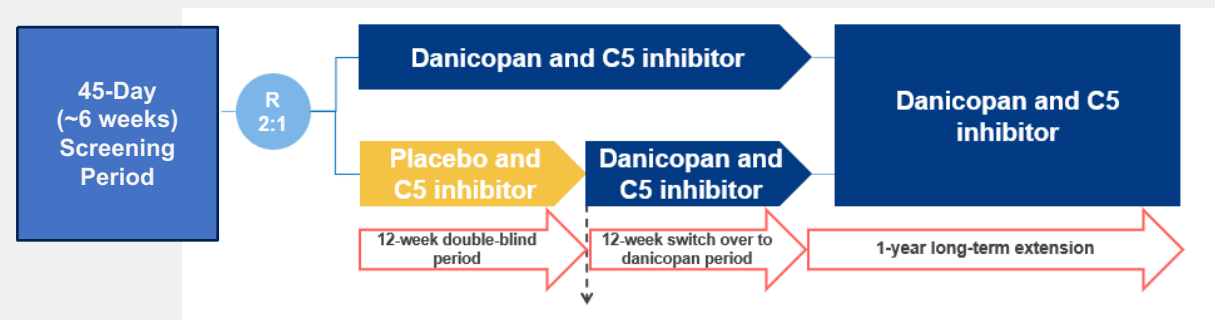


1. Wiles JA, et al. *Curr Med Chem*. 2020. 2 Kulasekararaj AG, et al. *Blood*. 2021. 3. Risitano AM, et al. *Haematologica* 2021.

AP, alternative pathway; cs-EVH, clinically significant EVH; EVH, extravascular hemolysis; FB, factor B; FD, factor D; IVH, intravascular hemolysis; MAC, membrane attack complex; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

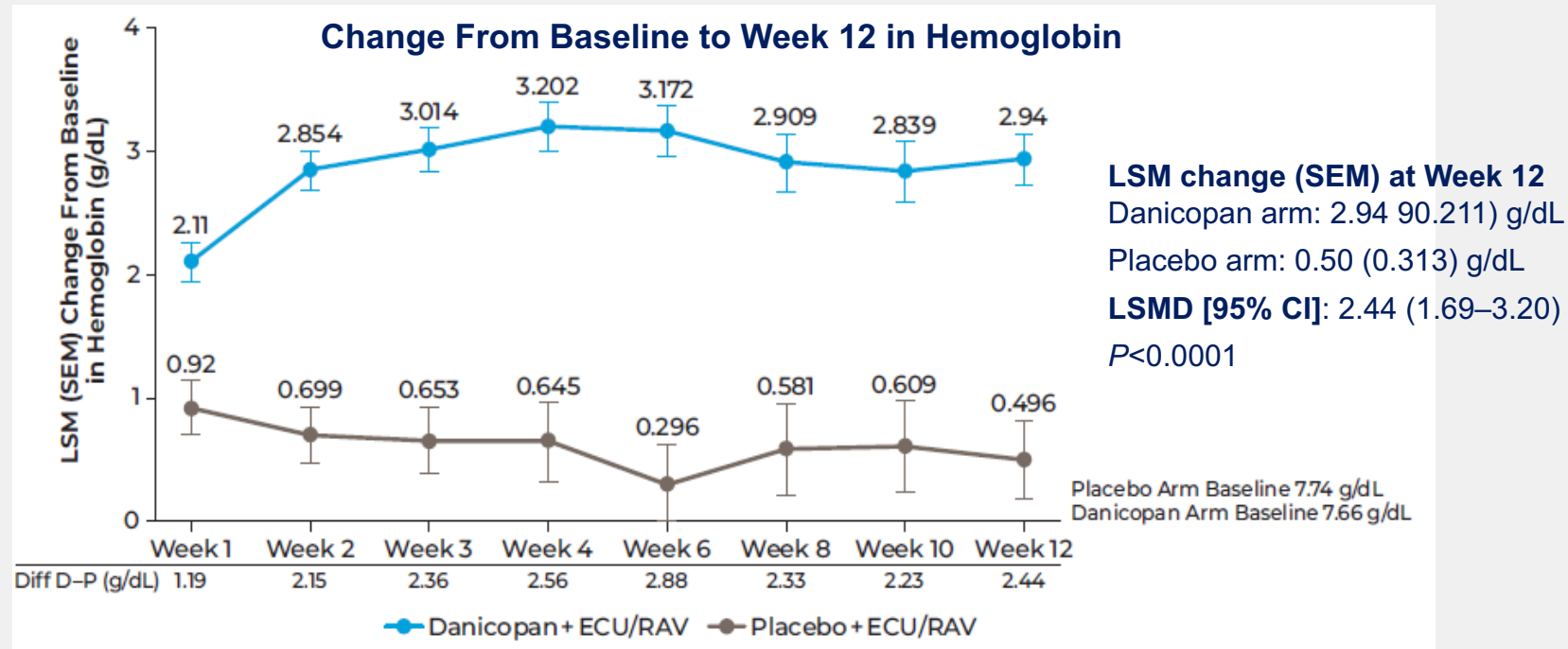
Methods

<p>Study Design</p>	<ul style="list-style-type: none"> Ongoing, phase 3, randomized, double-blind, placebo-controlled clinical trial 	<p>Dosing</p>	<ul style="list-style-type: none"> Initial danicopan dose of 150 mg TID <ul style="list-style-type: none"> Escalation to 200 mg TID permitted based on clinical response at the investigator's discretion
<p>Endpoints</p>	<ul style="list-style-type: none"> Primary endpoint: Change in Hgb from baseline at week 12 Key secondary endpoints at week 12: <ul style="list-style-type: none"> Proportion of participants with Hgb increase of ≥ 2 g/dL without transfusion Proportion of participants with transfusion avoidance Change from baseline in FACIT-F score and ARC Safety: TEAEs and laboratory abnormalities 	<p>Key Inclusion Criteria</p>	<ul style="list-style-type: none"> Age ≥ 18 years with PNH and cs-EVH, despite receiving stable eculizumab or ravulizumab treatment for ≥ 6 months
		<p>Data Analysis</p>	<ul style="list-style-type: none"> Statistical significance: <ul style="list-style-type: none"> 2-sided 0.018 for primary endpoint 2-sided 0.042 for key secondary endpoints Safety analysis performed using data from all participants who took ≥ 1 dose of the study drug <ul style="list-style-type: none"> Data analyzed descriptively



Methods

- Danicopan* as an add-on treatment to eculizumab or ravulizumab resulted in a statistically significant increase in Hb from baseline to week 12 vs placebo as add-on to eculizumab or ravulizumab

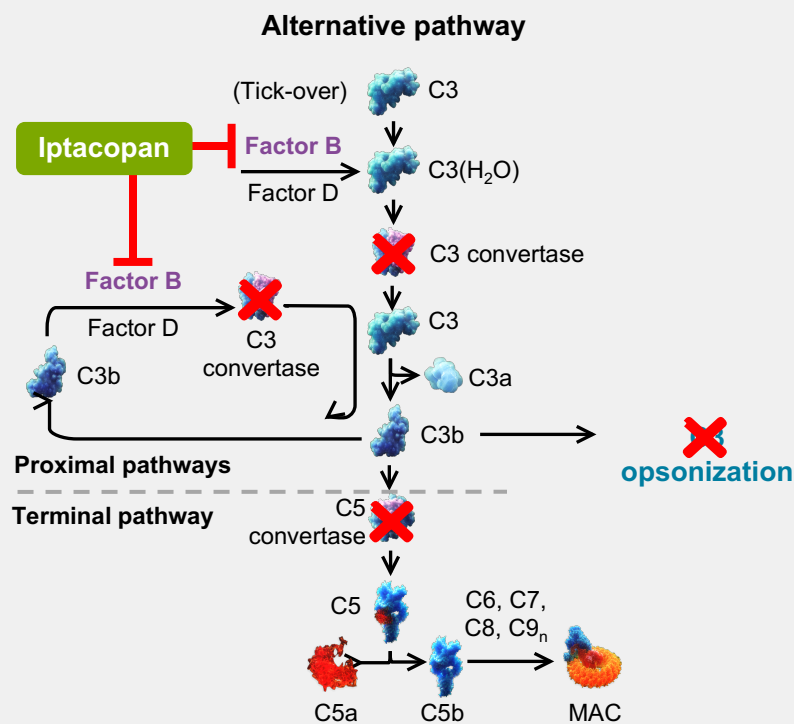


P<0.0001 for all data points.

D, danicopan; Diff, difference; ECU, eculizumab; Hgb, hemoglobin; LSM, least squares mean; P, placebo; RAV, ravulizumab; SE, standard error.

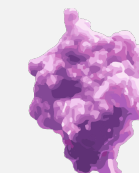
Lee J, Griffin M, Kim J et al. Addition of danicopan to ravulizumab or eculizumab in patients with paroxysmal nocturnal haemoglobinuria and clinically significant extravascular haemolysis (ALPHA): a double-blind, randomised, phase 3 trial. *The Lancet Haematology*, 10, e955-e965

Iptacopan



Iptacopan binds to the **active site** of factor B, **inhibiting** the activity of **C3 convertase**¹

Iptacopan



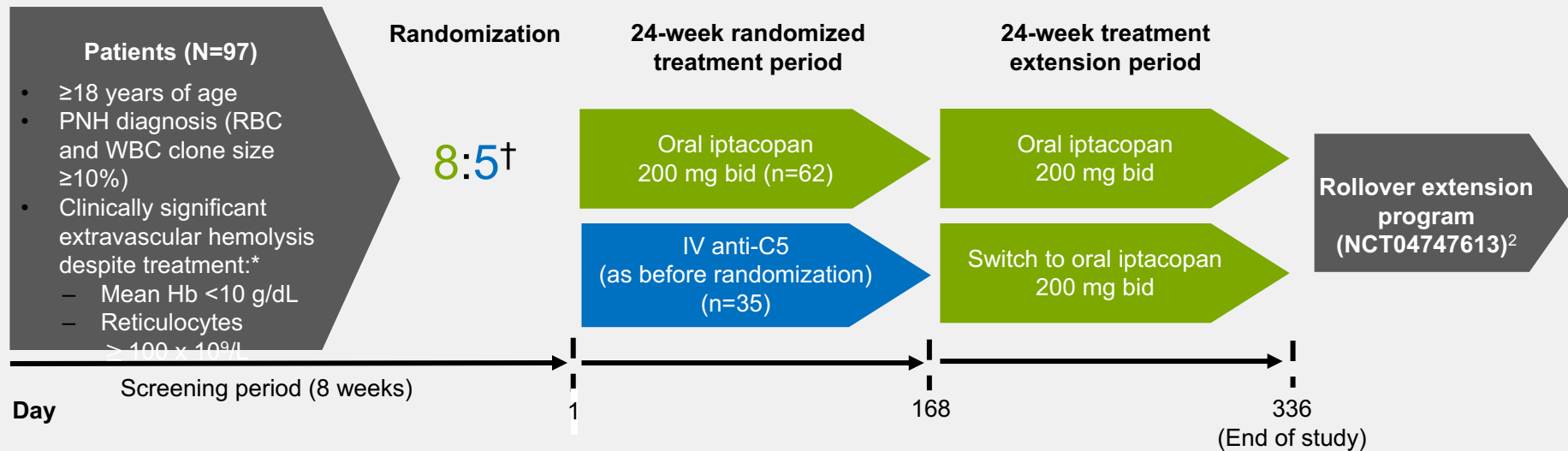
Factor B

Iptacopan **controlled intra- and extravascular hemolysis** in 10 patients with a suboptimal response to eculizumab, leading to **transfusion independence** and an **improved quality of life**²



Material from *The Lancet Haematology* is used with permission
 1. Schubart A et al. *Proc Natl Acad Sci USA* 2019;116:7926–31; 2. Risitano AM, Röth A, Soret J, et al. Addition of iptacopan, an oral factor B inhibitor, to eculizumab in patients with paroxysmal nocturnal haemoglobinuria and active haemolysis: an open-label, single-arm, phase 2, proof-of-concept trial. *Lancet Haematol.* 2021;8(5):e344–e354. doi:10.1016/S2352-3026(21)00028-4 Peffault de Latour R et al. Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria. *N Engl J Med.* 2024 Mar 14;390(11):994–1008.;

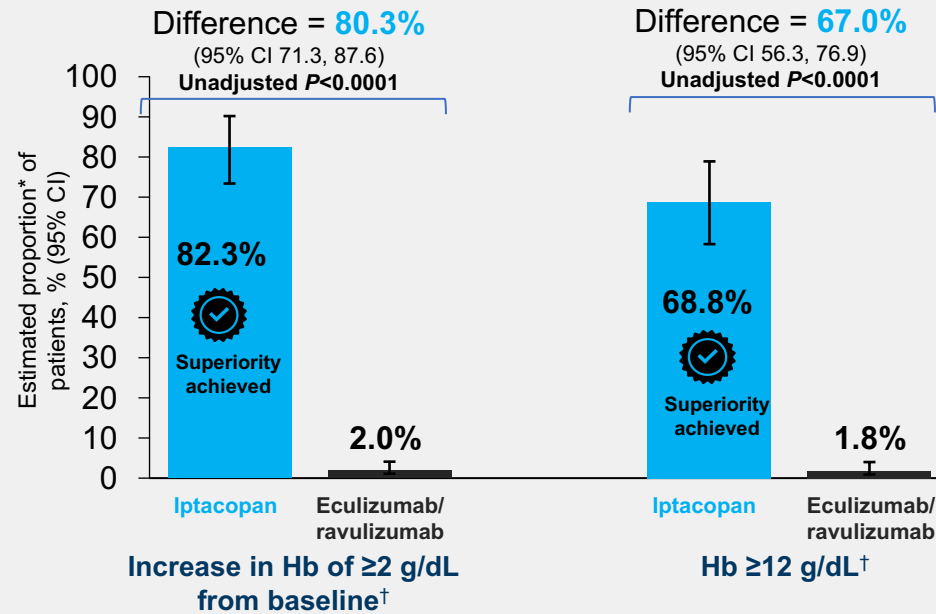
APPLY-PNH is an open-label, randomized, multicenter, Phase III trial investigating iptacopan* monotherapy in PNH patients with residual anemia despite anti-C5 therapy (NCT04558918)¹



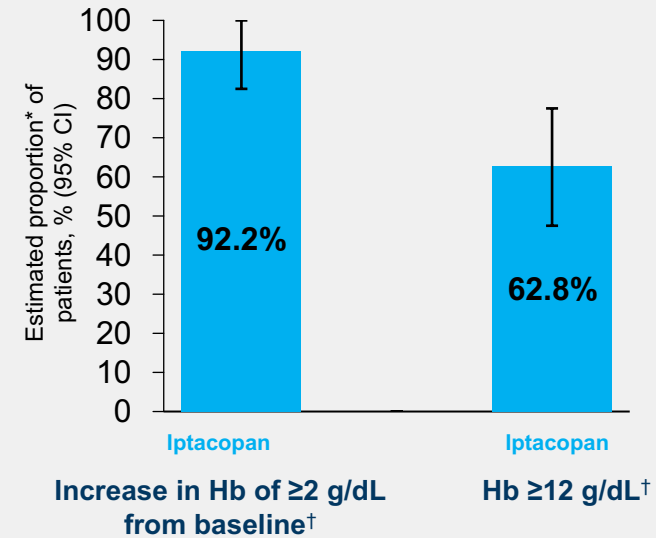
*With a stable regimen of eculizumab or ravulizumab for at least 6 months preceding randomization; [†]Stratified by prior anti-C5 treatment and RBC transfusions in the preceding 6 months bid, twice daily; Hb, hemoglobin; IV, intravenous; RBC, red blood cell; WBC, white blood cell
Peffault de Latour R et al. Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria. N Engl J Med. 2024 Mar 14;390(11):994-1008.

In Phase III trials, inhibition of factor B with oral iptacopan monotherapy led to clinically meaningful Hb improvements in the absence of RBCTs

Iptacopan (Phase III; APPLY-PNH)¹
(97 patients who were anemic despite receiving eculizumab/ravulizumab)



Iptacopan (Phase III; APPOINT-PNH)²
(40 complement inhibitor-naïve patients)



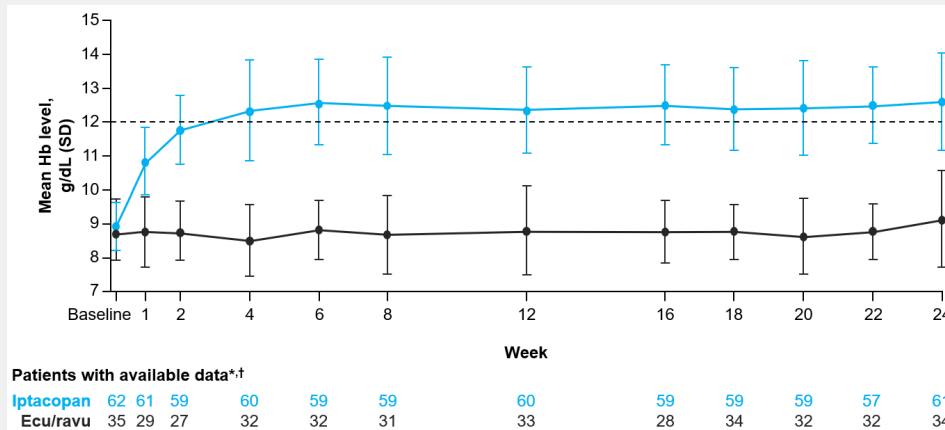
*Estimated proportions were calculated to reflect the population average probability of a patient meeting the endpoint criteria; [†]Assessed between Days 126 and 168 in the absence of (or meeting the criteria for) RBCTs between Days 14 and 168

1. Peffault de Latour R et al. Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria. N Engl J Med. 2024 Mar 14;390(11):994-1008;

In Phase III trials, inhibition of factor B with oral iptacopan monotherapy led to clinically meaningful Hb improvements in the absence of RBCTs

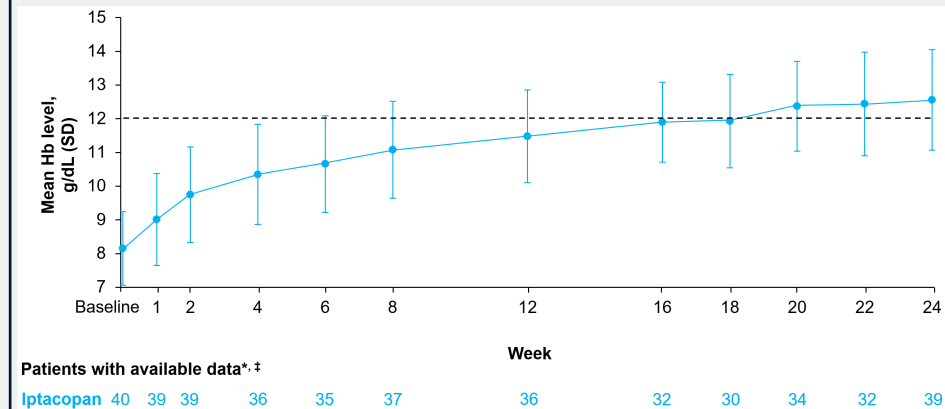


Iptacopan (Phase III; APPLY-PNH)¹
(97 patients who were anemic despite receiving eculizumab/ravulizumab)



Iptacopan was superior to eculizumab/ravulizumab for adjusted mean change in Hb from baseline,[§] with a difference of **+3.63 g/dL** (95% CI +3.18, +4.08; **unadjusted P<0.0001**) between treatment arms

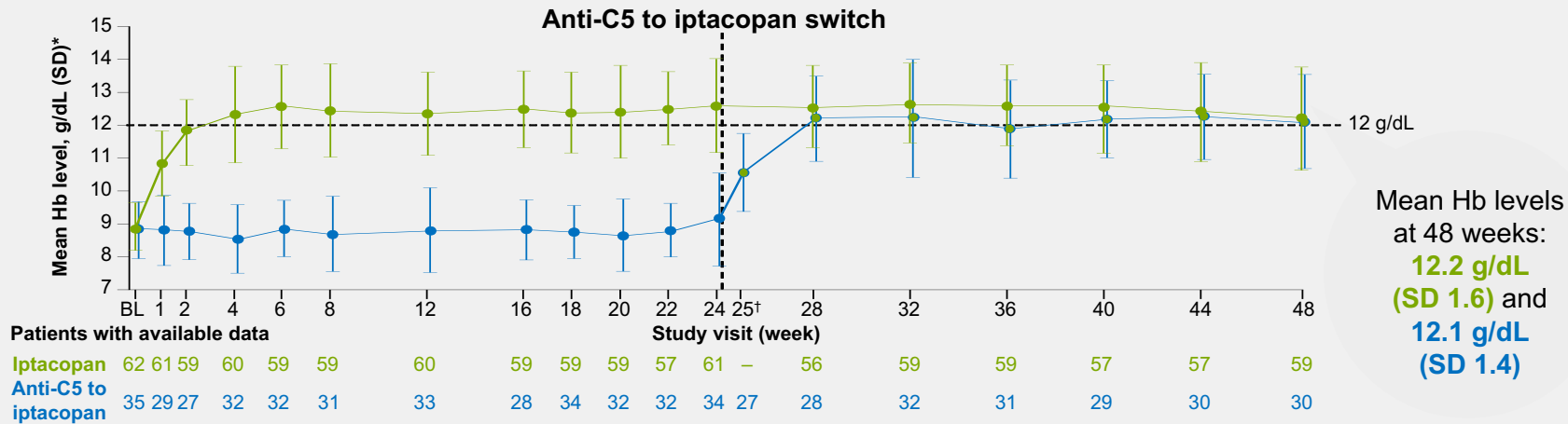
Iptacopan (Phase III; APPOINT-PNH)²
(40 complement inhibitor-naïve patients)



Iptacopan led to an adjusted mean change in Hb from baseline[§] of **+4.28 g/dL** (95% CI +3.87, +4.70)

¹Includes post-transfusion data; ²162 patients in the iptacopan arm and 21/35 patients in the eculizumab/ravulizumab arm had RBCTs between Days 14 and 168; ³RBCTs were received by 5/40 patients between Days 1 and 13 and by 0/40 patients between Days 14 and 168; [§]Assessed between Days 126 and 168 in the absence of (or meeting the criteria for) RBCTs between Days 14 and 168. Ecu, eculizumab; ravu, ravulizumab; SD, standard deviation
1. Peffault de Latour R et al. Blood 2022;140(Suppl 2):LBA-2; 2. Risitano AM et al. European Society for Blood and Marrow Transplantation (EBMT). Paris, France, 23–26 April 2023; abstract OS12-06

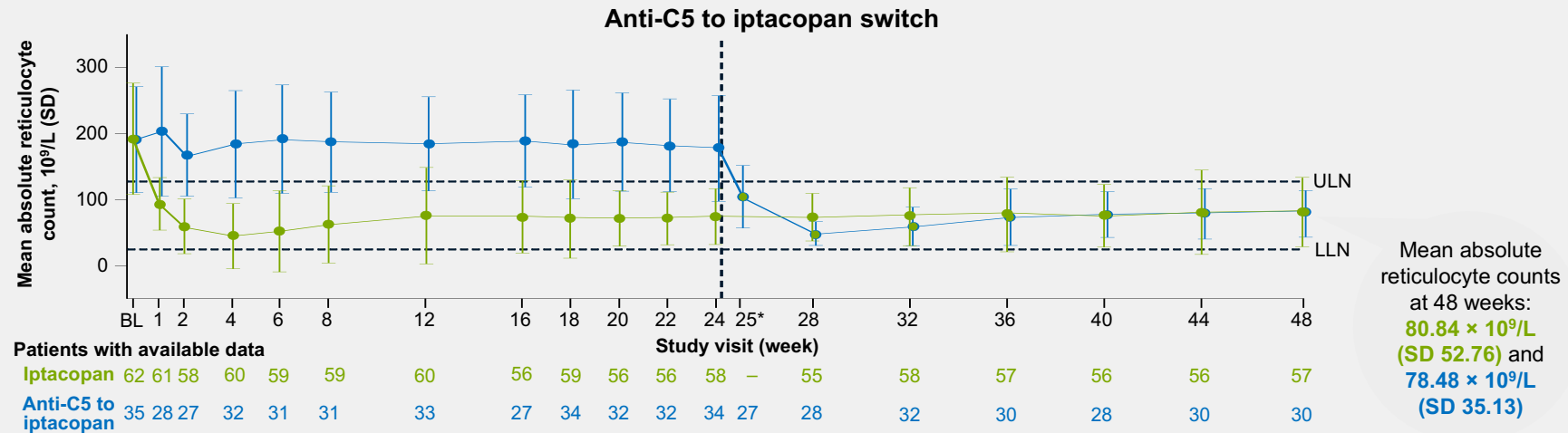
Increases in Hb and a mean normal/near-normal Hb level were maintained in the iptacopan arm and rapidly achieved in the anti-C5-to-iptacopan arm upon treatment switch



	Treatment arm	Adjusted mean change from baseline at Week 48 (95% CI)	Adjusted mean difference in change from baseline (95% CI): Week 48 vs Week 24
Change from baseline [‡] in Hb level (g/dL) [§]	iptacopan	+3.35 (3.04, 3.67)	-0.41 (-0.80, -0.01)
	Anti-C5 to iptacopan	+3.36 (2.94, 3.79)	+3.02 (2.49, 3.56)

*Includes post-transfusion data; †At Week 25, Hb data were only available for one patient in the iptacopan arm (Hb level: 13.9 g/dL); this was not a scheduled visit in the protocol for the iptacopan arm but was for the anti-C5-to-iptacopan arm. The value in the iptacopan arm is not plotted on the graph as one patient cannot be representative of the whole treatment group; ‡Change from baseline was analyzed using a mixed model of repeated measures that adjusted for covariates, including baseline Hb; §Analysis includes all central laboratory Hb data, including post-transfusion data; ||The data in this presentation are derived from the final APPLY-PNH dataset at trial completion. Following the submission of the ASH 2023 abstract, it was confirmed that another RBC transfusion was administered to a patient in the iptacopan arm during the 24-week randomized treatment period; therefore, there are minor numerical differences between this presentation and its published abstract. BL, baseline; CI, confidence interval; Hb, hemoglobin; SD, standard deviation.

A reduction in mean absolute reticulocyte count to within the normal range was maintained in the iptacopan arm and rapidly achieved in the anti-C5-to-iptacopan arm

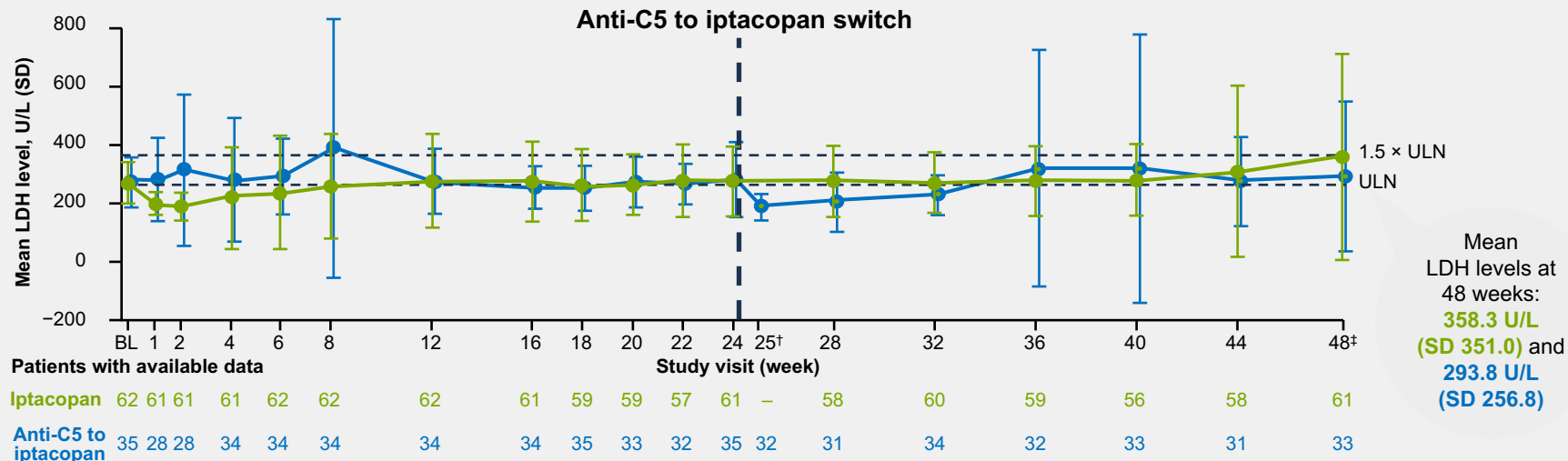


	Treatment arm	Adjusted mean change from baseline at Week 48 (95% CI)	Adjusted mean difference in change from baseline (95% CI): Week 48 vs Week 24
Change from baseline [†] in absolute reticulocyte count ($10^9/L$)	Iptacopan	-106.26 (-117.57, -94.96)	+9.92 (-4.40, 24.25)
	Anti-C5 to iptacopan	-107.95 (-123.18, -92.73)	-102.29 (-121.57, -83.02)

*At Week 25, absolute reticulocyte count data were only available for one patient in the iptacopan arm (absolute reticulocyte count: $76.00 \times 10^9/L$); this was not a scheduled visit in the protocol for the iptacopan arm but was for the anti-C5-to-iptacopan arm. The value in the iptacopan arm is not plotted on the graph as one patient cannot be representative of the whole treatment group;
[†]Change from baseline was analyzed using a mixed model of repeated measures that adjusted for covariates, including baseline absolute reticulocyte count.
 LLN, lower limit of normal; SD, standard deviation; ULN, upper limit of normal.

Mean LDH levels were generally maintained at $1.5 \times \text{ULN}$ in both treatment arms

- Mean **LDH levels** at **Week 48** were **consistent** with **baseline levels** in **both arms**, as shown by Week 48 geometric adjusted mean ratios to baseline that were close to 1.0 (**iptacopan arm: 1.11** [95% CI 1.02, 1.22]; **anti-C5-to-iptacopan arm: 0.99** [0.88, 1.11])*
- Mean **LDH levels** at **Week 48** were also **consistent** with the levels at **Week 24** in both arms (geometric adjusted mean ratio for Week 48 vs Week 24: **iptacopan arm, 1.12** [95% CI 1.00, 1.25]; **anti-C5-to-iptacopan arm, 0.99** [0.85, 1.15])*



*Log-transformed ratio to baseline was analyzed using a mixed model of repeated measures that adjusted for covariates, including baseline LDH; [†]At Week 25, LDH data were only available for one patient in the iptacopan arm (LDH level: 348.0 U/L); this was not a scheduled visit in the protocol for the iptacopan arm but was for the anti-C5-to-iptacopan arm. The value in the iptacopan arm is not plotted on the graph as one patient cannot be representative of the whole treatment group; [‡]Variability in LDH level in the iptacopan arm at Week 48 was driven by a few outliers. LDH, lactate dehydrogenase; SD, standard deviation; ULN, upper limit of normal.

All reported MAVEs were considered unrelated to iptacopan and resolved without iptacopan treatment discontinuation

- **Three patients** had MAVEs during the APPLY-PNH trial
- The **overall adjusted annualized rate of MAVEs** since initiation of iptacopan monotherapy, including iptacopan-treated patients in both treatment arms, was **0.04** (95% CI 0.01, 0.13)

Randomized treatment period

- One patient in the iptacopan arm had a **serious TEAE of transient ischemic attack**
 - The patient had a **concomitant serious TEAE of sick sinus syndrome**
 - The investigator considered the MAVE to be **unrelated to iptacopan** and likely caused by an episode of arrhythmia due to sick sinus syndrome
 - **Iptacopan treatment continued throughout the event**

Treatment extension period

- One patient in the anti-C5-to-iptacopan arm had a **serious TEAE of portal vein thrombosis**
 - The patient had decided to **discontinue heparin** prior to the MAVE and had a **history of portal vein thrombosis**
- One patient in the iptacopan arm had a **non-serious TEAE of transient ischemic attack**, which presented as **dysarthria**
- Both MAVEs were considered to be **unrelated to iptacopan**, and iptacopan treatment **continued throughout** the events

MAVE, major adverse vascular event; TEAE, treatment-emergent adverse event.

CODA · TRADUÇÃO PARA A PRÁTICA

O que sabemos hoje sobre iptacopana

12,3 g/dL

Hb média sustentada em 4 anos

95%

DHL <1,5×LSN no ano 4

87%

pacientes livres de transfusão

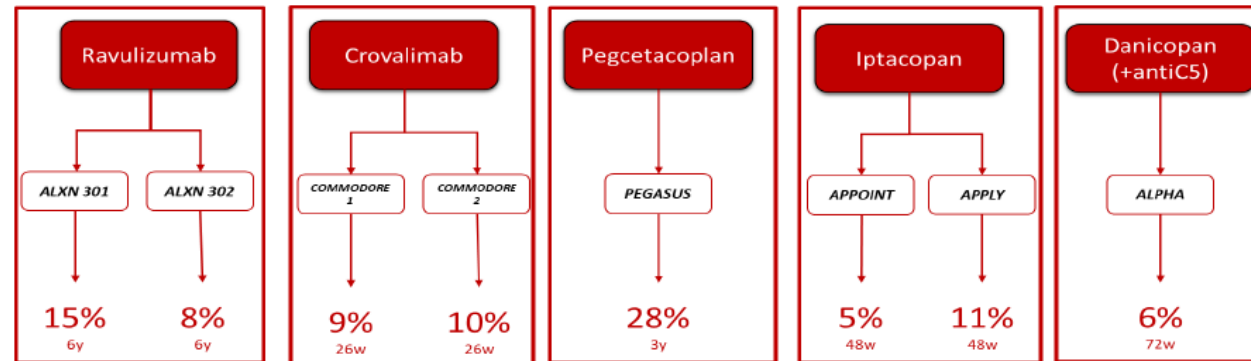
+8 pts

ganho FACIT-Fatigue sustentado




6 anos

sem novos sinais de segurança




FREQUENCY OF BREAKTHROUGH HEMOLYSIS (BTH) IN PNH WITH VARIOUS COMPLEMENT INHIBITORS



SEVERE BTH

- 1 Transfusion need 
- 2 Breakthrough thrombosis 
- 3 Need of increase / change anti-C drug 

PREDICTORS OF SEVERE BTH

- 1 Size of RBC PNH clone 
- 2 Suboptimal response to complement inhibition 
- 3 Comorbidities / higher infectious risk 

Conclusions: BTH may occur with all complement inhibitors, with a frequency of 10-15% over 6 months with eculizumab, crovalimab, and pegcetacoplan, and <5% with ravulizumab, iptacopan, and danicopan in combination with anti-C5. BTH is generally managed with transfusions and modifications of anti-complement therapy included anticipation of the next anti-C5 dose and addition of eculizumab in patients on proximal inhibitors. Breakthrough thromboses are rare, though anti-coagulant prophylaxis should be considered during severe episodes.

Downloaded from <http://ashpublications.org/blood/article-pdf/doi/10.1182/blood.2024.02.757428> by guest on 28 April 2025

Conclusions

- **Eculizumab for a long time the only option (q2 weeks, IV)**
- **Newer anti-C5 agents – ravulizumab (q8 weeks, IV), crovalimab (SC, monthly)**
- **Proximal inhibitors control EVH and IVH**
 - **Pegcetacoplan (C3 inhibition, 2x week, 30-60 minute infusion)**
 - **Danicopan (oral, TID, Factor D inhibitor, add-on)**
 - **Iptacopan (oral, BID, Factor B inhibitor)**
- **Better strategy, dual versus single blockade option question**
- **Long term effects still being defined for newer agents**
- **Different delivery methods could influence decision**
- **Payors, reimbursement**

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Obrigado

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Hospital A Beneficência Portuguesa



Contraindicações: Fabhalta® é contraindicado para iniciação em pacientes com infecção grave não solucionada causada por bactérias encapsuladas, incluindo *Streptococcus pneumoniae*, *Neisseria meningitidis* ou *Haemophilus influenzae* tipo B. **Interações**

Medicamentosas: Não se espera que tenha interações clinicamente relevantes com outros medicamentos.

Forma farmacêutica e apresentações: Fabhalta® 200 mg - embalagens contendo 56 cápsulas duras. Cada cápsula dura de Fabhalta® contém 200 mg de iptacopana (na forma de 225,8 mg de cloridrato de iptacopana monoidratado). **Indicações:** Fabhalta® é indicado para o tratamento de pacientes adultos com hemoglobinúria paroxística noturna (HPN) e glomerulopatia por complemento 3 (C3G). **Posologia:** 200 mg por via oral, duas vezes ao dia, pode ser administrado com ou sem alimento. • Troca de eculizumabe para Fabhalta® em pacientes com HPN: Fabhalta® deve ser iniciado no máximo 1 semana após a última dose de eculizumabe. • Troca de ravulizumabe para Fabhalta® em pacientes com HPN: Fabhalta® deve ser iniciado no máximo 6 semanas após a última dose de ravulizumabe. • Troca de outras terapias de HPN para Fabhalta®: considerar o intervalo de administração da dose e o modo de ação dos medicamentos anteriores. • Dose(s) esquecida(s): Administrar uma dose o mais rápido possível (mesmo que seja um pouco antes da próxima dose programada) e depois retomar o cronograma posológico regular. • Adesão ao cronograma posológico: orientar todos os pacientes sobre a importância da adesão ao cronograma posológico. Em pacientes com HPN, a adesão é importante para minimizar o risco de hemólise. • A descontinuação deste medicamento não é recomendada, a menos que seja clinicamente indicada, uma vez que a HPN e C3G são doenças que requerem tratamento crônico. **Pacientes pediátricos (< 18 anos de idade):** A segurança e a eficácia de Fabhalta® não foram estabelecidas. **Populações especiais: Comprometimento renal:** Não é necessário nenhum ajuste da dose em pacientes com comprometimento renal leve a moderado. Não há dados atualmente disponíveis em pacientes com comprometimento renal severo ou em diálise. O rim não é a principal via de eliminação. **Comprometimento hepático:** Não é necessário ajuste de dose para pacientes com comprometimento hepático leve, moderado ou severo. **Pacientes geriátricos:** Nenhum ajuste de dose é necessário. **Contraindicações:** • Hipersensibilidade à iptacopana ou a qualquer um dos excipientes. • Pacientes não vacinados atualmente contra *Neisseria meningitidis* e *Streptococcus pneumoniae* a menos que o risco de adiar o tratamento com Fabhalta® supere o risco de desenvolver uma infecção por essas bactérias encapsuladas. • Para iniciação em pacientes com infecção grave não solucionada causada por bactérias encapsuladas, incluindo *Streptococcus pneumoniae*, *Neisseria meningitidis* ou *Haemophilus influenzae* tipo B. **Advertências e Precauções: Infecções graves causadas por bactérias encapsuladas:** Inibidores do complemento, como Fabhalta®, podem predispor os indivíduos a infecções graves, com risco à vida ou fatais. Para reduzir o risco de infecção, os pacientes devem ser vacinados contra bactérias encapsuladas, incluindo *Neisseria meningitidis* e *Streptococcus pneumoniae*. Recomenda-se vacinação contra *Haemophilus influenzae* tipo B, se disponível. As vacinas devem ser administradas pelo menos 2 semanas antes da administração da primeira dose de Fabhalta®. Caso Fabhalta® deva ser iniciado antes da vacinação, administrar a vacina o mais rápido possível após a primeira dose de Fabhalta® e fornecer aos pacientes profilaxia antibacteriana até 2 semanas após a vacinação. Se necessário, os pacientes podem ser revacinados. Os pacientes devem ser informados e monitorados quanto aos primeiros sinais e sintomas de infecção bacteriana grave. Avaliar e tratar imediatamente os pacientes se houver suspeita de infecção bacteriana. **Monitoramento das manifestações de HPN após descontinuação de Fabhalta®:** Monitorar os pacientes por pelo menos duas semanas quanto a sinais e sintomas de hemólise. Os sinais e sintomas incluem níveis elevados de lactato desidrogenase (LDH), juntamente com diminuição súbita na hemoglobina ou no tamanho do clone de HPN, fadiga, hemoglobinúria, dor abdominal, dispneia, principais eventos adversos vasculares (MAVEs) incluindo trombose, disfagia ou disfunção erétil. Se a descontinuação de Fabhalta® for necessária, considerar terapia alternativa. Se ocorrer hemólise após a descontinuação de Fabhalta®, deve ser considerado o reinício do tratamento com Fabhalta®. **Gravidez, lactação, mulheres e homens com potencial reprodutivo: Gravidez:** Estudos de reprodução em animais não demonstraram risco de aumento de anormalidades fetais. Há riscos para a mãe e para o feto associados à HPN e C3G não tratadas. Podese considerar o uso em gestantes ou mulheres que planejam engravidar após uma avaliação dos riscos e benefícios. **Lactação:** Não se sabe se é transferido ao leite materno. Não há dados sobre os efeitos no lactente ou na produção de leite. Os benefícios da amamentação na saúde e no desenvolvimento devem ser considerados em conjunto com a necessidade clínica da mãe de usar Fabhalta® e os eventuais efeitos adversos em potencial (por exemplo, infecções graves decorrentes de bactérias encapsuladas) no lactente a partir do uso de Fabhalta® ou da condição subjacente materna. **Reações adversas: HPN: Muito comuns (≥ 10%):** infecção do trato respiratório superior, cefaleia, diarreia. **Comuns (≥ 1 a < 10%):** infecção do trato urinário, bronquite, diminuição da contagem de plaquetas, tontura, náusea, artralgia, dor abdominal. **Incomuns (≥ 0,1 a < 1%):** pneumonia bacteriana, urticária. **C3G: Muito comuns (≥ 10%):** infecção do trato respiratório superior. **Comuns (≥ 0,1 a < 1%):** infecção pneumocócica. **Interações medicamentosas:** Não se espera que tenha interações clinicamente relevantes com outros medicamentos. **USO ADULTO VENDA SOB PRESCRIÇÃO** Registro – 1.0068.1187 Informações completas para prescrição disponíveis à classe médica mediante solicitação. BSS 08.05.25. Esta mini-bula foi atualizada em 15/09/2025.

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Material destinado aos profissionais habilitados a prescrever e/ou dispensar medicamentos. Data de produção: Maio/2026. BR-38604

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