C5 inhibition as disease modifying treatment, present and future

Jens Panse

University Hospital RWTH Aachen

Disclosures of Jens Panse

Company name	Research support (to institution)	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Alexion/Astra Zeneca	x				x	x	
Amgen						x	
Apellis	x		x			x	
Novartis	x				x	x	
Omeros	x		x			x	
Pfizer	x		x			x	
Roche	x		x		x	x	
Sobi			x		x	x	

PNH -

Historical su
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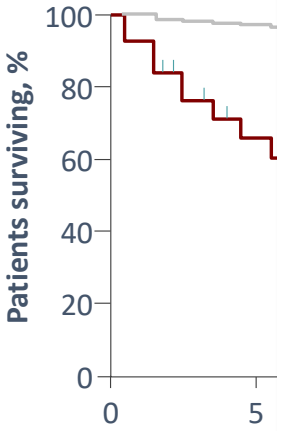


Median survival i
hospital be

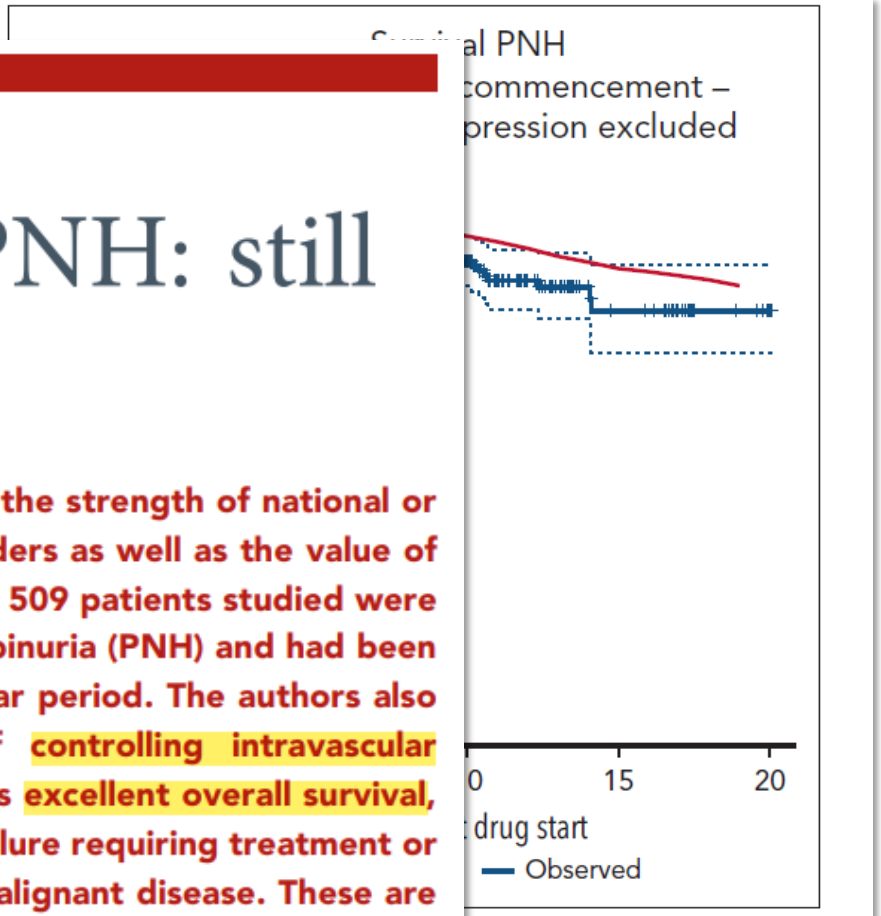
RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Kelly et al, page 1157

C5 inhibition in PNH: still effective and safe

Jeff Szer | The Royal Melbourne Hospital

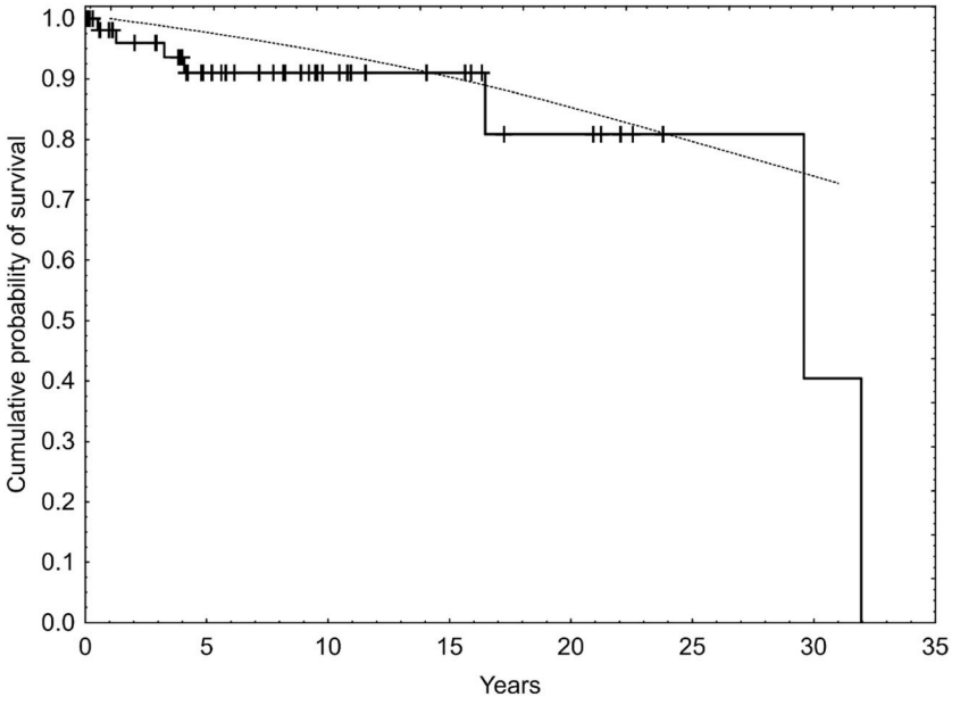
In this issue of *Blood*, Kelly et al[1] demonstrate the strength of national or regional centralized management of rare disorders as well as the value of consistent and complete collection of data. The 509 patients studied were diagnosed with paroxysmal nocturnal hemoglobinuria (PNH) and had been treated with C5 inhibitor therapy over a 20-year period. The authors also demonstrate the long-term effectiveness of controlling intravascular hemolysis and its downstream effects as well as excellent overall survival, particularly in patients without bone marrow failure requiring treatment or in those whose condition had evolved into a malignant disease. These are not surprising new findings but very valuable information for treating physicians.

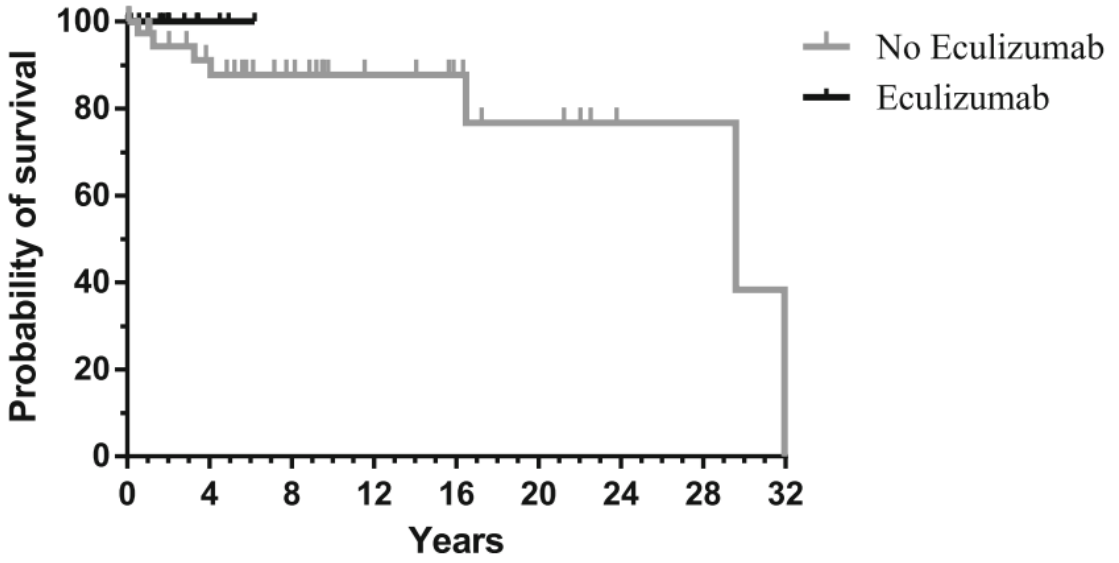


ing those with clonal evolution or

1. Hillmen P, et al; Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995 Nov 9;333(19):1253-8; **2.** Kelly RJ, et al: Treatment outcomes of complement protein C5 inhibition in 509 UK patients with paroxysmal nocturnal hemoglobinuria. Blood. 2024 Mar 21;143(12):1157-1166.

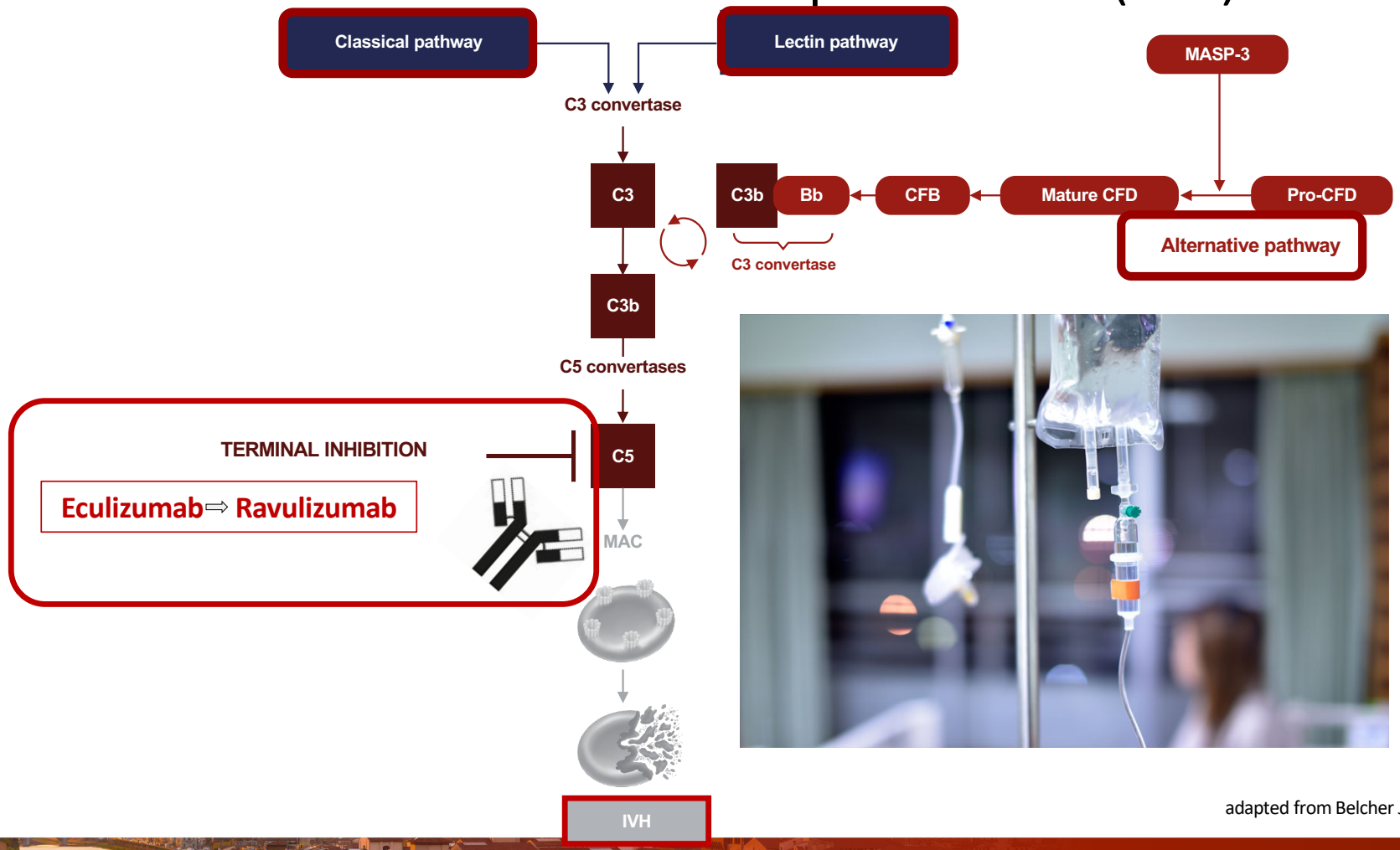
PNH – with terminal (C5) CI (Austria, N = 59)





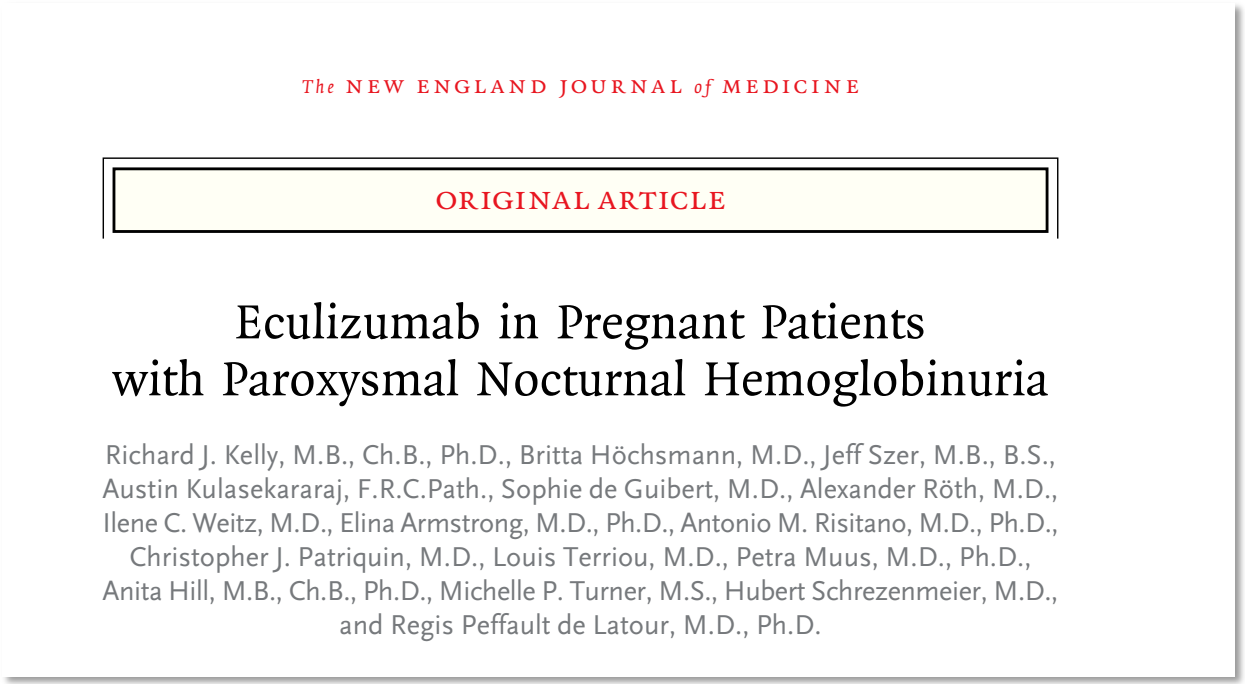
Füreder W, et al; Prognostic factors and follow-up parameters in patients with paroxysmal nocturnal hemoglobinuria (PNH): experience of the Austrian PNH network. Ann Hematol. 2020 Oct;99(10):2303-2313.

PNH – terminal complement (C5) inhibition



adapted from Belcher JD *et al. Transl Res.* 2022;249:1–12

C5I – disease modification



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Eculizumab in Pregnant Patients with Paroxysmal Nocturnal Hemoglobinuria

Richard J. Kelly, M.B., Ch.B., Ph.D., Britta Höchsmann, M.D., Jeff Szer, M.B., B.S., Austin Kulasekararaj, F.R.C.Path., Sophie de Guibert, M.D., Alexander Röth, M.D., Ilene C. Weitz, M.D., Elina Armstrong, M.D., Ph.D., Antonio M. Risitano, M.D., Ph.D., Christopher J. Patriquin, M.D., Louis Terriou, M.D., Petra Muus, M.D., Ph.D., Anita Hill, M.B., Ch.B., Ph.D., Michelle P. Turner, M.S., Hubert Schrezenmeier, M.D., and Regis Peffault de Latour, M.D., Ph.D.

before C5I

- **maternal mortality** 8% - 20.8% (TE primary cause of death; majority postpartum)
- **fetal mortality** 4% - 9%

with C5I

- **no maternal deaths**
- **no TE during pregnancy**
- postpartum TE in 2/75 pregnancies (3%)
- fetal mortality simimilar to previous reports
- BTH -> more frequent use / higher doses of eculizumab / both in 36 of 67 pregnancies (54%)

Kelly RJ, et al;. Eculizumab in Pregnant Patients with Paroxysmal Nocturnal Hemoglobinuria. NEJM 2015 Sep 10;373(11):1032-9

C5I – pregnancy with C5I

Ann Acad Med Singap 2024;53:371-85
https://doi.org/10.47102/annals-acadmedsg.202475

REVIEW ARTICLE

Consensus recommendations for optimising the diagnosis and treatment of paroxysmal nocturnal haemoglobinuria in Singapore

Yeow Tee Goh[1] *MMed*, Eng Soo Yap[2] *MRCP*, Chuen Wen Tan[1] *MRCP*, Daryl Tan[3] *MRCP*, Yvonne Su Ming Loh[4] *MRCP*, Yuh Shan Lee[5] *MRCP*, Lip Leong Chong[6] *MRCP*, Zi Yi Lim[7] *MBChB*, Hein Than[1] *MRCP*

Management of classic PNH		Level of evidence
Statement 5.2	Complement C5 inhibitors are indicated for the treatment of patients with PNH, with increased haemolysis (LDH >1.5 ULN), granulocyte PNH clone >10%, and one or more of the following criteria: • clinical symptoms indicative of high disease activity (weakness, fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia [Hb <10 g/dL], thrombosis, dysphagia and/or erectile dysfunction), regardless of transfusion history • history of thromboembolic events requiring anticoagulant therapy due to PNH • history of regular transfusions (at least 4 packs of RBC over the past 12 months) due to haemolysis • organ damage due to haemolysis (chronic renal failure or repeated episodes of acute renal failure; chest pain with New York Heart Association class III or IV; respiratory failure or an established diagnosis of pulmonary hypertension; and/or smooth muscle dystonia) • pregnancy with a high risk of thrombosis or history of gestational complications	2
Statement 5.3.1	Consider (1) increasing the dose of eculizumab, (2) decreasing the time between infusions or (3) switch-over from eculizumab to ravulizumab,[b] in case of inadequate response to eculizumab therapy (transfusion dependency due to intravascular haemolysis or failure to decrease serum LDH levels to <1.5 x ULN) or regular breakthrough haemolysis during eculizumab treatment (≥3 months).[c]	2
Statement 5.3.2	Switch-over from C5 to C3 inhibitor therapy[d] may be considered in case of any one of the following conditions: (1) breakthrough intravascular haemolysis during regular C5 inhibitor treatment (≥3 months) (2) clinically relevant C3-mediated extravascular haemolysis on C5 inhibitor treatment (≥3 months) (3) unprovoked thromboembolic event during C5 inhibitor therapy (4) unexplained severe fatigue and impaired quality of life despite C5 inhibitor therapy for ≥3 months (5) inadequate response to C5 inhibitor therapy (transfusion dependency due to intravascular haemolysis or failure to decrease serum LDH levels to <1.5 x ULN)	2
Statement 5.4	Vaccination against meningococcus with a tetravalent vaccine including serotypes A, C, Y and W135, along with vaccination against serotype B[e] is recommended at least 2 weeks before initiating treatment with C5 inhibitor therapy.	2
Statement 5.6	Complement C5 inhibitor therapy should ideally be continued for an extended duration. Discontinuation of treatment may be considered in selected cases with significant lack of clinical improvement, severe bone marrow failure, non-compliance/contraindications to treatment or due to patient's decision to stop the treatment.	2

Received: 13 February 2024 | Revised: 10 April 2024 | Accepted: 23 April 2024
DOI: 10.1002/ccr3.8900

CASE REPORT

Clinical Case Reports WILEY

Eculizumab for paroxysmal nocturnal hemoglobinuria: Two cases of successful pregnancy outcomes

Jovanka Ilic[1] | Borislava Pujic[2] | Branislava Jakovljevic[3] | Borivoj Sekulic[1,4] | Danijela Agic[1,4] | Amir El Farra[1,4] | Branimir Micanovic[1] | Tihomir Vejnovic[3,5] | Ivana Urosevic[1,4] | Aleksandar Savic[1,4]

Case Series

Pregnancy with Paroxysmal Nocturnal Hemoglobinuria: A Case Series with Review of the Literature

Yara Mohammad Al-Dosari[1,2], Hazza Al-Zahrani[3], Fahad Al-Mohareb[4], Shahrukh Hashmi[1,5]

[1]Internal Medicine Department, Bahrain Defence Force Hospital and Royal Medical Services, [2]King Faisal Specialist Hospital and Research Center, [3]Adult Hematology/Bone Marrow Transplantation Section, Oncology Center, King Faisal Specialist Hospital and Research Center, [4]Adult Hematology, HSCT Section, Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, [5]Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

Research letters

Eculizumab treatment in pregnant women with paroxysmal nocturnal hemoglobinuria: A Polish experience

Jarosław Czyż[1,A–D], Łukasz Szukalski[1,B,C,E,F], Adriana Szukalska[2,B,D], Bożena Katarzyna Budziszewska[1,B,F], Ewa Lech-Marańda[3,A,B,F], Joanna Zdziarska[4,B,E], Tomasz Sacha[4,A,B,E]

[1] Clinic of Hematology, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland
[2] Clinic of Hematology, Jan Biziel University Hospital No. 2 in Bydgoszcz, Poland
[3] Institute of Hematology and Transfusion Medicine, Warszawa, Poland
[4] Department of Hematology, Jagiellonian University Medical College, Kraków, Poland

Journal of Nephrology (2019) 32:17–25
https://doi.org/10.1007/s40620-018-0517-z

REVIEW

Eculizumab in pregnancy: a narrative overview

Laura Sarno[1] · Antonella Tufano[2] · Giuseppe Maria Maruotti[1] · Pasquale Martinelli[1] · Mario M. Balletta[3] · Domenico Russo[3]

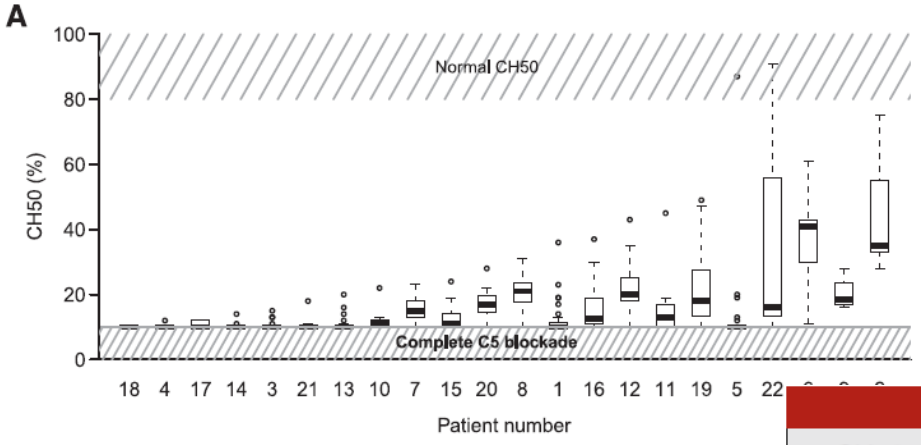
Received: 13 March 2018 / Accepted: 4 June 2018 / Published online: 29 August 2018

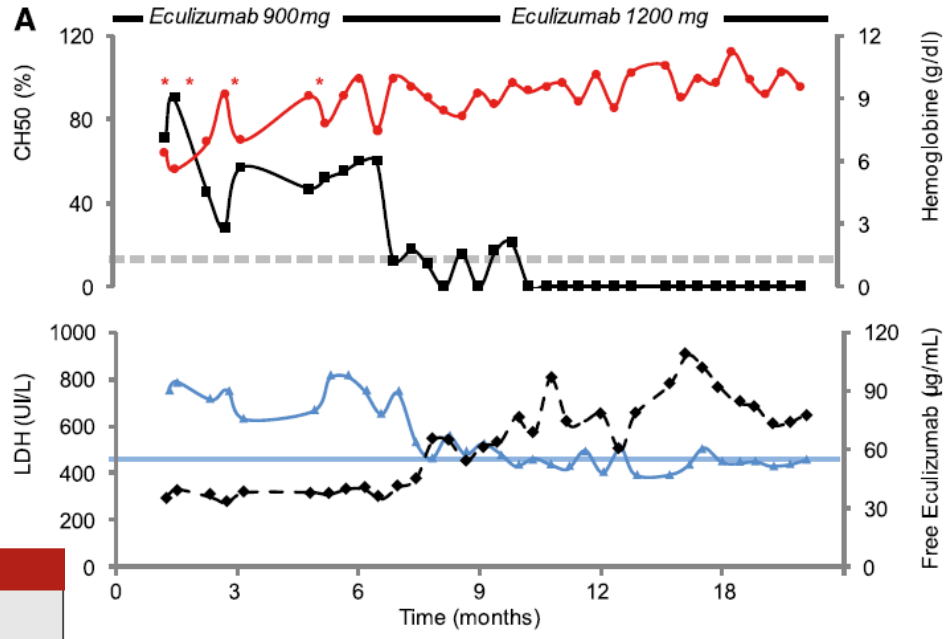
Goh YT et al; , Consensus recommendations for optimising the diagnosis and treatment of paroxysmal nocturnal haemoglobinuria in Singapore. Ann Acad Med Singap. 2024 Jun 28;53(6):371-385
Ilic J et al; Eculizumab for paroxysmal nocturnal hemoglobinuria: Two cases of successful pregnancy outcomes. Clin Case Rep. 2024 May 8;12(5):e8900
Czyż J, det al; Eculizumab treatment in pregnant women with paroxysmal nocturnal hemoglobinuria: A Polish experience. Adv Clin Exp Med. 2022 Jun;31(6):707-710
Al-Dosari et al; Pregnancy with Paroxysmal Nocturnal Hemoglobinuria: A Case Series with Review of the Literature. Saudi J Med Med Sci. 2021 May-Aug;9(2):178-189
Sarno L, et al; Eculizumab in pregnancy: a narrative overview. J Nephrol. 2019 Feb;32(1):17-25.

C5I – disease modification – drug modification

Assessing complement blockade in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab

Régis Peffault de Latour,[1,2] Véronique Fremeaux-Bacchi,[3,4] Raphaël Porcher,[5,6] Aliénor Xhaard,[1] Jérémie Rosain,[3,4] Diana Cadena Castaneda,[3] Paula Vieira-Martins,[3,4] Stéphane Roncelin,[3] Paula Rodriguez-Otero,[1] Aurélie Plessier,[7] Flore Sicre de Fontbrune,[1] Sarah Abbes,[1] Marie Robin,[1] and Gérard Socié[1,8,9]





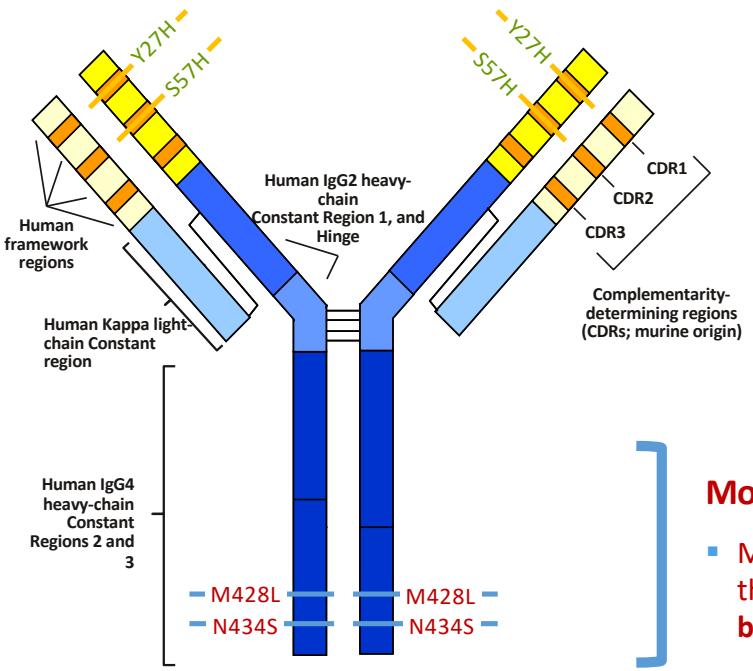
Key Points

- CH50 activity reflects C5 blockade in PNH patients treated with eculizumab and is directly related to circulating free eculizumab levels.
- Both CH50 and free eculizumab level markers look promising for the monitoring of complement blockade in patients with PNH receiving eculizumab.

Peffault de Latour et al. Blood 2015;125(5):775-83.

C5I – drug modification (2 x 4 = 8)

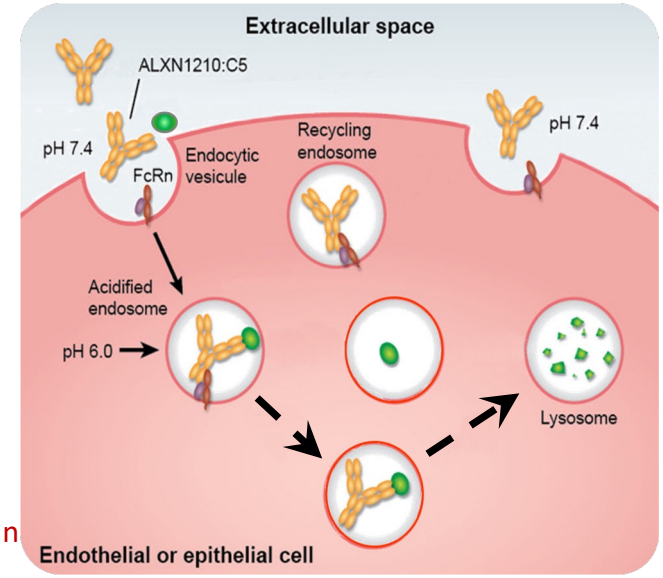
Eculizumab Backbone[1-3]



RAVULIZUMAB

Modifications to Promote Release of C5 in the Endosome[1,3]

- Replacement of Tyr-27 and Ser-57 in variable **heavy-chain** complementary-determining regions (CDRs) 1 and 2 with His residues was designed to **enhance pH-dependent dissociation from C5** in acidified endosomes



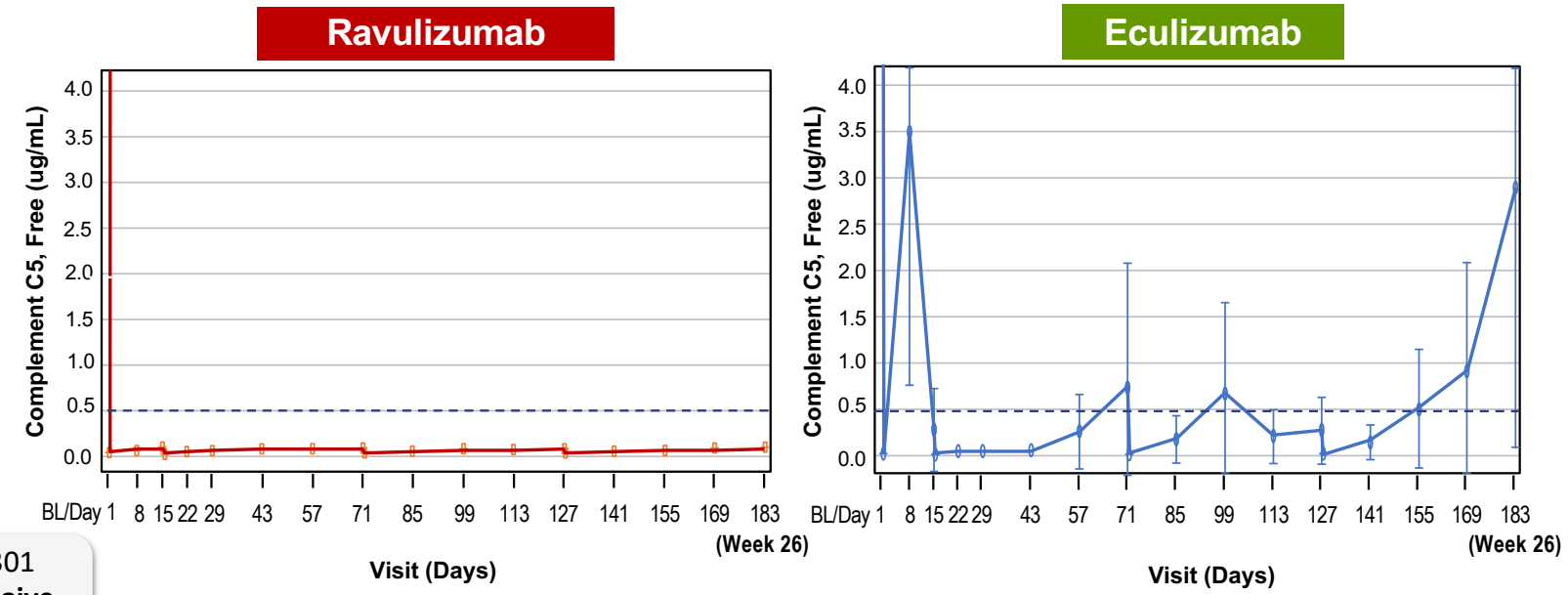
Modifications to Enhance FcRn Binding[1,3]

- Met-428 replaced with Leu and Asn-434 replaced with Ser in the heavy-chain CH3 domain to **enhance pH-dependent binding to FcRn**

1. Sheridan D, et al. *PLoS One*. 2018;13(4):e0195909. doi: 10.1371/journal.pone.0195909. 2. Rother R, et al. *Nat Biotechnol*. 2007;25(11):1256-1264. 3. Roth A, et al. *Blood Adv*. 2018;2(17):2176-2185.

C5I – drug modification – PK optimization

- Inhibition of serum free C5 (terminal complement)
- by the end of the first Ravulizumab infusion and sustained throughout the entire 26-week treatment period



ALXN1210-301
C5 Inhibitor **naive**
(N=246)

[a]BL is defined as the last nonmissing assessment value prior to first dose of study drug. bPlot shows serum free C5 concentrations at predose and end-of-infusion for days 1, 15, 71, and 127, and any time for the ravulizumab group and predose for the eculizumab group for all other visits, except day 183 data were from the end of the randomized treatment period for both treatment groups.

Lee JW, et al. *Blood.* 2019;133(6):530-539.

C5I – drug modification – PK optimization

Table 1. Summary of efficacy endpoints in the primary evaluation and extension periods.

Patients, *n* (%)	Ravulizumab–ravulizumab		Eculizumab–ravulizumab	
	Primary evaluation period* weeks 1–26 *n* = 125	Extension period† weeks 27–52 *n* = 124	Primary evaluation period* weeks 1–26 *n* = 121	Extension period† weeks 27–52 *n* = 119
LDH normalization	61 (48.8)	54 (43.5)	54 (44.6)	48 (40.3)
Transfusion avoidance	92 (73.6)	95 (76.6)	80 (66.1)	80 (67.2)
BTH	5 (4.0)	4 (3.2)	13 (10.7)	2 (1.6)
Stabilized hemoglobin	85 (68.0)	91 (73.4)	78 (64.5)	78 (65.5)
⩾3-point improvement in FACIT-Fatigue	77 (61.6)	80 (64.5)	71 (58.7)	68 (57.1)

*Full analysis set (all patients who received ⩾1 dose of study drug and had ⩾1 efficacy assessment after the first infusion).
†Extension set (all patients who entered the extension period).
BTH, breakthrough hemolysis; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase.

ALXN1210-301
C5 Inhibitor **naive**
(N=246)

Schrezenmeier H et al., Ther Adv Hematol 2020, Vol. 11: 1–14

Ravulizumab – pediatric patients (9 -17 years old)

REGULAR ARTICLE

blood advances

Pharmacokinetics, pharmacodynamics, efficacy, and safety of ravulizumab in pediatric paroxysmal nocturnal hemoglobinuria

Satheesh Chonat,[1] Alexander Kulagin,[2] Alexey Maschan,[3] Marije Bartels,[4] Jochen Buechner,[5] Rowena Punzalan,[6] Michael Richards,[7] Masayo Ogawa,[8] Eden Hicks,[9] Ji Yu,[9] André Baruchel,[10] and Austin G. Kulasekararaj[11]

[1]Department of Pediatrics, Emory University School of Medicine and Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, GA; [2]Department of Hematology, Transfusiology and Transplantology, RM Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russia; [3]Department of Pediatric Hematology and Oncology, Dmitry Rogachev National Medical Research Center for Pediatric Hematology, Moscow, Russia; [4]Department of Benign Hematology, Thrombosis and Hemostasis, Wilhelmina Children's Hospital, UMC Utrecht, Utrecht, The Netherlands; [5]Department of Pediatric Hematology and Oncology, Oslo University Hospital, Oslo, Norway; [6]Department of Pediatrics, Medical College of Wisconsin, Children's Wisconsin and Versiti Blood Center of Wisconsin, Milwaukee, WI; [7]Haemophilia Comprehensive Care Centre, Leeds Children's Hospital, Leeds, United Kingdom; [8]Alexion, AstraZeneca Rare Disease, Cheshire, CT; [9]Alexion, AstraZeneca Rare Disease, Boston, MA; [10]Department of Pediatric Hematology-Oncology, Hôpital Universitaire Robert-Debré, Assistance Publique–Hôpitaux de Paris, Université Paris Cité, Paris, France; and [11]Department of Haematology, King's College Hospital, National Institute of Health Research/Wellcome King's Clinical Research Facility, King's College London, London, United Kingdom

Pharmacokinetics, pharmacodynamics, efficacy, and safety of ravulizumab in pediatric paroxysmal nocturnal hemoglobinuria

Aim To evaluate ravulizumab treatment in pediatric patients with PNH who were eculizumab-naive or -experienced

Population
Stratified by prior eculizumab experience

Naive (n = 5): 20.0% 80.0%

Experienced (n = 8): 87.5% 12.5%

Study design

Screening → Primary evaluation period (26 weeks) *Loading and maintenance weight-based intravenous (IV) ravulizumab* → Extension period (Up to 4 years) *Maintenance weight-based IV ravulizumab*

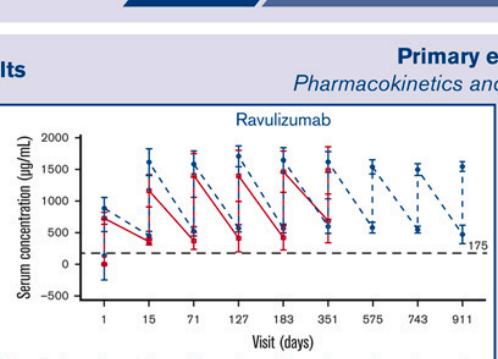
Maintenance IV ravulizumab

Weight	Frequency
<20 kg	4 weeks
≥20 kg	8 weeks

Results

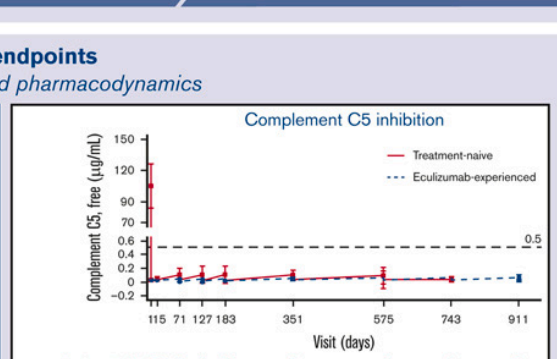
Primary endpoints
Pharmacokinetics and pharmacodynamics

Ravulizumab



Treatment-naive	5	5	5	5	5	4	0	0	0
Eculizumab-experienced	8	8	7	8	8	7	7	4	2

Complement C5 inhibition



Treatment-naive	5	5	5	5	5	5	4	1	0
Eculizumab-experienced	8	8	7	8	8	7	7	6	5

Secondary endpoints
Efficacy and safety

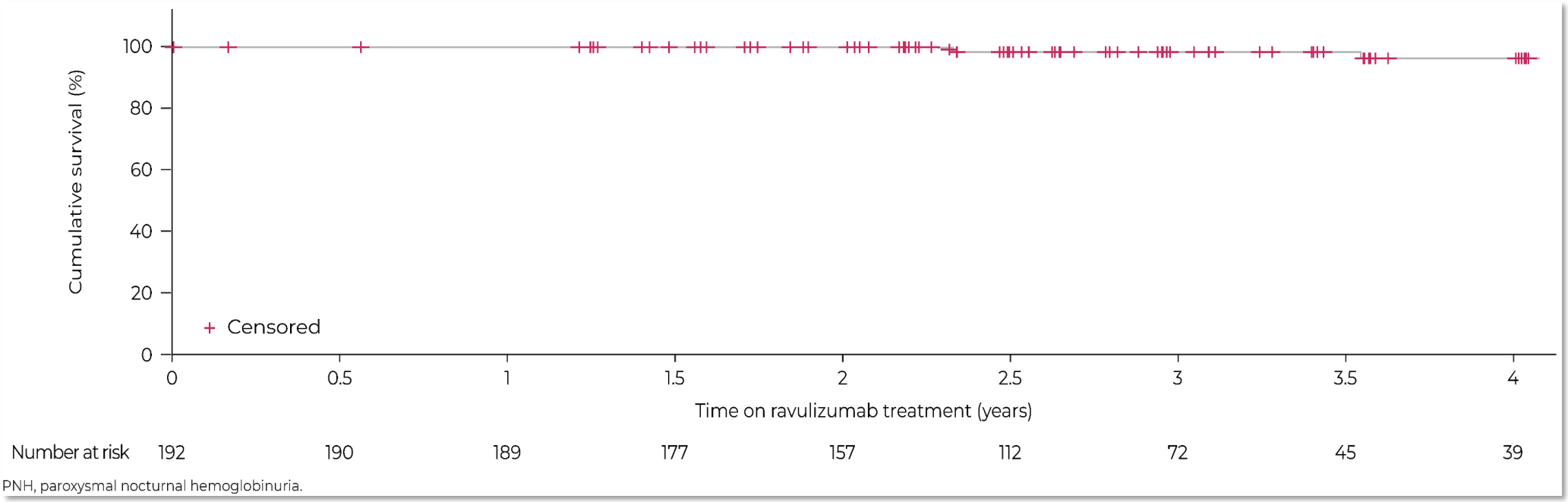
Overall, ravulizumab improved disease outcomes and maintained efficacy in eculizumab-naive and -experienced patients, respectively, with no new safety signals identified

Conclusion Ravulizumab was generally well tolerated, and provided immediate, complete, and sustained C5 inhibition, translating to clinical benefit for pediatric patients with PNH

Chonat S det al; Pharmacokinetics, pharmacodynamics, efficacy, and safety of ravulizumab in pediatric paroxysmal nocturnal hemoglobinuria. Blood Adv. 2024 Jun 11;8(11):2813-2824

C5I – Ravulizumab - survival

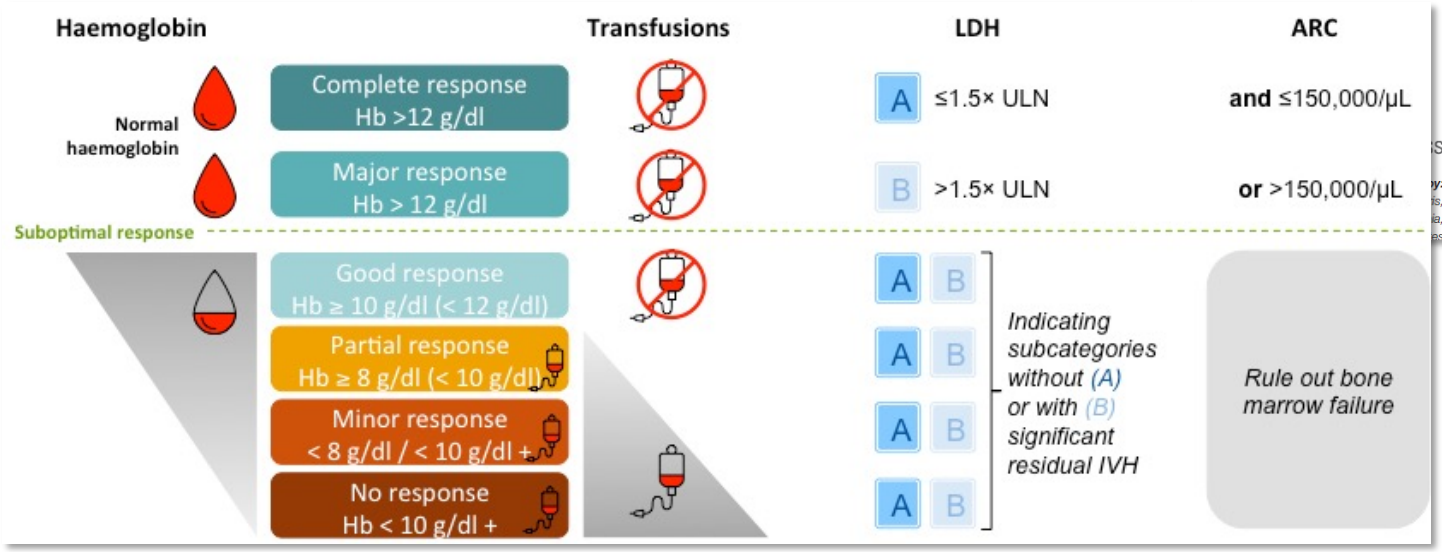
Overall survival of patients with PNH who received ravulizumab for up to 4 years



PNH, paroxysmal nocturnal hemoglobinuria.

Kulasekararaj AG et al. Presented at the European Hematology Association 2023 Hybrid Congress, 8–11 June 2023, Frankfurt, Germany. Poster P772

C5I – assessment of efficacy



frontiers in Immunology
REVIEW
published: 14 June 2019
doi: 10.3389/fimmu.2019.01157

Anti-complement Treatment for Paroxysmal Nocturnal Hemoglobinuria: Time for Proximal Complement Inhibition? A Position Paper From the SAAWP of the EBMT

Antonio M. Risitano[1,2], Serena Marotta[1,2], Patrizia Ricci[1], Luana Marano[1], Camilla Frieri[1], Fabiana Cacace[1], Michela Sica[3], Austin Kulasekararaj[3,4], Rodrigo T. Calado[5], Phillip Scheinberg[6], Rosario Notaro[3†] and Regis Peffault de Latour[2,7†] on behalf of the Severe Aplastic Anemia Working Party of the European group for Bone Marrow Transplantation*

Rissitano AM et al., *Front Immunol* 2019 June 2019 | Volume 10 | Article 1157

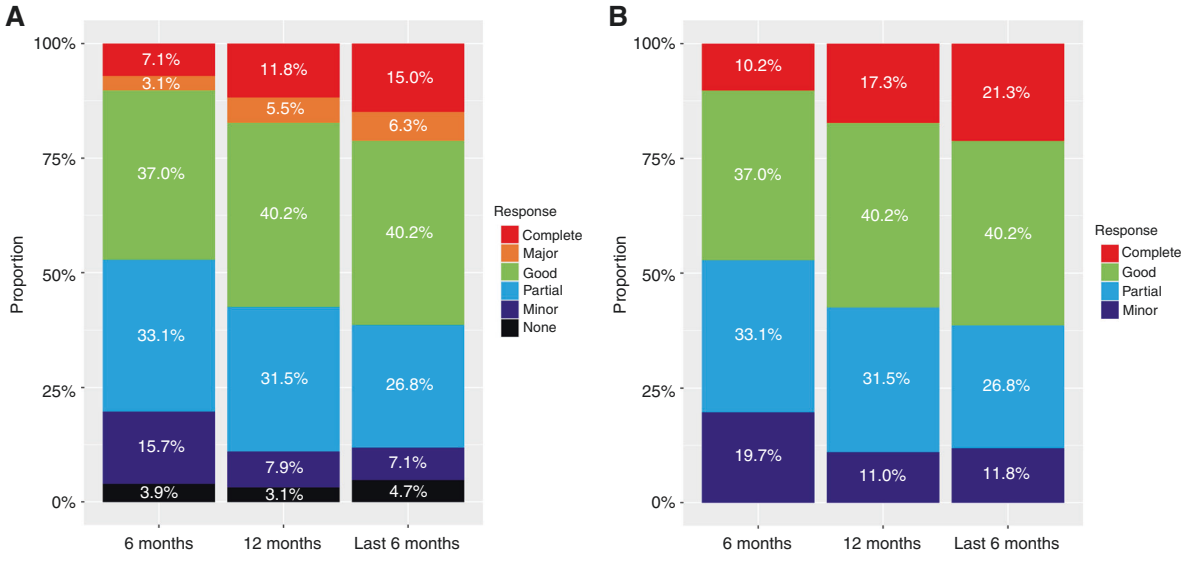
C5I – assessment of efficacy (N= 127)

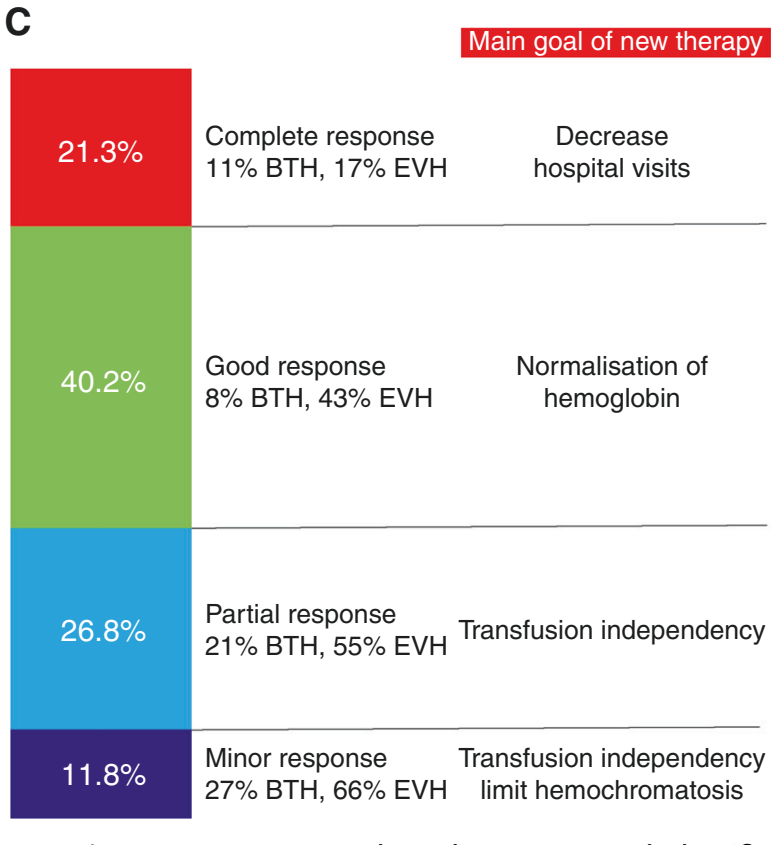
www.nature.com/bmt

CORRESPONDENCE

Categorizing hematological response to eculizumab in paroxysmal nocturnal hemoglobinuria: a multicenter real-life study

Paris, Naples/Avellino, London, Florence, São Paulo, and Ribeirão Preto





Debureaux, PE et al; Bone Marrow Transplantation (2021) 56:2600–2602

C5I – assessment of efficacy (N =94)

Received: 29 November 2022 | Revised: 15 February 2023 | Accepted: 17 February 2023
DOI: 10.1111/ejh.13946

ORIGINAL ARTICLE

European Journal of Haematology | WILEY

Nationwide study of eculizumab in paroxysmal nocturnal hemoglobinuria: Evaluation of treatment indications and outcomes

Charlotte C. M. Schaap[1] | Floor C. J. I. Heubel-Moenen[2] | Erfan Nur[3] | Marije Bartels[4] | Olivier W. H. van der Heijden[5] | Emiel de Jonge[6] | Frank W. M. B. Preijers[6] | Nicole M. A. Blijlevens[1] | Saskia M. C. Langemeijer[1] | on behalf of the Dutch PNH Working Group

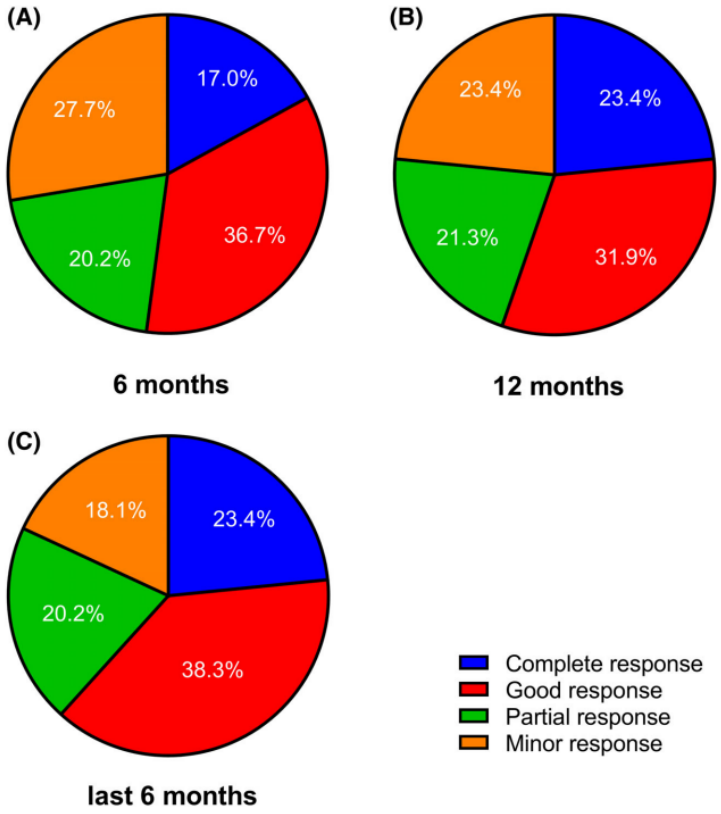
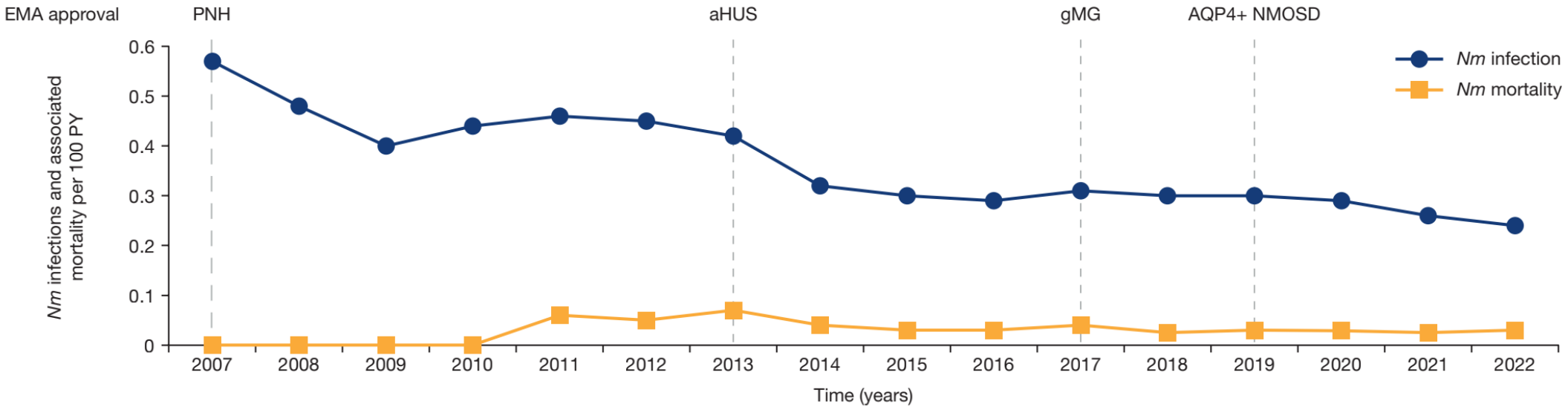


FIGURE 1 Hematological responses to eculizumab after 6 months (A), 12 months (B), and during long-term (C) eculizumab therapy. Data on hematological responses to eculizumab, according to classification in Table S1, were available from 94 out of 95 patients who received at least 1 year of eculizumab therapy. Responses during long-term eculizumab treatment were determined during the last 6 months of therapy before September 2021 (median treatment duration of 5.9 years [range 1.2–13.9 years]).

Debureaux, PE et al; Bone Marrow Transplantation (2021) 56:2600–2602

C5I – consequences – mitigation strategies

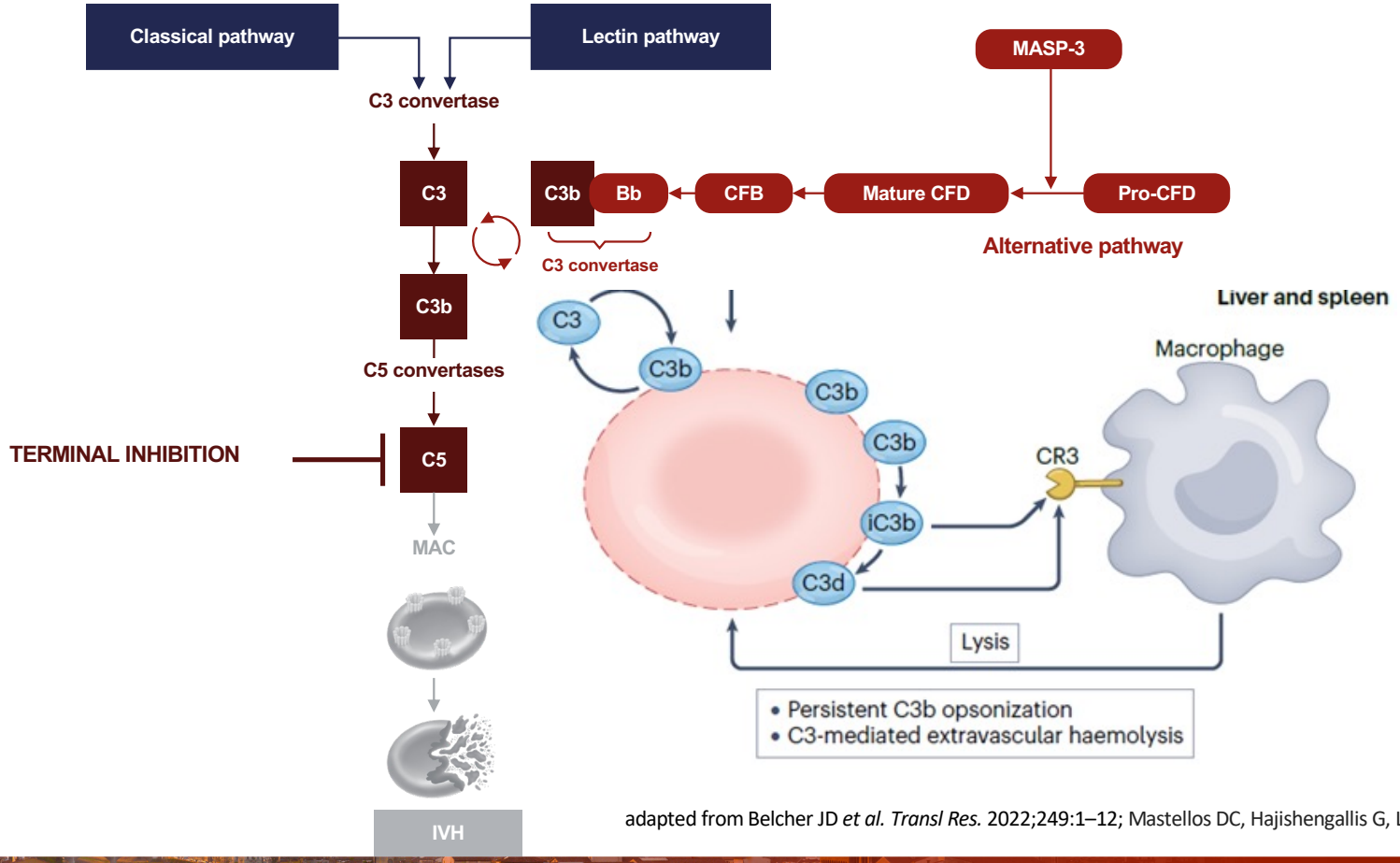
Rate of Nm infections and associated mortality per 100 PY among eculizumab-treated pts in the real-world setting:



PY	75	560	1414	2581	4083	6544	10 046	14 789	20 798	28 108	36 447	44 542	53 798	62 341	70 679	78 416
Nm infection	0.57	0.48	0.40	0.44	0.46	0.45	0.42	0.32	0.30	0.29	0.31	0.30	0.30	0.29	0.26	0.24
Nm mortality	0.00	0.00	0.00	0.00	0.06	0.05	0.07	0.04	0.03	0.03	0.04	0.02	0.03	0.03	0.03	0.03

Fam S et al. Presented at the 9th Congress of the European Academy of Neurology (EAN) 2023, 1–4 July 2023, Budapest, Hungary.

C5I – disease modification



- Hb⇧, LDH⇩
- TE ⇩
- Pulm. HTN ⇩
- Kidney insuff. ⇩
- Fatigue ⇩
- QoL⇧
- Survival⇧

adapted from Belcher JD *et al. Transl Res.* 2022;249:1–12; Mastellos DC, Hajishengallis G, Lambris JD. Nat Rev Immunol. 2024 Feb;24(2):118-141

C5I – EVH

There is no consensus definition for clinically significant EVH

Ravulizumab 302 clinical study		Real-world evidence: PNH DSP (Adelphi)	
Eculizumab (n = 94)	Ravulizumab (n = 94)	Eculizumab (n = 202)	Ravulizumab (n = 129)
20 (21.3%)	**19 (20.2%)**	**15 (7.4%)**	**10 (7.8%)**
Definition of csEVH used in ravulizumab 302 clinical study: • Eculizumab or ravulizumab treatment for up to 6 months • Symptomatic anemia (Hgb ≤ 9.5 g/dL) with ARC ≥ 120 × 10^9/L • With or without blood transfusion		Definition of csEVH used in Adelphi RWE: • Eculizumab or ravulizumab treatment for ≥3 months • Hgb ≤ 9.5 g/dL and moderate/severe symptomatic fatigue • With or without blood transfusion in the last 12 months	

ARC, absolute reticulocyte count; C5i, complement component 5 inhibitor; DSP, Disease Specific Program™; EVH, extravascular hemolysis; Hgb, hemoglobin; IVH, intravascular hemolysis; PNH, paroxysmal nocturnal hemoglobinuria; RWE, real-world evidence.

1. Kulasekararaj AG, et al. HemaSphere. 2023;7(S3):1427-1428. 2. Shammo J, et al. J Blood Med. 2022;13:425-437. 3. Kulasekararaj AG, et al. Blood. 2020;136(suppl 1):6-7.

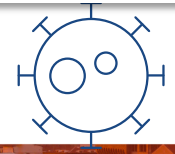
C5I – BTH beyond PK/PD

Reason	Cause	Prevalence	Mechanism	Clinical impact on hematological response	Corrective action
Intravascular hemolysis	Inherited C5 variants	Ultra-rare (<1%, usually in Japanese patients)	Intrinsic resistance due to impaired binding of eculizumab (and of	Minimal (but very significant for the few patients for whom there is no available treatment)	Switch to other investigational agents (mostly alternative C5 inhibitors)

TABLE 1

Aggregated allele frequencies for each of the three C5 polymorphisms linked to a poor eculizumab response in literature: the allele frequencies are aggregated with the study sample size weighted average

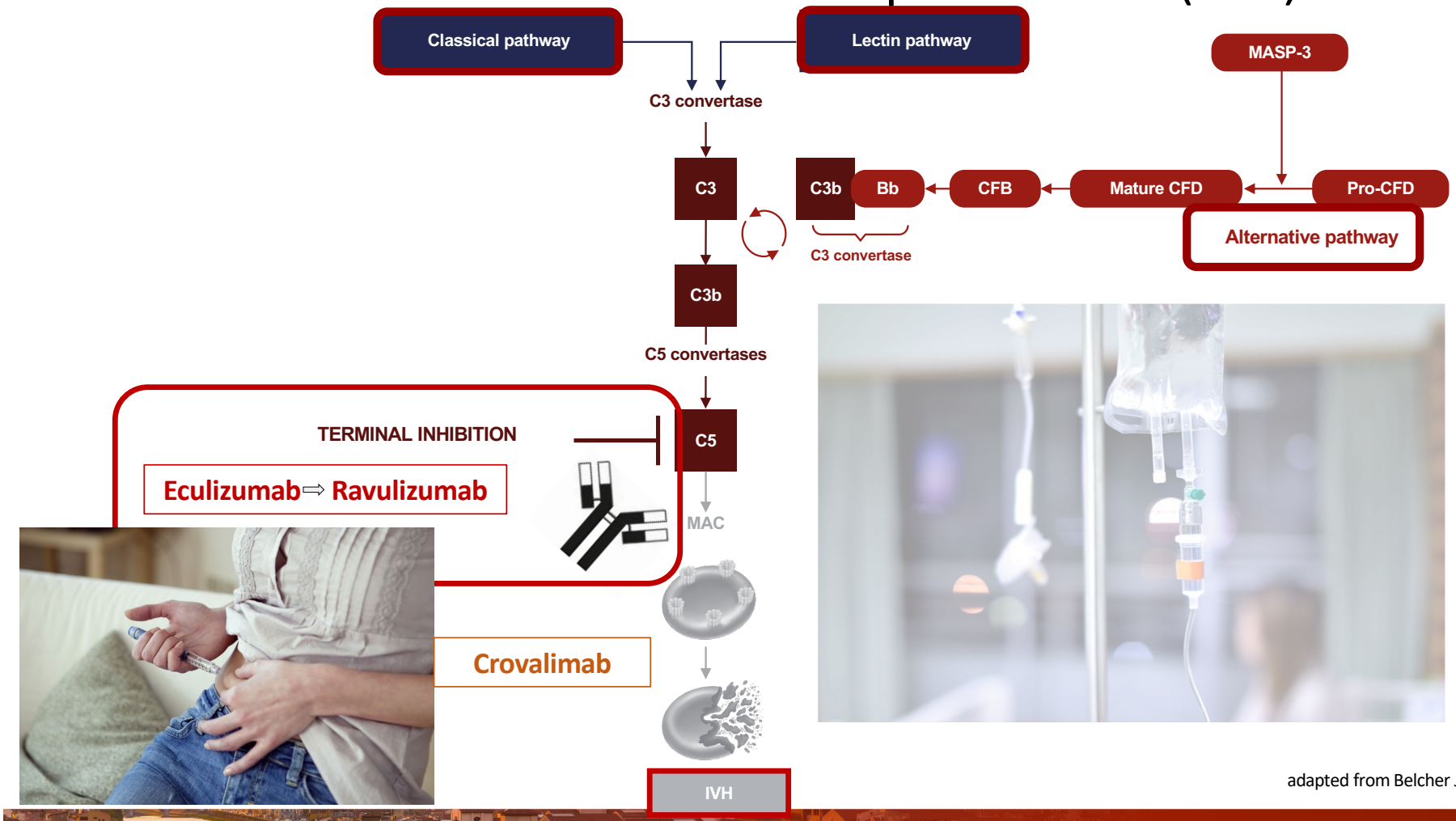
Population	p.Arg885His (%)	p.Arg885Cys (%)	p.Arg885Ser (%)
Global	0.0385	0.0191	0.000697
African	0	0.0211	0
East Asian	0.428	0	0
Japanese	1.83	0	0
Korean	1.28	0	0
European	0.00515	0.000962	0.00145
Finnish	0.00847	0.00282	0
Latino	0.00847	0.00282	0



PD-BTH
complement amplifying condition

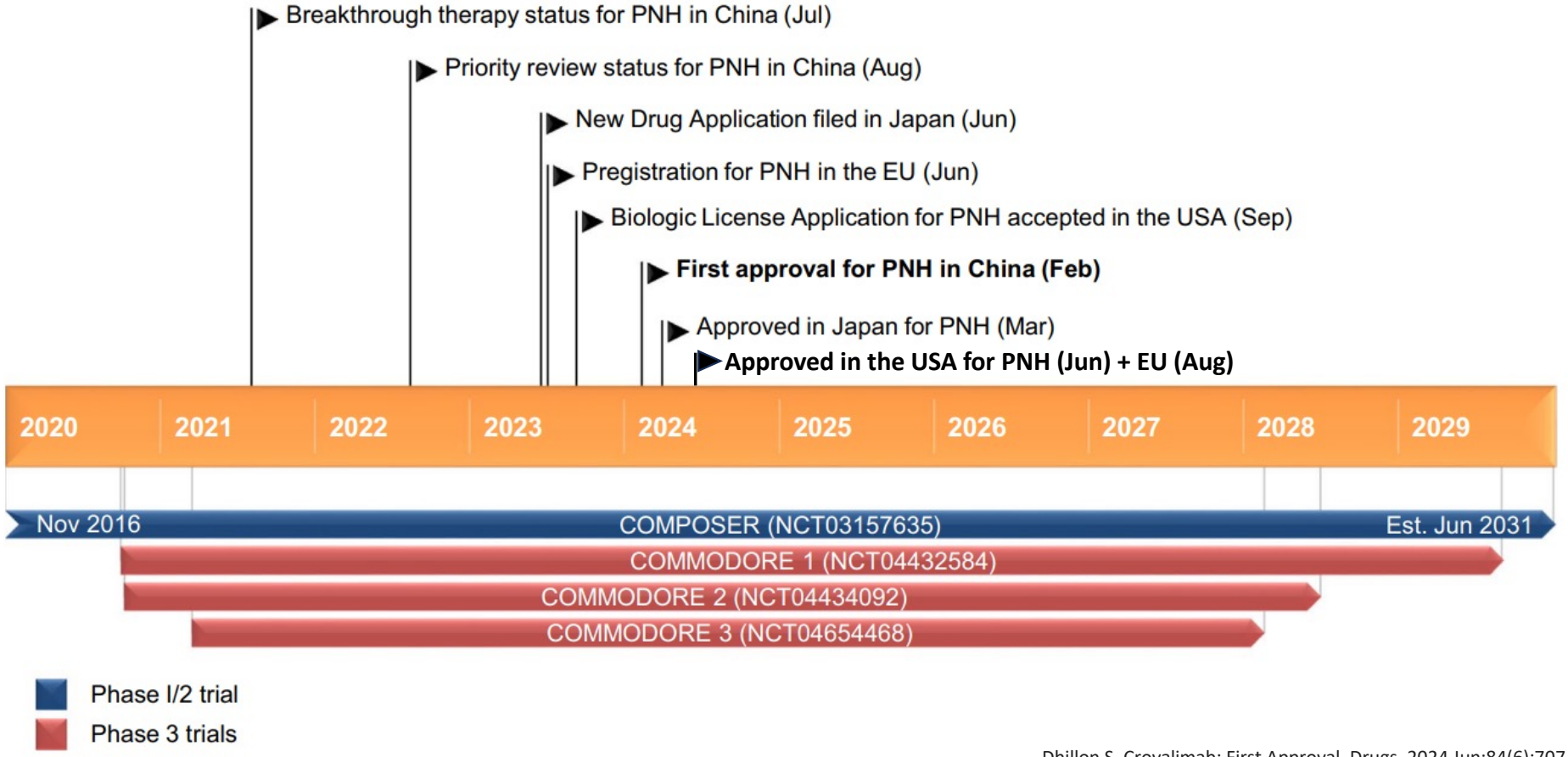
Rissitano AM et al., *Front Immunol* 2019 June 2019 | Volume 10 | Article 1157
Bouwman HB, Guchelaar HJ. Drug Discov Today. 2024 Sep;29(9):104134

PNH – terminal complement (C5) inhibition



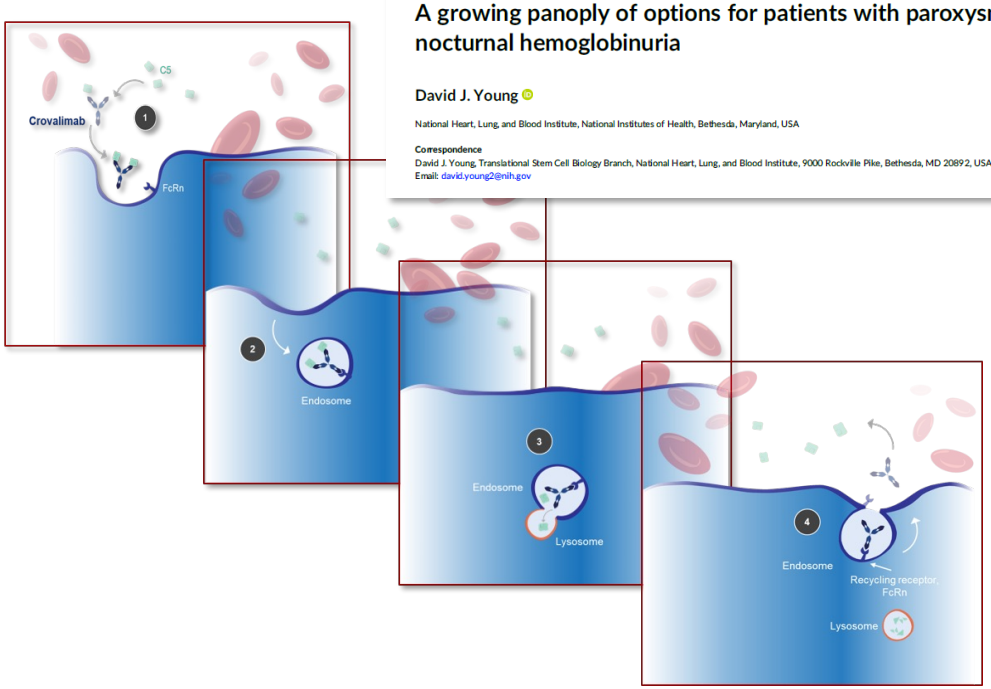
adapted from Belcher JD *et al. Transl Res.* 2022;249:1–12

C5I – Crovalimab



Dhillon S. Crovalimab: First Approval. Drugs. 2024 Jun;84(6):707-716

C5I – Crovalimab



Received: 15 June 2024 | Accepted: 17 June 2024
DOI: 10.1002/ajh.27426

COMMENTARY

A growing panoply of options for patients with paroxysmal nocturnal hemoglobinuria

David J. Young

National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA

Correspondence
David J. Young, Translational Stem Cell Biology Branch, National Heart, Lung, and Blood Institute, 9000 Rockville Pike, Bethesda, MD 20892, USA.
Email: david.young2@nih.gov

Received: 29 February 2024 | Revised: 10 May 2024 | Accepted: 29 May 2024
DOI: 10.1002/ajh.27412

RESEARCH ARTICLE

Phase 3 randomized COMMODORE 2 trial: Crovalimab versus eculizumab in patients with paroxysmal nocturnal hemoglobinuria naive to complement inhibition

Alexander Röth[1] | Guangsheng He[2] | Hongyan Tong[3] | Zenghua Lin[4] | Xiaoqin Wang[5] | Chatree Chai-Adisaksopha[6] | Je-Hwan Lee[7] | Andres Brodsky[8] | Chattree Hantaweepant[9] | Teresita E. Dumagay[10] | Roberta Demichelis-Gómez[11] | Ponlapat Rojnuckarin[12] | Jing Sun[13] | Martin Höglund[14] | Jun Ho Jang[15] | Anna Gaya[16] | Fernando Silva[17] | Naoshi Obara[18] | Richard J. Kelly[19] | Leigh Beveridge[20] | Simon Buatois[21] | Sammy Chebon[21] | Brittany Gentile[20] | Pontus Lundberg[21] | Sasha Sreckovic[20] | Jun-ichi Nishimura[22] | Antonio Risitano[23] | Bing Han[24]

Received: 29 February 2024 | Revised: 10 May 2024 | Accepted: 29 May 2024
DOI: 10.1002/ajh.27413

RESEARCH ARTICLE

Phase 3 randomized COMMODORE 1 trial: Crovalimab versus eculizumab in complement inhibitor-experienced patients with paroxysmal nocturnal hemoglobinuria

Phillip Scheinberg[1] | Diego Villa Clé[2] | Jin Seok Kim[3] | Erfan Nur[4,5] | Mustafa N. Yenerel[6] | Wilma Barcellini[7] | Debora Bonito[8] | Valentina Giai[9] | Marek Hus[10] | YooJin Lee[11] | Cristina Barrenetxea Lekue[12] | Jens Panse[13,14] | Yasutaka Ueda[15] | Simon Buatois[16] | Brittany Gentile[17] | Anna Kiialainen[16] | Himika Patel[17] | Sasha Sreckovic[17] | Marianne Uguen[16] | John Edwards[18] | Zsolt Nagy[19] | Austin G. Kulasekararaj[20,21]

Received: 30 May 2023 | Accepted: 7 June 2023
DOI: 10.1002/ajh.26998

RESEARCH ARTICLE

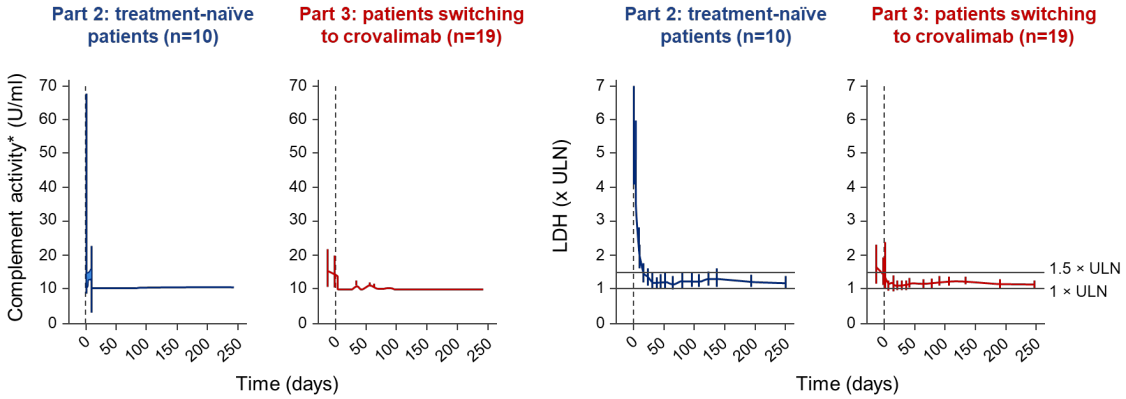
Efficacy and safety of the C5 inhibitor crovalimab in complement inhibitor-naive patients with PNH (COMMODORE 3): A multicenter, Phase 3, single-arm study

Hui Liu[1] | Linghui Xia[2] | Jianyu Weng[3] | Fengkui Zhang[4] | Chuan He[5] | Sujun Gao[6] | Jinsong Jia[7] | Alice C. Chang[8] | Pontus Lundberg[9] | Jane Shi[10] | Camelia S. Sima[11] | Alexandre Sostelly[12] | Sasha Sreckovic[13] | Zhenyu Xiao[14] | Zilu Zhang[15] | Rong Fu[1]

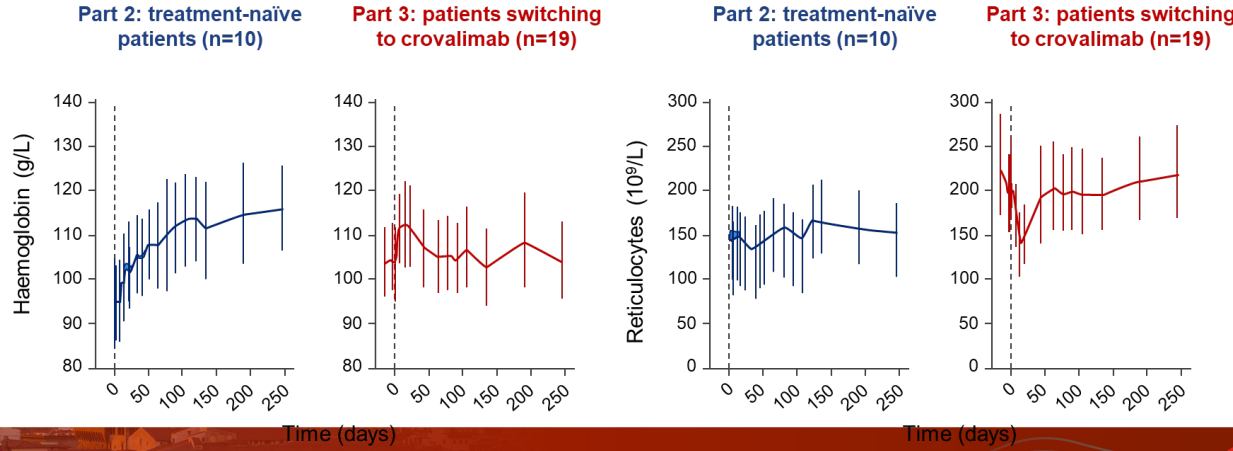
- Crovalimab binds to normal C5 as well as the R885H version (mutation within C5 α-chain) by binding to ß-chain

Fukuzawa T et al. Scientific Reports. 2017; 7: https://doi.org/10.1038/s41598-017-01087-7; Nishimura et al. NEJM. 2014; 13;370(7):632-9

C5I – Crovalimab (COMPOSER efficacy)

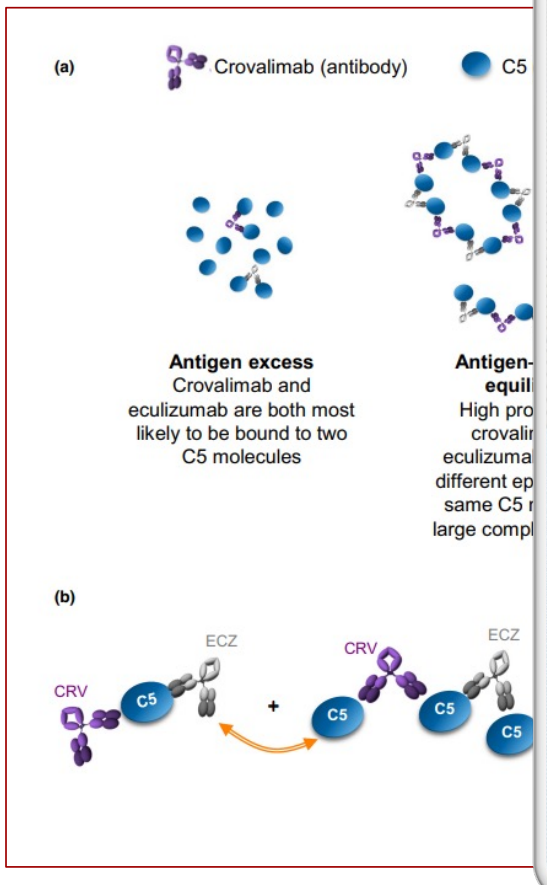


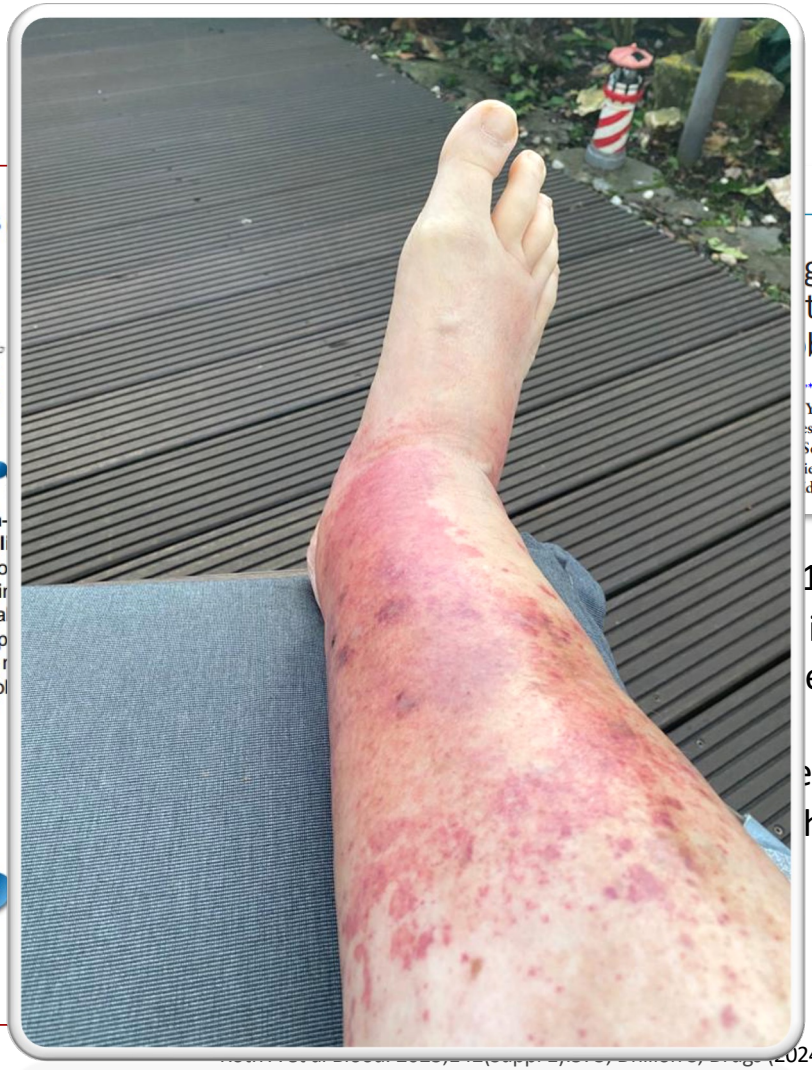
- Complement blocking +
- LDH decrease +
- Hb increase − +
- Reticulocyte decrease −



Röth A, et al. *Blood* 2020;135:912–920.

C5I – Crovali





g Drug–Target–Drug Complexes
ts With Paroxysmal Nocturnal
binuria Who Switch C5 Inhibitors

*, Antoine Soubret[2], Noriko Arase[3], Simon Buatois[2], Masaki Hotta[4], Yoshikazu Ito[5], Sasha Sreckovic[6], Hiroyuki Takamori[1], Christoph Bucher[2], s Hernández-Sánchez[7], Keisuke Gotanda[8], Gregor Jordan[9], Kenji Shinomiya[8], Seok Kim[10], Jens Panse[11], Régis Peffault de Latour[12], Alexander Röth[13], Eiichi Morii[14], ier[15], Yoshitaka Isaka[16], Simona Sica[17], Yuzuru Kanakura[1,18], Sung-Soo Yoon[19], do Paz-Priel[6,22] and Alexandre Sostelly[2,23]

185) of Ecu switch patients had
immune complex reactions (formerly
et-drug complexes [DTDCs])

nts in the phase 1/2 COMPOSER
h C5 codon 885 polymorphism

(2024) 84:707–716; Nishimura JI et al; Br J Haematol. 2022;198(3):e46–50

Licensed C5I

	Target	Dosing		BTH rates	Terminal 1/2-life	Disease modification	Fatigue Score
Eculizumab (+ biosimilars)	C5 α-chain	iv 5 x weekly, then 2-weekly	fixed dose (PK adjustments)	10.7% - 14.5%	271.7 ± 81.6 hours (11.3 days)	Hb ⇧ LDH ⇩ TE ⇩ Transfusion⇩ ARC ⇩ Fatigue⇧ QoL⇧	+ 5.2
Ravulizumab	C5 α-chain	iv 2 x 2-weekly then 8 weekly	weight based ≥ 40 < 60 kg ≥ 60 < 100 kg ≥ 100 kg	4% -6.2%	47.9 (8.9) days		+ 8.2
Crovalimab	C5 ß - chain	iv loading, 4 x weekly sc, 4-weekly sc	weight based (≥40 kg < 100 kg; ≥ 100 kg)	10.4%	58.7 days		+7.8

Wijnsma, K.L., *et al.* Pharmacology, Pharmacokinetics and Pharmacodynamics of Eculizumab, and Possibilities for an Individualized Approach to Eculizumab. *Clin Pharmacokinet* **58**, 859–874 (2019)

Dhillon S; Crovalimab: First Approval, Drugs (2024) 84:707–716

Peffault de Latour R, et al; Pharmacokinetic and pharmacodynamic effects of ravulizumab and eculizumab on complement component 5 in adults with paroxysmal nocturnal haemoglobinuria: results of two phase 3 randomised, multicentre studies. Br J Haematol. 2020 Nov;191(3):476-485

C5I – Costs

Opportunity Cost of Funding Drugs for Rare Diseases: The Cost-Effectiveness of Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

Doug Coyle, PhD, Matthew C. Cheung, MD, Gerald A. Evans, MD

Background. *Both ethical and economics concerns have been raised with respect to the funding of drugs for rare diseases. This article reports both the cost-effectiveness of eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and its associated opportunity costs.* ***Methods***. *Analysis compared eculizumab plus current standard of care v. current standard of care from a publicly funded health care system perspective. A Markov model covered the major consequences of PNH and treatment. Cost-effectiveness was assessed in terms of the incremental cost per life year and per quality-adjusted life year [QALY] gained. Opportunity costs were assessed by the health gains foregone and the alternative uses for the additional resources.* ***Results***. *Eculizumab is associated with greater life years (1.13), QALYs (2.45), and costs (CAN$5.24 million). The incremental cost per life year and per QALY gained is CAN$4.62 million and CAN$2.13 million, respectively. Based on established thresholds, the opportunity cost of funding eculizumab is 102.3 discounted QALYs per patient funded. Sensitivity and subgroup analysis confirmed the robustness of the results. If the acquisition cost of eculizumab was reduced by 98.5%, it could be considered cost-effective.* ***Limitations***. *The nature of rare diseases means that data are often sparse for the conduct of economic evaluations. When data were limited, assumptions were made that biased results in favor of eculizumab.* ***Conclusions***. *This study demonstrates the feasibility of conducting economic evaluations in the context of rare diseases. Eculizumab may provide substantive benefits to patients with PNH in terms of life expectancy and quality of life but at a high incremental cost and a substantial opportunity cost. Decision makers should fully consider the opportunity costs before making positive reimbursement decisions.* ***Key words***: *cost utility analysis; Markov models; probabilistic sensitivity analysis.* ***(Med Decis Making XXXX;XX:xx–xx)***

In conclusion, this study demonstrates that a decision to fund a treatment for a rare disease can have high opportunity costs associated with treatment. It is vital that decision makers have considered fully these opportunity costs and whether the manufacturer's requested price for the treatment is appropriate when making decisions in favor of reimbursement.

Viewpoint

Outrageous prices of orphan drugs: a call for collaboration

Lucio Luzzatto*, Hanna I Hyry*, Arrigo Schippati, Enrico Costa, Steven Simoens, Franz Schaefer, Jonathan C P Roos, Giampaolo Merlini, Helena Kääriäinen, Silvio Garattini, Carlo E Hollak, Giuseppe Remuzzi, on behalf of the Second Workshop on Orphan Drugs participants

Few instances of a single act of legislation have shifted industrial policy in the pharmaceutical industry like the Orphan Drugs Act did when it was signed in the USA in 1983. The Act was written to facilitate the development of drugs for rare diseases and health conditions,[1] and the incentives provided by the Act, such as 7 year exclusivity, tax credits of up to 50% of research and development costs, and access to research and development grants, resulted in the US Food and Drug Administration' (FDA) approving 575 drugs and biological products for rare diseases between 1983 and 2017—a real success. In 2000, the European Commission passed similar legislation for orphan medicinal products (OMPs). As a matter of fact, the diseases, not the drugs, are the orphans because all drugs are very expensive.[2] having marrying this success diseases. So-called orphanisation of common disorders, which is a direct result of the genomics era, enhances the scope for precision medicine and is expected to expand the scope further. At present, 40% of drugs with OMP status are approved for specific types of cancer.[3]

Free market competition is distorted in the case of OMPs. First, often only one drug is available, giving rise to a monopoly situation. Second, in some cases, several OMPs are available for the same disease; for example, three drugs are licensed for treatment of Gaucher's disease (imiglucerase, velaglucerase alfa, and taliglucerase alfa).[4] No evidence favours any one product over the other, and each drug costs about US$200 000 per patient per year. To an outside observer, this might look like a cartel

Lancet 2018; 392: 791–94
Published Online July 26, 2018
http://dx.doi.org/10.1016/S0140-6736(18)31069-9

*Contributed equally
Muhimbili University of Health and Allied Sciences, Dar-es-Salaam, Tanzania (Prof L Luzzatto MD); Department of Medicine, University of Cambridge, Cambridge, UK (H I Hyry MA, J C P Roos PhD); Rare Disease Unit, Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy

Received: 15 June 2024 | Accepted: 17 June 2024
DOI: 10.1002/ajh.27426

COMMENTARY

AJH WILEY

A growing panoply of options for patients with paroxysmal nocturnal hemoglobinuria

David J. Young

National Heart, Lung, and Blood Institute

Correspondence
David J. Young, Translational Stem Cell B
Email: david.young2@nih.gov

Algasidase beta (Fabrazyme)	Fabry disease
Imiglucerase (Cerezyme)	Imiglucerase (Cerezyme)
Laronidase (Aldurazyme)	Mucopolysaccharidosis I

Drug names are followed by brand names in parenthesis. Affected population

Table: The most expensive drugs

found in Japanese populations. Finally, whereas at its market introduction eculizumab was titled "the most expensive drug in the world"—prior to the advent of cell and gene therapies—the expansion of treatment options should exert economic pressures upon drug pricing in a field where, for better or worse, treatment decisions are greatly influenced by financial considerations.

As more agents see broader use, data will gradually become avail-

The European Journal of Health Economics (2023) 24:1455–1472
https://doi.org/10.1007/s10198-022-01556-5

ORIGINAL PAPER

Cost-effectiveness of ravulizumab compared with eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria in the Netherlands

S. W. Quist[2] · A. J. Postma[2] · K. J. Myrén[3] · L. A. de Jong[1] · M. J. Postma[1,4]

Received: 19 August 2021 / Accepted: 22 November 2022 / Published online: 12 January 2023

Abstract
Objectives The aim of this study w
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PharmacoEconomics (2020) 38:981–994
https://doi.org/10.1007/s40273-020-00929-z

ORIGINAL RESEARCH ARTICLE

Cost-Utility Analysis of Ravulizumab Compared with Eculizumab in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria

Thomas O'Connell[1] · Marric Buessing[1] · Scott Johnson[1] · Lufei Tu[1] · Simu K. Thomas[2] · Ioannis Tomazos[2]

Published online: 10 June 2020

rnal hemoglobinuria, characterized by intravascular hemolysis and venous thrombosis, can
n inhibitor of the complement system; however, patients may periodically experience break-
b is a newly approved treatment for paroxysmal nocturnal hemoglobinuria that may reduce
us improving health-related quality of life and reducing treatment costs.
study was to compare the costs and benefit of treatment with ravulizumab vs eculizumab in
nocturnal hemoglobinuria, from a US payer perspective.
s was conducted using a semi-Markov model, informed by clinical experts. Lifetime costs
e-years) (both discounted at 3% per annum) and incremental cost-effectiveness ratios were
n. Results are reported for an entire treated population and subgroups of eculizumab treat-
were characterized by assumptions of non-inferiority between treatments, in terms of break-
d blood transfusion requirements, and of variations in eculizumab dosing adjustments used
molysis.
is for the overall population, there was a positive impact on health-related quality of life
of 1.67) and costs were lower (−$1,673,465), for ravulizumab vs eculizumab. This led to a
tiveness ratio (−$1,000,818, indicating cost savings per quality-adjusted life-year gained).
provement and cost savings were also observed in all cohorts and scenario analyses.
xysmal nocturnal hemoglobinuria, ravulizumab is associated with improved health-related
quality of life and provides a large cost saving from the perspective of a US payer, when compared with eculizumab.

Coyle D, Cheung MC, Evans GA. Opportunity cost of funding drugs for rare diseases: the cost-effectiveness of eculizumab in paroxysmal nocturnal hemoglobinuria. Med Decis Making. 2014 Nov;34(8):1016-29
Luzzatto L, et al; Second Workshop on Orphan Drugs participants. Outrageous prices of orphan drugs: a call for collaboration. Lancet. 2018 Sep 1;392(10149):791-794
Quist SW, et al; Cost-effectiveness of ravulizumab compared with eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria in the Netherlands. Eur J Health Econ. 2023 Dec;24(9):1455-1472
O'Connell T,et al; Cost-Utility Analysis of Ravulizumab Compared with Eculizumab in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria. Pharmacoeconomics. 2020 Sep;38(9):981-994
Young DJ. A growing panoply of options for patients with paroxysmal nocturnal hemoglobinuria. Am J Hematol. 2024 Sep;99(9):1667-1669

C5I – availability - reimbursement

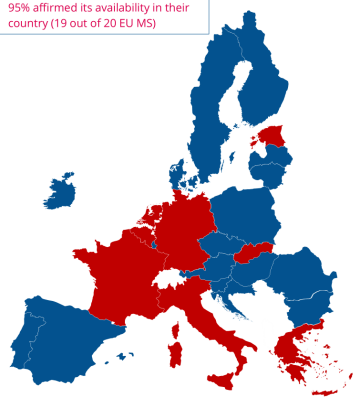
Eculizumab

95% affirmed its availability in their country (19 out of 20 EU MS)

Available in all centers and reimbursed via the National standard health care benefit package:

- Belgium
- Denmark
- Estonia
- France
- Germany
- Greece
- Italy
- Netherlands
- Slovakia

NOT at all available:
- Bulgaria



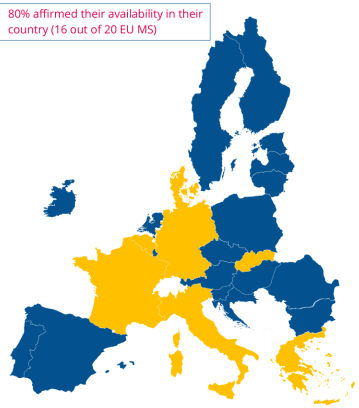
Ravulizumab

80% affirmed their availability in their country (16 out of 20 EU MS)

Available in all centers and reimbursed via the National standard health care benefit package:

- Belgium
- Denmark
- France
- Germany
- Greece
- Italy
- Slovakia

NOT at all available:
- Bulgaria
- Estonia
- Netherland
- Romania
- Portugal



CONCLUSION

- PNH drugs, exemplifying highly effective yet expensive treatments for rare diseases, face **limited and inequality accessibility across EU countries**
- If available in some countries, access to PNH drugs may be restricted to **specific centers**, primarily due to their costs
- Patient reimbursement is often complicated, which burdens the costs of healthcare systems and **undermines regulated reimbursement pathways** on access to PNH treatments
- **Discrepancies between regulation aim and reality**
- Even **specialists are not aware** about the difficulties on availability of drugs for patients

Eculizumab biosimilars

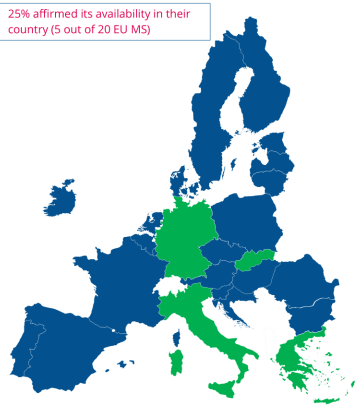
25% affirmed its availability in their country (5 out of 20 EU MS)

Available in all centers and reimbursed via the National standard health care benefit package:

- Germany
- Greece
- Italy
- Slovakia

NOT at all available:

- Bulgaria
- Austria
- Belgium
- Bulgaria
- Czechia
- Denmark
- Estonia
- France
- Hungary
- Lithuania
- Luxembourg
- Netherlands
- Poland
- Portugal
- Romania
- Spain



EHA 2024; Abstract P832 M. Pellegrini, M. Piggin, P. Burmester, R. Peffault de Latour, A.Risitano, C.Dufour, J.Panse, V. Gutierrez Valle, M.Del Mar Mañú Pereira, B. Gulbis, P. Fenaux

PNH – Guidelines – Singapore, China

Ann Acad Med Singap 2024;53:371-85
https://doi.org/10.47102/annals-acadmedsg.202475

REVIEW ARTICLE

Consensus recommendations for optimising the diagnosis and treatment of paroxysmal nocturnal haemoglobinuria in Singapore

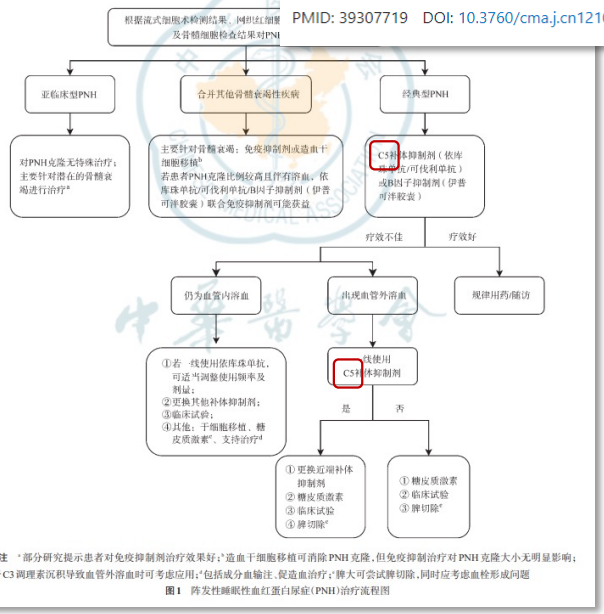
Yeow Tee Goh[1] *MMed*, Eng Soo Yap[2] *MRCP*, Chuen Wen Tan[1] *MRCP*, Daryl Tan[3] *MRCP*, Yvonne Su Ming Loh[4] *MRCP*, Yuh Shan Lee[5] *MRCP*, Lip Leong Chong[6] *MRCP*, Zi Yi Lim[7] *MBChB*, Hein Than[1] *MRCP*

Management of classic PNH		Level of evidence
Statement 5.2	Complement C5 inhibitors are indicated for the treatment of patients with PNH, with increased haemolysis (LDH >1.5 ULN), granulocyte PNH clone >10%, and one or more of the following criteria: • clinical symptoms indicative of high disease activity (weakness, fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia [Hb <10 g/dL], thrombosis, dysphagia and/or erectile dysfunction), regardless of transfusion history • history of thromboembolic events requiring anticoagulant therapy due to PNH • history of regular transfusions (at least 4 packs of RBC over the past 12 months) due to haemolysis • organ damage due to haemolysis (chronic renal failure or repeated episodes of acute renal failure; chest pain with New York Heart Association class III or IV; respiratory failure or an established diagnosis of pulmonary hypertension; and/or smooth muscle dystonia) • pregnancy with a high risk of thrombosis or history of gestational complications	2
Statement 5.3.1	Consider (1) increasing the dose of eculizumab, (2) decreasing the time between infusions or (3) switch-over from eculizumab to ravulizumab,[b] in case of inadequate response to eculizumab therapy (transfusion dependency due to intravascular haemolysis or failure to decrease serum LDH levels to <1.5 x ULN) or regular breakthrough haemolysis during eculizumab treatment (≥3 months).[c]	2
Statement 5.3.2	Switch-over from C5 to C3 inhibitor therapy[d] may be considered in case of any one of the following conditions: (1) breakthrough intravascular haemolysis during regular C5 inhibitor treatment (≥3 months) (2) clinically relevant C3-mediated extravascular haemolysis on C5 inhibitor treatment (≥3 months) (3) unprovoked thromboembolic event during C5 inhibitor therapy (4) unexplained severe fatigue and impaired quality of life despite C5 inhibitor therapy for ≥3 months (5) inadequate response to C5 inhibitor therapy (transfusion dependency due to intravascular haemolysis or failure to decrease serum LDH levels to <1.5 x ULN)	2
Statement 5.4	Vaccination against meningococcus with a tetravalent vaccine including serotypes A, C, Y and W135, along with vaccination against serotype B[e] is recommended at least 2 weeks before initiating treatment with C5 inhibitor therapy.	2
Statement 5.6	Complement C5 inhibitor therapy should ideally be continued for an extended duration. Discontinuation of treatment may be considered in selected cases with significant lack of clinical improvement, severe bone marrow failure, non-compliance/contraindications to treatment or due to patient's decision to stop the treatment.	2

中华血液学杂志2024年8月第45卷第8期 Chin J Hematol, August 2024, Vol. 45, No. 8

阵发性睡眠性血红蛋白尿症诊断与治疗中国指南(2024年版)

中华医学会血液学分会红细胞疾病(贫血)学组
通信作者:付蓉,天津医科大学总医院血液科,天津市骨髓衰竭及癌性造血克隆防治重点实验室,天津市血液病研究所,天津 300052,Email:florai@sina.com;张连生,兰州大学第二医院,兰州 730030,Email:zhanglianshen@medmail.com.cn
基金项目:国家自然科学基金面上项目(82270142)
DOI:10.3760/cma.j.cn121090-2024



注 [a]部分研究提示患者对免疫抑制剂治疗效果好;[b]造血干细胞移植可消除PNH克隆,但免疫抑制治疗对PNH克隆大小无明显影响;[c]由于C3调理素沉积导致血管外溶血时可考虑应用;[d]包括成分血输注、促造血治疗;[e]脾大可尝试脾切除,同时应考虑血栓形成问题

图1 阵发性睡眠性血红蛋白尿症(PNH)治疗流程图

Practice Guideline > Zhonghua Xue Ye Xue Za Zhi. 2024 Aug 14;45(8):727-737.
doi: 10.3760/cma.j.cn121090-20240624-00232.

[Guidelines for the diagnosis and management of paroxysmal nocturnal hemoglobinuria (2024)]

[Article in Chinese]

Red Blood Cell Disease (Anemia) Group, Chinese Society of Hematology, Chinese Medical Association

PMID: 39307719 DOI: 10.3760/cma.j.cn121090-20240624-00232

Goh YT et al; , Consensus recommendations for optimising the diagnosis and treatment of paroxysmal nocturnal haemoglobinuria in Singapore. Ann Acad Med Singap. 2024 Jun 28;53(6):371-385
Red Blood Cell Disease (Anemia) Group, Chinese Society of Hematology, Chinese Medical Association. [Guidelines for the diagnosis and management of paroxysmal nocturnal hemoglobinuria (2024)]. Zhonghua Xue Ye Xue Za Zhi. 2024 Aug 14;45(8):727-737

PNH – Guidelines – Germany/Switzerland/Austria

onkopedia

onkopedia leitlinien

Paroxysmale nächtliche Hämoglobinurie (PNH)

Inhaltsverzeichnis

Änderungen gegenüber Vorversion
Zusammenfassung
Grundlagen
Definition
Epidemiologie

ICD-10: D59.5

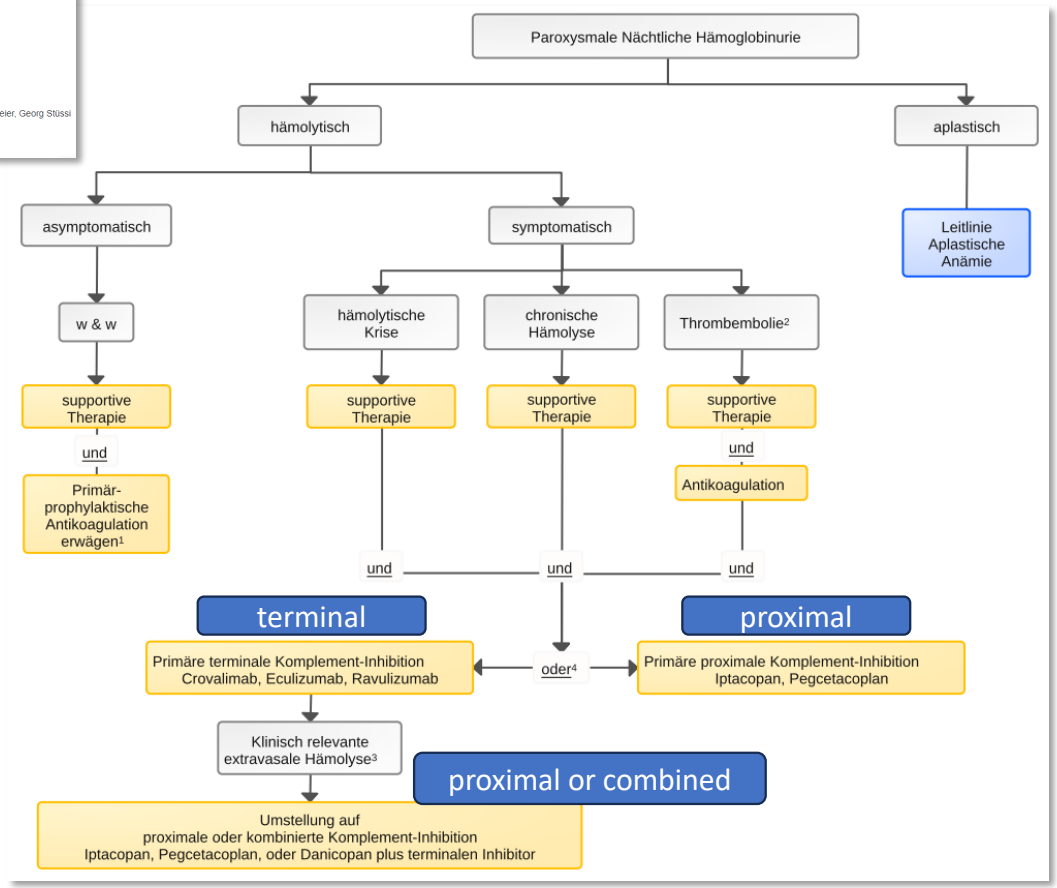
Stand: September 2024

Dies ist die aktuell gültige Version des Dokuments

Erstellung der Leitlinie: Regelwerk Interessenkonflikte Leitlinien-Report

Autoren: Jörg Schubert, Peter Bettelheim, Tim Henrik Brümmendorf, Pascale Olivia Burmester, Ulrike Göbel, Britta Höchsmann, Jens Panse, Alexander Röth, Hubert Schrezenmeier, Georg Stüssi

Beteiligte Fachgesellschaften: DGHO ÖGHO SGH+SSH SSMO SAKM SGMO



PNH – Guidelines - Canada

Journal of Blood Medicine

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Open Access Full Text Article

REVIEW

Paroxysmal Nocturnal Hemoglobinuria: Current Management, Unmet Needs, and Recommendations

Monika Oliver[1], Christopher J Patriquin[2]

[1]Department of Medicine, University of Alberta; Division of Hematology, University of Alberta Hospital, Edmonton, Albert
Medicine (Hematology), University of Toronto, Division of Medical Oncology & Hematology, University Health Network,

Correspondence: Christopher J Patriquin, Toronto General Hospital, 200 Elizabeth Street, Toronto, Ontario, M5G2C4, Can
Fax + 1-416-340-3799, Email christopher.patriquin@uhn.ca

Current Standard of Care

Standard of care (SOC) treatment for PNH varies broadly by country, with many nations still without any complement inhibition,[6] though this may be improving as clinical trials of novel agents expand geographically. The only curative therapy for PNH is an allogeneic hematopoietic stem cell transplant (HSCT); however, as transplant-related morbidity and mortality are significant, HSCT is reserved for PNH patients with concomitant severe aplastic anemia or other causes of bone marrow failure (BMF), where HSCT is worth the risk of addressing both conditions.[1,4,7] However, patients with a history of PNH-related thrombosis appear to do worse with HSCT and are best served by supportive care alone if targeted treatments are not available.[8,9] As transplant medicine evolves with less intensive conditioning regimens and improved graft-versus-host disease and infectious prophylaxis, HSCT may eventually move up in the treatment algorithm, especially in jurisdictions where anti-complement therapies are not available. Use of eculizumab prior to transplantation does not appear to affect engraftment or increase transplant complication rates,[10] and may protect against increased hemolysis when exposed to antithymocyte globulin.

Currently, the definitive treatment for hemolytic or thrombotic PNH is complement blockade. In Canada, as in many countries, first-line therapy is eculizumab or ravulizumab, monoclonal antibodies targeting terminal complement protein, C5, preventing its cleavage and participation in membrane attack complex formation. With C5 inhibition, IVH is substantially reduced, and major complications are prevented. Details regarding eculizumab and ravulizumab are

Oliver M, Patriquin CJ. Paroxysmal Nocturnal Hemoglobinuria: Current Management, Unmet Needs, and Recommendations. J Blood Med. 2023 Dec 6;14:613-628

PNH – Guidelines – Belgium

Received: 1 February 2018 | Revised: 21 May 2018 | Accepted: 22 May 2018

DOI: 10.1111/ejh.13166

REVIEW ARTICLE

WILEY European Journal of Haematology

Diagnosis and management of PNH: Review and recommendations from a Belgian expert panel

Timothy Devos[1,2] | Stef Meers[3] | Nancy Boeckx[4,5] | Andre Gothot[6] | Dries Deeren[7] | Bernard Chatelain[8] | Christian Chatelain[9] | Bérangère Devalet[9]

Indications for eculizumab treatment

Whether to treat or not should not be solely based on the size of the PNH clone. Under Belgian reimbursement restrictions, the need for four erythrocyte transfusions over the last 2 years is mandatory, despite the recent EMA-label that recommends treatment in case of clinical symptoms indicative of high disease activity, regardless of transfusion history, and with an LDH level ≥1.5 ULN (European public assessment reports [EPAR] for full details).[62] Clinical signs and symptoms include fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia, thrombosis, dysphagia and erectile dysfunction.

Patients with a large clone (>50% PNH granulocytes and >10% PNH RBC) coupled with a marked elevation of LDH level (indicator of intravascular haemolysis) and a robust reticulocyte count (indicator of adequate bone marrow reserve) are most likely to benefit from treatment with eculizumab. Therefore, starting treatment with eculizumab in patients with major PNH symptoms may be considered even in the absence of transfusion-dependent anaemia (recommendation level B).

Devos T, Meers S, Boeckx N, Gothot A, Deeren D, Chatelain B, Chatelain C, Devalet B. Diagnosis and management of PNH: Review and recommendations from a Belgian expert panel. Eur J Haematol. 2018 Dec;101(6):737-749.

PNH – Guidelines - Netherlands

Received: 29 November 2022 | Revised: 15 February 2023 | Accepted: 17 February 2023
DOI: 10.1111/ejh.13946

ORIGINAL ARTICLE

European Journal of Haematology
WILEY

Nationwide study of eculizumab in paroxysmal nocturnal hemoglobinuria: Evaluation of treatment indications and outcomes

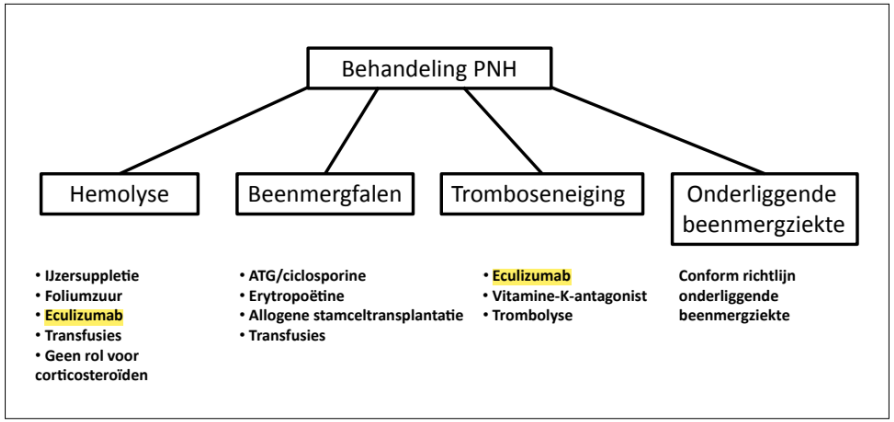
Charlotte C. M. Schaap[1] | Floor C. J. I. Heubel-Moenen[2] | Erfan Nur[3] | Marije Bartels[4] | Olivier W. H. van der Heijden[5] | Emiel de Jonge[6] | Frank W. M. B. Preijers[6] | Nicole M. A. Blijlevens[1] | Saskia M. C. Langemeijer[1] | on behalf of the Dutch PNH Working Group

NTVH RICHTLIJNEN 285

Samenvatting van de Nederlandse richtlijn voor de diagnostiek en behandeling van paroxysmale nachtelijke hemoglobinurie

Summary of the Dutch guideline for diagnostics and treatment of paroxysmal nocturnal hemoglobinuria

dr. S. Langemeijer[1], dr. S. Halkes[2], prof. dr. S. Zeerleder[3], prof. dr. H. Schouten[4], dr. P. te Boekhorst[5], dr. B. Span[6], dr. M. de Witte[7], dr. M. Bartels[8] en dr. P. Muus[9]



Schaap CCM, et al; Dutch PNH Working Group. Nationwide study of eculizumab in paroxysmal nocturnal hemoglobinuria: Evaluation of treatment indications and outcomes. Eur J Haematol. 2023 Jun;110(6):648-658
Langemeijer S et al; Summary of the Dutchguideline for diagnostics and treatment of paroxysmal nocturnalhemoglobinuria. Dutch J Haematol. 2018;15(6):285-292

C5I – there‘s more

Table 1. New and emerging agents for the treatment of paroxysmal nocturnal hemoglobinuria.

Agent	ROA	Dosing frequency	Development phase
Terminal (C5) inhibitors			
Coversin (nomacopan, rVa576; AKARI T			
Crovalimab (RO7112689 or SKY59; Hofi			
Ravulizumab 100 mg/mL (ULTOMIRIS®			
Ravulizumab SC (Alexion, AstraZeneca			
Pozelimab (REGN3918; Regeneron Phai			
Cemdisiran (ALN-CC5; Alnylam Pharma			
Tesidolumab (LFG316; Novartis)			
Zilucoplan (RA101495; RA Pharmaceuti			
Biosimilars			
ABP959 (eculizumab biosimilar; Amg			
SB12 (eculizumab biosimilar; Samsui			
Elizaria (eculizumab biosimilar; JSC (			
Pozelimab (SC)	Phase III trial		
PD and PK of REGN3918	Phase I	Healthy volunteers	Weyne J et al, Blood. 2018
NCT03946748	Phase II	PNH naive	Jang JH et al, Hemasphere. 2023[37]
Cemdisiran (SC)	Phase III trial		
PK and PD properties of Cemdisiran	Phase I	Healthy volunteers and PNH naive	Badri P. et al, Clin Pharmacokinet. 2021[34]
Pozelimab + Cemdisiran (NCT04888507)	Phase II	PNH in C5- inhibitor	Richard Kelly et al, Blood 2022[38]
ACCESS-1 (NCT05133531)	Phase III	PNH naïve	Ongoing NCT05133531 at clinicaltrials.gov
Tesidolumab (IV)			
NCT02534909	Phase II	C5 variant PNH naive	Nishimura JI et al, Haematologica. 2022[33]
Zilucopan (SC)			
NCT03078582	Phase II	PNH naive and PNH in C5-inhibitor	Hill A et al, EHA 2018, PF305
Coversin (SC)			
NCT02591862	Phase II	PNH in C5-inhibitor	Hill A et al, EHA 2018, PF 313

Abbreviations: IV, intravenous; PD, pharmacodynamics; PNH, paroxysmal nocturnal hemoglobinuria; PK, pharmacokinetics; SC, subcutaneous.

Lee JW, Brodsky RA, Nishimura JI, Kulasekararaj AG. The role of the alternative pathway in paroxysmal nocturnal hemoglobinuria and emerging treatments. Expert Rev Clin Pharmacol. **2022** Jul;15(7):851-861;
Versino F, Fattizzo B. Complement inhibition in paroxysmal nocturnal hemoglobinuria: From biology to therapy. Int J Lab Hematol. **2024** May;46 Suppl 1:43-54

C5I – Pozelimab (+ Cemdisiran)

EXPERT OPINION ON PHARMACOTHERAPY
2024, VOL. 25, NO. 11, 1421–1426
https://doi.org/10.1080/14656566.2024.2388267

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EDITORIAL

Check for updates

Pharmacotherapy for CD55 deficiency with CHAPLE disease: how close are we to a cure?

Salim Can [a,b,c], Melek Yorgun Altunbas[a,b,c] and Ahmet Ozen [a,b,c]

[a]Division of Allergy and Immunology, Department of Pediatrics, School of Medicine, Marmara University, Istanbul, Turkey; [b]Istanbul Jeffrey Modell Diagnostic Center for Primary Immunodeficiency Diseases, Istanbul, Turkey; [c]The Isil Berat Barlan Center for Translational Medicine, Istanbul, Turkey

ARTICLE HISTORY Received 24 May 2024; Accepted 31 July 2024

KEYWORDS CD55; CHAPLE disease; eculizumab; pozelimab; primary intestinal lymphangiectasia; protein-losing enteropathy

Litcher-Kelly et al. Orphanet Journal of Rare Diseases (2024) 19:290
https://doi.org/10.1186/s13023-024-03277-9

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Pozelimab for CHAPLE disease: results from in-trial interviews and clinical outcome assessments

Leighann Litcher-Kelly[1], Ahmet Ozen[2], Sarah Ollis[1], Hagit Baris Feldman[3], Andrew Yaworsky[1], Paolo Medrano[1], Voranush Chongsrisawa[4], Taylor Brackin[5], Lorah Perlee[5], Marisa Walker[1], Sharanya Pradeep[1], Michael J. Lenardo[6], Olivier A. Harari[5] and Jessica J. Jalbert[5*]

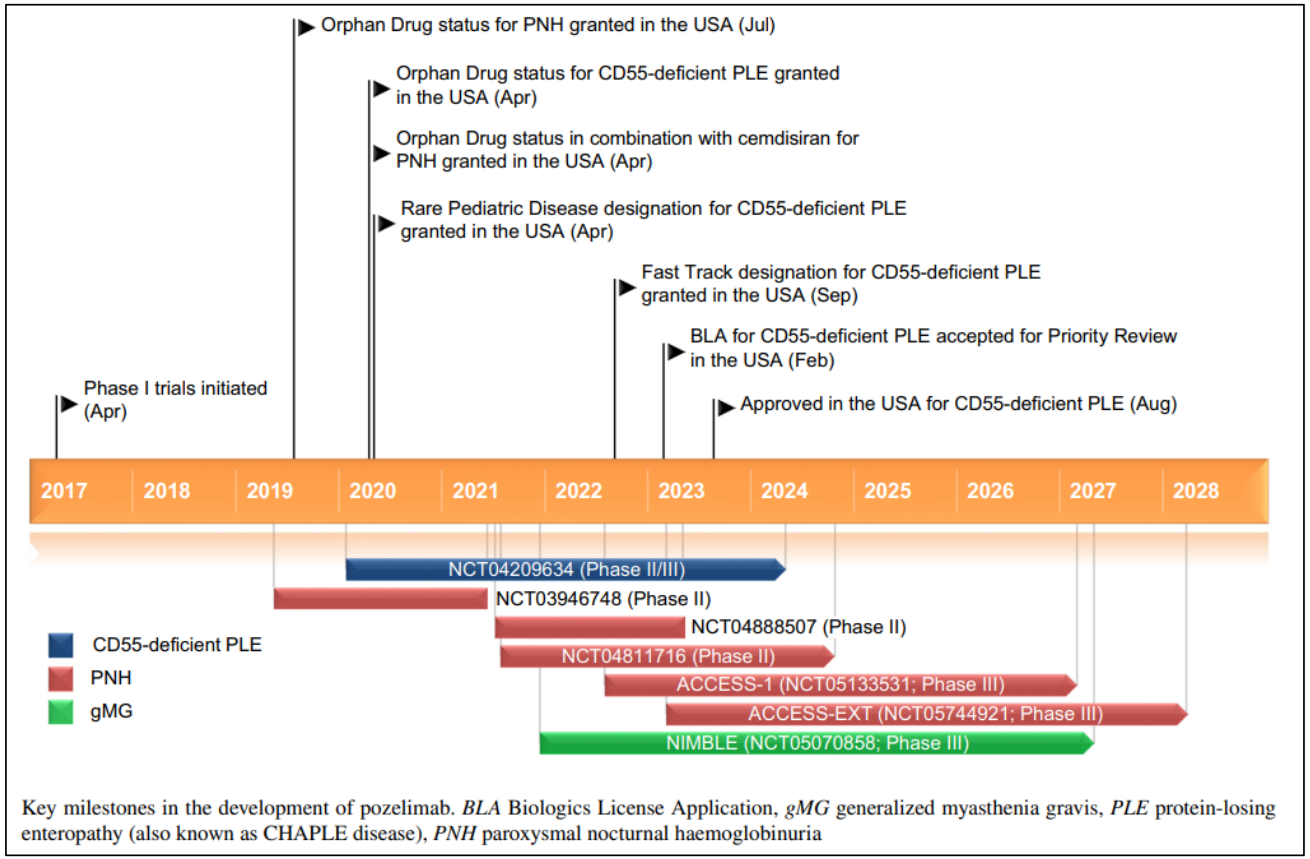
Evaluating the efficacy and safety of pozelimab in patients with CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy disease: an open-label phase 2 and 3 study

Ahmet Ozen, Voranush Chongsrisawat, Asena Pinar Sefer, Burcu Kolukisa, Jessica J Jalbert, Karoline A Meagher, Taylor Brackin, Hagit Baris Feldman, Safa Baris, Elif Karakoc-Aydiner, Rabia Ergelen, Ivan J Fuss, Heather Moorman, Narissara Suratannon, Kanya Suphapeetiporn, Lorah Perlee, Olivier A Harari, George D Yancopoulos, Michael J Lenardo, on behalf of the Pozelimab CHAPLE Working Group*

Summary

Background CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE) is an ultra-rare genetic disorder characterised by intestinal lymphatic damage.

Lancet 2024; 403: 645-56
Published Online



Key milestones in the development of pozelimab. *BLA* Biologics License Application, *gMG* generalized myasthenia gravis, *PLE* protein-losing enteropathy (also known as CHAPLE disease), *PNH* paroxysmal nocturnal haemoglobinuria

Litcher-Kelly L et al; Pozelimab for CHAPLE disease: results from in-trial interviews and clinical outcome assessments. Orphanet J Rare Dis. 2024 Aug 8;19(1); Can S et al; Pharmacotherapy for CD55 deficiency with CHAPLE disease: how close are we to a cure? Expert Opin Pharmacother. 2024 Aug;25(11):1421-1426; Hoy SM. Pozelimab: First Approval. Drugs. 2023 Nov;83(16):1551-1557

C5I – Pozelimab (+ Cemdisiran)

- N = 24 (naive / > 6 months to prior C5)
- iv loading 30 mg/kg bw, weekly sc 800 mg
- control of IVH (22/23)
- transfusion avoidance (21/24)
- control in one patient with a C5 variant known to be resistant to ecu/ravu blockage

Figure 1A. Percentage of patients with LDH ≤1.5 x ULN by visit during the phase 2 open-label trial

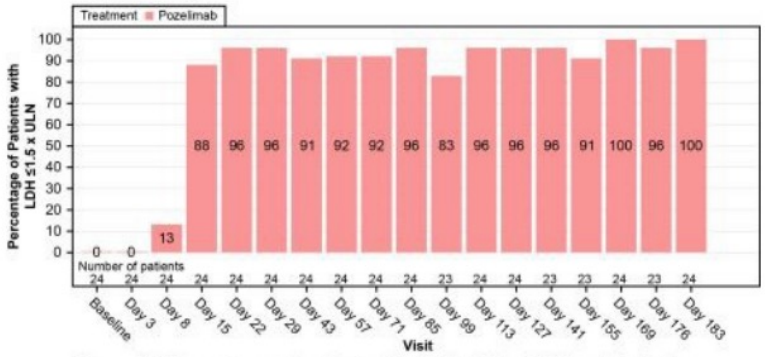
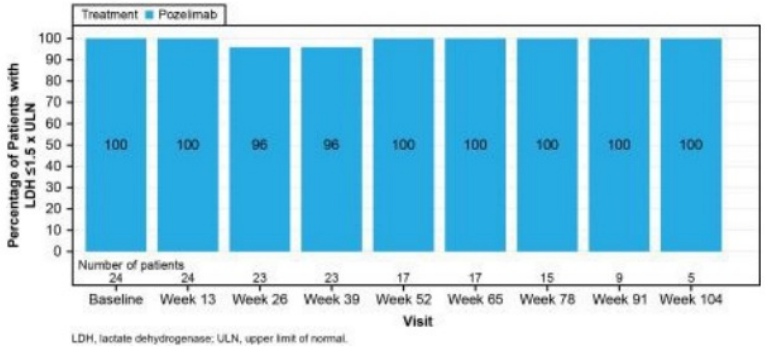


Figure 1B. Percentage of patients with LDH ≤1.5 x ULN by visit during the open-label extension trial



LDH, lactate dehydrogenase; ULN, upper limit of normal.

Jang JH, Wong R, Weyne J, et al. P775: long-term efficacy and safetyof pozelimab monotherapy in patients with paroxysmal nocturnalhemoglobinuria. Hemasphere. 2023;8(7Suppl):e4357016

C5I – Cemdisiran

Clinical Pharmacokinetics (2021) 60:365–378
https://doi.org/10.1007/s40262-020-00940-9

ORIGINAL RESEARCH ARTICLE

Pharmacokinetic and Pharmacodynamic Properties of Cemdisiran, an RNAi Therapeutic Targeting Complement Component 5, in Healthy Subjects and Patients with Paroxysmal Nocturnal Hemoglobinuria

Prajakta Badri[1] · Xuemin Jiang[2] · Anna Borodovsky[1] · Nader Najafian[3] · Jae Kim[1] · Valerie A. Clausen[1] · Varun Goel[1] · Bahru Habtemariam[1] · Gabriel J. Robbie[1]

Received: 20 December 2022 | Revised: 14 June 2023 | Accepted: 15 June 2023
DOI: 10.1002/jha2.748

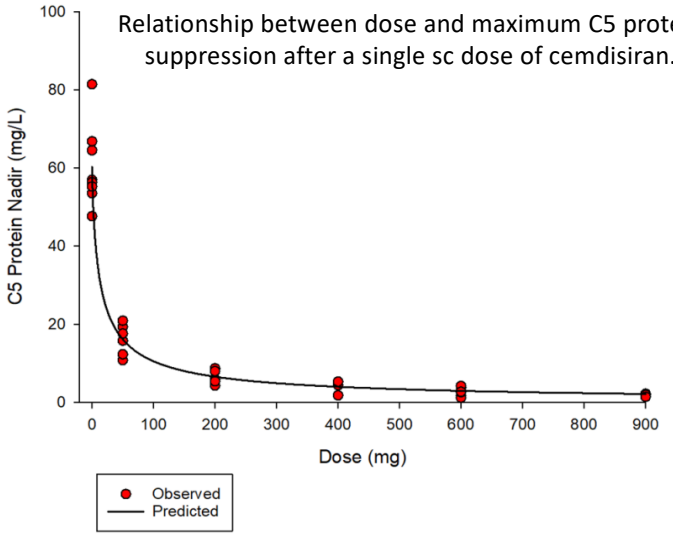
eJHaem

RESEARCH ARTICLE

Results of a phase 1/2 study of cemdisiran in healthy subjects and patients with paroxysmal nocturnal hemoglobinuria

Anna Gaya[1] | Talha Munir[2] | Alvaro Urbano-Ispizua[1,3] | Morag Griffin[2] | Jorg Taubel[4] | Jim Bush[5] | Ishir Bhan[6] | Anna Borodovsky[6] | Yue Wang[6] | Prajakta Badri[6] | Pushkal Garg[6]

Relationship between dose and maximum C5 protein suppression after a single sc dose of cemdisiran.



Abstract

Complement dysregulation underpins the physiopathology of paroxysmal nocturnal hemoglobinuria (PNH). Cemdisiran, an RNA interference investigational treatment, silences complement component 5 (C5) expression in the liver. Previously reported results showed sustained reduction in C5 levels following cemdisiran monotherapy, with >90% reduction in patients with PNH.

This phase 1/2 study evaluated single (Part A, $n = 32$; 50–900 mg) or multiple (Part B, $n = 24$; 100–600 mg) ascending doses of cemdisiran or placebo (double-blind, randomized 3:1) in healthy adults, or cemdisiran in patients with PNH who were naive to, or receiving, eculizumab (Part C, $n = 6$; 200 or 400 mg weekly; open-label). The primary objective was to assess the safety and tolerability of cemdisiran. Other assessments included change in complement activity, lactate dehydrogenase levels, and inhibition of hemolysis following cemdisiran treatment.

Cemdisiran was generally well tolerated in this study. Overall, 75%, 89%, and 100% of subjects in Parts A, B, and C, respectively, experienced ≥1 non-serious adverse event (AE). Most events were Grade 1 or 2 in severity and the most common AEs included nasopharyngitis and headache. Cemdisiran elicited robust, sustained reductions in the complement activity in healthy adults and patients with PNH. In Part C, exploratory analyses showed that cemdisiran monotherapy was insufficient to prevent hemolysis in patients with PNH as measured by serum lactate dehydrogenase levels. Cemdisiran and eculizumab combination therapy reduced the dose of eculizumab required to provide adequate control of intravascular hemolysis.

These results demonstrate a potential benefit of cemdisiran coadministration in patients who are inadequate responders to eculizumab alone.

Badri P et al; Clin Pharmacokinet. 2021 Mar;60(3):365-378; Gaya A et al; EJHaem. 2023 Jun 26;4(3):612-624

C5I – Pozelimab (+ Cemdisiran)

RECRUITING

NCT05744921

A Study in Adult Patients With **Paroxysmal Nocturnal Hemoglobinuria** (**PNH**) to Evaluate How Safe Long-term Treatment With Pozelimab + Cemdisiran Combination Therapy is and How Well it Works.

Conditions

Paroxysmal Nocturnal Hemoglobinuria

Locations

Toronto, Canada
Firenze, Italy
Firenze, Forence, Italy
Tsukuba, Japan

Show all 28 locations

COMPLETED

NCT04811716

Pozelimab and Cemdisiran Combination Treatment in Adult Participants With **Paroxysmal Nocturnal Hemoglobinuria** Who Have Received Pozelimab Monotherapy

Conditions

Paroxysmal Nocturnal Hemoglobinuria

Locations

Hong Kong, New Territories, Hong Kong
Budapest, Nagyvárad Tér 1, Hungary
Busan, Korea, Republic of
Seoul, Korea, Republic of (3)

Show all 13 locations

COMPLETED

NCT04888507

Pozelimab and Cemdisiran Combination Therapy in Adult Participants With **Paroxysmal Nocturnal Hemoglobinuria** Who Switch From Eculizumab Therapy

Conditions

Paroxysmal Nocturnal Hemoglobinuria

Locations

Leeds, United Kingdom

RECRUITING

NCT05133531

A Study to Evaluate How Safe Pozelimab + Cemdisiran Combination Therapy is and How Well it Works in Adult Patients With **Paroxysmal Nocturnal Hemoglobinuria** (**PNH**) Who Have Not Recently Received or Have Not Receive...

Conditions

Paroxysmal Nocturnal Hemoglobinuria

Locations

Whittier, California, United States
Toronto, Ontario, Canada
Thessaloniki, Greece
Budapest, Hungary

Show all 51 locations

Jang J, Wong R, Pavani R, et al. A phase 2, randomized trial evaluating the safety and efficacy of pozelimab and cemdisiran in patients with paroxysmal nocturnal hemoglobinuria [abstract no. P782]. HemaSphere. 2023;7(Suppl 3):1449–50.
Kelly R, Houghton N, Munir T, et al. A phase 2, open-label study evaluating the safety and efficacy of combination pozelimab and cemdisiran therapy in patients with paroxysmal nocturnal hemoglobinuria who switch from eculizumab [abstract no. P797]. HemaSphere. 2023;7(Suppl 3):1481–82.

ClinicalTrials.gov (access 01. Oct 2024)

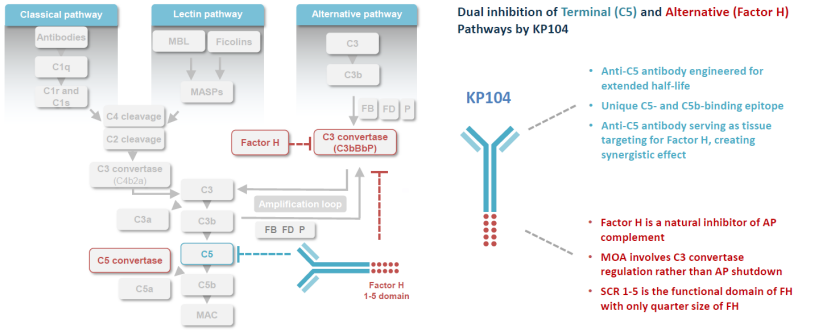
C5I + Factor H

KP104, A Bifunctional C5 Antibody/Factor H Fusion Protein, Effectively Controls Both Intravascular and Extravascular Hemolysis:
24/25-Week Results From An Ongoing Phase 2 Study In Complement Inhibitor-naïve Patients with PNH

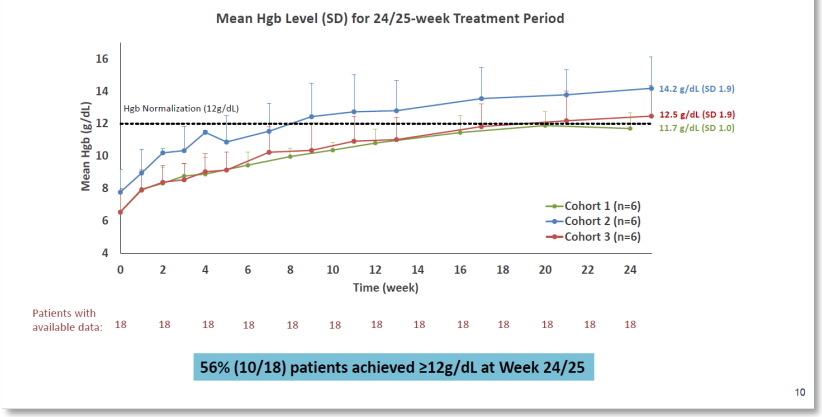
Fengkui Zhang*[1], Bing Han*[2], Li Zhang[1], Chen Yang [2], Chunrong Wang[3], Changhe Yue[3], Hui Yan[3], Jay Ma[4], Helen Fu [4], Chaomei He[4], Ping Tsui[4], Jingtao Wu[4], Richard Lee[4], Wenru Song[4]

[1]Institute of Hematology & Blood Diseases Hospital, Tianjin, China; [2]Peking Union Medical College Hospital, Beijing, China; [3]Kira Pharmaceuticals (Suzhou) Limited, China; [4]Kira Pharmaceuticals (US), Boston, MA, US; *Co-first author.

KP104: First-in-Class Dual Inhibitor of Alternative & Terminal Pathways



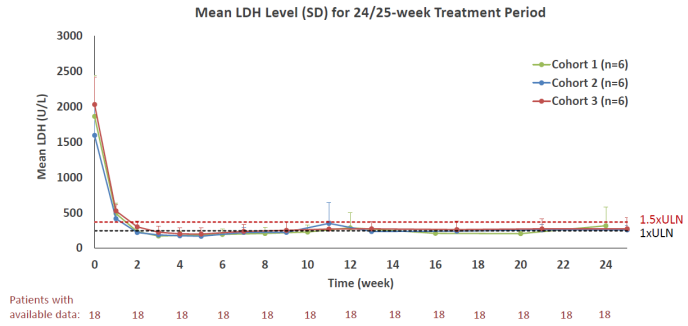
Rapid and Continued Increase in Hgb to Normal/Near-normal Level Through Week 24/25 (#1)



56% (10/18) patients achieved ≥12g/dL at Week 24/25

10

Rapid and Sustained LDH Reduction to Near Normal (1x ULN) Through 24/25 Weeks



72% (13/18) patients maintained <1 x ULN at Week 24/25

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Fengkui Zhang, et al; KP104, a Bifunctional C5 Antibody/Factor H Fusion Protein, Effectively Controls Both Intravascular and Extravascular Hemolysis: Interim Results from a Phase 2 Study in Complement Inhibitor-Naïve PNH Patients. *Blood* 2023; 142 (Supplement 1)

PNH – C5 Inhibition

C5α-chain Eculizumab
iv every 2 weeks

C5α-chain Eculizumab
biosimilars iv every 2 weeks

C5α-chain Ravulizumab
iv every 8 weeks

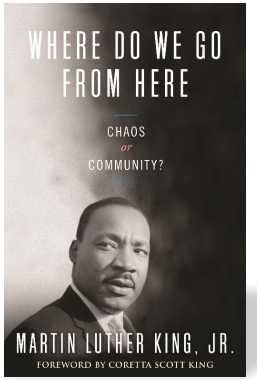
C5α-chain Ravulizumab
sc weekly

C5ß-chain Crovalimab
sc every 4 weeks

C5 + Factor H KP104
sc weekly/every 2 weeks

C5 + C5RNAi sc
weekly + every 2 weeks

C5 I others…



Thank you for your time

Paroxysmal Nocturnal Hemoglobinuria:
at the crossroads of somatic mutations, clonal expansion and immunity

Florence, October 3-4, 2024
Grand Hotel Baglioni

PNH – Guidelines – Central Europe

Adv Ther (2023) 40:2752–2772
https://doi.org/10.1007/s12325-023-02510-4

ORIGINAL RESEARCH

Complement Inhibition in Paroxysmal Nocturnal Hemoglobinuria (PNH): A Systematic Review and Expert Opinion from Central Europe on Special Patient Populations

Imre Bodó · Ismail Amine · Ana Boban · Horia Bumbea · Alexander Kulagin · Elena Lukina · Agnieszka Piekarska · Irena Preloznik Zupan · Juraj Sokol · Jerzy Windyga · Jaroslav Cermak

Received: February 10, 2023 / Accepted: March 28, 2023 / Published online: April 18, 2023

Hungary, Bulgaria, Coratia, Romania, Russia, Slovenia, Slovakia, Poland, Czech Republic

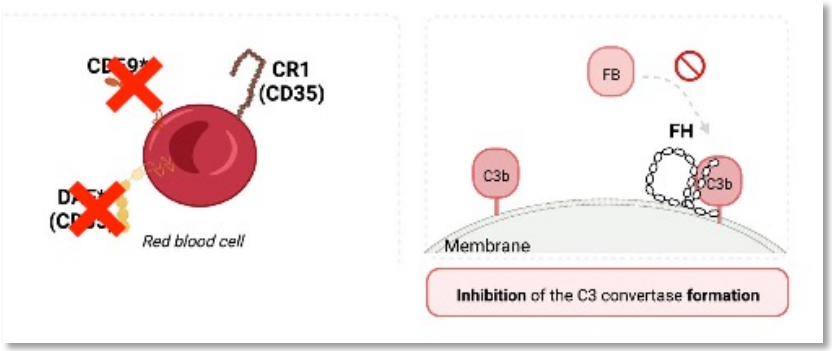
Table 2 Advantages and disadvantages of C5 and C3 inhibition

	C5 inhibition	C3 inhibition
Advantage(s)	• Several years of real-world data/experience • Clinically effective in a large proportion of patients • Very well tolerated, few side effects	• [a]Superior efficacy compared to C5 eculizumab in improving Hb and improvements in clinical and hematologic outcomes in patients with PNH (PEGASUS trial) • Current C3 inhibitor available as SQ treatment; option for self-administration • Well tolerated, few side effects
Disadvantage(s)	• Not effective in all patients • Accentuates C3-related extravascular hemolysis • Current C5 inhibitors available as IV treatments • *Neisseria meningitidis* vaccination required • High direct cost • High indirect cost (e.g., breakthrough hemolysis and loss of work/school productivity due to treatment regimen)	• Only one approved treatment is available in the EU • Twice weekly applications • Limited clinical and real-world data/experience • *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Hemophilus influenzae* vaccination required • High direct cost • Indirect cost unknown

[a]Superior efficacy was only for patients who remained anemic on a stable dose of eculizumab
C3 complement component 3, *C5* complement component 5, *EU* European Union, *Hb* hemoglobin, *PNH* paroxysmal nocturnal hemoglobinuria, *IV* intravenous, *SQ* subcutaneous

Bodó I, Amine I, Boban A, Bumbea H, Kulagin A, Lukina E, Piekarska A, Zupan IP, Sokol J, Windyga J, Cermak J. Complement Inhibition in Paroxysmal Nocturnal Hemoglobinuria (PNH): A Systematic Review and Expert Opinion from Central Europe on Special Patient Populations. Adv Ther. 2023 Jun;40(6):2752-2772

- residual complement regulators on PNH-erythrocytes (**CR1** & **soluble Factor H**) -> no IVH under low level/tick-over AP activity **BUT during CAC**
- C5 inhibition: PNH RBCs accumulate high densities of C3b, iC3b and C3dg
- clusters of C3b prime C5 (via conformational change) for C5 convertase clevage
- under **strong complement activation (CAC)**, conformational activation of C5 **cannot be inhibited** by different individual C5 inhibitors, hence **strong complement activation can override terminal pathway inhibition**



Duval A, Frémeaux-Bacchi V. Am J Hematol. 2023 May;98 Suppl 4:S5-S19; Harder et al. *Blood* 2017 **;** Kelly et al. *touchREVIEWS in Oncology & Haematology* 2022.

C5I – accross the globe - Turkey

Annals of Hematology (2021) 100:1667–1675
https://doi.org/10.1007/s00277-021-04554-4

ORIGINAL ARTICLE

Clinical characteristics and therapeutic outcomes of paroxysmal nocturnal hemoglobinuria patients in Turkey: a multicenter experience

Deniz Goren Sahin[1] · Olga Meltem Akay[2] · Muzaffer Keklik[3] · Vahap Okan[4] · Abdullah Karakus[5] · Cengiz Demir[6] · Mehmet Ali Erkurt[7] · Kadir Ilkkilic[8] · Rahsan Yildirim[9] · Gulsum Akgun Cagliyan[10] · Salih Aksu[11] · Mehmet Hilmi Dogu[12] · Mehmet Sinan Dal[13] · Volkan Karakus[14] · Ali Ihsan Gemici[15] · Hatice Terzi[16] · Engin Kelkitli[17] · Serdar Sivgin[18] · Ali Unal[3] · Mehmet Yilmaz[4] · Orhan Ayyildiz[5] · Serdal Korkmaz[19] · Bulent Eser[9] · Fevzi Altuntas[13,20]

Received: 23 April 2020 / Accepted: 2 May 2021 / Published online: 14 May 2021

- availability of Eculizumab 43/60 (71.6%) got Eculizumab
- reasons for not receiving Eculizumab: patient refusal (n=2) economic reasons (n=1), health insurance problems (n=1), asymptomatic (n=3)

- N = 60
- 28 males; 32 females
- median age 33 (range; 17–77) years
- 40/60 (66.6%) < 40 yo
- Hb 8.2 ± 2.17 g/dl (N = 46 classic PNH)

Table 2 Table showing past treatment (pre-eculizumab era) approaches for paroxysmal nocturnal hemoglobinuria patients (PNH) in our study group. Please note that these percentages have been calculated for the use of each drug alone and/or in combination therapy

Past treatments	Classic PNH ($n=46$)	PNH+AA/ PNH+MDS ($n=14$)
Oxymetholone (%)	-	4 (28.5)
Prednisolone (%)	21 (45.6)	7 (50)
Danazol (%)	3 (6.5)	3 (21.4)
Cyclosporine (%)	13 (28.2)	12 (85.7)
Azathioprine (%)	2 (4.3)	-
ATG (%)	3 (6.5)	8 (57.1)
HSCT (%)	3 (6.5)	3 (21.4)

AA, aplastic anemia; *MDS*, myelodysplastic syndrome; *ATG*, anti-thymocyte globulin; *HSCT*, hematopoietic stem cell transplantation

Sahin DG et al; Annals of Hematology (2021) 100:1667–1675

C5I – efficacy- Turkey

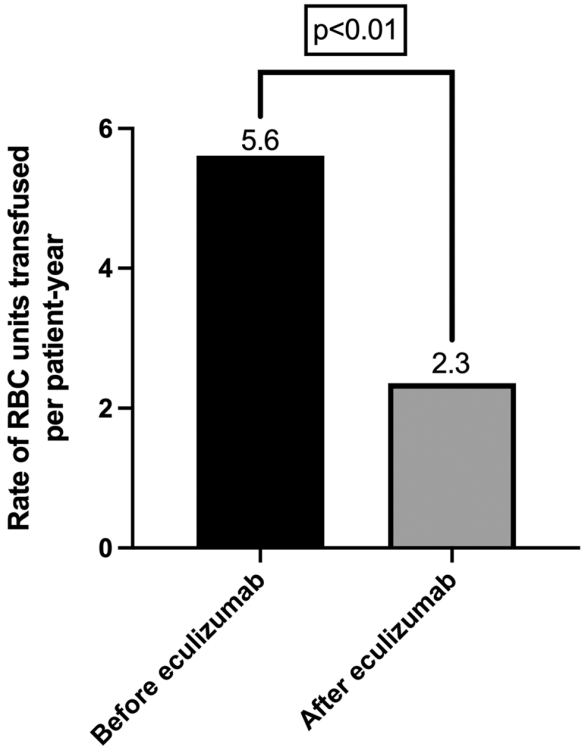


Fig. 2 Figure showing rate of the red blood cell units transfused in patients with PNH. After eculizumab treatment, transfusion need was significantly decreased

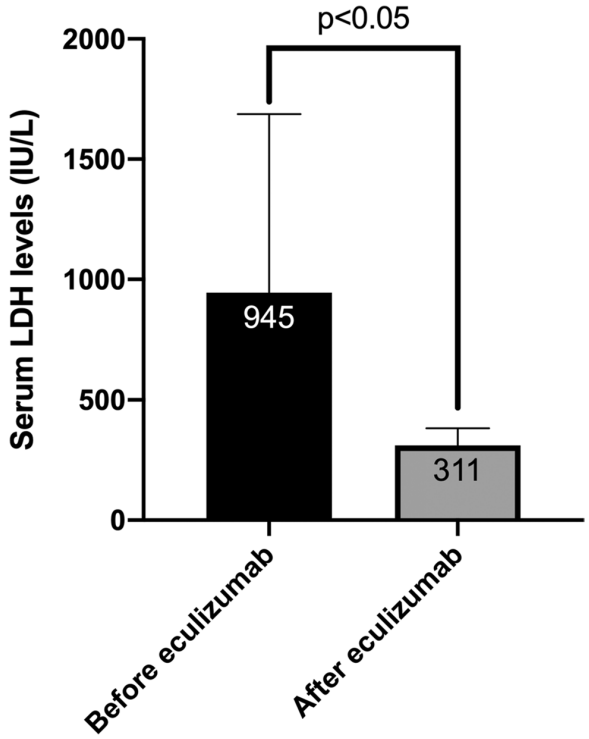


Fig. 3 Figure showing median LDH levels before and after starting eculizumab treatment

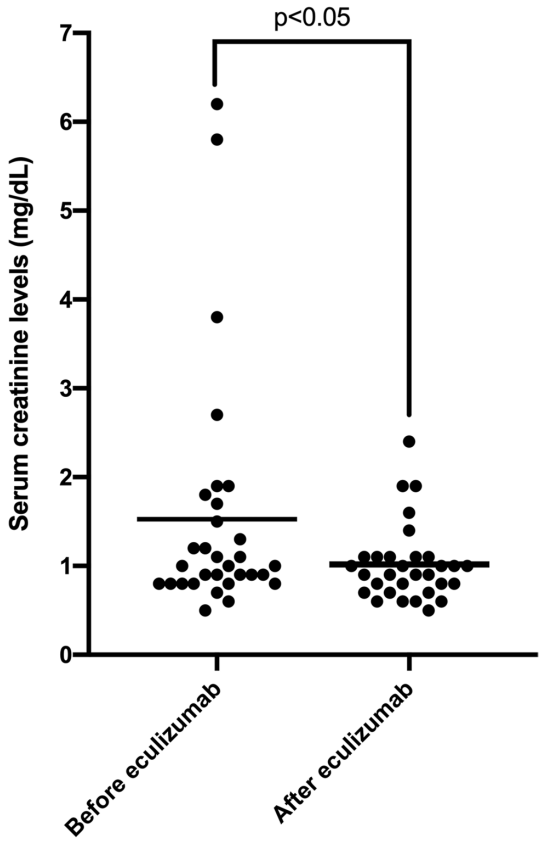


Fig. 4 Scatter dot plot graph showing significant decreased of mean creatinine levels after eculizumab treatment in PNH patients. Mean creatinine levels were 1.5 (±1.3) and 1.0 (±0.4) mg/dL before and after eculizumab therapy respectively ($p < 0.05$)

Sahin DG et al; Annals of Hematology (2021) 100:1667–1675