

# **PNH: a scientific journey from bench to the patient**

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United Kingdom

and

Chief Medical Advisor, Apellis Pharmaceuticals

# Disclosures – Peter Hillmen

Employment and equity:

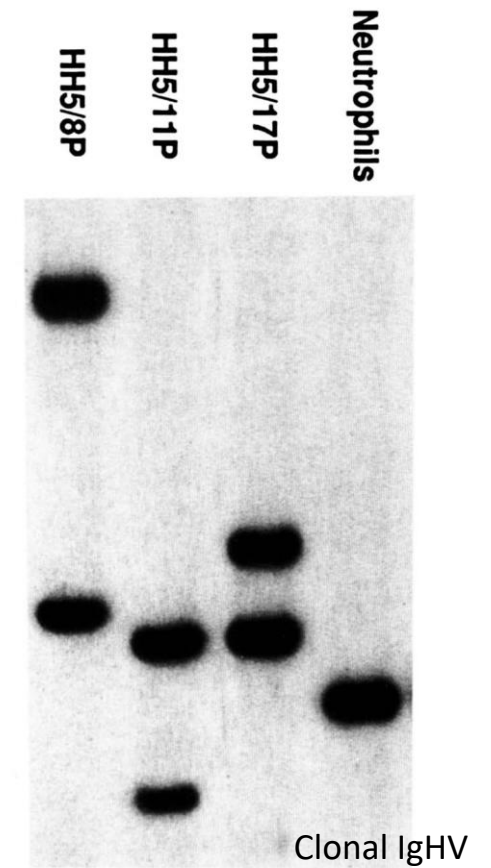
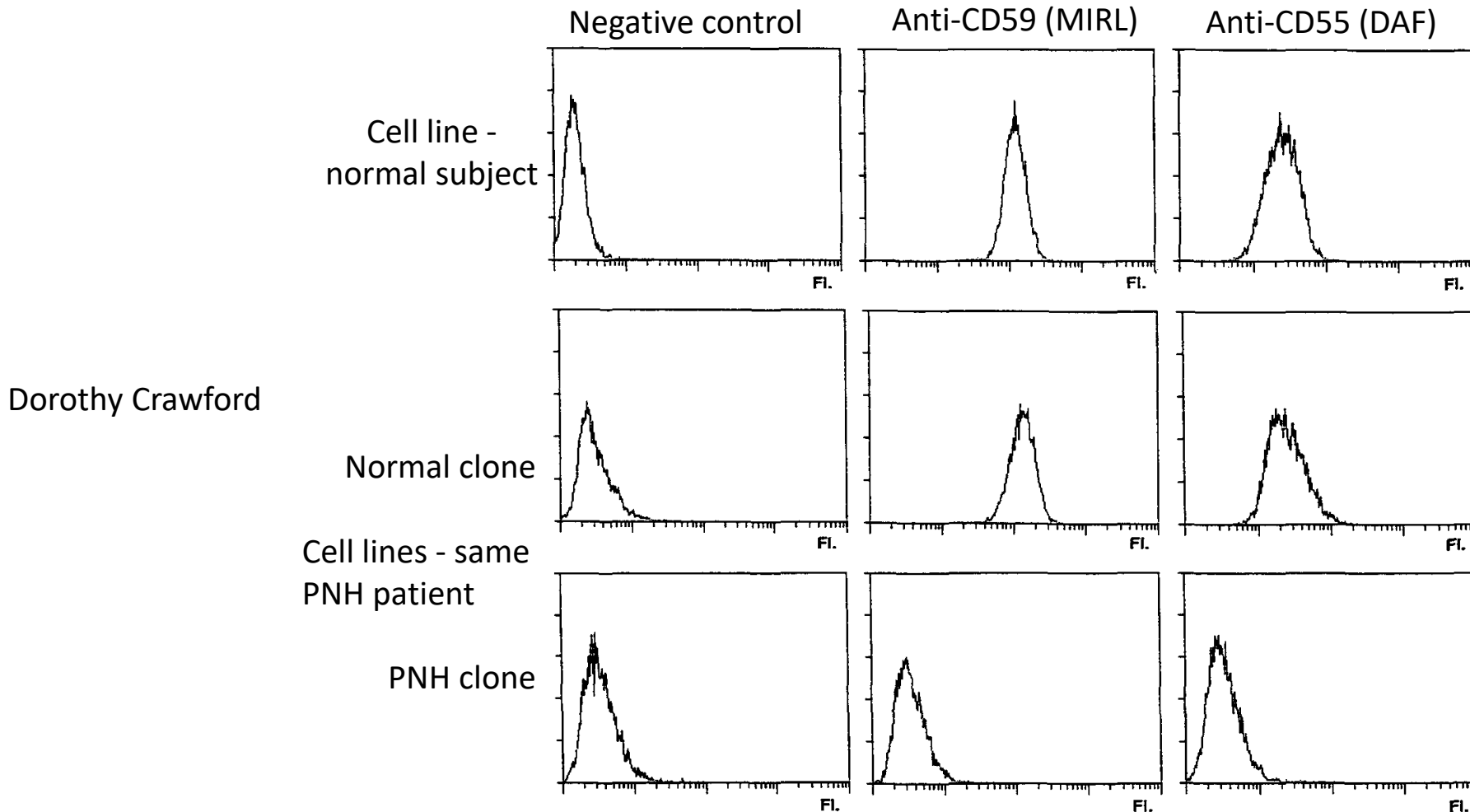
Apellis Pharmaceuticals since May 2022



# Production and Characterization of Lymphoblastoid Cell Lines With the Paroxysmal Nocturnal Hemoglobinuria Phenotype

By Peter Hillmen, Monica Bessler, Dorothy H. Crawford, and Lucio Luzzatto

*Blood*, Vol 81, No 1 (January 1), 1993: pp 193-199

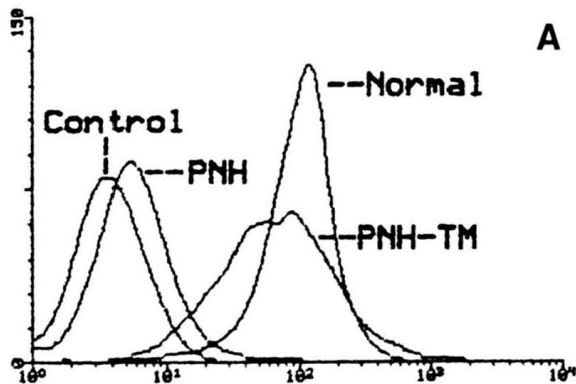


# Initial collaboration and anti-C5 MoAb

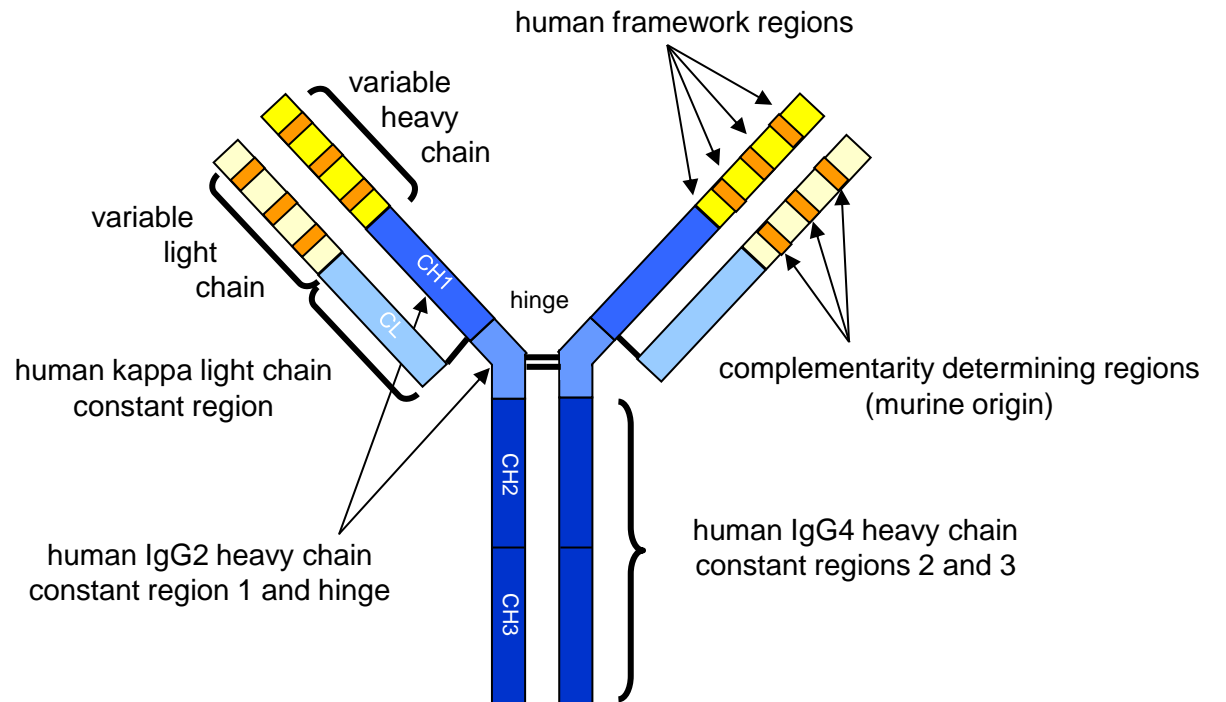
## Expression of Recombinant Transmembrane CD59 in Paroxysmal Nocturnal Hemoglobinuria B Cells Confers Resistance to Human Complement

By Russell P. Rother, Scott A. Rollins, John Mennone, Amy Chodera, Seth A. Fidel, Monica Bessler, Peter Hillmen, and Stephen P. Squinto

*Blood*, Vol 84, No 8 (October 15), 1994: pp 2604-2611



## h5G1.1-mAb (anti-C5 [eculizumab])



Initially being developed for autoimmune diseases and cardiac indications

# Visit New Haven Sept 1999



Lenny Bell

# Meeting in Leeds to discuss PNH Pilot study



Steve Squinto

Scott Rollins

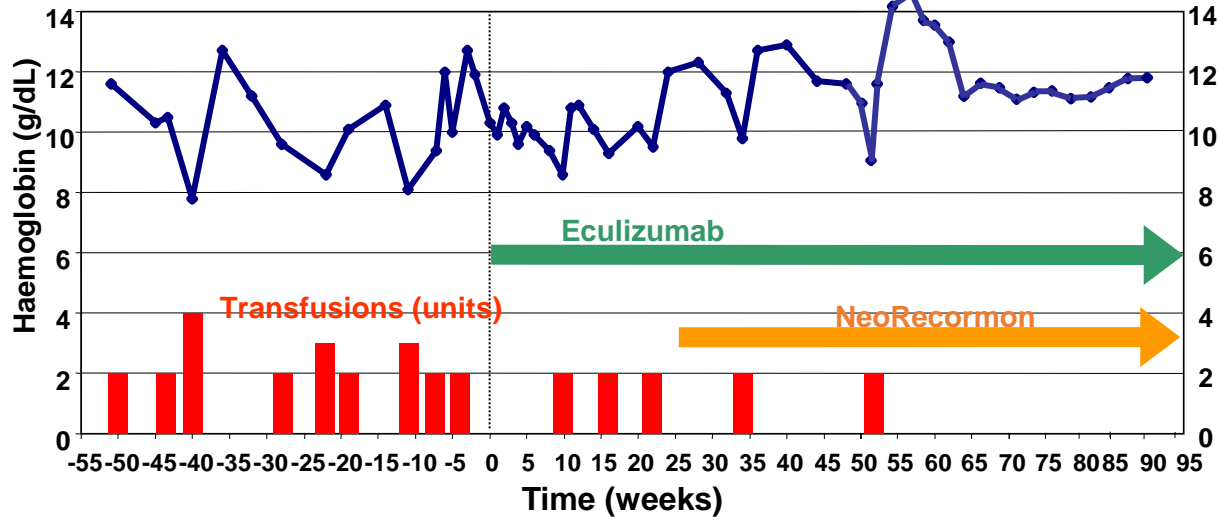
4<sup>th</sup> February 2002 – initial meeting  
22<sup>nd</sup> May 2002 – first patient treated

# First two patients with PNH in the PNH Pilot study

## D.L., 69yo man, teacher (eculizumab at 49yo)

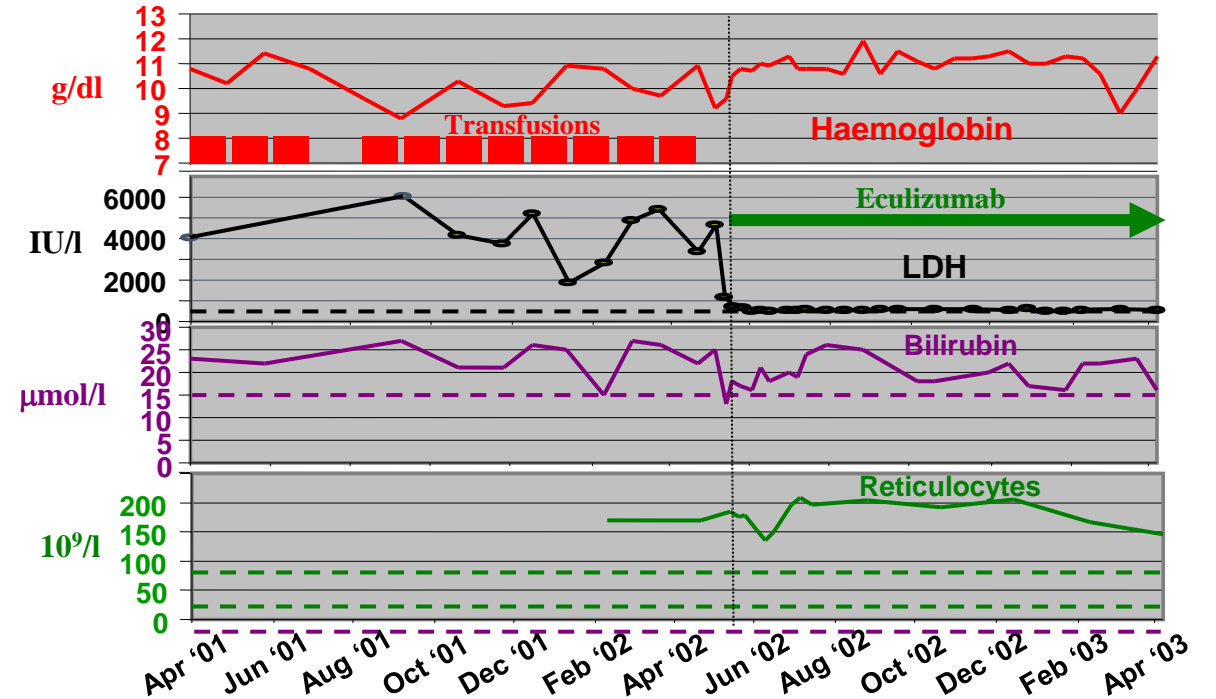
Diagnosed aplastic anemia 1988 - ALG (x2) + ciclosporin dependent  
 PNH diagnosed Sept. 1993. Hypoplastic with platelets  $80-100 \times 10^9/l$ .  
 Abdo pain, Erectile dysfunction, Severe lethargy. Transfused 24 units in  
 latest 12 months.

Started Eculizumab on 22<sup>nd</sup> May 2002 (remains on anti-complement  
 therapy)



## D.T., 79yo man, farmer (eculizumab at 59yo)

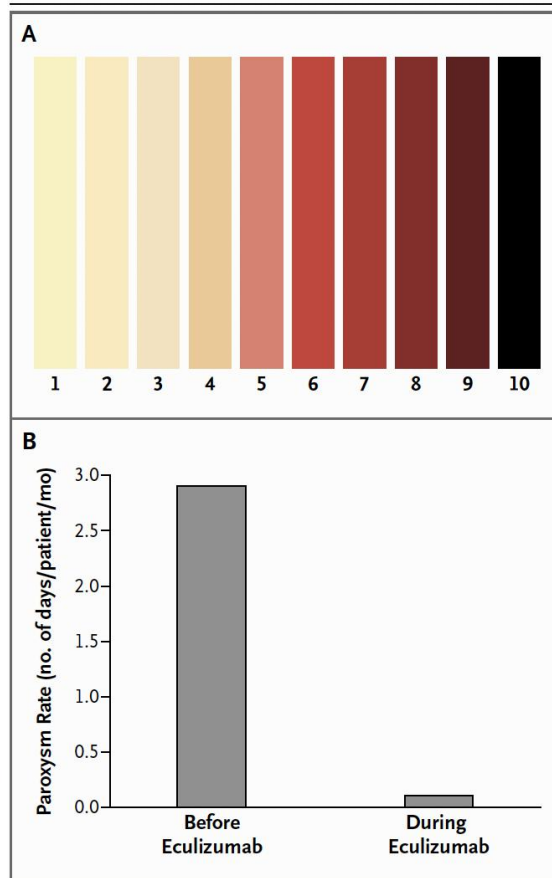
Diagnosed aplastic anaemia 1984 - ALG; PNH diagnosed 1987.  
 Hemoglobinuria, Abdo pain, Erectile dysfunction, Severe lethargy  
 Started Eculizumab on 29th May 2002 (now on ravulizumab)



## Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria

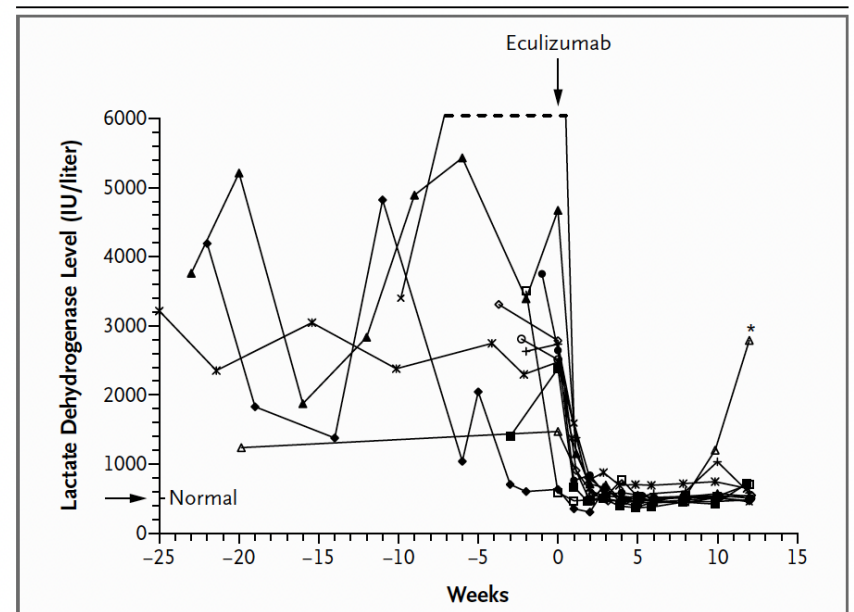
Peter Hillmen, M.B., Ph.D., Claire Hall, M.B., Ch.B., Judith C.W. Marsh, M.B., M.D., Modupe Elebute, M.B., M.D., Michael P. Bombara, B.S., Beth E. Petro, B.S., Matthew J. Cullen, B.Sc., Stephen J. Richards, Ph.D., Scott A. Rollins, Ph.D., Christopher F. Mojcik, M.D., Ph.D., and Russell P. Rother, Ph.D.

N Engl J Med 2004;350:552-9.



**Figure 4. Incidence of Paroxysms during Eculizumab Treatment.**

Panel A shows a urine color scale devised to monitor the incidence of paroxysms of hemoglobinuria in patients with paroxysmal nocturnal hemoglobinuria before and during treatment. A paroxysm was prospectively defined as a urine score of 6 or greater in this study. Panel B depicts the change in the paroxysm rate (defined as the mean number of days in paroxysm per patient per month) in nine patients 1 month before and during 12 weeks of eculizumab therapy. Pretreatment data on paroxysms were inadvertently not collected for two patients, and these two were therefore excluded from the analysis.



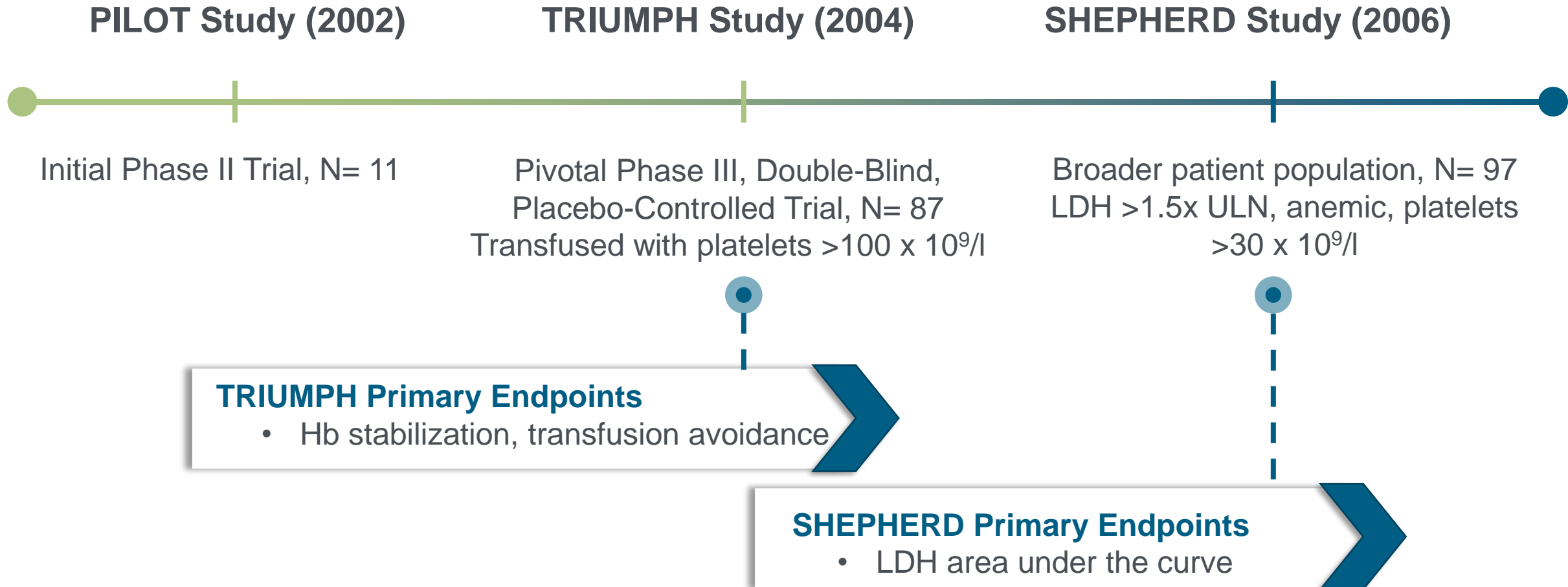
**Figure 2. Analysis of Lactate Dehydrogenase Levels, a Biochemical Indicator of Hemolysis, in 11 Patients with Paroxysmal Nocturnal Hemoglobinuria up to 25 Weeks before and during 12 Weeks of Eculizumab Treatment.**

The first dose of eculizumab is indicated by an arrow, as is the upper limit of the normal range of lactate dehydrogenase at the Leeds Teaching Hospital. The data point identified at week 12 by the asterisk represents a reading that was obtained from a duplicate serum sample since the original sample was lost. The dashed line represents off-scale points from one patient with a peak value of 12,100 IU per liter.

...ase levels. Interestingly, lactate dehydrogenase levels were reduced in most patients to just above the upper limit of normal. The slightly elevated levels of this enzyme during treatment with eculizumab could reflect persistent, low-level C3b-mediated extravascular hemolysis or, possibly, undefined



# Eculizumab clinical trials led to regulatory approval for PNH in 2007



Hb: hemoglobin; LDH: lactate dehydrogenase; PNH: paroxysmal nocturnal hemoglobinuria; ULN: upper limit of normal

Reference: 1. Hillmen P, et al. *NEJM*. 2004; 350:552-9. 2. Hillmen P, et al. *NEJM*. 2006;355:1233-43. 3. Brodsky RA, et al. *Blood*. 2008;111(4):1840-1847. 4. Hillmen P, et al. *Blood*. 2007;110(12):4123-4128. 5. Hillmen P, et al. *Br J Haematol*. 2013;162(1):62-73.

# Eculizumab clinical studies leading to Regulatory Approval for PNH in 2007

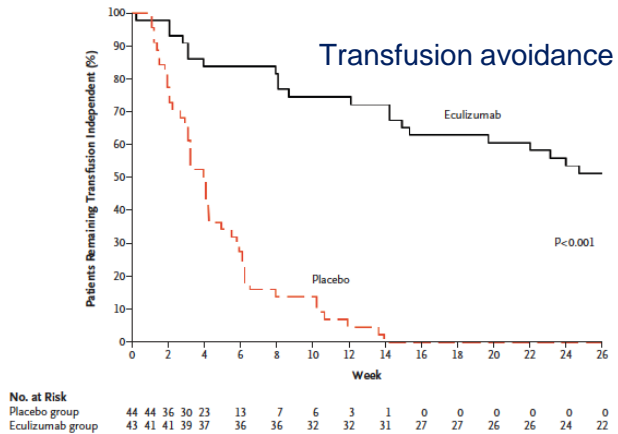
## PILOT Study (2002)<sup>1</sup>

Initial Phase II PNH Trial, N = 11

## TRIUMPH Study(2004)<sup>2</sup>

Pivotal Phase III, Double-Blind,  
Placebo-Controlled Trial, N = 87

Transfused with platelets >100 x 10<sup>9</sup>/l



## SHEPHERD Study (2005)<sup>3</sup>

Broader patient population, N = 97

LDH >1.5x ULN, anemic, platelets >30 x 10<sup>9</sup>/l

1. Hillmen P et al. *NEJM*. 2004; 350:552-9. 2. Hillmen P et al. *NEJM*. 2006;355:1233-43. 3. Brodsky RA, et al. *Blood*. 2008;111(4):1840-1847. 4. Hillmen P, et al. *Blood*. 2007;110(12):4123-4128. 5. Hillmen P, et al. *Br J Haematol*. 2013;162(1):62-73. 4. Socié G, et al. Poster presented at: 49th Annual Meeting of the American Society of Hematology; December 8-11, 2007; Atlanta, GA. Poster 891-III (appears in *Blood*. 2007;110:3672).

# Thrombosis in PNH is controlled by eculizumab

S.T., 28yo female, diagnosed PNH Nov 2003

Prophylactic warfarin

Oct 2004 → abdo pain, high INR, given FFP, stopped warfarin

Reduced thrombosis in the combined eculizumab Registration studies<sup>1</sup>

TE Events	Pilot	TRIUMPH Placebo	TRIUMPH Eculizumab	SHEPHERD	EXTENSION STUDIES
<b>Before eculizumab</b>					
No. patients	11	44	43	97	195
TE events, no.	5	11	16	91	124
Patient-years	161.7	470.4	309.0	718.3	1683.4
TE rate (per 100 pt-years)	3.09	2.34	5.18	12.67	<b>7.37</b>
<b>During eculizumab therapy</b>					
No. patients	11	44	43	97	195
TE events, no.	0	1	0	2	35
Patient-years	34.2	22.9	21.8	96.9	281.0
TE rate (per 100 pt-years)	0.00	4.38	0.00	2.06	<b>1.07</b>



## Thromboses Sept and Dec 2004

Dermal vein thrombosis  
 Mesenteric vein thrombosis  
 Left Internal Jugular Vein  
 Left Subclavian Vein  
 Proximal axillary veins  
 Budd-Chiari syndrome  
*plus*

Pulmonary embolism!

22nd Feb 2005: **bowel ischaemia**

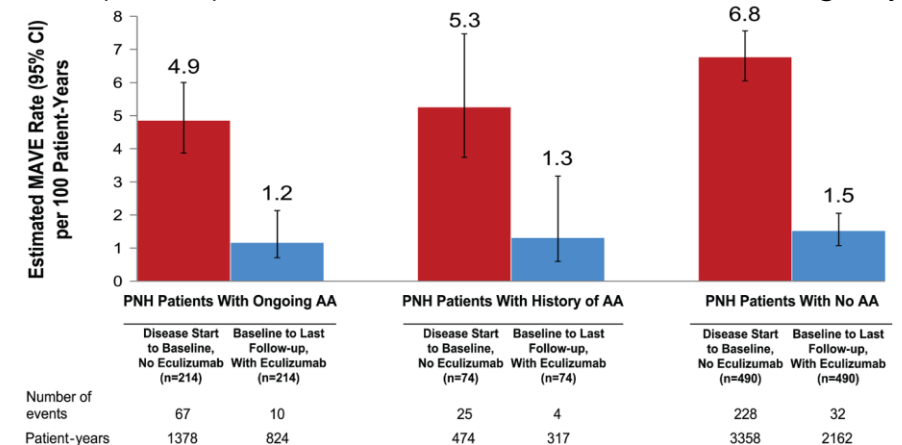
Apr 2005: ascites ++, TIPSS,  
 Malnourished

Jun 2005: SHEPHERD trial open  
 - But rbc <10% PNH due to  
 transfusions and not eligible  
 No transfusion for 10 days, PNH  
 rbc 10.1% - started eculizumab

Now:

Remains on anti-complement therapy  
 No further thrombosis  
 Completed degree in forensic medicine  
 No further thrombosis or abdo symptoms  
 Married; Adopted 3 children

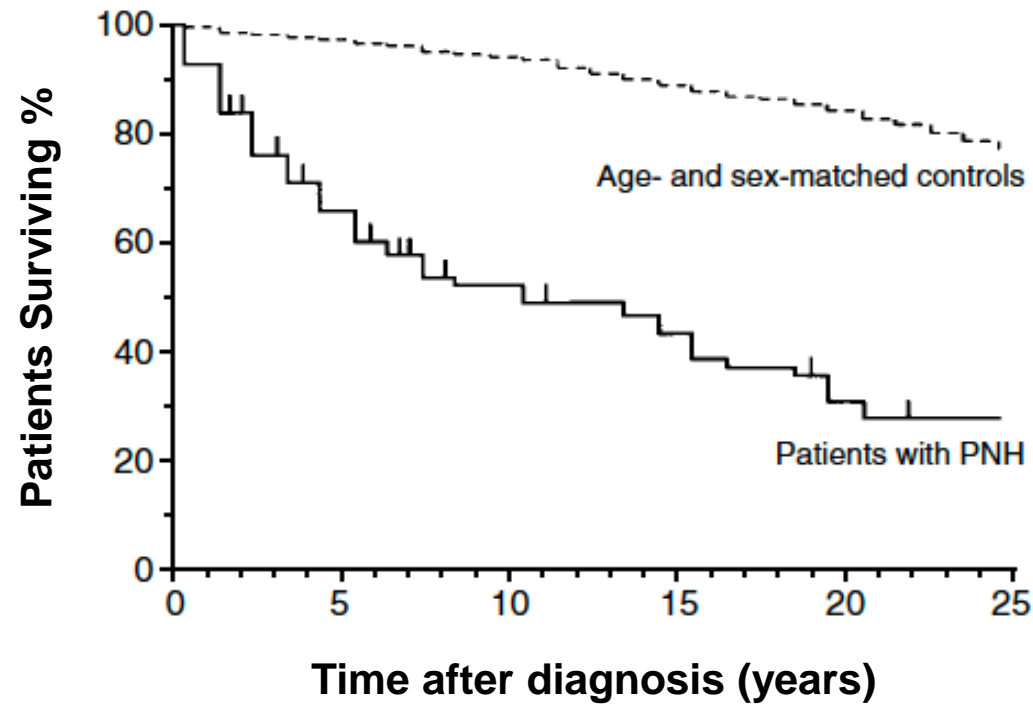
## Effectiveness of eculizumab preventing thrombosis (MAVE) in PNH in the International PNH Registry<sup>2</sup>



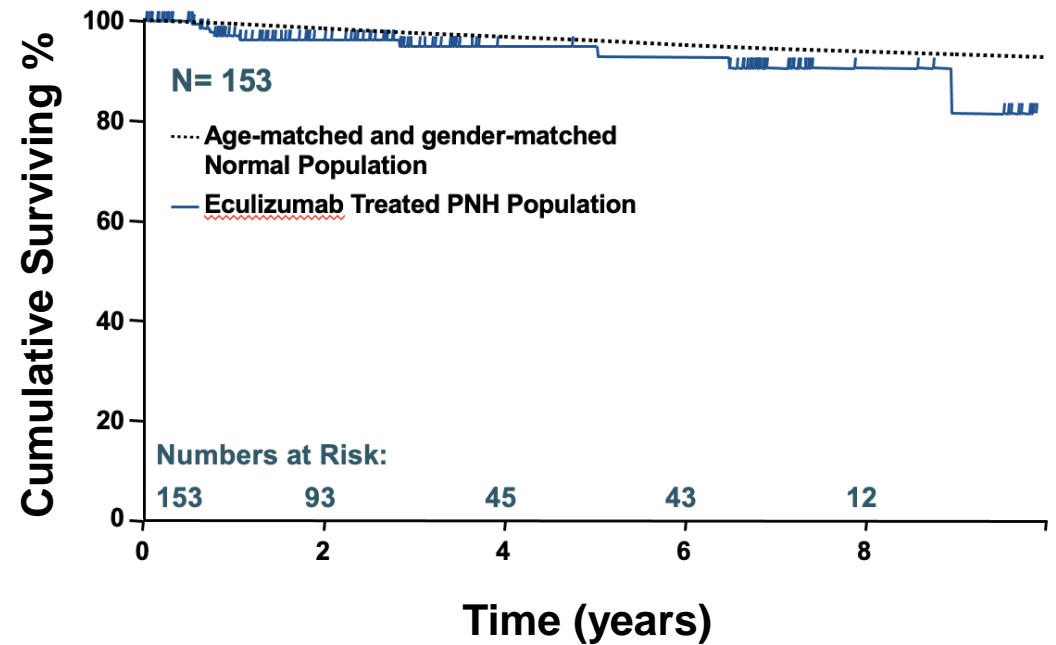
1. Hillmen et al. *Blood* 2007;110:4123-8; 2. Lee et al. *Am J Hematol.* 2019;94:E37-E41

# Survival in PNH with eculizumab

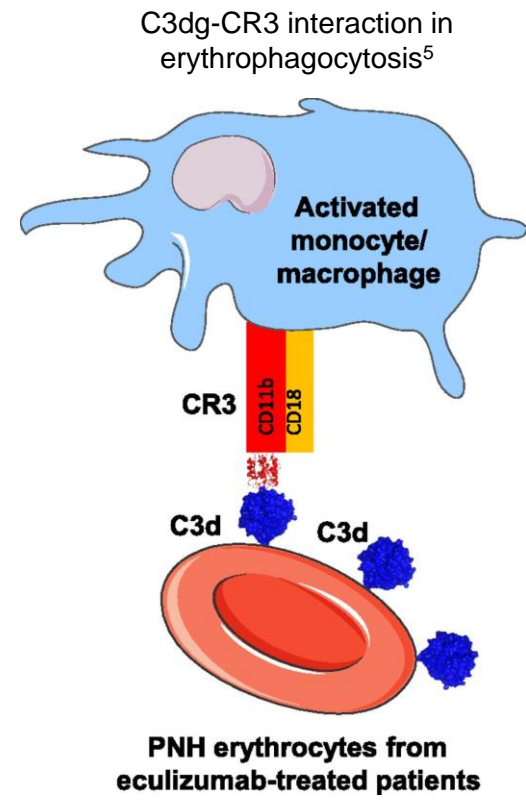
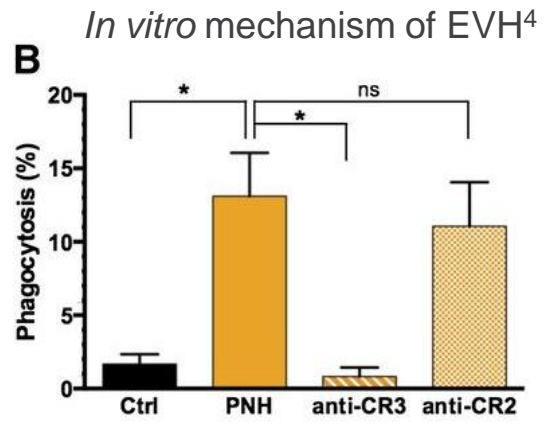
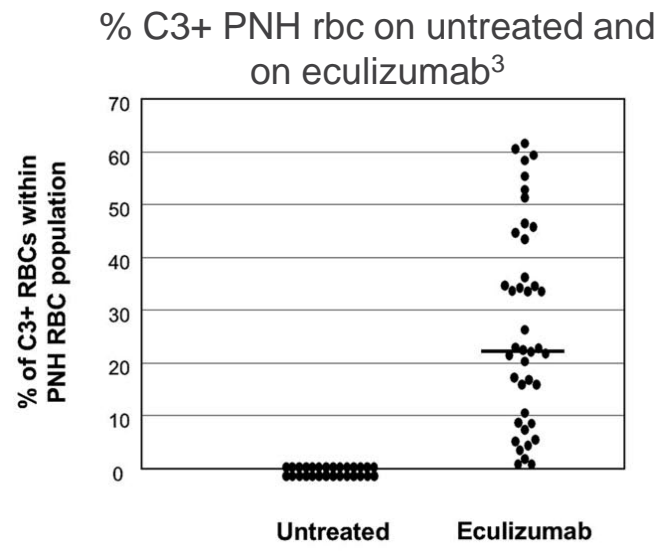
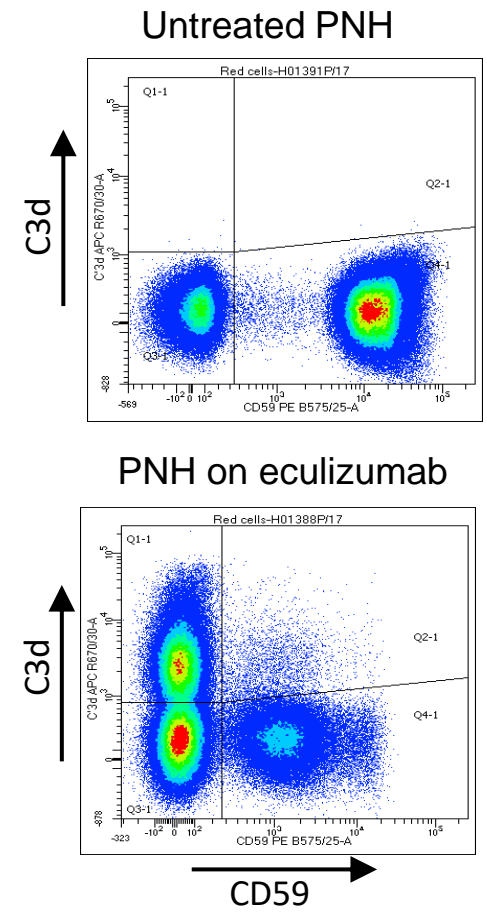
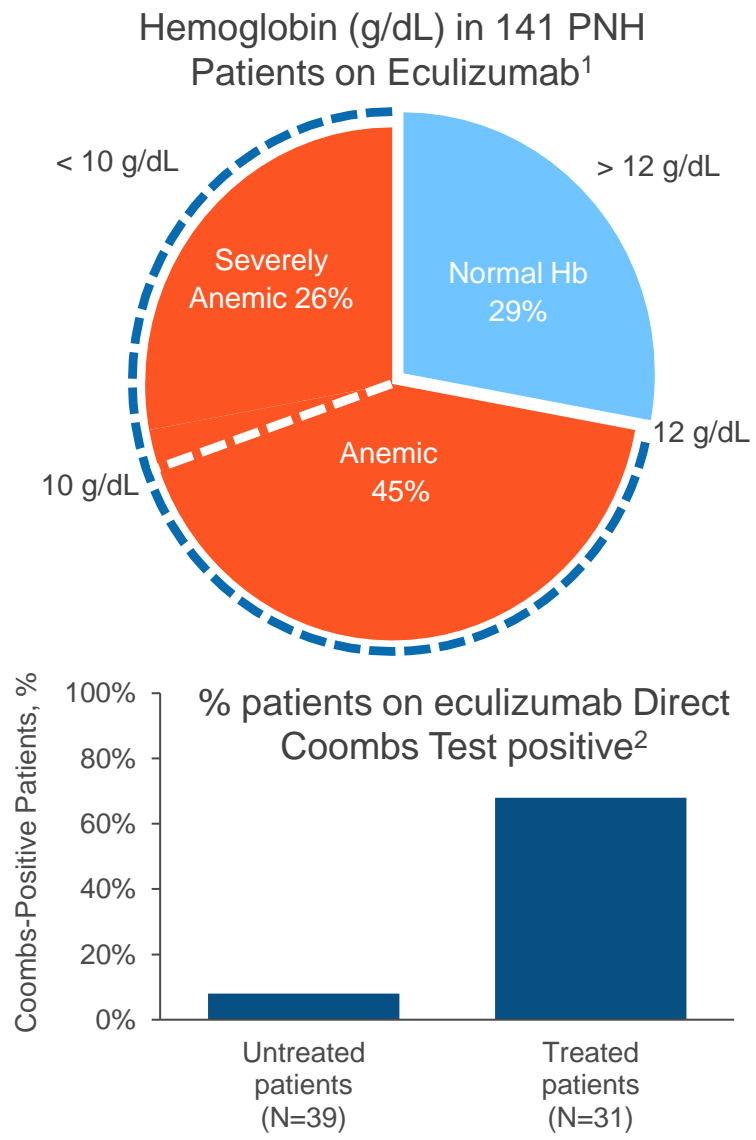
Historical survival from the time of diagnosis in 80 patients with PNH<sup>1</sup>



Overall survival of UK PNH patients treated with eculizumab vs normal population<sup>2</sup>



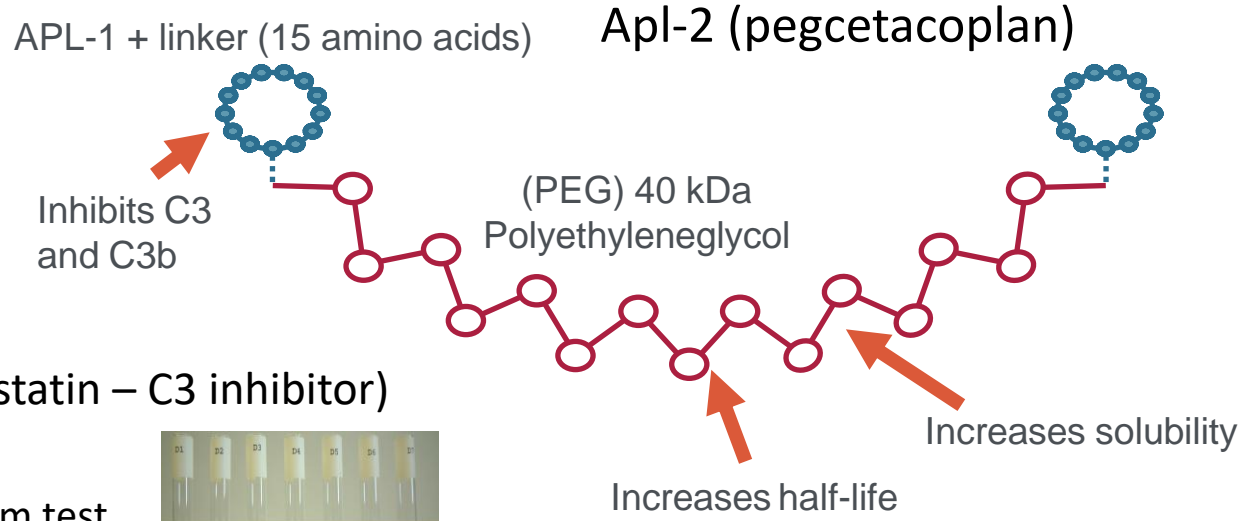
# C3 deposition and Extravascular Hemolysis in PNH treated with eculizumab



1. McKinley et al. *Blood*. 2017;130: Abst.3471. 2. Hill A, et al. *Haematologica*. 2010;95(4):567-573. 3. Risitano et al. *Blood*. 2009;113:4094-100. 4. Lin et al. *Blood*. 2015;126:891-4. 5. Lubka and Roumenina. *Blood*, 2015;126:828.

# Initial collaboration with respect to C3 inhibition

Pascal Deschatelets Cedric Francois

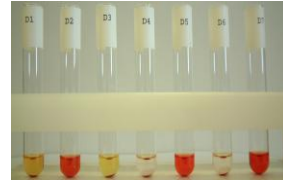


Apl-1 (2<sup>nd</sup> generation Compstatin – C3 inhibitor)

First collaboration 2012

*In vitro* analysis in a modified Ham test

Flow cytometry for CD59 and C3



## PEGASUS: Phase 3 study

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

**Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria**

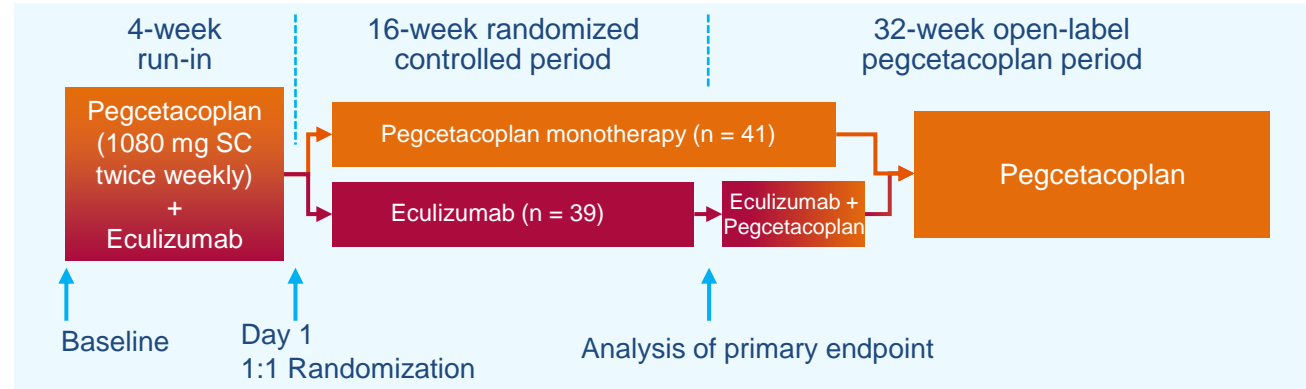
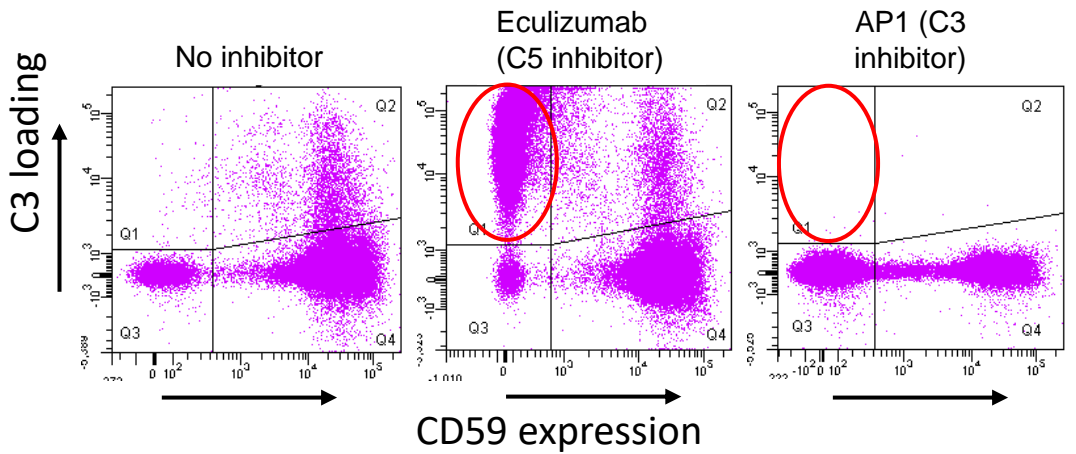
Peter Hillmen, M.B., Ch.B., Ph.D., Jeff Szer, M.B., B.S., Ilene Weitz, M.D., Alexander Röth, M.D., Britta Höchsmann, M.D., Jens Panse, M.D., Kensuke Usuki, M.D., Ph.D., Morag Griffin, B.M.Sc., M.B., Ch.B., Jean-Jacques Kiladjian, M.D., Ph.D., Carlos de Castro, M.D., Hisakazu Nishimori, M.D., Ph.D., Lisa Tan, R.N., Mohamed Hamdani, M.S., Pascal Deschatelets, Ph.D., Cedric Francois, M.D., Ph.D., Federico Grossi, M.D., Ph.D., Temitayo Ajayi, M.D., Antonio Risitano, M.D., Ph.D., and Régis Peffault de la Tour, M.D., Ph.D.

**N Engl J Med 2021;384:1028-37.**  
DOI: 10.1056/NEJMoa2029073

**Pegcetacoplan versus eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PEGASUS): 48-week follow-up of a randomised, open-label, phase 3, active-comparator, controlled trial**

Régis Peffault de la Tour, Jeff Szer, Ilene Weitz, Alexander Röth, Britta Höchsmann, Jens Panse, Kensuke Usuki, Morag Griffin, Jean-Jacques Kiladjian, Carlos M de Castro, Hisakazu Nishimori, Temitayo Ajayi, Mohammed Al-Adhami, Pascal Deschatelets, Cedric Francois, Federico Grossi, Antonio M Risitano, Peter Hillmen

**Lancet Haematol 2022; 9: e648-59.**



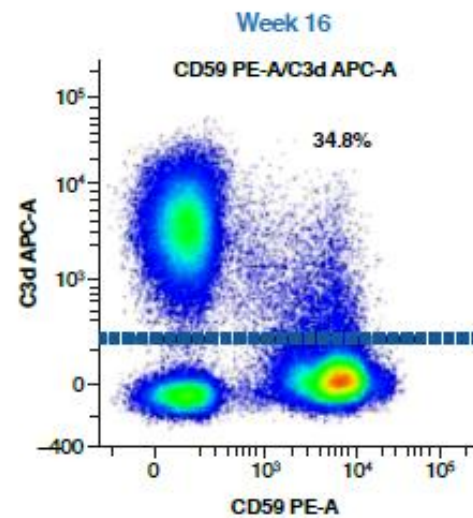
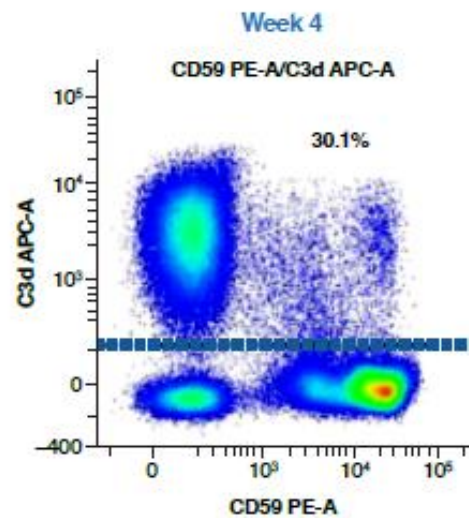
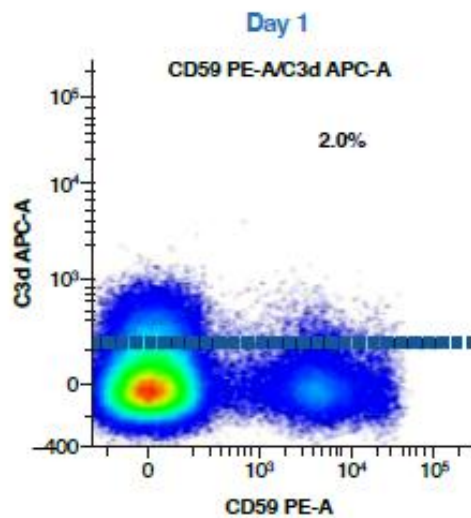
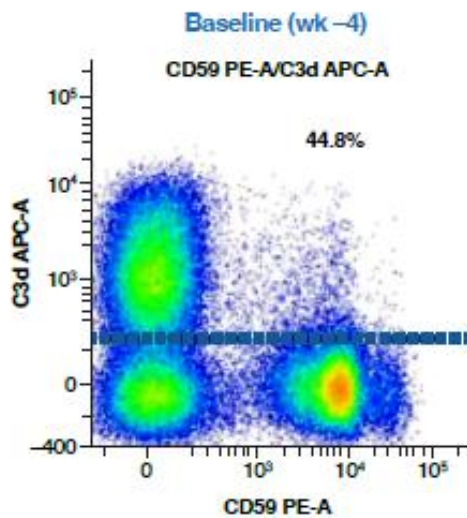
- Patients ≥18 years of age with PNH and hemoglobin <10.5 g/dL despite treatment with eculizumab
- Enrollment of patients with <4 transfusions was limited to ≤50%

Primary end-point: Week 16 change from baseline in hemoglobin level

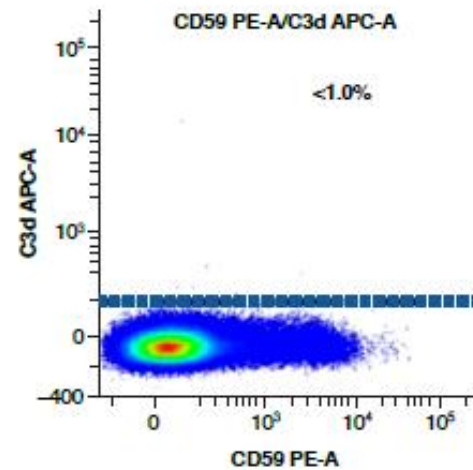
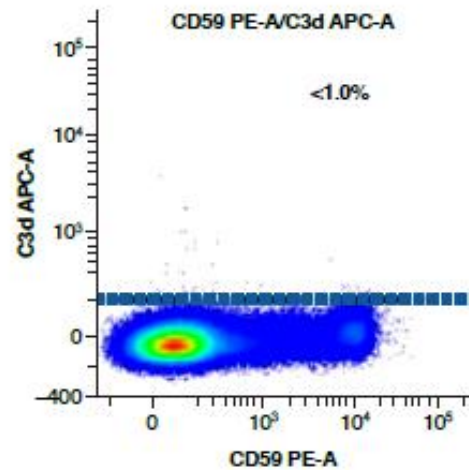
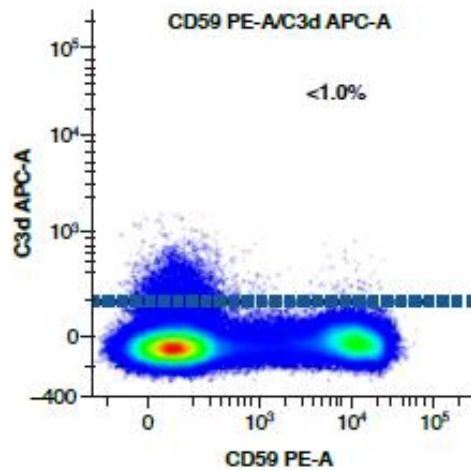
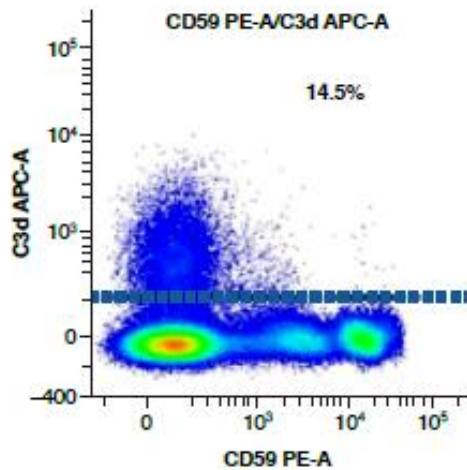
Kaudlay et al. Blood (2013) 122 (21): ASH abstract 2466.

# C3 staining in PNH receiving eculizumab or pegcetacoplan

Single patient  
randomized to  
eculizumab

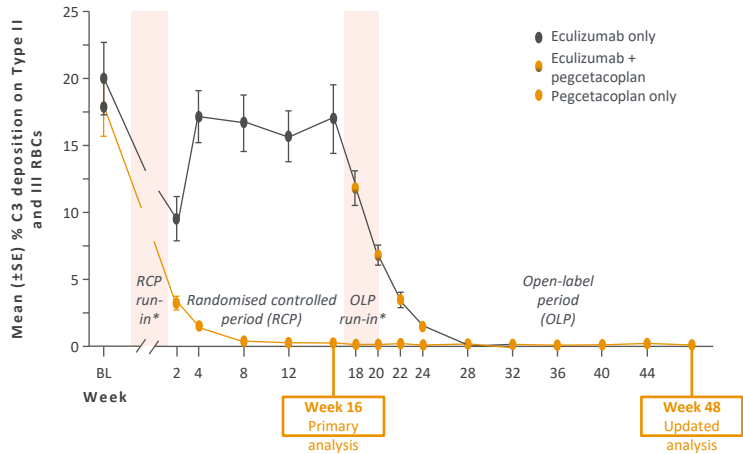


Single patient  
randomized to  
pegcetacoplan

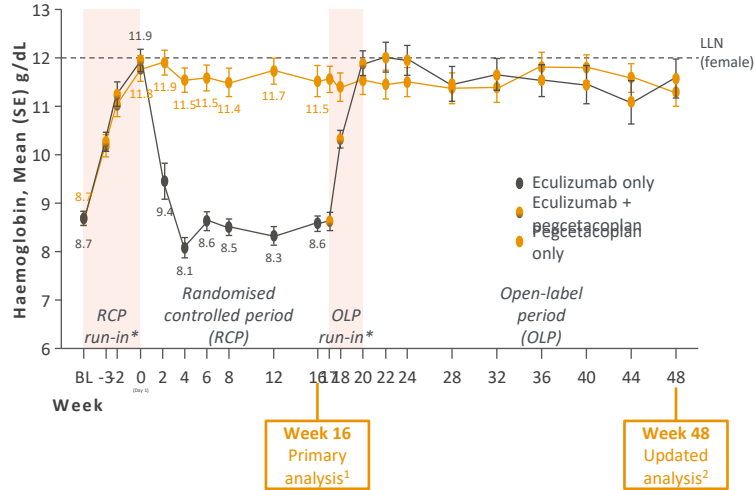


# PEGASUS Trial: Pegcetacoplan vs eculizumab in PNH

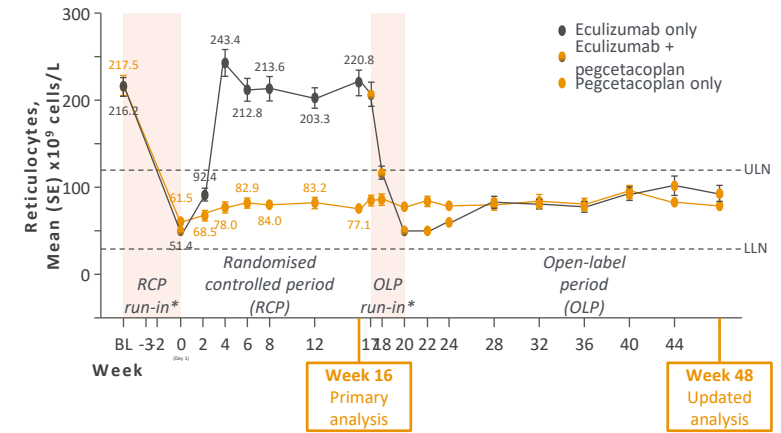
## % PNH Type II + III RBCs opsonised with C3



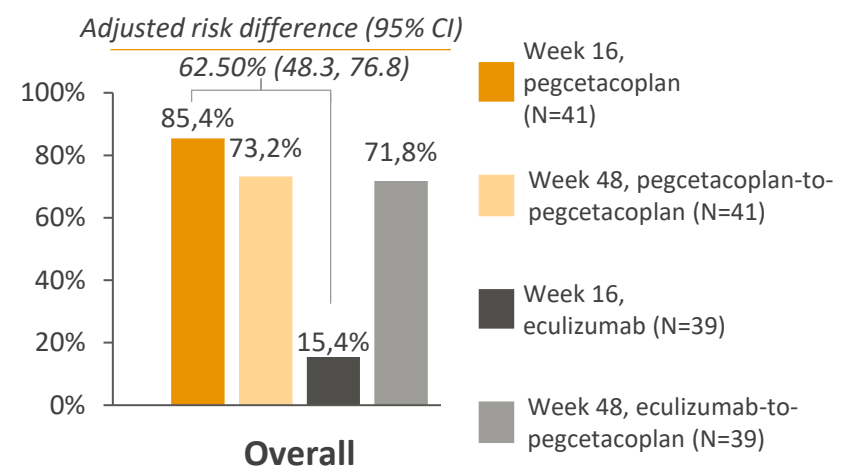
## Change in haemoglobin levels



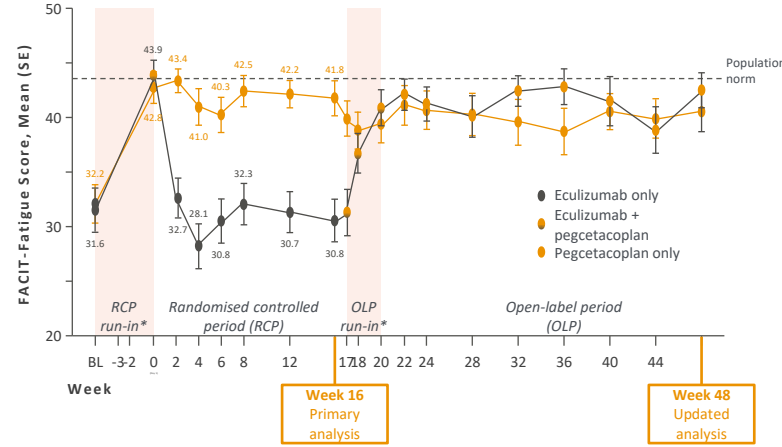
## Absolute reticulocyte count



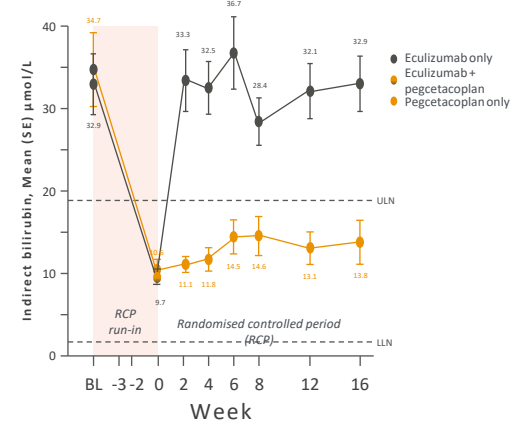
## Freedom from transfusions



## FACIT-Fatigue Scores



## Indirect bilirubin



\* Pegcetacoplan run-in periods: 1) before randomisation, for both pegcetacoplan-to-pegcetacoplan and eculizumab-to-pegcetacoplan treatment groups; and 2) before the open-label period (OLP), for the eculizumab-to-pegcetacoplan treatment group only. All observed/uncensored for transfusion data. BL, baseline; LLN, lower limit of normal; RCP, randomised controlled period; SE, standard error.

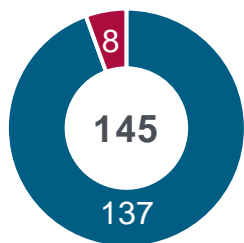
1. Hillmen et al. *N Engl J Med* 2021; 384: 1028-37; 2. Peffault de Latour et al. *Lancet Haematol* 2022; 9: e648-59



# Long Term Safety and Efficacy Study (307): Key Efficacy Takeaways<sup>1</sup>



## Efficacy data (48 week datacut):



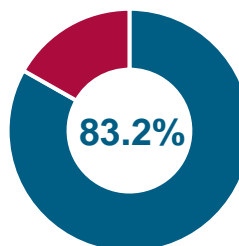
A total of **137 of 145 patients** who completed a previous pegcetacoplan trial chose to enter the extension study and 107 had received **48 weeks of treatment** at the time of data cutoff in addition to the treated time in the parent study



Exposure to pegcetacoplan ranged from **74 weeks in PRINCE** to **96 weeks in PEGASUS**



**Baseline hemoglobin, LDH, and FACIT-fatigue scores were well maintained** throughout the study



**Transfusion avoidance was achieved in 83.2%** of patients through Week 48



Pegcetacoplan **sustained improvements in hemoglobin, LDH, and fatigue** and reduced the need for transfusions in patients with PNH

FACIT-Fatigue, functional assessment of chronic illness therapy-fatigue; LDH: lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria

Reference: 1. Patriquin C, et al. Long-Term Safety and Efficacy of Pegcetacoplan Treatment in Adults with Paroxysmal Nocturnal Hemoglobinuria. Blood. 2022; 138 (Suppl 1).

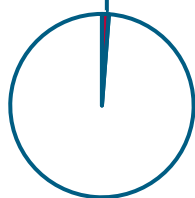
2. Patriquin et al. Presented at 64th American Society of Hematology (ASH) Annual Meeting; December 10-13, 2022; New Orleans, LA.

# Latest data showing additional safety experience with pegcetacoplan: post-hoc analysis of thrombosis and meningococcal infection<sup>1</sup>

## thrombosis



Pooled analysis of **seven pegcetacoplan clinical trials** and in the **post-marketing setting** (US, EU, and rest of the world) indicated there were:



**7 events of thrombosis** in 464 patients treated with PEG comprising 619.4 patient-years, equivalent to:

1.13 events  
100 patient-years

compared to

1.38 events  
100 patient-years

for patients treated with ravulizumab in clinical trials<sup>2</sup>

## meningococcal infection



As of November 2022, there have been **no cases of meningococcal infection** across all systemic pegcetacoplan trials, which comprise 619.4 patient years and 464 vaccinated patients.



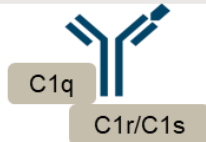
All patients were **vaccinated** against *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* Type B (Hib)

EU, European Union; PEG, pegcetacoplan; US, United States

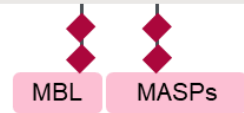
**Reference:** 1. Kelly I, et al. Submitted to the 1<sup>st</sup> International PNH Interest Group (IPIG) Conference; May 18-19, 2023; Harrogate, United Kingdom, Abstract. 2. Peffault de Latour, et al. Ravulizumab reduces the risk of thrombosis in adult patients with paroxysmal nocturnal hemoglobinuria and high disease activity: 2-year data from a phase III, openlabel study. *HemaSphere*. 2021;5(S2):109-110.

# Complement in Paroxysmal Nocturnal Haemoglobinuria

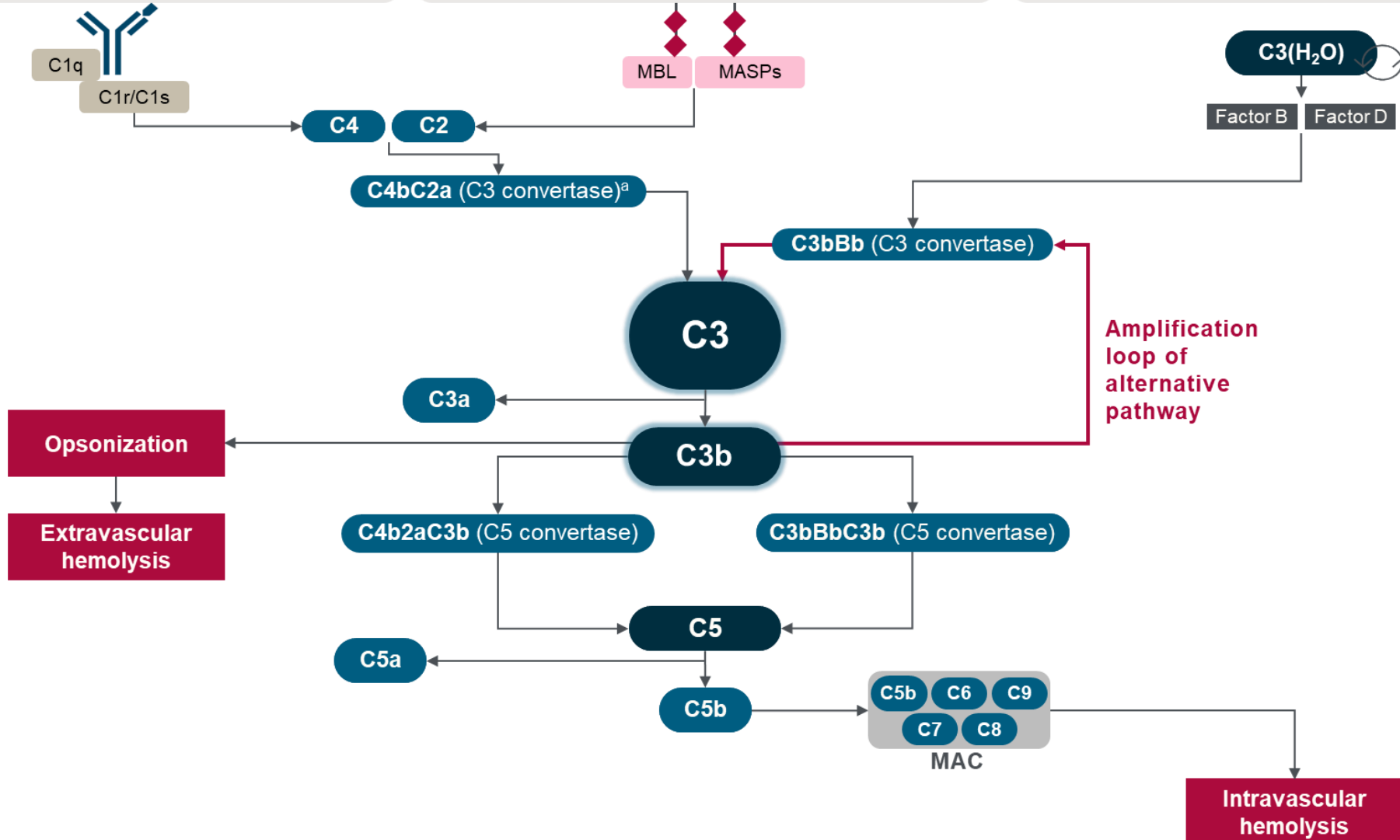
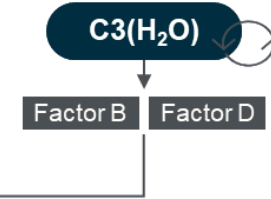
## Classical pathway



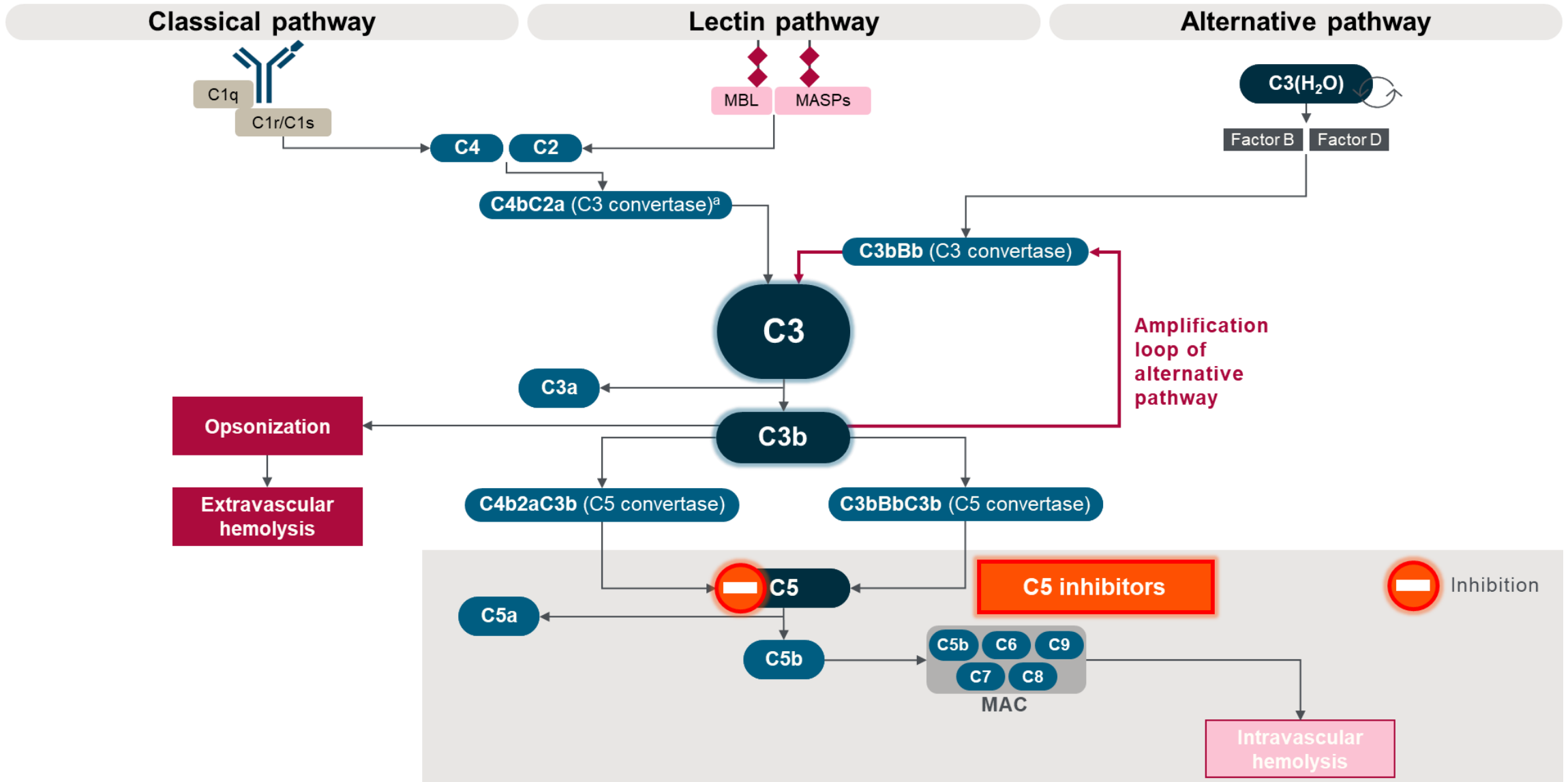
## Lectin pathway



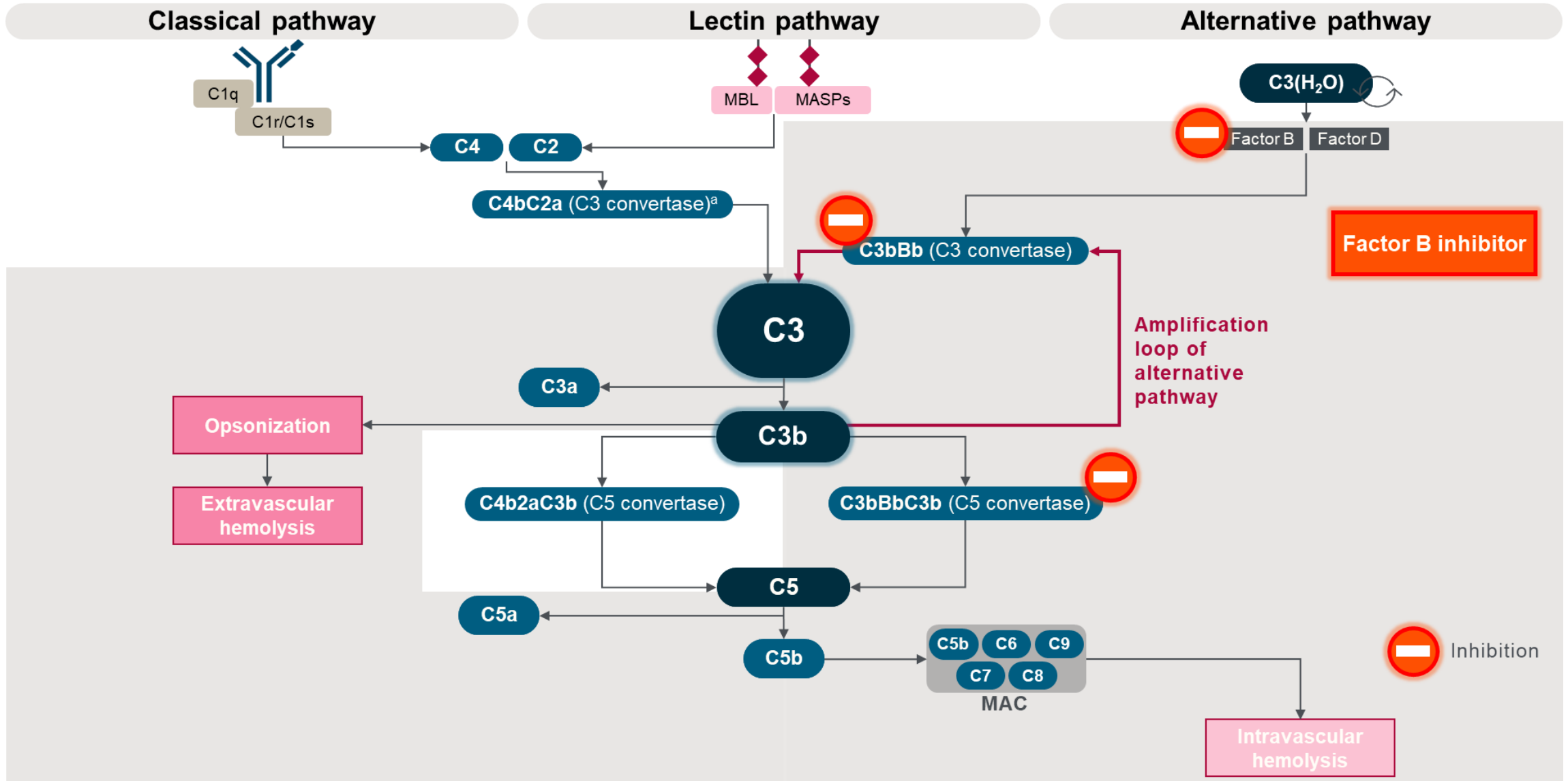
## Alternative pathway



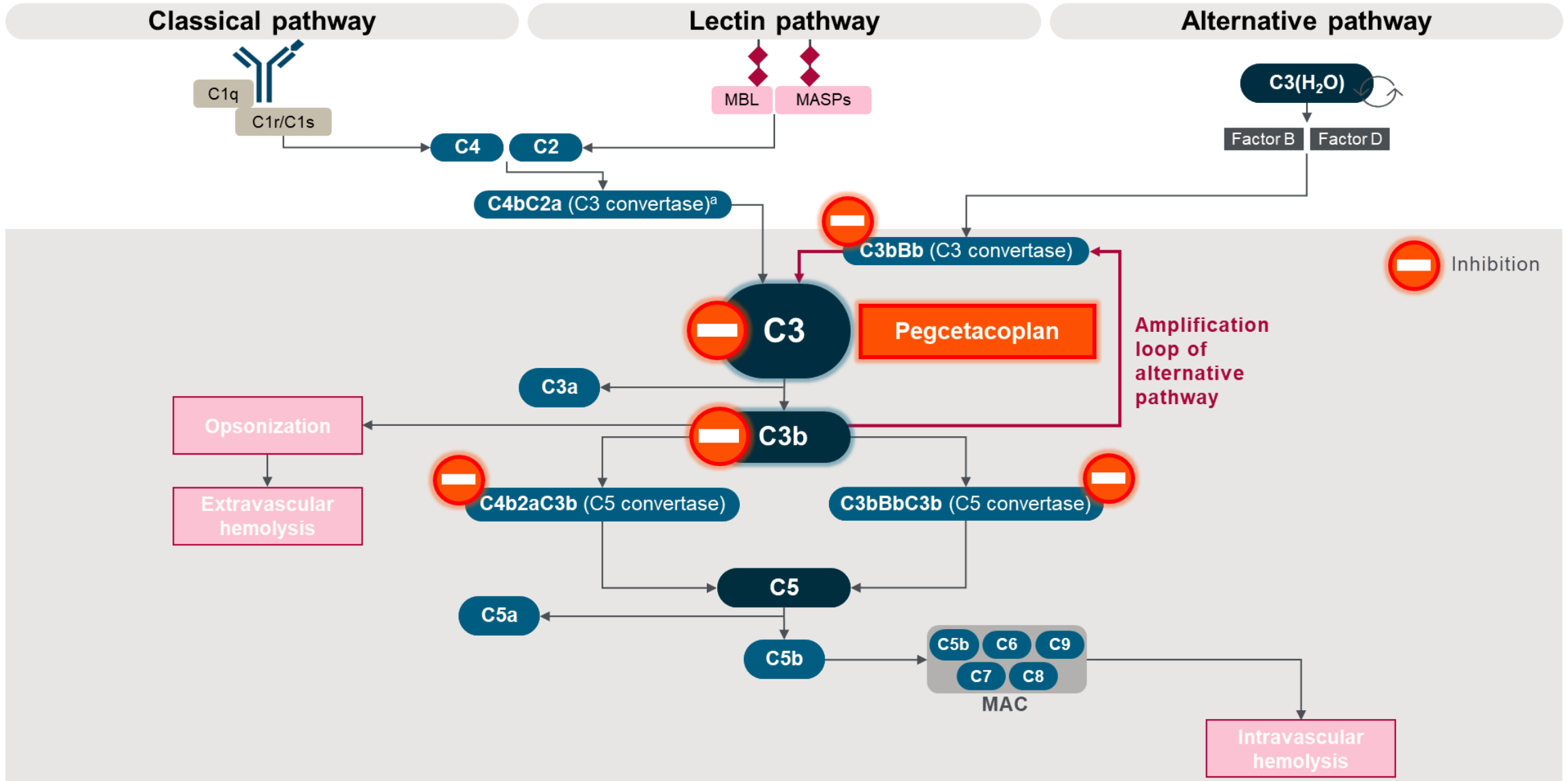
# C5 inhibitors in Paroxysmal Nocturnal Haemoglobinuria



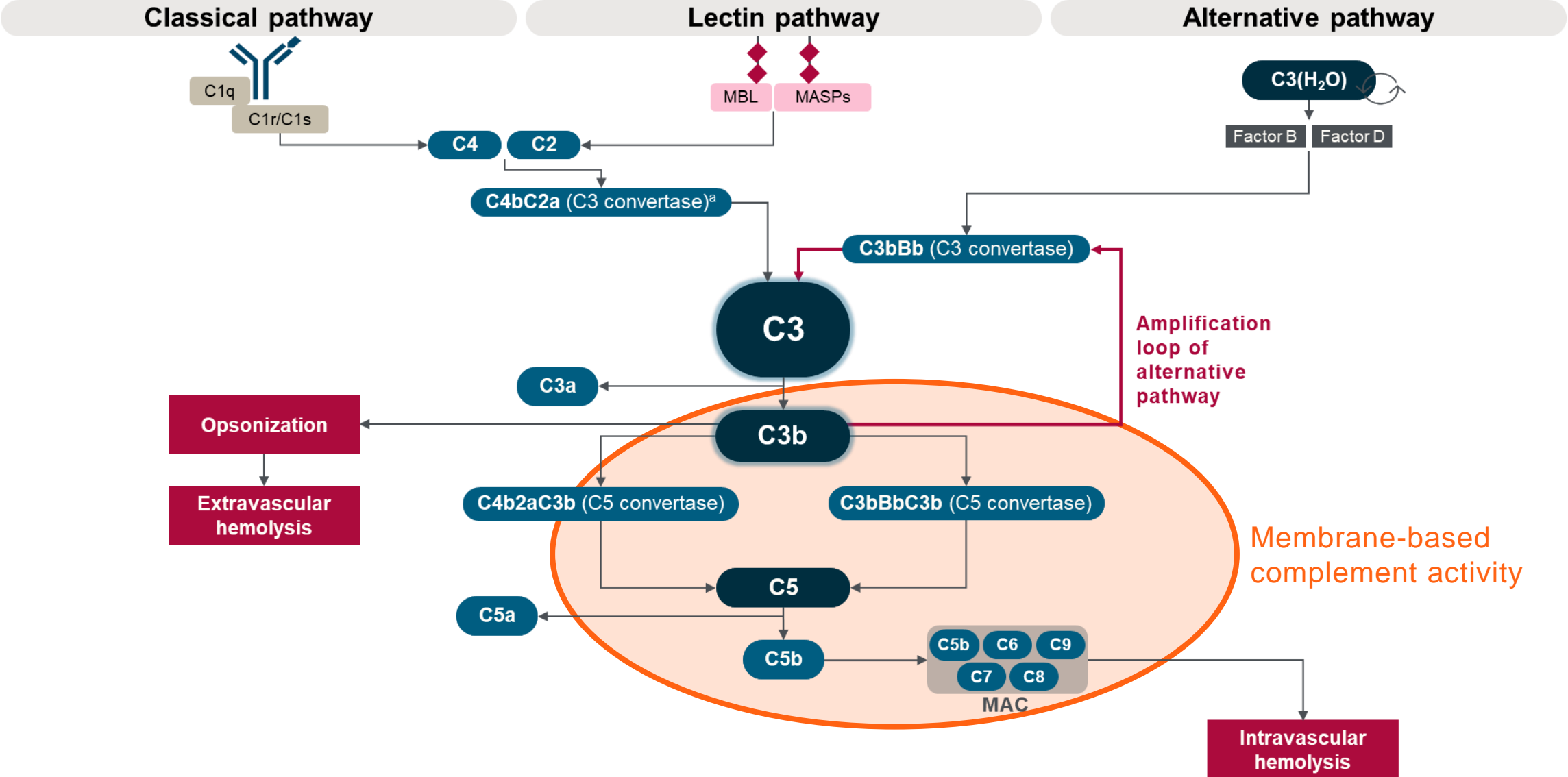
# Factor B inhibition in Paroxysmal Nocturnal Haemoglobinuria



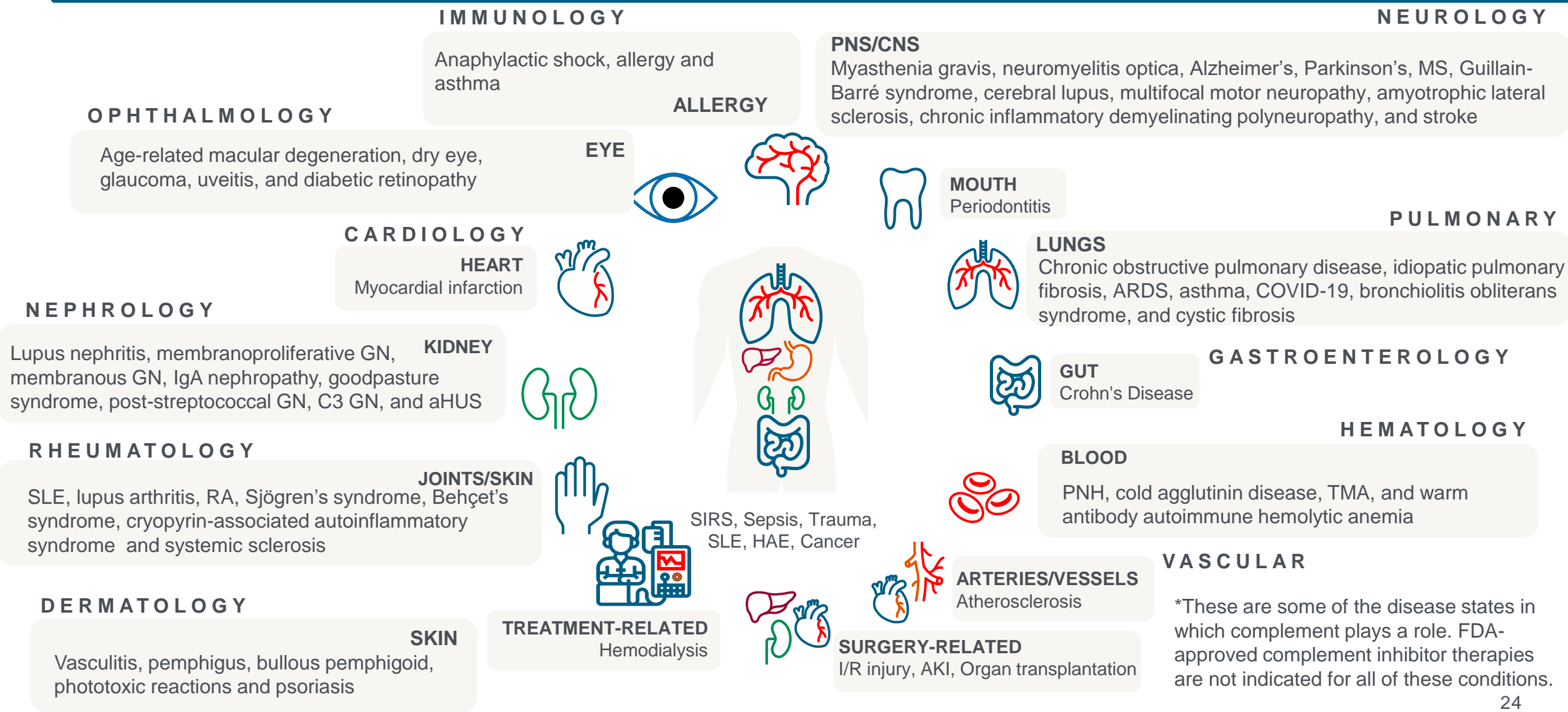
# Pegcetacoplan in Paroxysmal Nocturnal Haemoglobinuria



# Complement in Paroxysmal Nocturnal Haemoglobinuria



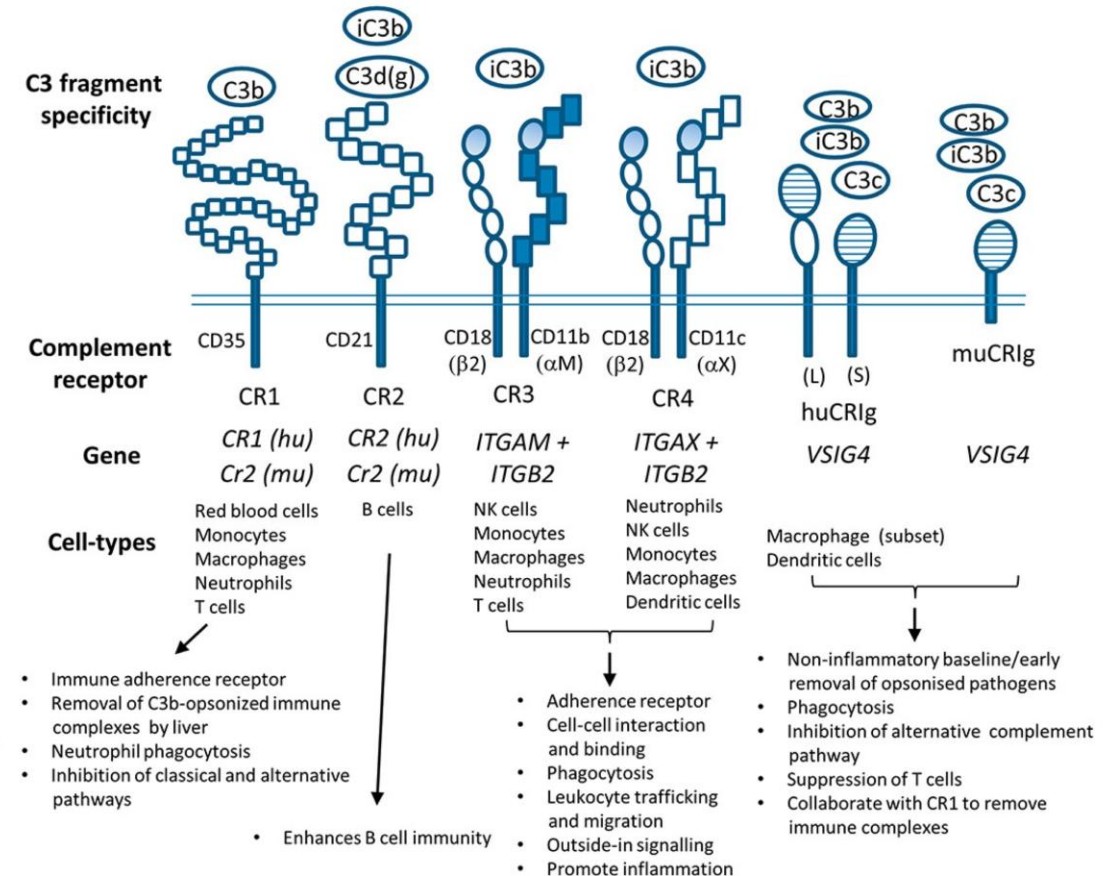
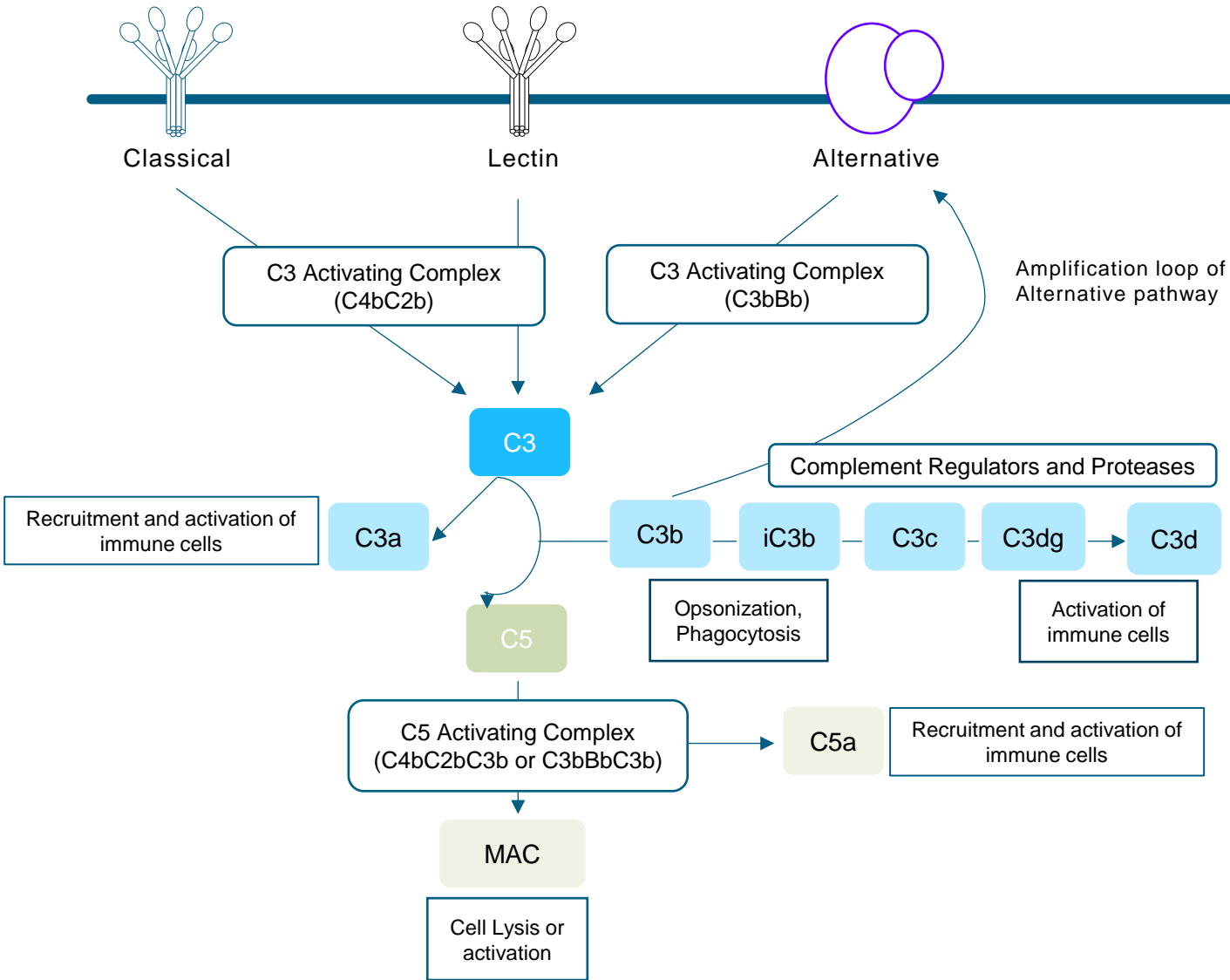
# Complement is dysregulated in many conditions\*



\*These are some of the disease states in which complement plays a role. FDA-approved complement inhibitor therapies are not indicated for all of these conditions.



# C3 opsonization critical to complement effects



# Multiple complement inhibitors in increasing indications



Complement inhibitor	Target	Disease state	First FDA approval
Eculizumab	C5	aHUS, gMG, NMOSD, PNH	March 2007
Ravulizumab	C5	aHUS, gMG, PNH	Dec 2018
Pegcetacoplan	C3	PNH	May 2021
Avacopan	C5a	ANCA associated vasculitis	Oct 2021
Sutimlimab	C1a	CAD	Feb 2022
Intravitreal pegcetacoplan	C3	Geographic atrophy due to AMD	Feb 2023
Intravitreal avacincaptad pegol	C5	Geographic atrophy due to AMD	Aug 2023
Iptacopan	Factor B	PNH, IgAN	Dec 2023
Danicopan*	Factor D	PNH (with C5i)	April 2024

aHUS: atypical hemolytic uremic syndrome; ANCA: antineutrophil cytoplasmic antibody; CAD: cold agglutinin disease; gMG: generalized myasthenia gravis; NMOSD: neuromyelitis optica spectrum disorder; PNH: paroxysmal nocturnal hemoglobinuria; Age-related macular degeneration

\*, add-on to C5i

# Conclusions

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01

Complement was a very early part of immunity to evolve

02

**Paroxysmal Nocturnal Hemoglobinuria (PNH)**

- Archetypal complement-dependent disorder
- Development of terminal and proximal complement inhibition
- Further understanding the biology of the disease

03

Targeting of C3 and the alternative complement pathway

04

C3 opsonization is central to the pathophysiology in many diseases (AMD, C3G, etc.)