Unmet needs in PNH

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Conflicts of interest

Advisory board : Sobi, Novartis.
Speakers bureau: Alexion, Novartis.

Discussion points

Navigating through "unmet needs" in PNH:

- **"Beginning of the history": improve survival and anemia**

- **"Unmet needs" in PNH patients on anti-C5 inhibitors:**

  - ✓ **Causes of residual anemia:**
    - **IVH: BTH PK and PD**
    - **EVH**
  - ✓ **Schedule and route of administration**
  - ✓ **Convenience**
  - ✓ **Special Setting**

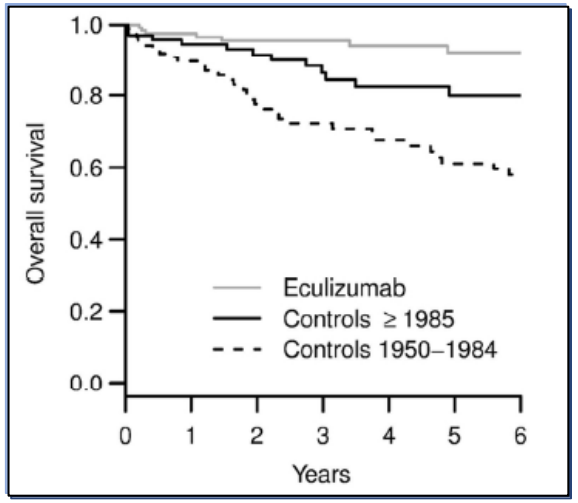
- **"Unmet needs" in PNH patients in the era of new complement inhibitors:**
  - ✓ **Open questions ?**

Impact of eculizumab treatment on paroxysmal nocturnal hemoglobinuria: a treatment versus no-treatment study *(Loschi et al, AJH 2016)*

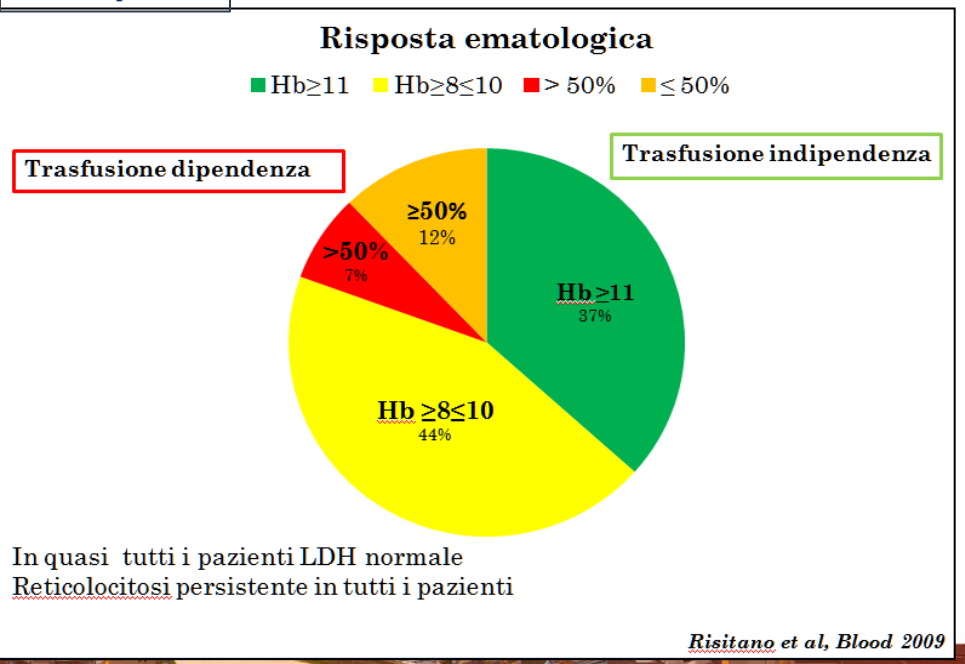
PNH patients with indication to eculizumab (clinically meaningful hemolysis and/or thrombosis)

- Eculizumab: n=123 (>2005)

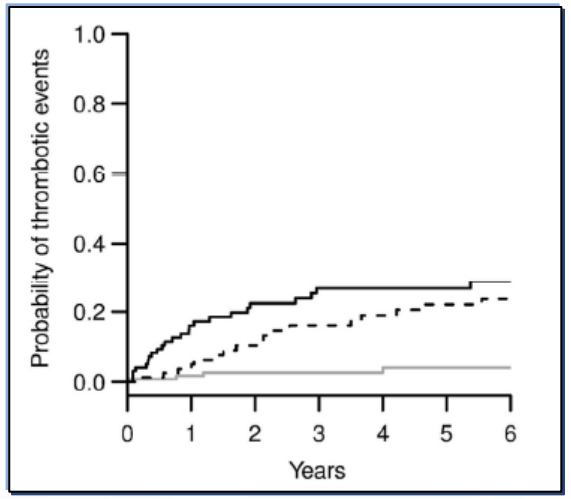
- Non-eculizumab: n=191



Italian experience



2009
Frist classification of haematological response



Response to Eculizumab and response categories – Historical background

2007
Eculizumab

2009
1st classification of haematological response

2019
2nd classification of haematological response

2021
Application of classification

Response category	Red blood cell transfusions	Hemoglobin level	LDH level*‡	ARC*
Complete response	None	≥12 g/dL	≤1.5x ULN	***and*** ≤150,000/μL§
Major response	None	≥12 g/dL	>1.5x ULN	***or*** >150,000/μL§
Good response	None	≥10 and <12 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure°
Partial response	None or occasional (≤2 every 6 months)	≥8 and <10 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure°
Minor response#	None or occasional (≤2 every 6 months) Regular (3–6 every 6 months) Reduction by ≥50%^	<8 g/dL <10 g/dL <10 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure°
No response#	Regular (>6 every 6 months)	<10 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure°

Risitano et al, 2019 Front Immunology

Tentative classification of hematological response to anti-complement agents in PNH

(Risitano et al, 2019)

Response category	Red blood cell transfusions	Hemoglobin level	LDH level*‡	ARC*
Complete response	None	≥12 g/dL	≤1.5x ULN	***and*** ≤150,000/μL§
Major response	None	≥12 g/dL	>1.5x ULN	***or*** >150,000/μL§
Good response	None	≥10 and <12 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure°
Partial response	None or occasional (≤2 every 6 months)	≥8 and <10 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure°
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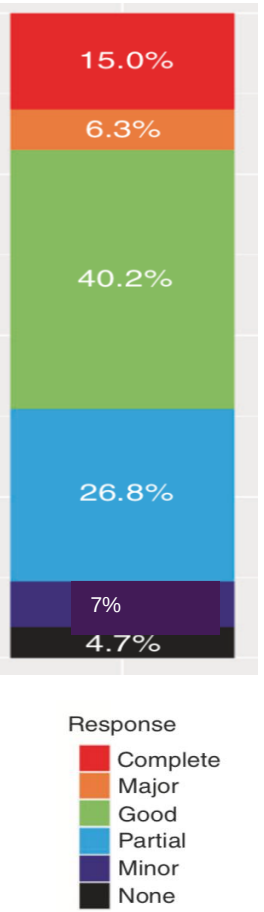
No response#	Regular (>6 every 6 months)	<10 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure°



Retrospective analysis on 160 PNH patients on eculizumab

Debureaux PE, Bone marrow transplantation 2021

“no” hematological response ≠ no clinical benefit

Discussion points

Navigating through "unmet needs" in PNH:

- **"Beginning of the history": improve survival and anemia** ✓

- **"Unmet needs" in PNH patients on anti-C5 inhibitors:**
  - ✓ **Causes of residual anemia:**
    - **IVH: BTH PK and PD**
    - **EVH**
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  - ✓ **Convenience**
  - ✓ **Special Setting**

- **"Unmet needs" in PNH patients in the era of new complement inhibitors:**
  - ✓ **Open questions ?**

What are the causes of residual anemia in patients treated with C5 inhibitors?

Intravascular hemolysis : BTH PK and PD (I)

2007
Eculizumab

BreakThrough Hemolysis

"Pharmacokinetic"

- Need to increase the dose (1200 mg) or reduce dosing intervals (10 days) of eculizumab

"Pharmacodynamic" (low-grade intravascular hemolysis)

Modification of the Eculizumab Dose to Successfully Manage Intravascular Breakthrough Hemolysis in Patients with Paroxysmal Nocturnal Hemoglobinuria.

Richard Kelly, MD, Louise Arnold, BSc, MA, Stephen Richards, PhD, Anita Hill, MD, Sandra vanBijnen, MD, Petra Muus, MD, PhD, Donna Dorr, RN, MSN, AOCN, Robert Brodsky, MD, Gus Khursigara, PhD, Russell P. Rother, PhD, Peter Hillmen, MBChB, PhD

Blood, 2008

Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria

Hillmen P et al, BJH 2013

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]

Blood, 2015

Intravascular hemolysis

2007
Eculizumab

2018
Ravulizumab

ID	Design	Schedule	Patient population	Primary endpoint
301	Phase III random VS Ecu	Every 8 w	Naïve pt	Efficacy (by LDH)
302	Phase III random VS Ecu	Every 8 w	Stable PNH responders	Efficacy (by LDH)

Table 1. Incidence of breakthrough hemolysis and overall temporal association.

	Study 301 (Naïve patients)		Study 302 (Patients stable on eculizumab)	
	Ravulizumab n=125	Eculizumab n=121	Ravulizumab n=97	Eculizumab n=98
Patients with BTH, n (%)	5 (4.0)	13 (10.7)	0 (0.0)	5 (5.1)
BTH events, n	5	15	0	7
BTH events with free C5 ≥0.5 μg/mL	0	7[a]	0	4[b]
BTH events with infection (with no free C5 elevation)	4	4	0	2
BTH events unrelated to elevated free C5 or infection[c]	1	4	0	1

n: total number of patients in treatment group; BTH: breakthrough hemolysis. [a]Two patients in the eculizumab group with suboptimal C5 inhibition also had concomitant infection. [b]One patient in the eculizumab group with suboptimal C5 inhibition also had concomitant infection. [c]These cases had neither suboptimal C5 inhibition nor concomitant infection identified to explain cause of breakthrough hemolysis.

Robert A. Brodsky et al., Haematologica 2020

Intravascular hemolysis

2007
Eculizumab

2016
Crovalimab

2024
Crovalimab approved

Crovalimab: anti-C5, SC, every 4w, effective in patients with a C5 R885H polymorphism.

Crovalimab (SC)	Phase III trial		
PK, PD and safety profile of anti-hC5 mAb	Phase I	PNH naive	Röth A et al, Blood. 2017
COMPOSER trial NCT03157635	Phase I/II	Healthy volunteers and PNH naive	Röth A et al, Blood. 2020[35]
COMMODORE 2 (NCT04434092)	Phase III	PNH naive	Ongoing NCT04434092 at clinicaltrials.gov
COMMODORE 1 (NCT04432584)	Phase III	PNH in C5-inhibitor	Ongoing NCT04432584 at clinicaltrials.gov

Versino e Fattizzo, 2024

Phase 3 randomized COMMODORE 2 trial: crovalimab vs eculizumab in patients with PNH naive to complement inhibition

Crovalimab allows for effective PNH treatment with subcutaneous self-administration every 4 weeks

Population
- PNH patients ≥18 years
- Body weight ≥40 kg
- LDH ≥2×ULN
- No previous complement inhibitor treatment

R 2:1

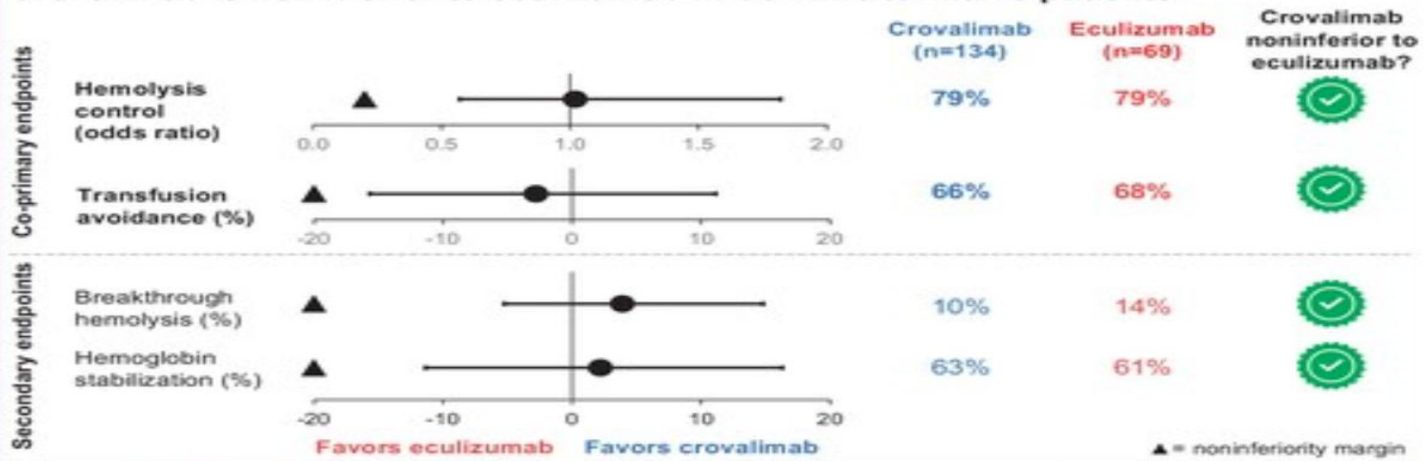
- Crovalimab (SC) Every 4 weeks* (home or in the clinic) → Crovalimab continuation
- Eculizumab (IV) Every 2 weeks* (clinical setting) → Switch to crovalimab

Primary treatment period 24 weeks

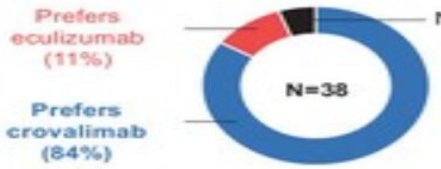
* Maintenance dosing following a loading series.

Crovalimab is well tolerated and has a safety profile comparable to eculizumab

Crovalimab is noninferior to eculizumab in C5 inhibitor-naive patients



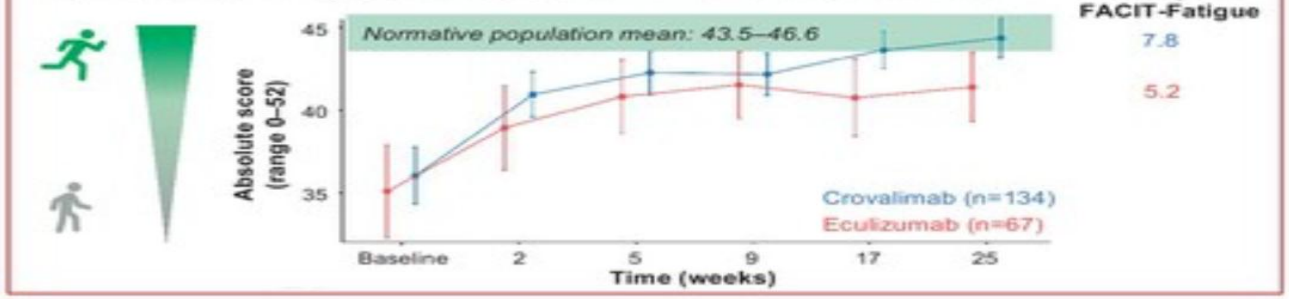
Most patients who switched from eculizumab to crovalimab preferred crovalimab due to reasons associated with self-administration, either at home or in the clinic



The top 3 reasons for crovalimab preference were:
1. The way treatment was given was easier
2. Fewer hospital visits associated with treatment
3. Time to administer treatment was shorter

Data are exploratory.

Clinically meaningful improvements in fatigue occurred in both arms, with a numerically greater improvement with crovalimab



Conclusions

- COMMODORE 2 met its co-primary efficacy endpoints, demonstrating noninferiority of crovalimab vs eculizumab for hemolysis control and transfusion avoidance, and showed that crovalimab has a well-tolerated safety profile
- These data highlight the overall favorable benefit–risk profile of crovalimab, which has the potential to reduce treatment burden by allowing for every-4-weeks subcutaneous injection with an option to self-administer at home

Alexander Röth, et al. *Am J Hematol*

Navigating through “unmet needs” in PNH:

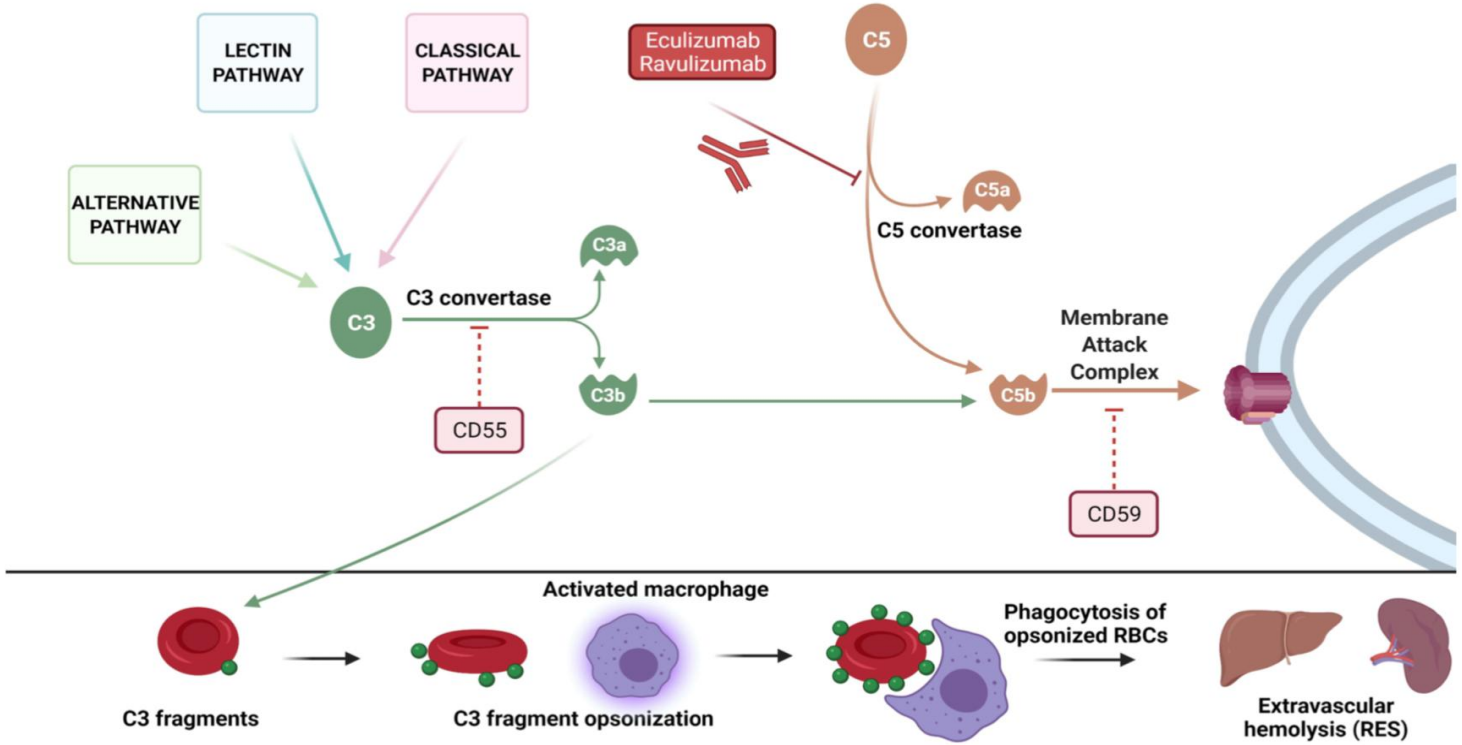
- “Beginning of the history”: improve survival and anemia ✓
- “Unmet needs” in PNH patients on anti-C5 inhibitors:
  - ✓ Causes of residual anemia: ✓
    - IVH: BTH PK and PD
    - EVH
  - ✓ Schedule and route of administration
  - ✓ Convenience
  - ✓ Special Setting
- “Unmet needs” in PNH patients in the era of new complement inhibitors:
  - ✓ Open questions ?

C3-mediated extravascular hemolysis (I)

2007
Eculizumab

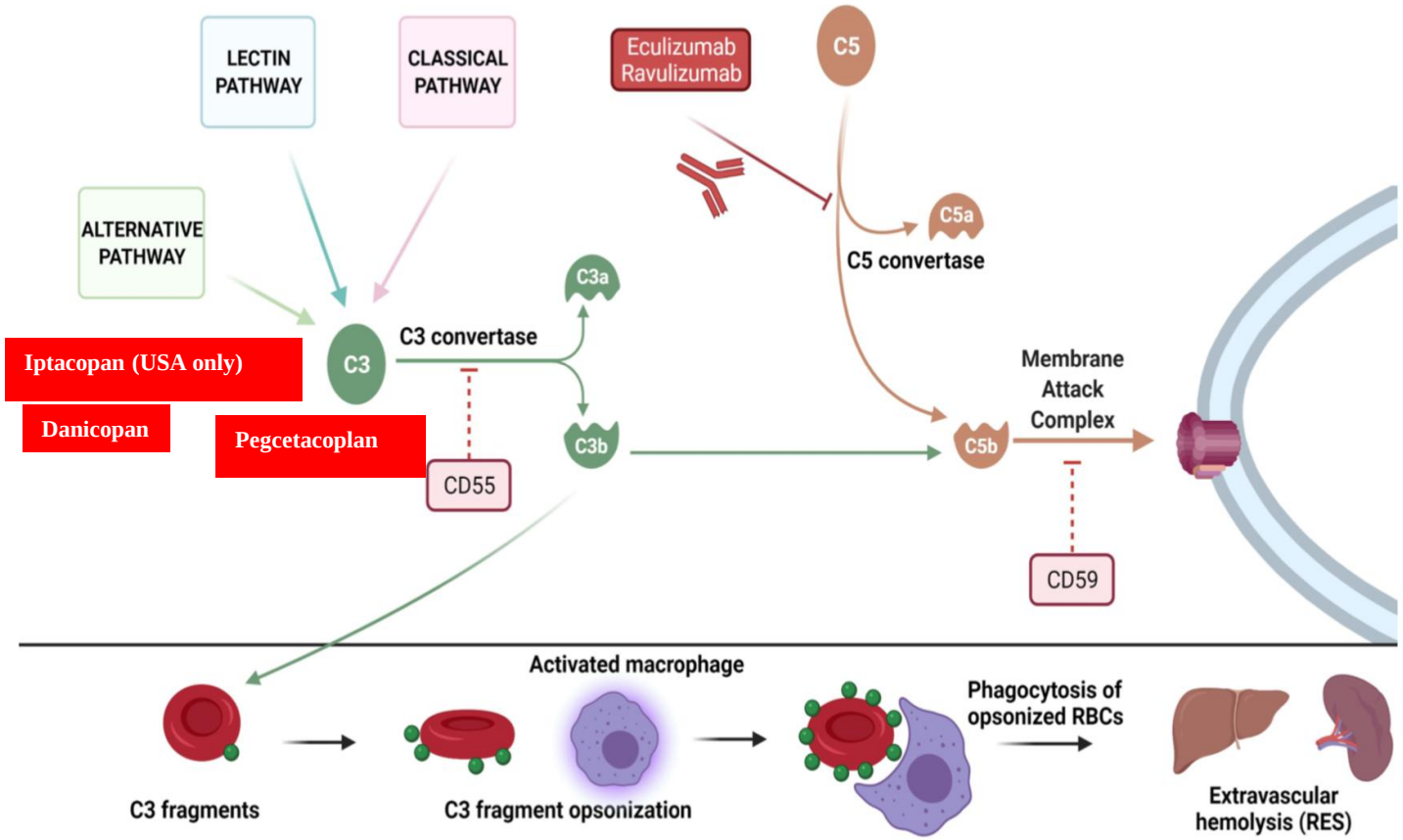
2009
C3-mediated extravascular hemolysis

Risitano A. et al, Blood 2009



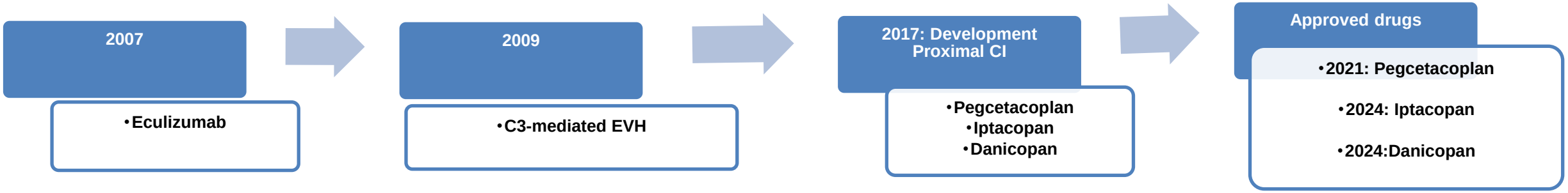
Gurnari C., 2021

C3-mediated extravascular hemolysis (II)



Gurnari C., 2021 (modified)

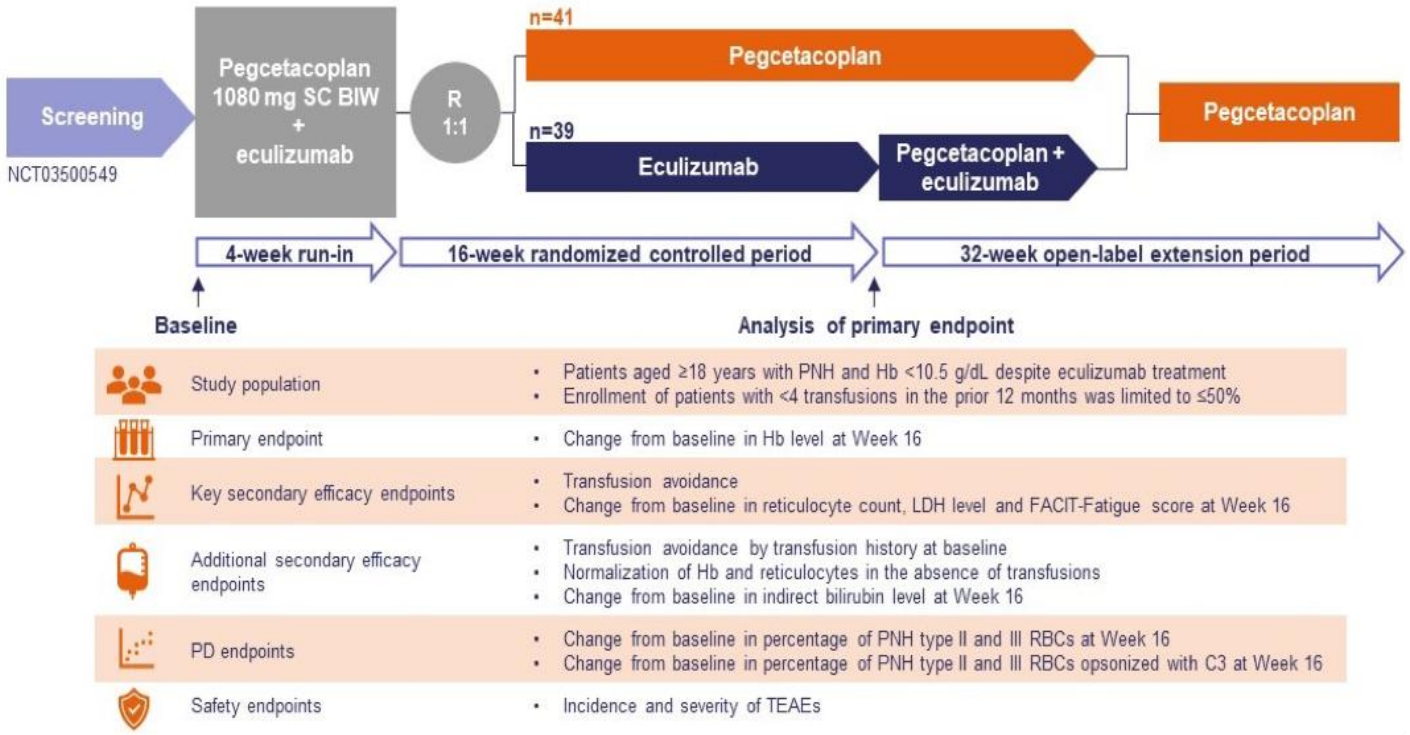
C3-mediated extravascular hemolysis (III)

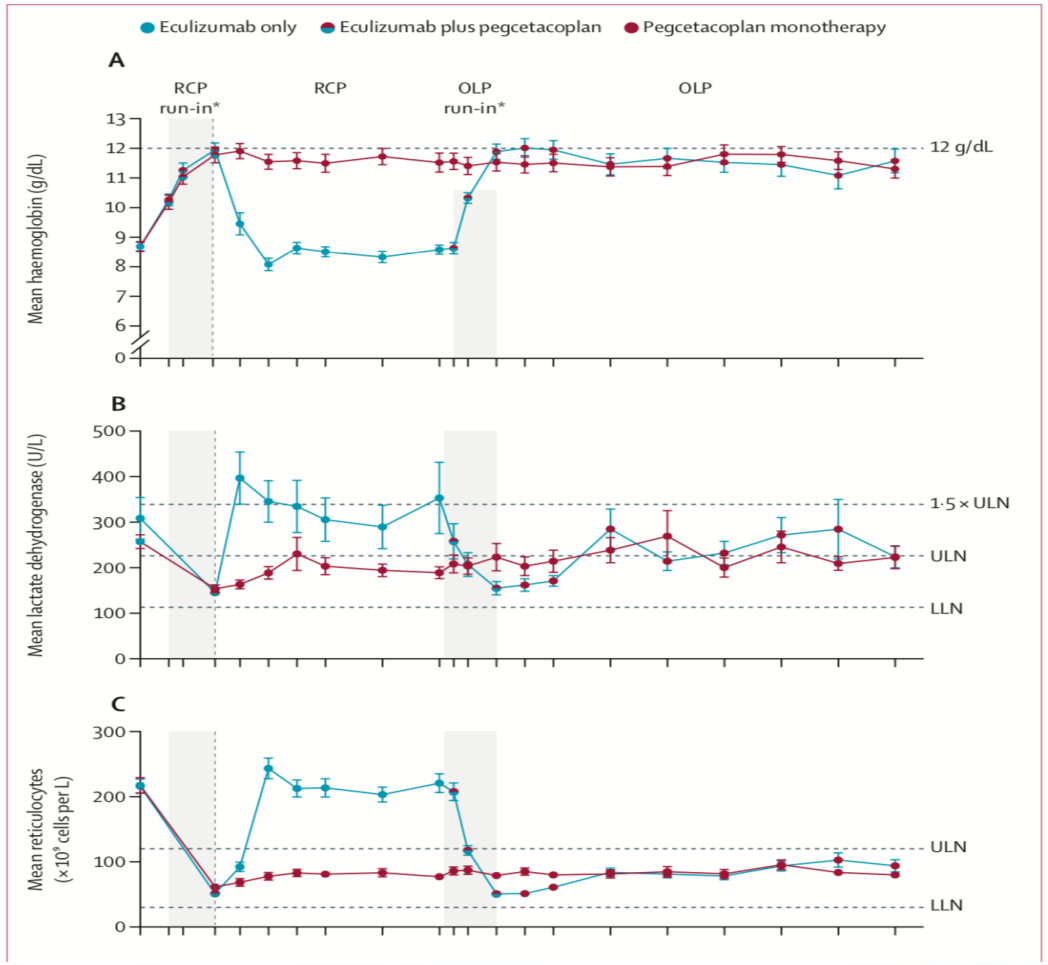


Compound	Target	Clinical ID	Design	Schedule	Patient population	Primary endpoints
PEGcetacoplan	C3	NCT02264639 (PHAROAH)	Phase Ia, open-label	MAD, daily	Poor responders (by Hb <10 gr/dl and transfusion requirement)	Safety and tolerability
		NCT02588833 (PADDOCK)	Phase Ib, open-label	MAD, daily	Naïve patients	Safety , tolerability efficacy (by LDH, Hb, hapto)
		NCT03593200 (PALOMINO)	Phase IIa, open-label	MD, daily	Naïve patients	Safety , tolerability efficacy (by LDH, hb, hapto),
		NCT04085601 (PRINCE)	Phase III random VS SC	Twice weekly	Naïve patients	Efficacy (by Hb, LDH)
		NCT03500549 (PEGASUS)	Phase III random VS Ecu	Twice weekly	Poor responders (by Hb <10.5 gr/dl)	Efficacy (by Hb)
Iptacopan	FB	NCT03439839	Phase II, open-label	BID	Poor responders (by LDH <1.5x ULN)	Efficacy (by LDH)
		NCT04820530 (APPOINT)	Phase III	BID	Naïve patients	Efficacy (by Hb)
		NCT04558918 (APPLY)	Phase III random VS Ecu	BID	Poor responders (by Hb <10, gr/dl)	Efficacy (by Hb)
Danicopan	FD	NCT03053102	Phase II	TID	PNH naive	Efficacy (by LDH)
		NCT03472885	Phase II	TID	PNH in C5 inhibitor	Efficacy (by Hb)
		ALPHA trial (NCT04469465)	Phase III	TID	PNH in C5 inhibitor	Efficacy (by Hb)

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

de Latour RP, Lancet Haematol. 2022





Pegcetacoplan: the first C3-inhibitor

PRINCE study

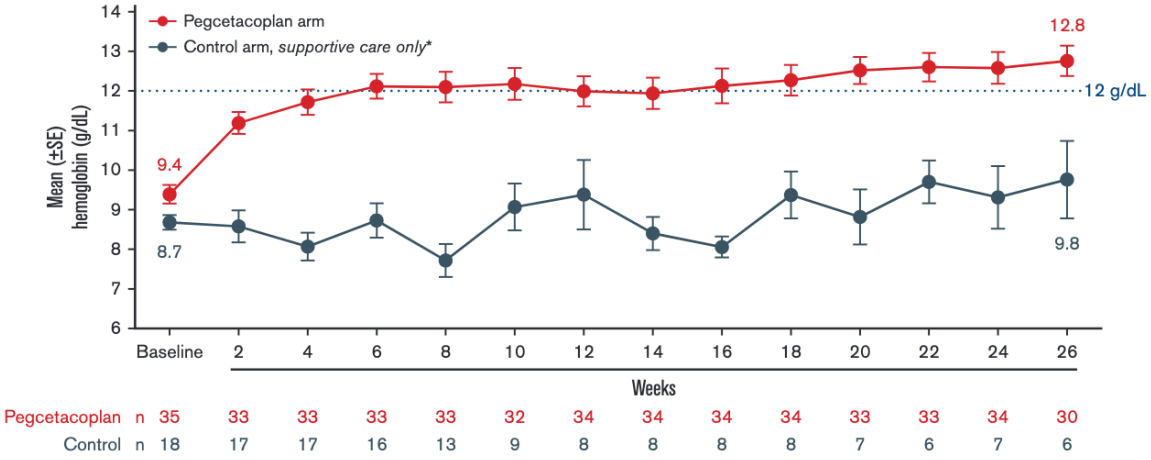
Pegcetacoplan controls hemolysis in complement inhibitor–naive patients with paroxysmal nocturnal hemoglobinuria

Raymond Siu Ming Wong, Blood Ad, 2024

A

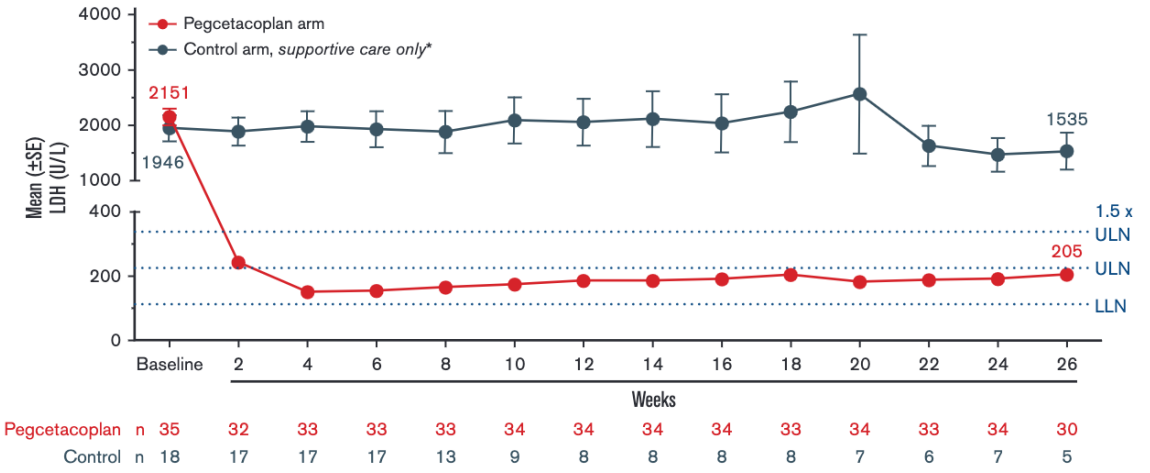
Coprimary end points	Pegcetacoplan arm (n = 35)	Control arm *supportive care only** (n = 18)	Difference 95% CI	*P* value
Hemoglobin stabilization, n (%)†	30 (85.7)	0 (0)	73.1 (57.2, 89.0)	<.0001
CFB in LDH levels, LS mean (SE), U/L‡	−1870.5 (101.0)	−400.1 (313.0)	−1470.4 (−2113.4, −827.3)	<.0001

B



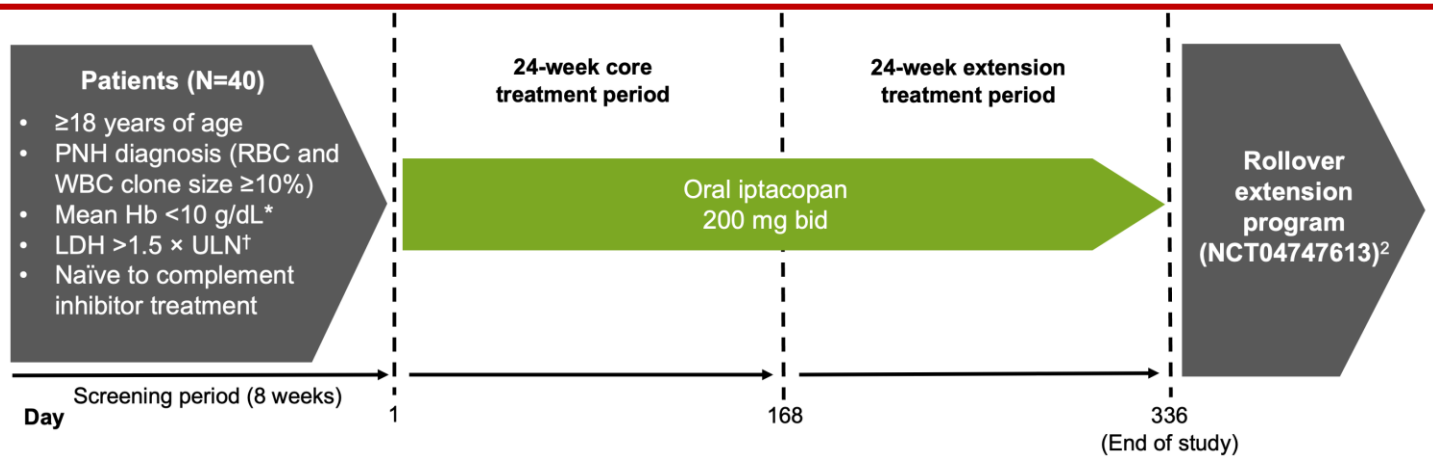
		Baseline	2	4	6	8	10	12	14	16	18	20	22	24	26
Pegcetacoplan	n	35	33	33	33	33	32	34	34	34	34	33	33	34	30
Control	n	18	17	17	16	13	9	8	8	8	8	7	6	7	6

C

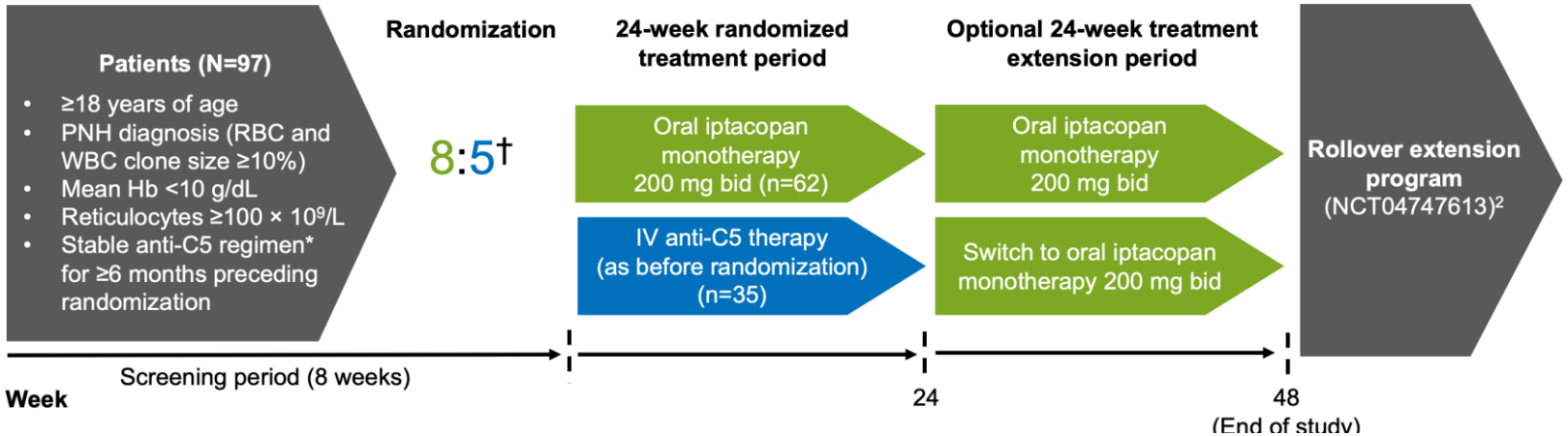


		Baseline	2	4	6	8	10	12	14	16	18	20	22	24	26
Pegcetacoplan	n	35	32	33	33	33	34	34	34	34	33	34	33	34	30
Control	n	18	17	17	17	13	9	8	8	8	8	7	6	7	5

Iptacopan: APPOINT

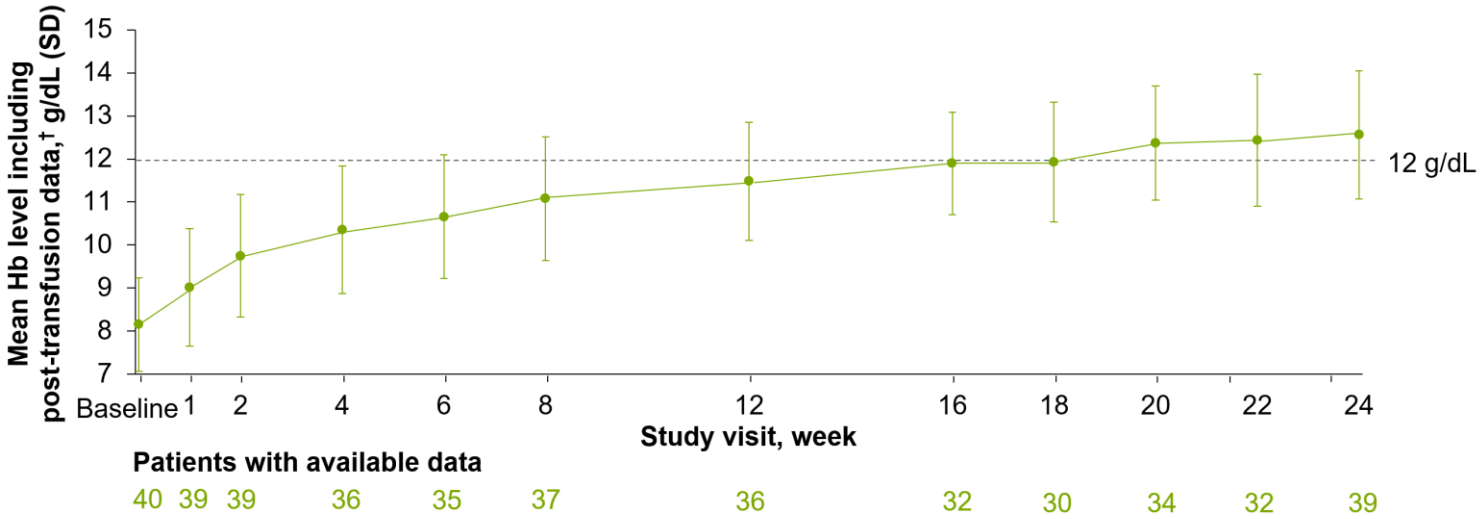


Iptacopan: APPLY

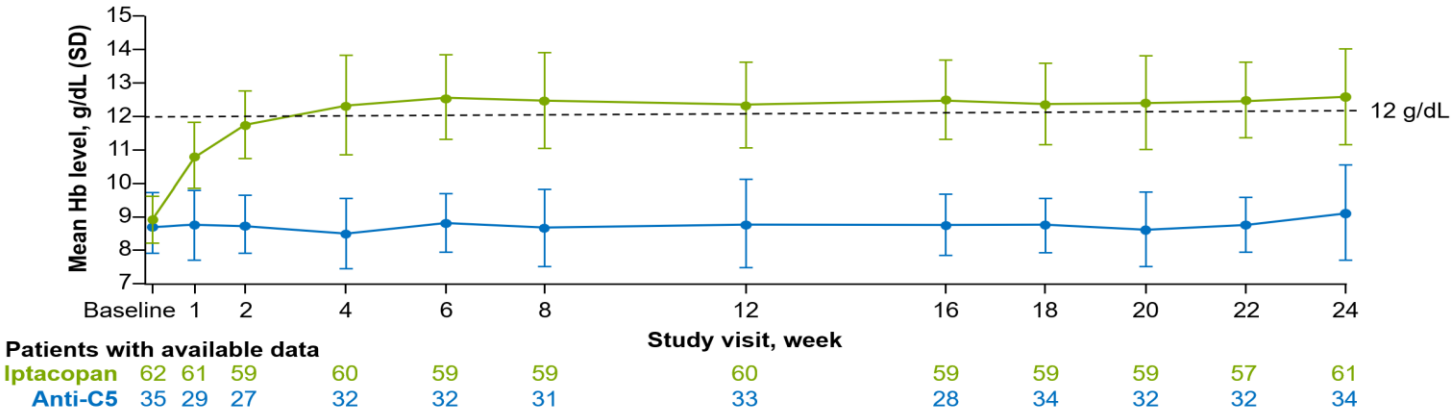


1.https://clinicaltrials.gov/study/NCT04820530 (Accessed October 2024)
2.https://clinicaltrials.gov/study/NCT04747613 (Accessed October 2024)
3.https://clinicaltrials.gov/study/NCT04558918 (Accessed October 2024)

Iptacopan: APPOINT



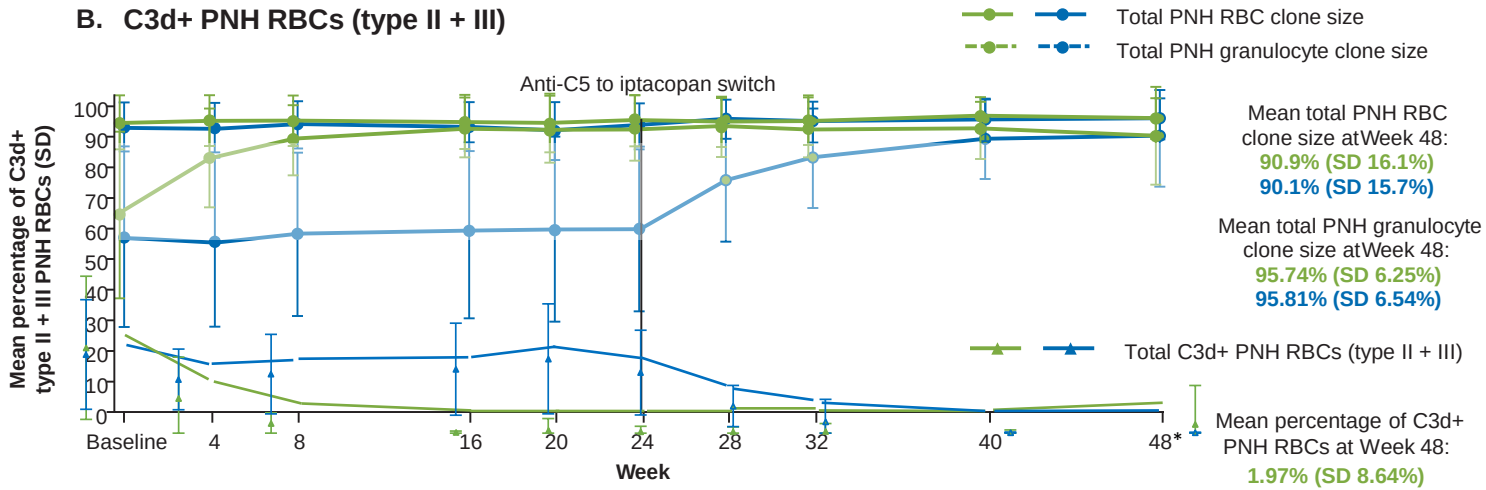
Iptacopan: APPLY



Peffault de Latour R *et al. N Engl J Med* 2024;390:994–1008

A. Total PNH RBC clone size (type II + III) and total PNH granulocyte clone size

B. C3d+ PNH RBCs (type II + III)



Patients with available total PNH RBC (granulocyte) clone size data

Iptacopan	62 (61)	57 (56)	57 (55)	56 (45)	53 (41)	60 (50)	60 (49)	56 (41)	60 (49)	61 (48)
Anti-C5 to iptacopan	35 (35)	28 (28)	32 (31)	28 (26)	32 (29)	33 (26)	30 (24)	32 (24)	29 (20)	30 (27)

Patients with available total C3 fragment deposition

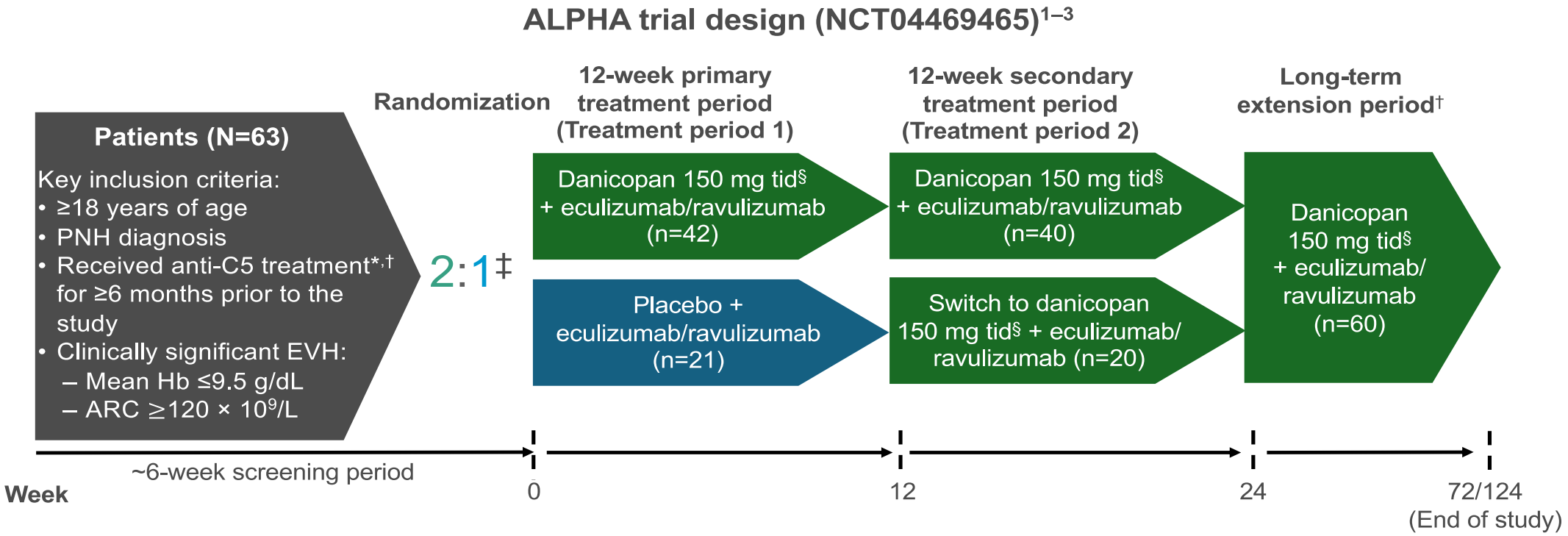
Iptacopan	61	55	52	43	38	47	48	41	44	47
Anti-C5 to iptacopan	34	28	31	28	31	31	27	25	21	16

*At Week 48, the mean in the iptacopan arm was skewed by a patient with C3 fragment deposition on type I, II and III PNH RBCs potentially associated with cold agglutinins.
PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SD, standard deviation.
Peffault de Latour R *et al. HemaSphere.* 2024;8(S1):1451-52. Abstract #P829.

Horneff, R.; Czech, B.; Yeh, M.; Surova, E. Three Years On: The Role of Pegcetacoplan in Paroxysmal Nocturnal Hemoglobinuria (PNH) since Its Initial Approval. Int. J. Mol. Sci. 2024, 25, 8698.

ALFA- Trial - Danicopan

ALPHA is a randomized, Phase III trial of danicopan, a factor D inhibitor assessed as combination therapy with anti-C5 treatment[1–3]

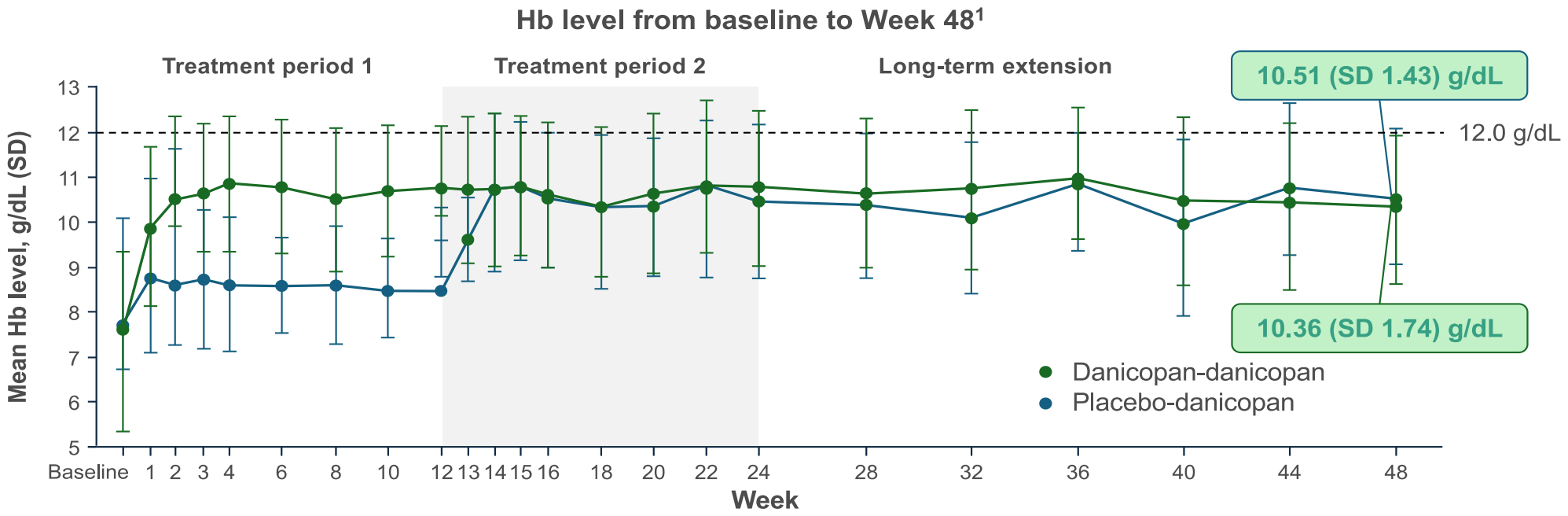


*Eculizumab or ravulizumab; †All patients will complete 72 weeks of long-term extension assessments. At the end of the first year of the long-term extension (Week 72), patients will have the choice to complete participation or continue to an optional second year; ‡Stratified by transfusion history, Hb level and patients enrolled from Japan; §Dosage could be escalated to 200 mg tid at the investigator's discretion. ARC, absolute reticulocyte count; ASH, American Society of Hematology; Hb, hemoglobin; tid, three times a day

1. ClinicalTrials.gov. NCT04469465. Available at: https://clinicaltrials.gov/ct2/show/NCT04469465 (accessed June 2024); 2. Lee JW *et al. Lancet Haematol* 2023;10:e955–65;
3. Kulasekararaj A et al Blood (2023) 142 (Supplement 1): 576.https://doi.org/10.1182/blood-2023-189863

ALFA- Trial - Danicopan

In ALPHA, improvements in Hb level were maintained through 48 weeks in the danicopan arm and rapidly achieved after switching treatment in the placebo-to-danicopan arm[1]



LSM change in Hb level from baseline, g/dL (SE)	Week 12		Week 24	
	Placebo + eculizumab/ravulizumab	Danicopan + eculizumab/ravulizumab	Placebo to danicopan + eculizumab/ravulizumab	Danicopan + eculizumab/ravulizumab
	+0.50 (0.31)	+2.94 (0.21)	+2.26 (0.34)	+3.17 (0.30)

Figure adapted from Kulasekararaj AG *et al.* ASH. San Diego, CA, 9–12 December 2023;oral 508
LSM, least squares mean; SD, standard deviation; SE, standard error

1. Kulasekararaj A et al Blood (2023) 142 (Supplement 1): 576.https://doi.org/10.1182/blood-2023-189863

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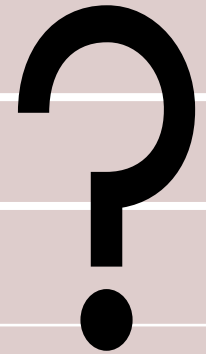
- **"Unmet needs" in PNH patients on anti-C5 inhibitors:**
  - ✓ **Causes of residual anemia:** ✓
    - **IVH: BTH PK and PD**
    - **EVH** ✓
  - ✓ **Schedule and route of administration**
  - ✓ **Convenience**
  - ✓ **Special Setting**
- **"Unmet needs" in PNH patients in the era of new complement inhibitors:**
  - ✓ **Open questions ?**

Schedule and route of administration and convenience

Compound	Target	RoA	Schedule	Convenience
Eculizumab	C5	IV	Every 14 days	
Ravulizumab	C5	IV	Every 8 weeks	
Crovalimab	C5	SC	Every 4 weeks	
PEGcetacoplan	C3	SC	Twice a week	
Iptacopan	FB	PER OS	BID	
Danicopan	FD	PER OS	TID	



1. Eculizumab - Summary of Product Characteristics. Accessed October 2024. Available at https://www.ema.europa.eu/en/documents/product-information/soliris-epar-product-information_en.pdf
2. Ravulizumab - Summary of Product Characteristics. Accessed October 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/ultomiris-epar-product-information_en.pdf
3. Crovalimab - Summary of Product Characteristics. Accessed October 2024. Available at https://www.ema.europa.eu/en/documents/product-information/piasky-epar-product-information_en.pdf
4. Pegcetacoplan - Summary of Product Characteristics. Accessed October 2024. Available at https://www.ema.europa.eu/en/documents/product-information/aspaveli-epar-product-information_en.pdf
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6. Danicopan - Summary of Product Characteristics. Accessed October 2024. Available at https://ec.europa.eu/health/documents/community-register/2024/20240419162306/anx_162306_en.pdf

Discussion points

Navigating through "unmet needs" in PNH:

- **"Beginning of the history": improve survival and anemia** ✓

- **"Unmet needs" in PNH patients on anti-C5 inhibitors:**

  - ✓ **Causes of residual anemia:** ✓
    - **IVH: BTH PK and PD**
    - **EVH** ✓

  - ✓ **Schedule and route of administration** ✓
  - ✓ **Convenience**

  - ✓ **Special Setting**

- **"Unmet needs" in PNH patients in the era of new complement inhibitors:**
  - ✓ **Open questions ?**

- **Don't forget different manifestations of the disease (PNH/AA)**

Special setting

Pediatric population and pregnancy

Compound	Target	RoA	Schedule	Trial in pediatric population	Pregnancy
Eculizumab	C5	IV	Every 14 days	NCT00867932	* 1
Ravulizumab	C5	IV	Every 8 weeks	NCT03406507	According to medical decision
Crovalimab	C5	SC	Every 4 weeks	OK >40KG	NO DATA
PEGcetacoplan	C3	SC	Twice a week	NCT04901936	One case report
Iptacopan	FB	PER OS	BID	NO DATA	NO DATA
Danicopan	FD	PER OS	TID	NCT06449001	NO DATA

*** Kelly, R.J.; Höchsmann, B.; Szer, J.; Kulasekararaj, A.; de Guibert, S.; Röth, A.; Weitz, I.C.; Armstrong, E.; Risitano, A.M.; Patriquin, C.J.; et al. Eculizumab in pregnant patients with paroxysmal nocturnal hemoglobinuria. N. Engl. J. Med. 2015, 373, 1032–1039.**

1. Eculizumab - Summary of Product Characteristics. Accessed October 2024. Available at https://www.ema.europa.eu/en/documents/product-information/soliris-epar-product-information_en.pdf
2. Ravulizumab - Summary of Product Characteristics. Accessed October 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/ultomiris-epar-product-information_en.pdf

How many questions has the scientific community answered?

Discussion points

Navigating through "unmet needs" in PNH:

- **"Beginning of the history": improve survival and anemia**

- **"Unmet needs" in PNH patients on anti-C5 inhibitors:**

  - ✓ **Causes of residual anemia:**
    - **IVH: BTH PK and PD**
    - **EVH**
  - ✓ **Schedule and route of administration**
  - ✓ **Convenience**
  - ✓ **Special Setting**

- **"Unmet needs" in PNH patients in the era of new complement inhibitors:**
  - ✓ **Open questions ?**

How many questions does the scientific community still have to answer?

“New” unmet needs in the current therapeutic scenario

“Update 2024”

Compound	Target	RoA	Schedule		FDA	EMA	TRIAL
Eculizumab	C5	IV	Every 14 days	1st line	✓	✓	TRIUMPH SHEPERD
Ravulizumab	C5	IV	Every 8 weeks	1st line	✓	✓	NCT02946463 (study 301) NCT03056040 (study 302)
Crovalimab	C5	SC	Every 4 weeks	1st line	✓	✓	NCT04432584 (COMMODORE 1) NCT04434092 (COMMODORE 2)
PEGcetacoplan	C3	SC	Twice a week	2nd line 1st line	✓	✓	NCT03500549 (PEGASUS) NCT04085601 (PRINCE)
Iptacopan	FB	PER OS	BID	1st / 2nd line	✓	✓	NCT04558918 (APPLY)
Danicopan	FD	PER OS	TID	“add-on therapy”	✓	✓	NCT04469465 (ALPHA III)

1. Eculizumab - Summary of Product Characteristics. Accessed October 2024. Available at https://www.ema.europa.eu/en/documents/product-information/soliris-epar-product-information_en.pdf
2. Ravulizumab - Summary of Product Characteristics. Accessed October 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/ultomiris-epar-product-information_en.pdf
3. Crovalimab - Summary of Product Characteristics. Accessed October 2024. Available at https://www.ema.europa.eu/en/documents/product-information/piasky-epar-product-information_en.pdf
4. Pegcetacoplan - Summary of Product Characteristics. Accessed October 2024. Available at https://www.ema.europa.eu/en/documents/product-information/aspaveli-epar-product-information_en.pdf
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6. Danicopan - Summary of Product Characteristics. Accessed October 2024. Available at https://ec.europa.eu/health/documents/community-register/2024/20240419162306/anx_162306_en.pdf

"NEW" UNMET NEEDS: OPEN QUESTIONS?

- How to menage severe possible BTH with about 100% PNH clone?
- Oral drugs: Intestinal absorption? Extreme situations: pt intubated in ICU?
- How to swich from one inhibitor to another?
- Pregnancy and pediatric population ?
- Long term safety
  - ✓ Immune dysfunction, cancers?
  - ✓ Infections?
- Cost and availability

NEXT STEP? ....TAILOR THERAPY?

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