european society for paediatric nephrology
espn

Complement-mediated kidney diseases in the era of complement inhibitors: future perspectives

Overview of Complement inhibitors: approved

ERKNet The European Rare Kidney Disease Reference Network

TransplantChild

European Reference Network Transplantation in Children

Funded by the European Union

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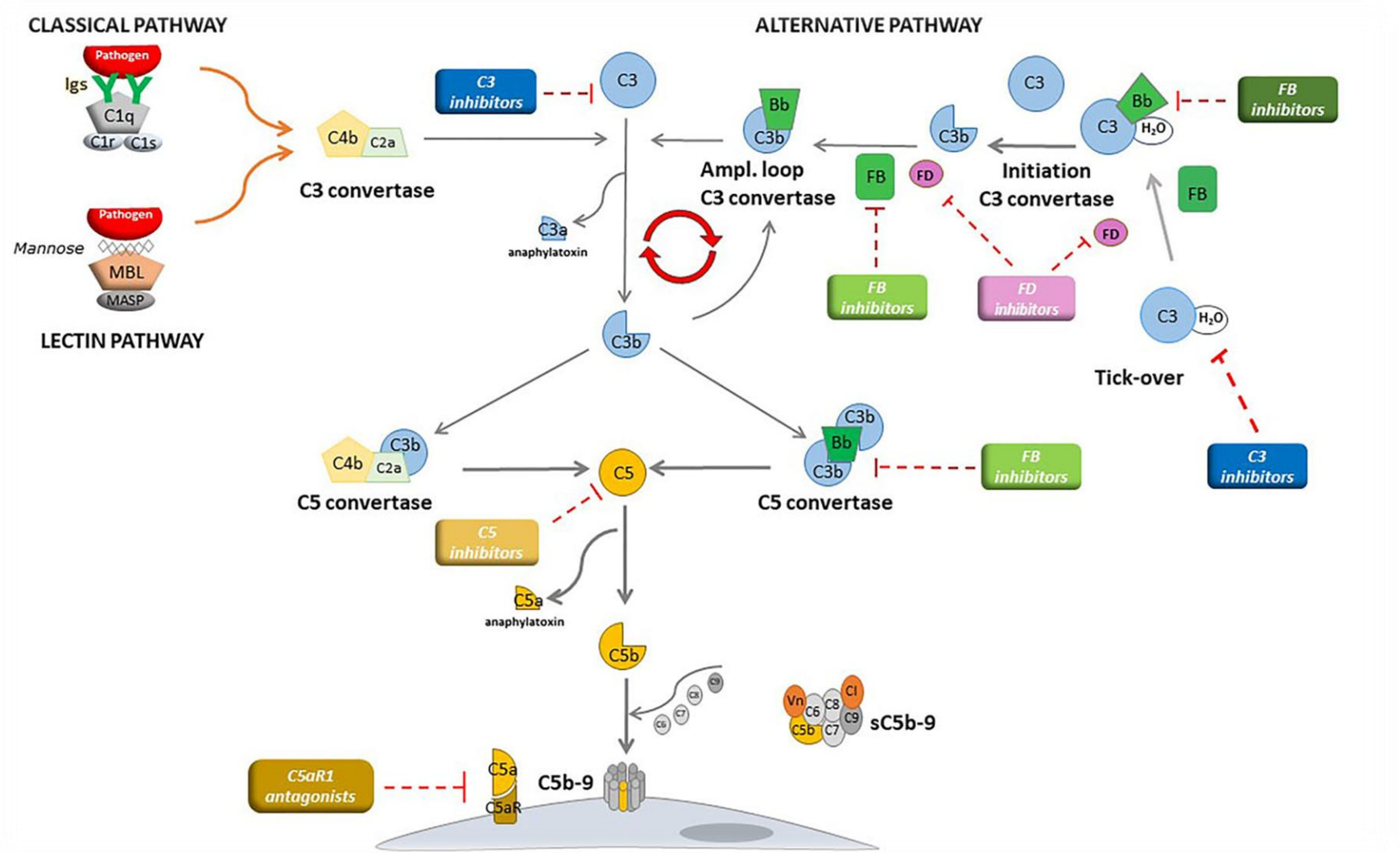
Disclosures

- Honoraria for lectures, educational events, or Advisory Boards for Astra Zeneca (Alexion), Recordati Rare Disease, Advicenne, Chiesi, Kyowa Kirim, Alnylam and Dicerna

- Site investigator for Apellis Pharmaceuticals and AstraZeneca Rare Diseases (Alexion)

- Member of the Scientific board if the Global aHUS Registry (Alexion),

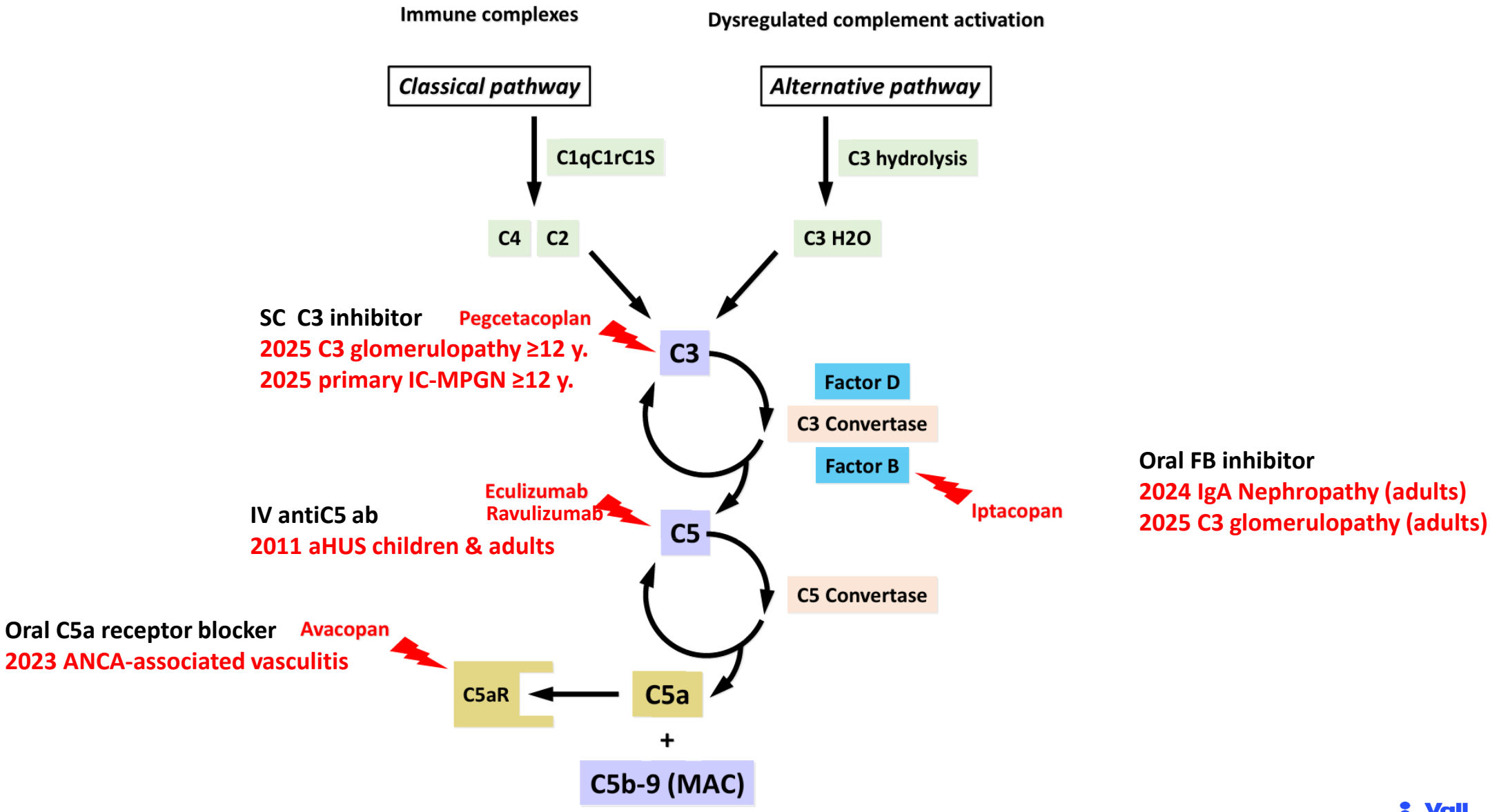
Targets of complement inhibitors



Noris M, Remuzzi G. NDT 2024

Vall d'Hebron

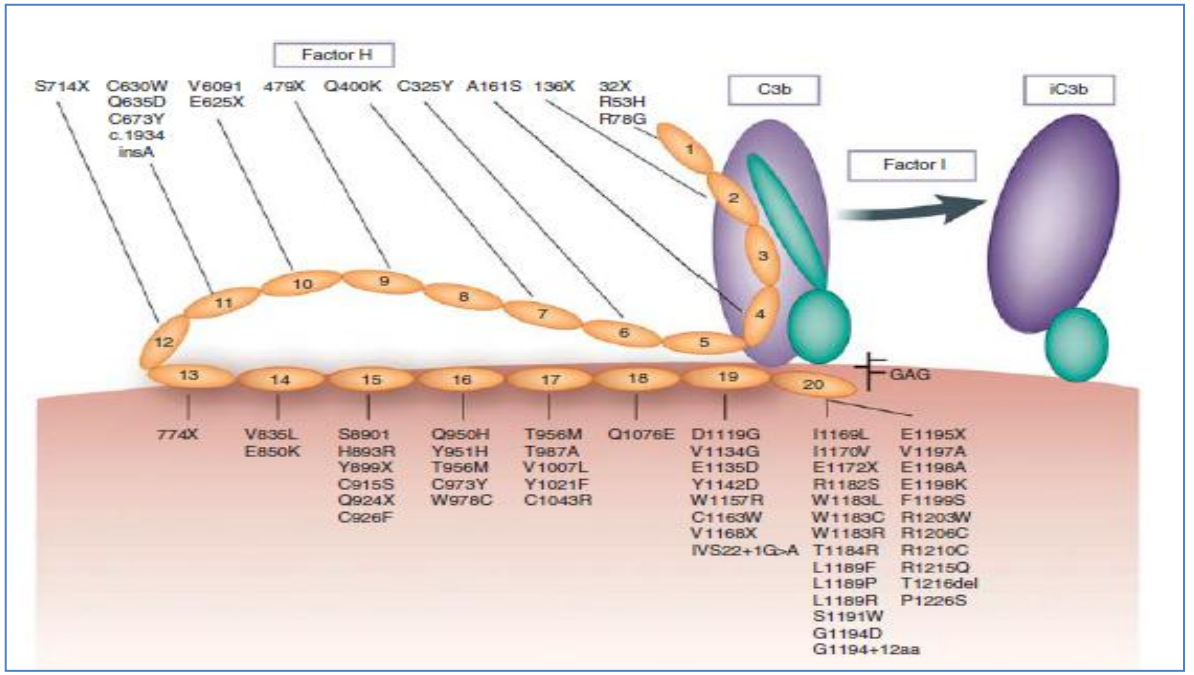
Complement inhibitors approved for kidney diseases

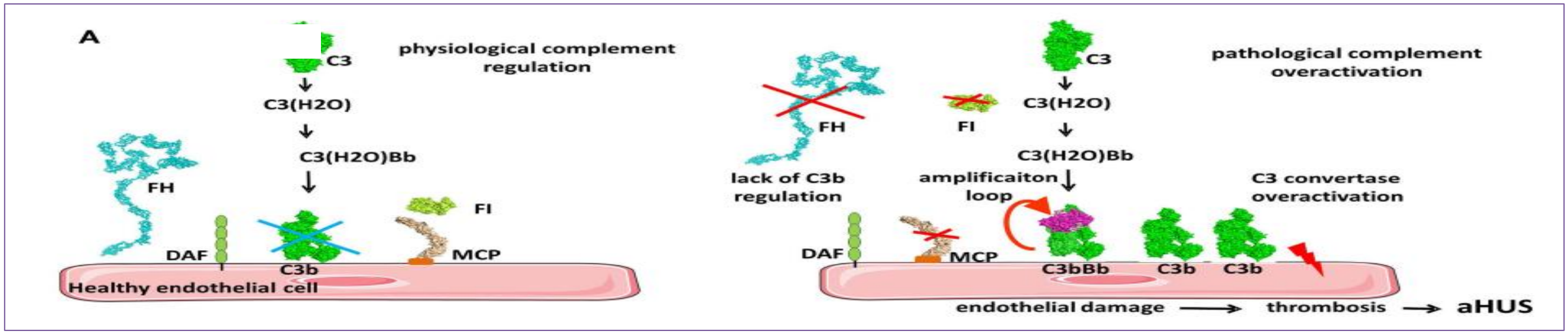


Modified from Emma F, John P. Kidney Int Rep 2025

Dysregulation of complement on the cell surface leads to aHUS

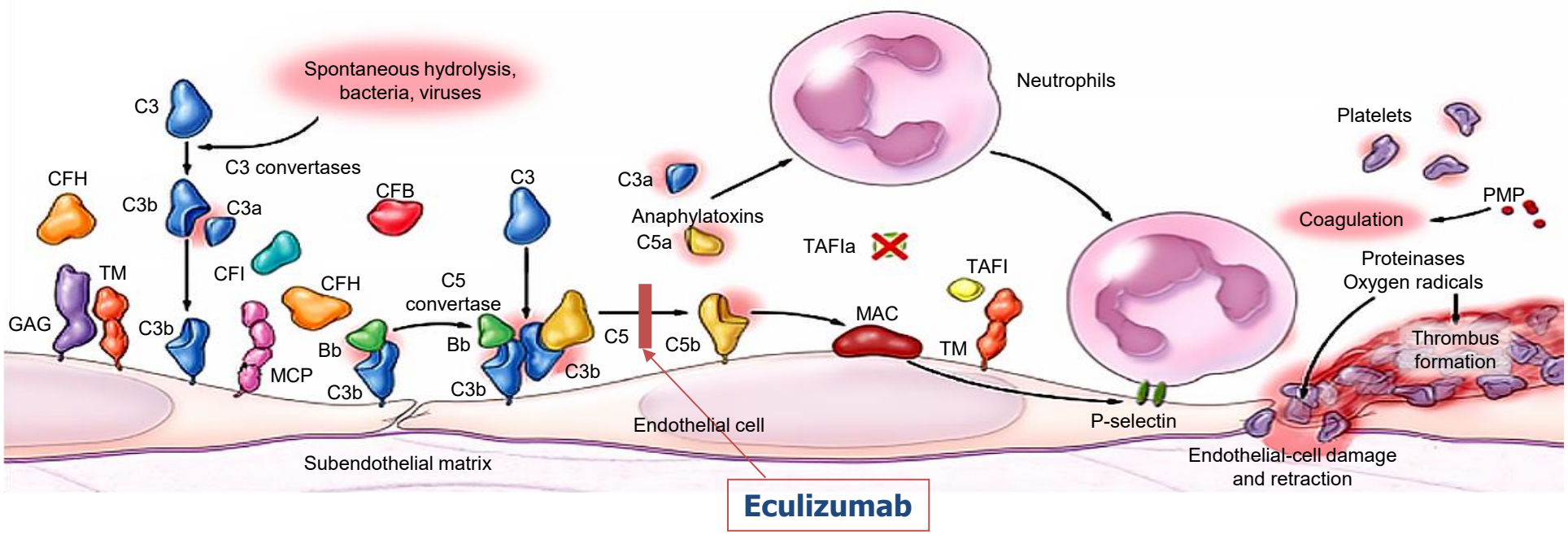
The pathogenic mechanism in aHUS is the endothelial damage at the renal microvasculature resulting from dysregulation of complement on the cell surface





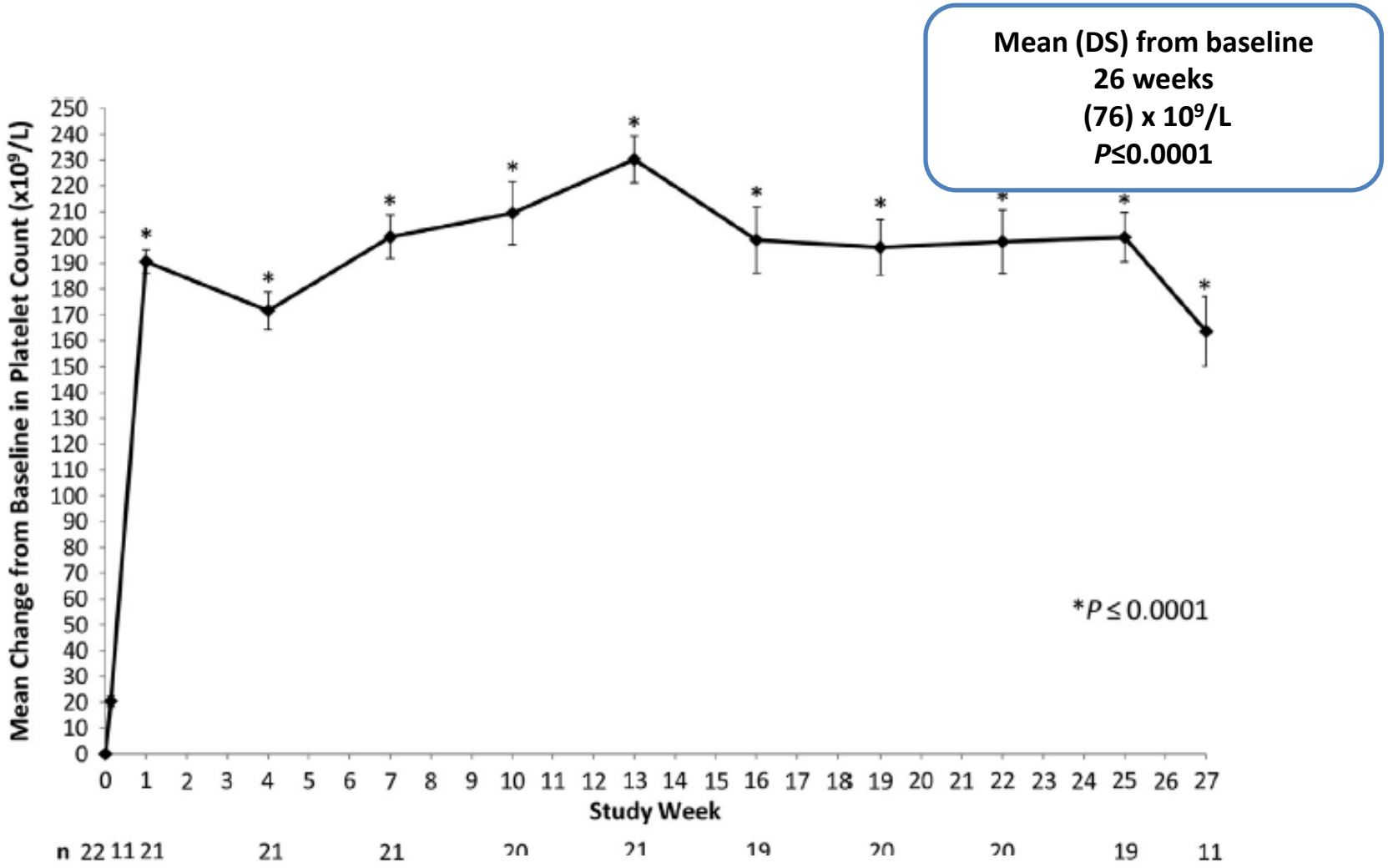
Merle et al. Frontiers in Immunology. June 2015

Eculizumab: Terminal Blockade of the Alternative Complement Pathway



Noris, Remuzzi. *N Engl J Med.* 2009;361:1676-87.

Eculizumab Treatment Resulted in Rapid and Sustained Improvement in Platelet Count in Pediatric Patients With aHUS

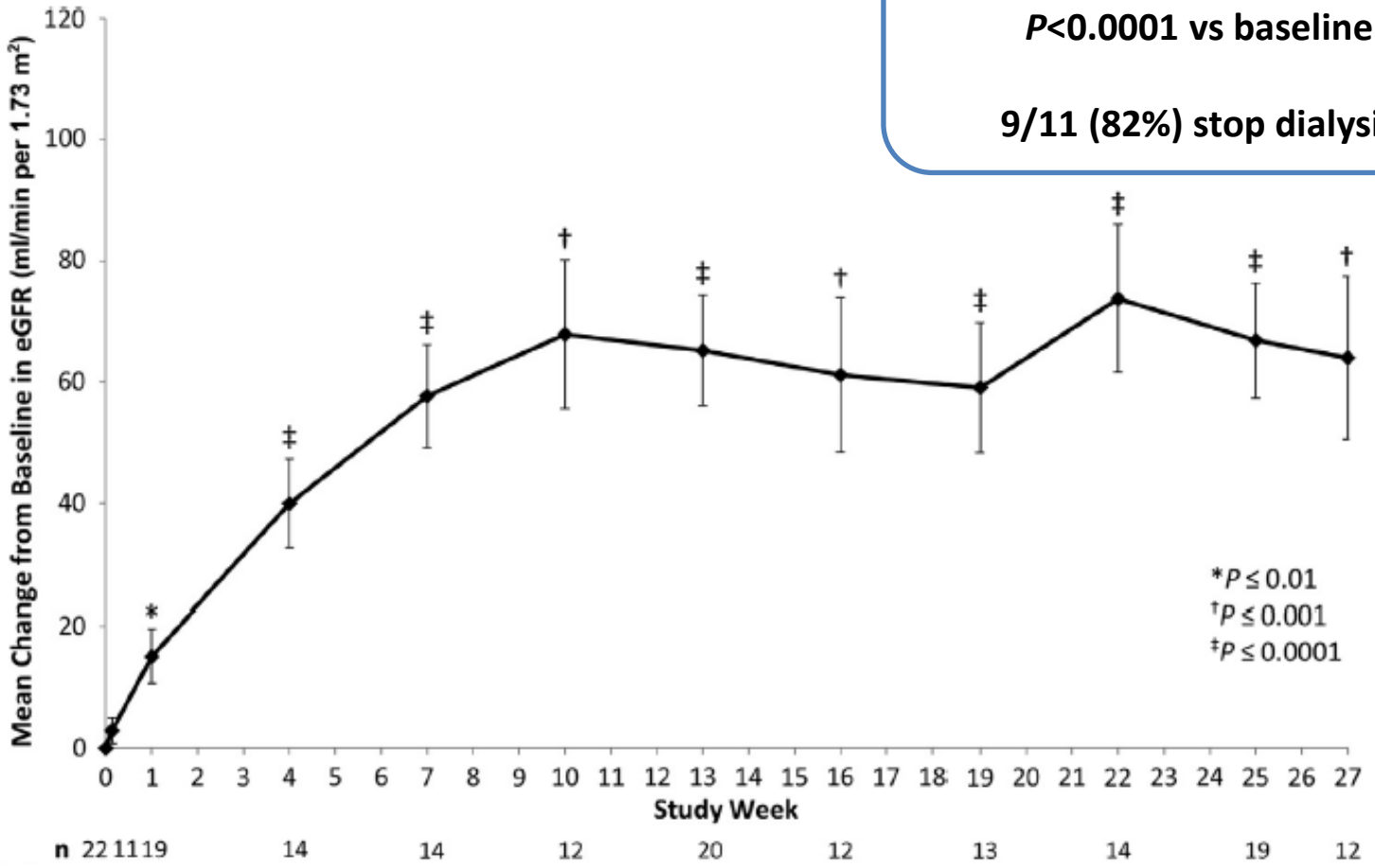


Greenbaum et al. Kidney Int. 2016;89(3):701-11.

Eculizumab Treatment in Pediatric Patients With aHUS Resulted in Continued Improvement in Renal Function

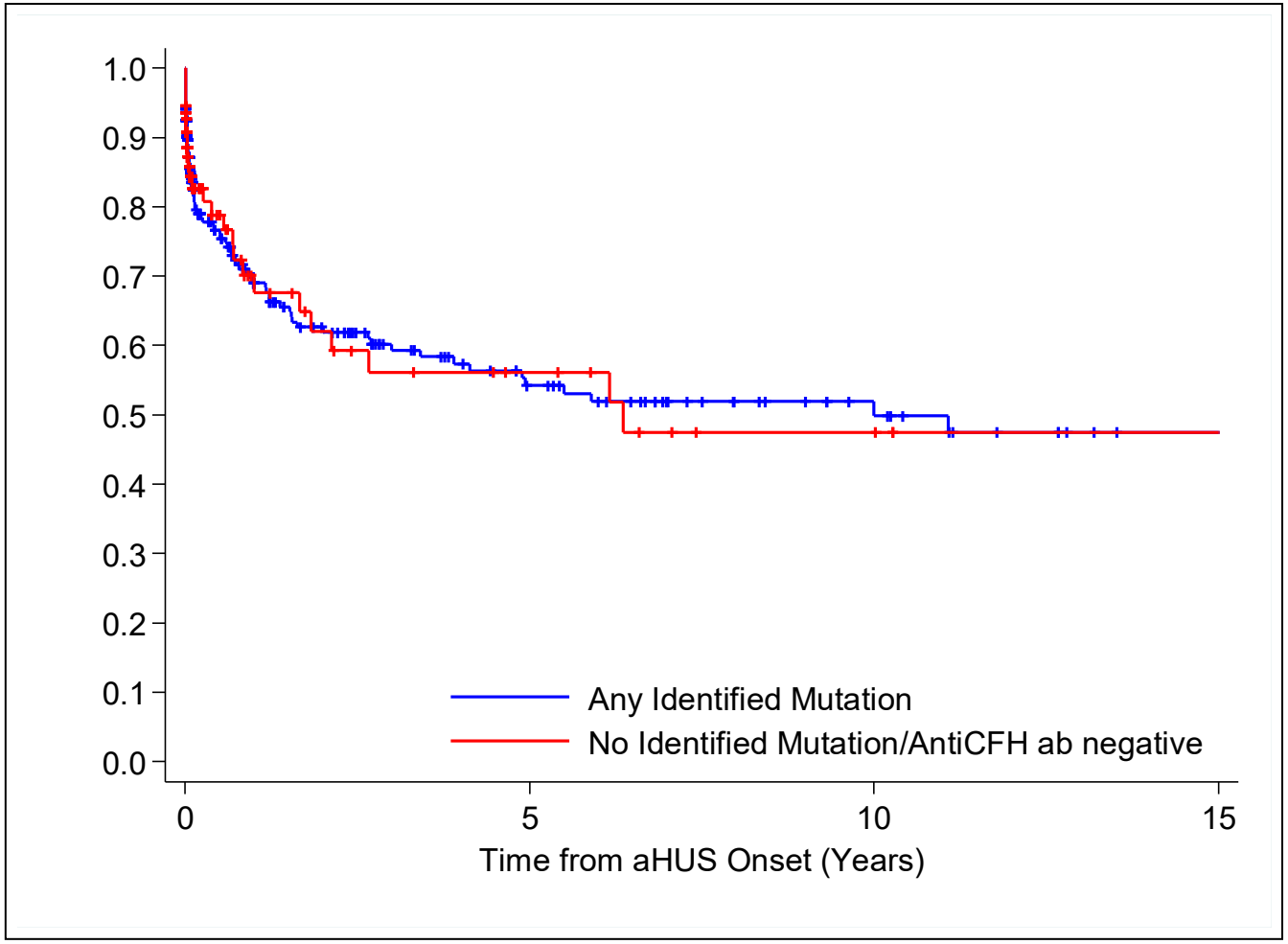
26 weeks:
64 mL/min/1.73 m^2
***P*<0.0001 vs baseline**

9/11 (82%) stop dialysis



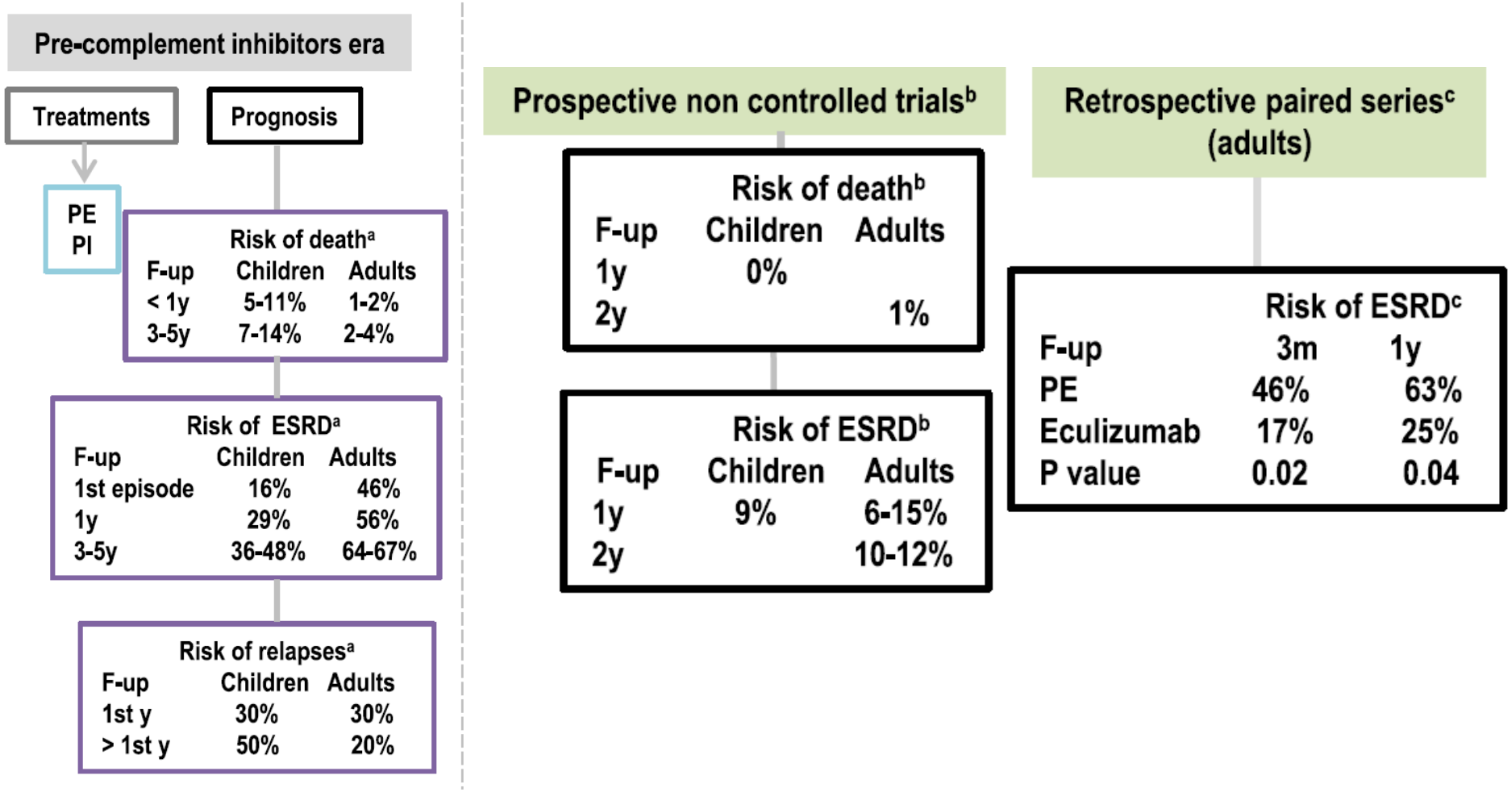
Greenbaum et al. Kidney Int. 2016;89(3):701-11.

Kidney survival in aHUS patients treated with eculizumab based on genetics



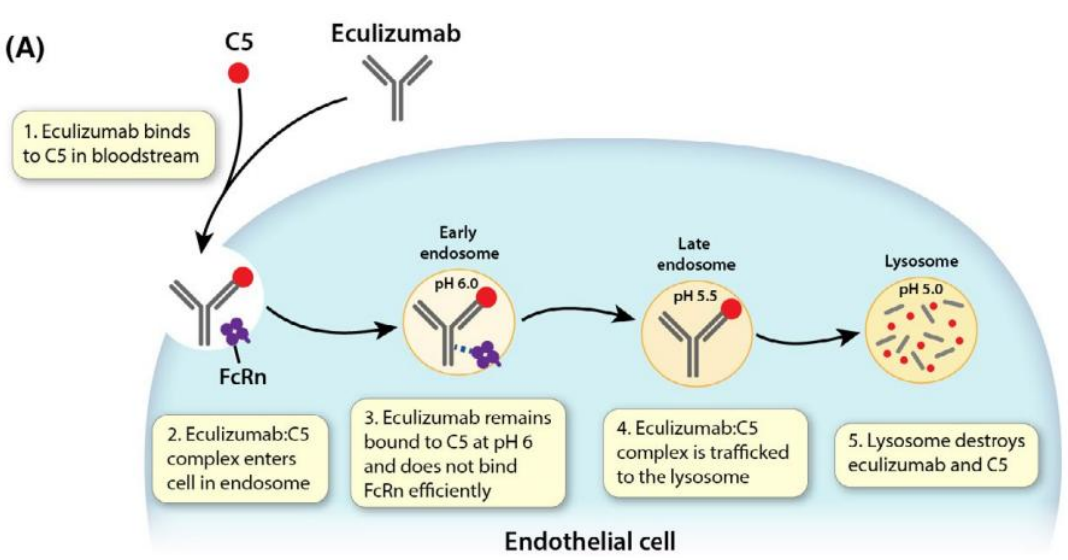
Schaefer et al, Kidney Int, 2018

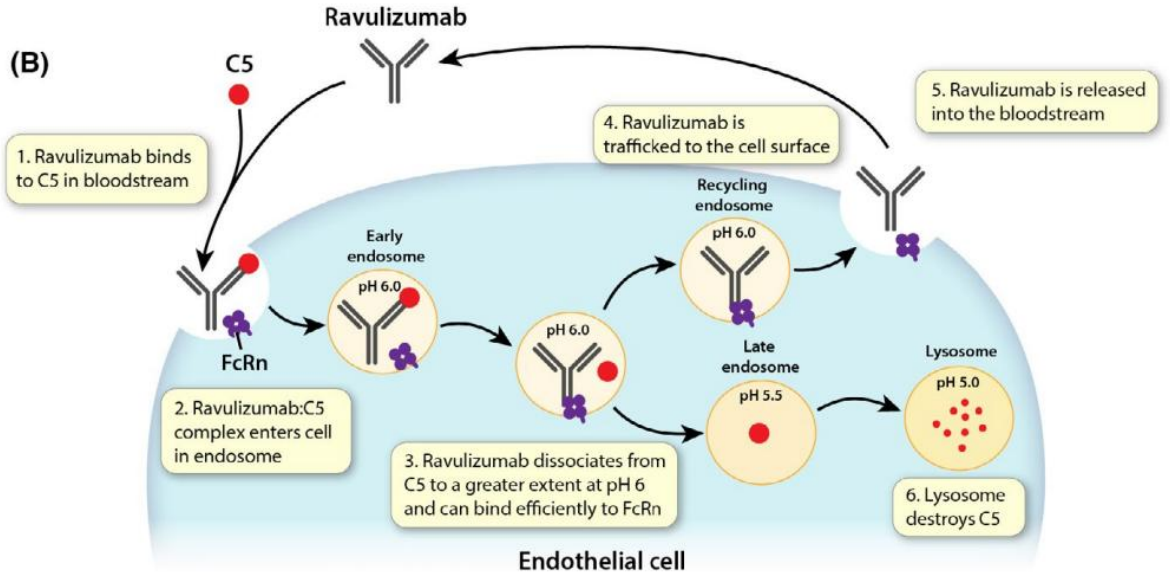
aHUS outcome before and after eculizumab



Fakhouri F, Loirat C. Semin Hematol. 2018

Diferences between eculizumab and ravulizumab

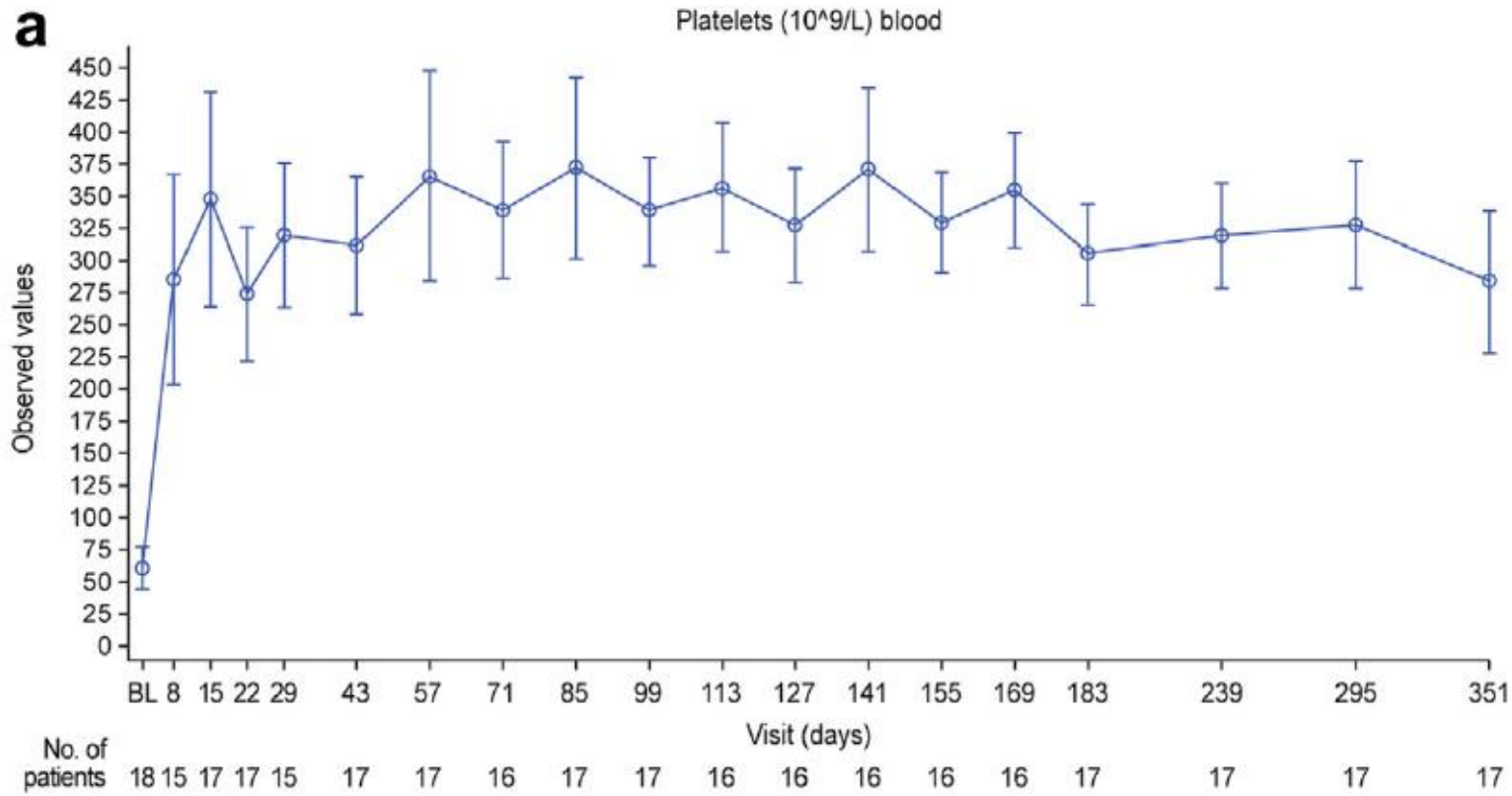




Ravulizumab was engineered by substituting 4 amino acids in eculizumab, which alter the molecule's binding affinity for C5 and FcRn at the endosomal pH. Ravulizumab binds to C5 in the bloodstream and enters the cell by endocytosis. At the lower pH in the endosome, ravulizumab dissociates from C5 to a greater extent and binds more efficiently to FcRn than does eculizumab, enabling ravulizumab trafficking from the endothelial cell back to the bloodstream, where it can bind to another C5 molecule. The C5 in the low pH lysosome is ultimately degraded.

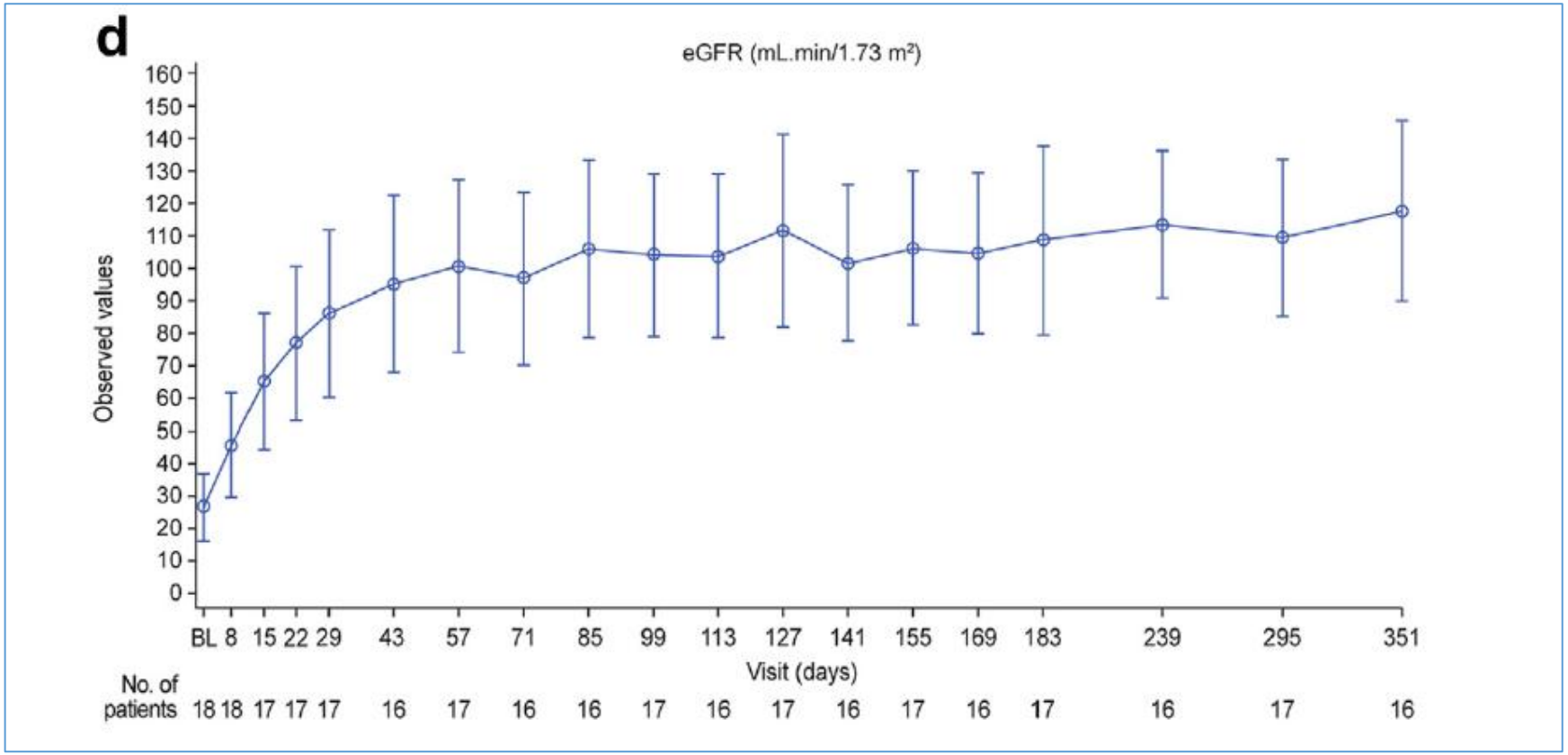
Dixon BP, Sabus A. J Clin Pharm Therm, 2022

Ravulizumab Treatment in Pediatric Patients With aHUS Resulted in Improvement of platelets



Ariceta et al Kidney Int. 2021

Ravulizumab Treatment in Pediatric Patients With aHUS Resulted in Improvement of renal function

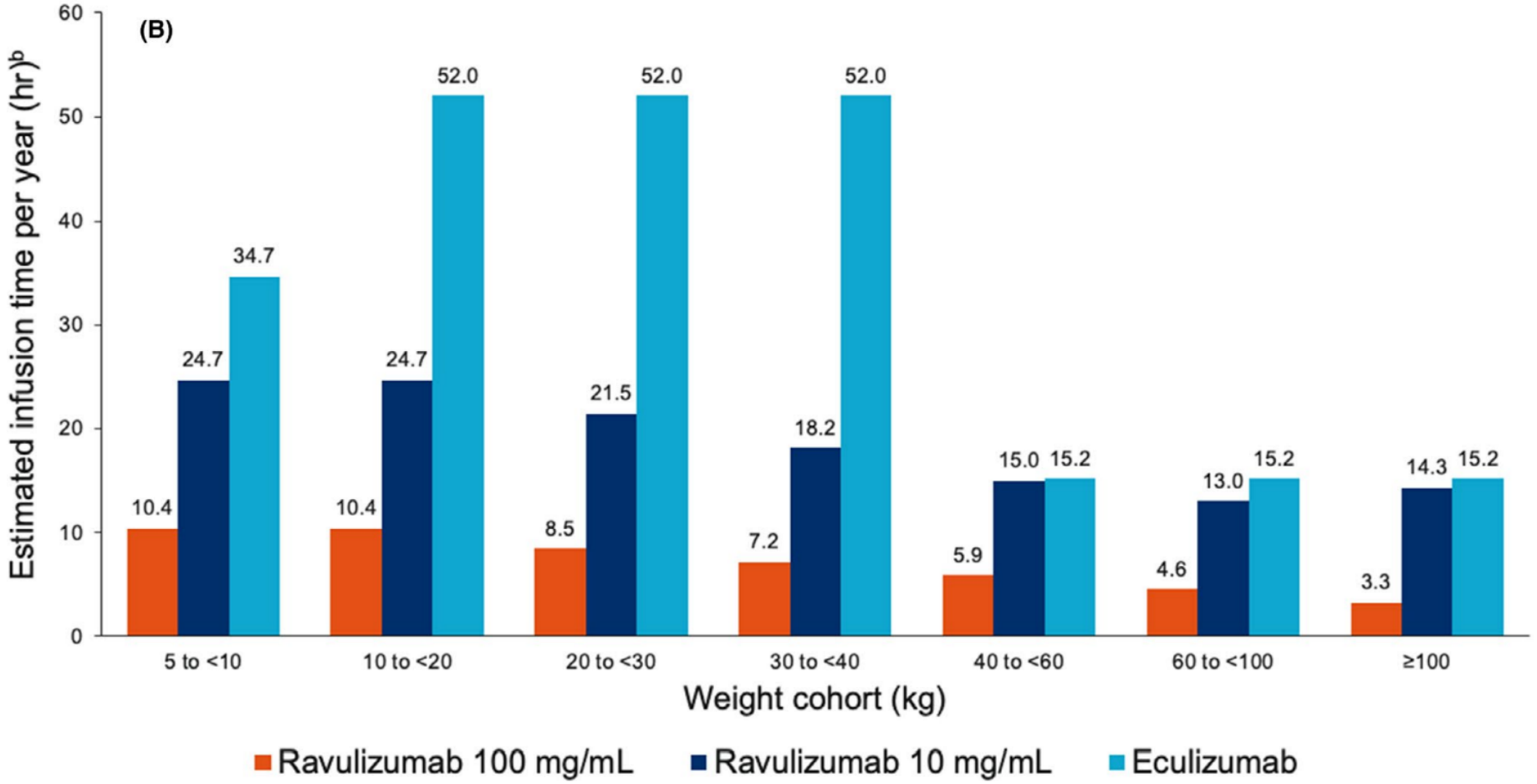


4 of 5 patients on dialysis at baseline were weaned off of dialysis after 29 days or less of exposure to ravulizumab

Median change in eGFR was **79.0 mL/min/1.73 m²** at Day 183

Ariceta et al Kidney Int. 2021

Estimated maintenance infusion time (hours) per year for ravulizumab 100 mg/mL, and eculizumab



Dixon BP, Sabus A. J Clin Pharm Therm, 2022

Points of discussion about anti-complement therapy in aHUS

Duration of C5 blockade: factors to consider

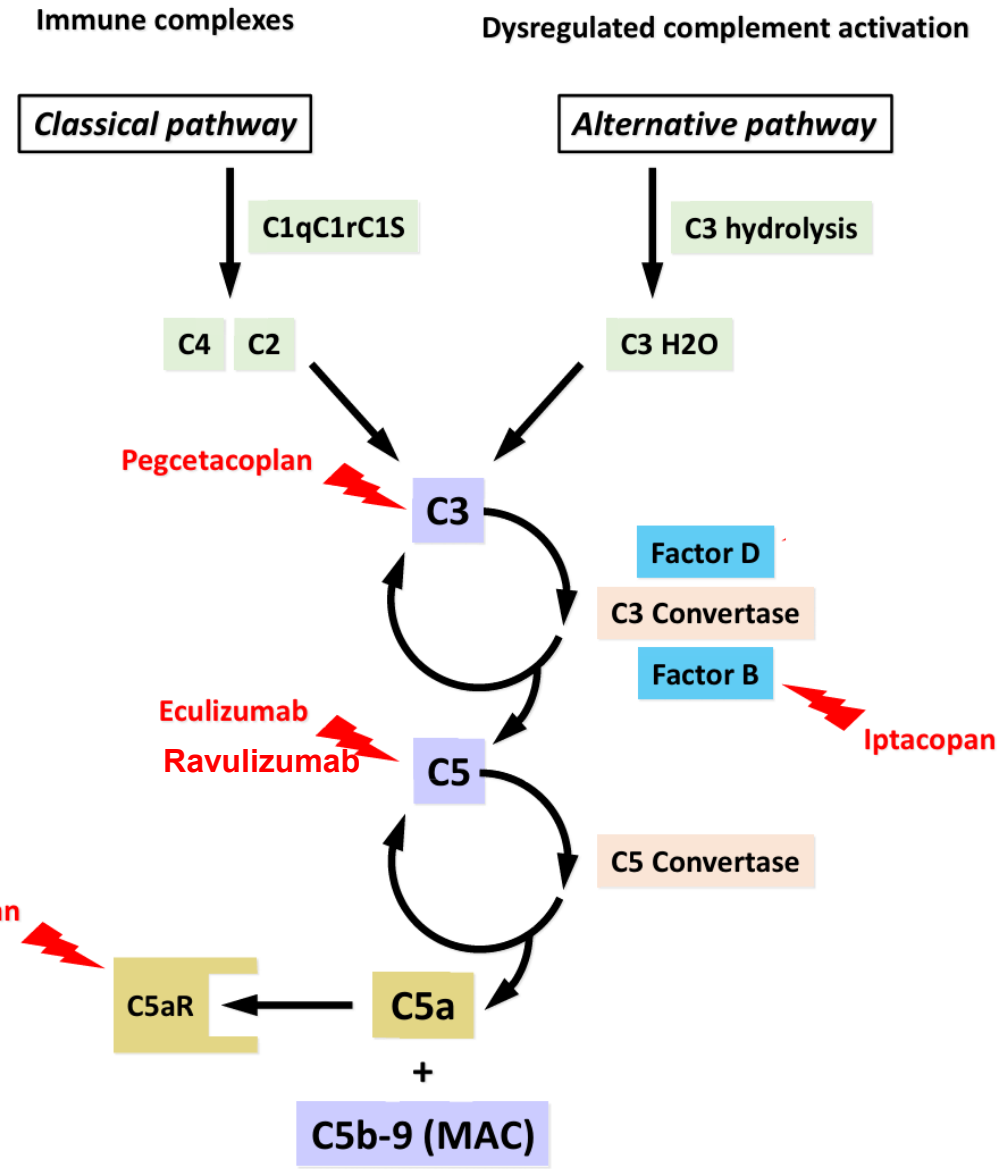
- genetic risk
- patient age
- native kidneys vs transplant
- eGFR

Infection risk

Resistance:

there is a rare intrinsic resistance to anti-C5 therapy in a subset of Japanese patients due to two polymorphisms in the C5 gene (p.Arg885His and p.Arg885Cys) which disrupt the eculizumab/ravulizumab target epitope

Complement inhibitors approved for kidney diseases



Oral C5a receptor blocker

2023 ANCA-associated vasculitis (AAV)

Modified from Emma F, John P. Kidney Int Rep 2025

Avacopan in ANCA-vasculitis (AAV)

- **Oral C5aR1 antagonist** (inhibits the proinflammatory effects of C5a, a powerful anaphylatoxin which recruits macrophages and neutrophils. A major advantage of avacopan is its more selective anti-inflammatory action, preserving host defense mechanisms that rely on MAC formation)

- **ADVOCATE trial** was a randomized, double-blind, double-dummy, controlled trial (avacopan vs. prednisone taper). NCT02994927

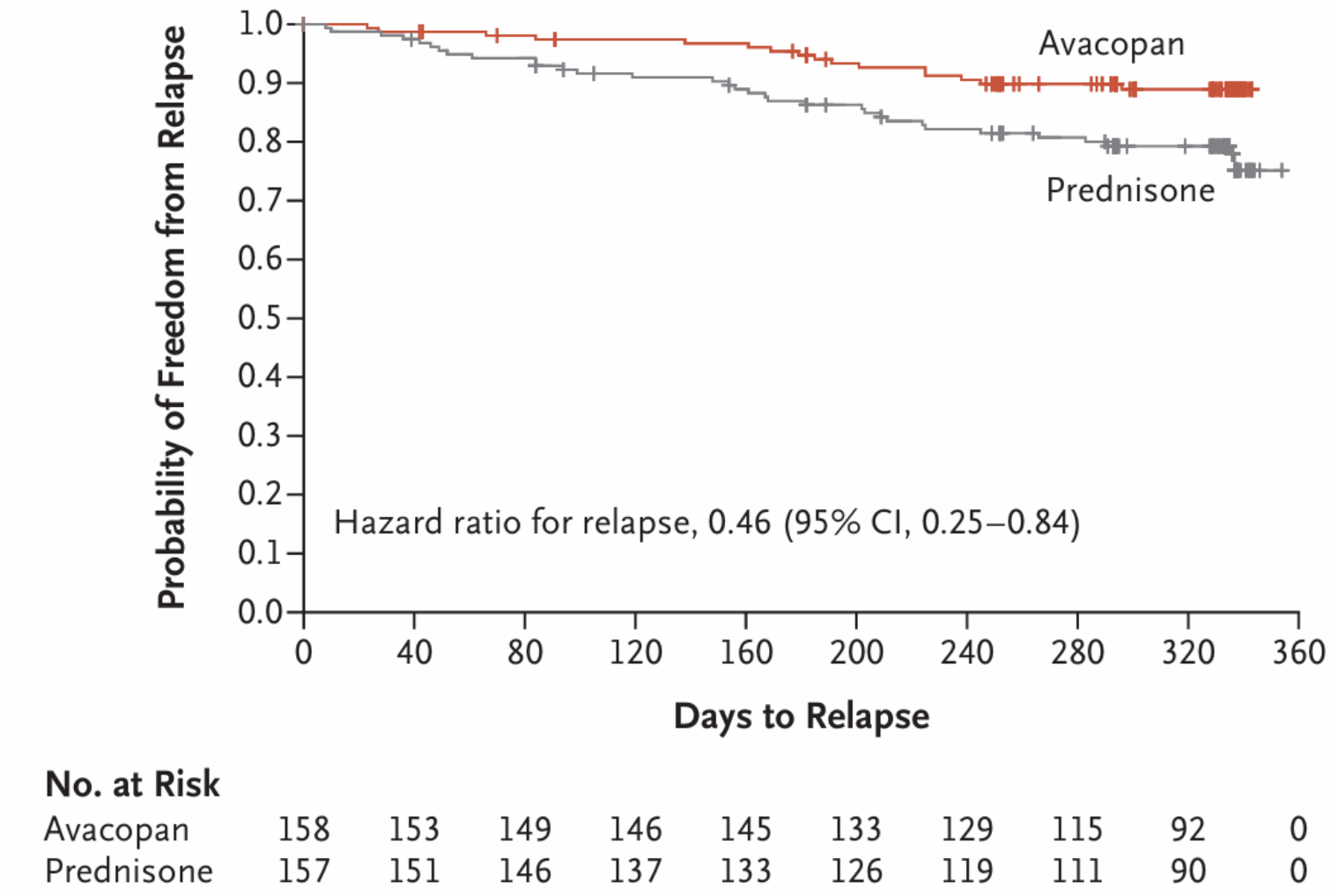
- **331 adult patients**

- **Inclusion criteria**:
  - diagnosed with granulomatosis with polyangiitis or micro polyangiitis
  - Treatment with rituximab or CFM
  - antiPR3^{+} or anti-MPO^{+}

- Patients randomized in a 1:1 ratio to receive oral avacopan (30 mg twice daily) or oral prednisone (60 mg daily tapered to discontinuation by week 21).

Jayne DRW. NEJM, 2021

ADVOCATE trial. Kaplan-Meier Plot of time to relapse



Efficacy: among patients with ANCA-associated vasculitis, avacopan was noninferior to prednisone with respect to remission at 26 weeks (72.3% vs 70.1%) and was superior with respect to sustained remission at 52 weeks (65.7% vs 54.9%)

Safety: The % of patients with serious adverse events was similar in the two groups.

Avacopan is used as an steroid sparing drug

Jayne DRW. NEJM, 2021

Vall d'Hebron

Systematic Review of Efficacy and Safety of Avacopan in Real-World Clinical Practice

Systematic review of real-world studies (N = 16)

447 patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV)
- 141 identified as Asian
- 113 identified as Caucasian
- 285 were MPO-positive

Induction therapy with:
- **Corticosteroids** (61%)
- **Rituximab** (54%)
- **Rituximab + cyclophosphamide** (32%)

Results

Time from AAV diagnosis or relapse and initiation of avacopan	**24 days** Range: 6-54 days
Clinical remission rates at 6 months N = 215	**89%** 95% CI: 0.84-0.93
Serious infection rates N = 327	**14%** 95% CI: 0.10-0.18
Hepatotoxicity rates N = 442, significant heterogeneity between populations	**6%** 95% CI: 0.03–0.14

KI REPORTS
Kidney International Reports

Berke I et al. 2026

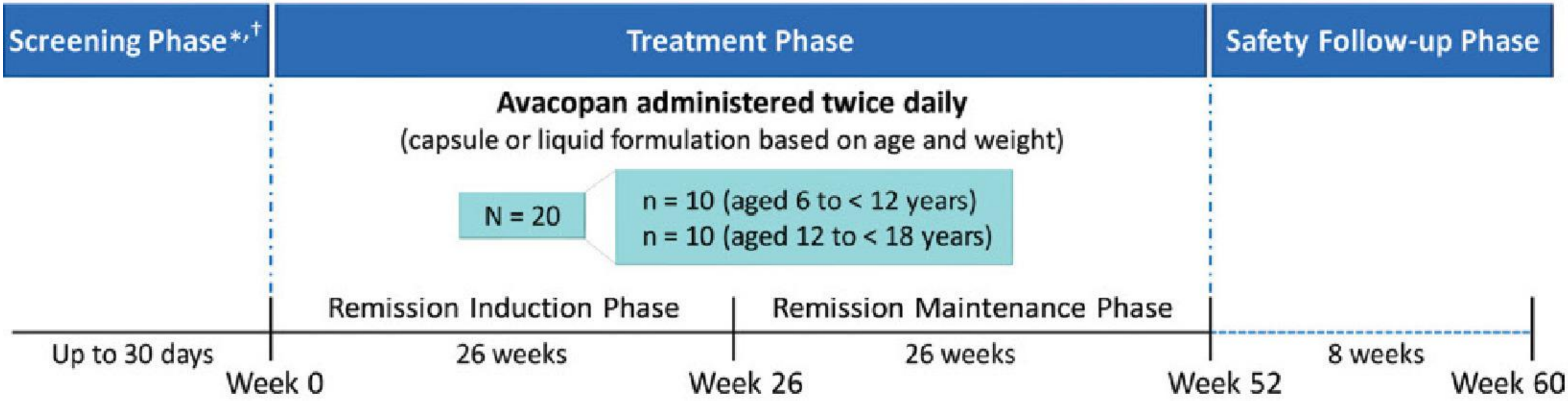
Visual abstract by:
Corina Teodosiu, MD
@CTeodosiu

Conclusions: Avacopan demonstrated favorable safety and high efficacy for AAV in real-world cohorts, with remission rates exceeding and serious infection rates comparable to those reported in clinical trials. Increased hepatotoxicity in certain populations warrants monitoring and further pharmacovigilance to clarify risk factors and guide patient selection.

Avacopan in ANCA-vasculitis (pediatric trial)

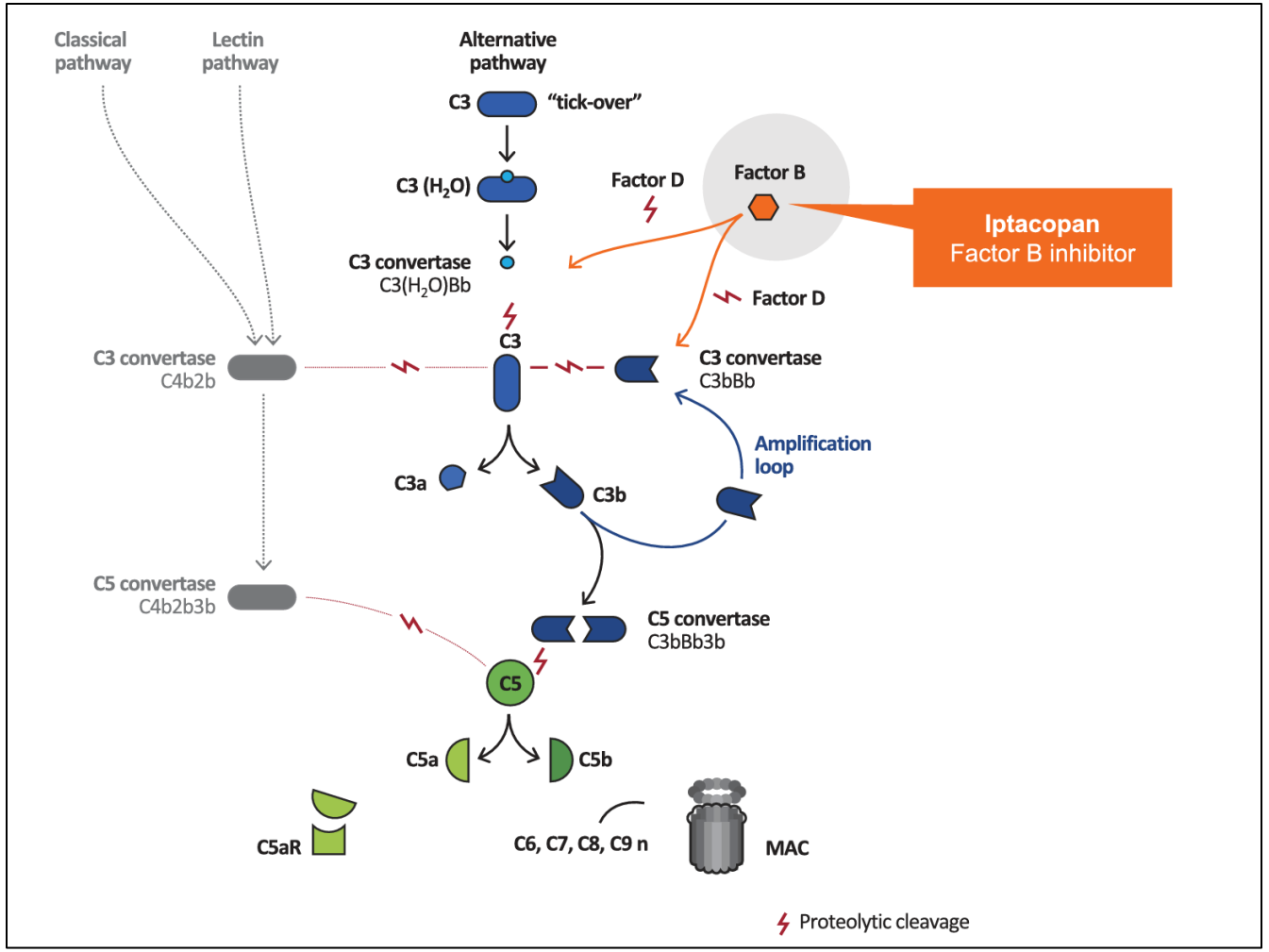
Ongoing trial in pediatric population with AAV

Phase 3, open-label, single-arm trial in progress designed to evaluate the efficacy, pharmacokinetics, and safety of avacopan when combined with a rituximab (RTX)- or cyclophosphamide (CYC)-containing regimen in pediatric patients with newly diagnosed or relapsing active GPA/MPA (NCT06321601).



iptacopan

Iptacopan is a small-molecule oral inhibitor of complement Factor B component of the alternative C3 convertase, that specifically binds to factor B and efficiently blocks the alternative pathway



Vivarelli M et al, KI Reports, 2024

APPLAUSE-IgAN (iptacopan) NCT04578834

- APPLAUSE-IgAN is a phase 3, double-blind, randomized, placebo-controlled trial
- Adult patients with biopsy-confirmed IgA nephropathy and UPCR ≥ 1g/g in 24h urine despite optimized supportive therapy.
- Patients were randomly assigned, in a 1:1 ratio, to receive oral iptacopan (200 mg) or placebo twice daily for 24 months (+ supportive therapy)
- 222 patients iptacopan group & 221 placebo group.
- **At month 9, the adjusted geometric mean 24-hour urinary protein-to-creatinine ratio was 38.3% (95% confidence interval, 26.0 to 48.6; two-sided P<0.001) lower with iptacopan than with placebo.**
- adverse events similar in the two groups; most events were mild to moderate in severity and reversible. No increased risk of infection was observed.

Perkovic V, et al. NEJM 2025

APPEAR-C3G (iptacopan)

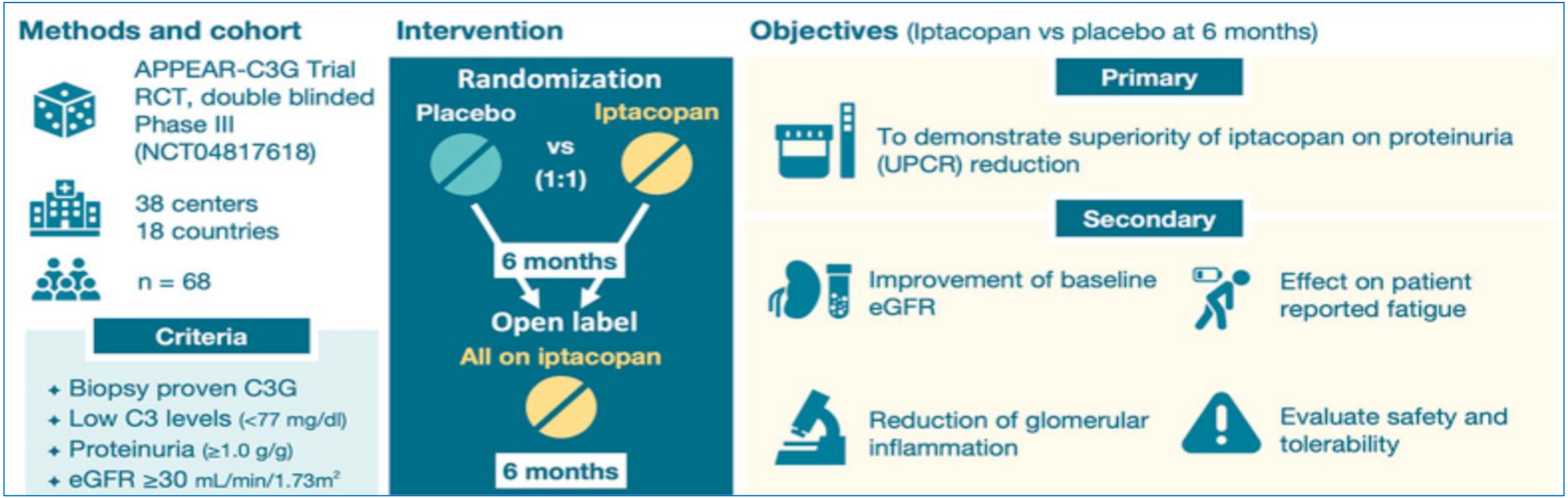
- APPEAR-C3G was a randomized, double-blind, parallel group, multicenter, placebo-controlled, phase 3 study of iptacopan versus placebo
- Adults (18 - 60 years)
- with biopsy-confirmed C3 glomerulopathy within 12 months of enrollment (native kidneys)
- reduced serum C3 concentration <77 mg/dL
- urine protein–creatinine ratio (UPCR) of 1.0 g/g or higher
- Iptacopan 200 mg BID (n=38) ; Placebo (n=36)

Kavanagh D et al, Lancet. 2025

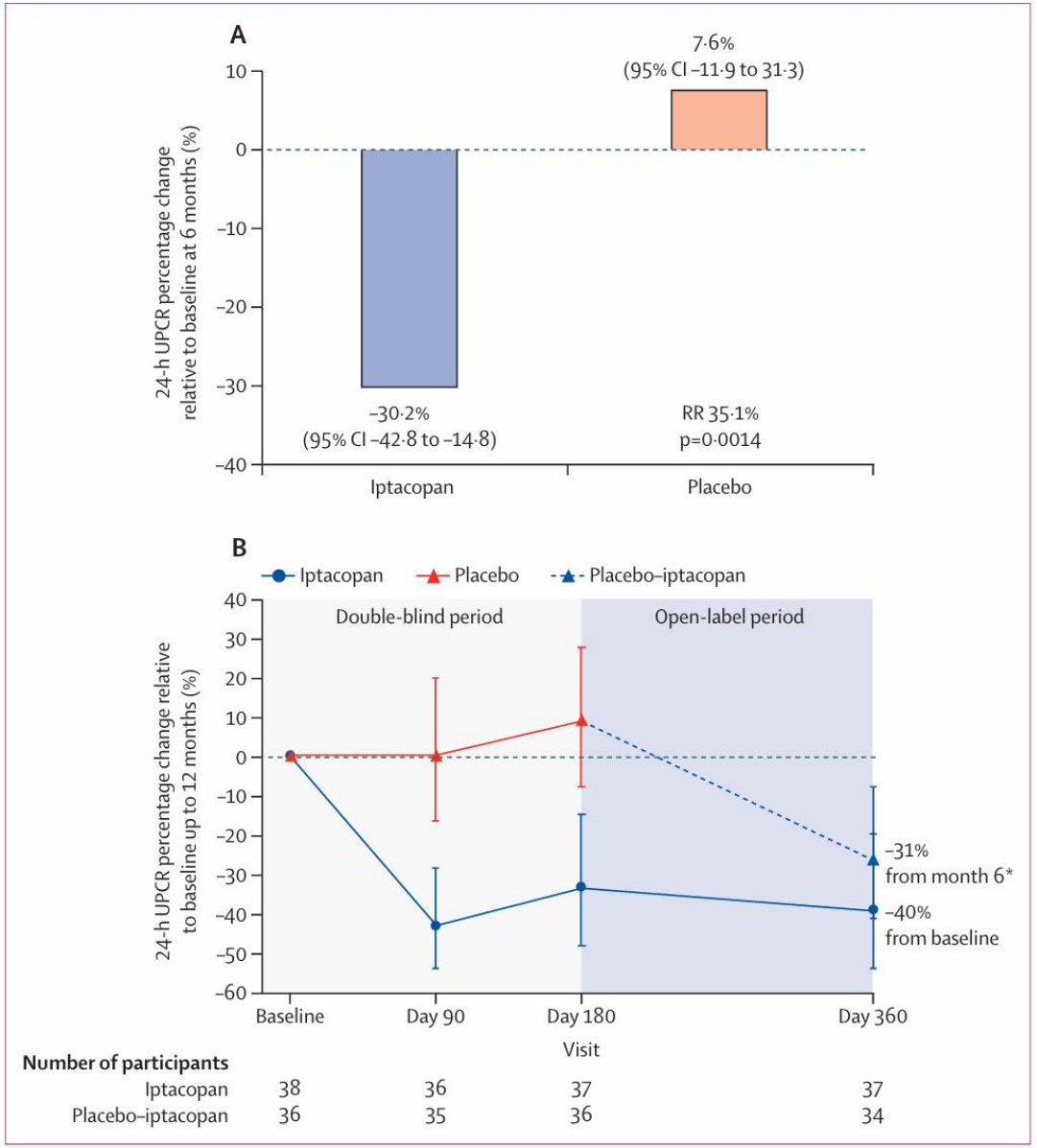
- **Iptacopan** (LNP023)

Alternative Complement Pathway Inhibition With Iptacopan for the Treatment of C3 Glomerulopathy-Study Design of the APPEAR-C3G Trial NCT04817618

AS Bomback et al.: APPEAR-C3G: Phase III Study Design and Rationale

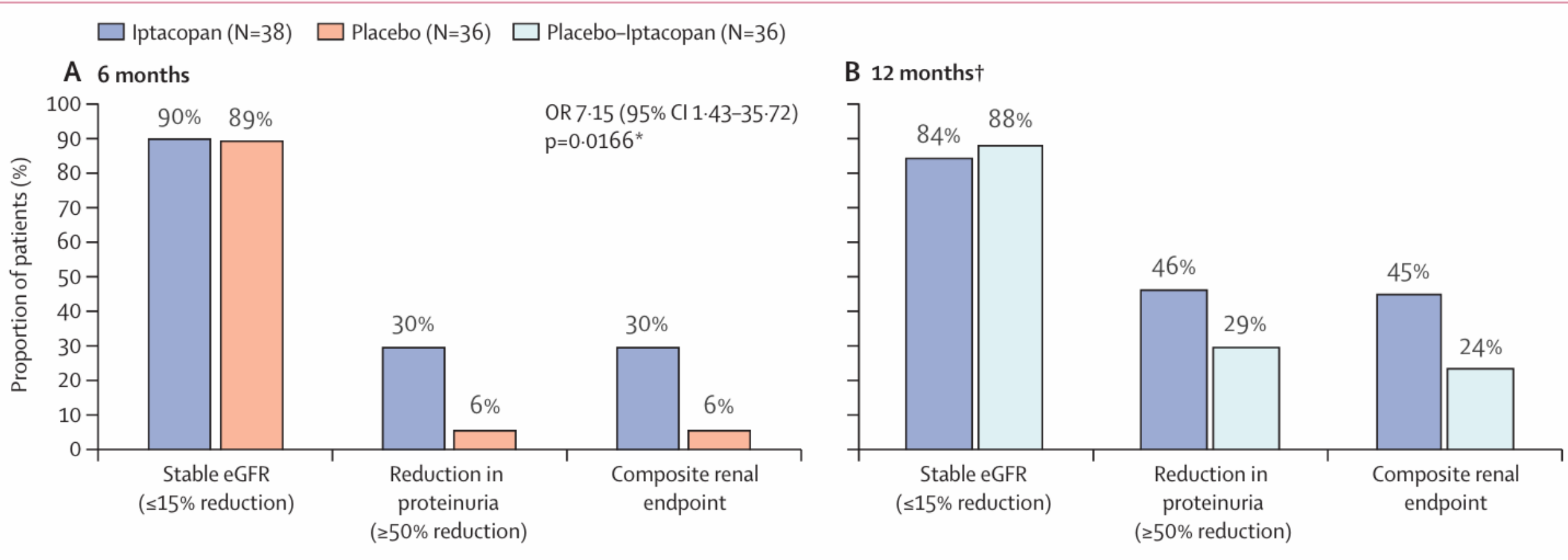


APPEAR-C3G % proteinuria reduction in GC3 treated with iptacopan



Kavanagh D et al, The Lancet 2025

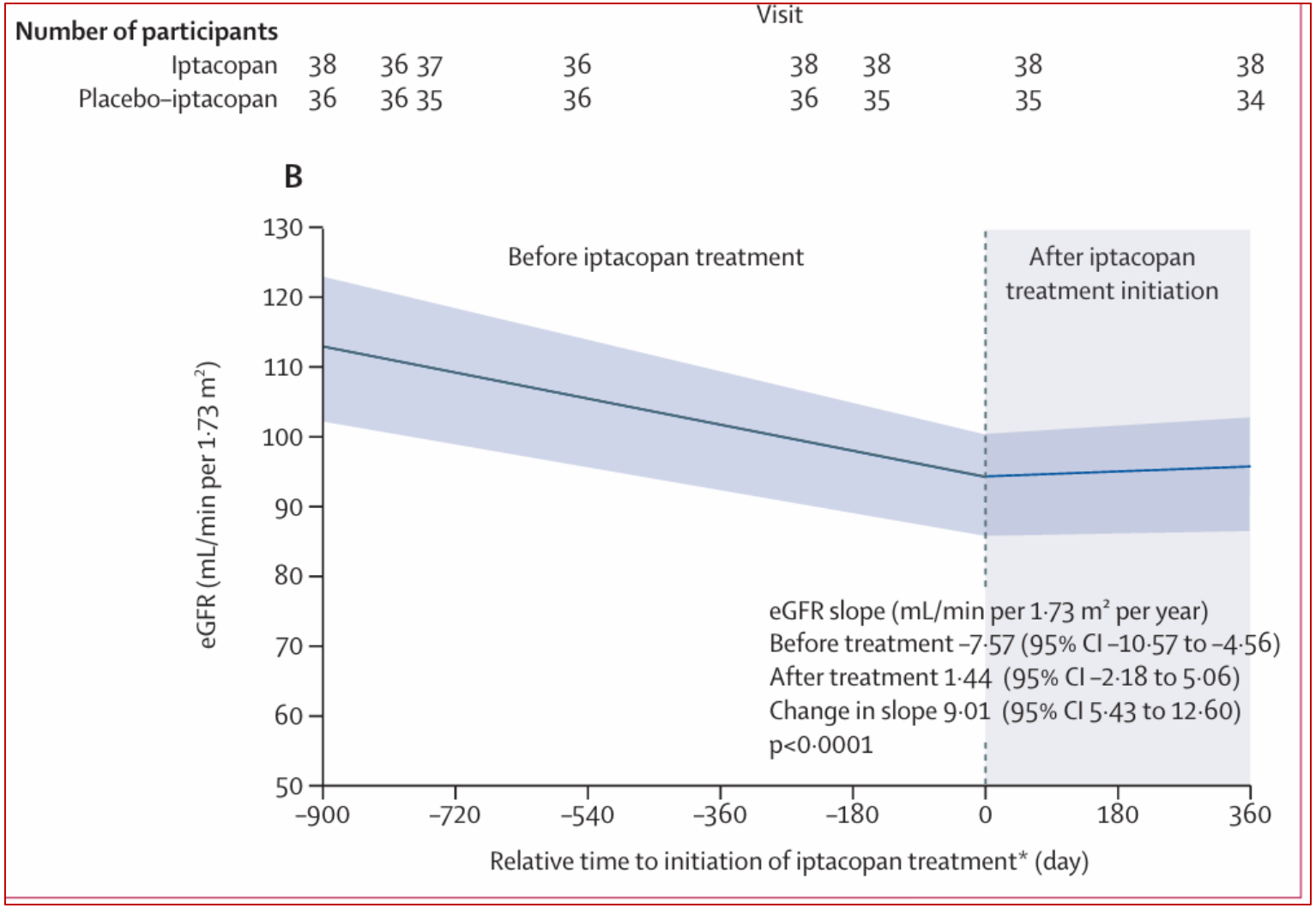
APPEAR-C3G % proteinuria reduction and eGFR in patients with GC3 treated with iptacopan



Composite renal endpoint (stable or improved eGFR [≤15% reduction] vs baseline + ≥50% reduction in UPCR from baseline to 6 months)

Kavanagh D et al, The Lancet 2025

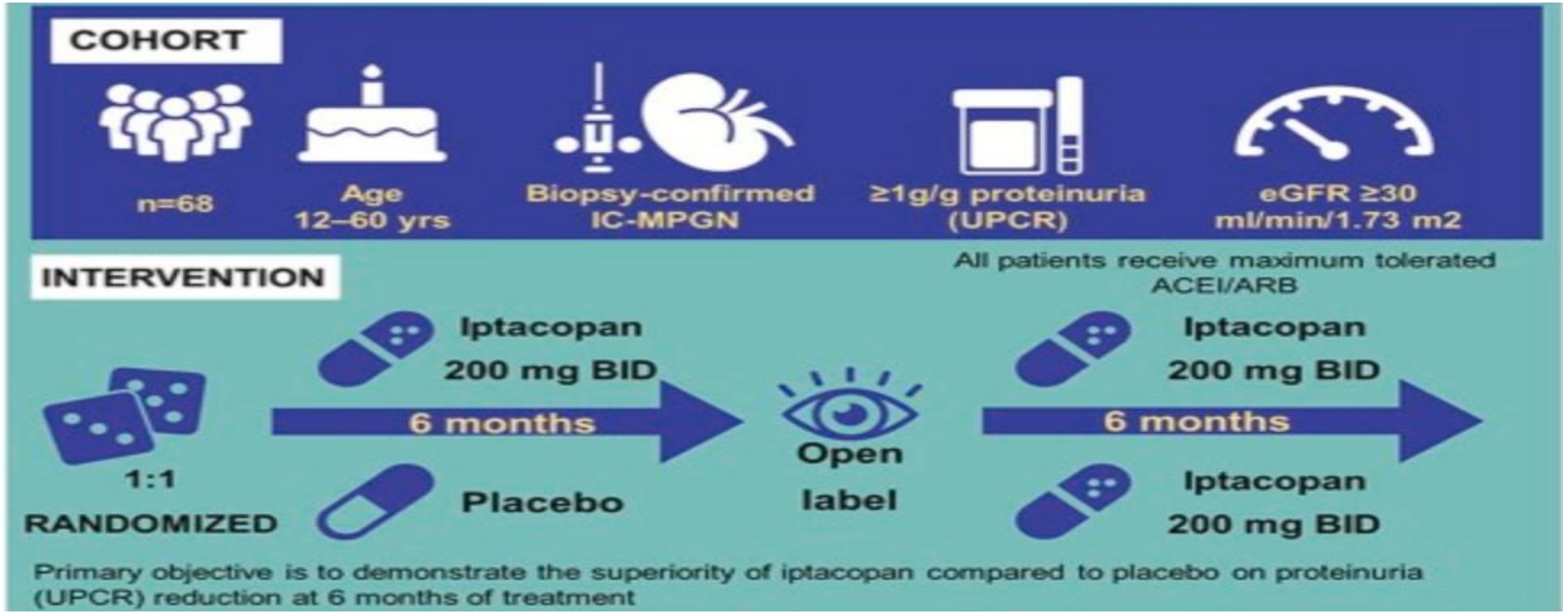
APPEAR-C3G: Effect of iptacopan 200 mg twice daily vs placebo on eGFR (N=74)



Kavanagh D et al, The Lancet 2025

News: Iptacopan

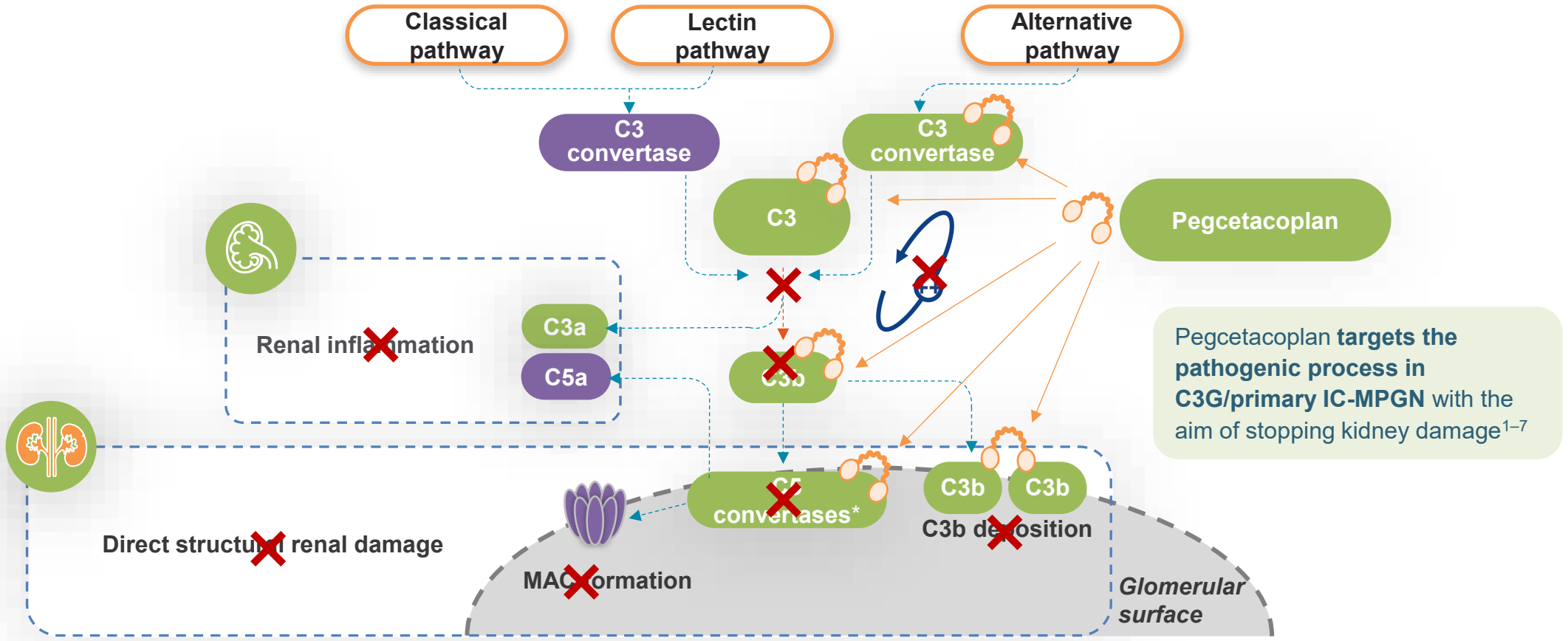
- Ongoing trial in adolescents with C3G (recruitment completed)
- Ongoing trial for IC-MPGN in patients 12-60 years of age NCT05755386



M Vivarelli et al.: APPARENT: Phase 3 Study Design and Rationale

Vall d'Hebron

Pegcetacoplan blocks C3 dysregulation and downstream complement activation



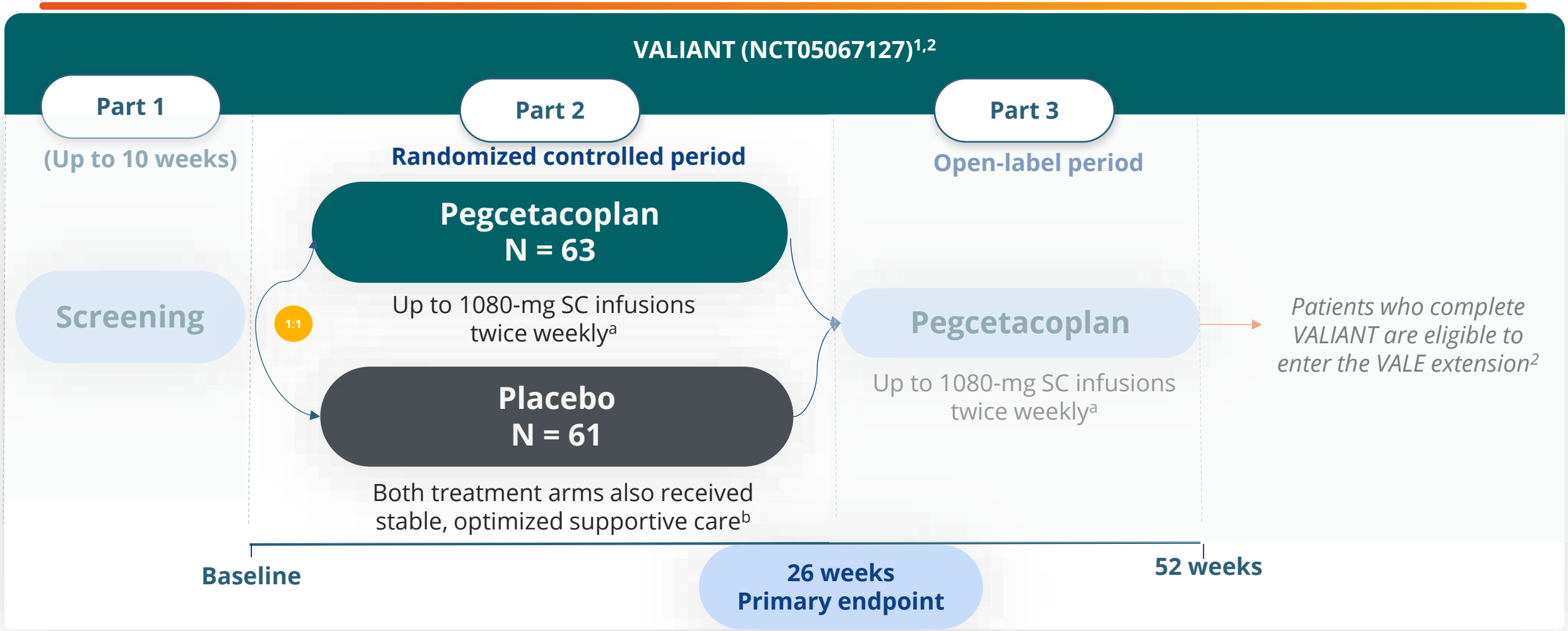
Pegcetacoplan **targets the pathogenic process in C3G/primary IC-MPGN** with the aim of stopping kidney damage[1–7]

*C5 convertases: C4b2aC3b and C3bBbC3b.

C3/5, complement 3/5; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; MAC, membrane attack complex.

1. Smith RJH, et al. *Nat Rev Nephrol.* 2019;15:129–143; **2.** Zipfel PF, et al. *Front Immunol.* 2019;10:2166; **3.** Meuleman MS, et al. *Semin Immunol.* 2022;60:101634; **4.** Dixon BP, et al. *Kidney Int Rep.* 2023;8:2284–93; **5.** EMPAVELI (pegcetacoplan). Apellis Pharmaceuticals, Inc. 2024; **6.** ASPAVELI (pegcetacoplan). Swedish Orphan Biovitrum AB; 2024; **7.** Lamers C, et al. *Nat Commun.* 2022;13:5519.

VALIANT: Double-Blind, Randomized, Placebo-Controlled Phase 3 Trial



.[a]All adults and adolescents weighing ≥50 kg self administered 1080 mg/20 mL. Adolescent patients weighing 30–34 kg received 540 mg/10 mL for the first 2 doses, then 648 mg/12 mL. Adolescent patients weighing 35–49 kg received 648 mg/12 mL for the first dose, then 810 mg/15 mL. [b]Stable, optimized antiproteinuric regimens: ACEis, ARBs, SGLT2is, MMF, and corticosteroids (prednisone ≤20 mg/d or equivalent) were permitted.

1. Dixon BP, et al. ASN Kidney Week 2023. Nov. 2–5, 2023. Abstract INFO12-SA. **2.** ClinicalTrials.gov. VALIANT. clinicaltrials.gov/study/NCT05067127. Accessed Sept. 18, 2024.

AEMPS. Pegcetacoplan 1080 mg solución para perfusión: ficha técnica. Madrid: AEMPS; 2021. Disponible en: https://cima.aemps.es/cima/dochtml/ft/1211595001/FT_1211595001.html

VALIANT: Eligibility criteria

Key eligibility criteria

Inclusion

- **Adolescents** (12–17 y) **or adults** (≥18 y)
- **Diagnosis of primary C3G or IC-MPGN (with or without previous renal transplant)**
- **MMF and corticosteroids (prednisone ≤20 mg/d or equivalent) permitted**

Exclusion

- **>50% global glomerulosclerosis or interstitial fibrosis on renal biopsy**

Other eligibility criteria

Inclusion

- Evidence of active disease
- ≥1 g/d of proteinuria on screening urine collection and UPCR ≥1 g/g in ≥2 first-morning spot urine samples
- eGFR ≥30 mL/min/1.73 m^2[a]
- Mandatory vaccination against *Streptococcus pneumoniae*, *Neisseria meningitidis* (types A, C, W, Y, and B), and *Haemophilus influenzae* (type B)
- Stable, optimized antiproteinuric regimens: ACEis, ARBs, SGLT2is

Exclusion

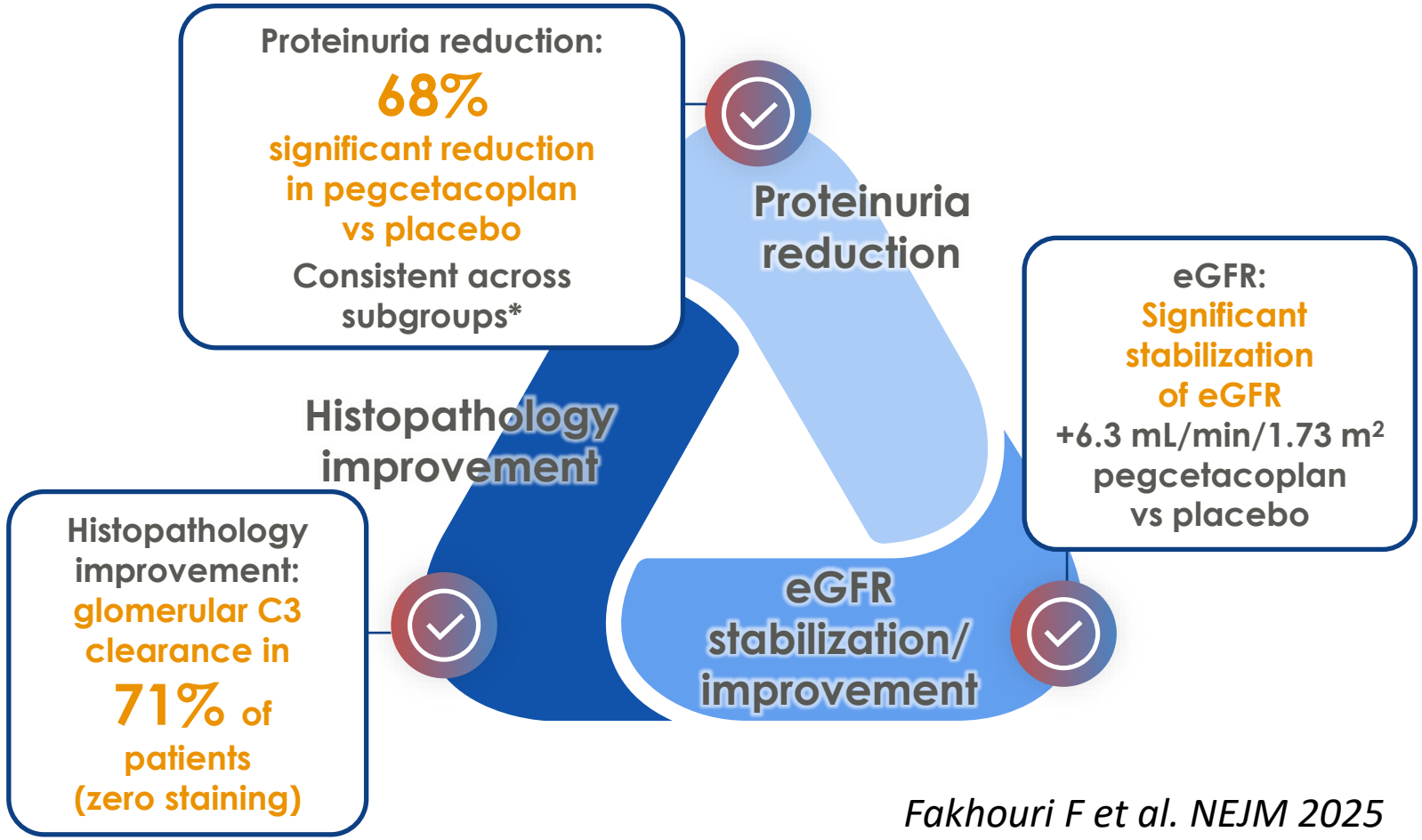
- Evidence of transplant rejection
- Diagnosis of secondary C3G or IC-MPGN
- Severe infection within 14 days prior to first dose
- Recurrent or chronic severe infections or history of meningococcal disease
- Previous exposure to pegcetacoplan or another complement inhibitor
- Evidence of improving renal disease

ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; C3G, complement 3 glomerulopathy; CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex membranoproliferative glomerulonephritis; MMF, mycophenolate mofetil; SGLT2is, sodium-glucose cotransporter-2 inhibitors; UPCR, urine protein-to-creatinine ratio.[a]Calculated using the CKD-Epi equation for adults or the Bedside Schwartz equation for adolescents **1.** Dixon BP, et al. ASN Kidney Week 2023. Nov. 2–5, 2023. Abstract INFO12-SA. **2.** ClinicalTrials.gov. VALIANT. clinicaltrials.gov/study/NCT05067127. Accessed Sept. 18, 2024.; AEMPS. Pegcetacoplan 1080 mg solución para perfusión: ficha técnica. Madrid: AEMPS; 2021. Disponible en: https://cima.aemps.es/cima/dochtml/ft/1211595001/FT_1211595001.html

VALIANT overall study results (26 weeks): **Pegcetacoplan's proven efficacy** in C3G and primary IC-MPGN[1]

Kidney Health Initiative (KHI) consensus[2]:

A **favorable treatment effect on three endpoints** (histopathology improvement, proteinuria reduction, eGFR stabilization) **provides convincing evidence of efficacy** for treatments targeting the complement pathway

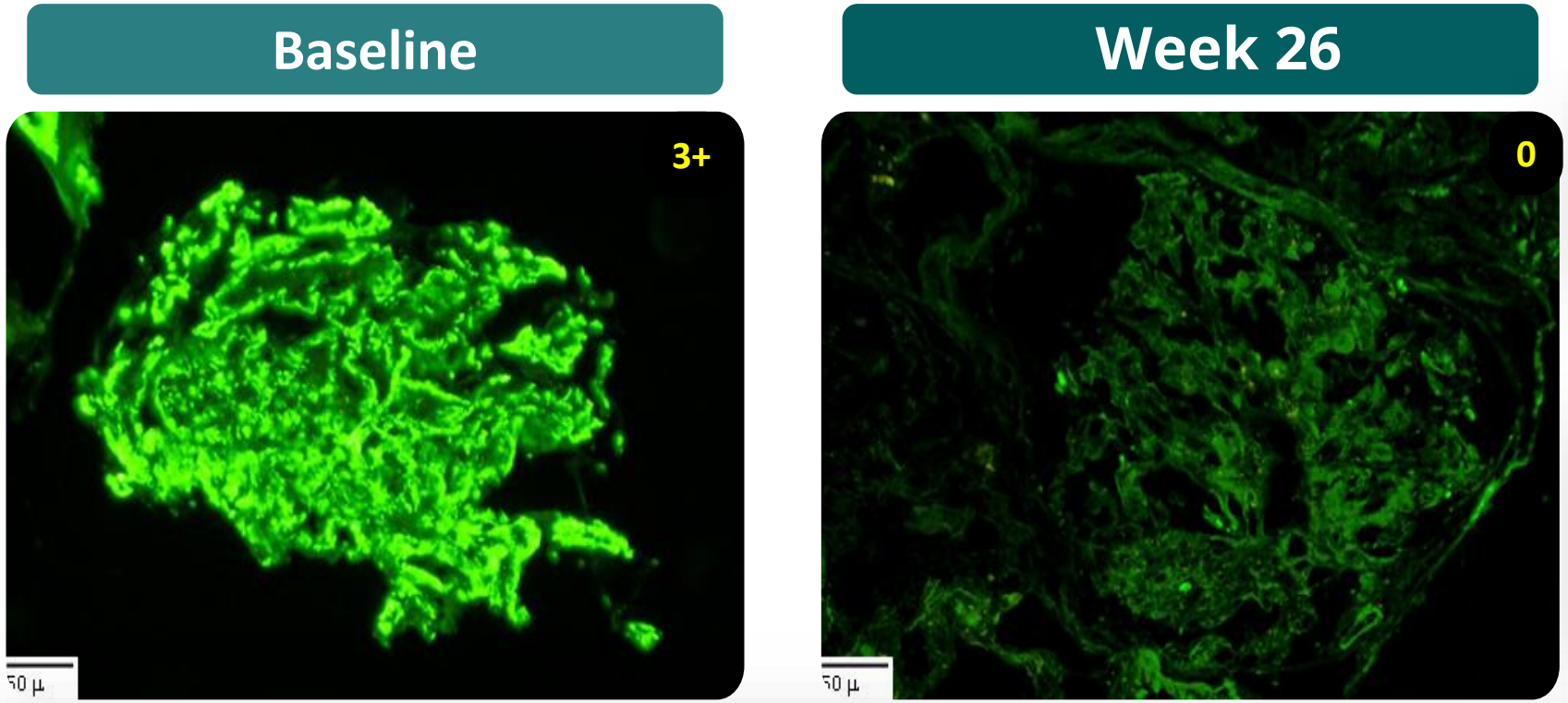


Fakhouri F et al. NEJM 2025

* Age group: adolescents and adults; Disease type: C3G and IC-MPGN; Transplant status: no transplant, post-transplant.
C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex membranoproliferative glomerulonephritis; KHI, Kidney Health Initiative.
1. Nester CM et al. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92) **2.** Nester C, et al. *Clin J Am Soc Nephrol* 2024;19:1201–8.

Key secondary endpoints: Pegcetacoplan Treatment Resulted in Clinically Significant Clearance of C3c From Renal Biopsies

Renal biopsies from a pegcetacoplan-treated C3G native kidney patient



Key secondary endpoint

Proportion with reduced C3c renal biopsy staining[a]

Pegcetacoplan	**74.3% (26/35)**
Placebo	11.8% (4/34)

Renal biopsies were not available for adolescents since they were not a mandatory requirement for this cohort

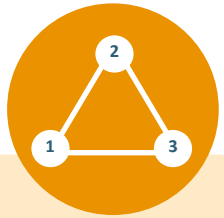
71.4% (25/35) of pegcetacoplan treated patients **achieved 0 intensity staining**

Fakhouri F et al. NEJM 2025

C3c, complement protein 3c; C3G, C3 glomerulopathy; OOM, orders of magnitude.
Intent-to-treat population (all randomized patients). [a]Difference defined as ≥2 OOM at week 26 vs baseline; in all adults. Baseline renal biopsies were not required for adolescent participants

AEMPS. Pegcetacoplan 1080 mg solución para perfusión: ficha técnica. Madrid: AEMPS; 2021. Disponible en: https://cima.aemps.es/cima/dochtml/ft/1211595001/FT_1211595001.html

VALIANT: 26-week data demonstrated efficacy of pegcetacoplan in adolescent patients with C3G and primary IC-MPGN



Kidney Health Initiative consensus[2]

Favourable treatment effect on **histopathology, proteinuria and eGFR**

74.5%
significant proteinuria reduction vs placebo*[1]

Proteinuria reduction

Stabilisation of eGFR +9.7 ml/min/1.73 m² vs placebo[1]

Histopathology improvement

eGFR stabilisation/ improvement

Glomerular C3 clearance in 71.4% of adult patients (zero staining)[1]

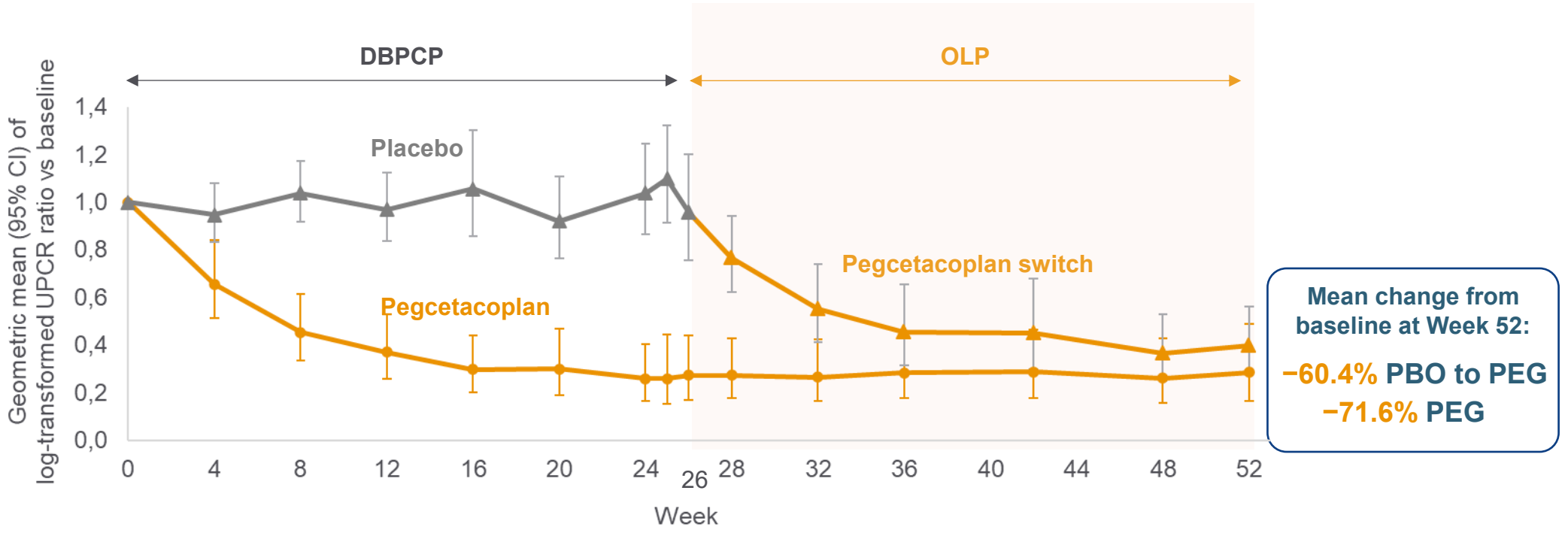
*p<0.0001.

C3, complement 3 protein; C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis.

1. Mastrangelo A, et al. Oral presentation at ERA 2025. 4–7 June 2025. (Abstract 3413); **2.** Nester C, et al. *Clin J Am Soc Nephrol.* 2024;19:1201–8

VALIANT: Robust proteinuria reductions at Week 26 were maintained through Week 52 also for adolescents

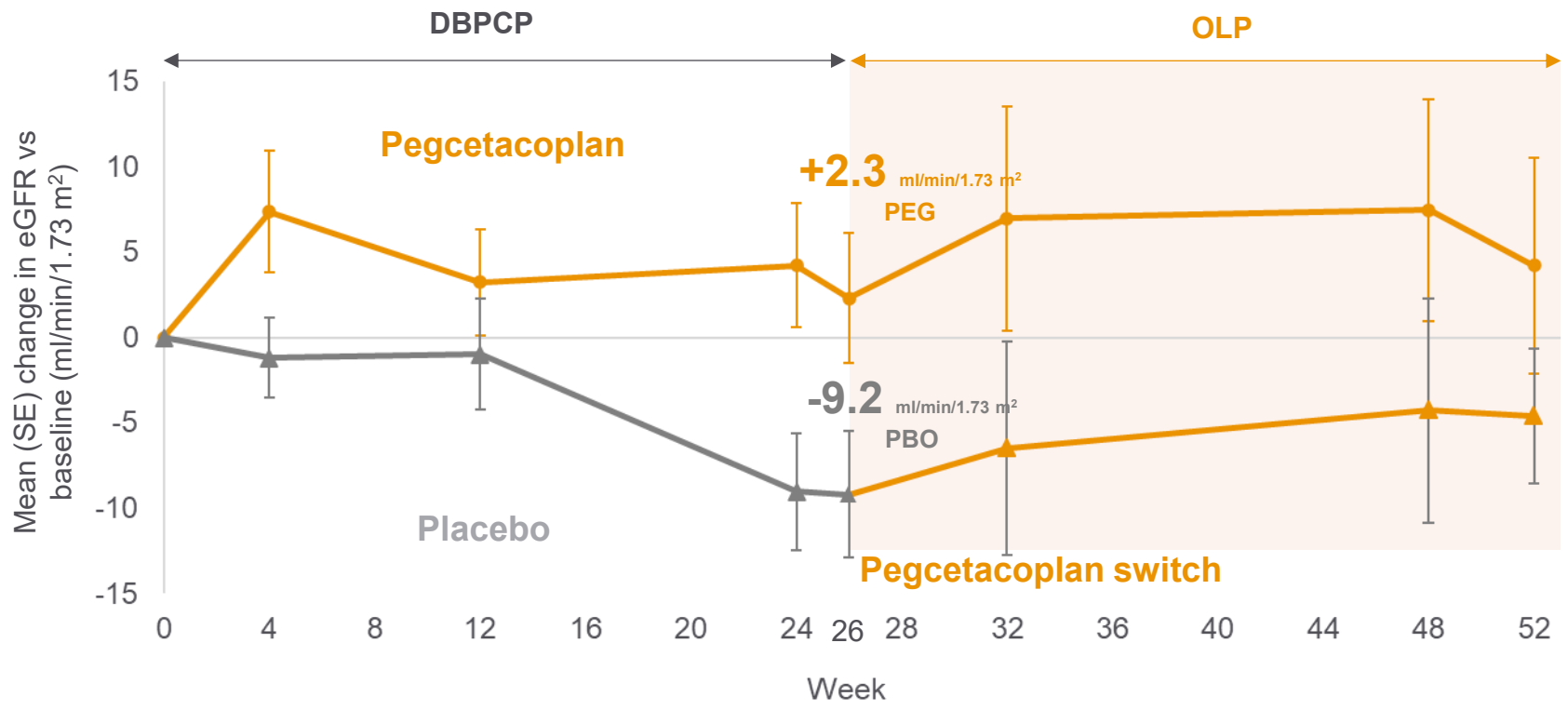
Change in proteinuria according to treatment group



CI, confidence interval; DBPCP, double-blind placebo-controlled period; OLP, open-label period; PBO, placebo; PEG, pegcetacoplan; UPCR, urine protein-to-creatinine ratio.

VALIANT: eGFR improved for both adolescent groups during pegcetacoplan treatment

Change in eGFR according to treatment group



Mean change from baseline at Week 52:

+4.2 ml/min/1.73 m² **PEG**

−4.6 ml/min/1.73 m² **PBO to PEG**

DBPCP, double-blind placebo-controlled period; eGFR, estimated glomerular filtration rate; OLP, open-label period; PBO, placebo; PEG, pegcetacoplan; SD, standard deviation.

VALIANT: TEAEs in adolescents over 52 weeks were consistent with the known safety profile for pegcetacoplan

Event, n (%)	Adolescent patients (n=53)
Any TEAE	46 (86.8)
Maximum severity	
Mild	21 (39.6)
Moderate	21 (39.6)
Severe	4 (7.5)
Treatment-related TEAE	23 (43.4)
Infusion-related TEAE	19 (35.8)
Serious TEAE (SAEs)	6 (11.3)
Treatment-related SAEs	1* (1.9)
TEAE leading to treatment withdrawal	2 (3.8)
TEAE leading to dose interruption	8 (15.1)
TEAE leading to study discontinuation	1 (1.9)†
TEAE leading to death	0 (0.0)
Rejection episodes	0 (0.0)
Graft loss	0 (0.0)

TEAE, treatment-emergent adverse event.
A TEAE is defined as any new adverse event that began, or any pre-existing condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. *1 Treatment-related SAE of pyrexia that was moderate and resolved. † One TAE of AKI considered non-related by the investigator

Thank you very much for your attention