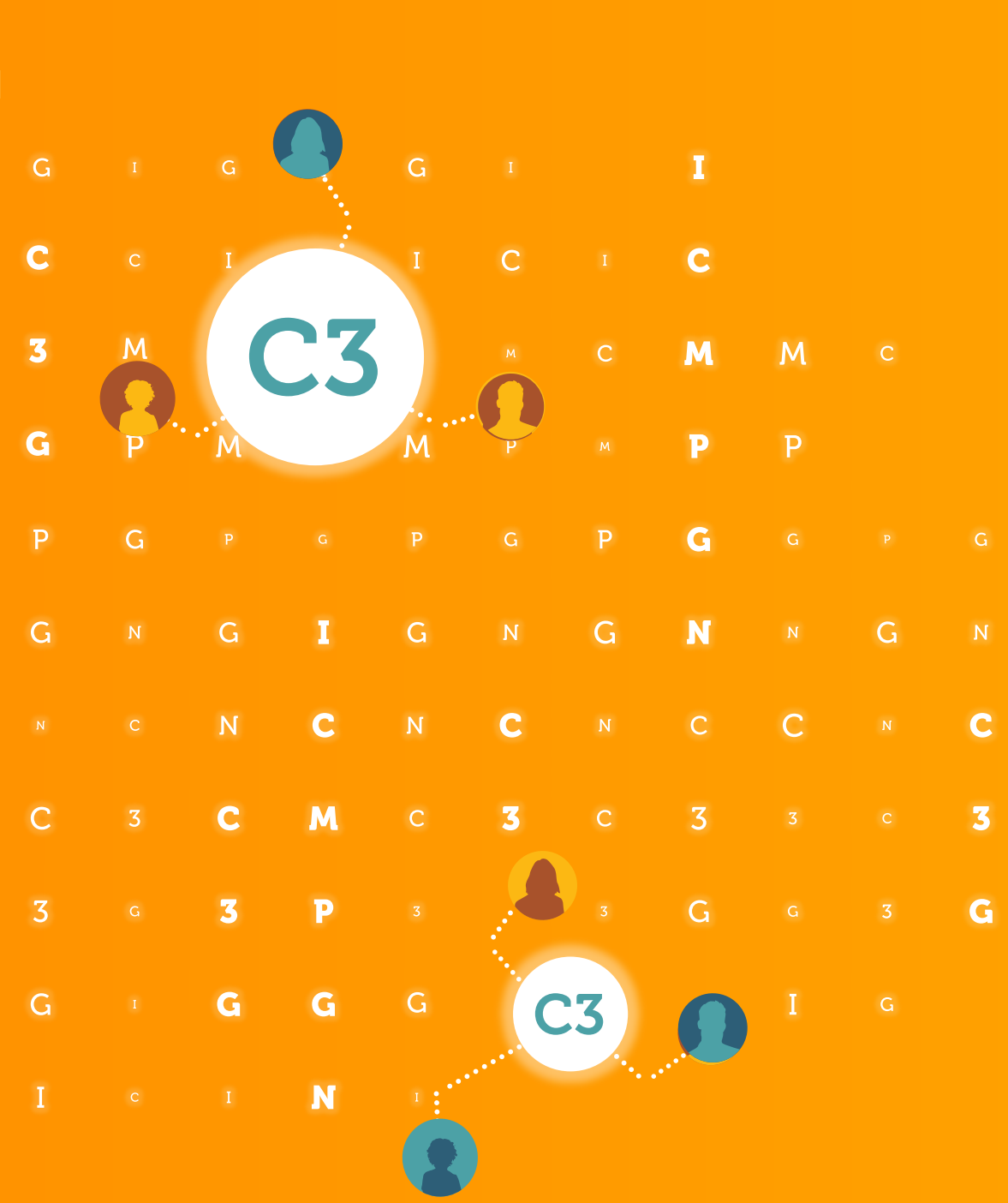

Decoding complement in C3G and primary IC-MPGN

Exploring evolving paths in care

Friday 17 October 2025
13.05–14.05 EEST

ESPN congress 2025
Athens, Greece

Date of preparation: October 2025
NP-43727

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Disclaimer and important information

This presentation serves educational purposes and is intended to provide information and stimulate discussion on selected topics in C3G and primary IC-MPGN

The intent is not to provide medical or any other type of advice. All treatment decisions should be up to the discretion of the healthcare provider and the patient, as each patients' situation may vary

This scientific event is a non-promotional symposium sponsored by Sobi and the speakers are being compensated for their involvement. The content, discussion and answers reflect the personal opinion of the speaker and may not represent those of Sobi

The therapeutics discussed herein may not be approved in every jurisdiction, and healthcare providers must always consult the applicable local regulatory authorities to determine whether the product is approved in their country

C3G, complement 3 glomerulopathy; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis.

Faculty

Sally Johnson
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Faculty disclosures

- **Sally Johnson** has received honoraria for speaking at symposia and for participation in advisory boards from Alexion, Novartis and Sobi. All monies are paid directly to employing institution
- **Francesca Diomedi Camassei** nothing to declare
- **Dieter Haffner** has received honoraria for speaking at symposia and/or participation in Advisory Boards from Advicenne, Biologix, Chiesi, Kyowa Kirin, Medison Pharma, recordati Rare diseases, SOBI and Ultragenyx. These funds were paid directly to him

  He has received research grants from Chiesi, Cystinosis Research Foundation, Else Kröner-Fresenius-Stiftung, German Research Foundation, and Kyowa Kirin. These funds were paid directly to employing institution

Symposium agenda

Time (EEST)	Presentation	Speaker
13.05–13.10	Chair's welcome	Dieter Haffner
13.10–13.25	Managing C3G and primary IC-MPGN in children: bridging clinical and molecular perspectives	Sally Johnson
13.25–13.40	Histopathology insights: paving the way for earlier diagnosis	Francesca Diomedi Camassei
13.40–13.55	Complement inhibition: from bench to clinical trials	Dieter Haffner
13.55–14.05	Closing remarks and Q&A	All speakers *Moderated by Dieter Haffner*

C3, complement 3; C3G, C3 glomerulopathy; GBM, glomerular basement membrane; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; EEST, Eastern European Summer Time; Q&A, questions and answers.

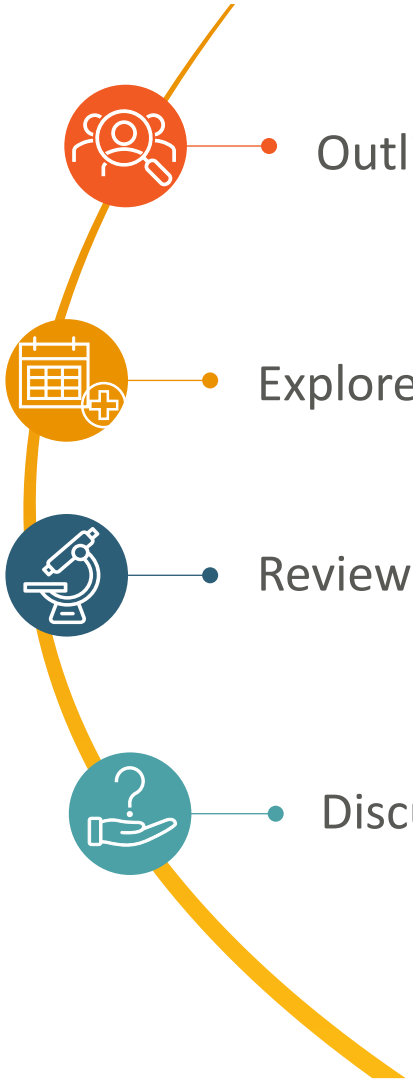
Today’s learning objectives

- Reflect on **current challenges and unmet needs** in children with C3G and primary IC-MPGN, highlighting **knowledge gaps driven by disease complexity and heterogeneity**
- Share expert guidance on **current challenges and unmet needs in diagnosis** and how to **improve diagnostic approaches** in children
- Share the **latest update on the new therapeutic targets** in investigation, focusing on **pegcetacoplan Phase 3 clinical trial** and new analyses presented at ESPN

C3G, C3 glomerulopathy; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis.

Managing C3G and primary IC-MPGN in children: bridging clinical and molecular perspectives

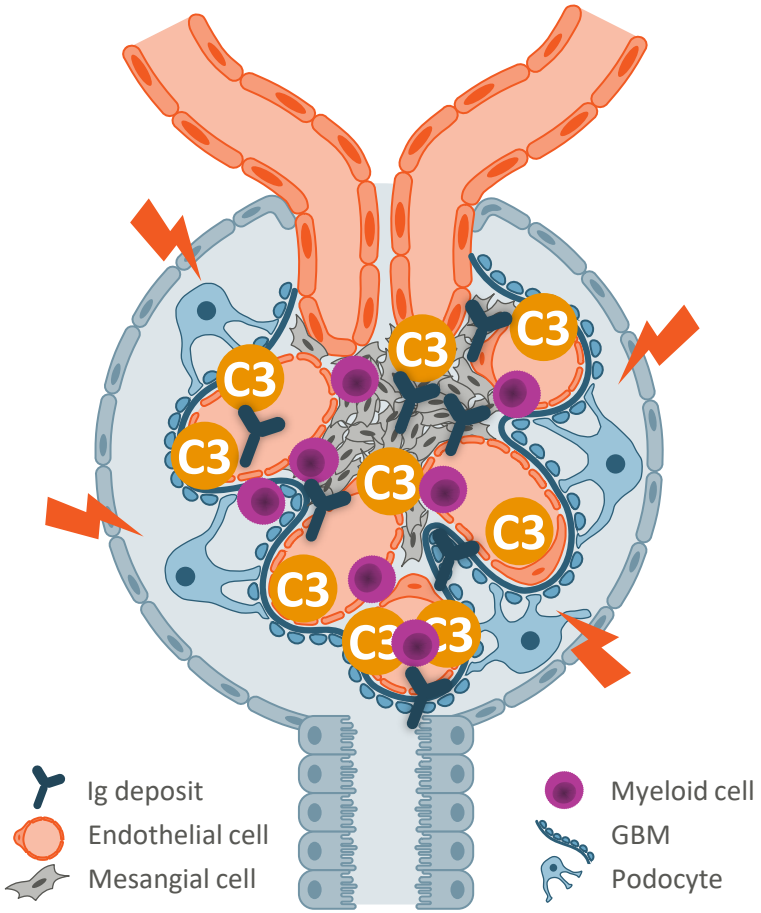
Today’s objective



- Outline the **clinical course** and **heterogeneity of C3G and primary IC-MPGN**
- Explore the importance of **differential diagnosis**
- Review the **molecular basis for C3G and primary IC-MPGN**
- Discuss how to assess **efficacy of treatment**

C3, complement 3; C3G, C3 glomerulopathy; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis.

C3G and primary IC-MPGN are rare complement-related kidney disorders[1]



Both diseases are defined by **glomerular inflammation and capillary wall thickening with C3 deposition**; in IC-MPGN, there is also Ig deposition[1]

The **diagnosis** is made by clinicopathological correlation following **kidney biopsy**[1]

- Light microscopy is used to identify the histological pattern
- **IF is used to identify complement deposition**

Although histological features are distinct, **C3G and primary IC-MPGN share** many similarities in terms of **clinical features and molecular basis**[1,2]

Image adapted from: Petr V & Thurman JM. *Nat Rev Nephrol* 2023;19:771–87.
C3, complement 3; C3G, C3 glomerulopathy; GBM, glomerular basement membrane; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IF, immunofluorescence; Ig, immunoglobulin.
1. Bomback AS, *et al*. *Kidney Int Rep* 2024;10:17–28; 2. Noris M & Remuzzi G. *Nephrol Dial Transplant* 2024;39:202–14.

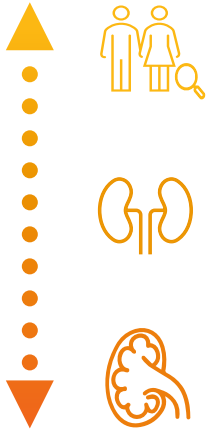
Presentation of C3G and primary IC-MPGN varies widely between patients[1]

Clinical signs of C3G or primary IC-MPGN in children

Signs of altered renal function are highly indicative[2]

- ❑ Proteinuria
- ❑ Haematuria
- ❑ Elevated serum creatinine
- ❑ Hypertension

Severity at presentation is heterogenous[2]



Asymptomatic urinary abnormalities

Nephrotic syndrome

Acute kidney injury (rare)

Low serum C3 levels are present in ~75% of children (compared with ~50% of adults)[3]

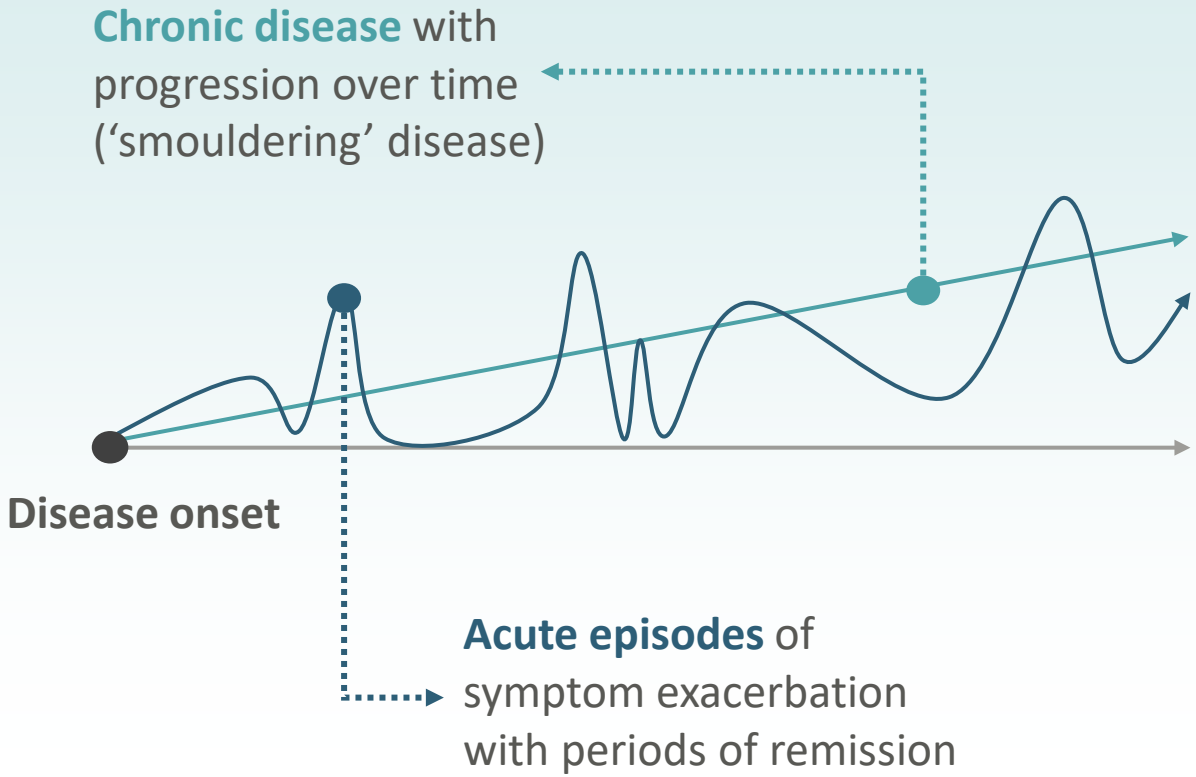
Serological complement assays are helpful to confirm diagnosis[2]

C3G, C3 glomerulopathy; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis.

1. Caravaca-Fontán F, *et al. Nephron* 2020;144:272–80; 2. Vivarelli M, *et al. Pediatr Nephrol* 2022;37:521–35; 3. Heiderscheit AK, *et al. Am J Med Genet C Semin Med Genet* 2022;190C:344–57.

Disease course is heterogeneous[1,2]

Disease course may be chronic, or with acute episodes[1,2]



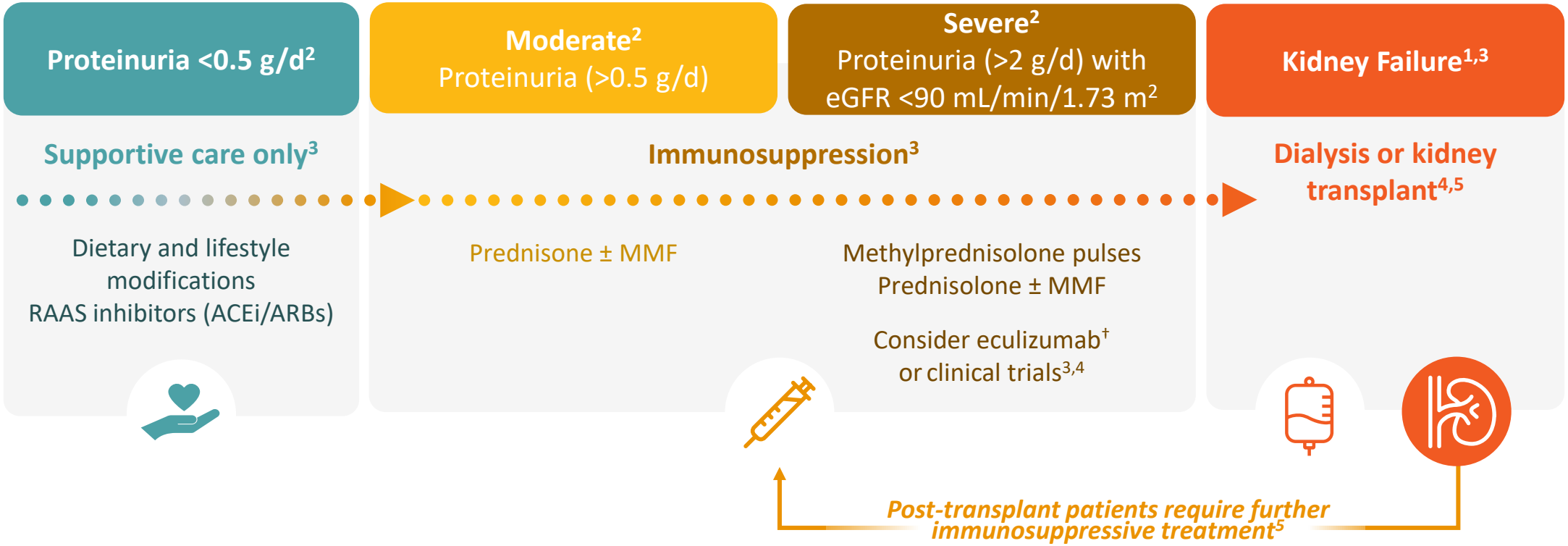
In children, **disease flares** are frequently associated with **infectious episodes**[2]

Regardless of disease severity at presentation, **timely intervention may allow slowing of disease progression** before significant kidney damage occurs[3,4]

1. Medjeral-Thomas NR, *et al. Clin J Am Soc Nephrol* 2014;9:46–53; 2. Vivarelli M, *et al. Pediatr Nephrol* 2022;37:521–35; 3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int* 2024;105:S117–S314; 4. Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43.

Without disease-modifying treatments, up to 50% of patients progress to kidney failure over 10 years[1]

After biopsy-confirmed diagnosis, all children should receive supportive care[2]



ACEi, angiotension converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; IV, intravenous; MMF, mycophenolate mofetil; RAAS, renin-angiotensin-aldosterone system.

1. Halfon M, et al. Kidney Int Rep 2024;10:75–86.; 2. Vivarelli M, *et al. Pediatr Nephrol* 2021;37:521–35; 3. Patry C, *et al. Pediatr Nephrol* 2024;39:3569–3580.

C3G and primary IC-MPGN have a substantial burden on paediatric patients

55% of paediatric patients experience **disease recurrence** within 5 years of renal transplant[1]

Patients experience **high rates of allograft loss due to disease recurrence** (C3G: **54–60%**; primary IC-MPGN: **43%**)[2,3*]

Increased **dependency on dialysis**, with significant impact on **cardiovascular health** and **deprioritisation on kidney transplant lists**[4–7]

CKD impacts **physical** (growth and development) and **psychological well-being** (mental health, academic performance and QOL)[8]

Current **immunosuppressive therapies** are **associated with a significant risk of adverse events**[3,9–11]

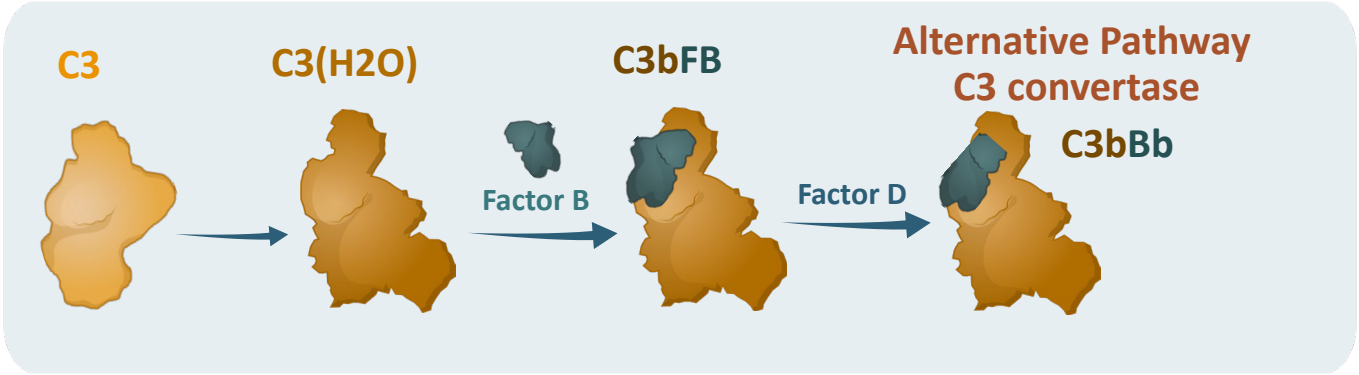
Glucocorticoids may result in **a negative effect on growth**[12]

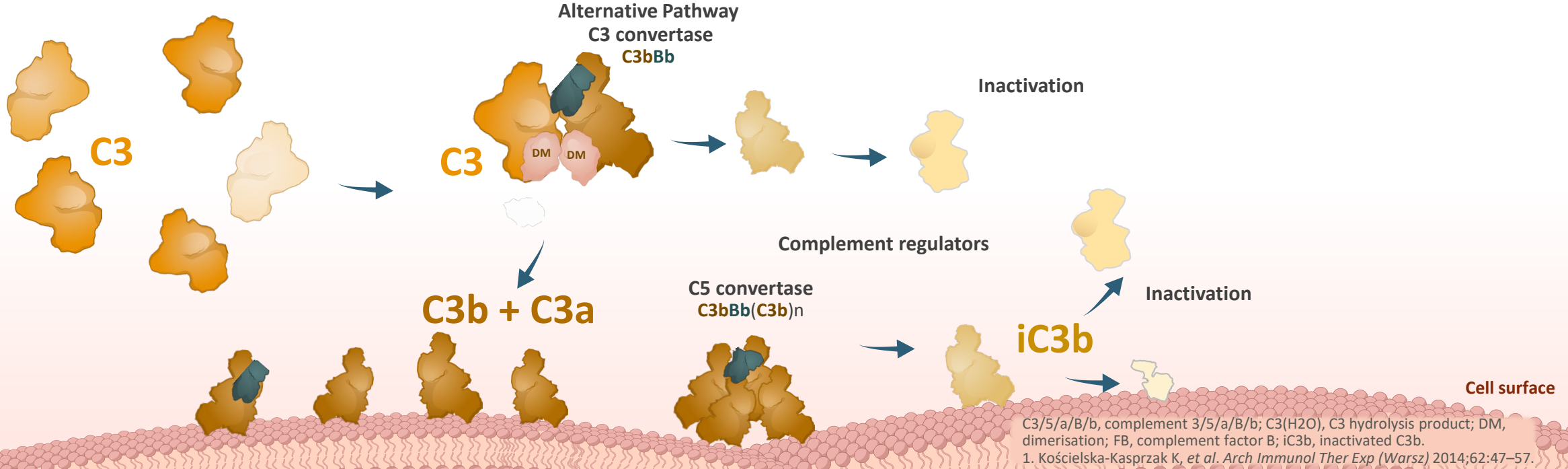
*Patient population inclusive of adult and paediatric patients. †Defined as need for dialysis therapy within the first week post-transplant.
C3G, C3 glomerulopathy; CKD, chronic kidney disease; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; QoL, quality of life.

1. Patry C, *et al. Pediatr Nephrol* 2024;39:3569–80; 2. Servais A, *et al. Kidney Int* 2012;82:454–64; 3. Noris M, *et al. Nephrol Dial Transplant* 2023;38:283–90; 4. Patry C, *et al. Pediatr Transplant* 2025;29:e70048; 5. Covic A, *et al. Nephrol Dial Transplant* 2006;21:729–35; 6. Wilson GJ, *et al. BMC Nephrol* 2019;20:417; 7. Parekh RS, *et al. J Pediatr* 2002;141:191–197; 8. Amatya K, *et al.* Chapter 20 – Pediatric and adolescent patients with CKD and ESRD. In: Cukor D, Cohen SD, Kimmel PL, editors. *Psychosocial Aspects of Chronic Kidney Disease*. 2021. Academic Press. pp 451–71; 9. Caravaca-Fontán F, et al. *Nephron* 2020;144:272–80; 10. Nester CM & Smith RJ. *Curr Opin Nephrol Hypertens* 2013;22:231–7; 11. Jefferson JA. *Clin J Am Soc Nephrol* 2018;13:1264–75; 12. Valavi E, *et al. J Pediatr* 2020;96;117–24.

The complement system is activated via the alternative, classical and lectin pathways[1]

The alternative pathway is constitutively active at a low level, constantly producing C3b. It does not require pathogen recognition to be activated[1]



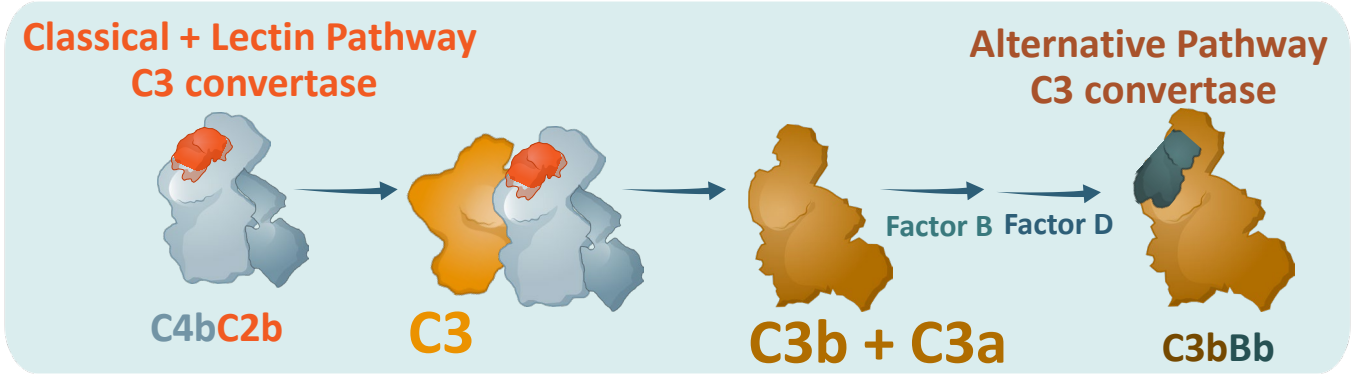


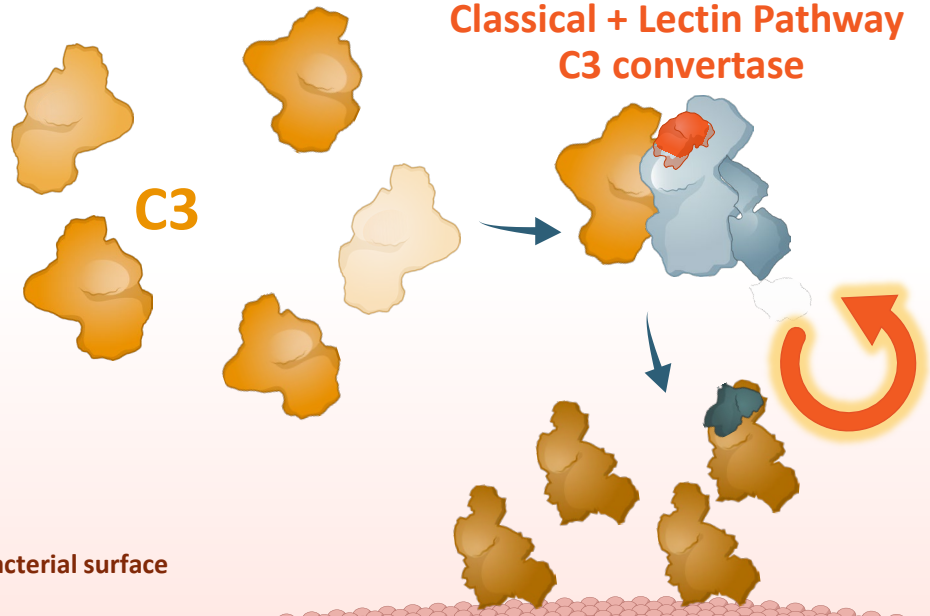
C3/5/a/B/b, complement 3/5/a/B/b; C3(H2O), C3 hydrolysis product; DM, dimerisation; FB, complement factor B; iC3b, inactivated C3b.

1. Kościelska-Kasprzak K, *et al*. *Arch Immunol Ther Exp (Warsz)* 2014;62:47–57.

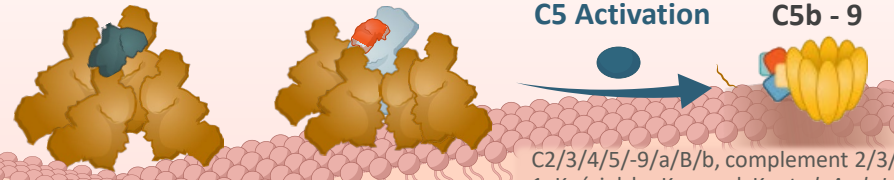
The complement system is activated via the alternative pathway, lectin pathway, or classical pathway[1]

Upon infection, after pathogen recognition, **classical and lectin pathways activate,** and the alternative pathway supports quick amplification for an effective response[1]





C3a and C5a anaphylatoxins: Immune cell recruitment

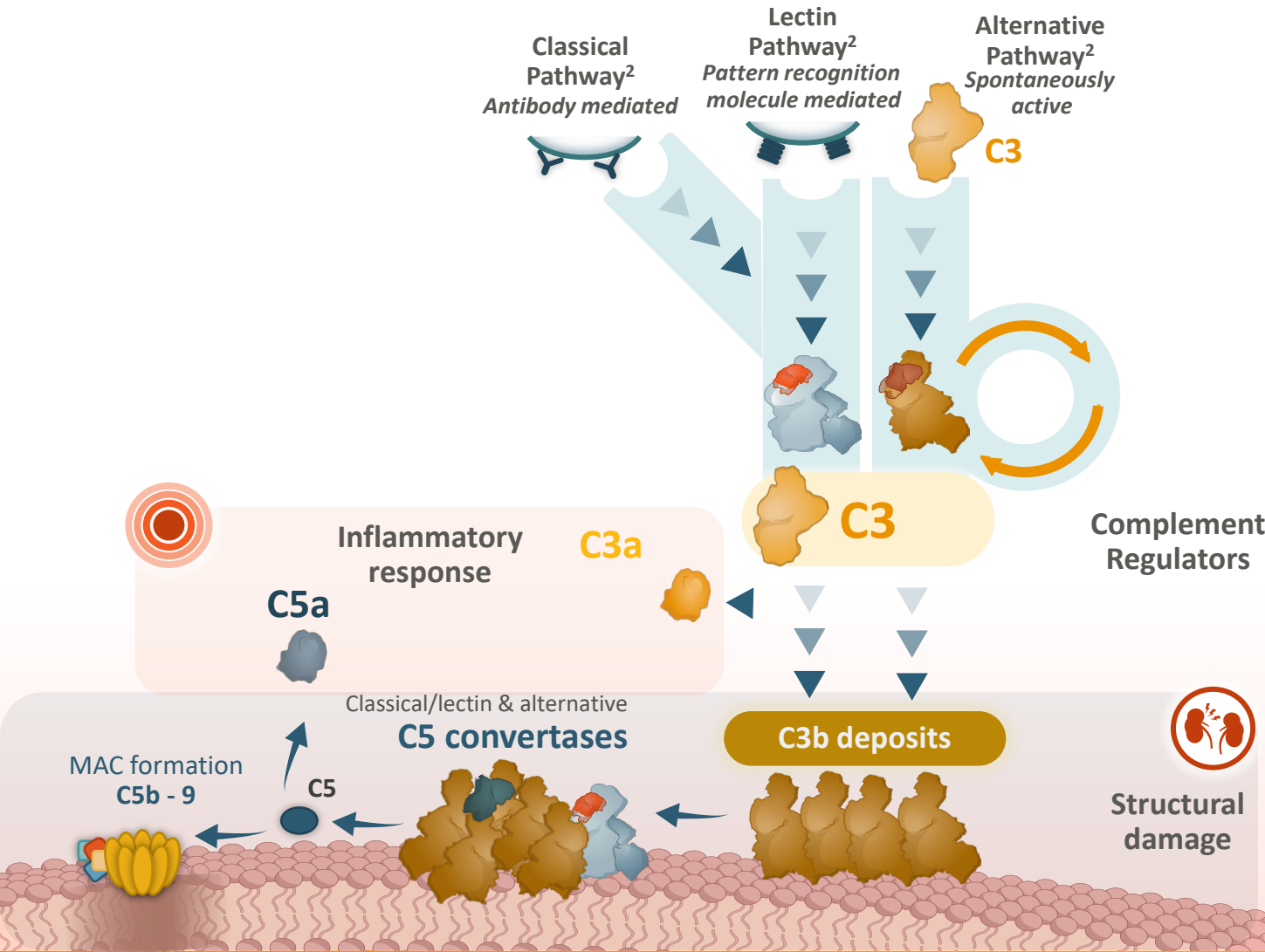


MAC formation: bacterial lysis

C2/3/4/5/-9/a/B/b, complement 2/3/4/5/-9/a/B/b; MAC, membrane attack complex.

1. Kościelska-Kasprzak K, *et al. Arch Immunol Ther Exp (Warsz)* 2014;62:47–57.

C3 is at the centre of disease pathophysiology in C3G and primary IC-MPGN[1,2]



Complement regulators prevent tissue damage[3,4]

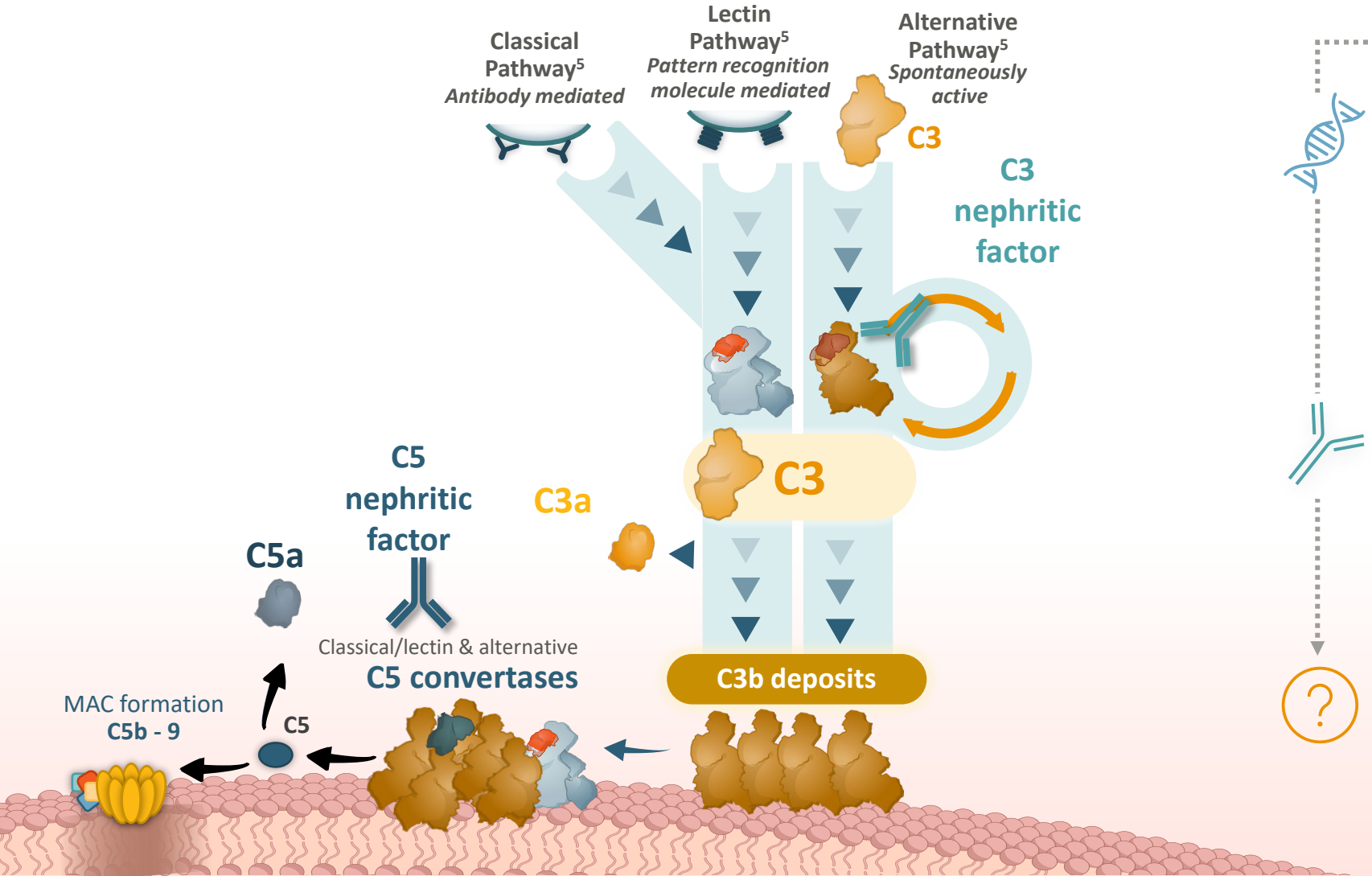
Defective complement regulation results in uncontrolled C3 activation, followed by abnormal complement deposition within the glomeruli[4]

C3 downstream effectors cause glomerular inflammation with recruitment of inflammatory cells and disruption of the glomerular basement membrane[1,2,5]

C3/5/-9/a/b, complement 3/5/-9/a/b;
C3G, C3 glomerulopathy; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis.

1. Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43; 2. Schena FP, *et al. Int J Mol Sci* 2020;21:525; 3. Zipfel PF, *et al. Front Immunol* 2019;10:2166; 4. Pickering M, *et al. Nat Genet* 2002;31:424–8; 5. Kościelska-Kasprzak K, *et al. Arch Immunol Ther Exp (Warsz)* 2014;62:47–57.

Heterogeneity in disease triggers may explain the heterogeneous presentation and disease course[1–4]



Disease triggers[1–4]

Gene variants

10–20% of patients carry variants in complement genes. Some variants are associated with human leukocyte antigens. **Familial cases are rare**

Autoantibodies

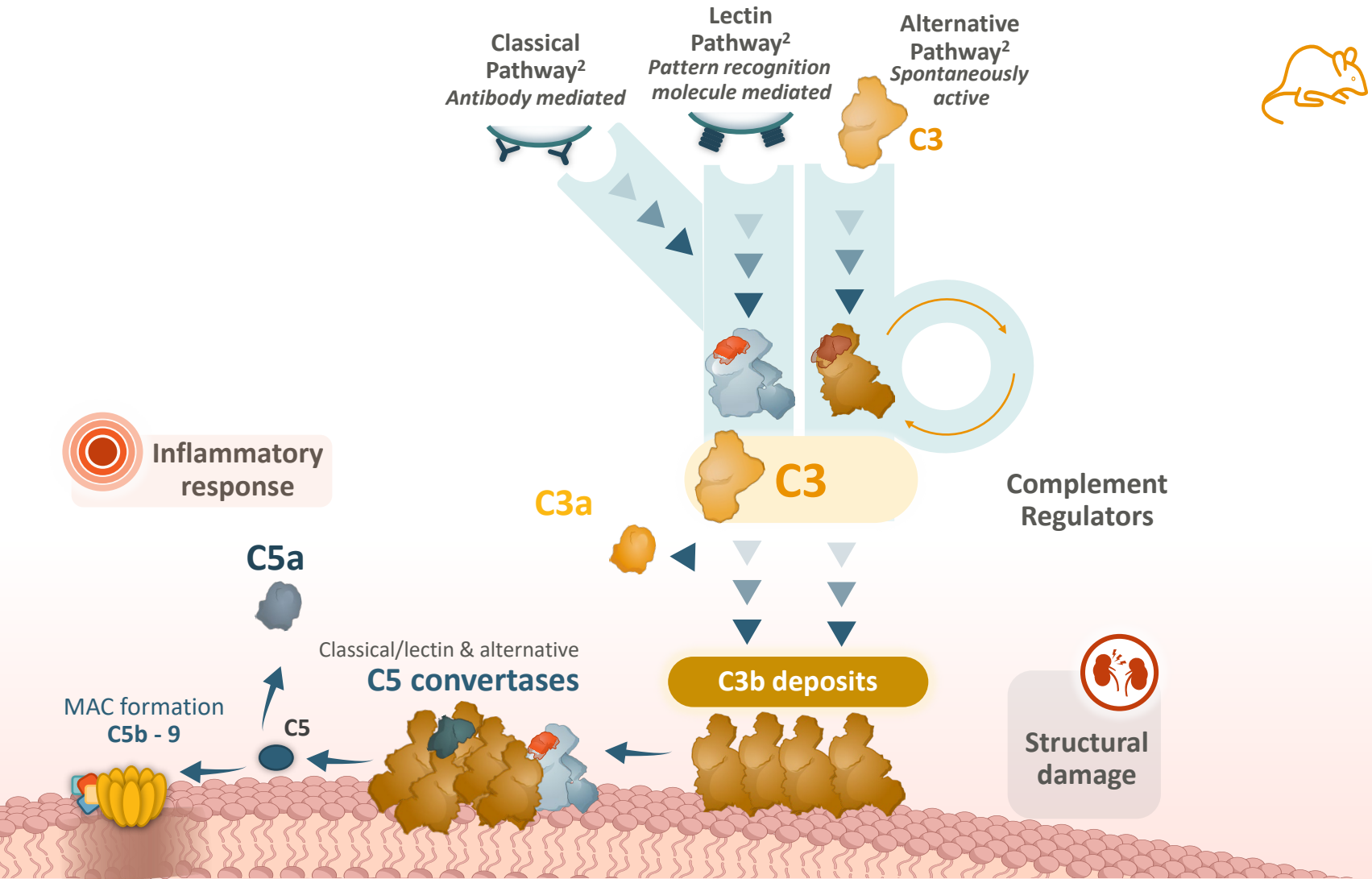
Approximately **50% of patients** have nephritic factors that stabilise C3/C5 convertase complexes

In some patients, **no autoantibodies or gene variants are detected**

C3/5/-9/a/b, complement 3/5/-9/a/b.

1. Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43; 2. Meuleman M-S, *et al. Semin Immunol* 2022;60:101634; 3. Xiao X, *et al. Mol Immunol* 2016;77:89–96; 4. Fakhouri F, *et al. Kidney Int* 2020;98:1135–48; 5. Kościelska-Kasprzak K, *et al. Arch Immunol Ther Exp (Warsz)* 2014;62:47–57.

C3G pathology does not develop when C3 activation is prevented in animal models[1]



In FH-deficient C3G models, **glomerular C3 is the first abnormality to develop**[1]

C3/5/-9/a/b, complement 3/5/-9/a/b; C3G, C3 glomerulopathy; FH, complement factor H; IS, immunosuppression.

1. Pickering M, *et al. Nat Genet* 2002;31:424–8; 2. Kościelska-Kasprzak K, *et al. Arch Immunol Ther Exp (Warsz)* 2014;62:47–57; 3. Pickering M, *et al. Proc Natl Acad Sci* 2006;103:9649–54; 4. Ruseva MM, *et al. J Am Soc Nephrol* 2016;27:405–16.

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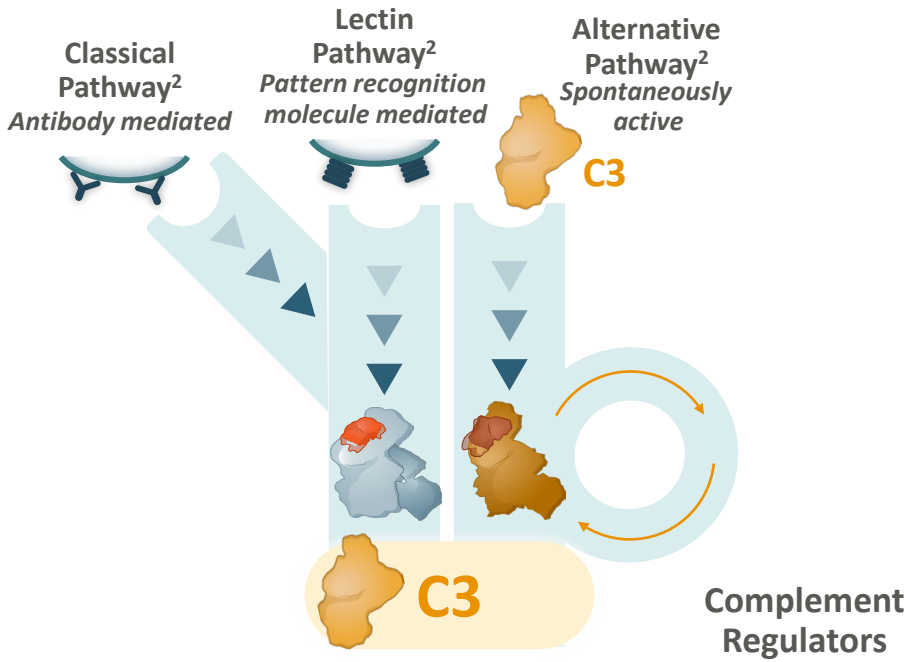

In FH-deficient C3G models, **glomerular C3 is the first abnormality to develop**[1]

If C3 activation is prevented, **no glomerular C3 occurs and C3G does not develop**[1]

C3/5/-9/a/b, complement 3/5/-9/a/b; C3G, C3 glomerulopathy; FH, complement factor H; IS, immunosuppression.

1. Pickering M, *et al. Nat Genet* 2002;31:424–8; 2. Kościelska-Kasprzak K, *et al. Arch Immunol Ther Exp (Warsz)* 2014;62:47–57; 3. Pickering M, *et al. Proc Natl Acad Sci* 2006;103:9649–54; 4. Ruseva MM, *et al. J Am Soc Nephrol* 2016;27:405–16.

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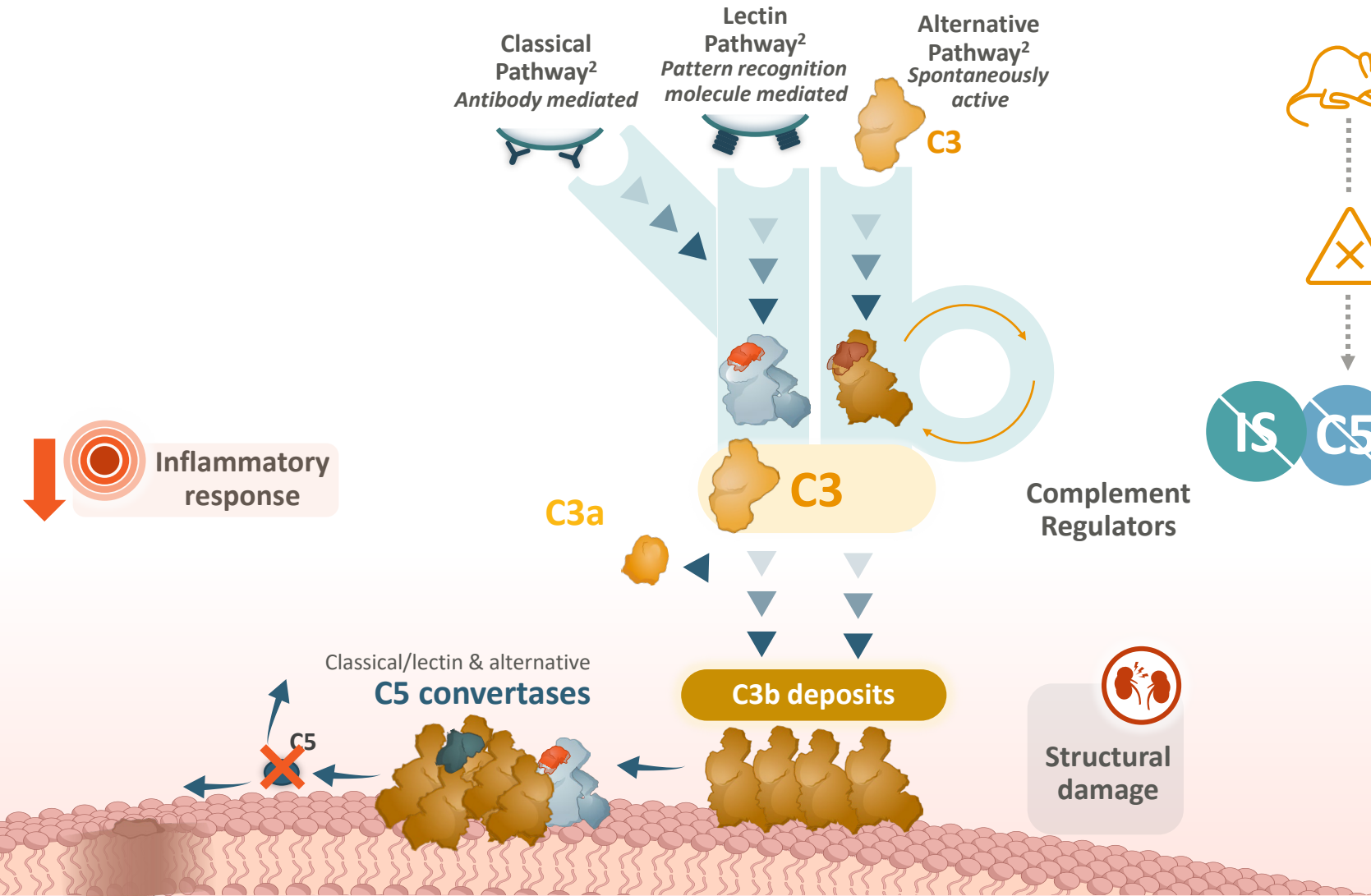


In FH-deficient C3G models, **glomerular C3 is the first abnormality to develop**[1]

If C3 activation is prevented, **no glomerular C3 occurs and C3G does not develop**[1]

IS and **C5 inhibition** reduce **inflammation but glomerular C3 remains unchanged** resulting in ongoing structural damage and failure to reduce the rate of kidney decline[3,4]

C3/5/-9/a/b, complement 3/5/-9/a/b; C3G, C3 glomerulopathy; FH, complement factor H; IS, immunosuppression.

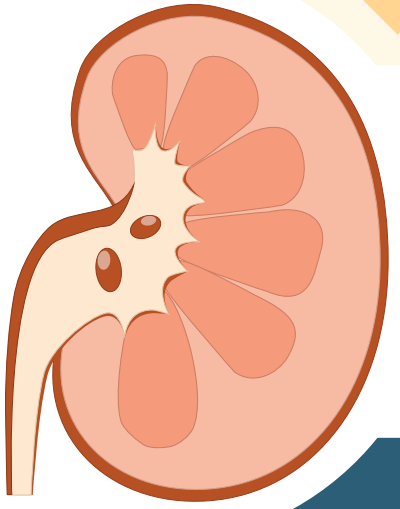
1. Pickering M, *et al. Nat Genet* 2002;31:424–8; 2. Kościelska-Kasprzak K, *et al. Arch Immunol Ther Exp (Warsz)* 2014;62:47–57; 3. Pickering M, *et al. Proc Natl Acad Sci* 2006;103:9649–54; 4. Ruseva MM, *et al. J Am Soc Nephrol* 2016;27:405–16.

Proteinuria reduction is associated with lower risk of kidney failure

RaDaR (N=371, median follow-up 11.0 years)[1]

50% reduction
or to <100 mg/mmol

in UPCR over 12 months was associated with lower risk of kidney failure.
(HR 0.40, 95% CI 0.28–0.56, p<0.0001 and HR 0.10, 95% CI 0.03–0.30, p<0.0001 respectively)



European multicentre cohort (N=225, median follow-up 3.7 years)[2]

>50% reduction
to <1 g/day

in proteinuria was associated with lower risk of the composite outcome (30% decline in eGFR or kidney failure) independent of other risk factors.
(HR 0.35, 95% CI 0.12–0.97, p=0.04)

GLOSEN (N=149, median follow-up 5.4 years)[3]

≥50% reduction

in proteinuria during follow-up time was associated with lower risk of kidney failure.
(HR 0.61, 95% CI 0.46–0.75, p=0.001)

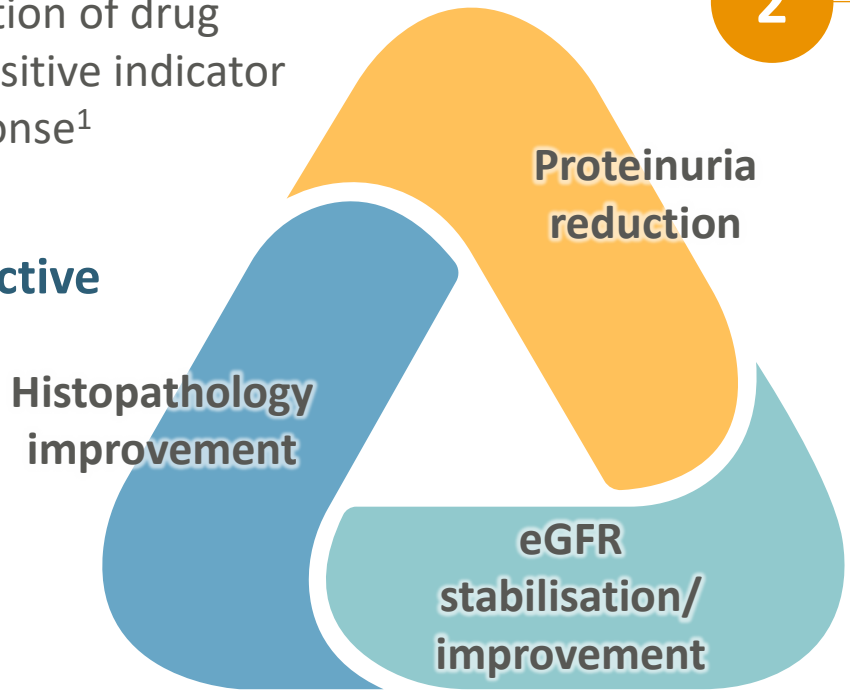
CI, confidence interval; GLOSEN, Spanish Group for the Study of Glomerular Diseases; HR, hazard ratio; RaDaR, The National Registry of Rare Kidney Diseases.

1. Masoud S, *et al. Kidney Int*. 2025;108:455-469; 2. Ghaddar M, *et al. Clin J Am Soc Nehprol* 2025; doi: 10.2215/CJN.0000000751 (online ahead of print); 3. Caravaca-Fontán F, *et al. Kidney Int Rep* 2025;10:1223–1236.

Effective complement inhibition should lead to glomerular C3 clearance, proteinuria reduction and eGFR stabilisation

1 **Clearance of glomerular C3** provides confirmation of drug activity and is a positive indicator of treatment response[1]

C3 is no longer active in the kidney



2 **Reduction in proteinuria reflects a positive treatment effect**[1]

Proteinuria has been validated as a surrogate endpoint for kidney failure, as it is a major **indicator of progression in several kidney diseases**[1,2]

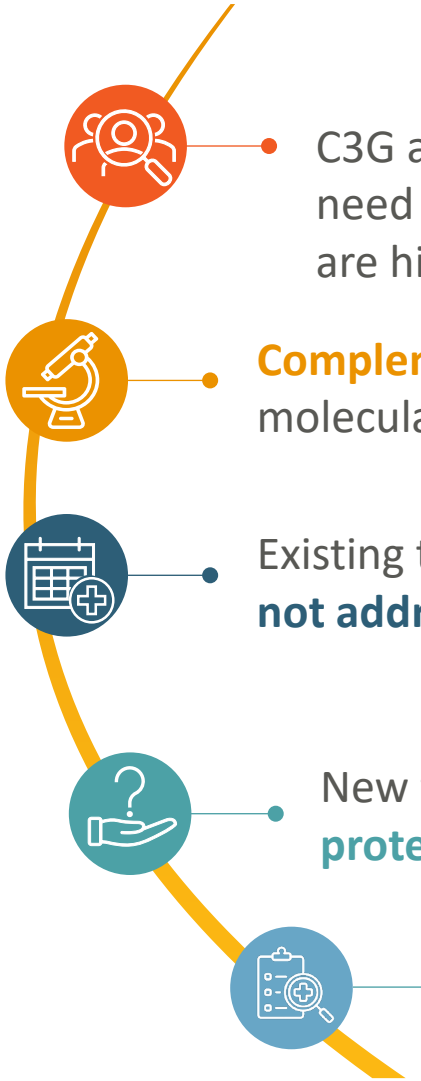
A **≥50% proteinuria reduction or proteinuria <100 mg/mmol** within 12 months of diagnosis is associated with a **lower risk** of **kidney failure**[2]

3 **Stabilisation/reduction in rate of decline for eGFR** over 6 months reflects treatment benefit[1]

C3, complement 3; eGFR, estimated glomerular filtration rate.

1. Nester C, *et al. Clin J Am Soc Nephrol* 2024;19:1201–8; 2. Masoud S, *et al. Kidney Int* 2025;108:455–69.

Take home messages



- C3G and primary IC-MPGN in children carry **long-term risk of kidney failure,** leading to need for **dialysis or transplantation**.[1,2] Rates of **disease recurrence and allograft loss** are high[3,4]
- **Complement dysregulation** and **deposition of glomerular C3** are at the centre of molecular pathogenesis[1]
- Existing treatments for paediatric patients with C3G and primary IC-MPGN **do not address underlying disease pathology**[1]
- New treatments need to target C3 to **reduce glomerular C3**, significantly reduce **proteinuria**, and **stabilise eGFR** to show evidence of treatment benefit[5]
- C3G and primary IC-MPGN share clinical features therefore diagnosis via assessment of **clinicopathological correlation** with histological findings following **kidney biopsy** is required[6]

C3, complement 3; C3G, C3 glomerulopathy; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis.

1. Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43; 2. Licht C, *et al*. Membranoproliferative glomerulonephritis and C3 glomerulopathy in children. In: *Pediatric Nephrology*. 2022. Springer Nature Switzerland, AG. pp 563–93; 3. Servais A, *et al*. *Kidney Int* 2012;82:454–64; 4. Noris M, *et al*. *Nephrol Dial Transplant* 2023;38:283–90; 5.Nester C, *et al. Clin J Am Soc Nephrol* 2024;19:1201–8; 6. Bomback AS, *et al*. *Kidney Int Rep* 2024;10:17–28.

Histopathology insights: paving the way for earlier diagnosis

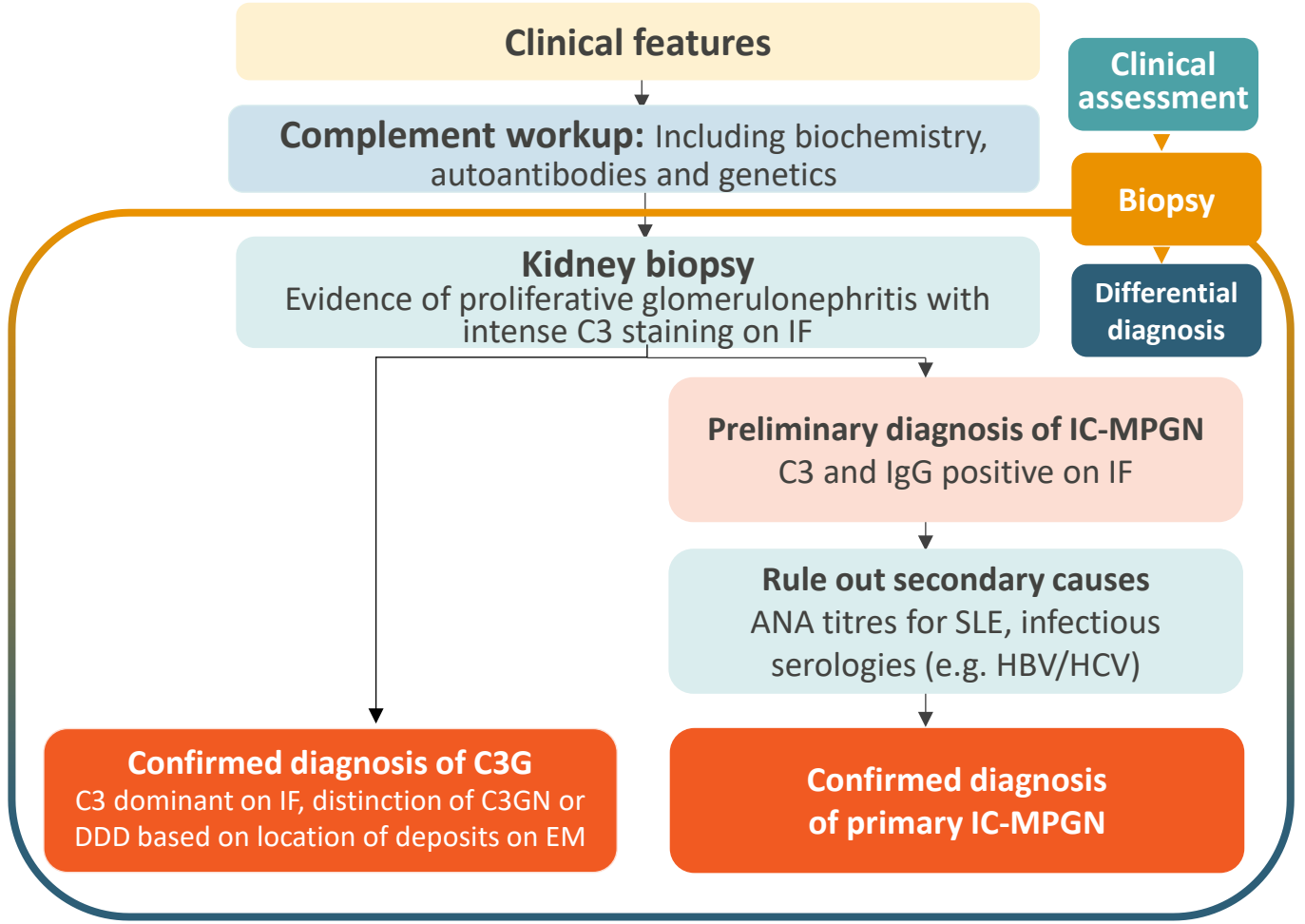
Accurate diagnosis of C3G/primary IC-MPGN relies on a multimodal approach, including definitive diagnosis via biopsy[1–5]

Early and accurate diagnosis is vital for timely management and longer kidney protection[4]

Biopsy is mandatory for diagnosis, with IF considered the gold standard[5]

Histological features overlap, therefore differential diagnosis via evaluation of history, clinical features and screening is key for better patient outcomes[5,6]

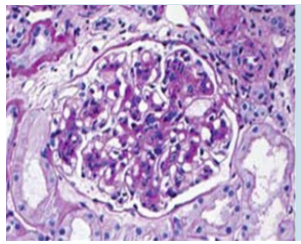
Example diagnostic pathway of C3G/primary IC-MPGN[1–3]



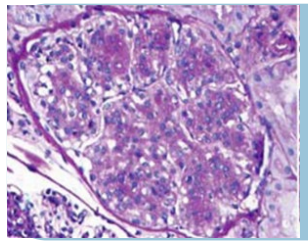
ANA, antinuclear antibody; C3, complement 3; C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; EM, electron microscopy; HBV; hepatitis B virus; HCV, hepatitis C virus; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IgG, immunoglobulin G; IF, immunofluorescence; SLE, systemic lupus erythematosus.

1. Vivarelli M, *et al. Pediatr Nephrol* 2021;37:521–35; 2. Noris M & Remuzzi G. *Nephrol Dial Transplant* 2024;2:202–14; 3. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int* 2021;100:S1–276; 4. Java A & Lindsey F. *Kidney Med* 2024;7:100928; 5. Abbas F, *et al. World J Transplant* 2018;8:203–19; 6. Bomback AS, et al. *KI reports* 2025;10:17–28.

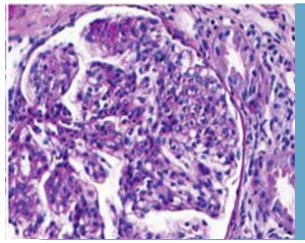
C3G and primary IC-MPGN present a spectrum of heterogeneous histological features[1–3]



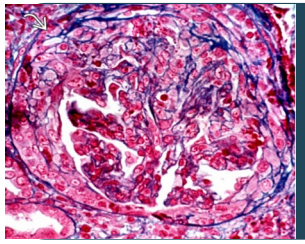
Mesangial proliferation 40%



Membrano-proliferative 50%



Endocapillary proliferation 7%



Extracapillary proliferation 3%

Proliferation ranges from **moderate** to **severe**[3]

Immunofluorescence is the **gold standard** for diagnosis[4]

Clinical assessment

Biopsy

Differential diagnosis

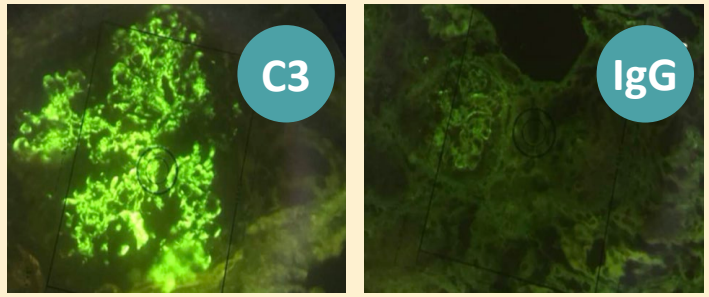
C3G, C3 glomerulopathy; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; MPGN, membranoproliferative glomerulonephritis.
Images and figures are taken from Dr. Diomedi's own research.

1. Hou J, et al. *Glomerular Dis* 2022;2:107–20; 2. Noris M & Remuzzi G. *Nephrol Dial Transplant* 2024;39:202–14; 3. Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43; 4. Abbas F, *et al. World J Transplant* 2018;8:203–19.

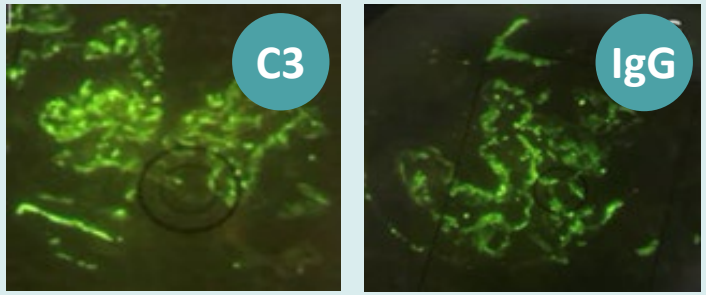
IF is the mainstay for diagnosing C3G and primary IC-MPGN but secondary causes must be excluded[1–3]

Clinical assessment
Biopsy
Differential diagnosis

C3 glomerulopathy (C3G)
No or few Igs | **C3 dominant***



C3/Ig deposits (IC-MPGN)
Ig positive | C3 co-dominant*



- PIGN
- Monoclonal gammopathies (> 50 years of age)[4]
- Infection-related glomerulopathies
- Autoimmune diseases

Main secondary MPGN causes to be excluded based on correlation between diagnostic findings and clinical history[1–3]

*C3 dominant: C3 is ≥2 orders of magnitude stronger than for any other common immune reactant.[5] . Images are taken from Mastrangelo A, *et al. Front Pediatr* 2020;8:205 with permission under CC by 4.0 license
C3G, C3 glomerulopathy; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis IF, immunofluorescence; PIGN, post-infectious glomerulonephritis.

1. Abbas F, *et al. World J Transplant* 2018;8:203–19; 2. Fervenza FC, *et al*. *Nephrol Dial Transplant* 2012;27:4288–94; 3. Noris M & Remuzzi G. *Nephrol Dial Transplant* 2024;39:202–14; 4. Smith RJH, *et al*. *Nat Rev Nephrol* 2019;15:129–43; 5. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int* 2021;100:S1–276.

C3GN vs DDD: the importance of EM

C3GN[1–3]

Mesangial C3 deposits, with variable **subendothelial** deposits

Less often, subepithelial and intramembranous deposits

DDD[1–3]

C3 deposition in the lamina densa of GBM of homogeneous, hyperosmiophilic material

Intramembranous deposits are confluent, elongated, and linear

- Mesangial deposits can also be seen
- Sometimes subepithelial deposits

DDD is associated with a worse prognosis than C3GN[1]

Images are redacted due to copyright restrictions.
C3, complement 3; C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; GN, glomerulonephritis; GBM, glomerular basement membrane; EM, electron microscopy.
Images from Barbour TD, *et al. Nephrol Dial Transplant* 2013;28:1685–93.
1. Barbour TD, *et al. Nephrol Dial Transplant* 2013;28:1685–93; 2. Ponticelli C, *et al. Front Med* 2023;10:1289812; 3. Hou J, *et al. Glomerular Dis* 2022;2:107–20.

Case study: a typical C3G case

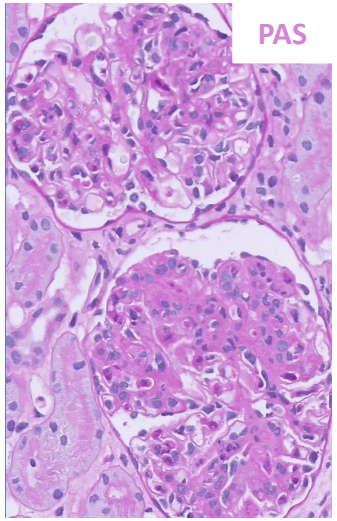
Clinical history:

- Microhaematuria
- Proteinuria (usually mild)
- Persistent low C3 (C4 usually normal)
- ± Hypertension
- ± CKD

Clinically: suspected C3G

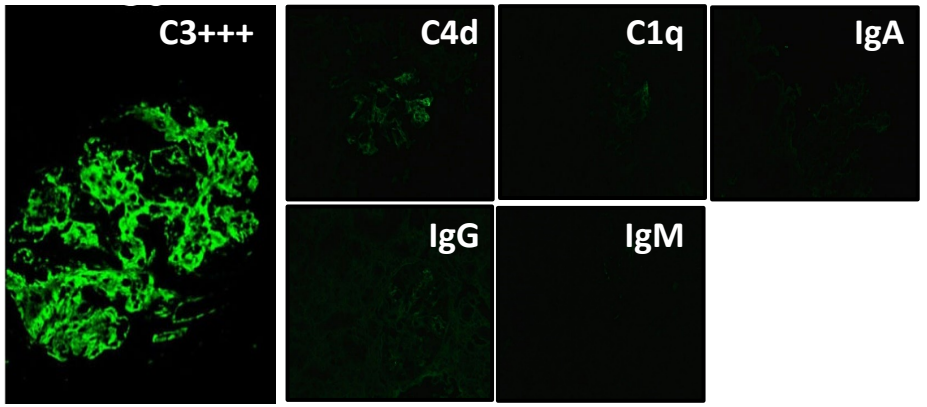
Biopsy results

Light microscopy



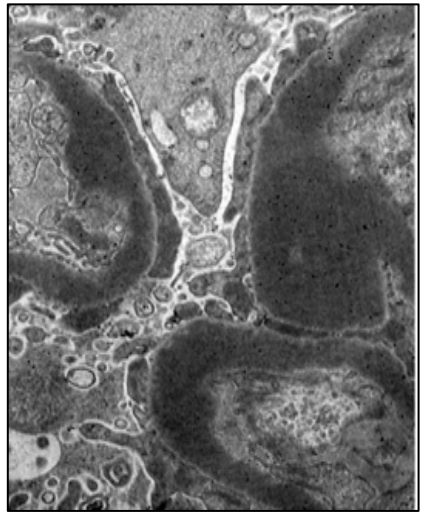
Glomerular proliferation

Immunofluorescence



C3-dominant staining by IF

Electron microscopy



Hyper-dense, ribbon-like, intramembranous deposits

DIAGNOSIS: C3G, DDD type

C1, complement 1; C3, complement 3; C3G, C3 glomerulopathy; C4, complement 4; CKD, chronic kidney disease; DDD, dense deposit disease; IF, immunofluorescence; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; PAS, Periodic-Acid-Schiff.
Based on a real patient case. Images are taken from Dr. Diomedi Camassei's own research.

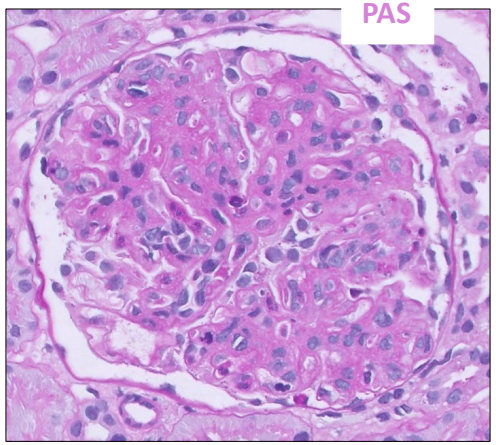
Case study: more suggestive of IC-MPGN

Clinical history:

- Microhaematuria
- Proteinuria (usually mild)
- Persistent low C3 (C4 can be low at presentation)
- ± Hypertension
- ± Chronic renal failure

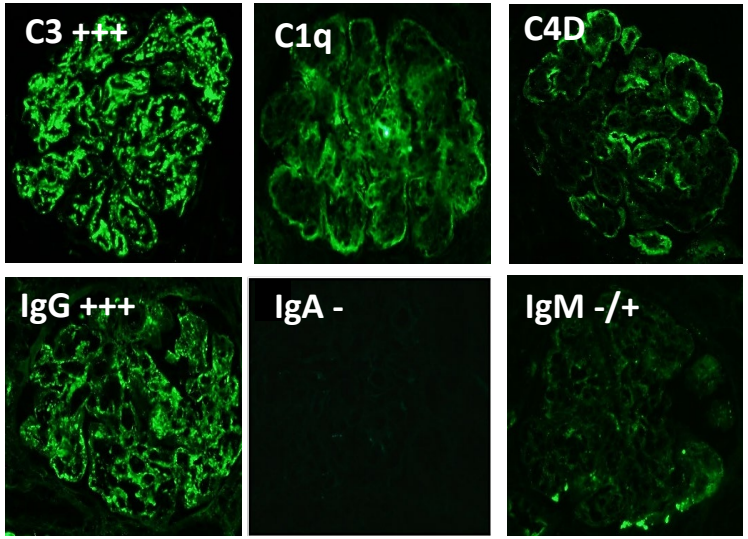
Biopsy results

Light microscopy



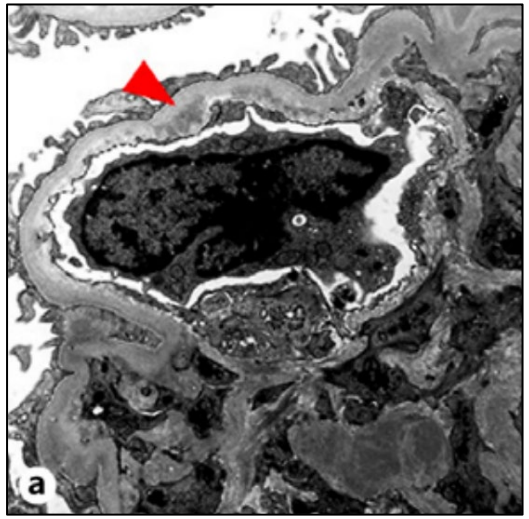
Membranoproliferative glomerulonephritis (MPGN)

Immunofluorescence



C3 and IgG codominant: classical pathway complement +

Electron microscopy



Sub-endothelial and mesangial deposits

DIAGNOSIS: suggested IC-MPGN

C1, complement 1; C3, complement 3; C3G, C3 glomerulopathy; C4, complement 4; DDD, dense deposit disease; IC-MPGN, IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IF, immunofluorescence; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; PAS, Periodic-Acid-Schiff.
Based on a real patient case. Images are taken from Dr. Diomedi Camassei's own research.

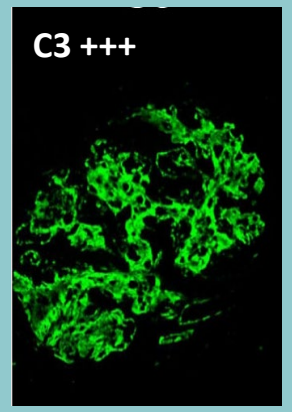
Case study: more suggestive of IC-MPGN

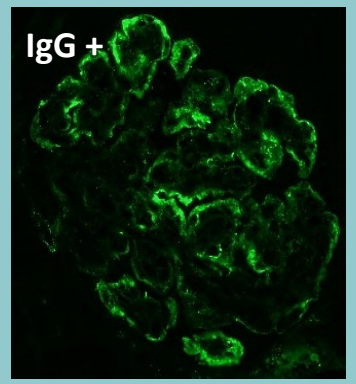
Clinical history:

- Microhaematuria
- Proteinuria (usually mild)
- Persistent low C3 (C4 can be low at presentation)
- ± Hypertension
- ± Chronic renal failure

Complement workup shows alternative pathway abnormalities:
C3NEF
High sC5b9

→ Second biopsy





C3G can start as primary IC-MPGN

DIAGNOSIS: C3G

C1, complement 1; C3, complement 3; C3G, C3 glomerulopathy; C4, complement 4; DDD, dense deposit disease; IC-MPGN, IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IF, immunofluorescence; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; PAS, Periodic-Acid-Schiff; NEF, nephritic factor; sC5b9, serum complement 5b9.
Based on a real patient case. Images are taken from Dr. Diomedi Camassei's own research.

Case study: a less typical C3G case

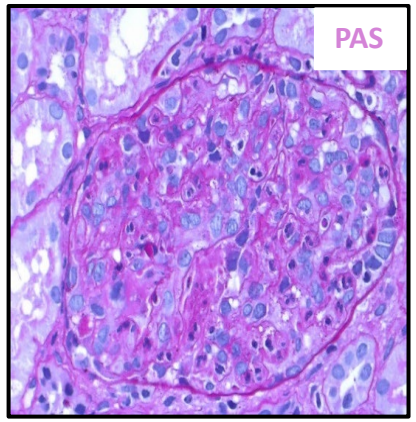
Clinical history:

- Previous infection
- Gross haematuria
- Peripheral oedema
- Acute renal failure
- Persistence of very low C3 (after 8 weeks)

Clinically: suspected C3G

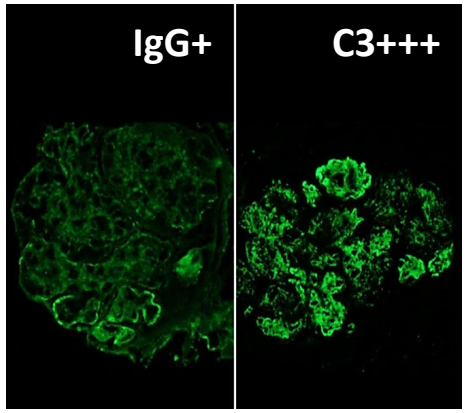
Biopsy results

Light microscopy



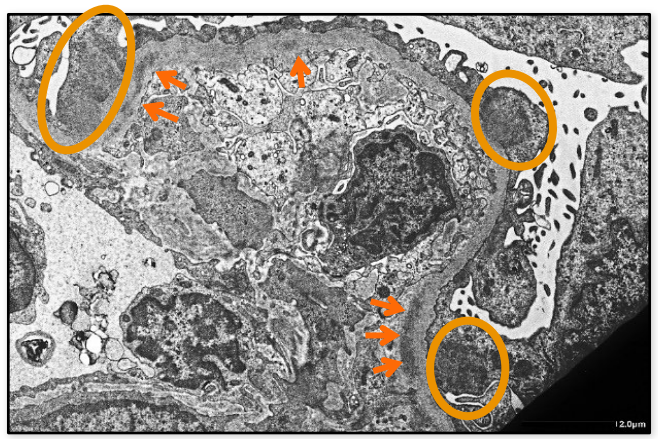
Diffuse endocapillary proliferation ("exudative GN")

Immunofluorescence



C3 dominant positivity

Electron microscopy



Many sub-epithelial deposits (humps)
Small sub-endothelial deposits

DIAGNOSIS: suggested PIGN with unusual features

C3, complement 3; C3G, C3 glomerulopathy; IgG, immunoglobulin G; PIGN, post-infectious glomerulonephritis.
Based on a real patient case. Images are taken from Dr. Diomedi Camassei's own research.

Case study: a less typical C3G case

Clinical history:

- Previous infection
- Gross haematuria
- Peripheral oedema
- Acute renal failure
- Persistence of very low C3 (after 8 weeks)

Clinically: suspected C3G

Biopsy results

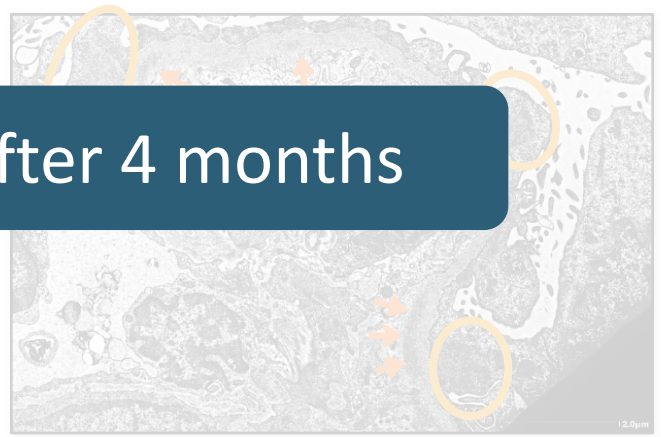
Light microscopy

Diffuse endocapillary proliferation ("exudative GN")

Immunofluorescence

C3 dominant positivity

Electron microscopy



Many sub-epithelial deposits (humps)
Small sub-endothelial deposits

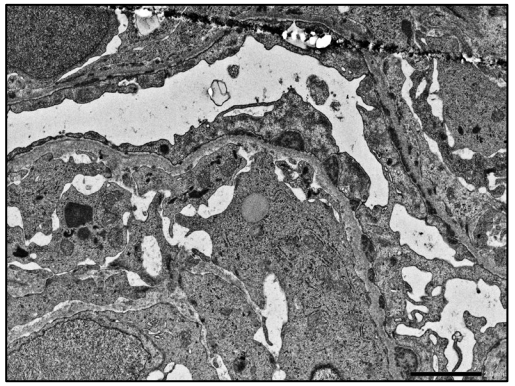
Patient had persistent low C3 after 4 months

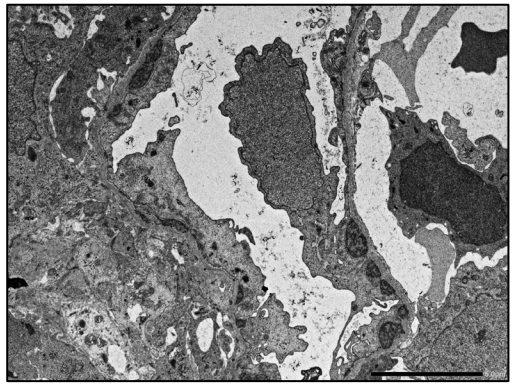
FINAL DIAGNOSIS: atypical post-infectious GN

C3, complement 3; C3G, C3 glomerulopathy; GN, glomerulonephritis; IgG, immunoglobulin G.
Based on a real patient case. Images are taken from Dr. Diomedi Camassei's own research.

LM and EM can support differentiation of PIGN from C3G/IC-MPGN

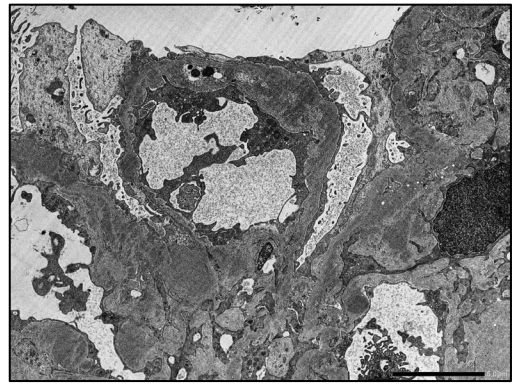
PIGN

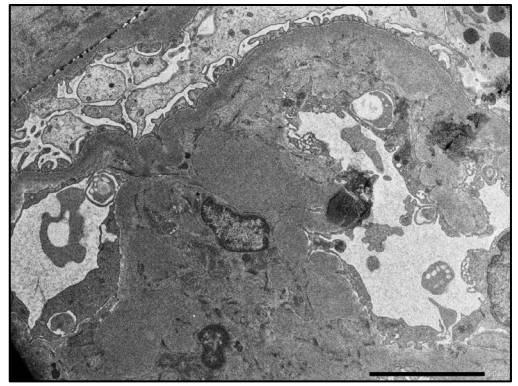




PIGN		C3G/ IC-MPGN
+++	Sub-epithelial humps	+/-
-	Subendothelial deposits	+++
Variable	Mesangial deposits	+++
+++	Endocapillary hypercellularity	Variable
-	Cellular interposition	++
-	GBM remodeling	++
+	Exudative GN	-

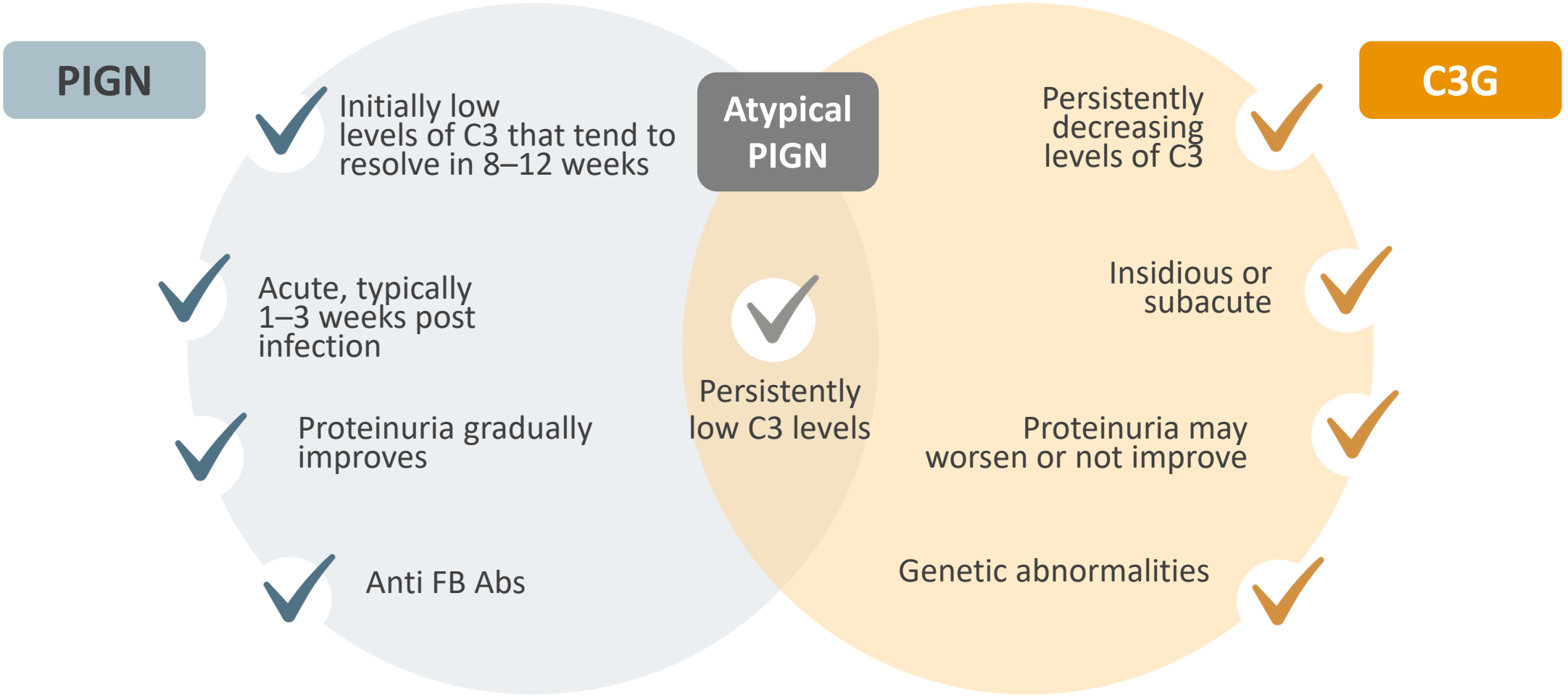
C3G/IC-MPGN





C3 glomerulopathy; EM, electron microscopy; GBM, glomerular basement membrane; GN, glomerulonephritis; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; LM, light microscopy; PIGN, post-infectious glomerulonephritis.
Images are taken from Dr. Diomedi Camassei's own research. Table is the expert opinion of Dr. Diomedi Camassei.

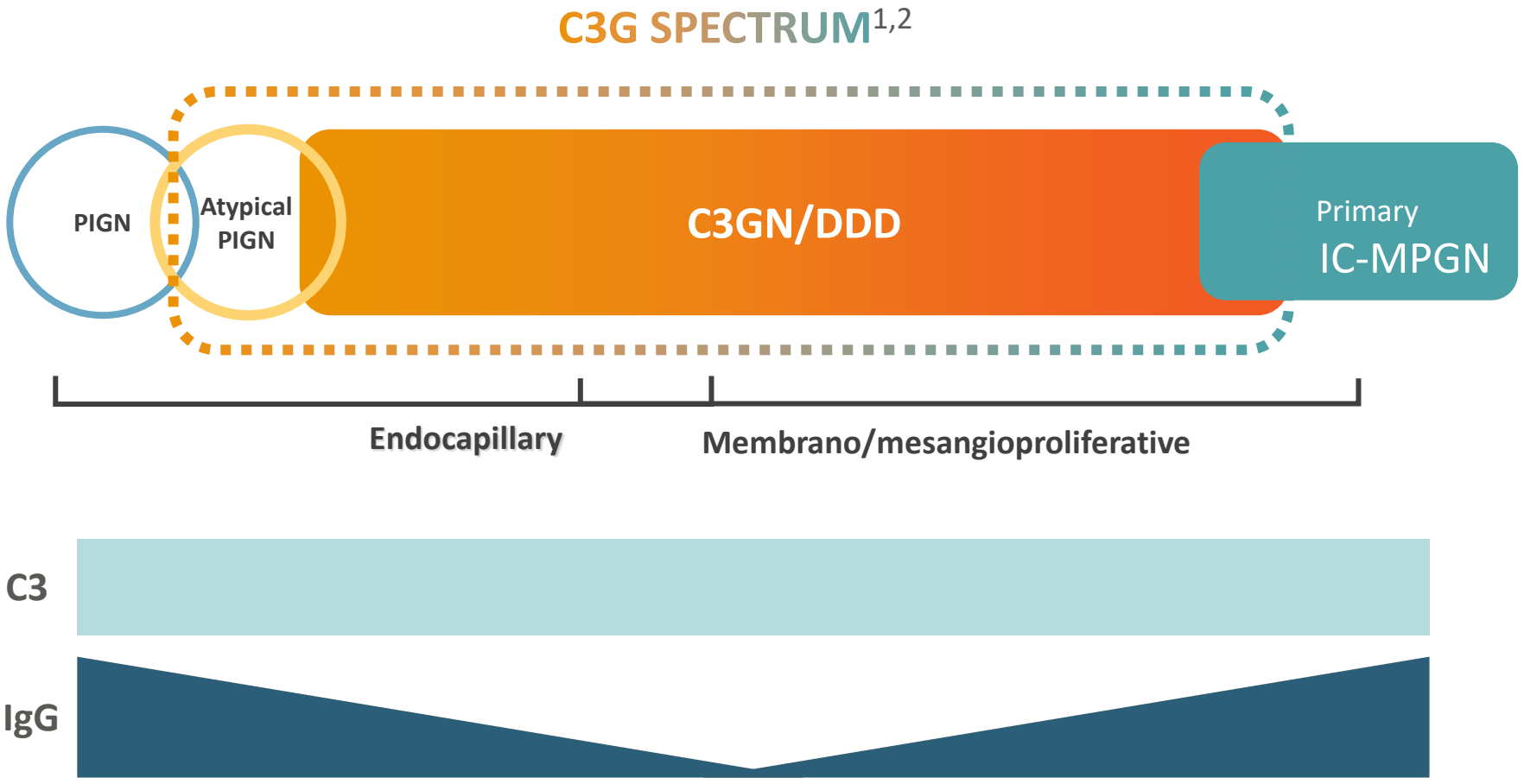
Differential diagnosis of C3G vs. PIGN requires a combination of histological and clinical findings[1–4]



Ab, antibody; C3, complement 3; C3G, C3 glomerulopathy; FB, Factor B; PIGN, post-infectious glomerulonephritis.

1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int* 2021;100:S1–S276; 2. Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43; Hou J, et al. *Glomerular Dis* 2022;2:107–20; 4. Expert opinion of Dr. Diomedi Camassei and Dr. Johnson.

C3G describes a spectrum of disorders that overlap in features



C3, complement 3; C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; CFHR, complement factor H related; DDD, dense deposit disease; GN, glomerulonephritis; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IgAN, immunoglobulin A nephropathy; PIGN, post-infectious glomerulonephritis.

1. Zipfel PF, *et al. Mol Immunol* 2015;67:21–30; 2. Hou J, et al. *Glomerular Dis* 2022;2:107–20.

Take home messages

Accurate diagnosis of C3G/primary IC-MPGN relies on **expert evaluation** of **histology**, **clinical features** and detailed **genetic** and **serological screening** for complement dysregulation[1–3]

Biopsy is mandatory for **diagnosis**, with IF considered the gold standard and EM needed to further define between C3GN and DDD[2,4]

Collaboration between **nephrologists** and **pathologists** is paramount for differential diagnosis, in order to assess **correlation** of **histological features** with **clinical course**[1]

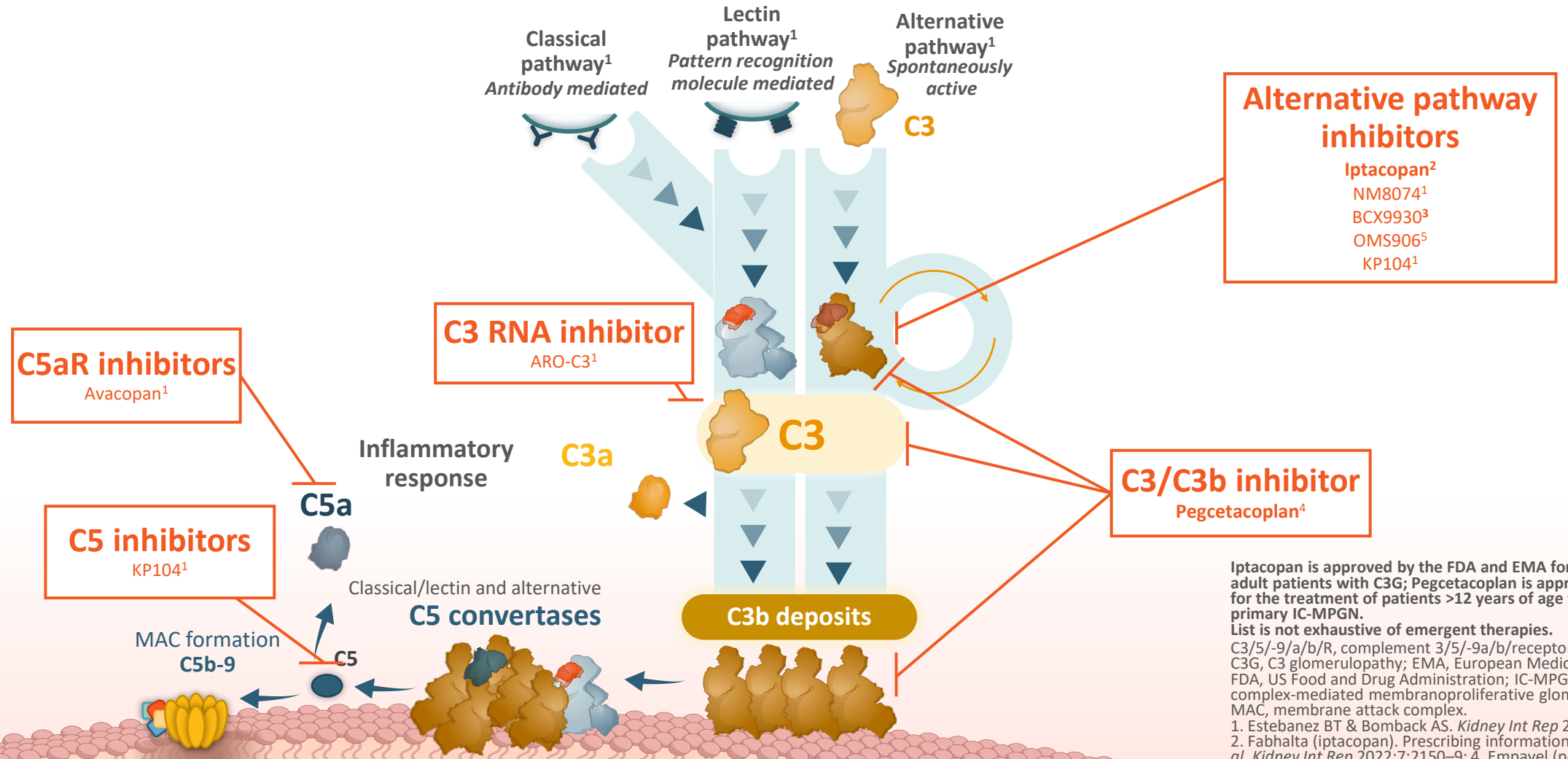
C3G, C3 glomerulopathy; DDD, dense deposit disease; EM, electron microscopy; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IF, immunofluorescence.

1. Java A & Lindsey F. *Kidney Med* 2024;7:100928; 2. Abbas F, *et al. World J Transplant* 2018;8:203–19; 3. Bomback AS, et al. *KI reports* 2025;10:17–28; 4. Hou J, *et al*. *Glomerular Dis* 2022;2:107–20.

Complement inhibition:

From bench to clinical trials

Emerging therapeutics for C3G and primary IC-MPGN target the complement pathway



Iptacopan is approved by the FDA and EMA for the treatment of adult patients with C3G; Pegcetacoplan is approved by the FDA for the treatment of patients >12 years of age with C3G or primary IC-MPGN.
List is not exhaustive of emergent therapies.

C3/5/-9/a/b/R, complement 3/5/-9a/b/receptor; C3G, C3 glomerulopathy; EMA, European Medicine Association; FDA, US Food and Drug Administration; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; MAC, membrane attack complex.

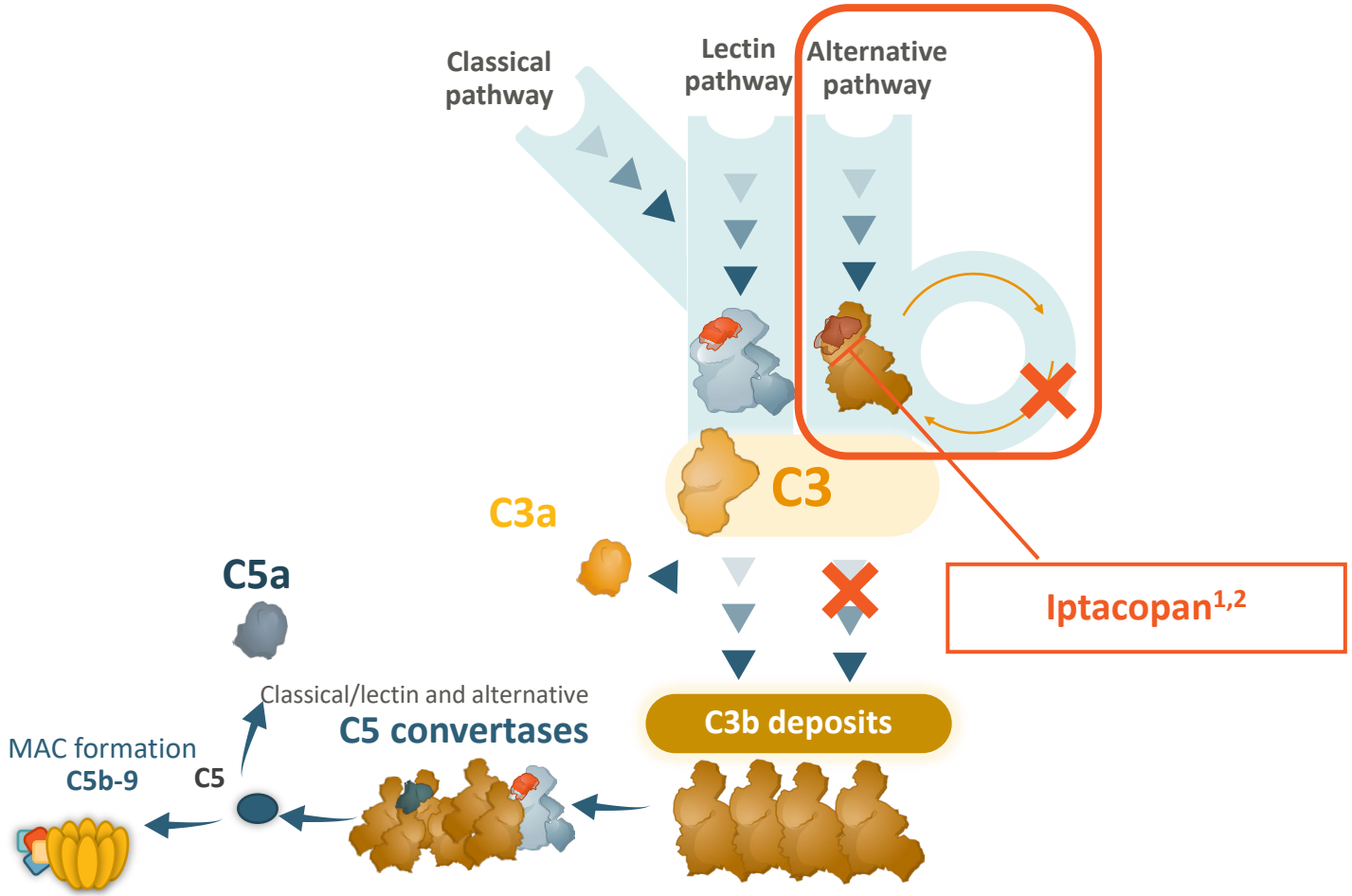
1. Estebanez BT & Bomback AS. *Kidney Int Rep* 2024;9:569–79; 2. Fabhalta (iptacopan). Prescribing information; 3. Bomback AS, *et al. Kidney Int Rep* 2022;7:2150–9; 4. Empavel (pegcetacoplan). Prescribing information; 5. Karnabeda O, *et al. Blood* 2023;142:573.

Iptacopan is a Factor B inhibitor approved for the treatment of adult patients with C3G

Iptacopan

A **small-molecule oral inhibitor of complement Factor B** component of the alternative convertase[1,2]

Approved for **adults with C3G**[3,4]
Currently under **Phase 3 investigation in adolescents with C3G and adults and adolescents with primary IC-MPGN** in the **APPEAR-C3G and APPARENT** trials, respectively[5,6]

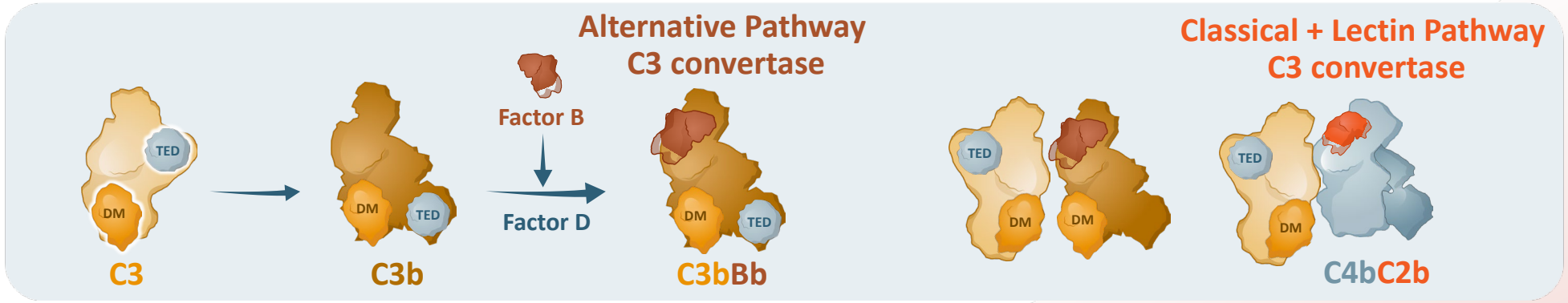


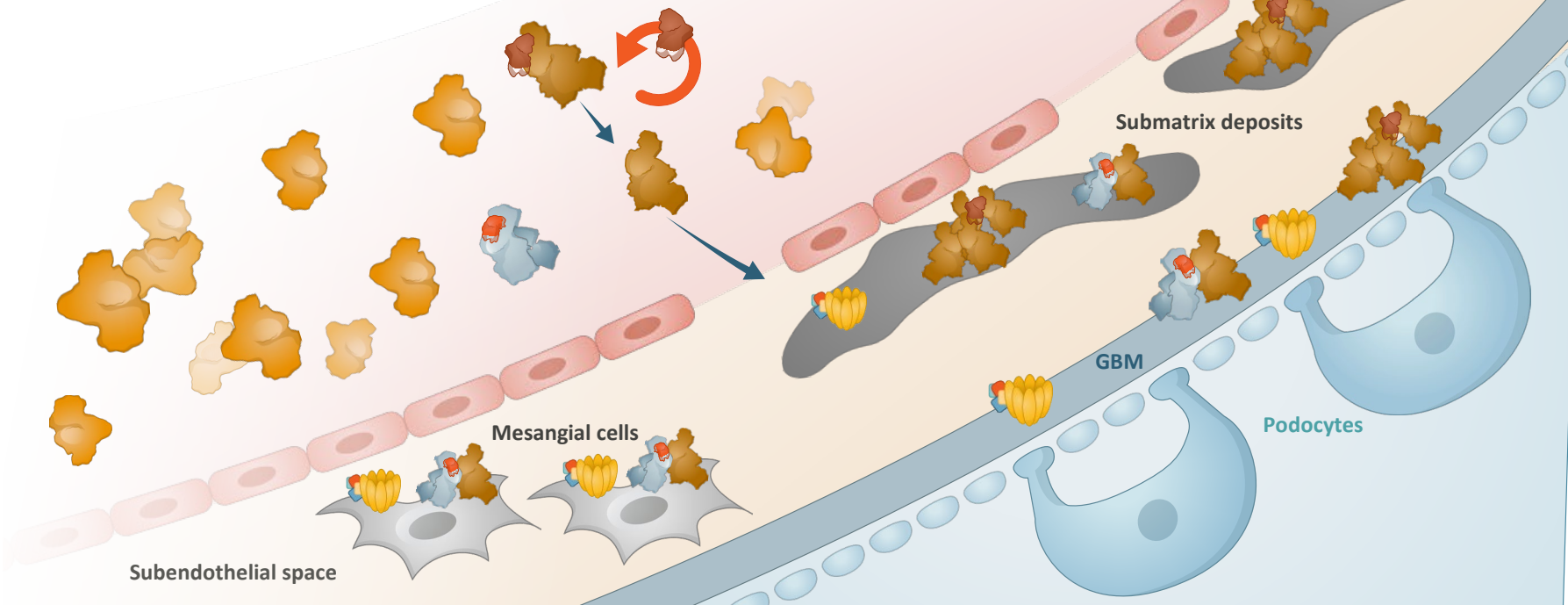
Iptacopan is approved by the FDA and EMA for the treatment of adult patients with C3G.

C3/3a/3b/5/5a/5b-9, complement 3/3a/3b/5/5a/5b-9; C3G, C3 glomerulopathy; EMA, European Medicine Association; FDA, US Food and Drug Administration; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; MAC, membrane attack complex. 1. Veldandi UK, *et al*. Presented at WCN 2023 (Poster WCN23-0584); 2. Bomback AS, *et al. Kidney Int Rep* 2022;7:2150–9; 3. FDA. 2025. Available at: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-adults-complement-3-glomerulopathy-rare-kidney-disease-reduce. Accessed October 2025; 4. EMA. 2024. Available at: https://www.ema.europa.eu/en/documents/procedural-steps-after/fabhalta-epar-procedural-steps-taken-scientific-information-after-authorisation-archive_en.pdf. Accessed October 2025; 5. ClinicalTrials.gov identifier: NCT05755386. Last update posted 6 August 2025. Accessed 7 October 2025; 6. ClinicalTrials.gov identifier: NCT04817618. Last update posted 4 March 2025. Accessed 7 October 2025.

Pegcetacoplan

Pegcetacoplan blocks C3 activation by all complement pathways[1,2]



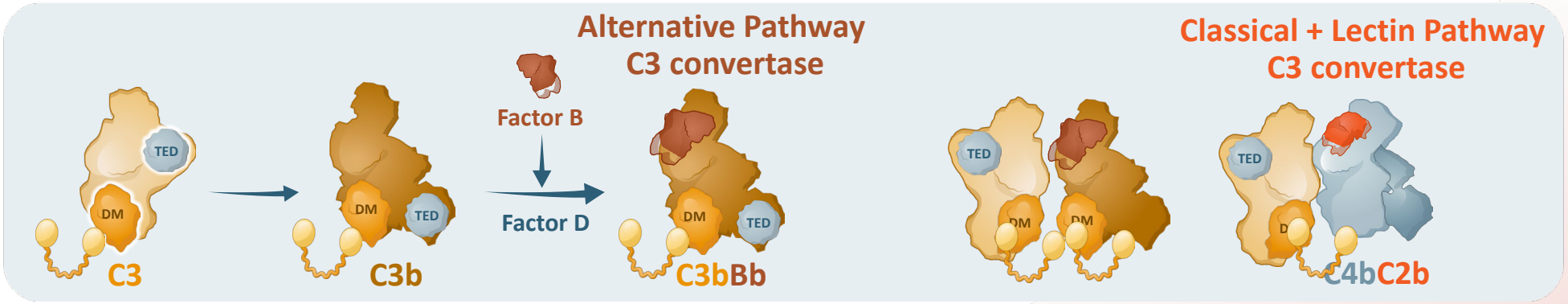


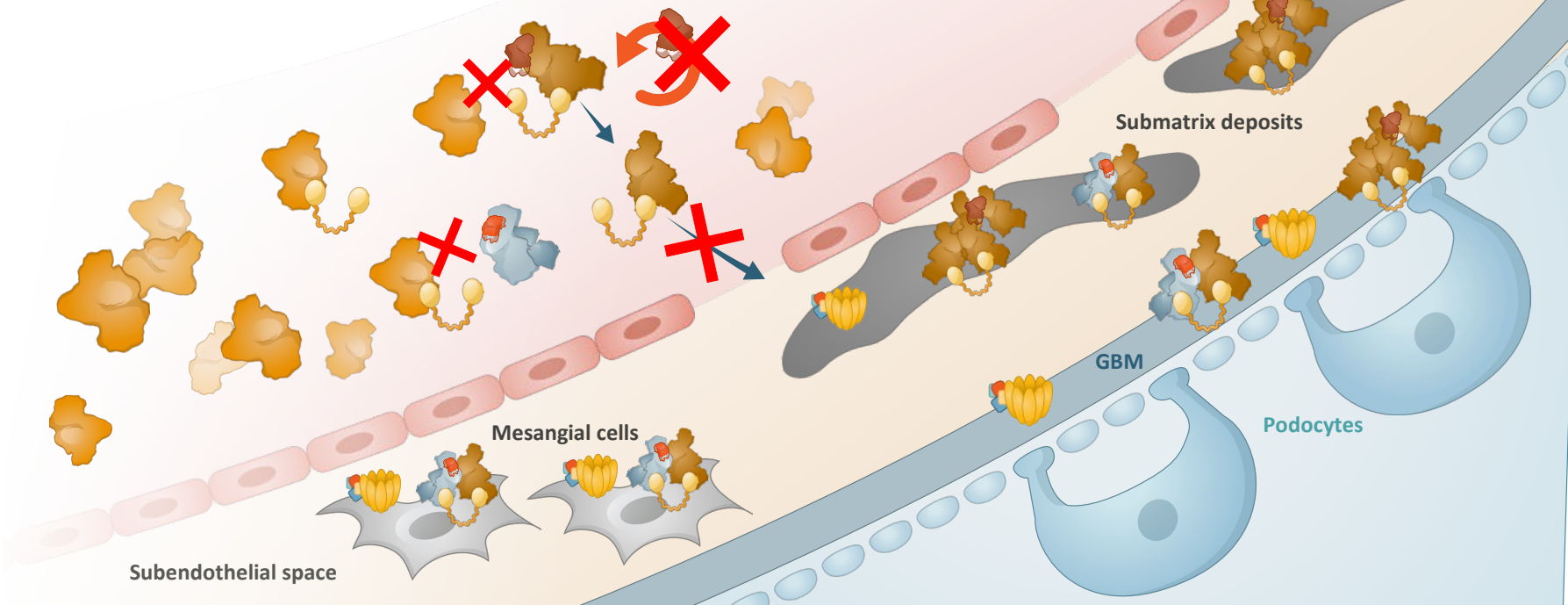
Pegcetacoplan is approved by the FDA for the treatment of C3G and primary IC-MPGN patients aged 12 years and older. Pegcetacoplan has not been reviewed or approved for these indications by the EMA or other regulatory authorities outside US.

C2/3/4/5/b, complement 2/3/4/5/b; C3G, C3 glomerulopathy; CP, classical pathway; DM, dimerization; GBM, glomerular basement membrane; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; TED, thioester domain.

1. Kolev M, *et al. Immunol Rev* 2023;313:358–75;
2. Nester CM, *et al.* Presented at American Society Nephrology 2024 (Oral SA-OR92).

Pegcetacoplan blocks C3 activation by all complement pathways[1,2]



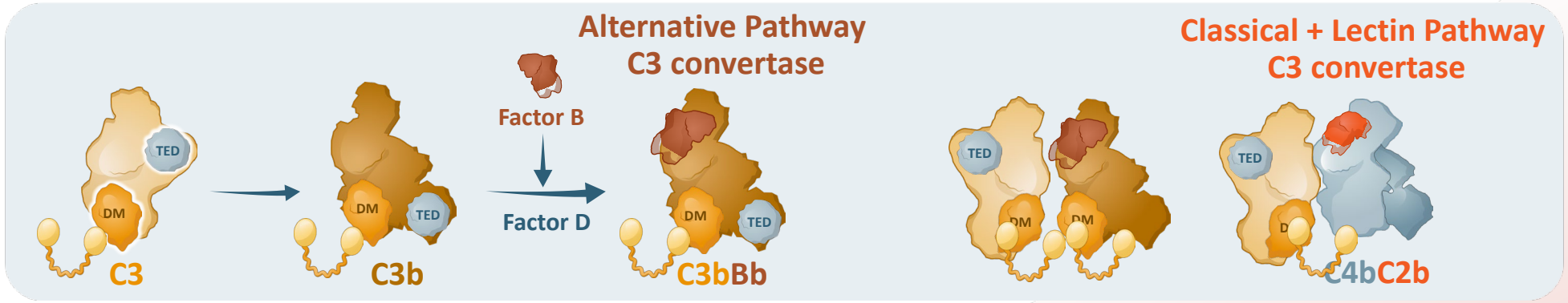


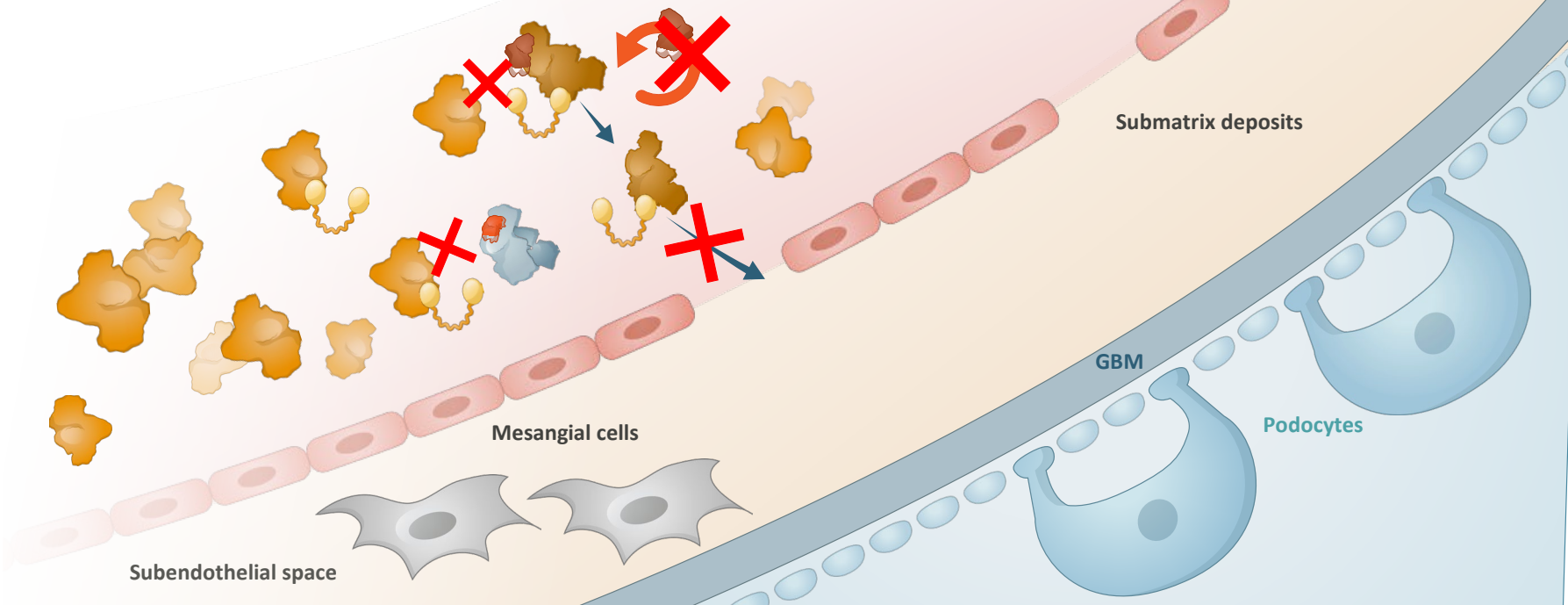
Pegcetacoplan is approved by the FDA for the treatment of C3G and primary IC-MPGN patients aged 12 years and older. Pegcetacoplan has not been reviewed or approved for these indications by the EMA or other regulatory authorities outside US.

C2/3/4/5/b, complement 2/3/4/5/b; C3G, C3 glomerulopathy; CP, classical pathway; DM, dimerization; GBM, glomerular basement membrane; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; TED, thioester domain.

1. Kolev M, *et al. Immunol Rev* 2023;313:358–75;
2. Nester CM, *et al.* Presented at American Society Nephrology 2024 (Oral SA-OR92).

Pegcetacoplan blocks C3 activation by all complement pathways[1,2]





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1. Kolev M, *et al. Immunol Rev* 2023;313:358–75;
2. Nester CM, *et al.* Presented at American Society Nephrology 2024 (Oral SA-OR92).

Pegcetacoplan is currently under investigation in a **broad population of patients** with C3G or primary IC-MPGN

Across ongoing clinical trials, >145 patients with C3G or primary IC-MPGN have received pegcetacoplan[1–8]

Phase 2		Phase 3	
DISCOVERY[1,2]	**NOBLE[3,4]**	**VALIANT[5,6]**	**VALE[7,8]**
8 patients (C3G)	13 patients	124 patients	All patients in VALIANT
≥16 years old	≥18 years old	≥12 years old	≥12 years old
Native kidneys	Transplanted kidneys	Native/transplanted kidneys	Native/transplanted kidneys
Open-label	Open-label	Placebo controlled	Open-label extension
NCT03453619	NCT04572854	NCT05067127	NCT05809531

ONGOING

Significant reduction in proteinuria and stabilised eGFR[2]

67% of pegcetacoplan-treated patients achieved zero C3 staining[9]

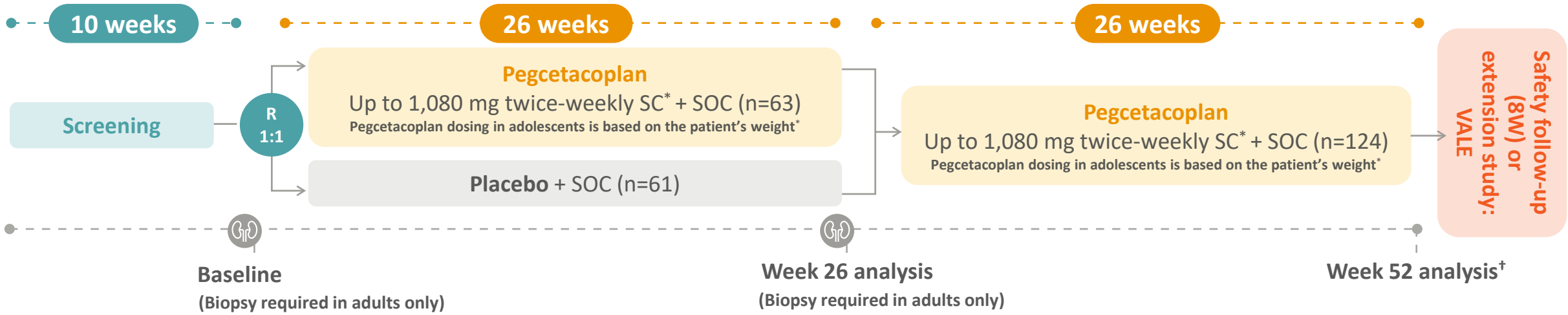
Pegcetacoplan is approved by the FDA for the treatment of C3G and primary IC-MPGN patients aged 12 years and older. Pegcetacoplan has not been reviewed or approved for these indications by the EMA or other regulatory authorities outside US.

C3/3c, complement 3/3c; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; US, United States.

1. Apellis Pharmaceuticals, Inc. Clinicaltrials.gov identifier: NCT03453619. Last update posted 13 February 2025. Accessed October 2025; 2. Dixon B, *et al. Kidney Int Rep* 2023;8:2284–93; 3. Apellis Pharmaceuticals, Inc. Clinicaltrials.gov identifier: NCT04572854. Last update posted 30 March 2025. Accessed October 2025; 4. Bomback AS, *et al. Kidney Int Rep* 2024;10:87–98; 5. Apellis Pharmaceuticals, Inc. Clinicaltrials.gov identifier: NCT05067127. Last update posted 8 June 2025. Accessed October 2025; 6. Nester CM, et al. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92); 7. Apellis Pharmaceuticals, Inc. Clinicaltrials.gov identifier: NCT05809531. Last update posted 28 March 2025. Accessed October 2025; 8. Nester C, *et al.* Presented at American Society of Nephrology Kidney Week 2024 (Poster SA-PO801); 9. Fakhouri F, *et al.* Presented at European Renal Association 2024 (Oral).

VALIANT: Phase 3 double-blind placebo-controlled trial in ≥12 year old, native/recurrent C3G/primary IC-MPGN[1–3]

Study design[1–3]



Study endpoints

Primary endpoint:
Change from baseline in log-transformed ratio of UPCR at Week 26 compared to placebo

Key secondary endpoints:
In all patients: composite renal endpoint;‡ ≥50% UPCR reduction; eGFR (all change from baseline to Week 26);
In adults: C3G activity score; reduction in C3 staining

Pegcetacoplan is approved by the FDA for the treatment of C3G and primary IC-MPGN patients aged 12 years and older. Pegcetacoplan has not been reviewed or approved for these indications by the EMA or other regulatory authorities outside US.

*All adults and adolescents weighing ≥50 kg self administered 1,080 mg/20 mL. Adolescent patients weighing 30–34 kg received 540 mg/10 mL for the first two 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. †The Week 52 biopsy was optional; ‡≤15% reduction in eGFR and ≥50% UPCR reduction vs BL.

C3, complement 3; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; R, randomised; SC, subcutaneous; SOC, standard of care; UPCR, urine protein-to-creatinine ratio; US, United States; W, week.

1. Dixon BP, *et al*. Presented at ASN 2023 (Abstract INFO12-SA); 2. Apellis Pharmaceuticals, Inc. ClinicalTrials.gov identifier: NCT05067127. Last updated 8 June 2025. Accessed October 2025;
3. Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

VALIANT: inclusion criteria and prespecified subgroups

Key inclusion criteria[1,2]

- **≥12 years of age** (weighing ≥30 kg)
- A **confirmed histological diagnosis** of C3G or primary IC-MPGN*
- **Proteinuria ≥1 g/day** and **eGFR ≥30 mL/min/1.73 m²**
- **Stable treatment regimen** for C3G/primary IC-MPGN

Prespecified subgroups[1–4]

- **Adults n=69**
- **Adolescents n=55**
- **C3G**
- **IC-MPGN**
- **Native kidney**
- **Transplanted**
- **IS-treated**
- **Non-IS treated**
- **≥3 g/g UPCR**

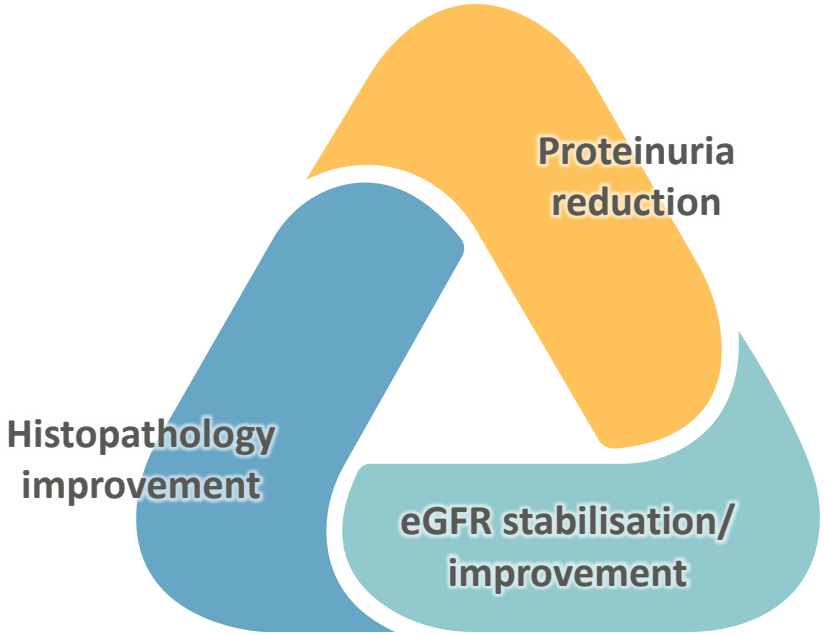
Pegcetacoplan is approved by the FDA for the treatment of C3G and primary IC-MPGN patients aged 12 years and older. Pegcetacoplan has not been reviewed or approved for these indications by the EMA or other regulatory authorities outside US.

*With or without previous renal transplant. C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IS, immunosuppression; UPCR, urine protein-to-creatine ratio; US, United States.

1. Apellis Pharmaceuticals, Inc. Clinicaltrials.gov identifier: NCT05067127. 8 June 2025. Accessed October 2025; 2. Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92); 3. Vivarelli M, *et al.* Presented at European Renal Association 2025; 4. Kavanagh D, *et al.* Presented at European Renal Association 2025.

In VALIANT, pegcetacoplan lowered proteinuria, stabilised eGFR and halted C3 deposition cross a diverse patient population

At Week 26:



Primary endpoint met

68% reduction in proteinuria vs placebo

51% of patients achieved **<1 g/g proteinuria**

+6.3 **mL/min/1.73 m²** difference in eGFR vs placebo

71.4% of adult pegcetacoplan-treated patients had no C3 deposits after treatment

Pegcetacoplan was well tolerated: frequency/severity of AEs was similar between arms and there were no encapsulated meningococcal infection cases*

Pegcetacoplan is approved by the FDA for the treatment of C3G and primary IC-MPGN patients aged 12 years and older. Pegcetacoplan has not been reviewed or approved for these indications by the EMA or other regulatory authorities outside US.
*Among the 4 reported serious infections (PEG: n=3; PBO: n=1).
C3, complement 3; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; PBO, placebo; TEAE, treatment-emergent adverse event; US, United States.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

In VALIANT, results were consistent regardless of age, disease type, severity, status and concomitant medication

Week 26	1 Histopathology **improvement** complete absence of C3 staining:	2 **Proteinuria reduction** vs placebo:	3 **eGFR stabilisation** vs placebo:
Overall population*,[1]	**71.4%** of patients	**68.1%** reduction	**stabilisation** +6.3 mL/min/1.73 m^2
Adolescents[2] N=55	**N/A***	**74.5%** reduction	**stabilisation** +9.7 mL/min/1.73 m^2
Post-transplant patients†,[3]	**100%** of patients	**64.9%** reduction	**stabilisation** +9.3 mL/min/1.73 m^2
Nephrotic range UPCR ≥3 g/g[4]	**84.6%** of patients	**72.1%** reduction	**stabilisation** +16.2 mL/min/1.73 m^2
Concomitant immunosuppression[5]	**65.4%** of patients	**70.3%** reduction	**stabilisation** +6.8 mL/min/1.73 m^2

Pegcetacoplan is approved by the FDA for the treatment of C3G and primary IC-MPGN patients aged 12 years and older. Pegcetacoplan has not been reviewed or approved for these indications by the EMA or other regulatory authorities outside US. *Adolescents made up 44% (n/N=55/124) of the total population; †One patient out of nine who underwent transplant was an adolescent.
C3, complement 3; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; UPCR, urine protein-to-creatine ratio; US, United States.
1. Nester CM, *et al*. Presented at American Society Nephrology 2024 (Oral SA-OR92); 2. Mastrangelo A, *et al*. Presented at European Renal Association 2025; 3. Oosterveld MJS, *et al*. Presented at European Renal Association 2025; 4. Vivarelli M, *et al*. Presented at European Renal Association 2025; 5. Kavanagh D, *et al*. Presented at European Renal Association 2025.

VALIANT: adolescent cohort results

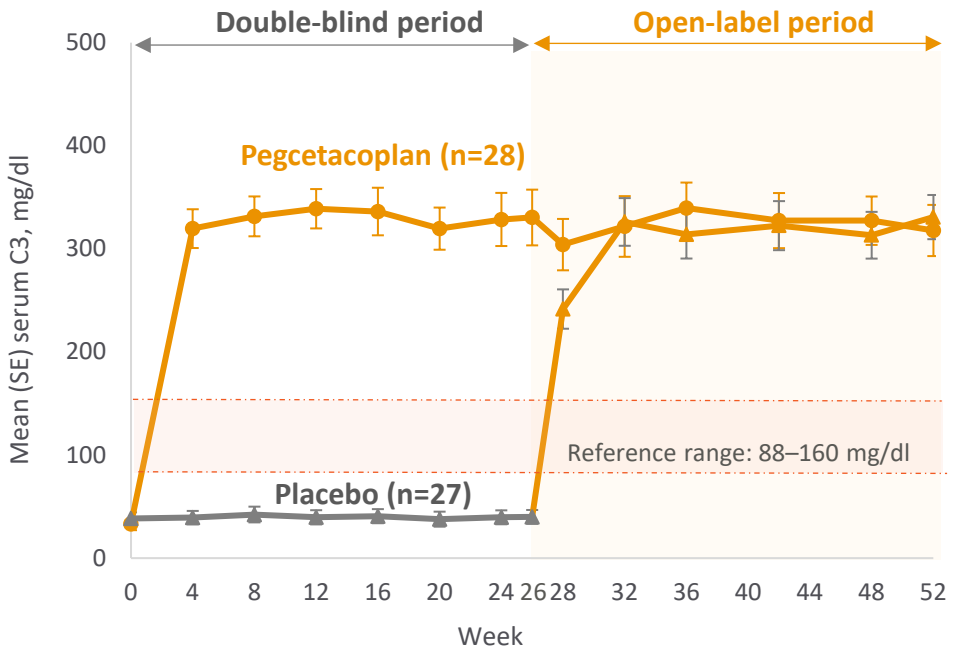
VALIANT: complement biomarkers restored after **pegcetacoplan treatment**

Change in serum complement biomarkers[1]

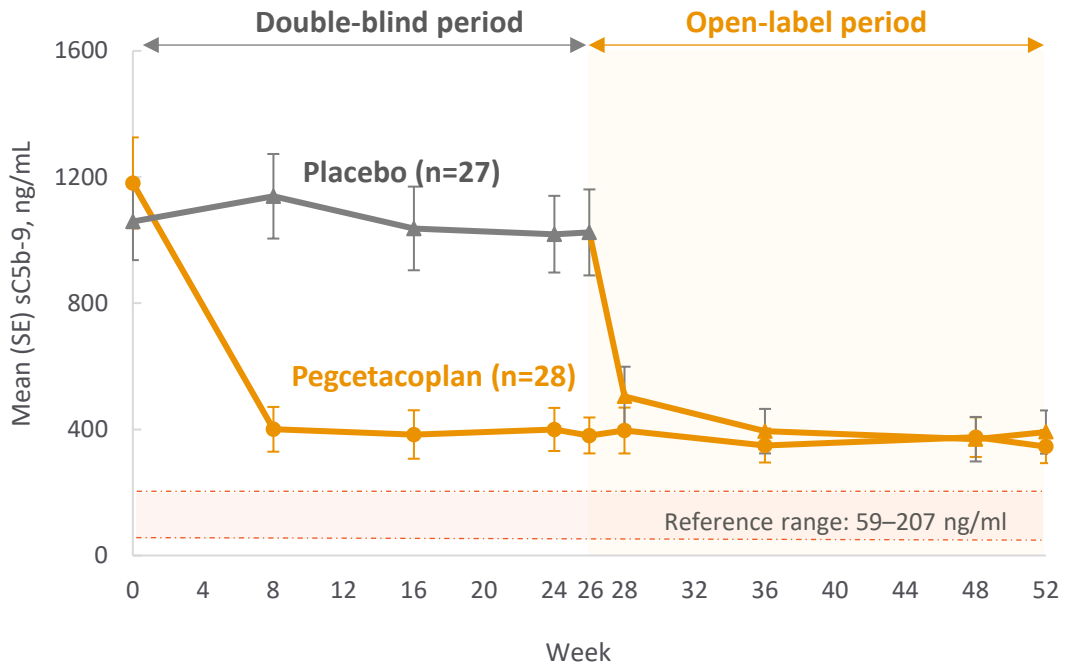
At week 52: 52/55*

Pegcetacoplan-treated patients achieved **C3 levels higher than the normal range†**

Change in serum C3 levels



Change in serum sC5b-9 levels



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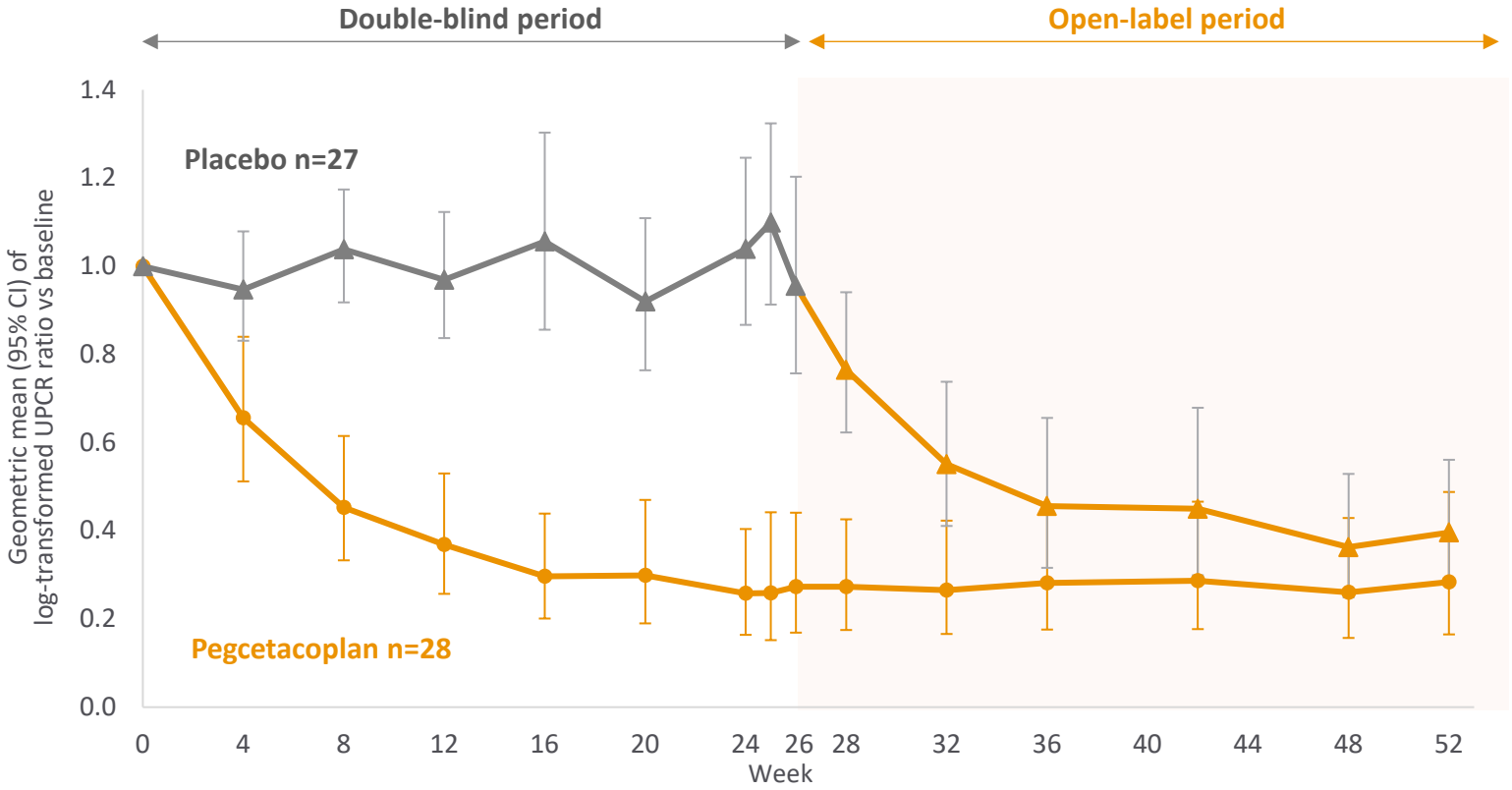
Pegcetacoplan has not been reviewed or approved for these indications by the EMA or other regulatory authorities outside US.

*One patient discontinued during the double-blind placebo-controlled period; two patients in the placebo arm discontinued during the double-blind placebo-controlled period. †Not all patients had low levels of sC3 at baseline.
C3/5/9/b, complement 3; C3G, C3 glomerulopathy; EMA, European Medicines Association; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; FDA, US Food and Drug Administration; SE, standard error; US, United States.

van de Kar, *et al.* Presented at European Society for Paediatric Nephrology annual meeting 2025.

In VALIANT, rapid **proteinuria reduction** was **sustained** across 52 weeks in adolescent patients

Change in proteinuria over 52 weeks



Pegcetacoplan-pegcetacoplan
Mean change from baseline at Week 52

-71.6%

-60.4%
placebo-pegcetacoplan

Placebo group achieved similar reduction in proteinuria when switching to pegcetacoplan

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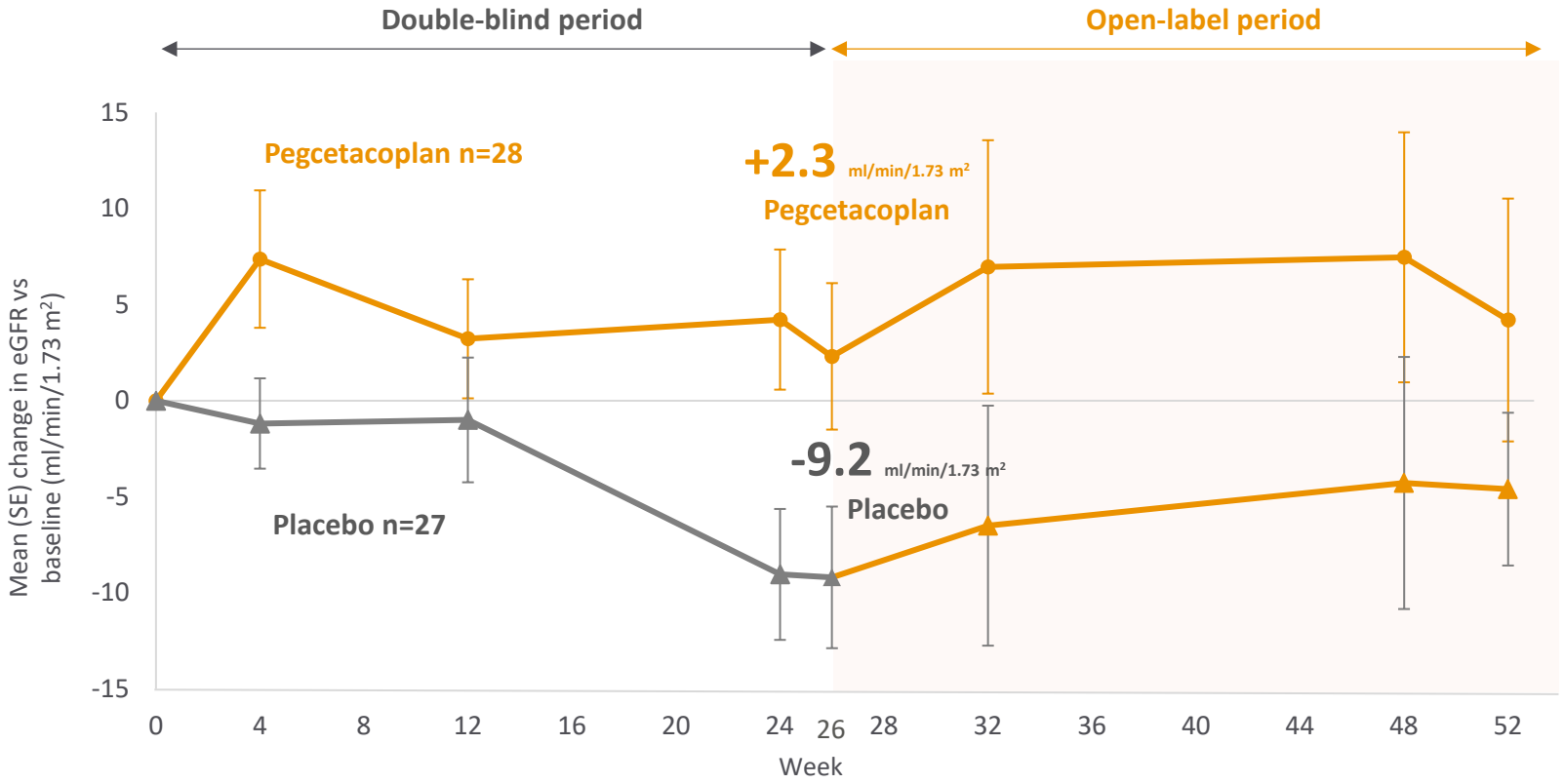
C3G, C3 glomerulopathy; CI, confidence interval; EMA, European Medicines Association; FDA, US Food and Drug Administration; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; PEG, pegcetacoplan; UPCR, urine protein-to-creatinine ratio; US, United States.
van de Kar, *et al.* Presented at European Society for Paediatric Nephrology annual meeting 2025.

In VALIANT, **eGFR stabilised after pegcetacoplan treatment** in adolescents

Change in eGFR over 52 weeks



Pegcetacoplan-pegcetacoplan
Mean change from baseline at Week 52

+4.2 mL/min/1.73 m²

-4.6 mL/min/1.73 m²

placebo-pegcetacoplan

Patients in the placebo group stabilised in eGFR when switching to pegcetacoplan

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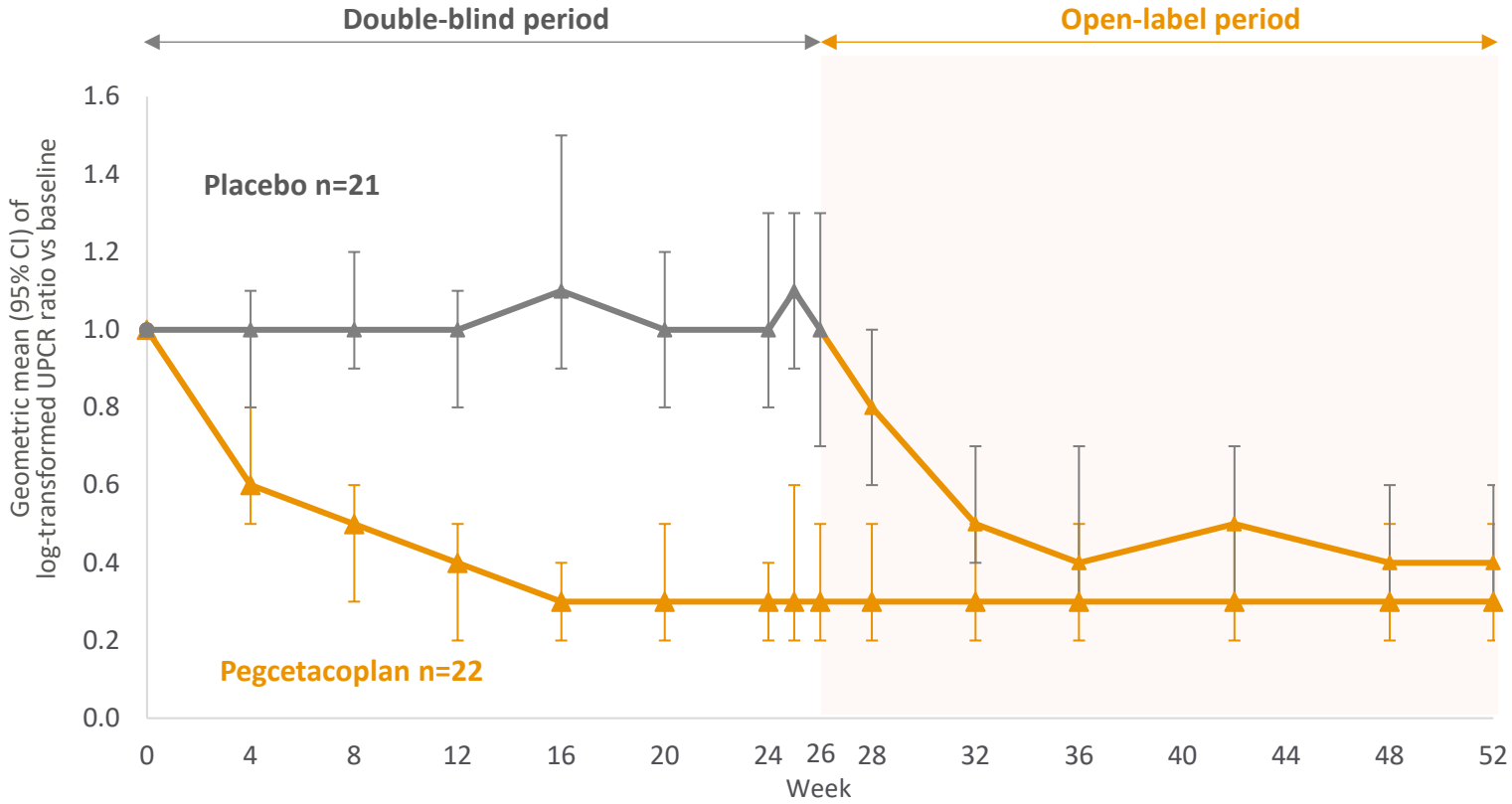
C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; EMA, European Medicines Association; US FDA, Food and Drug Administration; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; PEG, pegcetacoplan; SE, standard error.
van de Kar, *et al.* Presented at European Society for Paediatric Nephrology annual meeting 2025

VALIANT: adolescent patients + concomitant IS subgroup analysis

IS, immunosuppressant use.

In VALIANT, proteinuria reduction in patients with concomitant immunosuppression was consistent with the overall group

Change in proteinuria in patients with concomitant IS over 52 weeks



IS-pegcetacoplan-pegcetacoplan
Mean change from baseline at Week 52

-71.0%

-57.2%
IS-placebo-pegcetacoplan

Patients in the placebo arm experienced proteinuria reduction when switching to pegcetacoplan

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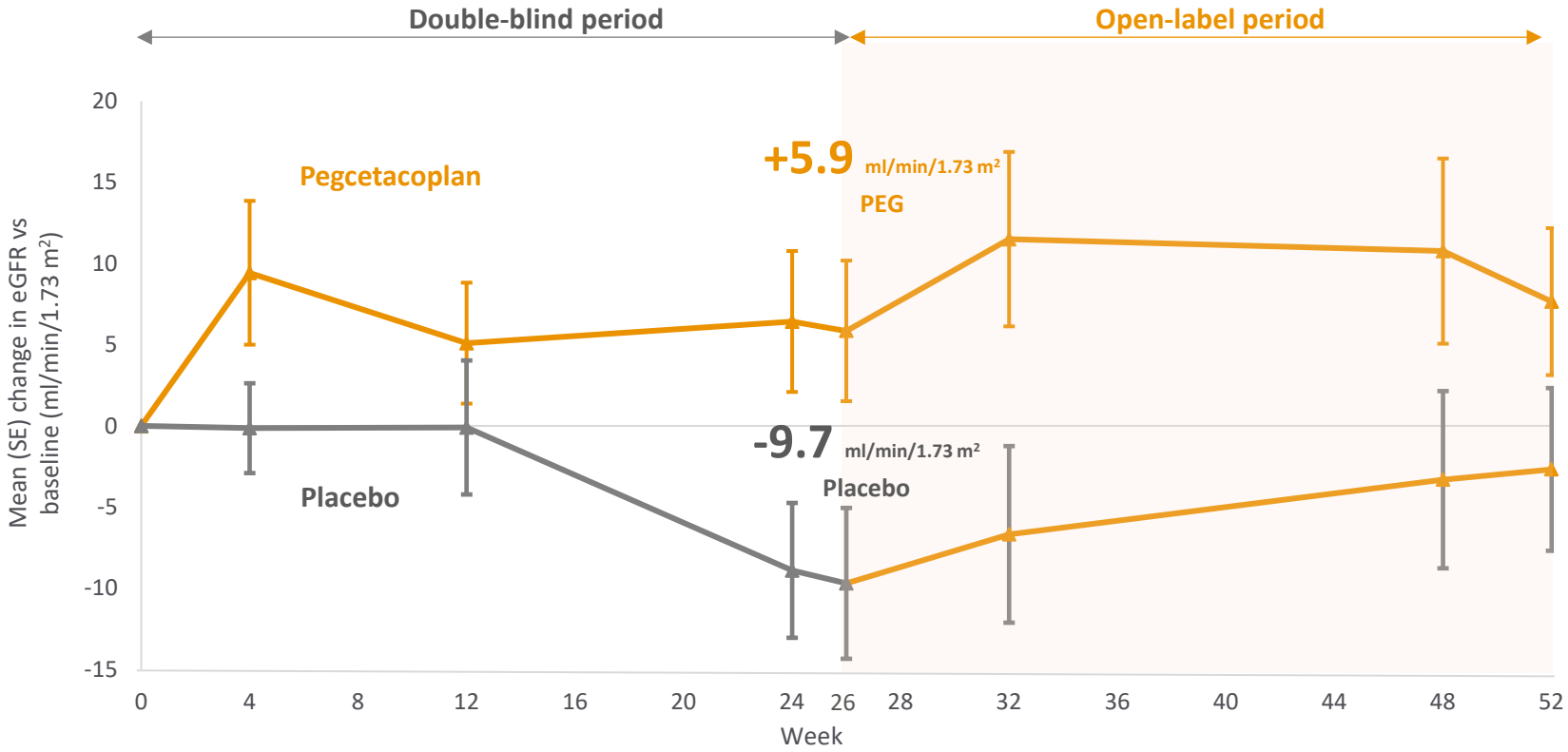
C3G, C3 glomerulopathy; CI, confidence interval; EMA, European Medicines Association; FDA, US Food and Drug Administration; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IS, immunosupressants and/or corticosteroids; PEG, pegcetacoplan; UPCR, urine protein-to-creatinine ratio; US, United States.
van de Kar, *et al.* Presented at European Society for Paediatric Nephrology annual meeting 2025.

In VALIANT, **eGFR improved after pegcetacoplan treatment** in patients receiving **concomitant immunosuppression**

Change in eGFR in patients with concomitant IS over 52 weeks



IS-pegcetacoplan-pegcetacoplan
Mean change from baseline at Week 52

+7.7 mL/min/1.73 m²

-2.7 mL/min/1.73 m²

IS-placebo-pegcetacoplan

Patients in the placebo arm had a mean improvement of 7 units after switching to pegcetacoplan

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IS, immunosuppressants and/or corticosteroids; PEG, pegcetacoplan; SE, standard error; US, United States.
van de Kar, *et al.* Presented at European Society for Paediatric Nephrology annual meeting 2025.

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

Event, n (%)	Adolescent patients (n=53)
Any treatment emergent adverse events	**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)**

Pegcetacoplan was well tolerated:

TEAE frequency/severity was similar between arms and there were no encapsulated meningococcal infection cases

1 serious TEAE (pyrexia) was considered related to treatment

There were 2 TEAEs leading to treatment withdrawal:

- Infusion site reaction, possibly-related
- Kidney failure considered non-related by the investigator. This patient also discontinued the study

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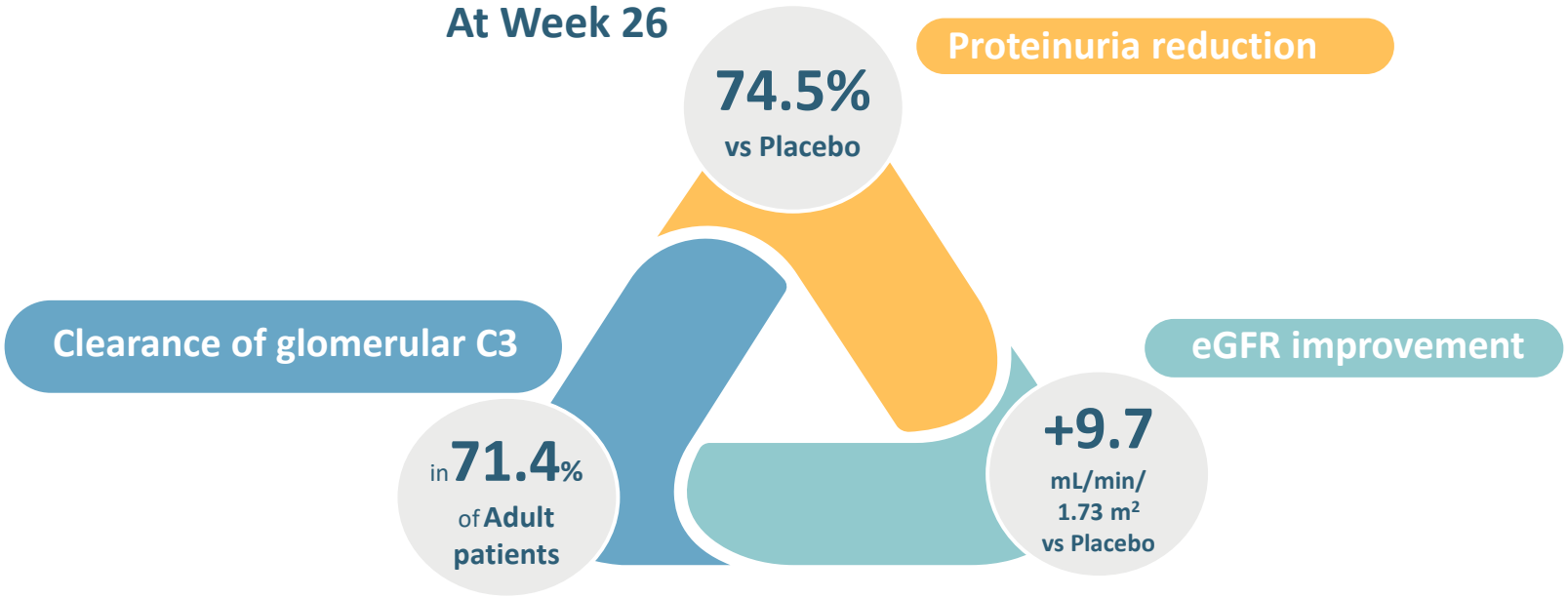
AKI, acute kidney injury; C3G, C3 glomerulopathy; EMA, European Medicines Association; FDA, US Food and Drug Administration; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; OLP, open-label period; RCP, randomised controlled period; SAE, serious adverse event; TEAE, treatment-emergent adverse event; US, United States.

van de Kar, *et al.* Presented at European Society for Paediatric Nephrology annual meeting 2025.

Overall, in VALIANT, pegcetacoplan was associated with positive patient outcomes in adolescents[1,2]



Pegcetacoplan was well tolerated: TEAE frequency/severity was similar between arms and there were no encapsulated meningococcal infection cases

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1. Nester CM, *et al*. Presented at American Society Nephrology 2024 (Oral SA-OR92); 2. Mastrangelo A, *et al*. Presented at European Renal Association 2025; 3. Fakhouri F, *et al*. Presented at European Renal Association 2025; 4. van de Kar, *et al.* Presented at European Society for Paediatric Nephrology annual meeting 2025.

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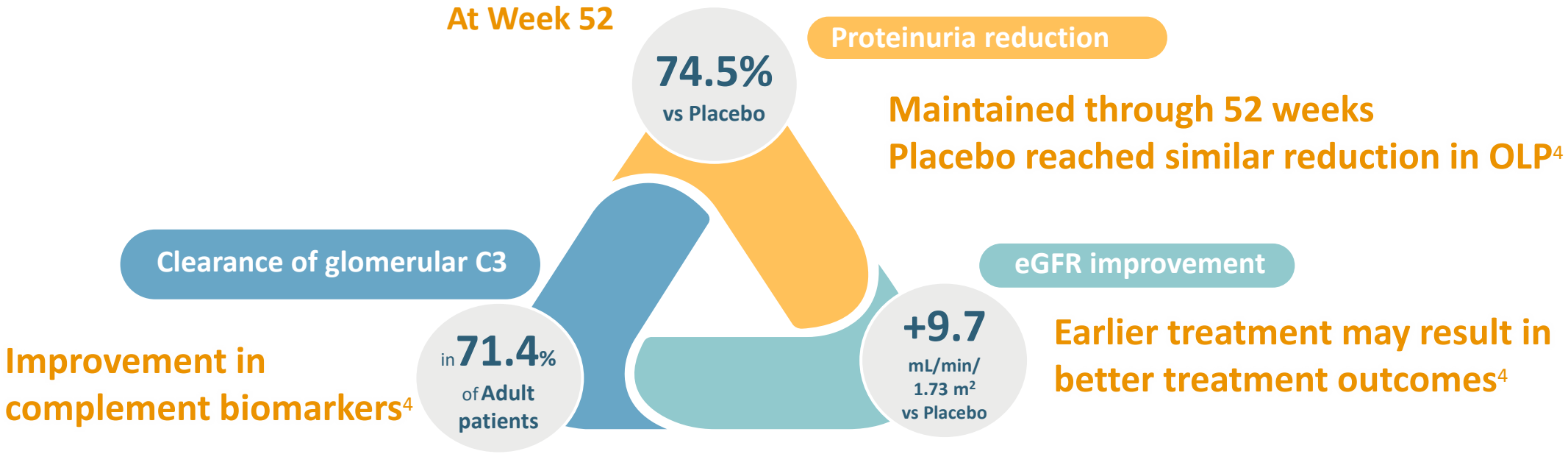

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Take home messages

- **Emerging therapeutics** for C3G and primary IC-MPGN **target** the **dysregulation** of the **complement pathway**[1–5]
- **Iptacopan** is a factor B inhibitor and is currently under investigation at **Phase 3** in adolescent C3G patients with native kidneys and adults and adolescents in primary IC-MPGN[6]
- **Pegcetacoplan**, a **C3/C3b inhibitor**, has shown significant **proteinuria reduction**, **eGFR stabilisation** and **clearance of glomerular C3 deposition** vs placebo. Clinical improvements were maintained up to 52 weeks in the Phase 3 VALIANT study[7]
- Outcomes of the **VALIANT** study demonstrate **consistent results across diverse patient populations**: patients with C3G or primary IC-MPGN regardless of age, use of concomitant medication, disease type or severity[7]

Iptacopan is approved by the FDA and EMA for the treatment of adult patients with C3G; Pegcetacoplan is approved by the FDA for the treatment of patients >12 years of age with C3G or primary IC-MPGN. Pegcetacoplan is approved by the FDA for the treatment of C3G and primary IC-MPGN patients aged 12 years and older. Pegcetacoplan has not been reviewed or approved for these indications by the EMA or other regulatory authorities outside US.

C3, complement 3; C3G, C3 glomerulopathy; EMA, European Medicines Association; FDA, Food and Drug Administration; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; US, United States.

1. Estebanez BT & Bomback AS. *Kidney Int Rep* 2024;9:569–79; 2. Bomback AS, *et al. Kidney Int Rep* 2022;7:2150–9; 3. Fabhalta (iptacopan). Prescribing information; 4. Empavel (pegcetacoplan). Prescribing information; 5. Karnabeda O, *et al. Blood* 2023;142:573; 6. Kavanagh D, *et al*. European Renal Association 2024; 7. Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).