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Pegcetacoplan Treatment Response in VALIANT/VALE: Impact of Genetic and Acquired Complement Dysregulation and Disease Type in C3G and Primary IC-MPGN

Marina Noris[1], Nicole Van De Kar[2], Daniel P Gale[3], Sophie Chauvet[4,5], Fernando Caravaca-Fontán[6], Julia Weinmann-Menke[7], Carla M Nester[8], Lucia Quintana-Gallardo[9], Johan Szamosi[9], Kathryn Gordon[10], Anwesha Mukherjee[10], Fadi Fakhouri[11]

[1]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy; [2]Radboud University Medical Center, Amalia Children's Hospital, Nijmegen, Netherlands; [3]University College London, London, United Kingdom; [4]Centre de Recherche des Cordeliers, Sorbonne Université, INSERM, Université Paris Cité, Inflammation, Complement and Cancer Team, Paris, France; [5]Department of Nephrology, European Hospital Georges Pompidou, APHP, Paris, France; [6]Department of Nephrology, Instituto de Investigación Hospital 12 de Octubre, Madrid, Spain; [7]Department of Nephrology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany; [8]University of Iowa, Stead Family Children's Hospital, Iowa City, IA, United States; [9]Swedish Orphan Biovitrum AB, Stockholm, Stockholm, Sweden; [10]Apellis Pharmaceuticals, Inc., Waltham, MA, United States; [11]Centre Hospitalier Universitaire Vaudois, Lausanne, Vaud, Switzerland

Disclosures

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- **KG** is an employee of Apellis Pharmaceuticals and may hold stock or stock options.
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- **FF** has received consultancy honorarium from Alexion, Astra Zeneca, Apellis, Novartis, Sobi and Roche.

ERA LEADING EUROPEAN NEPHROLOGY

C3G and primary IC-MPGN are heterogeneous **complement-related diseases** leading to irreversible kidney damage

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C3G and primary IC-MPGN are **highly heterogeneous**, with patients exhibiting a **broad spectrum** of clinical **severity** and a variable **disease course**[1]

Disease triggers differ but **C3 dysregulation**, observed by excessive glomerular **C3 deposition**, is the **common pathophysiological driver** leading to irreversible kidney damage[2,3]

Up to **50% of patients** progress to **kidney failure within 10 years** despite current standard of care[3]

C3G, C3 glomerulopathy; IC-MPGN, immune complex membranoproliferative glomerulonephritis.
1. Caravaca-Fontán et al. *Nephron* 2020 **2.** Noris & Remuzzi. *Nephrol Dial Transplant* 2024 **3.** Smith et al. *Nat Rev Nephrol* 2019.

In C3G and primary IC-MPGN, **excessive accumulation of glomerular C3 deposits leads to glomerular inflammation and scarring**[1,2]

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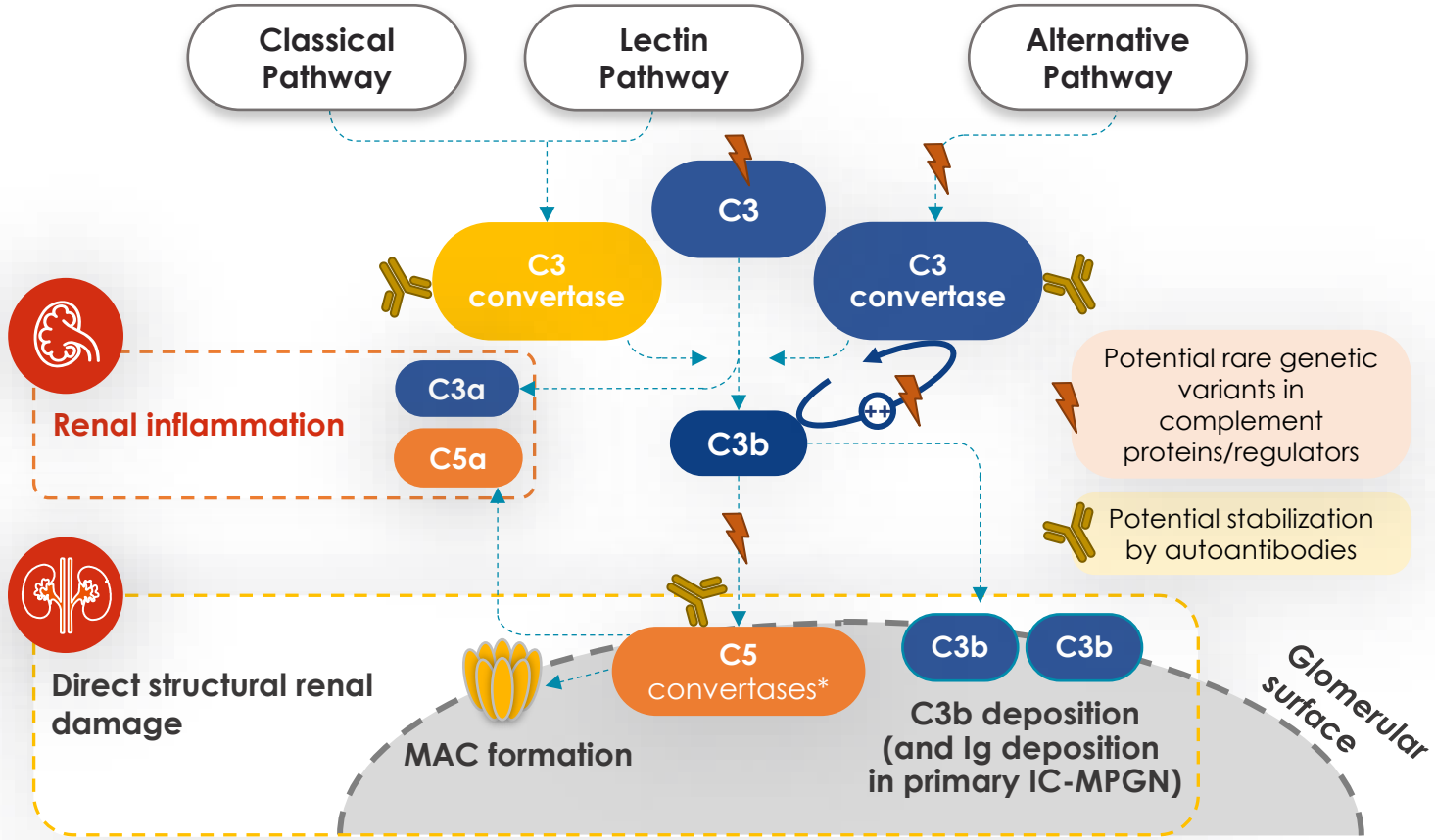

- In **primary IC-MPGN**, **Ig deposits** are a hallmark of disease in addition to C3 deposition, and a primary driver of classical pathway activation[3]
- **Genetic risk factors** and **acquired autoantibodies** affecting complement proteins or regulators have been identified in up to **20%** and **40-80%** of patients, respectively[4,5]
  - The impact of rare genetic variants and autoantibodies on patient outcomes remains unclear[3]
- In the remaining patients the disease trigger remains unknown[2]

* Including classical/lectin pathway C5 convertase and alternative pathway C5 convertase.
C3G, C3 glomerulopathy; IC-MPGN, immune complex membranoproliferative glomerulonephritis; Ig, immunoglobulin; MAC, membrane attack complex.
1. Fakhouri et al. *N Engl J Med* 2025 **2.** Kavanagh et al. *Kidney Int Rep* 2025 **3.** Bomback et al. *Kidney Int Rep* 2025
4. Meuleman *Clin J Am Soc Nephrol* 2023 **5.** Vivarelli *Kidney Int* 2024 **6.** Simon-Tillaux et al. ASN 2019; poster SA-PO609.

Pegcetacoplan aims to **control excessive glomerular C3 deposits** that may be the result of different disease triggers in C3G and primary IC-MPGN[1,2]

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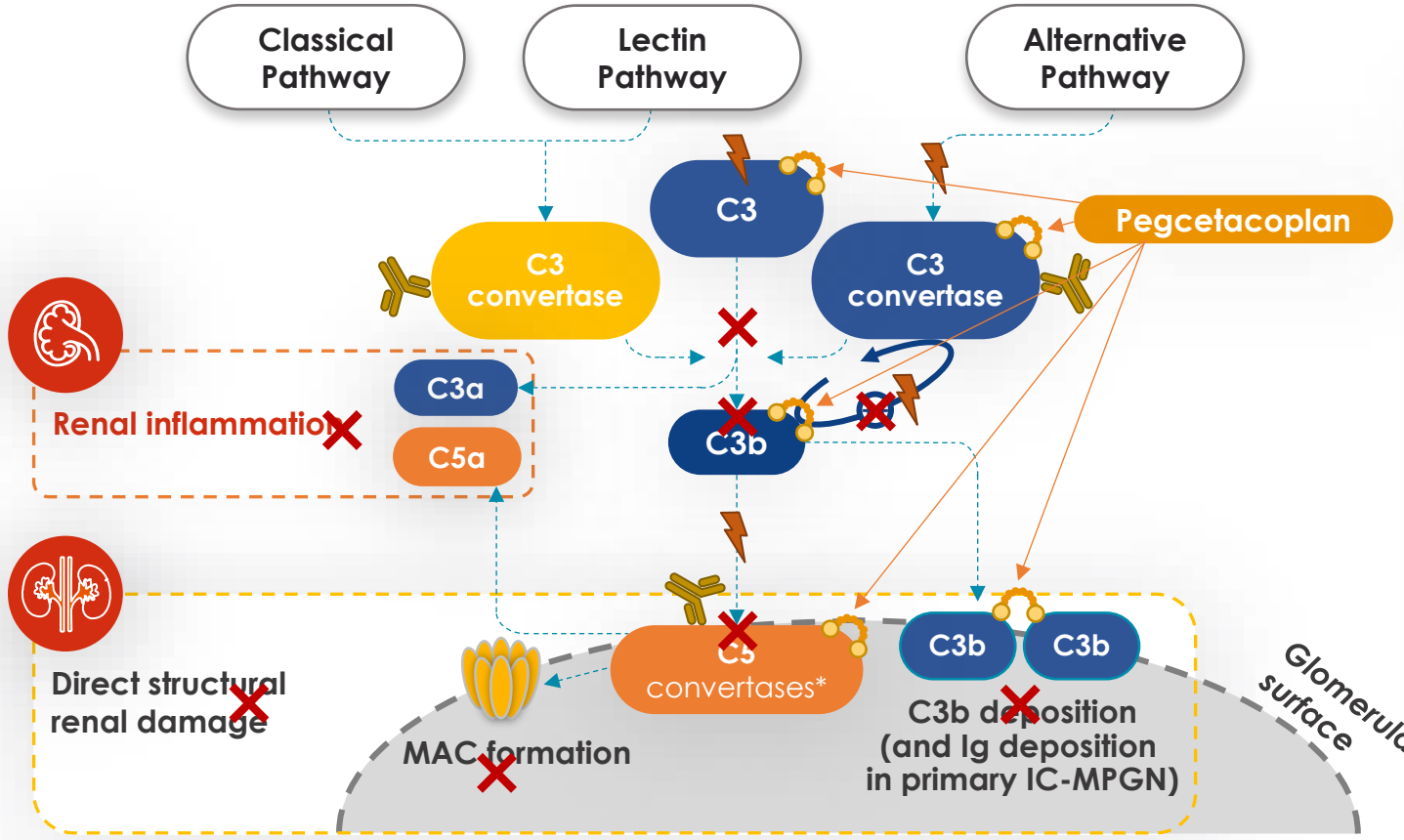

Pegcetacoplan binds C3 and C3b to:[1,2,6]

1. **Prevent C3 activation**, through all complement pathways and upstream autoantibodies
2. **Block the C3 amplification loop**, by directly inhibiting the alternative pathway C3 convertase
3. **Prevent C3 deposits** and downstream effectors

* Including classical/lectin pathway C5 convertase and alternative pathway C5 convertase.
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Aim: To evaluate **1-year pegcetacoplan** treatment effects in **patient subgroups of particular interest**

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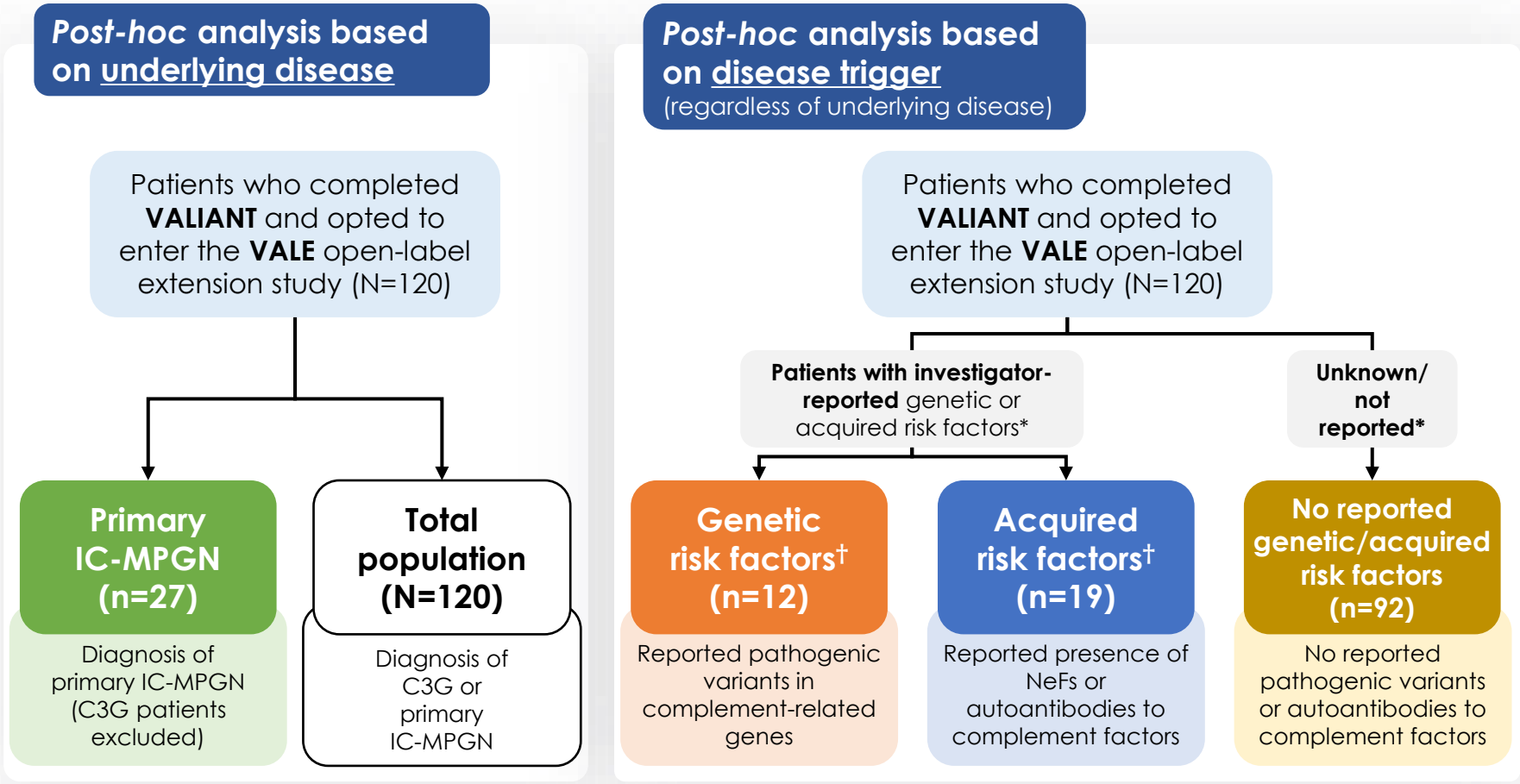
Method:

- Data from the Phase 3 VALIANT trial and its open-label extension (VALE) were pooled to enable a uniform evaluation of 1 year of pegcetacoplan exposure across all patients
- All data were time-aligned such that baseline represented pegcetacoplan initiation for all patients



* Testing for genetic and acquired risk factors was not mandatory for inclusion in VALIANT. Genetic and acquired risk factors were optionally reported by investigators and not assessed within the trial.
† Patients with reported genetic risk factors may also have had reported acquired risk factors, and *vice versa*.
C3G, C3 glomerulopathy; IC-MPGN, immune complex membranoproliferative glomerulonephritis; NeF, nephritic factor.

Baseline characteristics suggest **differences in disease duration and severity between groups**

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Baseline characteristic	Primary IC-MPGN (n=27)	Total population (N=124*)	Genetic risk factors (n=12)	Acquired risk factors (n=19)	No reported genetic/acquired risk factors (n=92)
Age, mean (SD), years	30.1 (19.2)	26.0 (15.9)	23.1 (12.5)	22.4 (14.5)	27.0 (16.6)
Adolescents (12–17 years), n (%)	12 (44.4)	55 (44.4)	5 (41.7)	12 (63.2)	38 (41.3)
Adults (≥18 years), n (%)	15 (55.6)	69 (55.6)	7 (58.3)	7 (36.8)	54 (58.7)
Sex, female, n (%)	16 (59.3)	70 (56.5)	9 (75.0)	12 (63.2)	50 (54.3)
Baseline triplicate first-morning spot UPCR, mean (SD), g/g	4.0 (3.3)	2.8 (2.2)	3.1 (2.3)	3.0 (2.0)	3.0 (2.5)
Baseline eGFR, mean (SD), mL/min/1.73 m²	67.6 (34.3)	82.8 (35.8)	71.2 (42.5)	88.8 (32.5)	78.0 (34.3)
Time since diagnosis, mean (SD), years	3.2 (2.6)	3.7 (3.5)	5.1 (4.3)	2.6 (2.1)	3.3 (2.6)

* Baseline characteristics at VALIANT study initiation.
IC-MPGN, immune complex membranoproliferative glomerulonephritis; eGFR, estimated glomerular filtration; SD, standard deviation; UPCR, urine protein:creatinine ratio.

Pegcetacoplan led to a sustained mean **UPCR reduction greater than 50% across subgroups**

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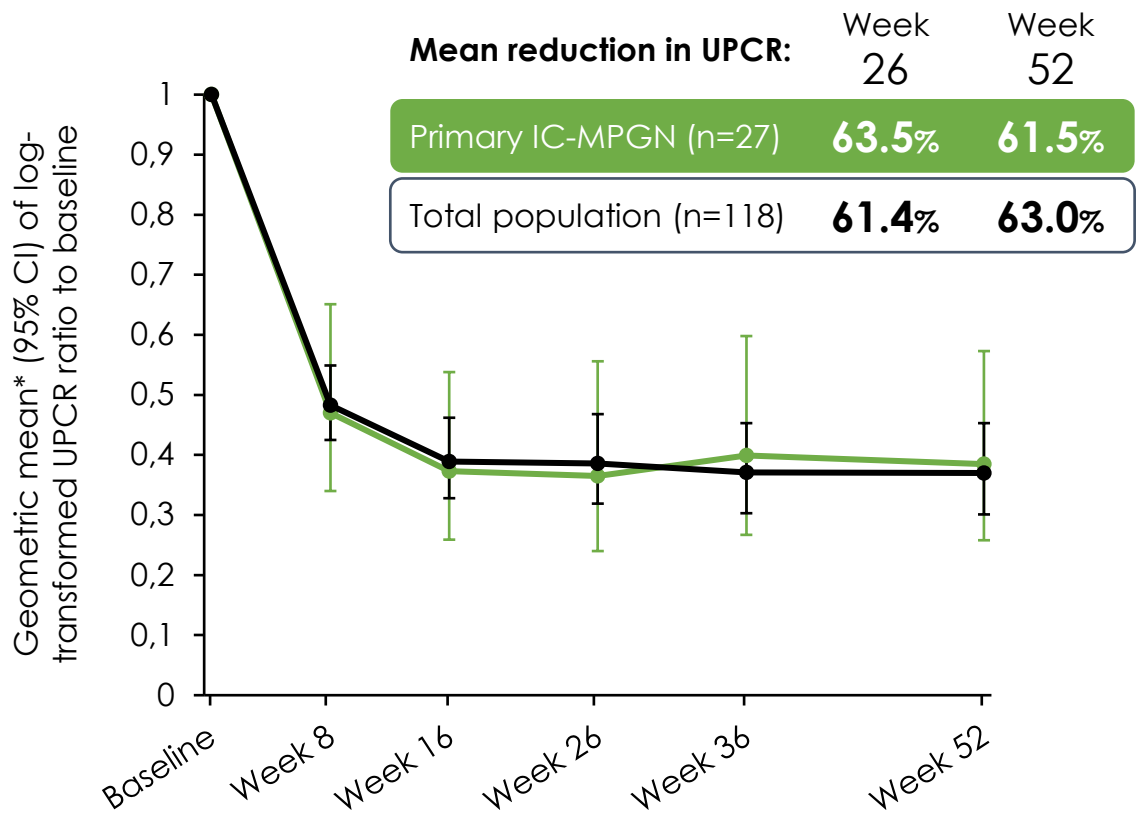
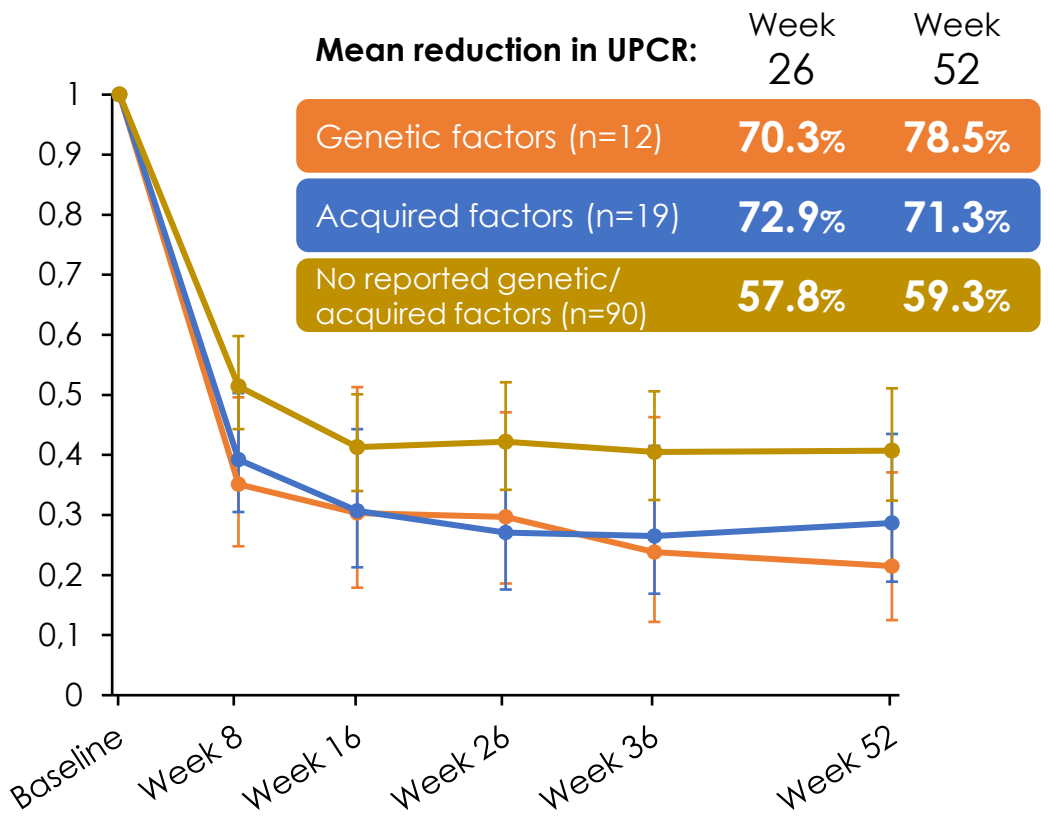
Change from time-aligned baseline in UPCR over time during pegcetacoplan treatment





* Geometric means and % change estimated from exponentiated LS mean differences from an MMRM of log-transformed UPCR.
n=number of patients included in each model.
CI, confidence interval, FMU; first morning urine; IC-MPGN, immune complex membranoproliferative glomerulonephritis; LS, least-squares; MMRM, mixed model for repeated measures; UPCR, urine protein:creatinine ratio.

Pegcetacoplan treatment led to a **rapid and sustained inhibition of overactive C3 in VALIANT**

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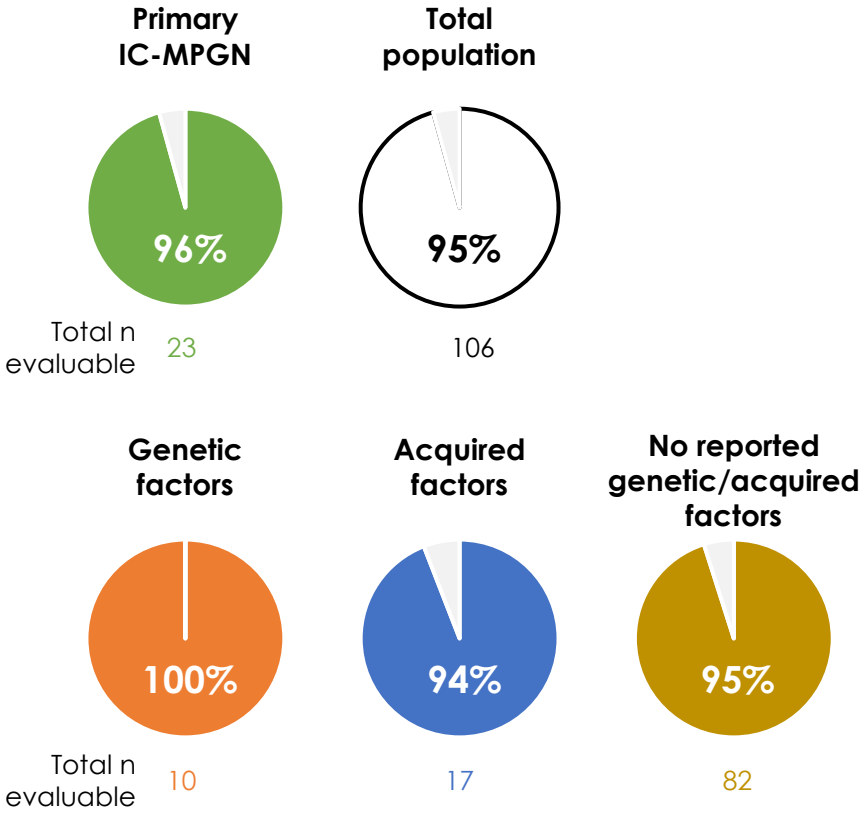
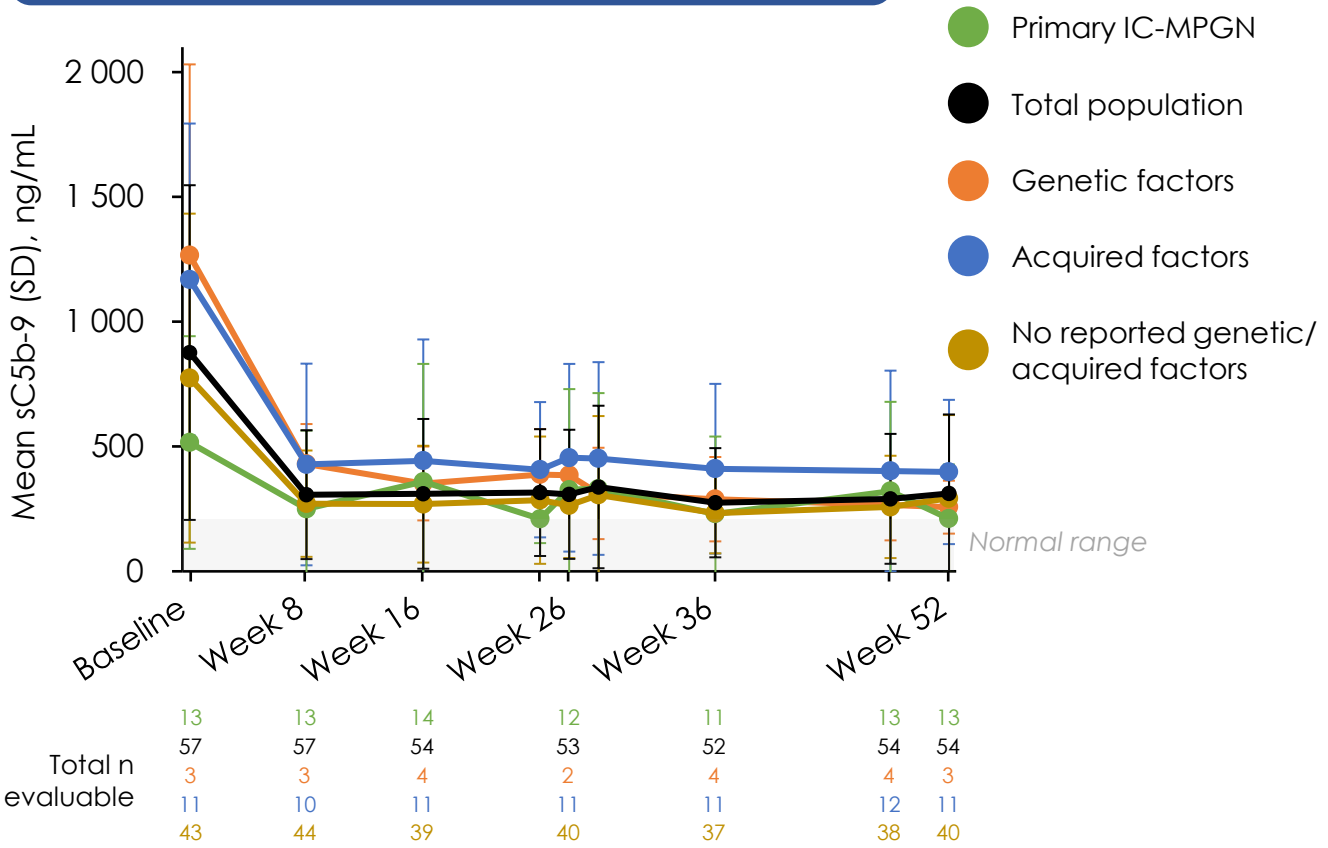
Normalization of soluble C3 levels* after 26 weeks of pegcetacoplan



Mean soluble C5b-9 levels over time in the pegcetacoplan-to-pegcetacoplan arm†



* Normalization of sC3 defined as >90 mg/dL.
† Normalization of sC5b-9 defined as <207 ng/mL.
IC-MPGN, immune complex membranoproliferative glomerulonephritis; pbo, placebo; peg, pegcetacoplan; sC3, soluble C3; sC5b-9, soluble C5b-9; SD, standard deviation.

Glomerular C3 reduction was generally consistent across subgroups at Week 26 in VALIANT

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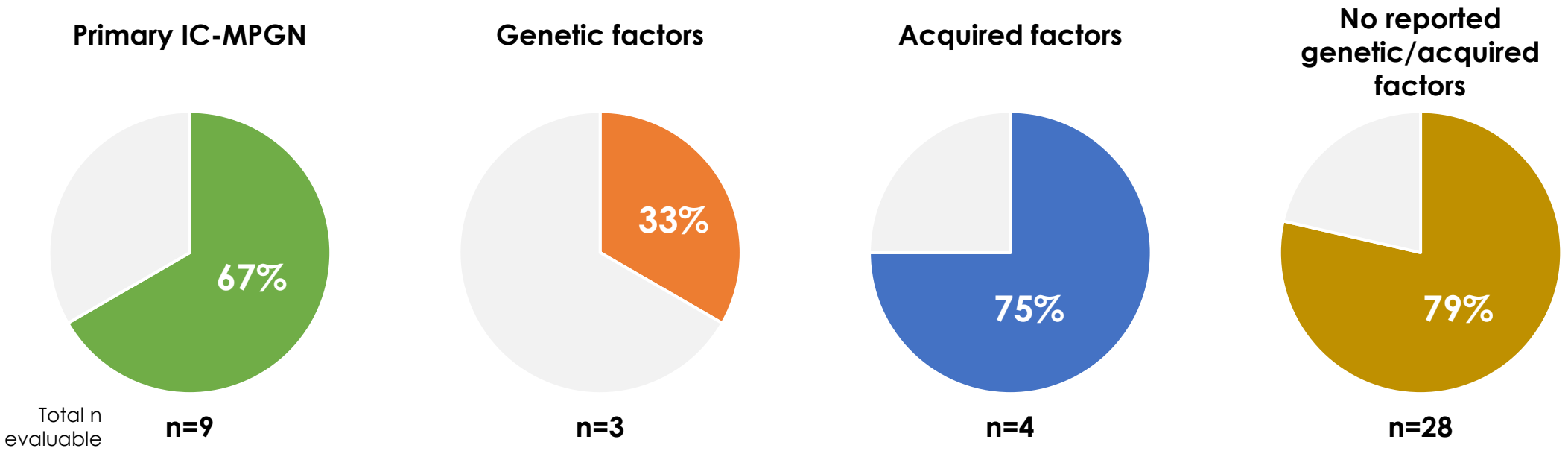
Proportion of patients with reduction in C3 staining in renal biopsy, defined as ≥2 OOM reduction at Week 26 vs baseline



In the **overall group**, **74%** (n=26/35) of patients had **≥2 OOM reduction in C3 staining** at Week 26[1]

IC-MPGN, immune complex membranoproliferative glomerulonephritis; OOM, orders of magnitude.

1. Fakhouri et al. *N Engl J Med* 2025.

Pegcetacoplan led to **stabilization of eGFR up to 1 year across subgroups**

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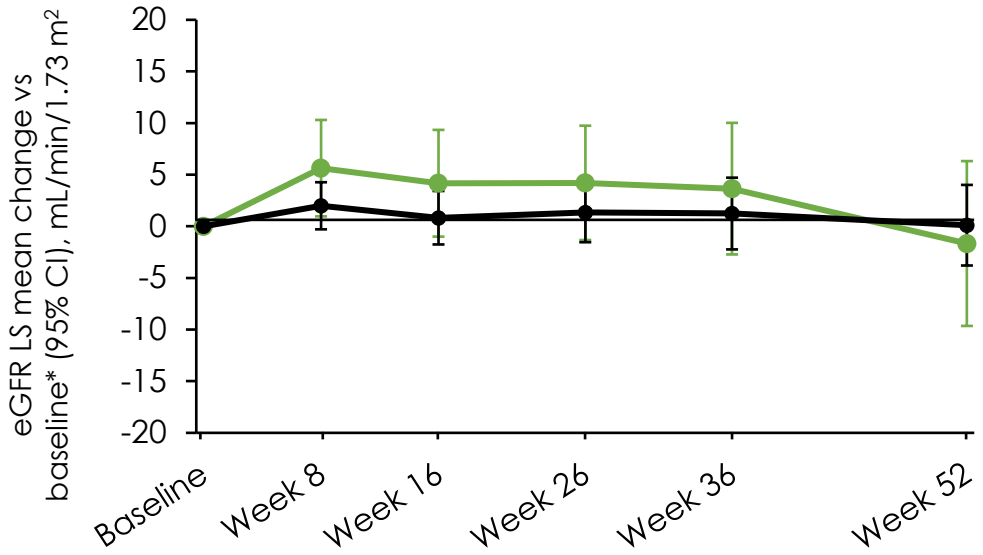
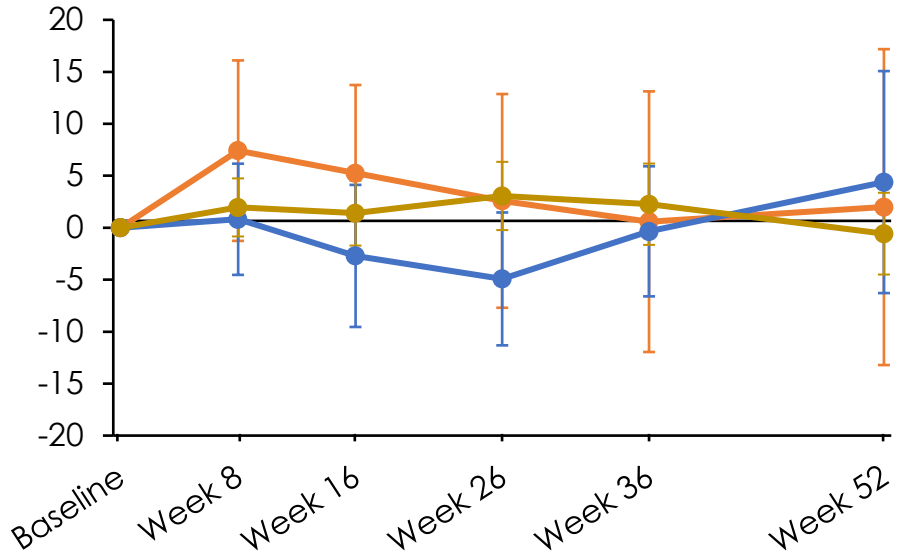
Change from time-aligned baseline in eGFR over time during pegcetacoplan treatment



Mean change in eGFR between baseline and 52 weeks:

Primary IC-MPGN (n=27)	**-1.7** mL/min/1.73 m²
Total population (n=118)	**+0.1** mL/min/1.73 m²



Mean change in eGFR between baseline and 52 weeks:

Genetic factors (n=12)	**+2.0** mL/min/1.73 m²
Acquired factors (n=19)	**+4.4** mL/min/1.73 m²
No reported genetic/ acquired factors (n=90)	**-0.6** mL/min/1.73 m²

* MMRM model of mean change from baseline in eGFR. n=number of patients included in each model.
CI, confidence interval; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex membranoproliferative glomerulonephritis; LS, least-squares; MMRM, mixed model for repeated measures.

Pegcetacoplan was **well-tolerated** and its **safety profile was consistent with previous reports**

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Patients, n (%) *Note: Due to overlap between subgroup populations, the same TEAE may be reported in >1 subgroup*	**Primary IC-MPGN (n=27)**	**Total population (N=120)**	**Genetic risk factors (n=12)**	**Acquired risk factors (n=19)**	**No reported genetic/acquired risk factors (n=92)**
TEAEs	22 (81.5)	106 (88.3)	10 (83.3)	18 (94.7)	81 (88.0)
Treatment-related TEAEs	12 (44.4)	53 (44.2)	2 (16.7)	8 (42.1)	44 (47.8)
Severe TEAEs	5 (22.7)*	11 (9.2)	1 (10.0)†	1 (5.6)‡	9 (11.1)§
Serious TEAEs	5 (18.5)	17 (14.2)	3 (25.0)	3 (15.8)	12 (13.0)
Common TEAEs (occurring in ≥10% of all subgroups					
Infusion site reaction	9 (33.3)	41 (34.2)	3 (25.0)	8 (42.1)	31 (33.7)
Nasopharyngitis	5 (18.5)	15 (12.5)	3 (25.0)	5 (26.3)	9 (9.8)
Influenza	5 (18.5)	13 (10.8)	2 (16.7)	3 (15.8)	10 (10.9)
Pyrexia	3 (11.1)	19 (15.8)	3 (25.0)	6 (31.6)	11 (12.0)
Encapsulated meningococcal infections	0	0	0	0	0
TEAE leading to discontinuation	3 (11.1)	4 (3.3)	0	0	4 (4.3)
Deaths§	1 (3.7)	1 (0.8)	0	0	1 (1.1)

Consistent with >3,500 patient-years of pegcetacoplan exposure‖[1]

TEAEs defined as any new AE that began, or any preexisting condition that worsened in severity, after the first dose of study drug in either VALIANT or VALE and ≤56 days beyond the last dose of study drug.
* n=22 evaluable patients. † n=10 evaluable patients. ‡ n=18 evaluable patients. § n=81 evaluable patients.
§ 1 death reported in total: due to COVID-19, unrelated to pegcetacoplan (counted in the "primary IC-MPGN" group, "total population" group, and in the "no reported genetic/acquired factors" group). ‖ As of 13 February 2026. Includes exposure in clinical trials and post-marketing across multiple indications.
AE, adverse event; IC-MPGN, immune complex membranoproliferative glomerulonephritis; TEAE, treatment-emergent AE.
1. Ayehu et al. NKF Spring Clinical Meetings 2026; poster.

Key takeaways

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Pegcetacoplan provides **benefits** in primary IC-MPGN as well as C3G patients, and **irrespective of the etiology of complement dysregulation**

Sustained reductions in **proteinuria** and **eGFR** stabilization were associated with **normalization of C3** and **glomerular C3 reduction in most patients,** and overall **safety** was **consistent** with outcomes previously observed for the total VALIANT population

This *post-hoc* analysis supports the **efficacy** of pegcetacoplan and its **mechanism of action** in a **broad patient population with different disease triggers**

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

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