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AST American Society of Transplantation | ASTS American Society of Transplant Surgeons | TTS The Transplantation Society

Pegcetacoplan for Posttransplant Patients with Complement 3 Glomerulopathy or Primary (Idiopathic) Immune-Complex Membranoproliferative Glomerulonephritis

An analysis of the Phase 2 NOBLE and Phase 3 VALIANT trials

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Disclosures

AB has received consulting fees from Amgen, Apellis, Catalyst, Genentech, Kezar, Novartis, Q32, Silence Therapeutics, and Visterra.

DK has received consultancy income from Alexion Pharmaceuticals & Astra Zenica, Novartis, Apellis, Gyroscope Therapeutics, Roche, Purespring Therapeutics, Samsung, Chemocentryx, Amgen, Silence Therapeutics and Sarepta. DK is authors of patent applications referencing recombinant complement factor I production and/or formation of the C3b/FH/FI trimolecular complex.

DZ has received consulting fees from Sobi, Apellis, and Novartis.

JZ and **OV** has nothing to disclose.

LLL is an employee of Swedish Orphan Biovitrum AB and holds stock or stock options.

EK is an employee of Apellis Pharmaceuticals, Inc. and may hold stock or stock options

LL was an employee of Apellis Pharmaceuticals, Inc. at the time of the study

FF has received consulting fees from, Alexion, Apellis, AstraZeneca, Biocryst, Novartis, Roche and Sobi.

C3G and primary (idiopathic) IC-MPGN often **recur after transplantation** despite conventional immunosuppression

C3G and primary IC-MPGN are rare, chronic, and heterogenous **complement-mediated diseases**

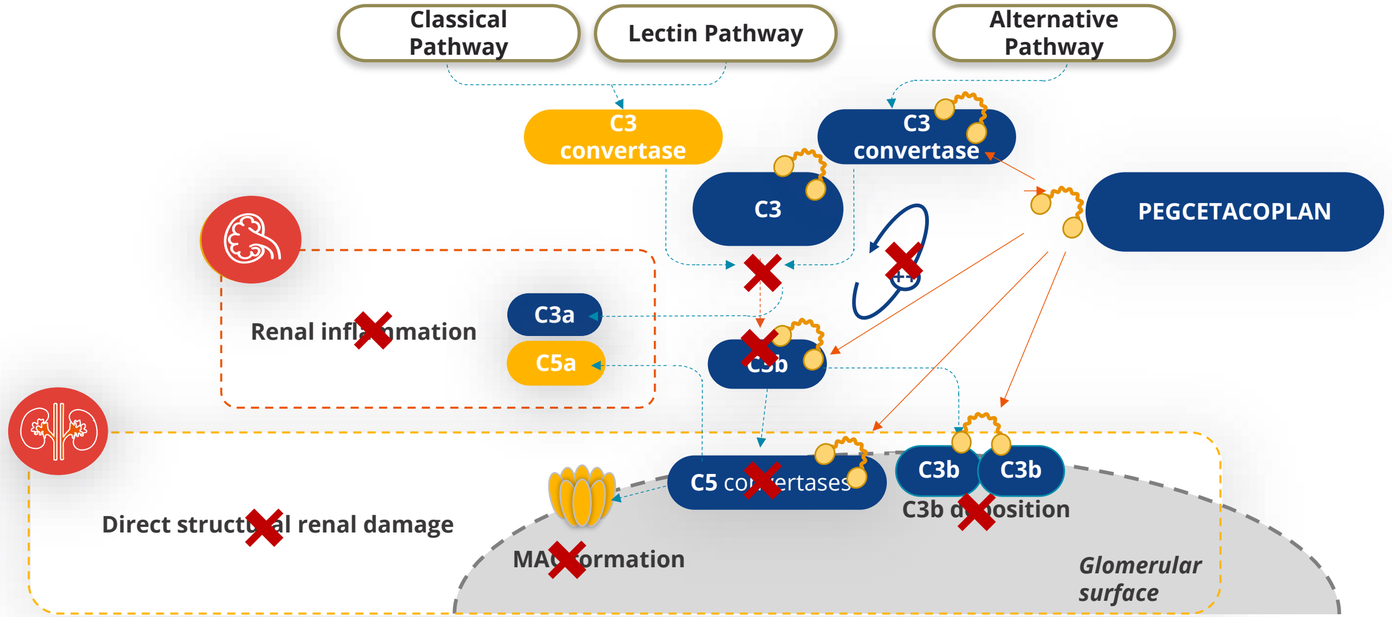
Disease is **driven by C3 overactivation**, resulting in the accumulation of C3 deposits in the glomeruli (in addition to immunoglobulins in IC-MPGN), leading to inflammation and progressive kidney damage that can result in permanent **loss of kidney function**, necessitating dialysis or transplantation[1,2]

Unfortunately, **disease recurrence and graft loss** after transplantation are likely,[3–7] with some estimates of posttransplant recurrence as high as 89%[7]

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

1. Bomback AS, et al. *Kidney Int Rep.* 2024.; 2. Mastrangelo A, et al. *Front Pediatr.* 2020;8:205; 3. Medjeral-Thomas NR, et al. *Clin J Am Soc Nephrol* 2014;9:46-53.; 4. Patry C, et al. *Pediatr Nephrol.* 2024;39(12):3569–3580.; 5. Tarragón B, et al. *Clin J Am Soc Nephrol.* 2024;19(8)1005-1015.; 6. Wong EKS, et al. *Clin J Am Soc Nephrol.* 2021;16(11):1639-1651.; 7. Zand L, et al. *J Am Soc Nephrol* 2014;25(5):1110-7.

Pegcetacoplan, a C3 and C3b inhibitor, **blocks C3 dysregulation and downstream complement activation** in C3G and primary IC-MPGN[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.; 2. Zipfel PF, et al. *Front Immunol* 2019.; 3. Meuleman MS, et al. *Semin Immunol* 2022.; 4. Dixon BP, et al. *Kidney Int Rep* 2023.; 5. EMPAVELI (pegcetacoplan). Apellis Pharmaceuticals, Inc.; 2024.; 6. ASPAVELI (pegcetacoplan). Swedish Orphan Biovitrum AB; 2024.; 7. Lamers C, et al. *Nat Commun* 2022.

Pegcetacoplan demonstrated **efficacy and tolerability** in studies including **posttransplant patients** with C3G and primary IC-MPGN

- In the **phase 2 NOBLE (NCT04572854)**[1] and **phase 3 VALIANT (NCT05067127)**[2] trials, **pegcetacoplan showed efficacy and favorable tolerability** for adolescents and adults with native or posttransplant recurrent C3G or primary IC-MPGN

- Pegcetacoplan improved disease parameters, including **clearance of glomerular C3**, **reduced proteinuria**, **stable eGFR**, increased serum C3, and normalization of plasma sC5b-9 in the overall study populations

- Here, we describe **pegcetacoplan for kidney transplant recipients** in these studies

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

1. Bomback A, et al. *Kidney Int Rep* 2024;10(1):87-98.; 2. Fakhouri F, et al. Pegcetacoplan for C3G and primary (idiopathic) IC-MPGN: 52-week results from the phase 3 VALIANT trial show sustained efficacy. Presented at ERA 2025. Vienna, Austria.

Eleven posttransplant patients with proteinuria ≥1 g/g at **baseline** received pegcetacoplan for at least **24 to 26 weeks**

NOBLE[1]

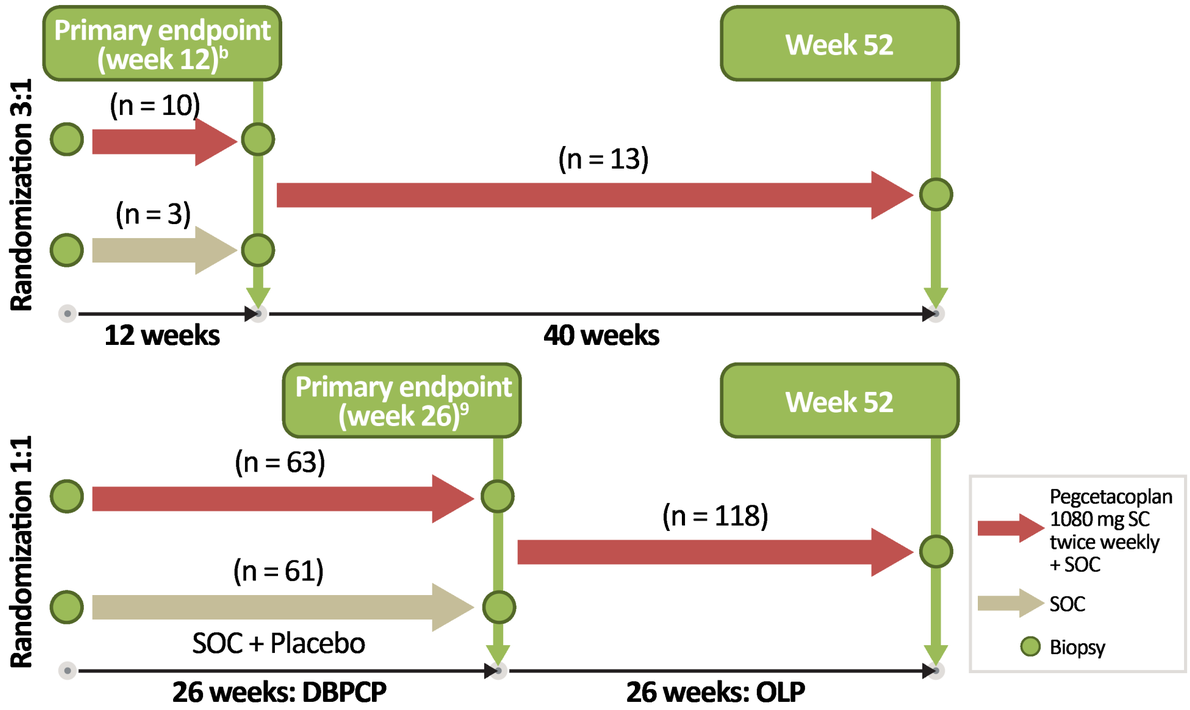
Included adults (≥18 years old) with biopsy-proven posttransplant recurrence of C3G or primary IC-MPGN with ≥2+ staining for C3 on kidney biopsy and eGFR ≥15 mL/min/1.73 m^2 (N = 13)

Six patients with ≥1 g/g proteinuria at baseline received pegcetacoplan for at least 24 weeks

VALIANT[2]

Included adolescents (12-17 years old) and adults (≥18 years old) with biopsy-proven native or posttransplant recurrent C3G or primary IC-MPGN with ≥2+ staining for C3 on kidney biopsy, eGFR ≥30 mL/min/1.73 m^2, and proteinuria ≥1 g/g[a] (N = 124)

Five patients received pegcetacoplan for at least 26 weeks



[a]Urine protein-to-creatinine ratio in at least 2 first-morning spot urine samples during screening. [b]Proportion of patients with reduction in renal biopsy C3 staining (defined as a decrease of ≥2 OOM) at Week 12 from baseline. [c]All patients completed the study through week 12 and entered the noncontrolled portion of the NOBLE study. [d]Log-transformed ratio of UPCR at week 26 compared with baseline. [e]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. [f]Stable, optimized antiproteinuric regimens: ACEis, ARBs, SGLT2is, MMF, and corticosteroids (prednisone ≤20 mg/d or equivalent) were permitted. [g]In the 61 (96.8%) patients from the pegcetacoplan group and 57 (93.4%) patients from the placebo group completed the RCP and entered the OLP.
ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; DBPCP, double-blind, placebo-controlled period; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex-membranoproliferative glomerulonephritis; MMF, mycophenolate mofetil; OLP, open-label period; OOM, order of magnitude; SC, subcutaneous; SGLT2is, sodium-glucose cotransporter-2 inhibitors; SOC, standard of care. 1. Bomback A, et al. *Kidney Int Rep* 2024;10(1):87-98. 2. Fakhouri F, et al. Pegcetacoplan for C3G and primary (idiopathic) IC-MPGN: 52-week results from the phase 3 VALIANT trial show sustained efficacy. Presented at ERA 2025. Vienna, Austria.

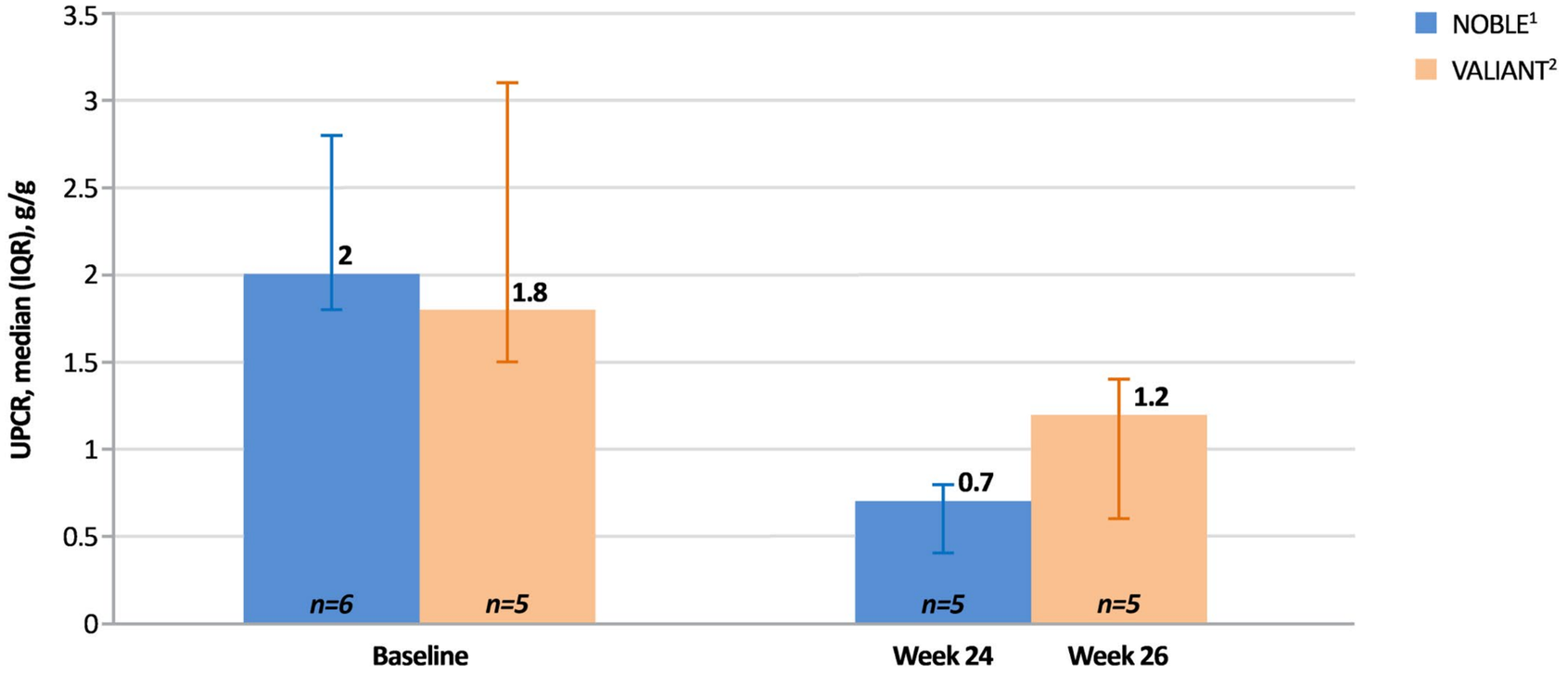
In the overall study populations, **demographics and baseline clinical characteristics** were relatively **balanced between treatment groups**

	NOBLE[1] (n=6)	VALIANT[2] (n=5)	Total (n=11)
Sex, n (%)			
Male	2 (33.3%)	3 (60.0%)	5 (45.5%)
Female	4 (66.7%)	2 (40.0%)	6 (54.5%)
Age, years, mean (SD)	36.8 (11.6)	41.4 (16.7)[a]	38.9 (13.6)
Disease, n (%)			
C3G	4 (66.7%)	5 (100%)	9 (81.8%)
IC-MPGN	2 (33.3%)	0	2 (18.2%)
Time since most recent transplant, years, mean (SD)	1.9 (0.81)	11.4 (6.70)	6.2 (6.54)
Time since most recent recurrence, years, mean (SD)	0.9 (0.61)	1.5 (1.51)	1.1 (1.09)

All patients were receiving standard posttransplant immunosuppressant therapy with or without glucocorticoids

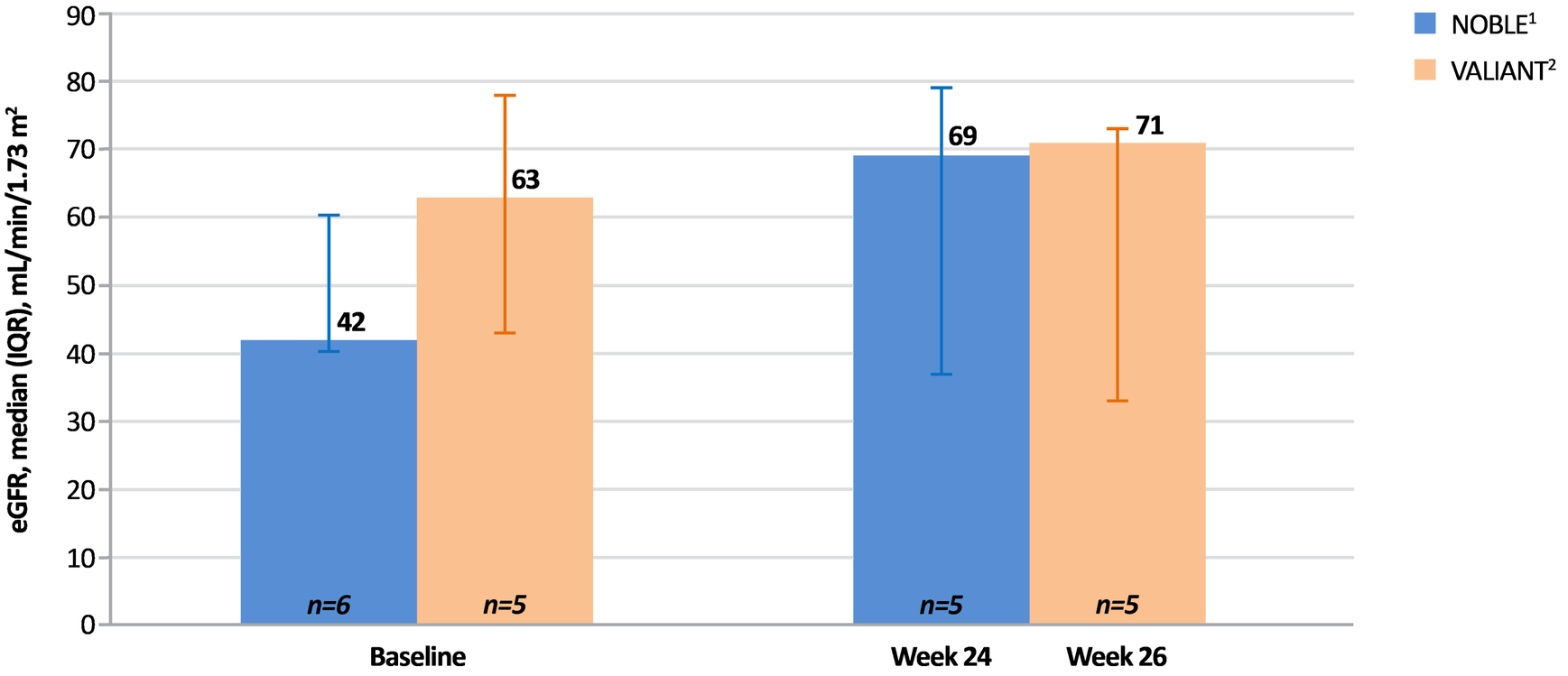
[a] One posttransplant patient in VALIANT was a pediatric patient (17 years old).
C3, complement protein 3; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; SD, standard deviation.
1. Bomback A, et al. *Kidney Int Rep* 2024;10(1):87-98. 2. Fakhouri F, et al. Pegcetacoplan for C3G and primary (idiopathic) IC-MPGN: 52-week results from the phase 3 VALIANT trial show sustained efficacy. Presented at ERA 2025. Vienna, Austria.

Efficacy: **Pegcetacoplan** led to **proteinuria[a] reductions** for posttransplant patients



[a]Based on triplicate first-morning spot urine.
IQR, interquartile range; UPCR, urine protein-to-creatinine ratio.
1. Bomback A, et al. *Kidney Int Rep* 2024;10(1):87-98. 2. Fakhouri F, et al. Pegcetacoplan for C3G and primary (idiopathic) IC-MPGN: 52-week results from the phase 3 VALIANT trial show sustained efficacy. Presented at ERA 2025. Vienna, Austria.

Efficacy: **eGFR was stable** for duration of studies for posttransplant patients



eGFR, estimated glomerular filtration rate; IQR, interquartile range.

1. Bomback A, et al. *Kidney Int Rep* 2024;10(1):87-98. 2. Fakhouri F, et al. Pegcetacoplan for C3G and primary (idiopathic) IC-MPGN: 52-week results from the phase 3 VALIANT trial show sustained efficacy. Presented at ERA 2025. Vienna, Austria.

Efficacy: **Glomerular C3 was reduced** at last timepoint assessed[a] for posttransplant patients[1-2]

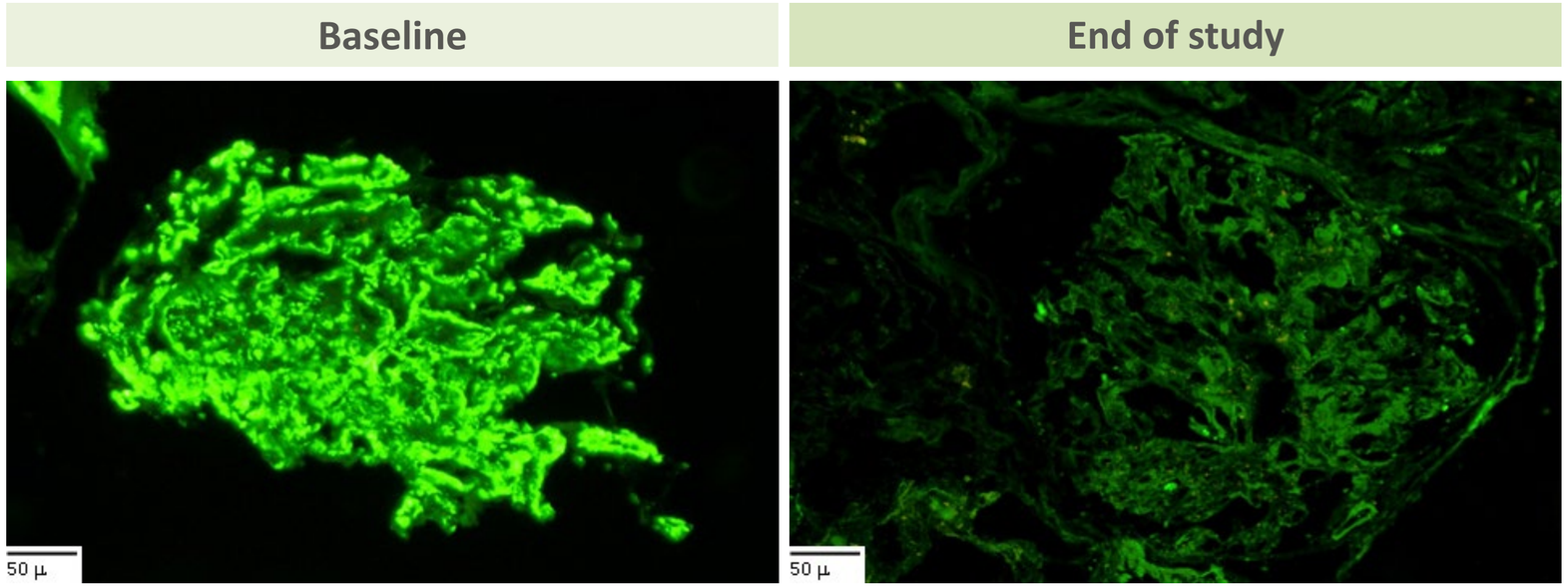
Staining was assessed on a standard 0-to-3 scale[1]

0: No staining

1+: Weak or minimal staining

2+: Moderate staining

3+: Strong or high-intensity staining



Change in C3 staining at Week 52 or 26 vs baseline	NOBLE[1]	VALIANT[2]
≥2 OOM reduction	60%	100%
-	-	-
Zero staining	40%	100%

[a]C3 staining was assessed with kidney biopsies at Weeks 12 and 52 during NOBLE and at Week 26 during VALIANT. Biopsies were not required for adolescent patients in VALIANT.
OOM, orders of magnitude.
1. Bomback A, et al. *Kidney Int Rep* 2024;10(1):87-98. 2. Fakhouri F, et al. Pegcetacoplan for C3G and primary (idiopathic) IC-MPGN: 52-week results from the phase 3 VALIANT trial show sustained efficacy. Presented at ERA 2025. Vienna, Austria.

Safety: **No new safety signals** were identified during 6 months of therapy

Safety, n (%)	NOBLE[1] (n=6)[a,b]		VALIAN2T (n=5)[c]	
TEAEs	5 (83.3%)		5 (100%)	
TEAEs reported as related to pegcetacoplan	2 (33.3%)	*One patient experienced mild-to-moderate flu and weight loss*	1 (20%)	*One patient experienced mild-to-moderate mucositis, elevated gamma-glutamyltransferase, and rosacea*
Serious TEAEs	1 (16.7%)	*One SAE of worsening neutropenia; drug was interrupted and the SAE resolved; drug was reintroduced*	0	
Serious TEAEs reported as related to pegcetacoplan	1 (16.7%)		0	
TEAEs leading to treatment discontinuation	1 (16.7%)	*Pegcetacoplan was withdrawn for the patient with TEAEs of flu and weight loss*	0	
Graft loss or rejection	0		0	

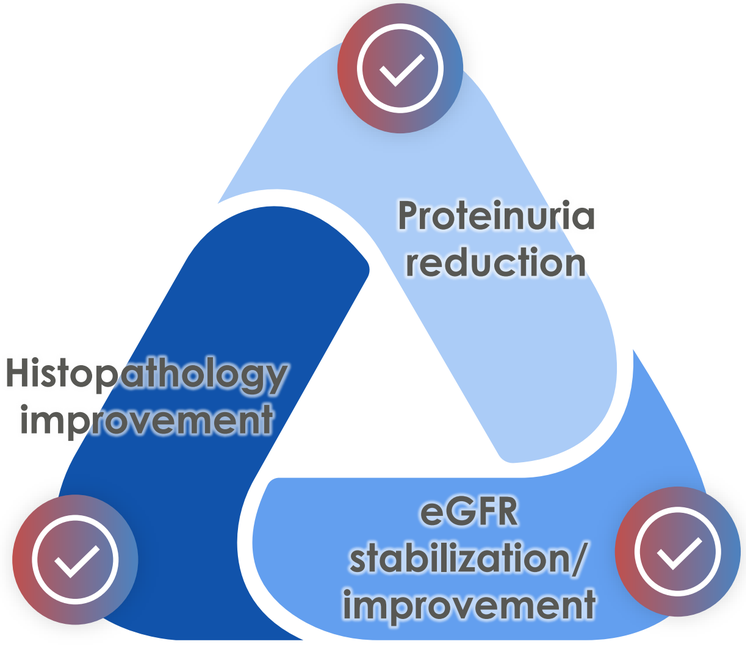
There were no reported infections caused by encapsulated bacteria among posttransplant patients

Safety findings among posttransplant patients were consistent with those of the overall NOBLE and VALIANT populations

[a]Patients with ≥1 g/g proteinuria at baseline. [b]Safety was assessed for 52-week data cutoff for NOBLE. [c]Includes posttransplant patients who received pegcetacoplan during the randomized controlled period.
SAE, serious adverse event; TEAE, treatment-emergent adverse event.
1. Bomback A, et al. *Kidney Int Rep* 2024;10(1):87-98. 2. Fakhouri F, et al. Pegcetacoplan for C3G and primary (idiopathic) IC-MPGN: 52-week results from the phase 3 VALIANT trial show sustained efficacy. Presented at ERA 2025. Vienna, Austria.

Pegcetacoplan demonstrated **efficacy and safety** for posttransplant patients

- With **6 months** of treatment, **pegcetacoplan** led to **robust and sustained clinical benefits** for posttransplant patients with C3G and primary IC-MPGN
- Pegcetacoplan was **safe and well tolerated** by most patients
- Results among the posttransplant subgroups were **consistent with the overall population**
- Longer-term data of pegcetacoplan efficacy and safety will be reported from the VALE[1] long-term extension study
- Pegcetacoplan received **FDA approval** in July 2025



1. ClinicalTrials.gov. VALE. https://clinicaltrials.gov/study/NCT05809531. Accessed 6 May 2025.

Thank You!

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