Pegcetacoplan for post-transplant 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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Andrew Bomback;[1] David Kavanagh;[2] Daniel Zecher;[3] Julien Zuber;[4] Ondrej Viklicky;[5] Li Li;[6] Luis López Lázaro;[7] Fadi Fakhouri[8]

[1]Columbia University Irving Medical Center, New York, NY, USA; [2]National Renal Complement Therapeutics Centre, Newcastle University, Newcastle, UK; [3]University Hospital Regensburg, Regensburg, Germany; [4]Necker-Enfants Malades Hospital, Paris, France; [5]Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [6]Apellis Pharmaceuticals, Inc., Waltham, MA, USA; [7]Swedish Orphan Biovitrum AB, Stockholm, Sweden; [8]Lausanne University Hospital, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

CONCLUSIONS

Pegcetacoplan was efficacious and well tolerated in post-transplant patients:

- Six months of pegcetacoplan treatment resulted in robust and sustained clinical benefits for post-transplant patients with complement 3 glomerulopathy (C3G) or primary (idiopathic) immune-complex membranoproliferative glomerulonephritis (IC-MPGN).
  - Reductions in proteinuria, stabilised estimated glomerular filtration rate (eGFR), and glomerular C3 clearance.
- No new safety signals were identified and no infections caused by encapsulated bacteria were reported.
- The efficacy and safety profile of pegcetacoplan in post-transplant patients is consistent with that in the overall pegcetacoplan-treated population.

BACKGROUND

- C3G and primary IC-MPGN often recur after transplantation despite conventional immunosuppression.[1–5]
- Pegcetacoplan is a targeted C3 and C3b inhibitor that acts centrally to block C3 dysregulation and downstream activation of the complement cascade in C3G and primary IC-MPGN.[6–12]
- The NOBLE (phase 2) and VALIANT (phase 3) trials showed that pegcetacoplan was efficacious (reduced proteinuria, stable eGFR, and glomerular C3 clearance) and well tolerated in adolescents/adults with native or post-transplant recurrent C3G or primary IC-MPGN.[13]

OBJECTIVE

- Using data from NOBLE and VALIANT, we describe the effect of pegcetacoplan in a subgroup of post-transplant patients with recurrent C3G or primary IC-MPGN.

METHODS

- The two trials included patients with biopsy-proven post-transplant recurrence of C3G and IC-MPGN, proteinuria ≥1 g/g (VALIANT), ≥2+ staining for C3 on kidney biopsy, and eGFR ≥15 mL/min/1.73 m^2 (NOBLE) or ≥30 mL/min/1.73 m^2 (VALIANT).
- NOBLE recruited patients ≥18 years and VALIANT recruited patients ≥12 years.
- In total, 11 post-transplant patients with proteinuria ≥1g/g received pegcetacoplan ≤1080 mg subcutaneously twice weekly (based on age and weight) for ≥24 weeks (NOBLE, n=6) or for ≥26 weeks (VALIANT, n=5); both treatment arms continued to receive optimised supportive care.
- Kidney biopsies were conducted at weeks 12 and 52 in NOBLE and at week 26 in VALIANT (optional for adolescents).
- Efficacy endpoints included:
  - Change from baseline in the log-transformed ratio of urine protein-to-creatinine ratio (UPCR) at week 24 (NOBLE) or week 26 (VALIANT).
  - Change in eGFR from baseline to week 24 (NOBLE) or week 26 (VALIANT).
  - C3 staining at the last timepoint assessed (NOBLE, week 52; VALIANT, week 26) – zero staining and a reduction in staining of at least two orders of magnitude.
- Treatment-emergent adverse event (TEAE) frequency, severity, and relatedness to study drug were recorded.

RESULTS

Efficacy

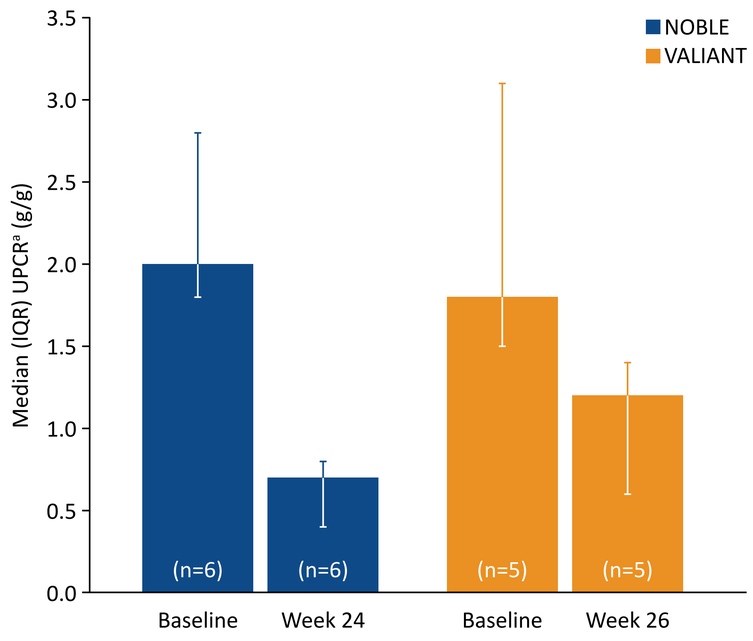
- Most patients in the analysis were adults (one patient from the VALIANT trial was 17 years old); patients were, on average, 6 years from their most recent transplant and had a recurrence of C3G or IC-MPGN in the last year (**Table 1**).
- All patients were receiving standard post-transplant immunosuppressant therapy with or without glucocorticoids.

Table 1: Demographics and baseline clinical characteristics

	NOBLE (n=6)	VALIANT (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 (100.0)	9 (81.8)
Primary IC-MPGN	2 (33.3)	0 (0.0)	2 (18.2)
Time since most recent transplant, years, mean (SD)	1.9 (0.8)	11.4 (6.7)	6.2 (6.5)
Time since most recent recurrence, years, mean (SD)	0.8 (0.6)	1.5 (1.5)	1.1 (1.1)

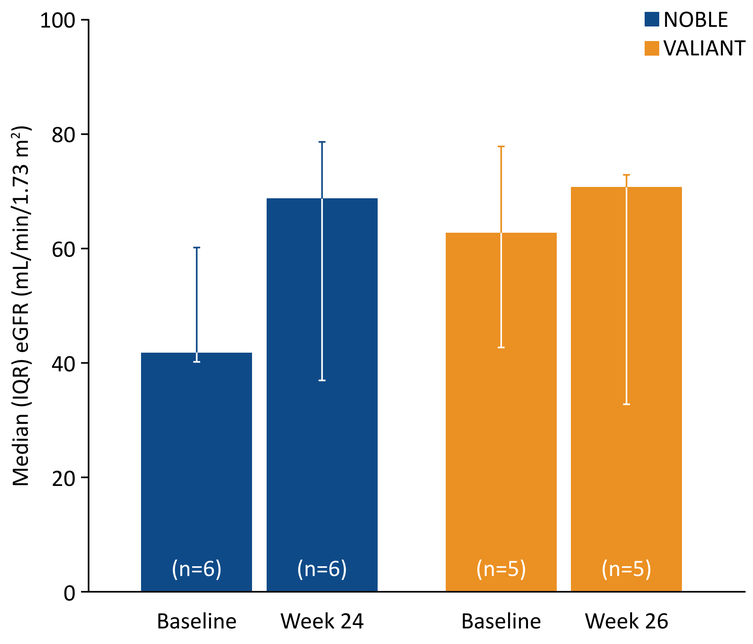
[a]One post-transplant patient in the VALIANT trial was 17 years old.
C3G, complement 3 glomerulopathy; IC-MPGN, immune complex-membranoproliferative glomerulonephritis; SD, standard deviation.

Figure 1: Change in proteinuria from baseline to week 24 (NOBLE) or week 26 (VALIANT)



[a]Based on triplicate first-morning spot urine.
IQR, interquartile range; UPCR, urine protein-to-creatinine ratio.

Figure 2: Change in eGFR from baseline to week 24 (NOBLE) or week 26 (VALIANT)



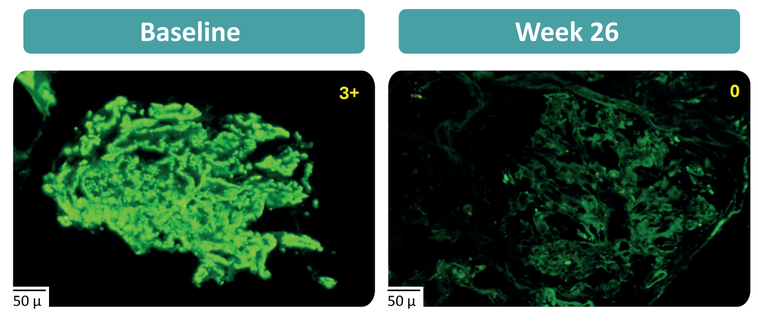
eGFR, estimated glomerular filtration rate; IQR, interquartile range.

- Pegcetacoplan treatment reduced proteinuria in the NOBLE and VALIANT trials (**Figure 1**).
- Pegcetacoplan stabilised eGFR for the duration of the two trials (**Figure 2**).
- At the last assessment (NOBLE, week 52; VALIANT, week 26), glomerular C3 staining was reduced by at least two orders of magnitude in 60% of NOBLE patients and in 100% of VALIANT patients; corresponding values for zero intensity staining were 40% and 100%, respectively (**Figure 3**).
- For all parameters, the effect of pegcetacoplan in post-transplant patients is consistent with that observed in the overall population of pegcetacoplan-treated patients from the two trials.[13]

Safety

- One patient in the NOBLE trial discontinued pegcetacoplan due to TEAEs of 'flu and weight loss (**Table 2**).
- No new safety signals were identified; no infections caused by encapsulated bacteria were reported, and there were no cases of graft loss/rejection.

Figure 3: Representative biopsies from a pegcetacoplan-treated patient with C3G in a native kidney (VALIANT)[14]



	NOBLE (12-week biopsy)	VALIANT (26-week biopsy)
Change from baseline in C3 staining		
≥2 OOM reduction	60%	100%
Zero staining	40%	100%

C3 staining was assessed with kidney biopsies at weeks 12 and 52 during NOBLE and at week 26 during VALIANT (optional for adolescents). Staining was assessed on a standard 3-point scale (0=no staining; 1+=weak/minimal staining; 2+=moderate staining; 3+=strong/high intensity staining).[15] All patients had ≥2+ staining for C3 on kidney biopsy at baseline.
C3G, complement 3 glomerulopathy; OOM, orders of magnitude.

Table 2: TEAEs reported in the two trials

	NOBLE (n=6)[a,b]	VALIANT (n=5)[c]
TEAEs	5 (83.3)	5 (100.0)
Related to pegcetacoplan	2 (33.3)[d]	1 (20.0)[e]
Serious TEAEs	1 (16.7)	0 (0.0)
Related to pegcetacoplan	1 (16.7)[f]	0 (0.0)
TEAEs leading to treatment discontinuation	1 (16.7)[g]	0 (0.0)
Graft loss or rejection	0 (0.0)	0 (0.0)

[a]Patients with proteinuria ≥1 g/g at baseline.
[b]Safety was assessed for 52 weeks.
[c]Includes post-transplant patients who received pegcetacoplan during the randomised controlled period.
[d]Mild-to-moderate 'flu and weight loss (one patient); possibly related.
[e]Mild-to-moderate mucositis, elevated gamma-glutamyltransferase, and rosacea (one patient); all possibly related.
[f]Worsening neutropenia (one patient); possibly related; drug was interrupted; event resolved; drug was reintroduced.
[g]Pegcetacoplan was withdrawn for the patient with TEAEs of 'flu and weight loss.
TEAE, treatment-emergent adverse event.

Abbreviations: C3, complement 3; C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex-membranoproliferative glomerulonephritis; TEAE, treatment-emergent adverse event; UPCR, urine protein-to-creatinine ratio.

References: 1. Medjeral-Thomas NR, *et al. Clin J Am Soc Nephrol* 2014;9:46–53. 2. Patry C, *et al. Pediatr Nephrol* 2024;39:3569–80. 3. Tarragón B, *et al. Clin J Am Soc Nephrol* 2024;19:1005–15. 4. Wong EKS, *et al. Clin J Am Soc Nephrol* 2021;16:1639–51. 5. Zand L, *et al. J Am Soc Nephrol* 2014;25:1110–7. 6. Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43. 7. Zipfel PF, *et al. Front Immunol* 2019;10:2166. 8. Meuleman MS, *et al. Semin Immunol* 2022;60:1016342. 9. Dixon BP, *et al. Kidney Int Rep* 2023;8:2284–93. 10. EMPAVELI® (pegcetacoplan) US PI 2024. 11. ASPAVELI® (pegcetacoplan) Summary of Product Characteristics 2024. 12. Lamers C, *et al. Nat Commun* 2022;13:5519. 13. Bomback A, *et al. Kidney Int Rep* 2024;10:87–98. 14. Vivarelli M, *et al.* Oral presentation at ERA 2025. 15. Pickering MC, *et al. Kidney Int* 2013;84:1079–89.

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