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Pegcetacoplan Treatment Appears to Halt Disease Progression in C3G and Primary (Idiopathic) IC-MPGN Patients: Results from the Phase 3 VALIANT Study

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CONCLUSIONS

In VALIANT, **pegcetacoplan** resulted in restoration of complement pathway function, as indicated by **increased serum C3** and **decreased soluble C5b-9** levels.

This was accompanied by significant and clinically meaningful improvements in the **three key efficacy measures** of proteinuria reduction, C3 deposit clearance, and eGFR stabilization in patients with C3G and primary IC-MPGN, indicating pegcetacoplan's **profound disease-modifying effect**.

Reduction in proteinuria across the cohort, a key predictor of lower kidney failure risk,[1-3] suggests pegcetacoplan may have a **long-term impact**, significantly increasing the number of patients with **improved prognoses** and a **reduced risk** of **kidney failure**.

INTRODUCTION

C3 glomerulopathy (C3G) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) are rare, progressive kidney diseases driven by C3 dysregulation.[4,5]

Pegcetacoplan, a targeted C3 and C3b inhibitor, **acts centrally to block downstream complement activation** that leads to **kidney damage**.[6–11]

A recent **Kidney Health Initiative consensus** highlighted the **importance of assessing treatment effect via three clinical endpoints**: proteinuria reduction, histopathology improvement, and estimated glomerular filtration rate (eGFR) stabilization.[1] In the VALIANT phase 3 study (NCT05067127) of pegcetacoplan in patients with native or posttransplant recurrent C3G/primary IC-MPGN, **26 weeks of treatment** led to **statistically significant reduction in proteinuria** (68.1% vs. placebo), **eGFR stabilization** (+6.3 mL/min/1.73 m^2 vs. placebo), and **reduction in C3 staining** on renal biopsies (0 intensity staining in >70% of pegcetacoplan-treated patients with evaluable biopsies).[12]

Proteinuria, a key contributor to the progression of several kidney diseases, has been proposed as a **surrogate endpoint** for **kidney failure**.[1-3] Registry data show that a **≥50% reduction in proteinuria** over time correlated with a significantly **lower risk of kidney failure** in C3G patients, and patients with urine protein-to-creatinine ratio **(UPCR) of <0.88 g/g** 12 months after diagnosis have an **87% reduction in kidney failure risk** over 20 years.[1-3]

AIM

Evaluate the 26-week results of the VALIANT study to assess **indicators** that suggest **pegcetacoplan** may provide a potential **long-term protective effect in preventing kidney failure**.

METHODS

Patients were randomized 1:1 to receive pegcetacoplan 1080 mg* (subcutaneously twice weekly) or placebo for 26 weeks as add-on to their stable treatment regimen.† **Primary efficacy endpoint was proteinuria reduction.**‡ Data on **serum biomarkers** were collected and a *post-hoc* analysis was carried out to investigate the **absolute proteinuria categories** at baseline and week 26. Treatment-emergent adverse events (**TEAEs**) were recorded.

*Weight-based dosing for adolescents. †Both arms received optimized supportive care. ‡Change in log-transformed ratio of triplicate first-morning urine UPCR at week 26 over baseline.

RESULTS

Complement biomarker response:

124 patients enrolled in VALIANT (63 pegcetacoplan, 61 placebo).

Pegcetacoplan treatment led to a **rapid, sustained response** in **serum complement C3** (**Figure 1A**) and **soluble C5b-9 (Figure 1B)** at **week 4**, which was **maintained** through **26 weeks.**

Shift in proteinuria:

In the **pegcetacoplan** arm at week 26 vs baseline, patient distribution across **proteinuria ranges shifted towards lower values** including a decrease in proportion of patients in higher UPCR ranges (**Figure 2**).

Twenty of 63 patients (31.7%) achieved proteinuria normalization with pegcetacoplan.

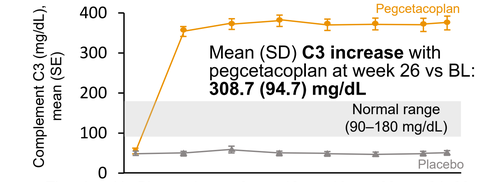
In contrast, in the **placebo** arm (**Figure 2**), there was **no increase** in the number of patients in low proteinuria ranges, while the proportion of patients in higher ranges stabilized or increased, as expected.

Safety:

TEAE frequency and severity were **similar** between arms (**Table 1**).

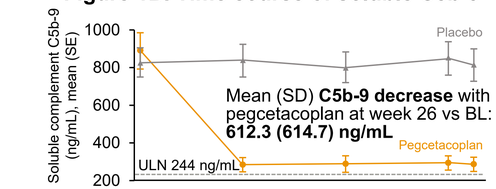
None of the 4 serious infections (3 pegcetacoplan; 1 placebo) were attributed to encapsulated bacteria.

Figure 1A. Time course of serum complement C3*



Time (week)	BL	4	8	12	16	20	24	26
Pegcetacoplan (n)	62	59	58	58	58	60	59	54
Placebo (n)	61	59	57	57	56	52	55	57

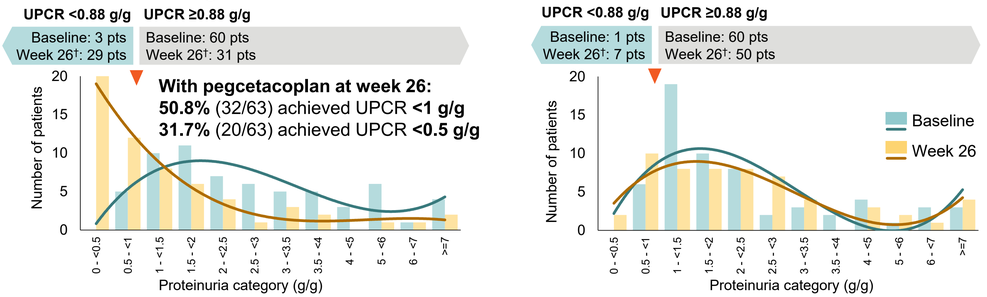
Figure 1B. Time course of soluble C5b-9*



Time (week)	BL	4	8	12	16	20	24	26
Pegcetacoplan (n)	56		57		54		50	53
Placebo (n)	57		53		52		46	45

*Data from pharmacodynamics set. BL, baseline; SD, standard deviation; SE, standard error; ULN, upper limit of normal.

Figure 2. Shift in absolute proteinuria at week 26 vs baseline



*Lines of best fit: polynomial function with 3 parameters. pts, patients; UPCR, urine protein-to-creatinine ratio. †Average UPCR of week 24 to 26 was used.

Table 1. TEAE frequency and severity

Patients, n (%)	Pegcetacoplan (N=63)	Placebo (N=61)
TEAEs	53 (84.1)	57 (93.4)
Treatment-related TEAEs	25 (39.7)	26 (42.6)
Severe TEAEs	3 (4.8)	4 (6.6)
Serious TEAEs	6 (9.5)	6 (9.8)
Serious infections		
COVID-19 pneumonia	1 (1.6)	0
Influenza	1 (1.6)	0
Pneumonia	1 (1.6)	0
Viral infection	0	1 (1.6)
TEAEs leading to treatment discontinuation	1 (1.6)	1 (1.6)
Deaths (COVID-19 pneumonia, unrelated to pegcetacoplan)	1 (1.6)	0

Safety population (all randomised and treated patients). TEAEs defined as any new AE that began, or any preexisting condition that worsened in severity, after the first dose of study drug and ≤56 days beyond the last dose of study drug. TEAE, treatment-emergent adverse event.

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DISCLOSURES **MDPG:** chairs the Rare Diseases Committee of the UK Kidney Association and reports fees for consulting and presenting from Novartis, Alexion, Calliditas, Sanofi, Britannia, and Travere. **ASB**: consulting fees from Amgen, Apellis, Catalyst, Genentech, Kezar, Novartis, Q32, Silence Therapeutics, and Visterra. **CL:** consulting fees from Apellis, Sobi, Novartis, and Alexion AstraZeneca. **CMN:** Associate Director for Molecular Otolaryngology and Renal Research Laboratory; receives NIH grant support (2R01DK110023-07); serves on advisory boards for Novartis, Apellis, Biocryst, and Alexion; participates as a site investigator for Novartis, Apellis, Biocryst, and Retrophin; is a member of the data safety monitoring board for Kira; serves as Chair of a data safety monitoring board for FIT4KID; and receives author royalties for UpToDate. **MCP** has received consulting fees from Alexion, Achillion, Annexon, Apellis, BioCryst, ChemoCentryx, Complement Therapeutics, Gemini, Gyroscope, MIRNA Therapeutics, Omeros, and Q32bio Pharma.**GR:** consultancy agreement with Alexion Pharmaceuticals Inc, Janssen Pharmaceutical, Akebia Therapeutics, Biocryst Pharmaceuticals, Menarini Ricerche SpA, AstraZeneca; speaker honoraria/travel reimbursement from Boehringer Ingelheim, Novartis. **NvdK:** consultancy fees from Roche, Novartis, Alexion, Sobi and Samsung. **ZW:** employee of Apellis Pharmaceuticals and holds stock or stock options. **JS** and **LQG:** employees of Swedish Orphan Biovitrum AB and may hold stock or stock options. **DD**: employee of Apellis Pharmaceuticals and may hold stock or stock options. **FF:** consultancy honorarium from Alexion, Astra Zeneca, Apellis, Novartis, Sobi and Roche.

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