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Pegcetacoplan treatment response in VALIANT/VALE: Impact of disease chronicity in C3G and primary IC-MPGN

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D. WALLACE[1], **A. AVILA**[2], **A. MASTRANGELO**[3], **F. PROVOT**[4], **D. ZECHER**[5], **C.M. NESTER**[6], **A.S. BOMBACK**[7], **L. QUINTANA-GALLARDO**[8], **J. SZAMOSI**[8], **G. AYEHU**[9], **A. MUKHERJEE**[9] **and F. FAKHOURI**[10]

[1] Royal Manchester Children's Hospital, Manchester, United Kingdom [2] Department of Nephrology, Hospital Universitario Doctor Peset, Valencia, Spain [3] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Lombardia, Italy [4] Department of Nephrology, Lille University Hospital, Lille, France [5] Department of Nephrology, University Hospital Regensburg, Regensburg, Germany [6] University of Iowa, Stead Family Children's Hospital, Iowa City, IA, United States [7] New York-Presbyterian/Columbia University Irving Medical Center, New York, NY, United States [8] Swedish Orphan Biovitrum AB, Stockholm, Sweden [9] Apellis Pharmaceuticals, Inc., Waltham, MA, United States [10] Centre Hospitalier Universitaire Vaudois, Lausanne, Vaud, Switzerland

INTRODUCTION

C3G and primary (idiopathic) IC-MPGN

Rare glomerular diseases driven by uncontrolled activation of C3, causing excessive glomerular deposition of C3 breakdown products[1,2]

Indicators of disease chronicity

High levels of interstitial fibrosis/tubular atrophy (IFTA) and low estimated glomerular filtration rate (eGFR) correlate with poor outcomes[3-5]. Cumulative structural damage can develop silently without acute signs[6].Current standard of care does not address the underlying pathologic mechanism[2], permitting irreversible kidney damage

Pegcetacoplan

Targeted C3/C3b inhibitor. In the Phase 3 VALIANT study, pegcetacoplan led to clearance of C3 deposits, proteinuria reduction, and eGFR stabilisation[7] – irrespective of age, disease subtype, proteinuria levels, or concomitant immunosuppression[7-9]

AIM & METHOD

Aim

***Post-hoc* analysis** evaluating the impact of baseline disease chronicity on 1-year clinical outcomes following pegcetacoplan treatment in patients with C3G and primary IC-MPGN

Dataset

Pooled data from the Phase 3 VALIANT trial and its open-label extension study (VALE) enabling a uniform evaluation of 1 year of pegcetacoplan exposure

Realigned baseline approach:

- Continuous pegcetacoplan arm: original VALIANT baseline; outcomes at 52 weeks
- Placebo to pegcetacoplan switch: Week 26 as new baseline (26 weeks VALIANT + 26 weeks VALE)
- Patients with >50% IFTA excluded from VALIANT

Patient stratification

- IFTA at baseline biopsy (≤25% or 26–50%)
- eGFR at baseline (>90, ≤90–≥60 or <60 mL/min/1.73 m^2)

Outcomes

Changes in proteinuria (based on urine protein:creatinine ratio [UPCR] from first morning urine) and eGFR over 52 weeks were analysed

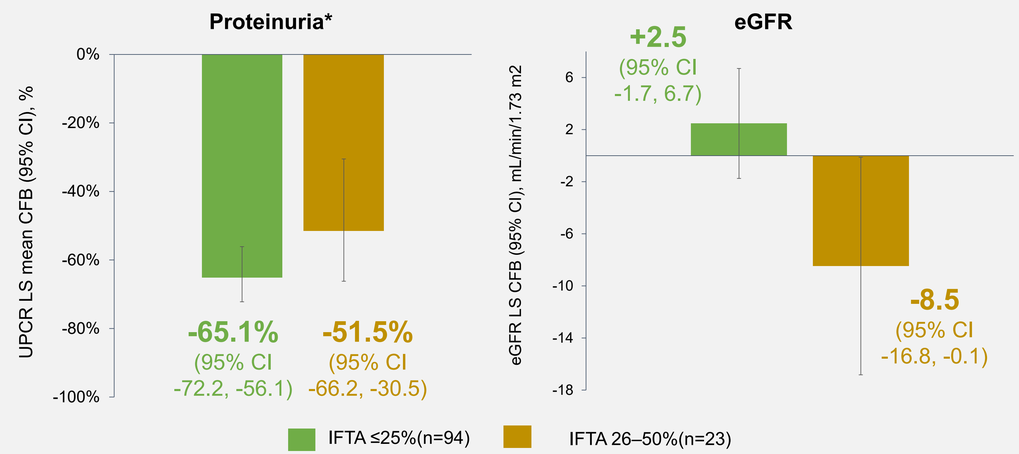
Time is Kidney

Pegcetacoplan reduces proteinuria by >50% indicating **effective suppression of ongoing complement-mediated disease regardless of baseline disease chronicity**

Data suggest that **patients with reduced eGFR may still derive clinical benefit from targeted C3 inhibition;** however, **eGFR stabilisation is maximised when treatment begins before significant kidney fibrosis**

These findings support early identification and intervention with targeted C3 inhibition before substantial fibrotic damage is established

FIGURE 1. Change from baseline in UPCR and eGFR at Week 52 by IFTA at baseline



* Geometric means and % change estimated from exponentiated LS mean differences from a MMRM of log-transformed UPCR.
CFB, change from baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; IFTA, interstitial fibrosis/tubular atrophy; LS, least squares; MMRM, mixed model for repeated measures; UPCR, urine protein:creatinine ratio.

RESULTS

119 (IFTA) and 120 (eGFR) patients were evaluable **(TABLE 1)**

IFTA-stratified

Proteinuria reductions were consistent **(FIGURE 1)**
IFTA ≤25%: eGFR stabilisation achieved over 52 weeks
IFTA 26–50%: experienced an eGFR decline from baseline despite proteinuria reduction (lower than placebo annualised rate of -15.6 mL/min/1.73 m^2/yr **(FIGURE 1)**

eGFR-stratified

Across all baseline eGFR strata, mean UPCR reduction >50% and eGFR stabilisation over the 52-weeks **(TABLE 2)**

TABLE 1. Characteristics at baseline by IFTA status and eGFR category

	Baseline IFTA in renal biopsy		Baseline eGFR (mL/min/1.73 m^2)		
	≤25% (n=96)	26-50% (n=23)	>90 (n=47)	≤90–≥60 (n=34)	<60 (n=39)
Age, mean (SD), years	23.8 (14.3)	34.7 (18.9)	18.1 (7.9)	25.2 (13.4)	36.7 (19.5)
Adolescents (12–17 years), n (%)	50 (52.1)	3 (13.0)	29 (61.7)	14 (41.2)	10 (25.6)
Adults (≥18 years), n (%)	46 (47.9)	20 (86.9)	18 (38.3)	20 (58.8)	29 (74.4)
Sex, female, n (%)	56 (58.3)	11 (47.8)	28 (59.6)	23 (67.6)	17 (43.6)
Baseline triplicate FMU UPCR, mean (SD), g/g	3.0 (2.5)	2.8 (1.8)	2.2 (1.5)	2.9 (2.0)	3.9 (3.1)
Baseline eGFR, mean (SD), mL/min/1.73 m^2	82.5 (34.0)	66.7 (35.0)	114.5 (17.2)	76.1 (9.7)	38.8 (10.8)
Underlying disease based on screening biopsy, n (%)					
C3G	70 (72.9)	21 (91.3)	38 (80.9)	24 (70.6)	30 (76.9)
Primary IC-MPGN	26 (27.1)	2 (8.7)	9 (19.1)	10 (29.4)	9 (23.1)
Time since diagnosis, mean (SD), years*	3.4 (2.6)	3.2 (3.4)	4.0 (2.7)	2.6 (2.5)	3.1 (2.9)

* For patients grouped by baseline IFTA: ≤25% n=90; 26-50% n=22. For patients grouped by baseline eGFR: >90 n=46; ≤90–≥60 n=33; <60 n=34.
C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; FMU, first-morning urine; IC-MPGN, immune complex-membranoproliferative glomerulonephritis; IFTA, interstitial fibrosis/tubular atrophy; SD, standard deviation; UPCR, urine protein:creatinine ratio.

TABLE 2. Change from baseline in UPCR and eGFR at Week 52 by baseline eGFR category

	Baseline eGFR (mL/min/1.73 m^2)		
	>90 (n=45)	≤90–≥60 (n=34)	<60 (n=39)
UPCR LS mean CFB (95% CI), %*	-63.8 (-73.0, -51.5)	-63.1 (-74.3, -47.1)	-63.1 (-74.0, -47.6)
eGFR LS mean CFB (95% CI), mL/min/1.73 m^2	+1.6 (-4.4, 7.7)	-3.3 (-11.8, 5.2)	+1.3 (-3.8, 6.4)

* Geometric means and % change estimated from exponentiated LS mean differences from a MMRM of log-transformed UPCR. CI, confidence interval; CFB, change from baseline to Week 52; eGFR, estimated glomerular filtration rate; LS, least squares; MMRM, mixed model for repeated measures; UPCR, urine protein:creatinine ratio.

CONCLUSIONS

1. **Effective complement suppression at all stages**: pegcetacoplan achieved ≥50% proteinuria reduction across disease categories
2. **IFTA — not eGFR alone — predicts eGFR response**: IFTA stratification revealed differential eGFR trajectories, reflecting potential irreversibility
3. **Low eGFR alone does not preclude benefit**: patients with low eGFR may still derive meaningful clinical benefit from targeted C3 inhibition
4. **Early intervention is key:** data suggest biological rationale for initiation of targeted C3 inhibition, before substantial fibrotic damage occurs

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DW has nothing to disclose. **AA** has been a consultant for Alexion, GSK, and Vifor, received honoraria from Alexion, GSK, and Vifor, has had advisory or leadership roles for Alexion and GSK, and has been involved in speakers bureaus for Alexion, Otsuka, and GSK. **AM** received consultant and speaker fees from Sobi. **FP** has been a consultant for Alexion, Astellas, and Sanofi, and has had advisory or leadership roles for Novartis, Sanofi, and Takeda. **DZ** has received consulting fees from Sobi, Apellis, and Novartis. **CMN** has received consultant fees from Alexion Pharmaceuticals, Apellis, Biocryst Pharmaceuticals, Novartis, and Vertex, DSMB fees from Silence Therapeutics and clinical trial support from Apellis, Biocryst Pharmaceuticals, Novartis, and Travere. **ASB** has received consulting fees from Amgen, Apellis, Catalyst, Genentech, Kezar, Novartis, Q32, Silence Therapeutics, and Visterra. **LQ-G** is an employee of Swedish Orphan Biovitrum AB and holds stock or stock options. **JS** is an employee of Swedish Orphan Biovitrum AB and holds stock or stock options. **GA** is an employee of Apellis Pharmaceuticals and may hold stock or stock options. **AM** is an employee of Apellis Pharmaceuticals and may hold stock or stock options. **FF** has received consultancy honorarium from Alexion, Astra Zeneca, Apellis, Novartis, Sobi and Roche.

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CONTACT INFORMATION
Sobi Medical Information
medical.info@sobi.com