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Clinical Efficacy Of Pegcetacoplan Versus Iptacopan In Patients With C3 Glomerulopathy: Indirect Treatment Comparison

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CONCLUSIONS

- In the absence of head-to-head studies, indirect treatment comparisons (ITCs) show pegcetacoplan offers greater proteinuria reduction, indicating a potential therapeutic benefit over iptacopan for patients with C3G
- Pegcetacoplan was associated with significantly greater reductions in proteinuria and more patients achieving the composite renal endpoint vs. iptacopan
- The relative improvement in reducing proteinuria at 6 months was maintained at 12 months, highlighting the potential of pegcetacoplan to deliver a sustained therapeutic effect
- These comparative effectiveness findings will help guide clinicians and payers to better understand the utility of new therapies to treat patients with C3G

INTRODUCTION

- C3G is a rare complement-mediated kidney disease, characterised by progressive loss of kidney function and poor prognosis, compounded by limited efficacy of SoC antiproteinuric and immunosuppressive therapies[1]
- Pegcetacoplan (C3/C3b inhibitor) and iptacopan (factor B inhibitor) are complement pathway inhibitors[2] Pegcetacoplan is approved for adults/adolescents with C3G or primary IC-MPGN[3] and iptacopan for adults with C3G[4]

OBJECTIVES

- In the absence of head-to-head trials, this analysis aimed to assess the relative efficacy of pegcetacoplan and iptacopan in patients with C3G using ITCs: Bucher and matching-adjusted indirect comparison (MAIC)

METHODS

Data sources

- The VALIANT (pegcetacoplan) and APPEAR-C3G (iptacopan) trials had similar designs but with some differences in eligibility (**Table 1**)

Table 1: Overview of the VALIANT and APPEAR-C3G trials

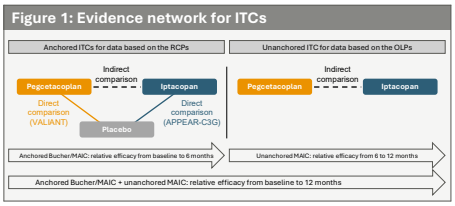
	VALIANT (NCT05067127)[5]	APPEAR-C3G (NCT04817618)[6]
Trial design	Phase 3 with 6-month RCP and 6-month OLP	
Key eligibility[b]	Adolescents (≥12 years and ≥30 kg) and adults	Adults (≥18 to ≤60 years)[a]
	C3G (native/post-transplant recurrent) or primary IC-MPGN	C3G (native only)
	No limit on baseline serum C3 levels	Baseline serum C3 <0.85 × LLN (<77 mg/dL)
	UPCR ≥1.0 g/g and eGFR ≥30 mL/min/1.73 m²	
	Prednisolone doses up to 20 mg/day permitted	Prednisolone doses up to 7.5 mg/day permitted
	SoC treatment for ≥12 weeks prior to randomisation	SoC treatment for ≥90 days prior to randomisation
Treatment[c]	Pegcetacoplan (up to 1080 mg twice per week)[d] (n=63) or placebo (n=61)	Iptacopan (200 mg twice per day) (n=38) or placebo (n=36)
1[e] endpoint	Log-transformed UPCR at 6 months	

[a] Enrollment ongoing in a separate cohort of adolescents. [b] Patients in VALIANT excluded from the MAIC: diagnosed with primary IC-MPGN; prior renal transplant; received >7.5 mg/day (or equivalent) of prednisone ≤90 days before study drug administration; and serum C3 levels ≥77 mg/dL. [c] During the double-blind period; all patients received pegcetacoplan or iptacopan during the OLP. [d] Lower weight-based dose of 648 mg or 810 mg used for some adolescents

Indirect treatment comparisons

- Relative treatment effects were estimated from baseline to 6 months based on two anchored ITCs, and from baseline to 12 months based on the anchored ITCs plus an unanchored ITC (**Figure 1**)

Figure 1: Evidence network for ITCs



Bucher

- Robust and straightforward methodology that preserves the internal validity conferred by randomisation and relative placebo effects of the included trials[7,8]
- Must be anchored (e.g. to placebo) and assume the studies are comparable with respect to study design, effect modifiers, and outcomes measured[7,8]
- Data were analysed for all available patients (i.e. the ITT populations) in VALIANT and APPEAR-C3G to preserve randomisation and the original sample size

MAIC

- Can be anchored or unanchored and use individual patient data from one trial and aggregate data from another trial and adjust between-trial differences in eligibility criteria and baseline characteristics[9,10]
- In both MAICs, the trials were first aligned by excluding patients in VALIANT who would be ineligible under the APPEAR-C3G criteria (**Table 1, Footnote b**)
- Propensity score weights were then estimated via logistic regression, using age as a prespecified prognostic variable, to approximate each VALIANT patient's probability of enrollment in APPEAR-C3G and to balance baseline characteristics across trials. Outcomes were subsequently analysed on the weighted populations

Outcomes

- Relative efficacy at 6 months was assessed for mean % reduction in log-transformed UPCR from baseline; proportion of patients who achieved UPCR <1 g/g; proportion of patients who achieved ≥50% UPCR reduction from baseline; proportion of patients who achieved the composite renal endpoint; and mean change in eGFR from baseline
- Relative efficacy at 12 months was assessed for mean reduction in log-transformed UPCR and mean change in eGFR
- A comparative assessment of glomerular C3 staining was not feasible due to differences in outcome measurement in the two trials

RESULTS

Relative efficacy: baseline to 6 months

- The Bucher analysis showed that pegcetacoplan was associated with a statistically significant improvement compared with iptacopan across three clinically relevant proteinuria outcomes and the composite endpoint (**Figures 2 and 3**)
- In the Bucher analysis, the mean change from baseline in eGFR between pegcetacoplan and iptacopan did not reach statistical significance
- Results from the anchored MAIC were generally consistent with the Bucher analysis across the five endpoints (**Figure 3**)

Relative efficacy: baseline to 12 months

- Mean change in UPCR from baseline to 12 months was significantly greater for pegcetacoplan vs. iptacopan (**Figure 4A**)
- Mean between-trial difference in eGFR change from baseline to 12 months was not significantly different between pegcetacoplan and iptacopan (**Figure 4B**)

Figure 2: Summary of proteinuria outcomes and the composite endpoint for pegcetacoplan vs. iptacopan at Month 6 (Bucher)

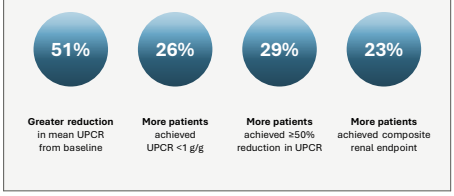
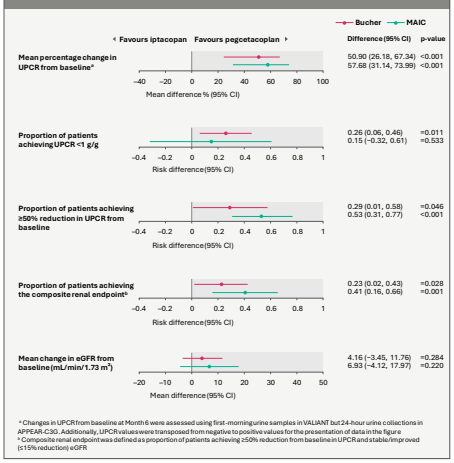
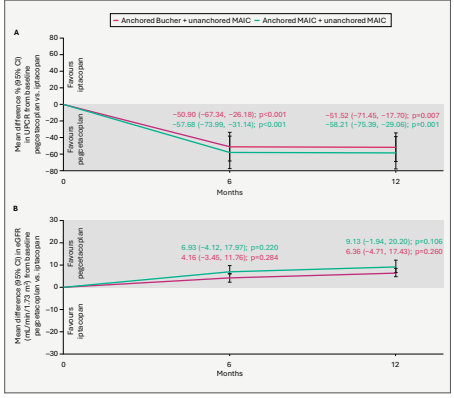


Figure 3: Summary of efficacy outcomes for pegcetacoplan vs. iptacopan from baseline to 6 months



* Changes in UPCR from baseline at Month 6 were assessed using first-morning urine samples in VALIANT but 24-hour urine collections in APPEAR-C3G. Additionally, UPCR values were transposed from negative to positive values for the presentation of data in the figure
* Composite renal endpoint was defined as a proportion of patients achieving ≥50% reduction from baseline in UPCR and stable/improved (≤15% reduction) eGFR

Figure 4: Mean change from baseline to 12 months for pegcetacoplan vs. iptacopan in UPCR (A) and in eGFR (B)



LIMITATIONS

- Individual patient data were available only for the pegcetacoplan trial and not for the iptacopan trial; thus, patient-level adjustment between trials was not feasible
- Anchored ITCs are potentially limited by assumptions about differences in trial design, reliance on reporting of trial characteristics and unknown differences not considered
- Unanchored MAICs rely on an assumption that all relevant confounding baseline factors are included in the weighting model

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ABBREVIATIONS

C3, complement component 3; C3G, C3 glomerulopathy; CI, confidence interval; eGFR, estimated glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; ITC, indirect treatment comparison; ITT, intent-to-treat; LLN, lower limit of normal; MAIC, matching-adjusted indirect comparison; OLP, open-label phase; RCP, randomised controlled period; SoC, standard of care; UPCR, urine protein–creatinine ratio.

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DISCLOSURES

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