The World Congress of Nephrology (WCN) 2025
New Delhi, India, February 6–9, 2025

Abstract specifications for WCN 2025

Abstract category: The Smart Kidney

Abstract topic: Clinical Glomerulonephritis

Character count: 1934/3,400 characters [including spaces, excluding tables and graphs if inserted as an image, author names and affiliations, and keywords]

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Standard of English: US or UK (Current: US)

Submission deadline: September 4, 2024

Notification of acceptance: October 15, 2024

Effect of Iptacopan on Proteinuria and Complement Biomarkers in IgA Nephropathy (IgAN): Interim Analysis of the Phase 3 APPLAUSE-IgAN Study

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Introduction: The alternative complement pathway (AP) plays a key role in IgAN pathogenesis and there is an unmet need for targeted disease-modifying treatments. In IgAN, the AP is often activated in urine but not in plasma, indicating renal complement activity. Iptacopan binds to Factor B and specifically inhibits the AP. In a Phase 2 study, iptacopan decreased plasma Bb and Wieslab activity, and urinary sC5b-9 decreased to almost healthy volunteer range. The APPLAUSE-IgAN trial is evaluating iptacopan vs placebo on top of optimized stable supportive therapy. In the pre-specified interim analysis (IA), iptacopan was superior to placebo in reducing proteinuria at Month 9 relative to baseline (24h urine protein–creatinine ratio reduction 38.3%; $P<0.0001$). Here, we present complement biomarker exploratory results from the IA.

Methods: APPLAUSE-IgAN (NCT04578834), a Phase 3, randomized, double-blind, placebo-controlled trial, enrolled adults with biopsy-confirmed IgAN with proteinuria ≥1 g/g despite stable supportive therapy. Patients were randomized 1:1 to iptacopan 200 mg or placebo twice daily for 24 months while remaining

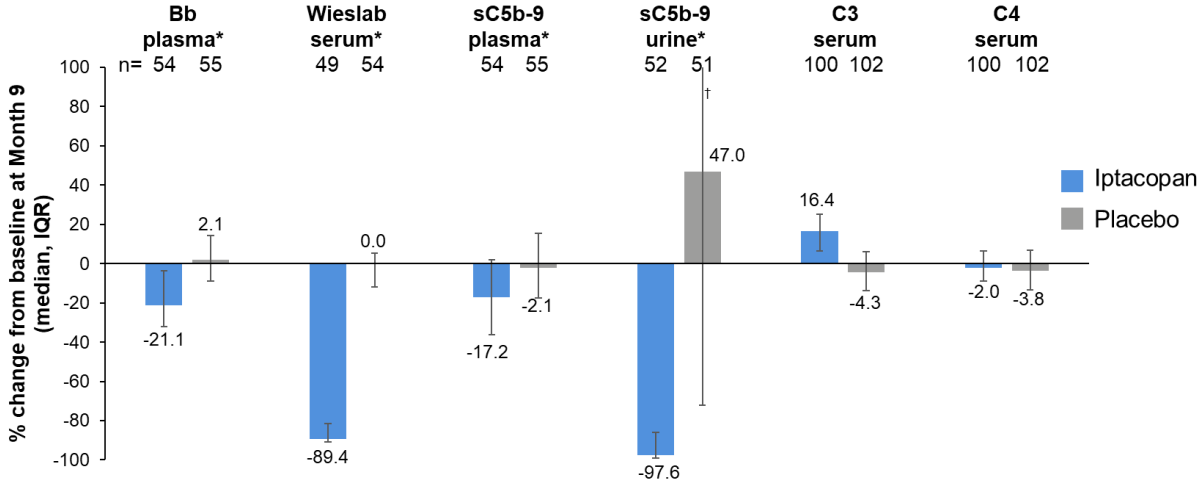
on supportive therapy. IA was performed when 250 patients reached Month 9 or discontinued the study. Change from baseline in biomarkers of complement activity was assessed: C3 and C4 in all patients; Bb, sC5b-9, and Wieslab were only assessed in a subset of patients.

Results: Iptacopan selectively inhibited the AP, with reductions in serum Wieslab activity, plasma Bb and sC5b-9, and increases in serum C3, while serum C4 was unchanged (**Figure**). Median decrease in urinary sC5b-9 was 97.6% (IQR 86.1–99.2) in the iptacopan arm; the Month 9 value was within the range observed in healthy individuals.

Conclusion: Iptacopan inhibited systemic and intrarenal activation of the AP in patients with IgAN at Month 9, supported by reductions in serum Wieslab, plasma Bb and sC5b-9, and urinary sC5b-9.

This abstract was also submitted for the ASN Kidney Week, 23–27 October 2024, San Diego, CA, USA.

Figure. Effect of iptacopan on biomarkers of complement activation at Month 9



*Available only in a subset of patients. †Y-axis truncated at 100; Q3 for urine sC5b-9 in placebo arm is 316.4.