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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KEY FINDINGS & CONCLUSIONS

- APPLAUSE-IgAN is the first Phase 3 study confirming the clinical benefit of alternative pathway inhibition in IgAN
- Combined evidence from the Phase 2 and Phase 3 studies suggest an **early systemic alternative pathway inhibition and reduction of intrarenal alternative pathway activation** which is sustained up to 9 months.
  - In the Phase 2 study, iptacopan treatment showed systemic inhibition of the alternative pathway and reduction of the urinary sC5b-9 to nearly healthy volunteers' range as early as Day 8
  - In the Phase 3 study, at Month 9 of treatment systemic alternative pathway inhibition and urinary sC5b-9 reduction was in the ranges observed in phase 2 at earlier treatment time points
- The study is ongoing and will continue per protocol until completion (final readout projected in 2025) to confirm long-term efficacy and safety

This study is sponsored by Novartis Pharma AG.
Poster presented at the ISN World Congress of Nephrology 2025 | 6–9 February 2025 | New Delhi, India.
Data was previously presented at American Society of Nephrology Kidney Week 2024 | 23–27 October 2024 San Diego, CA, USA.

INTRODUCTION

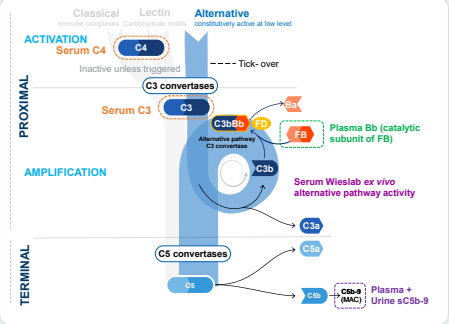
- IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide with a global incidence of 2.5/100,000/year[1]
- Overactivation of the complement system via the alternative pathway is a key driver of IgAN pathophysiology[2]
- Iptacopan, an oral, first-in-class, specific inhibitor of Factor B of the alternative complement pathway, is the first approved complement inhibitor in IgAN by the US FDA.[3] It selectively inhibits the alternative pathway and the amplification loop, leaving direct signaling from the lectin and classical pathways intact[4]
- The APPLAUSE-IgAN is a Phase 3, multicenter, randomized, double-blinded, placebo-controlled study (NCT04578834) evaluating the efficacy and safety of iptacopan vs placebo in patients with biopsy-confirmed IgAN and proteinuria ≥1 g/g (24h urine) despite optimized supportive therapy. Here, we discuss the interim results of the exploratory biomarker analyses of the APPLAUSE-IgAN study

METHODS

Biomarker exploratory analyses

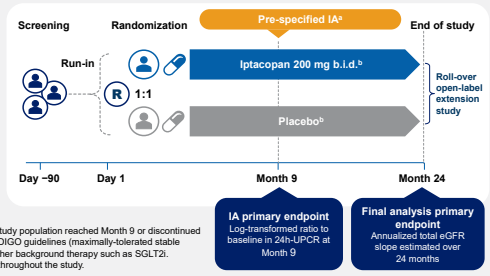
- Percentage change from baseline in biomarkers of complement activity:
  - **Serum**: C4, C3, Wieslab
  - **Plasma**: Bb (Catalytic subunit of FB), sC5b-9
  - **Urine**: sC5b-9

Figure 1. Complement pathway biomarkers



Study design

Figure 2. Study design



[a]Performed when the first 250 patients from main study population reached Month 9 or discontinued the study. [b]On top of optimal supportive care per KDIGO guidelines (maximally-tolerated stable [3 months] dose of RASi therapy) with or without other background therapy such as SGLT2i. Patients continued their supportive care treatment throughout the study.

Figure adapted from Rizk DV et al. Kidney Int Rep. 2023;8:968–979. Since APPLAUSE-IgAN is ongoing and remains double-blind, only data not disclosing patient-level information will be presented. Further, no interim eGFR data will be disclosed to avoid any bias on the primary endpoint at final analysis at the study end.

RESULTS

Table 1. Baseline demographic and disease characteristics were balanced across randomized arms

Parameters	Iptacopan N = 125	Placebo N = 125	Total N = 250
Age [years] – mean (SD)	39.3 (12.4)	39.6 (12.6)	39.4 (12.4)
Male – n (%)	71 (56.8)	60 (48.0)	131 (52.4)
Region – n (%)			
Asia	64 (51.2)	64 (51.2)	128 (51.2)
Baseline 24h-UPCR [g/g] – median (IQR)	1.81 (1.36–2.66)	1.87 (1.48–2.83)	1.85 (1.39–2.78)
Baseline eGFR [mL/min/1.73 m²] – mean (SD)	62.7 (26.0)	65.5 (26.7)	64.1 (26.3)
Time from kidney biopsy to baseline [years] – mean (SD)	1.7 (1.4)	1.6 (1.7)	1.7 (1.6)
MEST-C score[c] – n (%)			
M1	60.8	64.0	62.4
E1	28.8	28.8	28.8
S1	69.6	71.2	70.4
T1/T2	33.6/4.8	41.6/0.8	37.6/2.8
C1/C2	26.4/1.6	16.0/1.6	21.2/1.6

[c]Not all MEST-C components were available for all patients. Reproduced with permission from Perkovic V, et al. *N Engl J Med*. 2024.[5] ©*The New England Journal of Medicine* (2024).

- The interim analysis[d] results from the APPLAUSE-IgAN study demonstrated:
  - The superiority of iptacopan vs placebo in reducing proteinuria at Month 9 in patients with IgAN with persistent proteinuria ≥1 g/g despite receiving optimized supportive care (**24h-UPCR: 38.3%; 95% CI: 26.0, 48.6; P<0.0001**[e])
  - Iptacopan was well tolerated with a favorable safety profile

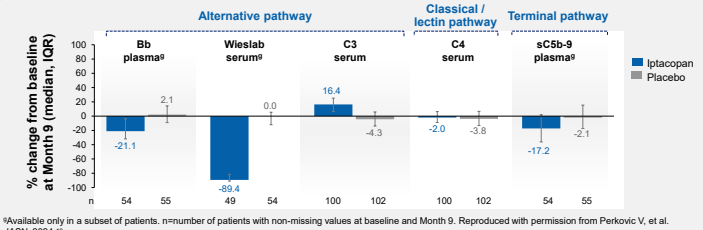
[d]Data presented at the ISN World Congress of Nephrology 2024 | 13–16 April 2024 | Buenos Aires, Argentina. [e]Significant at 1-sided multiplicity-adjusted alpha so that overall study type-I error was controlled at 1-sided 2.5%.

Table 2. Evidence of activation of complement pathway in urine at baseline but not in blood

Complement pathway biomarkers	Iptacopan N = 125	Placebo N = 125	Reference range
Serum C3, mg/L			
n	123	125	
Median (IQR)	1230.0 (1120.0–1434.0)	1310.0 (1140.0–1450.0)	900–1800[6]
Serum C4, mg/L			
n	123	125	
Median (IQR)	286.0 (230.0–334.0)	292.0 (256.0–349.0)	100–400[7]
Plasma Bb, ng/mL[f]			
n	66	71	
Median (IQR)	1935.0 (1550.0–2350.0)	1800.0 (1530.0–2190.0)	446–3920[8]
Plasma sC5b-9, ng/mL[f]			
n	67	72	
Median (IQR)	144.0 (120.0–177.0)	154.0 (126.0–179.0)	44.8–231[8]
Urine sC5b-9, pg/mL[f]			
n	69	70	
Median (IQR)	7801.0 (2553.0–20100.0)	6120.5 (1840.0–24380.0)	43.2–162.0[9]
Serum Wieslab, %[f]			
n	69	72	
Median (IQR)	78.6 (69.20–84.2)	79.8 (71.75–84.2)	21.1–>84.2[8]

[f]Available only in a subset of patients (approximately 150 biomarker sub study participants). N=number of all patients included in the analysis; n=number of patients providing sample for respective biomarker with non-missing measurements.

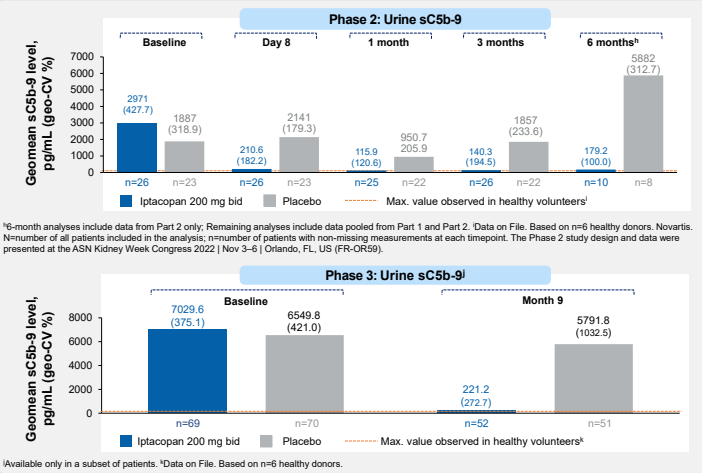
Figure 3. Changes in complement pathway biomarkers were consistent with selective alternative pathway inhibition



[g]Available only in a subset of patients. n=number of patients with non-missing values at baseline and Month 9. Reproduced with permission from Perkovic V, et al. *JASN*. 2024.[10]

Figure 4. Complement terminal pathway activity in the urine

- Phase 2 study: Iptacopan fully suppressed complement terminal pathway activity in the urine starting from Day 8 of treatment
- Phase 3 study: In the iptacopan arm, urinary sC5b-9 at Month 9 was near the range observed in healthy individuals



[h]6-month analyses include data from Part 2 only; Remaining analyses include data pooled from Part 1 and Part 2. [i]Data on File. Based on n=6 healthy donors. Novartis. N=number of all patients included in the analysis; n=number of patients with non-missing measurements at each timepoint. The Phase 2 study design and data were presented at the ASN Kidney Week Congress 2022 | Nov 3–6 | Orlando, FL, US (FR-OR59).

[j]Available only in a subset of patients. [k]Data on File. Based on n=6 healthy donors.

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Disclosures

DVR: Grants/research support/grants pending from Reata Pharmaceuticals, Travere Therapeutics (Retrophin), Pfizer Pharmaceuticals, Calliditas Therapeutics (Pharmalink), Otsuka Pharmaceuticals (Visterra), Vertex Pharmaceuticals, Chinook Pharmaceuticals, Vera Therapeutics, and LaRoche; consulting fees from Novartis, GSK, George Clinical, Eledon Pharmaceuticals, Otsuka Pharmaceuticals (Visterra), Calliditas Therapeutics (Pharmalink), Chinook Pharmaceuticals, LaRoche, Vera Therapeutics, and BioCryst; honorarium from Calliditas Therapeutics (Pharmalink), Chinook Pharmaceuticals, Otsuka Pharmaceuticals, Vera Therapeutics, BioCryst, Argenx; ownership in Reliant Glycosciences LLC. **DK, OP, TH, MAV, TM, RR**: Employee and shareholder of Novartis. **VP**: Serves as a Board Director for St. Vincent's Health Australia, George Clinical, and several Medical Research Institutes; and has received honoraria for Steering Committee roles, scientific presentations, and/or advisory board attendance from AstraZeneca, Boehringer Ingelheim, Janssen, Novo Nordisk, Novartis, Bayer, Chinook Therapeutics, Gilead, GlaxoSmithKline, Travere Therapeutics, Inc., and Otsuka.

Abbreviations

b.i.d., twice daily; CI, confidence interval; eGFR, estimated glomerular filtration rate; h, hour; IA, interim analysis; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; KDIGO, Kidney Disease Improving Global Outcomes; n, Number of patients with values non-missing/not imputed as per the intercurrent event handling strategy; N, Number of all patients included in the analysis (i.e. with non-missing baseline and covariates); RASi, renin-angiotensin system inhibitor; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SRI, severe renal impaired; TEAEs, treatment emergent adverse events; UPCR, urine protein–creatinine ratio.

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APPLAUSE-IgAN Primary Results Publication (NEJM 2024)