Efficacy and safety of iptacopan in patients with IgA nephropathy (IgAN): Interim analysis of the Phase 3 APPLAUSE-IgAN study

Dana V. Rizk[1], Dmitrij Kollins[2], Olympia Papachristofi[2], Thomas Hach[2], Severina Jacinto-Sanders[2], Tobias Merkel[2], Ronny Renfurm[2], Vlado Perkovic[3], on behalf of the APPLAUSE-IgAN Steering Committee

[1]University of Alabama at Birmingham, Birmingham, AL, USA; [2]Novartis Pharma AG, Basel, Switzerland; [3]University of New South Wales, Sydney, NSW, Australia

WCN25-AB-799

KEY FINDINGS & CONCLUSIONS

- **APPLAUSE-IgAN** demonstrated the **superiority of iptacopan vs placebo** on top of supportive care **in reducing proteinuria** at Month 9 in **patients with IgAN** with persistent proteinuria ≥1 g/g
- The treatment benefit of iptacopan over placebo on proteinuria was consistent across supportive analyses and subgroups studied
- Reduction in proteinuria was observed as early as the first post-baseline visit (Week 2)
- Iptacopan was well tolerated with a favorable safety profile
  - Overall, the incidence of TEAEs was generally balanced between the arms and the majority were mild to moderate in severity
- The study is ongoing and will continue in a blinded manner[a] per protocol until completion (final readout projected in 2025) to confirm long-term efficacy (annualized rate of total eGFR slope over 24 months) and safety over the 24-month treatment period

[a]Only limited interim results can be released.

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 National Kidney Foundation Spring Clinical Meetings 2024 | 14–18 May 2024 Long Beach, CA, USA.

INTRODUCTION

- IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide with a global incidence of 2.5/100,000/year.[1] Approximately 30% of patients with proteinuria 1–2 g/day progress to kidney failure within as little as 10 years[2]
- In IgA nephropathy, overactivation of the alternative complement pathway contributes to inflammation and glomerular injury.[3–6] Inhibition of Factor B prevents the formation of AP-related C3 convertase and the subsequent formation of C5 convertase[7]
- 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. The approval was based on a prespecified interim analysis of the ongoing Phase III APPLAUSE-IgAN trial in a population with baseline eGFR >30 ml/min/1.73 m^2 [8]

METHODS

- APPLAUSE-IgAN is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study (NCT04578834)

Eligibility criteria

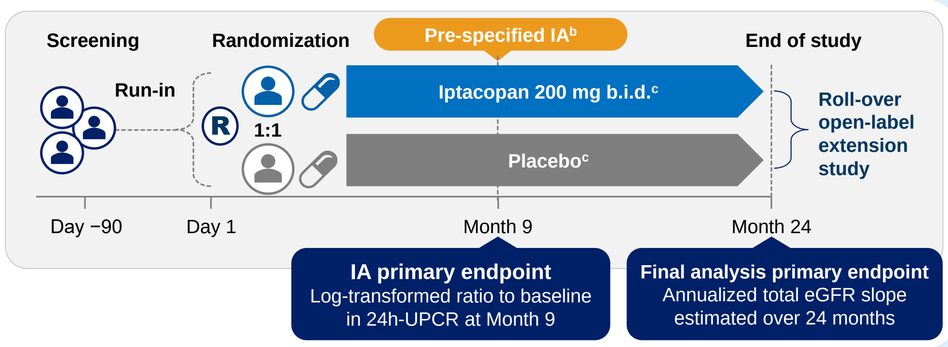
- Adults
- Biopsy-confirmed IgAN
- Proteinuria ≥1 g/g based on 24h urine (24h-UPCR) despite maximally tolerated RASi for ≥3 months, with or without SGLT2i

Main study population

eGFR ≥30 mL/min/1.73 m^2

SRI population

eGFR 20-<30 mL/min/1.73 m^2



[b]Performed when the first 250 patients from main study population reached Month 9 or discontinued the study. [c]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 are disclosed to avoid any bias on the primary endpoint at final analysis at the study end.

APPLAUSE-IgAN IA primary analysis approach

IA primary endpoint

- The primary endpoint of 24h-UPCR at Month 9 (log-transformed ratio to baseline) was analyzed using MMRM on 250 patients of the main study population who reached Month 9 or discontinued the study (IA-FAS)
- The primary analysis included all 24h-UPCR values collected from baseline
  - Up to and including the Month 9 visit or
  - Up to initiation of rescue/alternative medication or kidney replacement therapy. Measurements following these events were imputed to reflect worsening of disease

Additional analyses

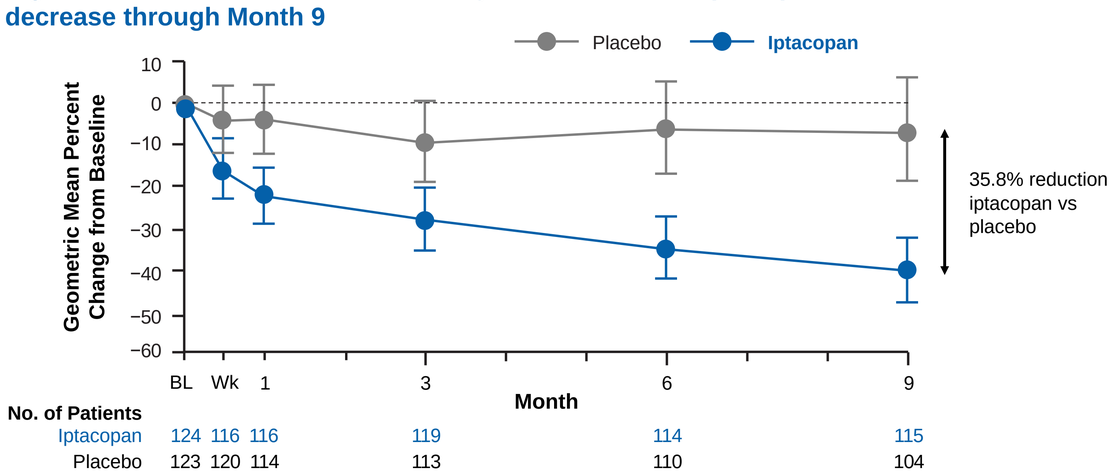
- Other secondary/exploratory efficacy endpoints were analyzed on the IA-FAS (n=250)
- Safety endpoints were descriptively summarized for all main study population patients who were randomized and received treatment at the IA data cut-off (n=443)

RESULTS

- Statistically significant and clinically meaningful reduction in 24h-UPCR (Relative percent reduction between arms: **38.3%**; 95% CI 26.0, 48.6; P<0.0001)[d]
- Proteinuria decreased as early as Week 2 in the iptacopan arm and continued to decrease through Month 9 (Relative percent reduction between arms: **35.8%**; 95% CI 22.6, 46.7; P<0.0001[e]; **Figure 1**)
- Proteinuria (24h-UPCR) reduction at Month 9 is consistent across prespecified subgroups (**Figure 2**) and across exploratory subgroups by baseline hematuria and MEST-C score (**Figure 3**)

[d]Significant at 1-sided multiplicity-adjusted alpha so that overall study type-I error was controlled at 1-sided 2.5%; [e]Nominal one-sided P-value.

Figure 1. Proteinuria decreased as early as Week 2 in the iptacopan arm and continued to decrease through Month 9

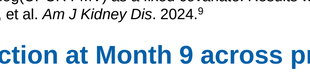


n: Number of patients with values non-missing and not imputed as per the intercurrent event handling strategy. Log transformed ratio to baseline was analyzed using MMRM including treatment, timepoint (as categorical variable), randomization strata as fixed effects, treatment*timepoint and timepoint*log(baseline UPCR FMV) as interaction terms and baseline log(UPCR FMV) as a fixed covariate. Results were back-transformed and are presented as percentages. Reproduced with permission from Rizk DV, et al. *Am J Kidney Dis*. 2024.[9]

Figure 2. Proteinuria (24h-UPCR) reduction at Month 9 across prespecified subgroups

Group	Iptacopan n/N	Placebo n/N	Iptacopan vs placebo % reduction (95% CI)
Overall	118/125	106/125	**38.3 (26.0, 48.6)**
Sex			
Male	68/71	49/60	35.5 (17.4, 49.7)
Female	50/54	57/65	42.6 (24.5, 56.4)
Geographic region			
Asia	63/64	55/64	31.6 (13.4, 46.0)
Non-Asia	55/61	51/61	45.5 (28.3, 58.5)
Baseline 24h-UPCR category			
≥1.5 g/g	73/80	76/91	41.2 (26.0, 53.2)
<1.5 g/g	45/45	30/34	27.3 (2.4, 45.9)
≥2 g/g	47/54	47/58	41.2 (20.9, 56.4)
<2 g/g	71/71	59/67	35.0 (18.8, 48.0)
Baseline eGFR category			
30–<45 mL/min/1.73 m^2	32/36	27/34	45.4 (25.3, 60.1)
≥45 mL/min/1.73 m^2	86/89	79/91	35.1 (19.0, 48.0)

P<0.0001[f] (Primary endpoint)

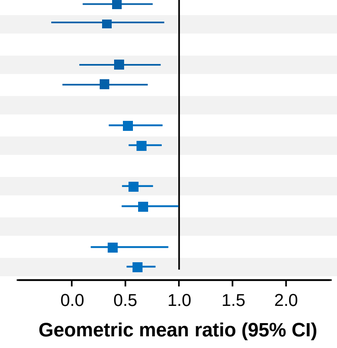


[f]One-sided. N: Number of all patients included in the analysis (with non-missing baseline and covariates). n: Number of patients with values non-missing/not imputed. Reproduced with permission from Perkovic V, et al. *N Engl J Med*. 2024.[10] ©*The New England Journal of Medicine* (2024).

Figure 3. Proteinuria (24h-UPCR) reduction at Month 9 across exploratory subgroups

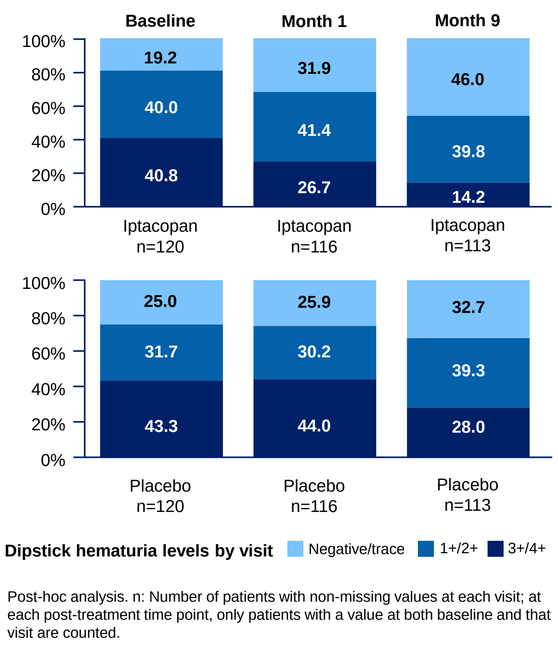
Group	Iptacopan n/N	Placebo n/N	Iptacopan vs placebo % reduction (95% CI)
Overall	118/125	106/125	**38.3 (26.0, 48.6)**
Dipstick hematuria at baseline			
≥1+	93/97	74/90	35.4 (21.8, 46.7)
Negative/trace	20/23	28/30	42.8 (6.1, 65.2)
M score[h]			
M1	69/76	66/80	44.3 (28.7, 56.5)
M0	40/40	35/39	20.8 (–6.1, 40.9)
E score[h]			
E1	32/36	30/36	39.2 (19.1, 54.3)
E0	76/79	69/81	37.4 (20.1, 50.9)
S score[h]			
S1	81/87	81/89	35.3 (19.2 to 48.2)
S0	27/28	19/29	39.4 (13.2 to 57.7)
T score[h]			
T1 or T2	46/48	44/53	34.4 (15.0 to 49.4)
T0	63/68	58/67	40.3 (21.8 to 54.5)
C score[h]			
C1 or C2	32/35	17/22	45.5 (15.0, 65.0)
C0	72/76	72/85	32.5 (15.2, 46.2)
M1 or E1 or C1/2[h]			
Yes	84/91	80/95	40.6 (26.1, 52.3)
No	25/25	21/24	31.5 (–0.3, 53.2)
M1 and E1 and C1/2[h]			
Yes	10/12	6/8	58.6 (9.5, 81.1)
No	99/104	95/111	36.2 (22.5, 47.5)

P<0.0001[g] (Primary endpoint)



[g]One-sided. [h]Based on qualifying biopsy as per inclusion criteria; assessed locally, documented by the investigator at screening. N: Number of all patients included in the analysis (with non-missing baseline and covariates). n: Number of patients with values non-missing/not imputed. For dual categories (M, E, and S), a score of 1 indicates evidence of respective lesions in biopsy specimens, and 0 the absence. For other categories (T and C), a higher score indicates a larger extent of the lesion. Reproduced with permission from Perkovic V, et al. *N Engl J Med*. 2024.[10] ©*The New England Journal of Medicine* (2024).

Figure 4. Changes in hematuria with iptacopan treatment



Post-hoc analysis. n: Number of patients with non-missing values at each visit; at each post-treatment time point, only patients with a value at both baseline and that visit are counted.

Table 1. Iptacopan tolerability and safety profile

Parameters	Iptacopan N = 222; n (%)	Placebo N = 221; n (%)
Adverse events		
TEAEs	138 (62.6)	153 (69.2)
Serious TEAEs	18 (8.1)	11 (5.0)
Severity of TEAEs[i]		
Mild	85 (38.3)	82 (37.1)
Moderate	46 (20.7)	64 (29.0)
Severe	7 (3.2)	7 (3.2)
TEAEs leading to treatment discontinuation	6 (2.7)	6 (2.7)
Most frequent or common TEAEs[j]		
COVID-19	31 (14.0)	37 (16.7)
Upper respiratory tract infection	20 (9.0)	16 (7.2)
Nasopharyngitis	11 (5.0)	16 (7.2)
Headache	9 (4.1)	12 (5.4)
Hypertension	4 (1.8)	13 (5.9)

Numbers (n) represent counts of subjects. [i]As assessed by the investigator. [j]Occurring in ≥5% in either treatment arm. Reproduced with permission from Perkovic V, et al. *N Engl J Med*. 2024.[10] ©*The New England Journal of Medicine* (2024).

- No deaths were reported in either arm

Acknowledgements

APPLAUSE-IgAN steering committee members: Drs. Vlado Perkovic, Dana V. Rizk, Jonathan Barratt, Brad Rovin, Naoki Kashihara, Bart Maes, Hong Zhang, and Hernán Trimarchi.

We thank the patients and their families and investigators and staff at participating study sites. Medical writing assistance was provided by Nupur Chaubey (Novartis Healthcare Pvt Ltd., Hyderabad, India).

References

1. McGrogan A, et al. *Nephrol Dial Transplant.* 2011;26(2):414–430; **2**. Reich HN, et al. *J Am Soc Nephrol.* 2007;18:3177–83; **3**. Rizk DV et al. *Front Immunol.* 2019;10:504; **4**. Boyd JK et al. *Kidney Int.* 2012;81:833-843; **5**. Onda K et al. *BMC Nephrol.* 2011;12:64; **6**. Maillard N et al. *J Am Soc Nephrol.* 2015;26:1503-1512; **7**. Merle NS et al. *Front Immunol.* 2015;6:257; **8**. FABHALTA® (iptacopan). Prescribing Information. Novartis Pharmaceuticals Corporation. 2024; **9**. Rizk DV, et al. *Am J Kidney Dis*. 2024;83:699-700. abstract. **10**. Perkovic V, et al. *N Engl J Med*. 2024. doi: 10.1056/NEJMoa2410316. Online ahead of print.

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, SJS, 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; BL, baseline, CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; FMV, first morning void; h, hour; IA, interim analysis; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease Improving Global Outcomes; MMRM, mixed model of repeated measures; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SRI, severe renal impaired; TEAE, treatment emergent adverse event; UPCR, urine protein−creatinine ratio; US FDA, United States Food and Drug Administration; Wk, week.

Scan to access:
APPLAUSE-IgAN Primary Results Publication (NEJM 2024)