Safety and efficacy of iptacopan in patients with IgA nephropathy (IgAN) with baseline eGFR 20–<30 mL/min: Phase 3 APPLAUSE-IgAN subcohort results

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WCN25-AB-797

KEY FINDINGS AND CONCLUSIONS

- APPLAUSE-IgAN is the first Phase 3 study confirming clinical benefit of alternative pathway inhibition in patients with IgAN
- Proteinuria reduction was observed with iptacopan in this low baseline eGFR (20–<30 mL/min/1.73 m^2) cohort consistent with the main study population
- Iptacopan was well tolerated in the entire study population, including patients with baseline eGFR 20–<30 mL/min/1.73 m^2

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.
Poster 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]
- Iptacopan specifically binds to Factor B and inhibits the alternative complement pathway (AP), which is a key driver of IgAN pathogenesis[2,3]
- Iptacopan (FABHALTA) is the first approved complement inhibitor in IgAN by the US FDA.[a] 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 [4]
- Clinical practice guidelines recommend avoidance of immunosuppression in patients with IgAN and eGFR <30 mL/min/1.73 m^2; treatment of this population is therefore limited to supportive care[5]
- Here, we present results from the pre-specified APPLAUSE-IgAN subcohort with baseline eGFR 20–<30 mL/min/1.73 m^2

[a]Iptacopan is approved for the reduction of proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a UPCR ≥1.5 g/g.

METHODS

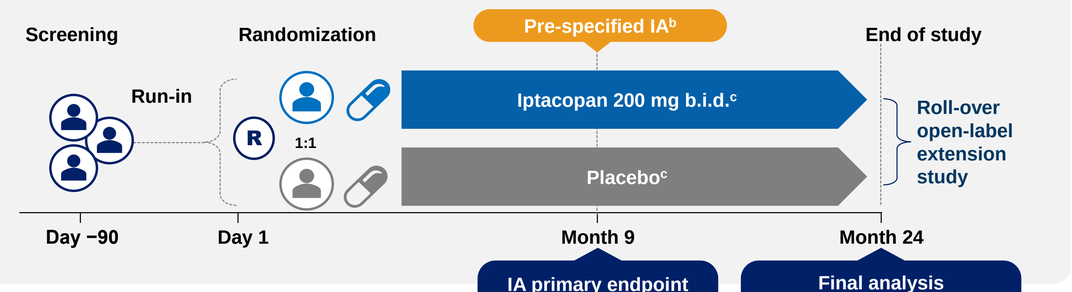
- APPLAUSE-IgAN (NCT04578834), a Phase III, randomized, double-blind, placebo-controlled trial, enrolled adults with biopsy-confirmed IgAN with proteinuria ≥1 g/g despite stable supportive therapy **(Figure 1)**
  - Main study population: Baseline eGFR ≥30 mL/min/1.73 m^2
  - Low eGFR cohort: Baseline eGFR 20–<30 mL/min/1.73 m^2
- Patients were randomized 1:1 to iptacopan 200 mg or placebo twice daily for 24 months while remaining on supportive therapy
- A prespecified interim analysis was conducted when 250 patients in the main population had completed (or discontinued the study prior to) the Month 9 visit
- Efficacy and safety analyses of the low eGFR cohort were descriptive and were performed on all patients randomized at the time of the interim analysis

Figure 1. APPLAUSE-IgAN study design

Eligibility criteria
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 D, 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

- The analysis included 27 patients (13 iptacopan, 14 placebo) randomized to the low baseline eGFR cohort at time of the interim analysis
- At data cut-off, 7 patients in the iptacopan and 9 in the placebo arm had discontinued treatment per protocol, most commonly due to reaching sustained 30% decline in eGFR or eGFR <15 mL/min/1.73 m^2 or commencing kidney replacement therapy
- Baseline demographics and disease characteristics were similar in the iptacopan vs placebo arms in the low eGFR cohort **(Table 1)**. At the time of interim analysis, there were no patients eligible for the low eGFR cohort from Asia. All patients received maximally approved/tolerated RASi doses

Table 1. Baseline patient characteristics

Parameters	Main study population		Low eGFR cohort	
	Iptacopan N = 125	Placebo N = 125	Iptacopan N = 13	Placebo N = 14
Age [years], mean (SD)	39.3 (12.4)	39.6 (12.6)	46.1 (10.0)	45.7 (11.3)
Male, n (%)	71 (56.8)	60 (48.0)	10 (76.9)	9 (64.3)
Female, n (%)	54 (43.2)	65 (52.0)	3 (23.1)	5 (35.7)
Region, n (%)				
Asia	64 (51.2)	64 (51.2)	0	0
Non-Asia	61 (48.8)	61 (48.8)	13 (100)	14 (100)
Baseline 24h-UPCR [g/g], median (IQR)	1.8 (1.4–2.7)	1.9 (1.5–2.8)	2.1 (1.7–2.5)	1.8 (1.4–2.4)
<2 g/g, n (%)	71 (56.8)	67 (53.6)	5 (38.5)	8 (57.1)
≥2 g/g, n (%)	54 (43.2)	58 (46.4)	8 (61.5)	6 (42.9)
Baseline eGFR [mL/min/1.73 m^2], mean (SD)	62.7 (26.0)	65.5 (26.7)	24.7 (2.8)	25.8 (2.9)
Time from kidney biopsy to baseline [years], mean (SD) MEST-C score[d], %	1.7 (1.4)	1.6 (1.7)	2.8 (4.1)	3.0 (2.0)
M1/M0	60.8/32.0	64.0/31.2	61.5/23.1	71.4/28.6
E1/E0	28.8/63.2	28.8/64.8	23.1/46.2	21.4/71.4
S1/S0	69.6/22.4	71.2/23.2	76.9/7.7	71.4/21.4
T1/T2/T0	33.6/4.8/54.4	41.6/0.8/53.6	61.5/7.7/23.1	57.1/0/35.7
C1/C2/C0	26.4/1.6/60.8	16.0/1.6/68.0	15.4/7.7/46.2	42.9/0/35.7
Systolic BP[e] [mmHg], mean (SD)	121.9 (10.7)	122.6 (10.8)	130.2 (9.1)	131.3 (16.0)
Diastolic BP[e] [mmHg], mean (SD)	77.7 (8.1)	78.3 (8.8)	81.7 (5.8)	83.5 (6.1)
ACEi/ARB use at baseline, n (%)	>98%[f]	>98%[f]	13 (100)	14 (100)
SGLT2i use at baseline, n (%)	18 (14.4)	14 (11.2)	2 (15.4)	2 (14.3)

[d]Not all MEST-C components were available for all patients. [e]Summarized for patients with measurements available in sitting position. [f]Number not shown to prevent unblinding of individual patient information. Data for main population reproduced with permission from Perkovic V, et al. *N Engl J Med*. 2024.[6] ©*The New England Journal of Medicine* (2024).

Proteinuria outcomes

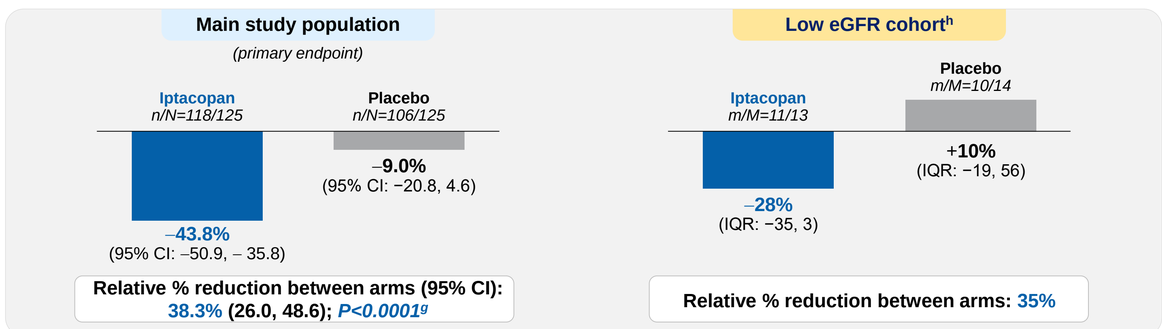
- In the low eGFR cohort at Month 9, there was a median reduction in 24h-UPCR in the iptacopan group of 28% relative to baseline, while there was an increase in the placebo group of 10% **(Table 2)**. These results correspond to an approximately 35% reduction in 24h-UPCR at Month 9 for iptacopan relative to placebo **(Figure 2)**

Table 2. Descriptive statistics of proteinuria outcomes in the low eGFR population

Proteinuria measure		Iptacopan (m/M=11/13)		Placebo (m/M=10/14)	
		Baseline	Month 9	Baseline	Month 9
24h-UPCR (g/g)	Median (IQR)	2.07 (1.68, 2.54)	1.49 (1.16, 2.24)	1.78 (1.40, 2.17)	2.06 (1.39, 3.38)
	% change from baseline, median (IQR)	-	–28 (–35, 3)	-	10 (–19, 56)
24h-UACR (g/g)	Median (IQR)	1.66 (1.26, 2.08)	1.17 (0.90, 1.60)	1.57 (1.09, 1.80)	1.71 (1.05, 2.50)
	% change from baseline, median (IQR)	-	–27 (–45, 3)	-	8 (–26, 46)

M: Number of all patients included in the analysis (i.e. with non-missing baseline). m: Number of patients with values non-missing at Month 9. Reproduced with permission from Rizk DV, et al. *JASN.* 2024.[7]

Figure 2: Percentage change from baseline in 24h-UPCR at Month 9



M: Number of all patients included in the analysis (i.e. with non-missing baseline). m: Number of patients with values non-missing at Month 9; N: Number of all patients included in the analysis (i.e. with non-missing baseline and covariates). n: Number of patients with values non-missing/not imputed as per the intercurrent event handling strategy at Month 9. [g]Significant at 1-sided multiplicity-adjusted alpha so that overall study type-I error was controlled at 1-sided 2.5%. [h]Descriptive statistics are presented.

Pharmacokinetic data

- Pharmacokinetic (PK) concentration-time data from 6 patients in the iptacopan arm with low eGFR (baseline eGFR 22−29 mL/min/1.73 m^2) showed an increase in steady state C_{max} (1.8-fold) and AUC_{tau} (2-fold) compared with 6 healthy volunteers
- This is consistent with exposure predictions from a physiological-based PK model and supports the use of iptacopan in patients with low eGFR

Safety

- Iptacopan was well tolerated in the low eGFR cohort, similar to the safety profile of the main study population (**Table 3**)
- At the time of interim analysis, SAEs had occurred in 2 patients in each arm and AEs leading to treatment discontinuation in 1 patient in each arm in the low eGFR cohort. The most frequent AE was COVID-19 (23.1% iptacopan, 35.7% placebo; **Table 4**)
- There were no clinically relevant changes in laboratory parameters for hematology, clinical chemistry, or vital signs (data not shown)

Table 3. Treatment-emergent adverse events

Parameters	Main study population		Low eGFR cohort	
	Iptacopan N = 222; n (%)	Placebo N = 221; n (%)	Iptacopan N = 13; n (%)	Placebo N = 14; n (%)
Adverse events				
TEAEs	138 (62.6)	153 (69.2)	11 (84.6)	11 (78.6)
Serious TEAEs	18 (8.1)	11 (5.0)	2 (15.4)	2 (14.3)
TEAEs classed as severe	7 (3.2)	7 (3.2)	3 (23.1)	2 (14.3)
TEAEs leading to treatment discontinuation	6 (2.7)	6 (2.7)	1 (7.7)	1 (7.1)

Numbers (n) represent counts of subjects. MedDRA version 26.0 has been used for AE reporting. A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.

Table 4. Most common TEAEs in the low eGFR population

Parameters	Iptacopan N = 13; n (%)	Placebo N = 14; n (%)
Adverse events occurring in ≥2 patients in either treatment arm		
COVID-19	3 (23.1)	5 (35.7)
Chronic kidney disease	1 (7.7)	2 (14.3)
Hyperkalemia	1 (7.7)	3 (21.4)
Hypertension	1 (7.7)	2 (14.3)
Benign prostatic hyperplasia[i]	2 (7.4)	
Diarrhea[i]	2 (7.4)	

[i]Pooled data are given for those TEAEs that would result in unblinding if listed separately under each treatment arm. Numbers (n) represent counts of subjects. MedDRA version 26.0 has been used for AE reporting. A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.

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).

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Disclosures

DVR: Consulting fees from Otsuka, Chinook Therapeutics, George Clinical, BioCryst, Novartis, Vera Therapeutics, Eledon. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Travere Therapeutics, Calliditas, Novartis, Otsuka. Support for attending meetings and/or travel from Otsuka, Novartis. Co-founder and co-owner of Reliant Glycosciences LLC. **DK, OP, TH, SJS, TM, RS, KK, RR:** Novartis employee. **VP:** Board Director for St. Vincents Health Australia, George Clinical, and several Medical Research Institutes; honoraria from AstraZeneca Boehringer Ingelheim, Janssen, Novo Nordisk, Novartis, Bayer, Chinook Therapeutics, Gilead, GlaxoSmithKline, Travere Therapeutics, Inc., and Otsuka.

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin II receptor blocker; AUC, area under the curve; BP, blood pressure; 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; PK, pharmacokinetic; RASi, renin-angiotensin system inhibitor; SAE, serious adverse event; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UACR, urine albumin–creatinine ratio; UPCR, urine protein–creatinine ratio; US FDA, United States Food and Drug Administration; TEAEs, treatment emergent adverse events.

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