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# Efficacy and safety of iptacopan in patients with IgA nephropathy: Interim results from the Phase 3 APPLAUSE-IgAN study

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## KEY FINDINGS & CONCLUSIONS

- APPLAUSE-IgAN is the first Phase 3 study to confirm the potential role of alternative complement pathway inhibition in IgA nephropathy
- This study met its pre-specified interim analysis primary endpoint, demonstrating superiority of iptacopan vs placebo in proteinuria reduction at Month 9

Select results will be presented at the oral presentation: **Monday 15 April 2024 at 15:25–15:35 ART**

This study is sponsored by Novartis Pharma AG
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## Introduction

- IgA nephropathy, with a global incidence of 2.5/100,000/year, is the most common primary glomerulonephritis[1]
- Approximately 30% of patients with proteinuria 1–2 g/day progress to kidney failure within 10 years[2]
- There is strong evidence for involvement of the alternative complement pathway (AP) in disease pathogenesis[3], but currently no approved therapies specifically target the complement-mediated inflammatory process in IgA nephropathy
- Iptacopan is an oral, proximal complement inhibitor that targets Factor B to selectively inhibit the AP while leaving the direct signaling from the lectin and classical pathways intact[4,5]
- Inhibition of Factor B prevents the activity of AP-related C3 convertase and the subsequent formation of C5 convertase[6]
- In December 2023, iptacopan was approved by the US FDA as the first oral monotherapy for the treatment of adults with paroxysmal nocturnal hemoglobinuria[7]

## Methods

### Study design

- APPLAUSE-IgAN is an ongoing, Phase 3, multicenter, randomized, placebo-controlled study (NCT04578834) evaluating the efficacy and safety of iptacopan vs placebo in patients with biopsy-confirmed IgA nephropathy and proteinuria ≥1 g/g (24h urine) despite optimized supportive therapy

**Interim analysis primary endpoint**

- The primary endpoint of 24h-UPCR at Month 9 (log-transformed ratio to baseline) was analyzed using MMRM
- The primary analysis included all 24h-UPCR on 250 patients of the main study population reached Month 9 or discontinued the study 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 intercurrent events were imputed in the iptacopan arm to reflect a poor response/worsening of disease

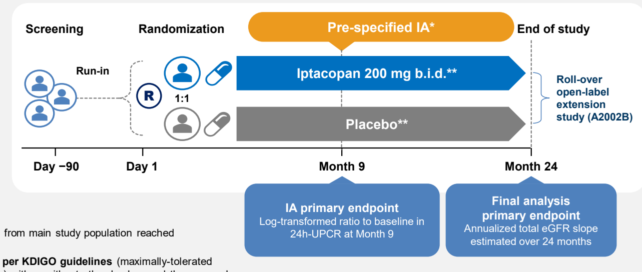
**Additional analyses**

- UPCR reduction was also evaluated from first morning void, using the same approach as the primary analysis
- Safety endpoints were descriptively summarized on all 443 patients of main study population received treatment at the data cut-off

**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$^2$

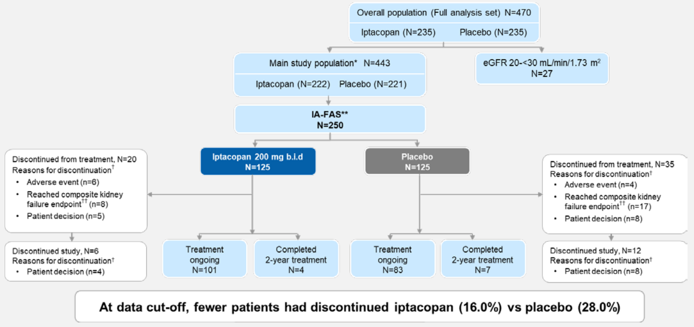
**SRI population**
eGFR 20-<30 mL/min/1.73 m$^2$




*Performed when the first 250 patients from main study population reached Month 9 or discontinued the study.
****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.

## Results

### Patient disposition at the IA data cut-off




All disposition events in the IA efficacy data set until the data cut-off are presented. *Used for safety analysis. **Used for efficacy analysis, the subset of the first 250 main study population patients who completed the Month 9 or discontinued the study prior to the IA cut-off. †Only the most frequent reasons for discontinuation are presented to maintain blinding. ††Either sustained ≥30% decline in eGFR relative to baseline, or sustained eGFR <15 mL/min/1.73 m², or maintenance dialysis, or receipt of kidney transplant, or death from kidney failure.

### Baseline demographic and disease characteristics

| | 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) |
| Female – n (%) | 54 (43.2) | 65 (52.0) | 119 (47.6) |
| Region, Asia – n (%) | 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 m$^2$] – mean (SD) | 62.7 (26.0) | 65.5 (26.7) | 64.1 (26.3) |

- The Phase 3 APPLAUSE-IgAN study met its pre-specified interim analysis primary endpoint, demonstrating superiority of iptacopan vs placebo in proteinuria reduction at Month 9[8]
- The safety profile of iptacopan (200 mg b.i.d.) was consistent with previously reported data[8]
- The primary efficacy and key safety results will be presented in the oral presentation on **Monday 15 April 2024 at 15:25–15:35 ART**

### Acknowledgements

APPLAUSE-IgAN steering committee members: Drs. Jonathan Barratt, Brad Rovin, Naoki Kashihara, Bart Maes, Hong Zhang, and Hernán Trimarchi.
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### Disclosures

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### Abbreviations

AE, adverse event; AP, alternative complement pathway; b.i.d., twice daily; eGFR, estimated glomerular filtration rate; FAS, full analysis set; h, hour; IA, interim analysis; IgA, IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease Improving Global Outcomes; MMRM, mixed model for repeated measures; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SRI, severe renal impairment; UPCR, urine protein–creatinine ratio; US FDA United States Food and Drug Administration.

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