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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 confirming clinical benefit of alternative pathway inhibition in IgAN
- Iptacopan was superior vs placebo in reducing proteinuria at Month 9: reduction relative to placebo 38.3%, *P*<0.0001
- Iptacopan was well tolerated with a favorable safety profile
- The study is ongoing in order to confirm long-term efficacy (annualized rate of total eGFR slope over 24 months) and safety

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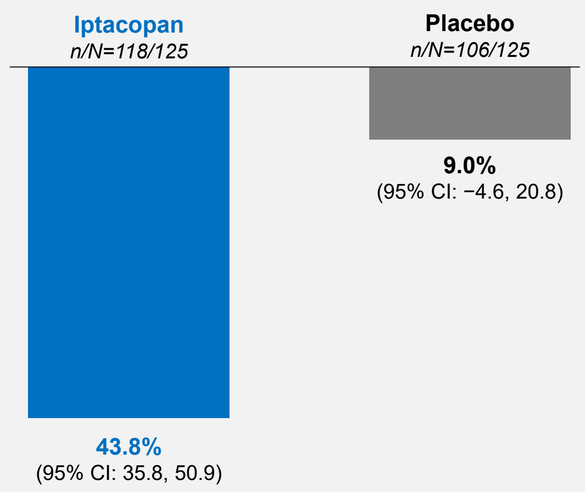
INTRODUCTION

- IgAN, 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 as little as 10 years[2]
- There is strong evidence for involvement of the alternative complement pathway in disease pathogenesis, but currently no approved therapies specifically target the complement-mediated inflammatory process in IgAN
- Iptacopan is an oral, first-in-class, specific inhibitor of Factor B of the alternative complement pathway that leaves direct signaling from the lectin and classical pathways intact[3]

RESULTS

Iptacopan achieved a statistically significant, clinically meaningful reduction in 24h-UPCR at Month 9

Primary endpoint: Reduction in 24h-UPCR at Month 9



Relative % reduction between arms (95% CI): 38.3% (26.0, 48.6); *P<0.0001**

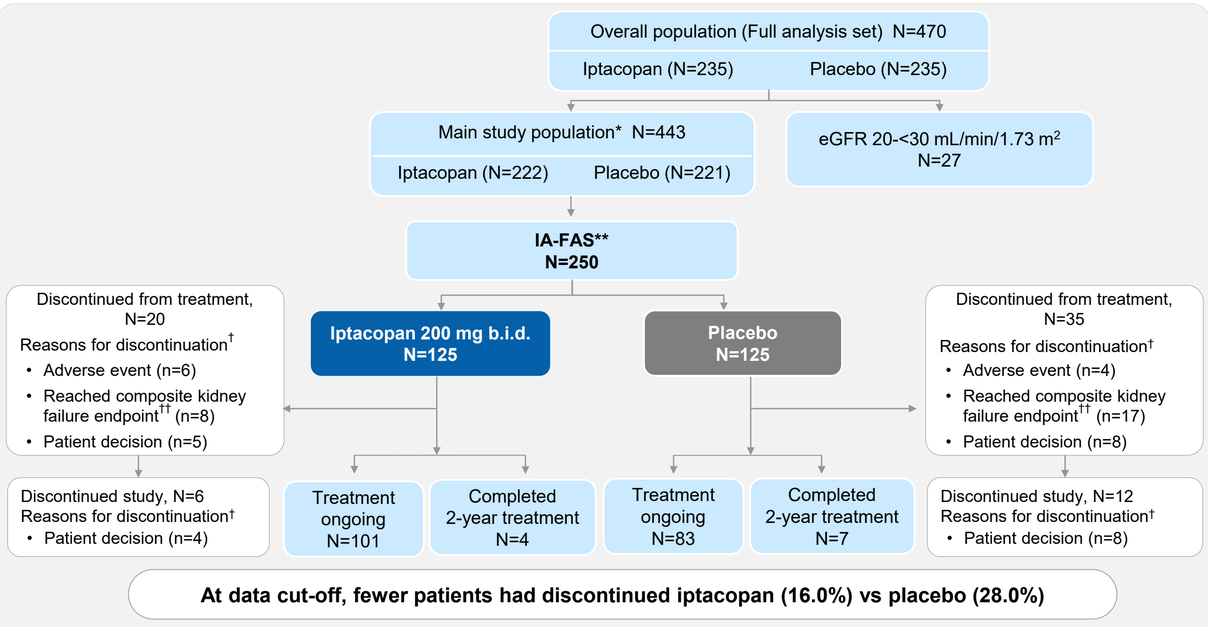
N: Number of all patients included in the analysis (i.e. with non-missing baseline and covariates). n: Number of patients with values non-missing/not imputed as per the intercurrent event handling strategy. *Significant at 1-sided multiplicity-adjusted alpha so that overall study type-I error was controlled at 1-sided 2.5%.

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)
Region – n (%)			
Asia	64 (51.2)	64 (51.2)	128 (51.2)
Non-Asia	61 (48.8)	61 (48.8)	122 (48.8)
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* – (%)			
M1/M0	60.8/32.0	64.0/31.2	62.4/31.6
E1/E0	28.8/63.2	28.8/64.8	28.8/64.0
S1/S0	69.6/22.4	71.2/23.2	70.4/22.8
T1/T2/T0	33.6/4.8/54.4	41.6/0.8/53.6	37.6/2.8/54.0
C1/C2/C0	26.4/1.6/60.8	16.0/1.6/68.0	21.2/1.6/64.4
Systolic blood pressure [mmHg] – mean (SD)**	121.9 (10.7)	122.6 (10.8)	122.3 (10.7)
Diastolic blood pressure [mmHg] – mean (SD)**	77.7 (8.1)	78.3 (8.8)	78.0 (8.4)
ACEi/ARB use at baseline – n (%)	*Blinded*†	*Blinded*†	248 (99.2)
SGLT2i use at baseline – n (%)	18 (14.4)	14 (11.2)	32 (12.8)

*Not all MEST-C components were available for all patients; **SBP, DBP are summarized for 249 patients with measurements available in sitting position. †Data not shown to prevent unblinding of the patient information.

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 visit 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.

Iptacopan was well tolerated with a favorable safety profile

	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		
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*		
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. *Occurring in ≥5% in either treatment arm. No death was reported in either arm.

METHODS

Study design

- APPLAUSE-IgAN* is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study (NCT04578834) evaluating the efficacy and safety of iptacopan vs placebo in adults with biopsy confirmed IgAN

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 values of 250 patients of the main study population who reached Month 9 or discontinued the study:
  - 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 worsening of disease

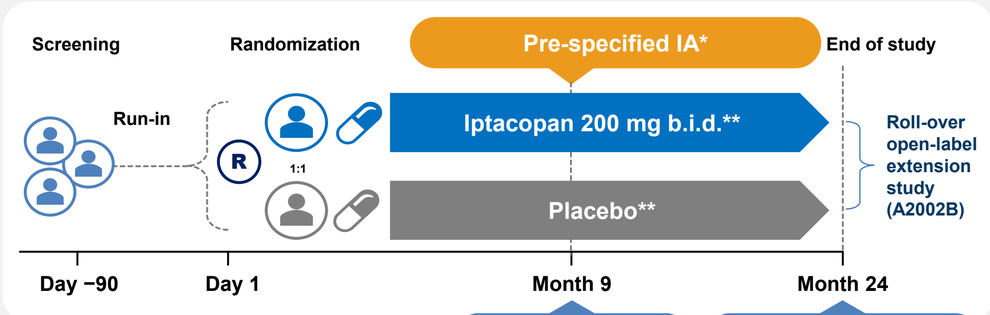
Additional analyses

- Safety endpoints were descriptively summarized on all 443 patients of main study population who had 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 m²

SRI population
eGFR 20-<30 mL/min/1.73 m²



*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.

*Since APPLAUSE-IgAN is ongoing and remains double-blind, only data not disclosing patient-level information are presented. Further, no interim eGFR data are disclosed to avoid any bias on the primary endpoint at final analysis at the study end.

Acknowledgements

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References

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Disclosures

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Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; b.i.d., twice daily; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; h, hour; IA, interim analysis; IA-FAS, interim analysis full analysis set; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; KDIGO, Kidney Disease Improving Global Outcomes; MMRM, mixed model of repeated measures; RASi, renin-angiotensin system inhibitor; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SRI, severe renal impairment; TEAEs, treatment emergent adverse events; UPCR, urine protein-creatinine ratio.

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