Efficacy and Safety of Iptacopan in Patients with IgA Nephropathy: Interim Results from the Phase 3 APPLAUSE-IgAN Study

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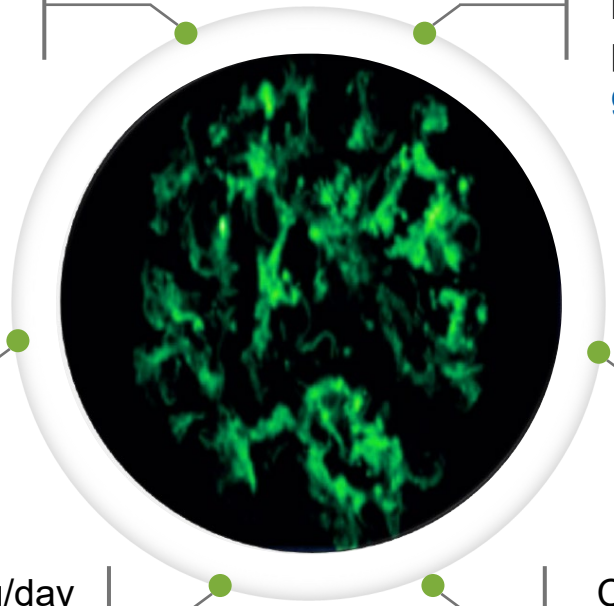
IgA nephropathy is the most common primary glomerulonephritis[1]

Global incidence of IgAN is **2.5/100,000/year**[2]

Multi-hit model: Gd-IgA1–containing immune complexes in the glomerular mesangium trigger downstream pathways, including the **complement system**, leading to **glomerular inflammation and injury**[3]



Heterogeneous autoimmune disease; presentation varies from **asymptomatic microscopic hematuria** to sustained **proteinuria**, **hypertension**, and **rapid deterioration of kidney function**[4-8]

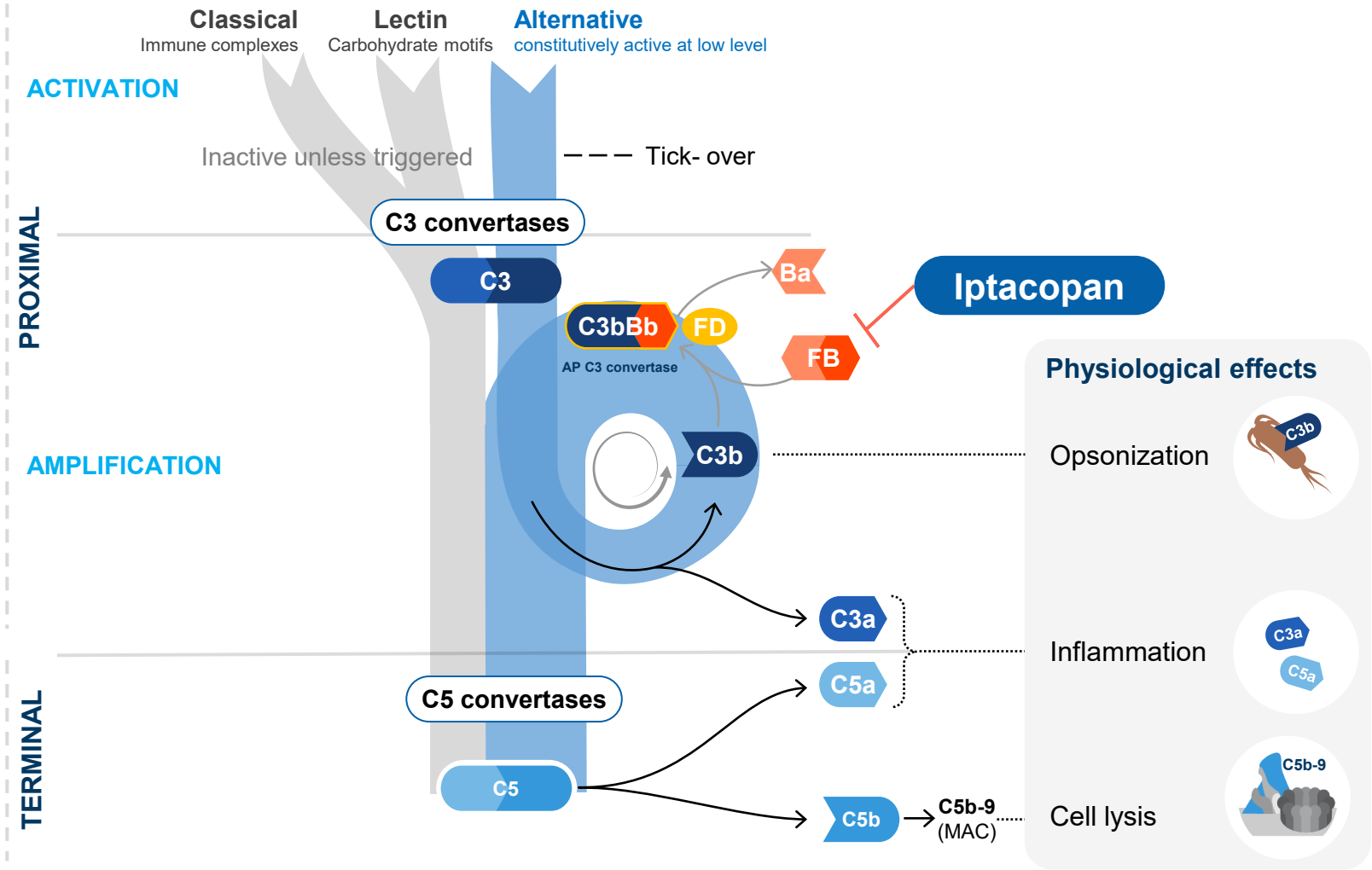
Overactivation of the complement system via the **alternative pathway** is a **key driver** of IgAN pathophysiology[9,10]

Approximately 30% of patients with proteinuria 1–2 g/day progress to kidney failure within as little as 10 years[11]

Currently, no approved therapies specifically target the complement-mediated inflammatory process in IgAN[12]

Gd-IgA1, galactose-deficient immunoglobulin A1; IgAN, immunoglobulin A nephropathy. 1. Penfold RS, et al. *Int J Nephrol Renovasc Dis*. 2018;11:137–48; 2. McGrogan A, et al. *Nephrol Dial Transplant*. 2011;26:414–30; 3. Knoppova B, et al. *J Clin Med*. 2021;10:4501; 4. Lafayette RA, Kelebouris E. *Am J Nephrol*. 2018;47:43–52; 5. Rajasekaran A, et al. *Am J Med Sci*. 2021;361:176–194; 6. Zhang H, Barratt J. *Semin Immunopathol.* 2021;43:707–15; 7. https://www.niddk.nih.gov/health-information/kidney-disease/iga-nephropathy#symptoms (Last accessed Mar 10, 2024); 8. https://rarediseases.org/rare-diseases/iga-nephropathy/ (Last accessed Mar 10, 2024); 9. Medjeral-Thomas NR and O'Shaughnessy MM. *Adv Chronic Kidney Dis*. 2020;27:111–119; 10. Rizk DV, et al. *Front Immunol*. 2019;10:504; 11. Reich HN, et al. *J Am Soc Nephrol*. 2007;18:3177–83; 12. Lim RS, et al. *J Clin Med*. 2024;13:947.

Iptacopan is an oral, first-in-class, specific inhibitor of factor B of the alternative complement pathway



- Inhibition of Factor B prevents the formation of AP-related C3 convertase and the subsequent formation of C5 convertase[1]
- Iptacopan selectively inhibits the AP while leaving direct signaling from the lectin and classical pathways intact[2]
- In December 2023, iptacopan was approved by US FDA as the first oral monotherapy for the treatment of adults with PNH[3]

AP, alternative complement pathway; MAC, membrane attack complex; PNH, paroxysmal nocturnal hemoglobinuria; US FDA, United States Food and Drug Administration.

1. Merle NS et al. *Front Immunol*. 2015;6:257; 2. Schubart A et al. *Prot Natl Acad Sci USA*. 2019;116:7926–31; 3. FABHALTA® (iptacopan). Prescribing Information. Novartis Pharmaceuticals Corporation. 2023.

APPLAUSE-IgAN: Phase 3, multicenter, randomized, double-blinded, placebo-controlled study (NCT04578834)

- The APPLAUSE-IgAN study is 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

Eligibility criteria

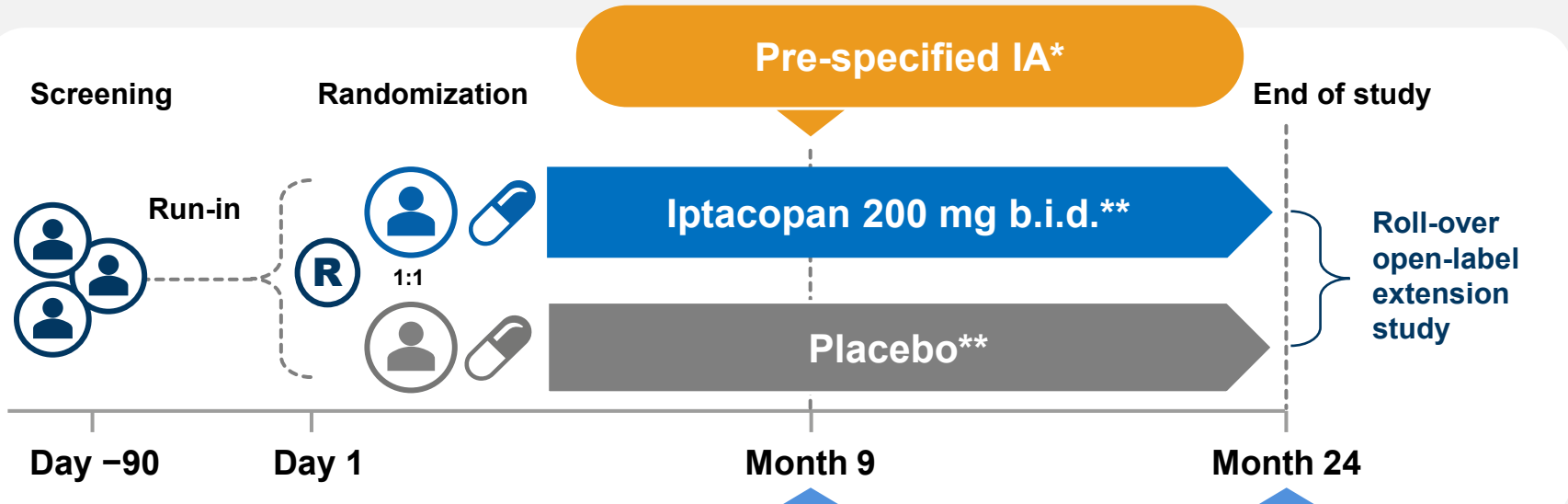
- Adults
- Biopsy-confirmed IgAN
- Proteinuria ≥1 g/g based on 24h urine (24h-UPCR) despite maximally tolerated RASi for ≥3 months, with or without SGLT2i

Main study population

eGFR ≥30 mL/min/1.73 m^2

SRI population

eGFR 20–<30 mL/min/1.73 m^2



*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 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. b.i.d., twice daily; eGFR, estimated glomerular filtration rate; h, hour; IA, interim analysis; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease Improving Global Outcomes; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SRI, severe renal impaired; UPCR, urine protein–creatinine ratio.

APPLAUSE-IgAN IA primary analysis approach

IA primary endpoint

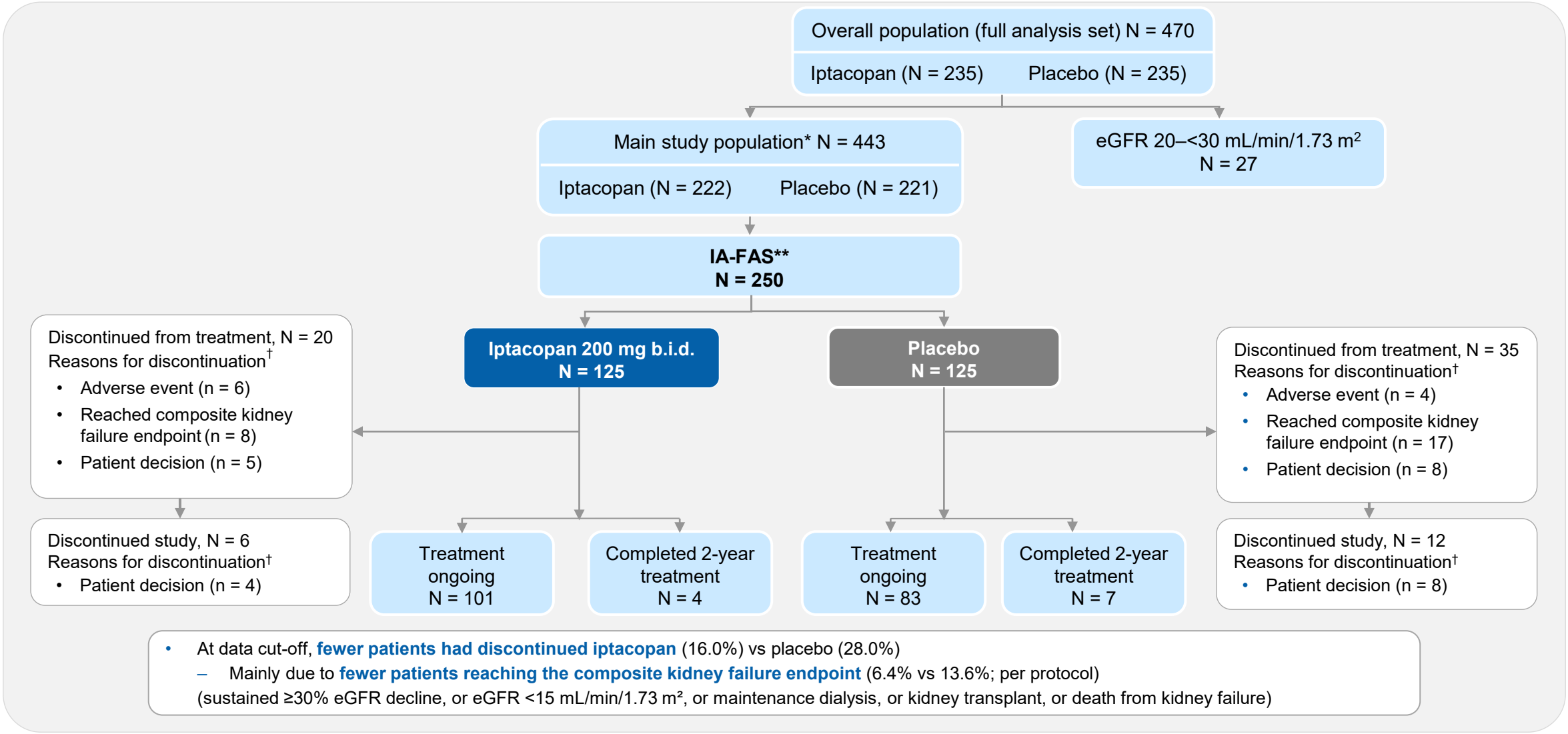
- The primary endpoint of 24h-UPCR at Month 9 (log-transformed ratio to baseline) was analyzed using MMRM on 250 patients of the main study population who reached Month 9 or discontinued the study (IA-FAS)
- The primary analysis included all 24h-UPCR values collected from baseline
  - Up to and including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

Additional analysis

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

h, hour; IA, interim analysis; IA-FAS, interim analysis full analysis set; IgAN, immunoglobulin A nephropathy; MMRM, mixed model of repeated measures; UPCR, urine protein–creatinine ratio.

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 Month 9. †Only the most frequent reasons for discontinuation are presented to maintain blinding. b.i.d., twice daily; eGFR, estimated glomerular filtration rate; IA-FAS, interim analysis full analysis set.

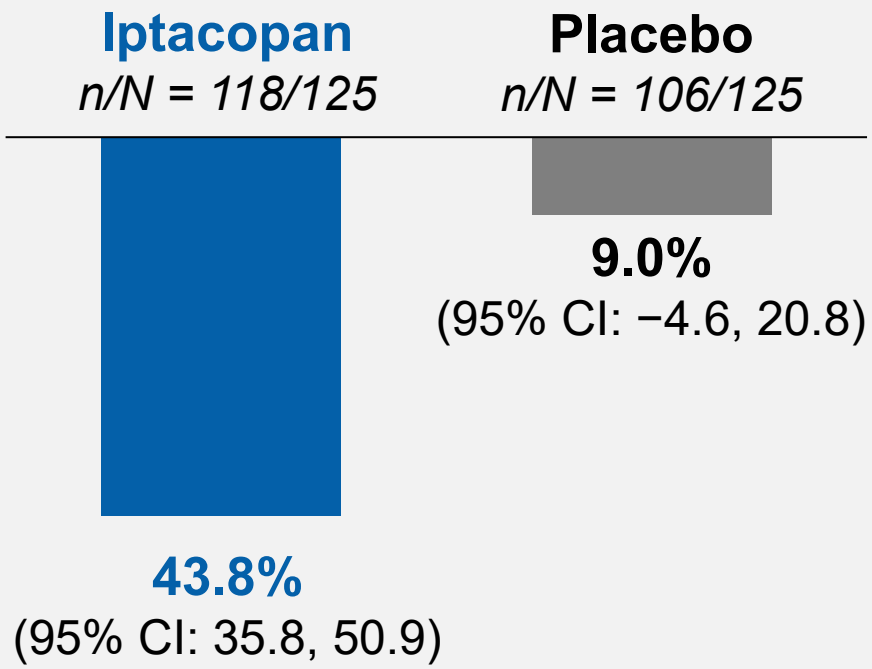
Baseline demographic and disease characteristics were balanced across randomized arms

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)
Female – n (%)	54 (43.2)	65 (52.0)	119 (47.6)
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)
<2 g/g – n (%)	71 (56.8)	67 (53.6)	138 (55.2)
≥2 g/g – n (%)	54 (43.2)	58 (46.4)	112 (44.8)
Baseline eGFR [mL/min/1.73m^2] – mean (SD)	62.7 (26.0)	65.5 (26.7)	64.1 (26.3)
30 to <45 mL/min/1.73m^2 – n (%)	36 (28.8)	34 (27.2)	70 (28.0)
≥45 mL/min/1.73m^2 – n (%)	89 (71.2)	91 (72.8)	180 (72.0)
Time from kidney biopsy to baseline [years] – mean (SD)	1.7 (1.4)	1.6 (1.7)	1.7 (1.6)
MEST-C score* – n (%)			
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 (%)	>98%†	>98%†	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. **Summarized for 249 patients with measurements available in sitting position. †n not shown to prevent unblinding of individual patient information. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range; h, hour; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UPCR, urine protein–creatinine ratio.

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

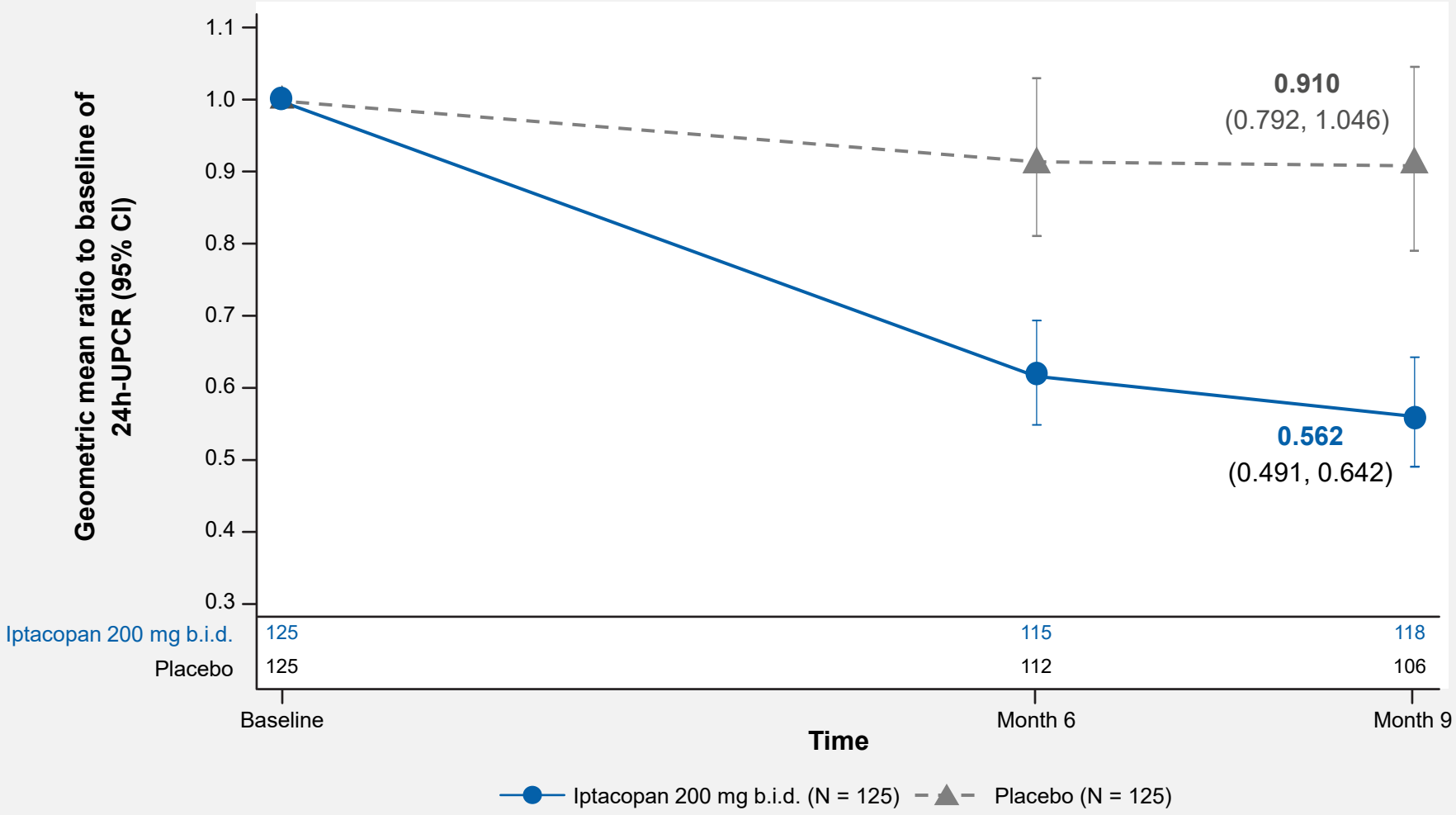
Primary endpoint: Reduction in 24h-UPCR from baseline at Month 9



Relative percent reduction between iptacopan and placebo at Month 9 (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%. CI, confidence interval; h, hour; UPCR, urine protein–creatinine ratio.

Proteinuria reduction was observed at Month 6 and proteinuria continued to decrease through Month 9



b.i.d., twice daily; CI, confidence interval; h, hour; UPCR, urine protein–creatinine ratio.

APPLAUSE-IgAN shows robust results across analyses and consistent proteinuria reduction among different proteinuria endpoints

Low number of imputations for primary analysis

- For primary analysis, data after start of alternative/rescue medication or KRT were imputed to reflect worsening of disease

Reasons for data imputation up to Month 9	Iptacopan N = 125; n (%)	Placebo N = 125; n (%)
Initiation of alternative/rescue medication after baseline	2 (1.6%)	**10 (8.0%)**
Initiation of KRT	0	0

Consistent efficacy results among different proteinuria endpoints

- A supportive analysis with all UPCR values included and no imputation (ITT or treatment policy) gave consistent results **37.9% (95% CI: 25.8, 48.0)**
- Reduction in UPCR-FMV was **35.8% (95% CI: 22.6%, 46.7%)**

CI, confidence interval; FMV, first morning void; IgAN, immunoglobulin A nephropathy; ITT, intent-to-treat; KRT, kidney replacement therapy; UPCR, urine protein–creatinine ratio.

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)

- Overall, the incidence of TEAEs was generally balanced between the arms
- The majority of TEAEs were mild to moderate in severity
- No death was reported in either arm

Numbers (n) represent counts of subjects. *Occurring in ≥5% in either treatment arm. TEAEs, treatment emergent adverse events.

Conclusions

- **APPLAUSE-IgAN** is the first Phase 3 study confirming clinical benefit of alternative pathway inhibition in IgAN
- This 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
  - Statistically significant and clinically meaningful reduction in 24h-UPCR (**38.3%**; 95% CI: 26.0, 48.6; *P*<0.0001) was achieved following 9 months of treatment with iptacopan
- Iptacopan was well tolerated with a favorable safety profile
  - Overall, the incidence of TEAEs was generally balanced between the arms and the majority of TEAEs were mild to moderate in severity
- The study is ongoing and will continue 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

eGFR, estimated glomerular filtration rate; h, hour; IgAN, immunoglobulin A nephropathy; TEAEs, treatment emergent adverse events; UPCR, urine protein–creatinine ratio.

Acknowledgments

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