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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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Introduction: Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis, with strong evidence for involvement of the alternative complement pathway (AP) in its pathogenesis, but no currently approved therapies specifically target the complement-mediated inflammatory process. Iptacopan binds to Factor B and inhibits the AP, leaving direct signaling from the lectin and classical pathways intact. The Phase 3 APPLAUSE-IgAN study is evaluating the efficacy and safety of iptacopan vs placebo on top of optimized supportive therapy in patients with IgAN. Here, we present results of the pre-specified interim analysis (IA).

Methods: APPLAUSE-IgAN (NCT04578834), a Phase 3, multicenter, randomized, double-blind, placebo-controlled study, enrolled adults with biopsy-confirmed IgAN with proteinuria ≥1 g/g based on 24h urine (24h-UPCR) despite maximally tolerated RASi for ≥3 months, with or without SGLT2i. The main study population had an estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m^2 at baseline. Patients were randomized (1:1) to receive iptacopan 200 mg or placebo b.i.d. for 24 months while remaining on supportive therapy. The pre-specified IA was performed when the first 250 patients reached Month (M) 9 or discontinued the study. The primary objective of the IA was to demonstrate superiority of iptacopan vs placebo in reducing proteinuria at M9 by measuring log-transformed ratio to baseline in 24h-UPCR. The effect on proteinuria was also evaluated from first morning void (FMV).

Results: The IA efficacy analysis included 250 patients and the safety analysis included all 443 randomized patients comprising the main study population at the time of data cut-off. Baseline demographics and disease characteristics were balanced across randomized groups, with approximately half of the patients from Asia; in the iptacopan vs placebo arms, median (IQR) 24h-UPCR was 1.8 (1.4-2.7) vs 1.9 (1.5-2.8) g/g and mean (SD) eGFR was 62.7 (26.0) vs 65.5 (26.7) mL/min/1.73m^2. All except 2 patients in the placebo arm received maximally approved and/or tolerated RASi doses. At data cut-off, fewer patients had discontinued iptacopan (16.0%) vs placebo (28.0%), mainly due to fewer patients reaching the composite kidney failure endpoint (6.4% vs 13.6%; per protocol; **Figure**). Iptacopan was superior to placebo in reducing proteinuria (24h-UPCR) from baseline at M9, with a reduction of 38.3% (95% CI: 26.0% to 48.6%; 1-sided $p<0.0001$) vs placebo (**Table**). Consistent with the primary analysis, reduction in UPCR-FMV from baseline at M9 with iptacopan vs placebo was 35.8% (95% CI: 22.6% to 46.7%). Rescue therapies initiated after baseline were used more frequently in the placebo arm. Most treatment-emergent adverse events (AEs) were mild to moderate in severity. Treatment-emergent serious AEs were reported in 18 (8.1%) and 11 (5.0%) patients in the iptacopan and placebo arms, respectively. No deaths were reported.

Conclusions: APPLAUSE-IgAN is the first Phase 3 study to confirm the potential role of AP inhibition in the clinical management of IgAN. The trial demonstrated the superiority of iptacopan vs placebo in reducing proteinuria at M9. Iptacopan was well tolerated with a favorable safety profile.

Figure: Patient disposition

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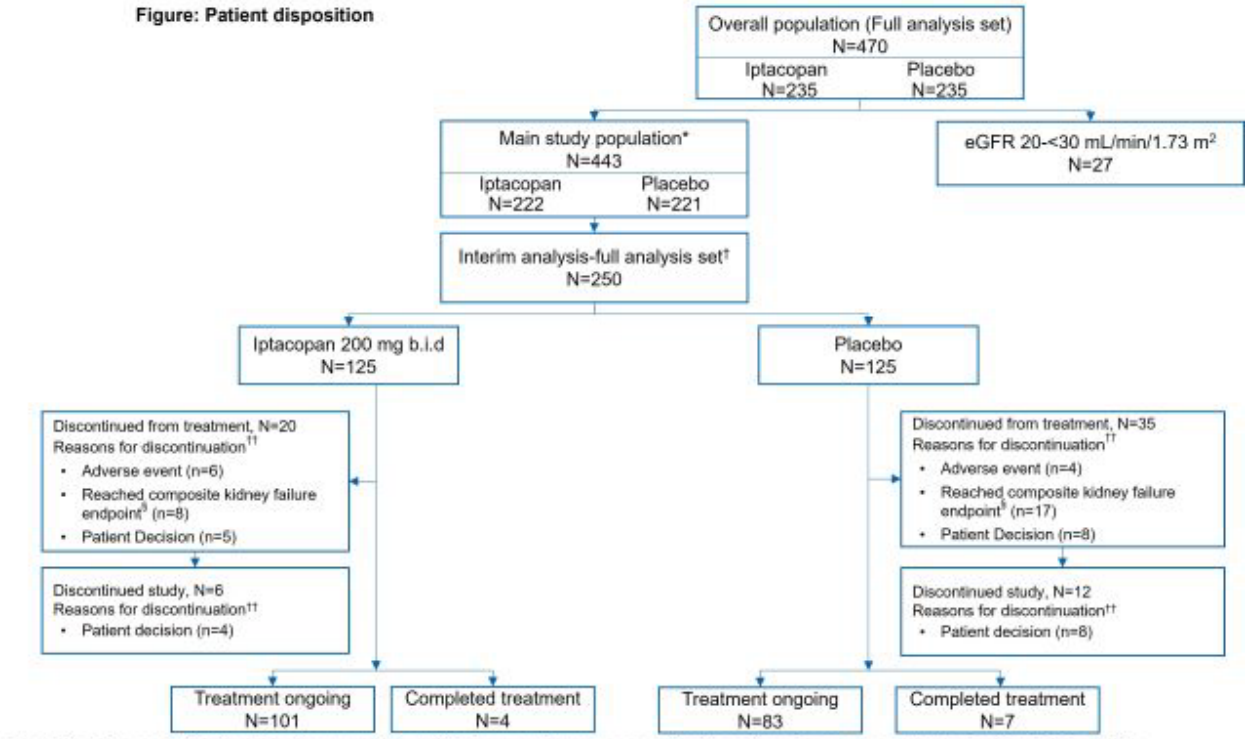

*Used for safety analysis. †Used for efficacy analysis. ††Only the most frequent reasons for discontinuation are presented to maintain blinding. §Either sustained ≥30% decline in eGFR relative to baseline, or sustained eGFR <15 mL/min/1.73 m², or maintenance dialysis, or receipt of kidney transplant, or death from kidney failure.

Table: Repeated measures analysis of log ratio to baseline in UPCR (from 24-hour urine collection) at 9 months

	Treatment	n/N	Geometric adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. vs Placebo		
				Geometric mean ratio % (95% CI)	% Reduction (95% CI)	1-sided p-value
Month 9	Iptacopan	118/125	0.562 (0.491, 0.642)	0.617 (0.514, 0.740)	38.3 (26.0, 48.6)	<0.0001*
	Placebo	106/125	0.910 (0.792, 1.046)			

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 as per the intercurrent event handling strategy.
Log transformed ratio to baseline was analyzed using a MMRM including treatment, timepoint (as categorical variable), randomization strata as fixed effects, treatment*timepoint and timepoint*log (baseline 24h-UPCR) as interaction terms and baseline log (24h-UPCR) as a fixed covariate. Results were back-transformed and expressed as geometric means.
*Significant at 1-sided multiplicity-adjusted alpha so that overall study type-I error was controlled at 1-sided 2.5%.
b.i.d., twice daily; CI, confidence interval; MMRM, mixed model for repeated measures; UPCR, urine protein creatinine ratio.