Title

Efficacy and safety of iptacopan in IgA nephropathy: Results of a randomized double-blind placebo-controlled Phase 2 study at 6 months

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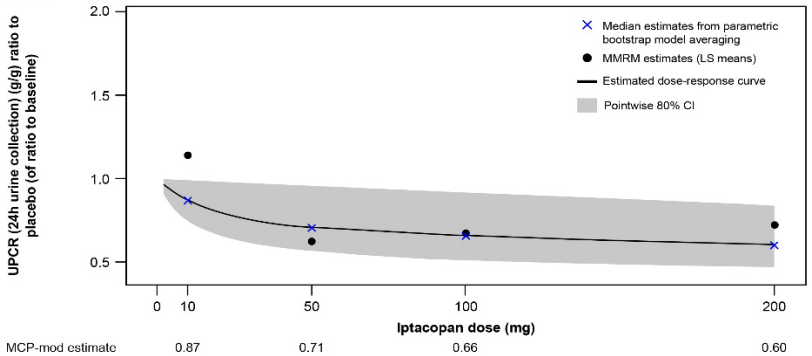
Introduction: No approved targeted therapies currently exist for IgA nephropathy (IgAN). Targeting the alternative complement pathway (AP) is an attractive therapeutic strategy given its role in the pathogenesis of IgAN. Iptacopan (LNP023) is a first-in-class, oral, potent and highly selective inhibitor of factor B of AP.

Methods: This randomized, double-blind, dose-ranging, parallel-group adaptive design Phase 2 study (NCT03373461) enrolled patients with biopsy-confirmed IgAN (within the previous 3 years), urine protein-to-creatinine ratio (UPCR) ≥0.8 g/g or urine protein ≥0.75 g/24 h, and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2. Part 1 of the study enrolled patients for a 3-month treatment period; Part 2 of the study enrolled patients for a 6-month treatment period; both Parts comprised a 3-month treatment-free follow-up. Patients were randomized to one of the four iptacopan arms (10, 50, 100 [in Part 2 only], and 200 mg bid) or placebo. In this analysis, we report efficacy and biomarker data assessed at 6 months and treatment-emergent adverse events (AEs) assessed for the entire study duration. In addition to the pre-specified efficacy analysis of Part 2 at 6 months, *Post hoc* analyses combining data from Parts 1 and 2 were also performed.

Results: 46 and 66 patients were randomized in Parts 1 and 2, respectively. In Part 2, 58 patients completed 6 months of treatment. Demographic and baseline characteristics were generally well-balanced across all arms. The primary analysis yielded a statistically significant dose-response effect (1-sided p=0.038) of iptacopan versus placebo at 3 months, with maximal reduction in UPCR achieved with iptacopan 200 mg bid (23%; 80% CI: 8–34% using MCP-mod; *Primary results were presented at 58th ERA-EDTA Congress 2021 as late-breaking clinical trial*). UPCR continued to decrease between 3 and 6 months in the higher dosed iptacopan arms in Part 2, albeit with a wider 80% CI reflecting the smaller sample size. To allow better comparison with the primary analysis at 3 months, a *Post hoc* analysis of pooled data from Parts 1 and 2 was performed. The results indicated UPCR reduction from baseline up to 6 months in iptacopan 200 mg bid arm by up to 40% (80% CI: 16–53% using MCP-mod model) and at least 28% (80% CI: 3–46% using MMRM model) versus placebo (Figure 1). Sustained inhibition of AP biomarkers including plasma Bb, serum Wieslab, and urinary C5b-9 through 6 months was also observed with all doses of iptacopan above 10 mg bid (Figure 2). Iptacopan had a well-tolerated safety profile, with no deaths, no serious adverse events (SAEs) suspected to be treatment-related, and no serious infections caused by encapsulated bacteria.

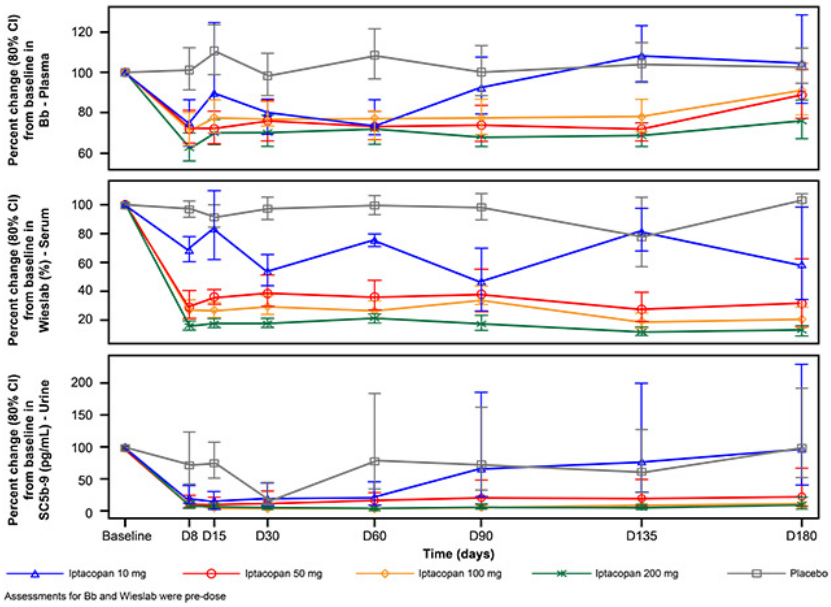
Conclusion: Iptacopan was well tolerated and led to continuous reduction in proteinuria and strong inhibition of AP activity through 6 months in patients with IgAN. These data are consistent with previous findings from the interim analysis at 3 months and support further evaluation of iptacopan in the ongoing Phase 3 APPLAUSE-IgAN trial (NCT04578834).

Figure 1



MCP-mod estimate (80% CI)	0.87 (0.75, 0.99)	0.71 (0.57, 0.96)	0.66 (0.51, 0.92)	0.60 (0.47, 0.84)
MMRM estimate (80% CI)	1.14 (0.83, 1.57)	0.62 (0.45, 0.85)	0.67 (0.50, 0.90)	0.72 (0.54, 0.97)

Figure 2



Assessments for Bb and Wieslab were pre-dose