Effect of iptacopan on proteinuria and complement biomarkers over time in IgA nephropathy

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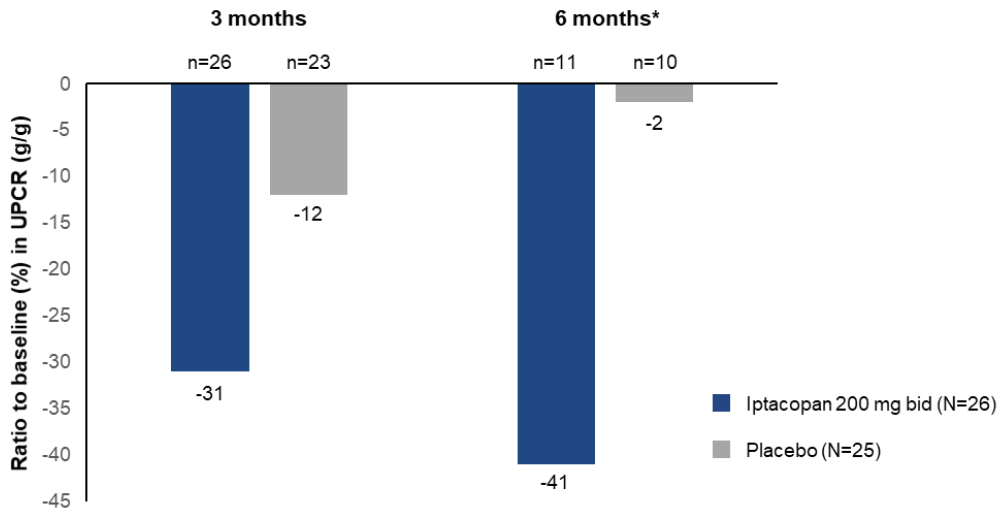
Background: The alternative complement pathway (AP) plays a key role in the pathogenesis of IgA nephropathy (IgAN). Iptacopan (LNP023) is an oral, first in class, highly-potent, selective inhibitor of factor B (FB). In a Phase 2 study, iptacopan treatment led to a dose dependent reduction in proteinuria and inhibition of AP in patients with IgAN.

Methods: This parallel-group adaptive design Phase 2 study (NCT03373461) randomized biopsy-confirmed IgAN patients to one of the four iptacopan doses (10, 50, 100, or 200 mg bid) or placebo for either a 3-month (m) (Part 1; N=46) or 6-m (Part 2; N=66) treatment period. In this analysis, we report changes in proteinuria (ratio to baseline in UPCR), and biomarkers of complement activity (plasma Bb, FB, properdin, C3 and C4, and serum Wieslab activity) with iptacopan 200 mg bid (n=26) vs placebo (n=25) at 3 m (pooled part 1 and 2 data) and 6 m (part 2).

Results: UPCR fell by 31% (80% CI: 23–39%) and 41% (49–31%) from baseline to 3- and 6-m (post-hoc analysis of part 1 and 2) in the iptacopan arm vs 12% (0–20%) and 2% (-20–23%) in the placebo arm (Figure 1A). Iptacopan selectively inhibited AP as demonstrated by changes in Wieslab activity, Bb, FB, properdin levels (Figure 1B) and small increases in C3; C4 levels remained largely unchanged indicating that iptacopan does not inhibit classical/lectin pathway (Figure 1B).

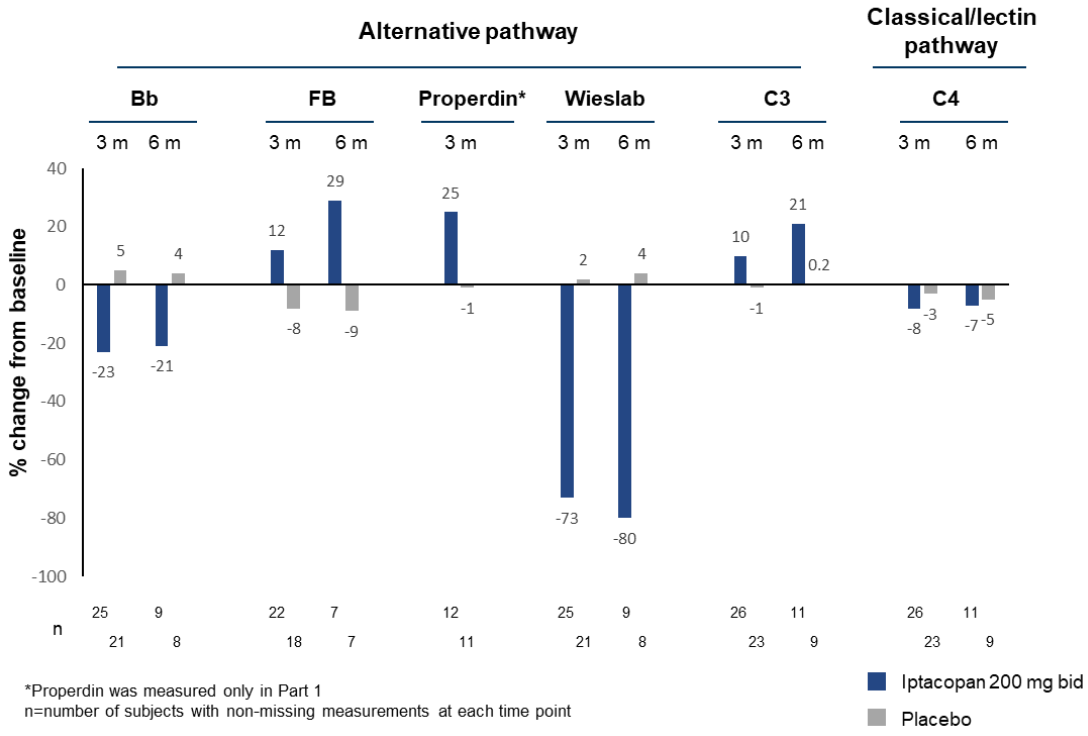
Conclusion: In accordance with its mechanism of action, iptacopan 200 mg bid attenuates activation of AP and results in clinically meaningful reductions in proteinuria in patients with IgAN.

Figure 1A: Effect of iptacopan on proteinuria reduction



*Post-hoc analysis of data pooled from Part 1 and Part 2
N=number of subjects included in the analysis; n=number of subjects with non-missing measurements at baseline and at 3- or 6 -months

Figure 1B: Effect of iptacopan on biomarkers of complement activation



*Properdin was measured only in Part 1
n=number of subjects with non-missing measurements at each time point