Background and Aims:

IgA nephropathy (IgAN) is a major cause of chronic kidney disease (CKD) and kidney failure. There are currently no approved treatments and management is focused on supportive care to slow the progression of CKD. There are multiple lines of evidence that suggest a role for alternative complement pathway activation in driving glomerular inflammation and worse outcomes in IgAN. Targeting the alternative pathway is thus a logical avenue for therapeutic intervention. Iptacopan is a first-in-class, orally administered, potent and highly selective inhibitor of factor B and the alternative complement pathway. We conducted a randomized, double-blind, placebo-controlled, dose-ranging, parallel-group adaptive design phase 2 study of iptacopan in adult IgAN patients.

Method: In Part 1, 46 IgAN patients were randomised to three doses of iptacopan or placebo for a 90 days treatment period. Guided by the Part 1 interim analysis (IA 1) results, an additional 66 patients were then randomised to four doses of iptacopan or placebo in Part 2 for a 180 days treatment period. The final primary endpoint data from Part 1 and Part 2 of the study up to Day 90 of treatment were pooled and evaluated (N=112) in the second IA (IA 2), reported here. The primary goal is to evaluate the dose response effect of iptacopan versus placebo on the reduction in urinary protein to creatinine ratio (UPCR 24h) at 90 days of treatment. Secondary endpoints include safety and tolerability of iptacopan, eGFR, and biomarkers reflecting activity of the alternative complement pathway.

Results: 112 patients were randomised in this study (Parts 1 and 2 combined): placebo (25); iptacopan 10mg (20); 50mg (19); 100mg (22); 200mg (26). Treatment groups were mostly balanced in terms of demography and baseline characteristics. Treatment discontinuations were reported in 4 patients (3.6% of the total) and were caused by 3 adverse events (2 in placebo arm vs 1 in iptacopan arms) and 1 protocol deviation. The median duration of exposure to iptacopan at the time of IA2 cut-off was 92 days (10mg); 91 days (50mg); 115.5 days (100mg); 91.5 days (200mg) and 91 days (placebo). The primary analysis yielded a statistically significant dose response effect (1-sided p=0.038) of iptacopan versus placebo, and suggested a 23% reduction (80% confidence intervals 8-34%) in UPCR 24h in the 200 mg b.i.d. arm vs placebo at 90 days(figure). There were also trends to lower first morning void UPCR levels and stabilisation of eGFR (figure). In parallel, iptacopan treatment was associated with a dose-dependent reduction in serum levels of the Wieslab assay, and a fall in urine excretion of soluble C5b-9 (creatinine-normalized) and plasma levels of Bb, with a maximal effect observed from Day 8 onwards. Most treatment-emergent adverse events (AE) up to Day 90 were mild (92%) or moderate (8%). No severe AEs and no deaths were reported. The most common AEs overall were headache (11.6%), back pain (6.3%), diarrhoea (6.3%), nasopharyngitis (6.3%) and vomiting (6.3%) with no evidence of a relation to the dose taken.

Conclusion: This is the first study to report the safety and efficacy of selective alternative pathway inhibition in IgAN. Iptacopan treatment was well tolerated and resulted in a dose dependent inhibition of measures of alternative pathway activity. Inhibition of alternative pathway activation with iptacopan was associated with a significant dose-dependent reduction in UPCR and a trend to eGFR stabilization. These data support further evaluating iptacopan in IgAN in the APPLAUSE trial (NCT04578834).

Figure:

Fig 1. IgAN Phase 2 (LNP023X2203) – Adaptive, seamless design

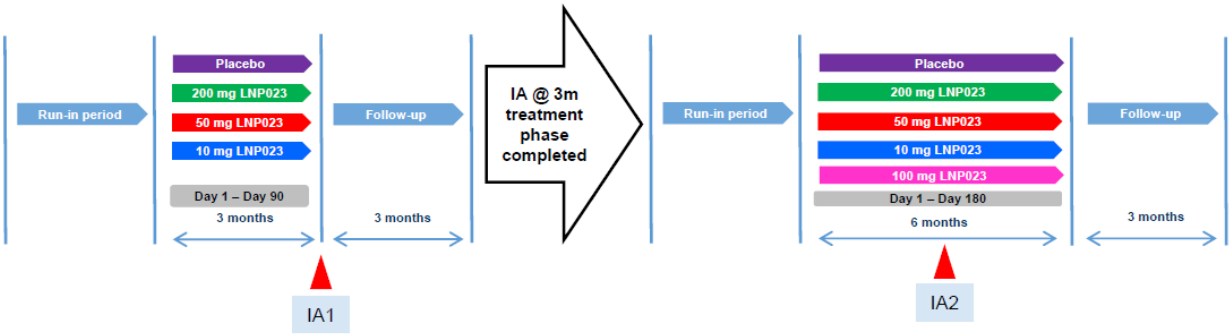
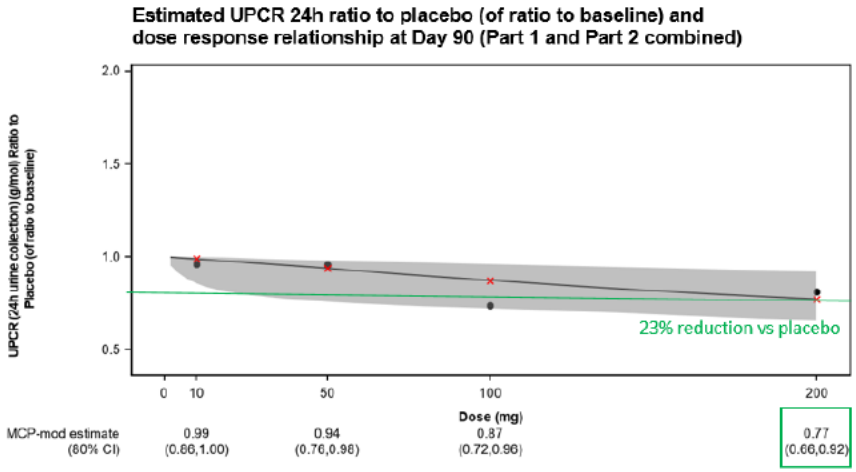


Fig 2. Efficacy/dose response of iptacopan versus placebo



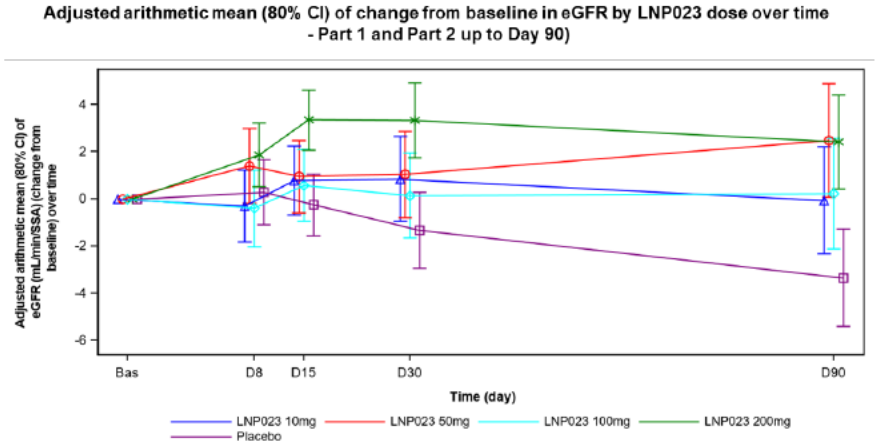


Fig 3. Biomarker response of iptacopan versus placebo