Title: An open-label, non-randomized extension study to evaluate the long-term efficacy, safety and tolerability of LNP023 in subjects with C3 glomerulopathy: Interim analysis of a Phase 2 study

***Author List**:* Nester C, Eisenberger U, Karras A, Lightstone L, Praga M, Remuzzi G, Soler MJ, Liu J, Meier M, Tawfik R, Junge G, Biondani A, Trapani AJ, Webb NJA, Wong E

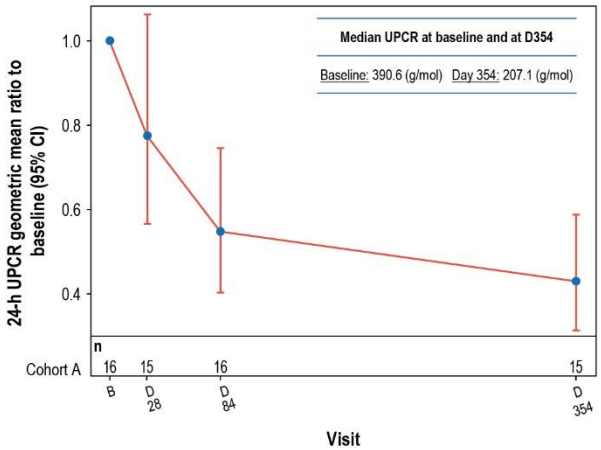
Background: Iptacopan (LNP023) is an oral, first-in-class, selective inhibitor of factor B, a key component of the alternative complement pathway (AP). We have previously reported data from a Ph2 study in native and recurrent C3G (NCT03832114) showing that 12W iptacopan treatment results in a 45% reduction in proteinuria in native C3G. Here we present the effects of 12M iptacopan treatment.

Methods: Adults with native (CoA) or recurrent C3G post kidney transplant (CoB) received iptacopan for at least 12W before entering this Ph2 extension trial (NCT03955445). The primary efficacy objective was to assess the effect of iptacopan on a composite endpoint of 1) stable/improved eGFR [≤10% reduction from baseline], 2) ≥50% reduction from baseline in UPCR, and 3) ≥50% increase from baseline in serum C3 after 12M treatment.

Results: Of 27 patients completing the 12W Ph2 study, 26 (16CoA, 10CoB) entered the extension for treatment with iptacopan 200mg b.i.d. 53% of CoA patients met the composite renal endpoint criteria at 12M; proteinuria was reduced by 57% (p<0.0001; Fig1), eGFR increased by 6.83 mL/min/1.73 m^2 (p=0.0174; Fig2) and C3 increased by 253% (p<0.0001). eGFR was stable and C3 levels increased by 96% in CoB. Proteinuria reduction was not assessed in CoB as median baseline proteinuria was normal (18.4g/moL). Iptacopan was generally well-tolerated and most AEs were of mild severity in both cohorts. Biomarkers demonstrated substantial AP inhibition.

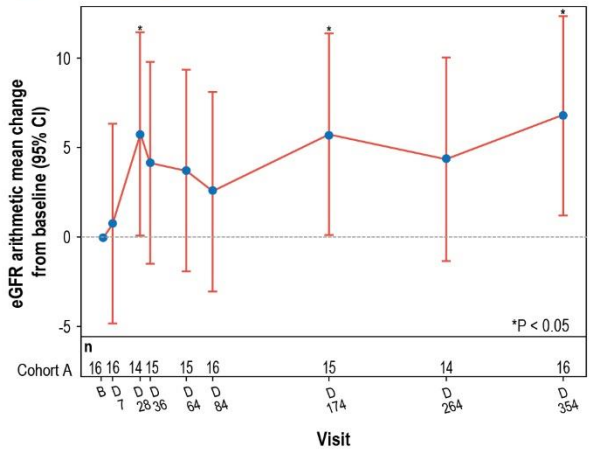
Conclusion: Long-term treatment with iptacopan results in further proteinuria reduction and eGFR improvement beyond that previously reported following 12W treatment in native C3G. Stable eGFR was seen in recurrent C3G, with stable increases in serum C3 levels found in both cohorts. The ongoing Ph3 APPEAR-C3G (NCT04817618) study is evaluating the efficacy of iptacopan in native C3G patients.

Figure 1: Primary endpoint Cohort A – UPCR



57% reduction in UPCR **(p<0.0001)**

Figure 2: Primary endpoint Cohort A – eGFR



+6.83 mL/min/1.73 m^2 **(p=0.0174)** increase in eGFR