Iptacopan (LNP023): a novel oral complement alternative pathway factor B inhibitor safely and effectively stabilises eGFR in C3 glomerulopathy

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Background and Aims: Iptacopan (LNP023) is a highly selective oral low molecular weight inhibitor of Factor B, a key complement alternative pathway protease. We have previously reported data from an interim analysis (IA) of a Phase 2 study in patients with native C3G (NCT03832114) showing that a 12-week course of iptacopan results in a 49% reduction in proteinuria with no adverse safety findings (ASN 2020 SU-OR39). The aim of this analysis was to determine whether iptacopan treatment altered eGFR slope in this same population.

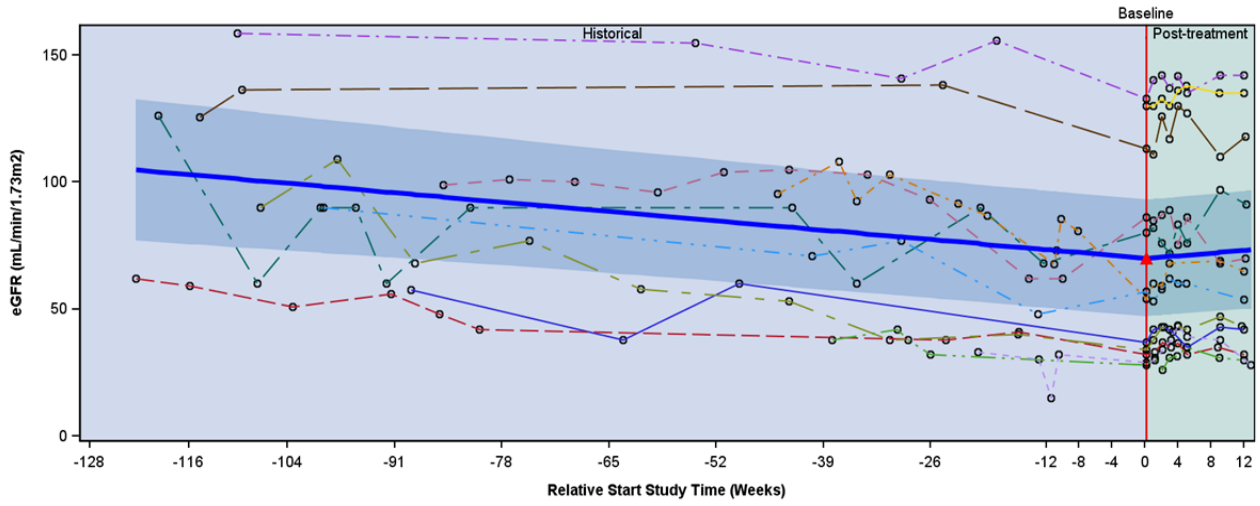
Method: Adults with biopsy-proven native C3G received open-label iptacopan for 12w (10-100mg bid during w1-3 then 200mg bid w4-12). All had proteinuria >1g/24h, low plasma C3, were receiving maximally tolerated stable ACEi/ARB and were vaccinated against *N. meningitidis, H. influenzae and S. pneumoniae*. On study completion, all patients received ongoing iptacopan in a long-term extension study (NCT03955445). Historical data were collected on eGFR (CKD-EPI) for the two-year period prior to patients entering the study or since diagnosis where this was less than two years, and were compared with those obtained in the IA following the commencement of iptacopan. A generalized linear mixed model, with a common intercept, a pre-treatment slope and a change in the slope following iptacopan treatment was used to predict the pre-post iptacopan change in eGFR over time.

Results: 12 patients (10 male, 2 female; 11 C3GN, 1 DDD) participated in the IA. Study baseline mean (SD) age was 26.1 (12.1) yrs, geometric mean (CV%) urine PCR 397 (56) g/mol and eGFR 57.9 (65.5) ml/min/1.73m^2. Complete data sets were collected for all 12 patients; one patient entered the study immediately following biopsy diagnosis. During the two years prior to the iptacopan treatment, the mean eGFR slope was -14.8 ml/min/1.73m^2/year (p=0.0016), consistent with the known natural history of native C3G (Nephron 2020; 144: 272–280). Treatment with iptacopan was associated with a mean increase in eGFR of 3.1 ml/min/1.73m^2 from baseline to 12w, corresponding to a mean predicted eGFR preservation of 6.4 ml/min/1.73m^2 over 12w as a result of iptacopan administration (Figure 1, p=0.0459). Data collected in seven patients who entered the extension study confirmed ongoing eGFR stability until 25 weeks. There were no deaths or SAEs related to iptacopan and no AEs leading to iptacopan discontinuation in this patient cohort.

Conclusion: 12 weeks treatment with iptacopan 200mg bid in patients with C3G resulted in statistically significant and clinically important improvement in eGFR slope with favourable safety and tolerability in addition to significantly reducing proteinuria. Extended

iptacopan treatment up to 25 weeks resulted in ongoing stability of eGFR, suggesting that this may result in clinically relevant prolongation of the time to or even potentially prevention of the development of kidney failure.

Figure:



Legend: Individual patient eGFR slopes (n=12) for up to 2 years prior to (blue zone) and following (green zone) commencement of 12w course of iptacopan. Mean eGFR slope indicated by bold blue line