Abstract: SU-OR39

LNP023: A Novel Oral Complement Alternative Pathway Factor B Inhibitor Safely and Effectively Reduces Proteinuria in C3 Glomerulopathy

Session Information

- Halfway Through the Marathon: Clinical Candidates in Development
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- 1203 Glomerular Diseases: Clinical, Outcomes, and Trials

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Background

LNP023 is a highly selective oral low molecular weight inhibitor of complement Factor B, a key alternative pathway (AP) protease. The aim of the preliminary interim analysis (IA) of this Phase 2 study (NCT03832114) was to determine whether LNP023 safely and effectively reduces proteinuria in patients with C3 glomerulopathy (C3G).

Methods

Adults with biopsy-proven native C3G received open-label LNP023 for 12w (10-100mg bid during w1-3 then 200mg bid w4-12). All had proteinuria >1g/24h, low plasma C3, stable

ACEi/ARB and were vaccinated vs. encapsulated bacteria. Complement inhibition was measured by the *ex vivo* Wieslab assay and fragment Bb and soluble C5b-9 (sC5b-9) levels. Study primary end-point was the ratio of UPCR at 12w vs. baseline. On study completion, all patients received ongoing LNP023 in a long-term extension study (NCT03955445).

Results

7 patients completed therapy at the time of this IA: mean (range) age 25 (18-39)y, median (range) eGFR 80 (29-130)ml/min/1.73m^2. There were no treatment discontinuations. UPCR levels fell by 53% (80% CI 40-64%) from a Geo-Mean (Geo-CV%) value of 399 (67.6)mg/mmol at baseline to 187 (104.3)mg/mmol at 12w, p=0.0035. eGFR improved or stabilised; median (IQR) change +4.0 ml/min/1.73m2 (-0.5 - +7.5ml/min/1.73m^2). There were no deaths or treatment-emergent SAEs. Blood and urine complement biomarkers confirmed abnormal pre-dosing AP activity in all. Plasma C3 levels recovered, with complete normalisation in 5/7 at 12w. LNP023 inhibited AP activity, with maximal effects obtained at 100mg to 200mg bid (median percent changes from BL at maximum inhibition were Wieslab: -66.3% (N=5), plasma Bb: -13.6% (N=5), plasma SC5b-9 (N=6): -75.9%, urine SC5b-9: -94.9% (N=4)). There was little impact of reduced eGFR on LNP023 systemic exposure. In 6 patients who have entered the long-term extension study to date there has been further reduction in proteinuria; Geo-CV% UPCR value at 6m was 129 (109.9)mg/mmol, a fall of 67.7% from baseline.

Conclusion

LNP023 200mg bid resulted in AP blockade and reduced proteinuria in patients with C3G treated for 12w with excellent safety and tolerability. Extended treatment resulted in further proteinuria reduction.

Funding

- Commercial Support