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Title: ALTERNATIVE COM**P**LEMENT **P**ATHWAY INHIBITION WITH IPTACOPAN TO ARREST DIS**EA**SE P**R**OGRESSION IN **C3 G**LOMERULOPATHY (APPEAR-C3G): A PHASE 3 STUDY

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Background: Complement 3 glomerulopathy (C3G) is a rare kidney disease characterized by dysregulation of the alternative pathway (AP) of the complement system. Around 50% of patients progress to kidney failure within 10 years of diagnosis. Currently, there are no approved therapies for C3G. Iptacopan (LNP023) is an oral, first-in-class, potent and selective inhibitor of factor B, a key regulator of the AP. In a previously reported phase 2 study, 12 weeks treatment with iptacopan was associated with 45% reduction in proteinuria (p=0.0003), stabilization of eGFR in native kidneys of C3G patients and reduction in C3 deposit scores on renal biopsy in patients with recurrent C3G after transplantation (p=0.03). Iptacopan showed a favorable safety and tolerability profile in both cohorts.

Methods: APPEAR-C3G (clinicaltrials.gov; NCT04817618) is a randomized, double blind, placebo-controlled pivotal Phase 3 study to evaluate the efficacy and safety of iptacopan in patients with native C3G. Sixty eight adults (≥ 18 and ≤ 60 years of age) with biopsy-confirmed C3G, reduced C3 and eGFRs (<77 mg/dL and ≥30 mL/min/1.73m^2, respectively) and increased proteinuria (≥1.0 g/g) will be enrolled globally. All patients will have received maximally tolerated ACEi/ARBs and vaccinations against encapsulated bacteria. Patients with any organ transplantation, monoclonal gammopathy of undetermined significance, progressive crescentic GN and >50% interstitial fibrosis/tubular atrophy will be excluded. Patients will be randomized 1:1 to receive either iptacopan 200 mg bid or placebo for six months, followed by open-label treatment with iptacopan 200 mg bid for all patients for another six months. Randomization will be stratified according to whether or not patients are receiving ongoing corticosteroid or mycophenolic acid treatment. The primary objective is to demonstrate the superiority of iptacopan versus placebo on proteinuria reduction as measured by UPCR (24h urine collection) at six months. The key secondary endpoint will be kidney function measured by eGFR. eGFR data will be retrospectively collected for the two years prior to enrollment to further support assessment of the effect of iptacopan on eGFR slope. All patients will undergo mandatory renal biopsy prior to, and following the, six-month course of blinded therapy and again at month 12 (voluntary). A blinded central pathology review committee will assess histological disease total activity score (Bomback et al. Kidney Int 2018) as well as C3 deposition evaluating correlation of histopathologic improvements with the complement biomarker profile and renal functional benefits of iptacopan. Additional secondary endpoints include patient-reported outcomes (PROs) using the FACIT-Fatigue score and the SF-36, EQ-5D-5L and PGIS questionnaires to assess symptoms, functioning and well-being apart from safety parameters.

Concluding remarks: This Phase 3 study will provide valuable evidence towards the efficacy and safety of iptacopan in C3G patients with native kidney disease.