Abstract submission deadline: Wednesday, July 07 2021, 2:00 p.m. EDT. (20:00 CET)

Title: Alternative com**P**lement **P**athway inhibition with iptacopan to arrest dis**EA**se p**R**ogression in **C3 G**lomerulopathy (APPEAR-C3G)

***Author List**:* Smith RJH, Kavanagh D, Tawfik R, Trapani AJ, Wang Y, Webb NJA, Vivarelli M, Bomback AS

Background: Complement 3 glomerulopathy (C3G) is a rare kidney disease characterized by dysregulation of the alternative pathway (AP) of the complement system. About 50% of patients progress to kidney failure within 10 years of diagnosis. Currently, there are no approved therapeutic agents for C3G. Iptacopan (LNP023) is an oral, first-in-class, potent and selective inhibitor of factor B, a key component of the AP. In a phase 2 study, treatment with iptacopan was associated with a statistically significant reduction in proteinuria and stabilization of eGFR in patients with C3G.

Methods: APPEAR-C3G (NCT04817618) is a randomized, double-blind, placebo-controlled pivotal Phase 3 study to evaluate the efficacy and safety of iptacopan in patients with native kidney C3G. 68 adults with biopsy-confirmed C3G, reduced C3 (<77 mg/dL), proteinuria ≥1.0 g/g and eGFR ≥30 mL/min/1.73m^2 will be enrolled. All patients will have received maximally tolerated ACEi/ARBs and vaccination against encapsulated bacteria. Patients with any organ transplant, progressive crescentic GN, monoclonal gammopathy of undetermined significance, and kidney biopsy with >50% interstitial fibrosis/tubular atrophy will be excluded. Patients will be randomized 1:1 to receive either iptacopan 200 mg bid or placebo for 6 months, followed by open-label treatment with iptacopan 200 mg bid for all patients for 6 months. Patients will be stratified by corticosteroid or mycophenolic acid treatment at randomization. The primary objective is to demonstrate the superiority of iptacopan versus placebo on proteinuria reduction as measured by UPCR (24h urine collection) at 6 months. Key secondary endpoints will assess kidney function measured by eGFR, a proteinuria-eGFR composite endpoint, histological disease total activity score, patient-reported fatigue, and safety parameters. Using functional, biomarker and histopathological assessments, this study aims to demonstrate clinical benefits of AP inhibition with iptacopan in C3G.

Concluding remarks: This study will provide valuable evidence towards efficacy and safety of iptacopan in C3G.