APPLAUSE-IgAN:
A multi-center, randomized, double-blind, placebo controlled, parallel group, phase III study to evaluate the efficacy and safety of LNP023 in primary IgA nephropathy patients

Background:

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. It is an autoimmune disease characterized by predominant IgA deposition in the glomerular mesangium leading to local inflammation and subsequent decline in kidney function. Currently there is no disease-specific therapy for IgAN. The KDIGO 2020 guidelines recommend long-term supportive therapy with an ACEi or ARB, with or without high dose corticosteroids or immunosuppressants, for blood pressure control and proteinuria reduction.

In recent years, mounting evidence have supported an important role for complement activation in disease onset and progression of IgAN. The alternative complement pathway (AP) and lectin complement pathway (LP) are found to be activated in 75-90% and 17-25% of IgAN patients respectively (Floege et al 2014, Maillard et al 2015). Factor B (FB) is an essential component of C3- and C5-convertases. LNP023 (iptacopan) is an oral, first-in-class, highly potent selective inhibitor of FB and thereby inhibits C3 and C5 convertases as well as the amplification of the classic and lectin complement pathways.

Currently, LNP023 is being evaluated in an ongoing adaptive seamless double-blind and placebo-controlled dose-ranging Phase 2 study (CLNP023X2203, Part 1 and Part 2) in patients with biopsy-confirmed IgAN and elevated proteinuria [urine protein to creatinine ratio (UPCR) ≥ 0.75 g/g]. An interim analysis (IA) at 90 days of treatment in the Part 1 study showed that LNP023 administered up to 200 mg b.i.d for 90 days was safe, well tolerated and may be effective in reducing proteinuria. A further IA combining participants in Part 1 and Part 2 will be completed in early 2021 and a phase 3 trial is being designed aiming to start in early 2021.

Aim: In a multicenter, randomized, double-blind, placebo-controlled parallel-group design, the Phase 3 study APPLAUSE-IgAN (CLNP023A2301) aims to evaluate the efficacy and safety of LNP023 compared to placebo in addition to supportive therapy on proteinuria reduction and slowing kidney disease progression in primary IgAN patients.

Method:
Adult patients with primary IgAN diagnosed based on kidney biopsy and elevated proteinuria (UPCR ≥ 1 g/g) will be recruited to the study. A run-in period will ensure that patients have received ACEi/ARB at a maximally tolerated dose for at least 90 days and receive required vaccinations at least 2 weeks prior to first dosing. Patients will be randomized in a 1:1 ratio to either LNP023 200 mg or matching placebo b.i.d. for a 24-month treatment period.

The trial will enroll approximately 450 participants, aiming for 430 with eGFR ≥30 mL /min/1.73m^2 (main study population) and approximately 20 participants with eGFR 20 to <30 mL/min/1.73m^2 (severe renal impairment/SRI population) which will primarily provide PK and safety information for that group and will not be included in efficacy analyses.

Primary objectives:

1) At interim analysis (when approximately 250 patients have completed the 9 months visit): to demonstrate superiority of LNP023 vs. placebo in the reduction of proteinuria. The IA results may be submitted to support accelerated/conditional approval.
2) At final analysis (when approximately 430 patients have completed 24 months of active treatment) to demonstrate superiority of LNP023 vs. placebo in slowing kidney disease progression measured by the annualized total slope of eGFR decline over 24 months.

Results: recruitment will start in Q1 2021.

Conclusion: This trial will define the effects of LNP023, a promising new therapy for IgAN, in reducing proteinuria and slowing loss of kidney function over 2 years.

Figure: Study Design