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

P220

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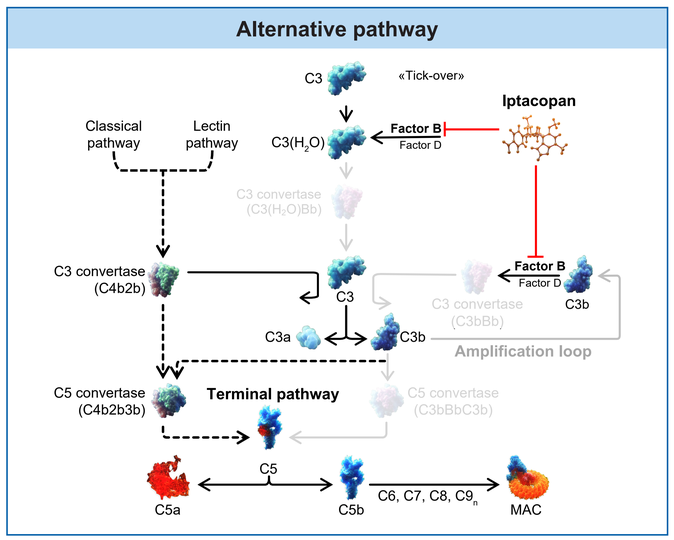
Introduction

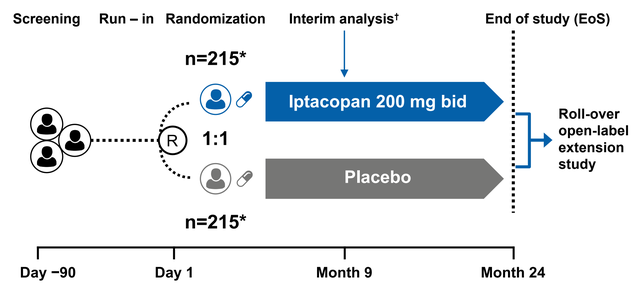
- **IgAN** is characterized by deposition of IgA1-containing immune complexes in the glomerular mesangium, leading to inflammation and glomerular injury[1]
- There is histologic evidence of the involvement of the **alternative complement pathway** (AP) in ~90% of patients[2] **(Figure 1)**
  - Co-deposition of C3, properdin and FH with immune complexes in the mesangium is common[2]
- There are no effective and well-tolerated targeted therapies approved for IgAN that slow or prevent progression to kidney failure[3,4]
- **Iptacopan (LNP023)** is an oral, highly potent, selective inhibitor of factor B (FB), a key protease of the AP[5,6]
- Iptacopan binds to FB to suppress the activity of C3 convertase – this prevents downstream generation of the C5 convertase complex, opsonization and formation of C5a anaphylatoxins and membrane attack complex (MAC)[5,6] **(Figure 1)**

Figure 1: Iptacopan: A selective inhibitor of the AP with a unique mechanism of action



Study design

Figure 2: Phase III study design – A multicenter, randomized, double-blind, placebo-controlled and parallel-group study[7]



Status: Recruiting (FPFV 25 Jan 2021)
Estimated study (NCT04578834) completion: Jan 2025

bid: twice daily, FPFV: first patient first visit.
*Main population only, severe renal impairment population (n~20) is not depicted.
†Planned when ~250 participants complete 9 months of treatment.

Patient population

- Biopsy-confirmed IgAN patients with elevated proteinuria (UPCR ≥1 g/g) despite being on stable doses of ACEi/ARB for at least 90 days[7]

Primary objectives

- **At interim analysis:** To assess superiority of iptacopan versus placebo in reduction of proteinuria (UPCR from 24-h urine collection) at 9 months[7]
- **At final analysis:** To assess superiority of iptacopan versus placebo in slowing progression of IgAN measured by annualized total slope of eGFR decline over 24 months[7]

Sample size

- **Main cohort** (eGFR ≥30 mL/min/1.73 m^2): ~430 patients[7]
- **Severe renal impairment cohort** (eGFR 20–29 mL/min/1.73 m^2): ~20 patients (not included in the primary analysis)[7]

Study endpoints

Interim analysis[7]

- **Primary endpoint:** Reduction in proteinuria (UPCR from 24-h urine collection) at 9 months
- **Key secondary endpoints‡**
  - Proportion of patients reaching proteinuria <1 g/g of UPCR (sampled from 24-h urine collection) at 9 months§
  - Annualized total eGFR slope estimated over 12 months
  - Change from baseline to 9 months in the fatigue scale measured by FACIT-Fatigue questionnaire
  - Safety and tolerability from baseline to 9 months

Final analysis[7]

- **Primary endpoint:** Annualized total eGFR slope estimated over 24 months
- **Key secondary endpoints**
  - Log-transformed ratio to baseline in UPCR (sampled from 24-h urine collection) at 9 months
  - Proportion of patients reaching proteinuria <1 g/g of UPCR at 9 months
  - Time to first occurrence of composite kidney failure endpoint‖
  - Change from baseline to 9 months in the fatigue scale measured by FACIT-Fatigue questionnaire
  - Safety and tolerability from baseline to EoS

‡Not adjusted for multiplicity. §Without receiving other background therapy or initiating KRT. ‖Defined as either sustained ≥30% decline eGFR from baseline, eGFR <15 mL/min/1.73 m^2, maintenance dialysis, receipt of kidney transplant, or death from kidney failure

Key eligibility criteria¶

Key inclusion criteria[7]

- Age ≥18 years with biopsy-confirmed IgAN#
- Proteinuria (UPCR of ≥1 g/g [113 mg/mmol]) at screening and completion of the run-in period
- On supportive care, including locally approved maximal daily dose or maximally tolerated stable dose of ACEi/ARB for ≥90 days before study treatment. If taking diuretics, antihypertensive medication, or other background medication for IgAN, their doses should be stable for ≥90 days before study treatment
- Vaccination against *Neisseria meningitides (required); Streptococcus pneumoniae and Haemophilus influenzae* (if available and according to local regulation)

Key exclusion criteria[7]

- Secondary IgAN
- HIV, HBV & HCV, malignancy in the past, major concurrent comorbidities
- SBP >140 mmHg or DBP >90 mmHg at randomization
- Previous treatment with immunosuppressive or immunomodulatory agents within 90 days prior to the study treatment
- Bacterial, viral or fungal infection within 14 days prior to randomization
- ≥50% decline in eGFR within 3 months prior to screening, acute kidney injury, nephrotic syndrome
- Prior transplantation

¶Eligibility criteria included here refer to the main cohort only. #eGFR ≥45 mL/min/1.73 m^2: biopsy within 5 years, eGFR 30 to <45 mL/min/1.73 m^2: biopsy within 2 years with <50% tubulointerstitial fibrosis, eGFR 20 to <30 mL/min/1.73 m^2: biopsy at any time

ACEi: angiotensin – converting enzyme inhibitor, AP: alternative complement pathway, ARB: angiotensin receptor blocker, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, EoS: end of study, FACIT: functional assessment of chronic illness therapy, FB: factor B, FH: factor H, HBV: hepatitis B virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus, IgA1: immunoglobulin A1, IgAN: immunoglobulin A nephropathy, IST: immunosuppressive therapy, KRT: kidney replacement therapy, MAC: membrane attack complex, SBP: systolic blood pressure, UPCR: urine protein – to – creatinine ratio, vs: versus.

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Disclosures:

VP and JB are co-chairs of the steering committee for LNP023 trials in IgAN; BR, HZ, NK, BM, and DVR are members of the steering committee for LNP023 trials in IgAN; HZ has received funds from Janssen; BM is a national leader for ASCEND-ND and -D trials (GSK), NefIgArd trial (Calliditas), DUPLEX and PROTECT trials (Retrophin); WW, MM, DK, OP, and AC are employees of the study sponsor (Novartis).

This scientific information may include data/information on investigational uses of compounds/drugs that have not yet been approved by regulatory authorities.

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