APPLAUSE–IgAN: Phase III study on efficacy and safety of iptacopan (LNP023) in primary IgA nephropathy

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on behalf of the Iptacopan IgAN Program Steering Committee

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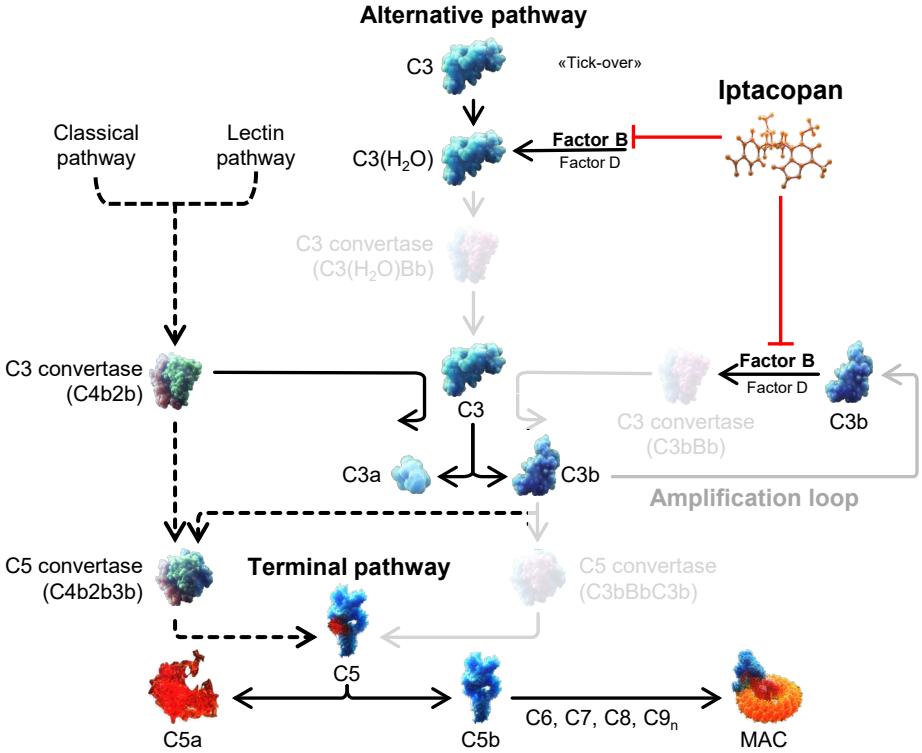
Disclosures

Prof. Barratt reports Co-Chairing the Steering Committee for Iptacopan trials in IgAN

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

- **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]
  - Co-deposition of C3, properdin and FH with immune complexes in the mesangium is common[2]
- **Iptacopan** is an oral, highly potent, selective inhibitor of factor B (FB), a key protease of the AP[3,4]
- 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 MAC[3,4]
- Analysis of the **Phase II** study suggested ~23% reduction in proteinuria (UPCR 24h) with iptacopan 200 mg bid vs. placebo at 3 months of treatment[5]



AP, alternative complement pathway; bid, twice daily; FB, factor B, FH, factor H; IgA1, immunoglobulin A1; IgAN, IgA nephropathy; MAC, membrane attack complex; vs, versus

1. Lai KN et al. Nat Rev Dis Primers 2016;2:16001; 2. Maillard N et al. J Am Soc Nephrol 2015;26:1503-12; 3. Schubart A et al. PNAS 2019;116(16):7926-931; 4. Rizk DV, et al. Front Immunol 2019;10;504; 5. Data on file

Study design

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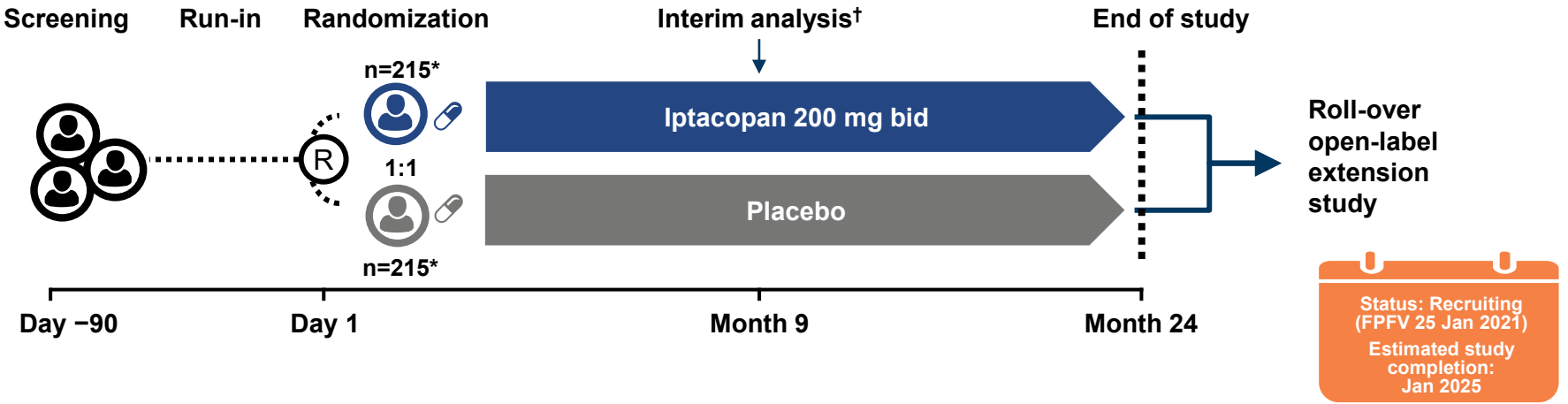

Study design	A multicenter, randomized, double-blind, placebo-controlled and parallel-group study
Patient population	Biopsy-confirmed IgAN patients with elevated proteinuria (UPCR ≥1 g/g) despite being on stable doses of ACEi/ARB for at least 90 days
Primary objectives	• **At IA**: To assess superiority of iptacopan versus placebo in reduction of proteinuria (UPCR from 24-h urine collection) at 9 months • **At EoS**: To assess superiority of iptacopan versus placebo in slowing progression of IgAN measured by annualized total slope of eGFR decline over 24 months
Sample size	• **Main cohort** (eGFR ≥30 mL/min/1.73 m^2): ~430 pts • **Severe Renal Impairment cohort** (eGFR 20–29 mL/min/1.73 m^2): ~20 pts (not included in the primary analysis)

*Main population only, severe renal impairment population (n~20) is not depicted;
†Planned when ~250 participants complete 9 months of treatment
ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; bid, twice daily; eGFR, estimated glomerular filtration rate; EoS, end of study; FPFV, first patient first visit; IgAN, immunoglobulin A nephropathy; pts, patients; IA, interim analysis; UPCR, urine protein-to-creatinine ratio

1. https://clinicaltrials.gov/ct2/show/NCT04578834 (Last accessed: 20 April 2021).

Study endpoints

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Interim analysis

- **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

- **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

¥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

eGFR, estimated glomerular filtration rate; EoS, end of study; FACIT, Functional Assessment of Chronic Illness Therapy; IgAN, immunoglobulin A nephropathy; IST, immunosuppressive therapy; KRT, kidney replacement therapy; UPCR, urine protein-to-creatinine ratio.

1. Data on file; 2. https://clinicaltrials.gov/ct2/show/NCT04578834 (Last accessed: 20 April 2021).

Key eligibility criteria*

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Key inclusion criteria

- 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 recommended or maximally tolerated stable dose of ACEi/ARB for ≥90 days before study treatment
- Vaccination against *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*

Key exclusion criteria

- 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
- 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 inhibitors; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgAN, IgA nephropathy; SBP, systolic blood pressure; UPCR, urine protein-to-creatinine ratio.

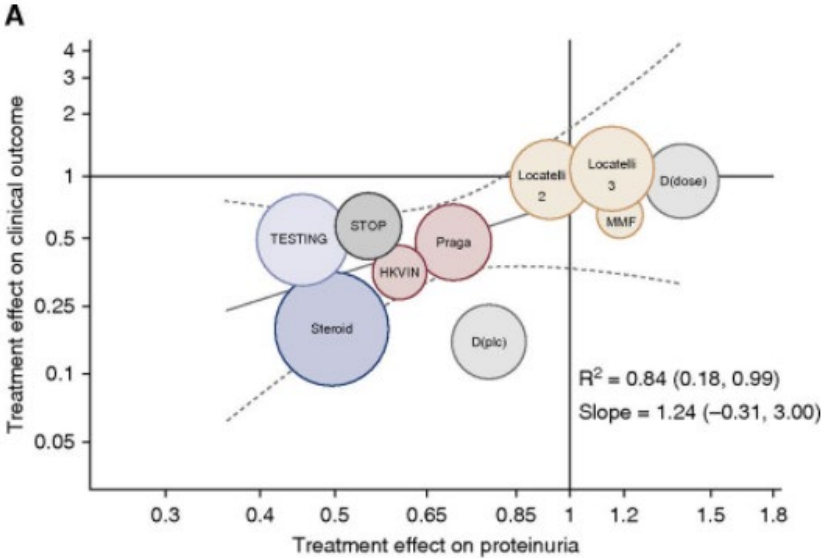
1. https://clinicaltrials.gov/ct2/show/NCT04578834 (Last accessed: 20 April 2021); 2. Data on file

Back-up

‘Proteinuria reduction’ as a surrogate endpoint for IgAN

- The alternative complement pathway (AP) plays an important role in the pathogenesis of IgAN; therefore inhibition of AP with **iptacopan (LNP023)**, an oral, highly potent selective inhibitor of Factor B, may provide an attractive therapeutic strategy[1].
- A meta-analysis of 13 RCTs in IgAN patients showed higher proteinuria was related to worse kidney outcomes or death[2]
- Early reduction of proteinuria is a useful surrogate endpoint in IgAN, predicting reduced risk of kidney failure[2]

Treatment benefits of novel therapies on changes in proteinuria[2]



AP, alternative complement pathway; FB, Factor B; IgAN, IgA nephropathy; RCTs, randomized controlled trials

1. Rizk DV, et al. Front Immunol 2019;10;504; 2. Thompson A, et al. Clin J Am Soc Nephrol. 2019;14(3):469-481.