Alternative complement pathway inhibition with iptacopan to arrest disease progression in C3 Glomerulopathy (APPEAR-C3G): A Phase 3 study

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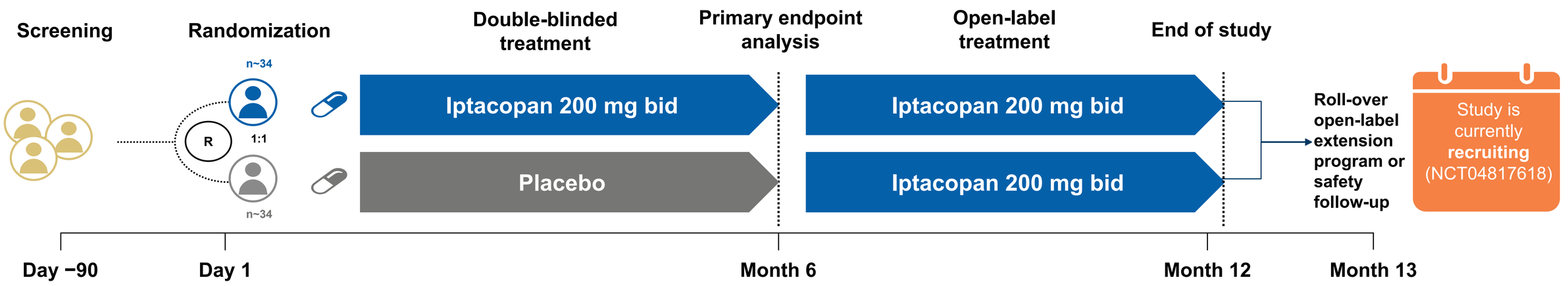
APPEAR-C3G

Introduction

- C3 glomerulopathy (C3G) is a rare kidney disease caused by dysregulation of the alternative complement pathway (AP)[1]
- Iptacopan (LNP023) is an oral, highly potent, and selective small-molecule inhibitor of complement Factor B, a key regulator of the AP[2]
- In a previously reported Phase II study, 12 weeks treatment with iptacopan was associated with a 45% reduction in **proteinuria** (p=0.0003)[3], stabilization of **eGFR**[4] in patients with native C3G, and reduction in **C3 deposit scores** on kidney biopsy in patients with recurrent C3G after kidney transplantation (p=0.03)[3]
- Iptacopan showed a favorable safety and tolerability profile in both cohorts, providing rationale for this Phase 3 trial

Study Design



Patients will be stratified by corticosteroid or mycophenolic acid treatment at randomization

Primary Objectives[5]

- To demonstrate the superiority of iptacopan versus placebo on proteinuria (urine protein:creatinine ratio [UPCR]) reduction following 6 months of treatment (double-blinded treatment period)

Key Secondary Objectives[5]

- To evaluate the effect of iptacopan vs. placebo on the following in the double-blind treatment period:
  - Change from baseline in eGFR at 6 months
  - Proportion of patients meeting the composite renal endpoint (stable or improved eGFR from baseline [≤15% reduction] and a ≥50% reduction from baseline in UPCR) at 6 months
  - Change from baseline in disease total activity score in a kidney biopsy and patient reported fatigue (FACIT-Fatigue score) at 6 months
- Safety and tolerability

Statistical Analysis

- The primary analysis will be carried out using a mixed model for repeated measures (MMRM) approach for the log ratio to baseline in UPCR at 6 months. Similarly, change from baseline in eGFR and fatigue total score will be assessed using a MMRM model.
- A logistic regression model will be used to assess the proportion of participants meeting the composite renal endpoint

Inclusion Criteria[5*]

- Male and female participants aged ≥18 years and ≤60 years
- Biopsy-confirmed diagnosis of C3G
- Reduced C3 (<0.85 X LLN)
- UPCR ≥1.0 g/g
- eGFR[†] or measured GFR ≥30 mL/min/1.73 m^2
- On maximally recommended or tolerated dose of ACEi or ARB for ≥90 days
- Stable dose of any other immunosuppressive or other medications such as, but not limited to, mycophenolic acids, corticosteroids, and mineralocorticoid receptor antagonists
- Vaccination against *Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae*

Key Exclusion Criteria[5*]

- Solid organ transplantation including kidney transplantation
- Rapidly progressive crescentic GN
- Renal biopsy with interstitial fibrosis/tubular atrophy >50%
- MGUS
- A history of recurrent invasive infections caused by encapsulated organisms
- Use of complement inhibitors within 6 months prior to screening or use of immunosuppressants (except mycophenolic acid), cyclophosphamide or systemic corticosteroids at a dose >7.5 mg/day (or equivalent for a similar medication) within 90 days of study drug administration

Conclusion

- This study will provide valuable evidence towards the efficacy and safety in C3G patients with native kidney disease, and is pivotal for the registration of iptacopan in C3G

***Other protocol-defined eligibility criteria may apply**

†Using the CKD-EPI formula for ≥18 years

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AP, alternative complement pathway; ARB, angiotensin receptor blocker; bid, twice daily; C3, complement protein 3; C3G, C3 glomerulopathy; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; GN, glomerulonephritis; LLN, lower limit of normal; MGUS, monoclonal gammopathy of undetermined significance; MMRM, mixed model for repeated measures; QR, quick response; UPCR, urine protein:creatinine ratio

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