A multicenter, randomized, double-blind, placebo-controlled Phase 3 study (APPARENT) to assess the efficacy and safety of iptacopan in idiopathic (primary) immune complex-mediated membranoproliferative glomerulonephritis

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Study aim and design

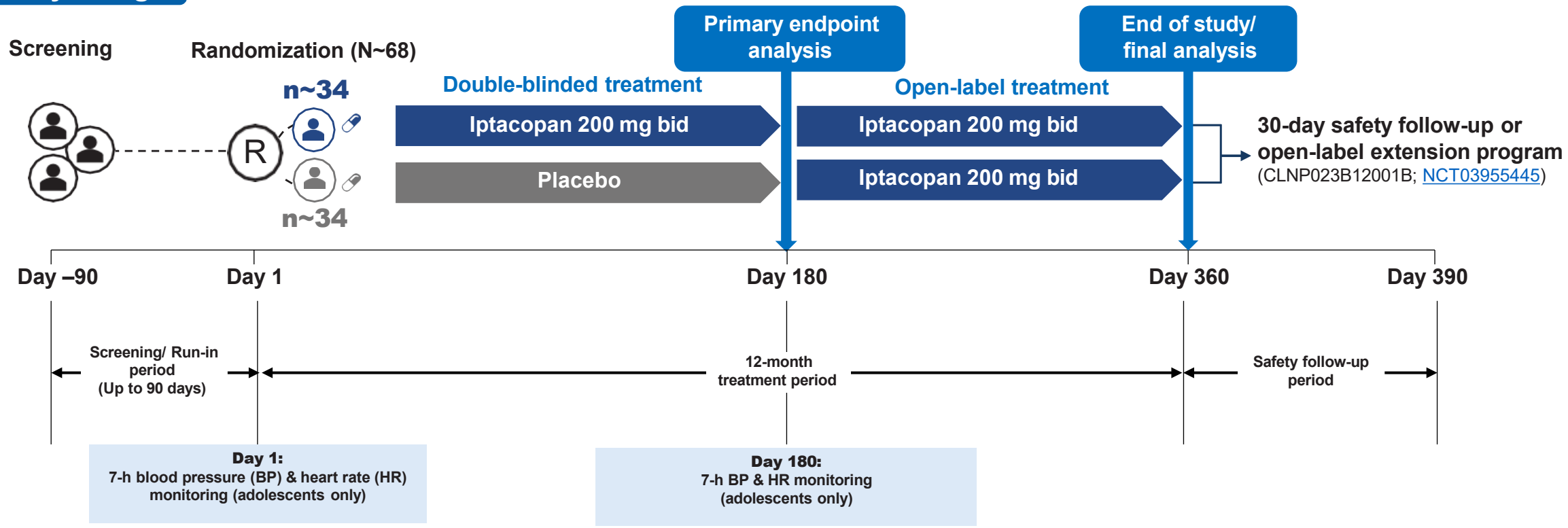
Aim

To **evaluate the clinical efficacy and safety of iptacopan** compared with placebo in adolescent and adult patients with IC-MPGN

Population

~68 adult and adolescent patients with biopsy-confirmed idiopathic IC-MPGN and a **minimum of 10 adolescents**

Study design



Key objectives and endpoints

Primary objective and endpoint

Double-blind period

- ***Primary objective:*** To demonstrate the superiority of iptacopan versus placebo on reducing proteinuria at 6 months
- ***Primary endpoint:*** Log-transformed ratio to baseline in UPCR (sampled from a 24-h urine collection) at 6 months

Open-label period

- ***Primary objective:*** To assess the effect of iptacopan on proteinuria at 12 months
- ***Primary endpoints:***
  - Log-transformed ratio to baseline in UPCR at the 12-month visit (both study treatment arms)
  - Log-transformed ratio to 6-month visit in UPCR at the 12-month visit in the placebo arm (iptacopan treatment period)

Secondary objectives

- To demonstrate the superiority of iptacopan versus placebo in improving:
  - eGFR
  - The proportion of patients achieving a composite renal endpoint (a stable or improved eGFR [≤15% reduction in eGFR] and a ≥50% reduction in UPCR compared with the baseline visit)
  - Patient-reported fatigue
- To perform cardiovascular surveillance (adolescents only)
- To evaluate the safety and tolerability of iptacopan

Key eligibility criteria

Key inclusion criteria

- **Age ≥12 and ≤60 years** at screening
- **Diagnosis of idiopathic IC-MPGN** as confirmed by kidney biopsy within 12 months (adults) or within 3 years (adolescents) prior to enrollment
- **UPCR ≥1.0 g/g** (FMV sample at both Day –75 and –15)
- eGFR **≥30 mL/min/1.73m² (modified Schwartz) at Screening and Day –15**
- Maximally **recommended / tolerated ACE/ARB therapy** for ≥90 days
- **Doses of other antiproteinuric medications** including MPA, corticosteroids (max 7.5mg prednisolone daily), SGLT2i or stable for ≥90 days prior to randomization
- **Vaccination** against *Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae infections*

Key exclusion criteria

- **Cell or solid organ transplantation**, including kidney transplantation
- Diagnosed with **secondary (non-idiopathic) IC-MPGN** due to, for example: viral, bacterial, and protozoa/other infections; autoimmune diseases; monoclonal gammopathy; fibrillary glomerulonephritis
- Rapidly **progressive crescentic glomerulonephritis** (defined as a 50% decline in the eGFR within 3 months) with kidney biopsy findings of glomerular crescent formation seen in ≥50% of glomeruli
- Kidney biopsy showing **interstitial fibrosis/tubular atrophy >50% or post-infectious GN**
- A history of **recurrent invasive infections** caused by encapsulated organisms, e.g., *N. meningitidis* and *S. pneumoniae*
- Use of non-MPA or corticosteroid immunosuppressive agents within 90d and **complement inhibitors** within 6 months prior to the screening