A Phase 3 study to support iptacopan registration in atypical hemolytic uremic syndrome (aHUS): Overview of APPELHUS study design considerations

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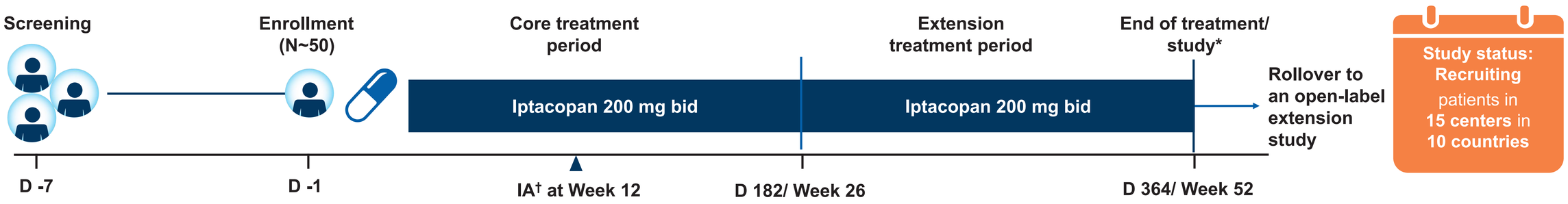
APPELHUS

Introduction

- aHUS is a rare, progressive and life-threatening form of TMA caused by dysregulation of the AP[1,2]
- Inhibiting AP is therefore an attractive therapeutic strategy to slow aHUS disease progression[3]
- Iptacopan (LNP023) is an oral, first-in-class, highly potent, selective inhibitor of factor B, a key regulator of the AP[4]
- In Phase 2 studies in patients with IgAN[5], PNH[6] and C3G[7] iptacopan inhibited the AP, showed clinically relevant benefits, and was well tolerated[5-7]
- The well-established role of AP dysregulation in aHUS pathophysiology, the positive results with iptacopan in IgAN[5], C3G[7] and PNH[6] Phase 2 studies, coupled with the efficacy of complement inhibitor therapies in aHUS, provide a strong rationale to evaluate iptacopan directly in this pivotal Phase 3 trial for patients with aHUS

Study Design

APPELHUS (Alternative Pathway Phase III to Evaluate LNP023 in aHUS): A global, multicenter, single-arm, open-label, Phase 3 study (NCT04889430) evaluating the efficacy and safety of iptacopan 200 mg bid in patients with aHUS naïve to complement inhibitor therapy[8]



*End of Study: when safety follow-up phone call has been placed 7 days post end of treatment for a last AE monitoring; after completing the end of treatment visit, a patient may rollover to an open-label extension study or proceed to End of Study
†IA when approx. 8 participants complete 12 weeks of treatment. IA will provide preliminary evidence of efficacy and safety of iptacopan in patients with aHUS who are treatment naive

Inclusion Criteria[8‡]

- Patients aged ≥18 years, with evidence of TMA, including
  - Platelet count <150×10^9/L
  - LDH ≥1.5×ULN
  - Hemoglobin ≤LLN
  - Serum creatinine ≥ULN
- Vaccinations for *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* at least 2 weeks prior to treatment initiation
  - If treatment has to start earlier than 2 weeks post vaccination or before vaccination, administer prophylactic antibiotics at the start of study treatment and for at least 2 weeks after vaccination
- Among patients with a kidney transplant
  - Known history of aHUS prior to current kidney transplantation, or
  - No known history of aHUS, and persistent evidence of TMA at least 4 days after modifying the immunosuppressive regimen

Key Exclusion Criteria[8‡]

- Treatment with complement inhibitors, including anti-C5 antibody
- ADAMTS13 deficiency (<5% activity), and/or Shiga toxin-related HUS, and/or Positive direct Coombs test
- Identified drug exposure-related HUS or HUS related to known genetic defects of cobalamin C metabolism or known diacylglycerol kinase ε mediated aHUS
- Receiving PE/PI, for ≥28 days, prior to the start of screening for the current TMA
- BMT/HSCT, heart, lung, small bowel, pancreas, or liver transplantation
- Kidney disease other than aHUS or chronic kidney failure or family history of non-complement mediated genetic kidney disease
- Sepsis, severe systemic infection, COVID-19 infection, systemic infection which confounds an accurate diagnosis or management of aHUS
- Active infection or history of recurrent invasive infections caused by encapsulated bacteria
- Systemic sclerosis (scleroderma), systemic lupus erythematosus, or antiphospholipid antibody positivity or syndrome
- Chronic hemodialysis or peritoneal dialysis

Primary Endpoints[8]

- Proportion of patients achieving complete TMA response[§] without the use of PE/PI or anti-C5 antibody during 26 weeks of study treatment
- Long-term (one-year) efficacy, safety and tolerability of iptacopan evaluated during the extension period

Secondary Endpoints[8]

- To evaluate the effect of iptacopan on the following, during 26 weeks of treatment:
  - Time to achieve complete TMA response
  - Proportion of patients with increase from baseline in hemoglobin levels ≥2 g/dL[¶]
  - Proportion of patients on dialysis (for current TMA event), who no longer require dialysis
  - Change from baseline in eGFR, CKD stage, hematologic parameters (platelets, LDH, and hemoglobin), and patient-reported outcomes (as measured by FACIT-Fatigue, EQ-5D-5L, PGIS, and SF-36 v2 questionnaires)
- Safety and tolerability

Statistical Analysis

- The primary endpoint of TMA response in iptacopan treated patients will be evaluated in the context of benefits reported for eculizumab and ravulizumab
- TMA response rate and its 95% CI will be calculated based on asymptotic Gaussian approximation with continuity correction, and this will be compared with a pre-determined threshold based on the two historical trials of eculizumab[9] and ravulizumab[10] in patients with aHUS
- A lower bound of the CI greater than the pre-determined threshold would suggest that iptacopan preserves a significant proportion of the treatment effect relative to current standard of care
- The long-term safety and tolerability will be assessed by descriptive analysis

Conclusion

- The study will determine if iptacopan is safe and efficacious in patients with aHUS

Abbreviations: AE adverse event; aHUS, atypical hemolytic uremic syndrome; AP, alternative complement pathway; bid, twice daily; BMT, bone marrow transplantation; C3G, complement 3 glomerulopathy; CI, confidence interval; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQol 5-level EQ-5D version; FACIT, Functional Assessment Of Chronic Illness Therapy; HSCT, hematopoietic stem cell transplantation; HUS, hemolytic uremic syndrome; IA, interim analysis; IgAN, immunoglobulin A nephropathy; LDH, lactate dehydrogenase; LLN, lower limit of normal; PE, plasma exchange; PGIS, Patient Global Impression of Severity; PI, plasma infusion; PNH, paroxysmal nocturnal hemoglobinuria; SF-36 v2, Short-form 36 health survey questionnaire version 2; TMA, thrombotic microangiopathy; ULN, upper limit of normal.

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‡Other protocol-defined eligibility criteria may apply; §Defined as (1) hematological normalization in platelet count (platelet count ≥150×10^9/L) and LDH (below ULN), and (2) improvement in kidney function (≥25% serum creatinine reduction from baseline), maintained for two measurements obtained at least four weeks apart, and any measurement in between; ¶As observed at two measurements obtained at least 4 weeks apart and any measurement in between during 26 weeks of study treatment.

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