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Evaluation of iptacopan in atypical hemolytic uremic syndrome: Design and rationale of the Phase 3 open-label multicenter APPELHUS study

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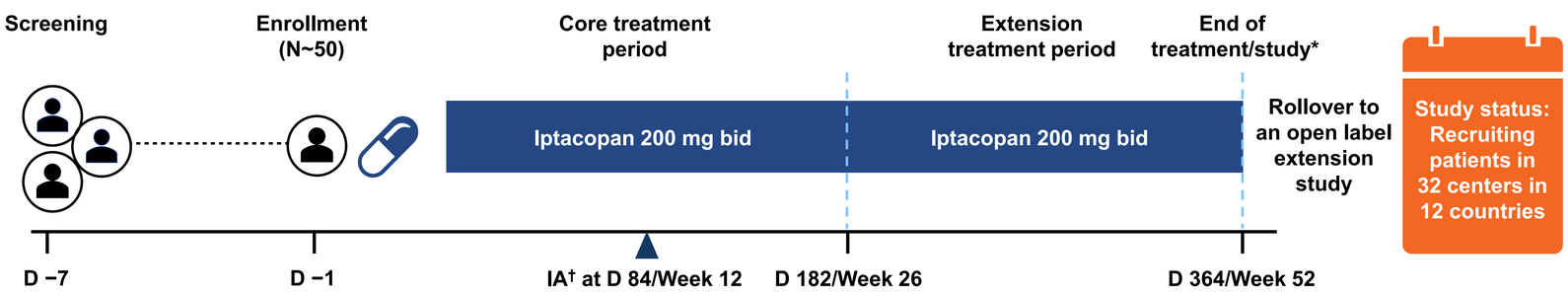
APPELHUS

Conclusion

- The study determines whether iptacopan is safe and efficacious in patients with aHUS

Figure 1. 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[1]



*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 ~ 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 naïve.

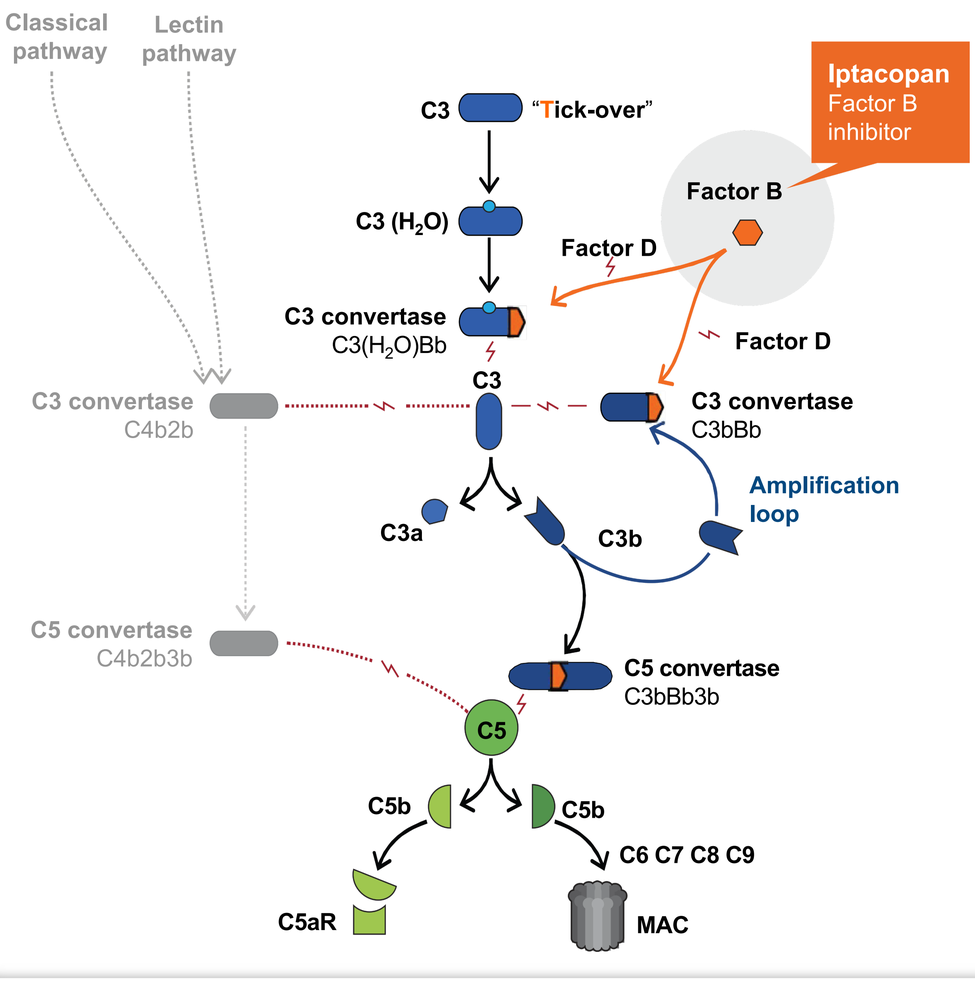
Statistical analysis

- The primary endpoint is complete TMA response and will be evaluated when all participants complete 26 weeks of treatment
- TMA response rate and its 95% CI will be calculated based on asymptotic Gaussian approximation with continuity correction, and the lower bound of the CI will be compared with a predetermined threshold based on the two historical trials of eculizumab[2] and ravulizumab[3] in patients with aHUS
- The long-term safety and tolerability will be assessed at Week 52 by descriptive analysis

Background: aHUS and AP inhibition

- aHUS is a rare, progressive, and life-threatening form of TMA caused by dysregulation of the AP[4,5]
- Inhibiting the AP is therefore an attractive therapeutic strategy to slow aHUS disease progression[6]
- Iptacopan is a proximal complement inhibitor that targets Factor B to selectively inhibit the AP while leaving the direct signaling from the lectin and classical pathways intact[7–9]. Inhibition of Factor B prevents the activity of AP–related C3 convertase and the subsequent formation of C5 convertase[7]
- In Phase 2 studies in patients with IgAN,[10] PNH,[8] and C3G,[11] iptacopan showed clinically-relevant benefits, and was well tolerated[8,10,11]
- The well-established role of AP dysregulation in aHUS pathophysiology and the positive results with iptacopan in 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

Figure 2. Alternative pathway



Inclusion criteria[1]*

- 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 *Hemophilus influenzae* at least 2 weeks prior to first study drug administration
  - 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

*Other protocol-defined eligibility criteria may apply

Exclusion criteria[1]*

- 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, and systemic infection that 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

*Other protocol-defined eligibility criteria may apply

Primary endpoints[1]

- 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 (1-year) efficacy, safety, and tolerability of iptacopan evaluated during the extension period at Week 52

*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 4 weeks apart, and any measurement in between obtained at least 4 weeks apart and any measurement in between during 26 weeks of study treatment

Secondary endpoints[1]

- To evaluate the effect of iptacopan during 26 weeks of treatment on the following:
  - 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)

*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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Abbreviations

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif; AE, adverse event; aHUS, atypical hemolytic uremic syndrome; AP, alternative pathway; bid, twice daily; BMT, bone marrow transplantation; C, complement; C3G, complement 3 glomerulopathy; CI, confidence interval; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; D, day; 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; IA, interim analysis; IgAN, immunoglobulin A nephropathy; LDH, lactate dehydrogenase, LLN, lower limit of normal; MAC, membrane attack complex; 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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