ISN Frontiers Meetings Abstract

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

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Introduction

Atypical hemolytic uremic syndrome (aHUS) is a rare, progressive and life threatening form of thrombotic microangiopathy (TMA). It is caused by dysregulation of the alternative complement pathway (AP); inhibiting AP is therefore an attractive therapeutic strategy to slow aHUS disease progression. Iptacopan (LNP023) is an oral, first-in-class, highly potent, selective inhibitor of factor B, a key regulator of the AP. In Phase 2 studies in patients with paroxysmal nocturnal hemoglobinuria (PNH) and in those with C3 glomerulopathy (C3G), iptacopan inhibited AP, demonstrated clinically relevant benefits and was well tolerated. Iptacopan thus has the potential to become an effective and safe treatment for aHUS, with a lower treatment burden due to oral administration. The efficacy and safety of iptacopan demonstrated in Phase 2 studies in C3G and PNH, coupled with the established efficacy of complement inhibitor therapies in aHUS provide a strong rationale to directly evaluate its benefits in aHUS patients in a Phase 3 trial to support iptacopan registration.

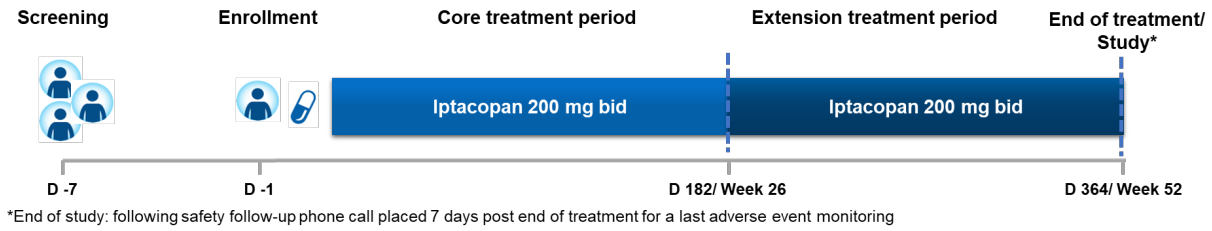
Methods

The APPELHUS (Alternative Pathway Phase III to Evaluate LNP023 in aHUS) study (NCT04889430) is a global, multicenter, single-arm, open label, Phase 3 study evaluating the efficacy and safety of iptacopan 200 mg twice daily in 50 adult aHUS patients naïve to complement inhibitor therapy. The study comprises a 26-week core treatment period followed by a 26-week extension treatment period. In the absence of Phase 2 data with iptacopan in aHUS patients, an interim analysis will be performed when approximately 8 participants complete 12 weeks of treatment. Eligible patients must have evidence of TMA (platelet count $<150\times10^9$/L, LDH ≥1.5×upper limit of normal [ULN], hemoglobin ≤lower limit of normal, serum creatinine ≥ULN). Key exclusion criteria include treatment with complement inhibitors, ADAMTS13 deficiency (<5% activity), Shiga toxin-related HUS, positive Coombs test and other causes of TMA. The primary endpoint is the proportion of patients achieving complete TMA response without the use of plasma exchange/plasma infusion and anti-C5 antibody during 26 weeks of iptacopan treatment. TMA response in iptacopan treated patients will be evaluated in the context of benefits reported for eculizumab and ravulizumab. The calculated

TMA response rate will be compared with a pre-determined threshold based on the two historical trials of eculizumab and ravulizumab in patients with aHUS. A two-sided 95% confidence interval (CI) for the primary endpoint will be calculated based on asymptotic Gaussian approximation with continuity correction. A lower bound above the pre-determined threshold suggests that iptacopan preserves a significant proportion of the treatment effect relative to current standard of care. Secondary endpoints include time to complete TMA response; change from baseline in hemoglobin (≥2 g/dL), eGFR, chronic kidney disease stage, hematologic parameters (platelets, LDH and hemoglobin), dialysis requirement status, and patient-reported fatigue scores; safety; and tolerability. Long-term efficacy, safety and tolerability of iptacopan will be evaluated during the extension period.

Conclusion

APPELHUS will determine if iptacopan is safe and efficacious in patients with aHUS.



*End of study: following safety follow-up phone call placed 7 days post end of treatment for a last adverse event monitoring

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