Cardiovascular Renal Metabolism Franchise

Efficacy and Safety of Iptacopan in Patients with aHUS Naïve to Complement Inhibitor Therapy: Design of a Single-arm, Open-Label Phase III Study

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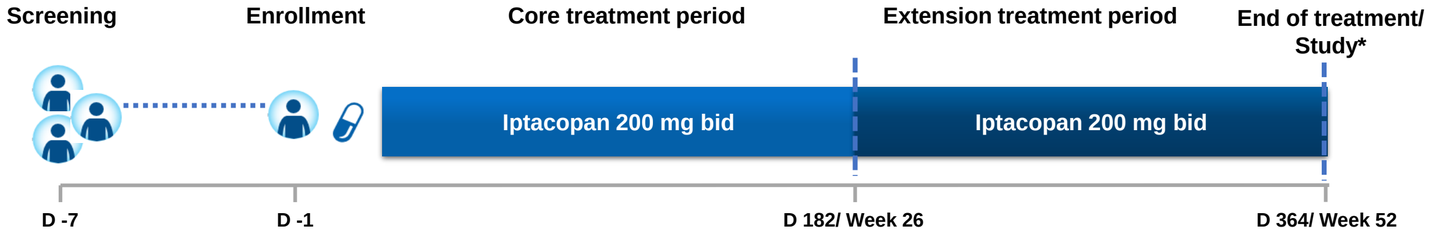
APPELHUS

Introduction

- Atypical hemolytic uremic syndrome (aHUS) is a life-threatening, ultra-rare form of thrombotic microangiopathy (TMA) characterized by acute kidney injury, thrombocytopenia, and microangiopathic hemolytic anemia[1,2]
- aHUS is caused by dysregulation of the alternative complement pathway (AP)[1,2]
- Iptacopan (LNP023) is a novel, first in class, oral, highly potent, selective, small-molecule inhibitor of complement Factor B, a key protease of the AP[3]
- In proof-of concept Phase II studies, iptacopan inhibits AP, reduces proteinuria in patients with C3 glomerulopathy[4] and reduces LDH levels and normalizes haemoglobin levels in patients with paroxysmal nocturnal hemoglobinuria[5], supporting the rationale for evaluating its potential benefits in patients with aHUS

Study Design[6]

APPELHUS (Alternative Pathway Phase III to Evaluate LNP023 in aHUS): A global, multicenter, single-arm, open label, Phase III study (NCT04889430)



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

Primary Objectives[6]

- To assess the proportion of patients treated with iptacopan achieving complete TMA response† during 26 weeks of study treatment (core treatment period)
- Long term safety, tolerability and efficacy after 52 weeks of treatment (extension period)

Key Secondary Objectives[6]

- To assess the effect of iptacopan on the following during 26 weeks of treatment:
  - Time to complete TMA response†
  - Proportion of patients
    - achieving an increase from baseline in hemoglobin levels of ≥2 g/dL
    - On dialysis (for current TMA event) who no longer require dialysis
- Change from baseline to 26 weeks in
  - Hematological parameters (platelets, LDH, hemoglobin)
  - eGFR
  - CKD stage
  - Patient-reported overall fatigue severity and HRQoL
- Safety and tolerability

Key Inclusion and Exclusion Criteria

Inclusion[6,¶]

- Aged >18 years
- Evidence of TMA including:
  - Platelet count (<150x10^9/L)
  - LDH≥1.5xULN and hemoglobin ≤LLN
  - Serum creatinine ≥ULN
- Prior vaccination for *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae*
  - Patients without prior vaccination should receive prophylactic antibiotics prior to 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[6,¶]

- Treatment with complement inhibitors (including anti-C5 antibody)
- ADAMTS13 deficiency and/or Shiga Toxin-related HUS and/or positive Coombs test
- Identified drug exposure-related HUS or HUS related to known genetic defects of cobalamin C metabolism or known DGKE mediated aHUS
- Systemic infections that impact diagnosis/ management of aHUS
- Liver disease or injury at screening
- Sepsis, severe systemic infection or COVID-19
- Scleroderma, systemic lupus erythematosus, or antiphospholipid antibody positivity or syndrome
- Active/history of recurrent invasive infections from encapsulated bacteria
- Chronic hemo- or peritoneal dialysis
- PE/PI for ≥28 days prior to the start of screening for the current TMA
- Heart, lung, small bowel, pancreas, liver transplant or bone marrow/hematopoietic stem cell transplantation
- Kidney disease other than aHUS

Statistical Analysis

A two-sided 95% confidence interval for the primary endpoint will be calculated based on asymptotic Gaussian approximation with continuity correction. The calculated TMA response rate will be compared to a pre-defined threshold that has been chosen based on the two historical trials with eculizumab[7] and ravulizumab[8] that are comparable in study design, population and efficacy endpoints.

Study Status: Recruiting

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Scan QR Code for full trial details

†Complete TMA response is defined as (1) hematological normalisation in platelet count (platelet count ≥150x10^9/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

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Abbreviations

aHUS, atypical hemolytic uremic syndrome; AP, alternative pathway; bid, twice a day; CKD, chronic kidney disease; D, day; DGKE, diacylglycerol kinase ε; eGFR, estimated glomerular filtration rate; HRQoL, health-related quality of life; LDH, lactate dehydrogenase; LLN, lower limit of normal; PE, plasma exchange; PI, plasma infusion; TMA, thrombotic microangiopathy; ULN, upper limit of normal`

Disclaimer

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