Title: AN ADAPTIVE, DOSE-EXPLORATION, PHASE 2 TRIAL EVALUATING EFFICACY AND SAFETY OF IPTACOPAN IN COMBINATION WITH STANDARD-OF-CARE WITH AND WITHOUT ORAL CORTICOSTEROIDS IN ACTIVE LUPUS NEPHRITIS

Introduction

Lupus nephritis (LN) is a renal manifestation seen in up to 60% of patients with systemic lupus erythematosus. With the current standard of care (SoC: high-dose followed by tapering oral corticosteroids [CS] plus cyclophosphamide or mycophenolate mofetil/sodium [MMF/MPS]) only 30–50% of patients achieve a complete clinical renal response, and up to 35% of responders may relapse. Further, 10-20% of patients progress to kidney failure within 10 years of diagnosis. Chronic CS therapy is associated with short and long-term adverse events. In LN, complement activation by immune complexes through the classical pathway and subsequent amplification by the alternative complement pathway (AP) is a key driver of kidney injury. Nearly 30% of patients with LN also have anti-C3 autoantibodies that contribute to overactivation of the AP. Thus, a targeted therapy to prevent activation of the AP might be beneficial. This study aims to evaluate the efficacy and safety of iptacopan (an oral proximal complement inhibitor that specifically binds to factor B and inhibits the AP) as an add-on to current SoC with or without oral CS in patients with active LN.

Methods

This Phase 2 adaptive, randomized, double-blind, dose-exploration, parallel-group, placebo-controlled, multicenter trial consists of two parts of 52 weeks each (Figure, NCT05268289). In total, ~240 participants (≥18 years) with Class III or IV, with or without co-existing class V features, active LN, positive for anti-nuclear antibodies, 24-hr UPCR ≥1.5 g/g and eGFR ≥30 mL/min/1.73 m^2, will be randomized. Part 1 (N~80) will evaluate whether the use of iptacopan 200 mg twice daily (b.i.d), compared with placebo, is efficacious and safe in combination with MMF/MPS and CS . An interim analysis (IA) will be performed when ~80 patients in Part 1 have completed the Week 24 visit. If iptacopan is found to be effective (in terms of reduction in proteinuria and other renal endpoints) and safe, Part 2 (N~160) will be initiated to evaluate the efficacy and safety of (i) iptacopan 50 mg b.i.d + MMF/MPS + CS, and (ii) iptacopan 200 mg b.i.d + MMF/MPS without CS . The SoC treatment in the control arms of Part 1 and Part 2 is identical (MMF/MPS + CS), and control patients from both parts will be pooled at the primary and final analysis to achieve greater power.

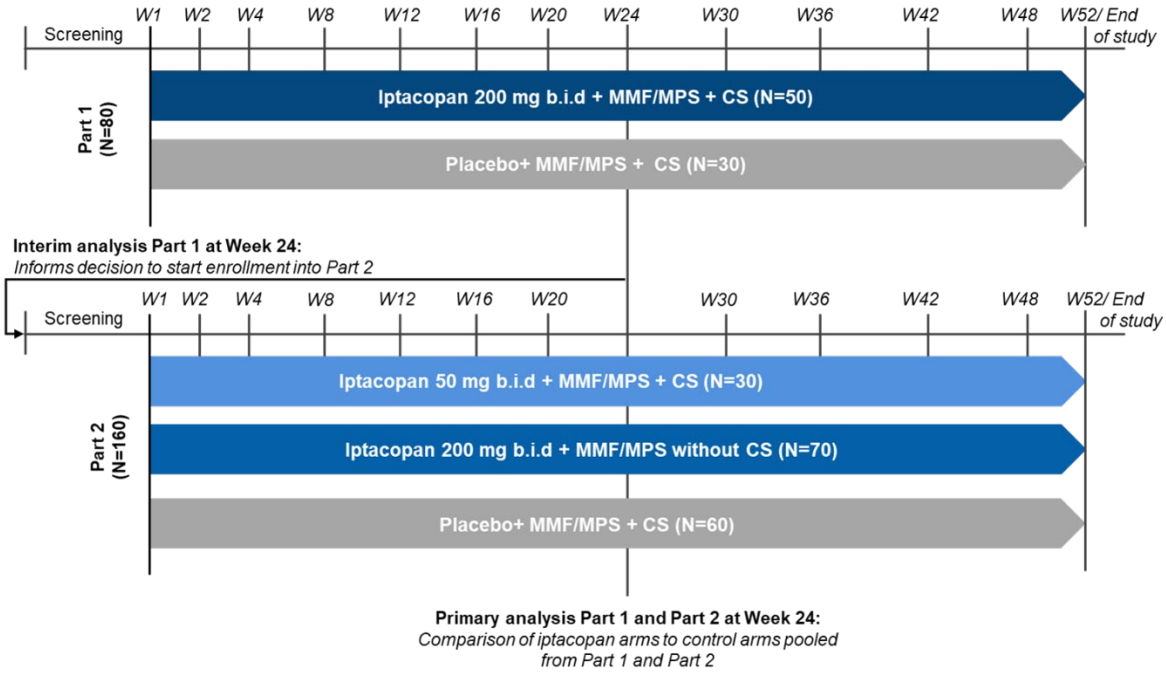
The primary objective is to compare the proportion of patients that achieve complete renal response at Week 24 in the absence of renal flares with the following regimens: iptacopan 200 mg b.i.d + MMF/MPS + CS; iptacopan 50 mg b.i.d + MMF/MPS + CS; iptacopan 200 mg b.i.d + MMF/MPS without CS, versus control. Patient-reported outcomes for fatigue, disease activity scores and safety will also be evaluated.

Results

Study recruitment is ongoing.

Conclusion

This adaptive proof-of-concept and dose-exploration Phase 2 study is designed to ascertain whether iptacopan can improve outcomes in patients with LN while also allowing reduction (or elimination) of oral CS.



Key words: LN, clinical trial, alternative complement pathway

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Category: AKI, Electrolytes, Acid-base Disorders, Tropical Diseases, RPGN and Pregnancy

Topic: Clinical Glomerulonephritis

Transparency declaration and ethics statement:
This study is conducted according to International Council for Harmonization E6 Guidelines for Good Clinical Practice that have their origin in the Declaration of Helsinki.

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