Dual JAK/ROCK Inhibition in Rheumatoid Arthritis: Results of a Phase II Study Of CPL'116

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BACKGROUND

Despite various treatments, the first-line approach for rheumatoid arthritis (RA) has long relied on disease-modifying antirheumatic drugs like methotrexate (MTX), often with glucocorticoids. Still, many patients fail to achieve satisfactory responses. The challenge for the new therapies is to ensure both effectiveness and safety, especially given RA's link to increased cardiovascular risk.[1]

CPL'116 is a new dual kinase inhibitor, with enhanced selectivity toward both JAK and Rho-associated kinases (ROCK). By targeting these two pathways, it offers to modulate immune responses and provide cardioprotective and antifibrotic effects, making CPL'116 a compelling candidate for treating autoimmune diseases like RA.[1]

OBJECTIVES

To determine the safety and efficacy of CPL'116 in patients suffering from RA who have had an inadequate response to MTX.[1]

METHODS

This was a 12-week, Phase II, randomised, double blind, placebo-controlled, parallel group study evaluating the safety and efficacy of CPL'116 in patients with moderate-to-severe RA with inadequate response to MTX. After completing all screening evaluations, eligible patients were randomly assigned (1:1:1:1) to one of the four treatment groups: CPL'116 60 mg, 120 mg, 240 mg, or placebo. All treatments were administered orally twice daily.

RESULTS

Hundred and six patients were randomised to receive either placebo or CPL'116. Most were females (75%), and the mean age of the participants was 54.4 (±10.5) years. Ninety-nine patients completed the treatment period (placebo group: 27/28 [96%]; CPL'116 60 mg group: 24/27 [89%]; CPL'116 120 mg group: 25/25 [100%]; and

CPL'116 240 mg group: 23/26 [89%]). One hundred and seventy adverse events (AE), mild or moderate, were recorded during the study. Treatment-related AEs accounted for 92 cases (54.1%). There were two serious AEs (1.2%), and three participants (2.8%) discontinued the study medication permanently due to AEs. There were no AEs leading to dose reduction or death.

CPL'116 improved patients' condition measured with Disease Activity Score-28 for RA with CRP (DAS28-CRP) in a dose-dependent manner. Decrease from baseline in the DAS28-CRP score at Week 12 compared to placebo (LS MD) was 0.145 (p=0.67), 0.564 (p=0.10), and 0.887 (p=0.01) for doses of 60, 120 and 240 mg, respectively. A statistically significant benefit over placebo was seen as early as Week 4. Notably, the remission rate (DAS28-CRP <2.6) for CPL'116 240 mg exceeded 45% throughout the study.

Tender Joint Count (TJC) and Swollen Joint Count (SJC) significantly decreased during treatment. At Week 12, both measures showed statistically significant improvements for the two highest CPL'116 doses: in the 120 mg group, TJC dropped by 10.76 (p=0.017) and SJC by 7.92 (p=0.032); in the 240 mg group, TJC dropped by 8.88 (p=0.037) and SJC by 7.92 (p=0.029).

Physician's Global Assessment (PhGA) of Arthritis showed a decreasing trend throughout the study for all the CPL'116 doses, reaching significance at the 120 mg dose at Weeks 8 and 12.

With respect to patient-reported outcomes, Patient's Assessment of Arthritis Pain (PAAP) and Patient's Global Assessment of Arthritis (PtGA) showed a consistent decline over the study. Mean PAAP dropped from 61.72 (±17.41) on Day 1 to 33.56 (±23.13) on Day 85, while PtGA decreased from 63.82 (±17.22) to 34.48 (±23.16) over the same period.

Most vital signs and ECG recordings remained stable. Importantly, there were no significant changes in biochemical parameters such as lipid profile, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), red blood cell and platelet count, haematocrit, and haemoglobin, which are characteristic of the JAK inhibitor group.

CONCLUSION

The authors present the first dual JAK/ROCK inhibitor as a possible therapeutic option for patients suffering from RA. CPL'116 demonstrated dose-dependent response and was effective in alleviating RA symptoms, reaching statistical significance at the highest dose. Moreover, the studied drug was well tolerated and presented superior to other JAKi safety profile. Taken together, CPL'116 is a promising treatment for RA and other autoimmune diseases, especially with fibrotic components, like RA-associated interstitial lung disease or idiopathic pulmonary fibrosis.[1]

Reference

1. Wieczorek M et al. Dual JAK/ROCK inhibition in rheumatoid arthritis – results of a phase 2 study of CPL'116. OP0193. EULAR Congress, 11-14 June, 2025.