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# Upadacitinib Versus Placebo or Adalimumab in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double-Blind, Randomized Controlled Trial

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## Abstract

**Objective:** To evaluate the efficacy, including capacity for inhibition of radiographic progression, and safety of upadacitinib, a JAK1-selective inhibitor, as compared to placebo or adalimumab in patients with rheumatoid arthritis (RA) who have experienced an inadequate response to methotrexate (MTX).

**Methods:** In total, 1,629 RA patients with an inadequate response to MTX were randomized (2:2:1) to receive upadacitinib (15 mg once daily), placebo, or adalimumab (40 mg every other week) while continuing to take a stable background dose of MTX. The primary end points were achievement of an American College of Rheumatology 20% (ACR20) improvement response and a Disease Activity Score in 28 joints using C-reactive protein level (DAS28-CRP) of <2.6 in the upadacitinib group compared to the placebo group at week 12; inhibition of radiographic progression was evaluated at week 26. The study was also designed and powered to test for the noninferiority and superiority of upadacitinib compared to adalimumab, as measured both clinically and functionally.

**Results:** At week 12, both primary end points were met in patients receiving upadacitinib compared to those receiving placebo ($P \leq 0.001$). An ACR20 improvement response was achieved by 71% of patients in the upadacitinib group compared to 36% in the placebo group, and a DAS28-CRP score of <2.6 was observed in 29% of patients receiving upadacitinib compared to 6% of patients receiving placebo. Upadacitinib was superior to adalimumab based on the ACR50 response rate, achievement of a DAS28-CRP score of ≤3.2, change in pain severity score, and change in the Health Assessment Questionnaire disability index. At week 26, more patients receiving upadacitinib than those receiving placebo or adalimumab achieved low disease activity or remission ($P \leq 0.001$). Radiographic progression was significantly inhibited in patients receiving upadacitinib and was observed in fewer upadacitinib-treated patients than placebo-treated patients ($P \leq 0.001$). Up to week 26, adverse events (AEs), including serious infections, were comparable between the upadacitinib and adalimumab groups. The proportions of patients with serious AEs and AEs leading to discontinuation were highest in the adalimumab group; the proportions of patients with herpes zoster and those with creatine phosphokinase (CPK) elevations were highest in the upadacitinib group. Three malignancies, 5 major adverse cardiovascular events, and 4 deaths were reported among the groups, but none occurred in patients receiving upadacitinib. Six venous thromboembolic events were reported (1 in the placebo group, 2 in the upadacitinib group, and 3 in the adalimumab group).

**Conclusion:** Upadacitinib was superior to placebo and adalimumab for improving signs, symptoms, and physical function in RA patients who were receiving background MTX. In addition, radiographic progression was significantly inhibited by upadacitinib as compared to placebo. The overall safety profile of upadacitinib was generally similar to that of adalimumab, except for higher rates of herpes zoster and CPK elevations in patients receiving upadacitinib.

**Trial registration:** ClinicalTrials.gov NCT02629159.