Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial

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RobotReviewer report

Risk of bias table

trial	design	n	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
Burmester GR, 2018	RCT	???	+	+	+	+

Characteristics of studies

Burmester GR, 2018

Population	1. Eligible patients were aged at least 18 years with active rheumatoid arthritis for 3 months or more, and fulfilled the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis.
Intervention	1. Procedures Permitted background csDMARDs were oral and parenteral methotrexate (15‚Äì25 mg per week; or ‚â•10 mg per week in patients who could not tolerate methotrexate at ‚â•12@BULLET5 mg per week), sulfasalazine (‚â§3000 mg per day), hydroxychloroquine (‚â§400 mg per day), chloroquine (‚â§250 mg per day), and leflunomide (‚â§20 mg per day); up to two concomitant background csDMARDs were allowed, with the exception of the combination of methotrexate and leflunomide. 2. An extended-release formulation, allowing once-daily dosing with upadacitinib (15 mg and 30 mg, which provide plasma exposures equivalent to immediaterelease 6 mg twice daily and 12 mg twice daily, respectively), was developed for phase 3 studies in rheumatoid arthritis. 3. Patients were assigned to receive once-daily extended-release formulation of upadacitinib at 15 mg or 30 mg, or to receive placebo for 12 weeks.
Outcomes	1. 16 Key secondary endpoints at week 12 were the proportions of patients who achieved 50% or 70% improvement in the ACR criteria (ACR50 or ACR70

responses); DAS28(CRP) less than 2@BULLET6; low disease activity as defined by clinical See Online for appendix Articles disease activity index (CDAI) of 10 or less; changes from baseline in DAS28(CRP), health assessment questionnaire‚Äìdisability index (HAQ-DI), short form-36 (SF-36) physical component summary (PCS), fatigue using the Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-F), and duration of morning stiffness; and the proportion of patients who achieved ACR20 at week 1.

2. Similar to the RA-BUILD trial, treatment with a JAK inhibitor in SELECT-NEXT (upadacitinib) resulted in rapid, significant improvements in clinical outcomes, as well as in multiple patient-reported outcomes (pain, patient's global assessment of disease activity, Health Assessment Questionnaire-Disability Index, and morning stiffness duration and severity).
3. Efficacy, patient-reported outcomes, laboratory assessments , adverse event assessments, local urine pregnancy tests, vital signs, height, and weight were measured at weeks 1, 2, 4, 8, and 12.

Bias	Judgement	Support for judgement
Random sequence generation	low	1. Randomisation and masking We randomly assigned patients (2:2:1:1) using interactive response technology with a randomisation schedule generated by the data sciences department at AbbVie. 2. Patients who were randomly assigned to receive upadacitinib at baseline continued to receive upadacitinib from week 12 onwards, remaining masked to allocation (appendix). 3. We calculated treatment compliance on the basis of the number of tablets taken, divided by the number of days the patient was exposed to study drug.
Allocation concealment	low	1. Patients, investigators, and the funder were masked to allocation. 2. Randomisation and masking We randomly assigned patients (2:2:1:1) using interactive response technology with a randomisation schedule generated by the data sciences department at AbbVie. 3. The placebo and study drug were identical in appearance.
Blinding of participants and personnel	low	1. Patients, investigators, and the funder were masked to allocation. 2. The placebo and study drug were identical in appearance. 3. The study had a 12-week placebo-controlled, double-blind period, followed by an ongoing double-blind extension of up to 5 years.
Blinding of outcome assessment	low	1. The study had a 12-week placebo-controlled, double-blind period, followed by an ongoing double-blind extension of up to 5 years. 2. AbbVie Inc was the study sponsor, contributed to study design, data collection, analysis and interpretation, and to writing, reviewing, and approval of the final version of the manuscript. 3. The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.