Upadacitinib for the treatment of active non-radiographic axial spondyloarthritis (SELECT-AXIS 2): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Upadacitinib, a Janus kinase inhibitor, has been shown to be effective in patients with ankylosing spondylitis. We aimed to assess the efficacy and safety of upadacitinib in non-radiographic axial spondyloarthritis.

Methods The SELECT-AXIS 2 non-radiographic axial spondyloarthritis study was a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial at 113 sites across 23 countries (Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, France, Germany, Hungary, Israel, Japan, Mexico, Poland, Russia, Slovakia, South Korea, Spain, Taiwan, Turkey, Ukraine, and the USA). Eligible adults had active non-radiographic axial spondyloarthritis, with objective signs of inflammation based on MRI or elevated C-reactive protein and an inadequate response to non-steroidal anti-inflammatory drugs. Patients were randomly assigned (1:1) to receive oral upadacitinib 15 mg once daily or placebo using interactive response technology. Random treatment assignment was stratified by MRI inflammation in the sacroiliac joints and screening high-sensitivity C-reactive protein status (MRI-positive and C-reactive protein-positive, MRI-positive and C-reactive protein-negative, and MRI-negative and C-reactive protein-positive) and previous exposure to biologic disease-modifying antirheumatic drugs (yes *vs* no). Treatment assignment was masked from patients, investigators, study site personnel, and the study sponsor. The primary endpoint was the proportion of patients with an Assessment of SpondyloArthritis international Society 40 (ASAS40) response at week 14. Analyses were performed on the full analysis set of patients, who underwent random allocation and received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT04169373.

Findings Between Nov 26, 2019, and May 20, 2021, 314 patients with active non-radiographic axial spondyloarthritis were enrolled into the study, and 313 received study drug (156 in the upadacitinib group and 157 in the placebo group); 295 (94%) patients (145 in the upadacitinib group and 150 in the placebo group) received treatment for the full 14 weeks. A significantly higher ASAS40 response rate was achieved with upadacitinib compared with placebo at week 14 (70 [45%] of 156 patients *vs* 35 [23%] of 157 patients; p<0·0001; treatment difference 22%, 95% CI 12–32). The rate of adverse events up to week 14 was similar in the upadacitinib group (75 [48%] of 156 patients) and placebo group (72 [46%] of 157 patients). Serious adverse events and adverse events leading to discontinuation of study drug occurred in four (3%) of 156 patients in the upadacitinib group and two (1%) of 157 patients in the placebo group. Few patients had serious infections or herpes zoster in either treatment group (each event occurred in two [1%] of 156 patients in the upadacitinib group and one [1%] of 157 patients in the placebo group). Five (3%) of 156 patients in the upadacitinib group had neutropenia; no events of neutropenia occurred in the placebo group. No opportunistic infections, malignancies, major adverse cardiovascular events, venous thromboembolic events, or deaths were reported with upadacitinib treatment.

Interpretation Upadacitinib significantly improved the signs and symptoms of non-radiographic axial spondyloarthritis compared with placebo at week 14. These findings support the potential of upadacitinib as a new therapeutic option in patients with active non-radiographic axial spondyloarthritis.

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Introduction

Axial spondyloarthritis is a chronic inflammatory rheumatic disease of the spine and sacroiliac joints, with an estimated prevalence of up to 1·4%,[1] encompassing non-radiographic axial spondyloarthritis and radiographic axial spondyloarthritis, also known as ankylosing spondylitis.[1,2] Patients with non-radiographic axial spondyloarthritis and ankylosing spondylitis share common epidemiological, genetic, and clinical features, such as inflammatory back pain, functional impairment, and extra-musculoskeletal manifestations, as well as similar disease burden,[3–5] response to therapy,[6–10] and treatment recommendations.[11,12] However, radiographic findings serve as an important differentiating characteristic, as patients with non-radiographic axial spondyloarthritis do not fulfil the criteria for radiographic sacroiliitis.[1] Additionally, patients with

Research in context

Evidence before this study

We searched PubMed for articles published in English between Jan 1, 2012, and April 7, 2022, using the search terms "non-radiographic axial spondyloarthritis" and "Janus kinase inhibitors". Ten articles were retrieved describing the disease, treatment landscape, and the 2019 American College of Rheumatology treatment recommendations. Axial spondyloarthritis is a rheumatic disease that manifests as inflammation of the spine and sacroiliac joints and is classified into two subtypes: radiographic axial spondyloarthritis (also termed ankylosing spondylitis) and non-radiographic axial spondyloarthritis. Only treatments with two different modes of action, tumour necrosis factor inhibitors and interleukin-17 inhibitors, are approved for non-radiographic axial spondyloarthritis. Janus kinase (JAK) inhibitors have been shown to be effective in ankylosing spondylitis but, to our knowledge, no randomised trials have investigated JAK inhibitors in non-radiographic axial spondyloarthritis.

Added value of this study

SELECT-AXIS 2 is the first phase 3 clinical trial to investigate the efficacy and safety of upadacitinib, a JAK inhibitor, for the treatment of non-radiographic axial spondyloarthritis. Upadacitinib met the primary endpoint of Assessment of SpondyloArthritis international Society 40 response and 12 of 14 ranked secondary endpoints at week 14 versus placebo. Patients treated with upadacitinib had significant improvements in disease activity, pain, objective signs of inflammation, and quality of life compared with placebo. Treatment with upadacitinib was well tolerated, and the safety profile of upadacitinib was consistent with what has been observed in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. This trial showed, for the first time to our knowledge, the potential use of upadacitinib as an oral treatment option in patients with non-radiographic axial spondyloarthritis.

Implications of all the available evidence

The results from this phase 3 trial show that upadacitinib could be a safe and effective treatment option for patients with non-radiographic axial spondyloarthritis, who might prefer to use an oral therapy. The findings from this trial complement those observed in SELECT-AXIS 1 in patients with ankylosing spondylitis, showing the potential use of upadacitinib across the full spectrum of patients with axial spondyloarthritis, including those who have not received treatment or have had an inadequate response to biological therapy. The SELECT-AXIS 2 trial of patients with non-radiographic axial spondyloarthritis is ongoing to assess the long-term efficacy and safety of upadacitinib in patients with non-radiographic axial spondyloarthritis.

non-radiographic axial spondyloarthritis are more frequently female, have lower C-reactive protein levels, and are less likely to be HLA-B27-positive compared with patients with ankylosing spondylitis.[1,4] Non-radiographic axial spondyloarthritis is considered an earlier form of axial spondyloarthritis that can progress to ankylosing spondylitis, particularly in patients with certain predictors for radiographic progression, including elevated C-reactive protein levels, active inflammation on MRI of the sacroiliac joints, and positive HLA-B27 status.[1]

Because of the overall disease burden and the progressive nature of axial spondyloarthritis, treatment is recommended to manage signs and symptoms. International treatment recommendations advise using non-steroidal anti-inflammatory drugs (NSAIDs) as a first-line therapy for axial spondyloarthritis.[11,12] In patients who do not respond to NSAIDs, biologic disease-modifying antirheumatic drugs (bDMARDs), such as tumour necrosis factor (TNF) inhibitors or interleukin-17 (IL-17) inhibitors are available to treat axial spondyloarthritis.[3] The Janus kinase (JAK) pathway has been found to play a part in the pathogenesis of axial spondyloarthritis,[13] and JAK inhibitors have emerged as an alternative, oral treatment option in patients with ankylosing spondylitis.[1,14,15] Upadacitinib is engineered for greater inhibitory potency for JAK1 versus other JAK isoforms; similarly, filgotinib is a JAK1 selective inhibitor.[16] Other JAK inhibitor compounds have different selectivity profiles, such as baricitinib, a selective JAK1 and JAK2 inhibitor, and tofacitinib, a potent inhibitor of JAK1 and JAK3 that is less active against JAK2 and tyrosine kinase 2.[16]

Upadacitinib 15 mg once daily has been shown to be safe and effective in improving the signs and symptoms of ankylosing spondylitis for 2 years in a phase 2/3 clinical trial of patients naive to bDMARDs.[17–19] Overall, few treatment options are available for non-radiographic axial spondyloarthritis and, to our knowledge, no clinical trials have evaluated a JAK inhibitor in patients with non-radiographic axial spondyloarthritis. Therefore, we aimed to investigate the efficacy and safety of upadacitinib 15 mg in a population with non-radiographic axial spondyloarthritis, including patients who were naïve to or had an inadequate response to bDMARDs.

Methods

Study design and participants

See Online for appendix

SELECT-AXIS 2 is a phase 3 programme that was conducted under a master protocol with two separate axial spondyloarthritis studies (appendix p 1). The SELECT-AXIS 2 non-radiographic axial spondyloarthritis study is a randomised, double-blind, placebo-controlled, multicentre trial that comprises a 35-day screening period; a 52-week, randomised, double-blind,

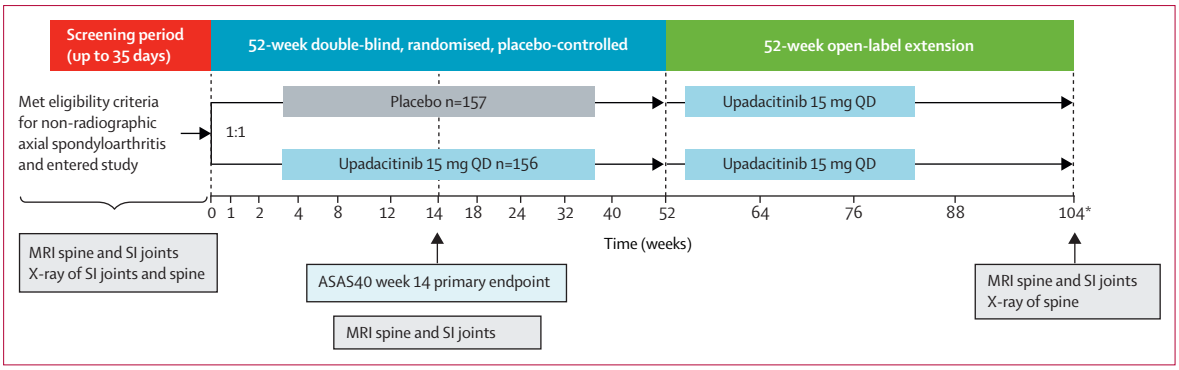

Figure 1: **SELECT-AXIS 2 non-radiographic axial spondyloarthritis study design**
ASAS40=Assessment of SpondyloArthritis international Society 40 response. QD=once daily. SI=sacroiliac. *Patients in remission at week 104 could enter a remission-withdrawal period until flare or week 152.

parallel-group, placebo-controlled period; and a 52-week open-label extension period (figure 1). Here, we report the primary 14-week results of this study.

Patients were enrolled at 113 sites in 23 countries (Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, France, Germany, Hungary, Israel, Japan, Mexico, Poland, Russia, Slovakia, South Korea, Spain, Taiwan, Turkey, Ukraine, and the USA) across North America, South America, Europe, and Asia. The study was approved by an institutional review board or ethics committee at each study site and conducted according to the Declaration of Helsinki, International Council for Harmonisation guidelines, and local laws and regulations.

Eligible patients aged 18 years and older had a clinical diagnosis of non-radiographic axial spondyloarthritis and fulfilled the 2009 Assessment of SpondyloArthritis international Society (ASAS) classification criteria.[20] Patients who met the radiographic criterion of the modified New York criteria for ankylosing spondylitis (based on central evaluation of radiographs of the sacroiliac joints by two readers plus an adjudicator if necessary) were excluded from the study.[20] Additional key inclusion criteria were active disease at both screening and baseline (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] and patient's assessment of total back pain score ≥4 on a 0–10 scale) and at least one objective sign of active inflammation at screening based on MRI of the sacroiliac joints, high-sensitivity C-reactive protein greater than the upper limit of normal (ULN; 2·87 mg/L), or both. MRIs were assessed by two primary readers and an adjudicator in case of disagreement, and a positive MRI for sacroiliitis was defined by the ASAS/Outcome Measures in Rheumatology Clinical Trials definition.[20,21] Patients must have had an inadequate response to at least two NSAIDs or intolerance to or contraindication for NSAIDs. Previous treatment with at most one bDMARD (either TNF inhibitor or IL-17 inhibitor) was allowed for at least 20% but no more than 35% of enrolled patients who had to discontinue the previous bDMARD because of either lack of efficacy (after ≥12 weeks at an adequate dose) or intolerance (regardless of treatment duration). A washout period for bDMARD treatment before the first dose of study drug was required and based on the half-life of the specific agent (appendix p 1). Patients who showed lack of efficacy for both a TNF inhibitor and IL-17 inhibitor were excluded from the study. Stable doses of background medications could be continued, including conventional synthetic DMARDs, oral corticosteroids, and NSAIDs. Exclusion criteria included a history of an inflammatory arthritis cause other than axial spondyloarthritis (including but not limited to rheumatoid arthritis, psoriatic arthritis, mixed connective tissue disease, systemic lupus erythematosus, reactive arthritis, scleroderma, polymyositis, or dermatomyositis) and previous treatment with a JAK inhibitor. All patients gave written informed consent before study entry.

Randomisation and masking

Patients were randomly assigned (1:1) to upadacitinib or matched placebo. Interactive response technology was used to assign patients a unique identification number at the screening visit based on a randomisation schedule generated by the sponsor's (AbbVie; North Chicago, IL, USA) statistics department. Random treatment assignment was stratified by MRI inflammation in the sacroiliac joints and screening high-sensitivity C-reactive protein status (MRI-positive and C-reactive protein-positive, MRI-positive and C-reactive protein-negative, and MRI-negative and C-reactive protein-positive) and previous exposure to bDMARDs (yes *vs* no). Study sites in Japan and China each had a separate randomisation schedule stratified by MRI inflammation and screening high-sensitivity C-reactive protein status, as categorised above. Treatment assignment was masked from patients, investigators, study site personnel, and the study sponsor. Upadacitinib and placebo were administered as tablets identical in appearance to preserve the study masking.

Procedures

Patients were randomly assigned to receive oral upadacitinib 15 mg once daily or matched placebo through 14 weeks. Study visits and data collection were conducted

at weeks 0 (baseline), 1, 2, 4, 8, 12, and 14. The majority of the reported outcomes were assessed at all post-baseline visits (weeks 1, 2, 4, 8, 12, and 14). Changes from baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) MRI spine and sacroiliac joint scores, Bath Ankylosing Spondylitis Metrology Index (BASMI), and tender and swollen joint counts were evaluated only at week 14; change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) was evaluated at all visits except weeks 2 and 12; change from baseline in ASAS Health Index was evaluated at all visits except week 12; and change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) was evaluated at all visits except weeks 1, 2, and 12. Imaging-related efficacy endpoints included the assessment of sacroiliac joint and spine MRI scans at week 14 using the SPARCC score methodology.[22,23] For MRI efficacy assessments, two primary readers masked to treatment assignment and imaging timepoints independently reviewed MRI scans, and a third reader was used to adjudicate discrepancies between the primary readers if the differences in spine and sacroiliac joint SPARCC change scores exceeded a certain mean absolute difference threshold (appendix p 1).[17,24] Intra-reader and inter-reader reliability for MRI sacroiliitis were calculated for the change from baseline based on intra-class correlation coefficients using the MRI scores that contributed to the final SPARCC sacroiliac joint scores.

Outcomes

The primary endpoint was the proportion of patients with an ASAS40 response at week 14 (appendix p 2).[25]

Secondary endpoints with multiplicity adjustment at week 14 were changes from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS)[26] based on C-reactive protein and SPARCC MRI sacroiliac joint inflammation score;[23] the proportions of patients with a 50% improvement in BASDAI and ASDAS inactive disease (appendix p 2); changes from baseline in patient assessment of total back pain and patient assessment of nocturnal back pain; the proportions of patients with low disease activity (appendix p 2)[26] and ASAS partial remission; changes from baseline in the following outcomes: Bath Ankylosing Spondylitis Functional Index (BASFI), ASQoL, and ASAS Health Index; the proportion of patients with a 20% improvement in ASAS; and changes from baseline in linear BASMI and MASES (appendix p 10). Assessment of MASES was performed in the subgroup of patients with pre-existing enthesitis, defined as MASES greater than 0 at baseline. Additional efficacy outcomes without multiplicity adjustment included ASDAS major improvement and clinically important improvement (appendix p 2),[27] changes from baseline in individual ASAS and ASDAS components,[25] and SPARCC MRI spine inflammation score.[22] Other measures of disease activity included tender and swollen joint counts and the six questions of the BASDAI related to fatigue, spinal pain, joint pain or swelling, local tenderness, and morning stiffness. A decrease from baseline in scores for all continuous endpoints indicates improvement.

Treatment-emergent adverse events, defined as adverse events with an onset after the first dose of study drug and up to 30 days after the last dose of study drug, and clinical laboratory testing were assessed up to week 14. Adverse events were classified using the Medical Dictionary for Regulatory Activities version 24.0.

Statistical analysis

Efficacy analyses were conducted in the full analysis set, which comprised all randomly assigned patients who received at least one dose of study treatment. A sample size of 304 patients (with a 1:1 randomisation ratio) was planned to achieve at least 90% power for the ASAS40 response rate of upadacitinib versus placebo (assuming 42% and 17% response rates, respectively; appendix p 1) using a two-sided χ^2 test at a 0·05 significance level. Additionally, the sample size provided at least 80% power for evaluating most multiplicity-controlled secondary endpoints. A per-protocol analysis of the primary endpoint was performed, excluding patients with major protocol deviations. The primary endpoint was also assessed in patients who were bDMARD-naive versus those who had an inadequate response to bDMARDs and who had previous exposure to a TNF inhibitor versus previous exposure to an IL-17 inhibitor. Safety evaluations were based on the safety analysis set, which included all patients who received at least one dose of study treatment. Binary endpoints were analysed using the Cochran-Mantel-Haenszel test stratified by the main stratification factor of positivity for MRI inflammation in the sacroiliac joints and screening high-sensitivity C-reactive protein status (MRI-positive and C-reactive protein-positive, MRI-positive and C-reactive protein-negative, and MRI-negative and C-reactive protein-positive). Non-responder imputation incorporating multiple imputation was used for handling missing data and intercurrent events. Study enrolment occurred during the COVID-19 pandemic; therefore, multiple imputation was used to impute missing data because of COVID-19 or logistical restrictions. Subsequent visits after study drug discontinuation or missing data for other reasons were considered non-responders. For each binary endpoint, the Cochran-Mantel-Haenszel test was performed on 30 datasets generated by non-responder imputation incorporating multiple imputation, and results were synthesised following Rubin's rule. The number of responders was calculated based on the total number of patients and the multiple imputation-aggregated response rates. Continuous endpoints were assessed using a mixed-effect model for repeated measures and observed patient data were included. The mixed-effect model incorporated the fixed effects of treatment, visit, treatment-by-visit interaction, main stratification factor, and the continuous fixed covariate of baseline measurement. An ANCOVA

model was used to evaluate the changes from baseline in MRI SPARCC sacroiliac joint inflammation score at week 14 and included the interaction between the treatment group and the stratification factor. Changes in MRI SPARCC sacroiliac joint and spine inflammation scores were calculated using the two primary readers' average scores or the average of the two closest scores of three readers in adjudicated cases. Primary and secondary endpoints were evaluated using a sequential multiple testing procedure to control the family-wise type I error rate at the two-sided significance level of 0·05 (appendix p 10). Post-hoc subgroup analyses were conducted for the primary endpoint by previous bDMARD exposure (naive *vs* inadequate response), the type of previous bDMARD used (TNF inhibitor *vs* IL-17 inhibitor), and baseline MRI sacroiliitis and screening high-sensitivity C-reactive protein status (MRI-positive and high-sensitivity C-reactive protein-positive *vs* MRI-positive and high-sensitivity C-reactive protein-negative *vs* MRI-negative and high-sensitivity C-reactive protein-positive). Additionally, post-hoc logistic regression adjusting for the stratification factor was conducted, and odds ratios and corresponding 95% CIs were presented for the multiplicity-controlled binary endpoints.

Ongoing safety monitoring was conducted during regular intervals throughout the study by an independent external data monitoring committee. Major adverse cardiovascular events and venous thromboembolic events were adjudicated in a masked fashion by an independent cardiovascular adjudication committee.

All analyses were done using SAS version 9.4. The trial is registered with ClinicalTrials.gov, NCT04169373.

Role of the funding source

The funder of the study was involved in the study design, data collection, data analysis, data interpretation, and writing of the report.

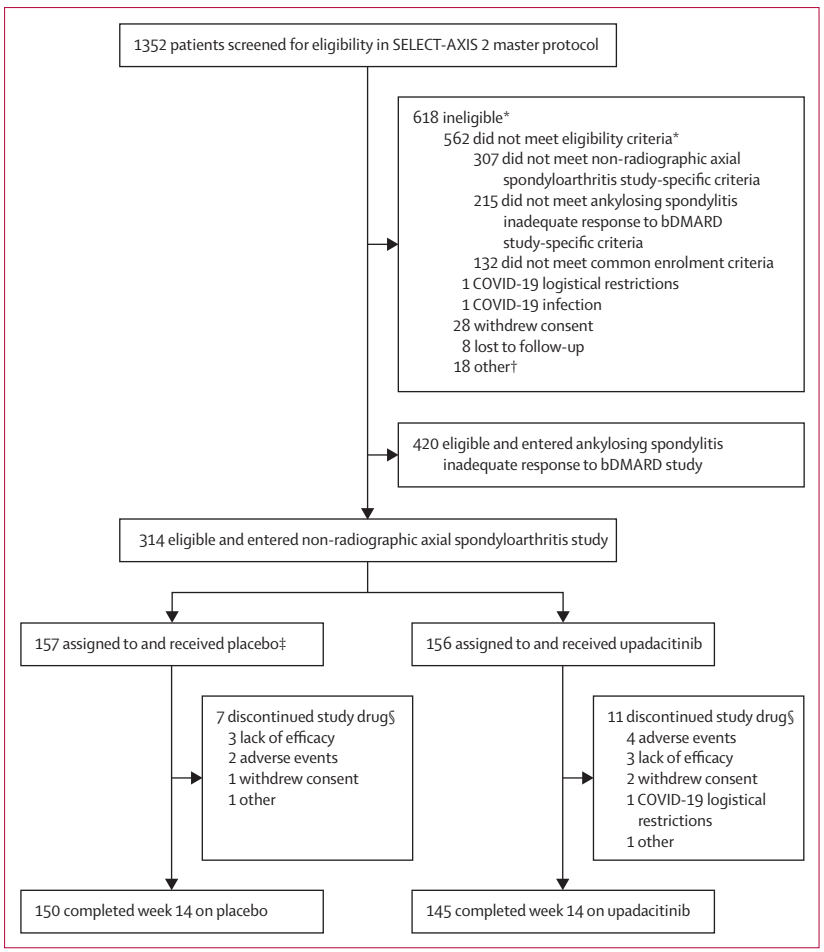

Figure 2: **Trial profile**
bDMARD=biologic disease-modifying antirheumatic drug. *Patients could have been ineligible due to multiple criteria or reasons; ineligibility details due to study eligibility criteria are presented in the appendix (p 3). †Imaging, site, or system issues. ‡One patient in the placebo group decided not to participate after random allocation and discontinued the study before receiving study drug. §Primary reason for discontinuation presented.

Results

Between Nov 26, 2019, and May 20, 2021, 1352 patients were assessed for eligibility to participate in the SELECT-AXIS 2 programme, of whom 618 (46%) were ineligible (figure 2; appendix p 3). 314 patients were enrolled into the non-radiographic axial spondyloarthritis study, 158 (50%) in the placebo group and 156 (50%) in the upadacitinib group. 295 (150 [96%] of 157 patients in the placebo group and 145 [93%] of 156 patients in the upadacitinib group) of 313 patients who received study drug completed 14 weeks of double-blinded treatment. The most frequent primary reasons for premature discontinuation of study drug were adverse events in the upadacitinib group (four [3%] of 156 patients) and lack of efficacy in the placebo group (three [2%] of 157 patients). Details of protocol deviations are shown in the appendix (p 4). Baseline characteristics were similar between the treatment groups and generally consistent with a population with this disease (table 1). Most patients were female (183 [59%] of 313 patients) with a mean age of 42·1 years (SD 12·2), a mean symptom duration of 9·1 years (8·0), and a mean duration since diagnosis of 4·4 years (5·7). Most patients were HLA-B27 positive (183 [59%] of 309 patients) and had elevated high-sensitivity C-reactive protein (249 [80%] of 313 patients with high-sensitivity C-reactive protein greater than the ULN [2·87 mg/L]; 183 [59%] of 313 patients with high-sensitivity C-reactive protein >5 mg/L at screening). 136 (44%) of 313 patients were MRI-positive with active sacroiliitis. Patients had active disease, as indicated by a mean BASDAI of 6·9 (SD 1·3), mean ASDAS (C-reactive protein) of 3·6 (0·7), and mean patient assessment of total back pain score of 7·3 (1·5). Most patients used concomitant therapy with NSAIDs (234 [75%] of 313 patients) followed by conventional synthetic DMARDs (91 [29%] of 313 patients) and oral corticosteroids (35 [11%] of 313 patients) at baseline. 103 (33%) patients had previous bDMARD exposure (84 patients with TNF inhibitor

	Placebo group (n=157)	Upadacitinib group (n=156)
Sex		
Female	94 (60%)	89 (57%)
Male	63 (40%)	67 (43%)
Age, years	42·5 (12·4)	41·6 (12·0)
Body-mass index, kg/m²	27·7 (5·2)	28·2 (6·4)
Race		
White	127 (81%)	134 (86%)
Asian	28 (18%)	19 (12%)
African American	1 (1%)	2 (1%)
American Indian or Alaska Native	0	1 (1%)
Multiple	1 (1%)	0
Region		
North America	19 (12%)	26 (17%)
South or Central America	13 (8%)	12 (8%)
Western Europe	19 (12%)	24 (15%)
Eastern Europe	72 (46%)	68 (44%)
Asia*	27 (17%)	19 (12%)
Other†	7 (5%)	7 (5%)
HLA B27-positive	93 (60%)	90 (59%)
Time since non-radiographic axial spondyloarthritis diagnosis, years	4·4 (5·8)	4·5 (5·5)
Symptom duration, years‡	9·2 (8·1)	9·0 (7·9)
Concomitant therapy		
Non-steroidal anti-inflammatory drugs	113 (72%)	121 (78%)
Oral corticosteroids	17 (11%)	18 (12%)
Conventional synthetic DMARDs	50 (32%)	41 (26%)
Previous biologic DMARD therapy	54 (34%)	49 (31%)
Biologic DMARD washout period, weeks	47·8 (60·8)	65·2 (105·1)
Total back pain (0–10 NRS)§	7·3 (1·4)	7·2 (1·6)
Nocturnal back pain (0–10 NRS)¶	7·0 (1·6)	6·7 (1·9)
Patient global assessment of disease activity (0–10 NRS)	7·3 (1·4)	7·0 (1·6)
Morning stiffness (0–10 NRS)‖	6·7 (1·7)	6·6 (1·8)
Ankylosing Spondylitis Disease Activity Score (C-reactive protein)	3·7 (0·6)	3·6 (0·7)
BASDAI score	6·9 (1·2)	6·8 (1·3)
Bath Ankylosing Spondylitis Functional Index score	6·0 (2·1)	5·9 (2·1)
Bath Ankylosing Spondylitis Metrology Index score**	3·1 (1·3)	3·0 (1·4)
MASES score††	4·7 (3·2)	4·7 (3·1)
Enthesitis (MASES >0)	125 (80%)	125 (80%)
hsCRP at screening, mg/L	10·5 (13·5)	13·6 (24·8)
hsCRP greater than upper limit of normal (2·87 mg/L) at screening	126 (80%)	123 (79%)
hsCRP >5 mg/L at screening	84 (54%)	99 (64%)
SPARCC MRI sacroiliac joint score‡‡	3·5 (7·6)	4·4 (8·7)
SPARCC MRI spine score‡‡	1·4 (3·7)	2·7 (6·9)
MRI-positive at screening§§	66 (42%)	70 (45%)

(Table 1 continues on next page)

exposure only, 16 patients with IL-17 inhibitor exposure only, and three patients who had protocol deviations with both TNF inhibitor and IL-17 inhibitor exposure); among those patients, 76 (74%) and 20 (19%) discontinued previous bDMARD therapy because of lack of efficacy (without intolerance) or intolerance (without lack of efficacy). Patients with an inadequate response to bDMARD therapy were more frequently female, current or former smokers, older, had a higher body-mass index (BMI), had a longer disease duration, and had fewer objective signs of inflammation (lower high-sensitivity C-reactive protein and SPARCC MRI sacroiliac joint and spine scores at screening) than patients who were bDMARD-naive (appendix p 5). At screening, 38 (37%) of 103 patients with an inadequate response to bDMARDs and 98 (47%) of 210 bDMARD-naive patients had active inflammation on MRI of the sacroiliac joints (appendix p 6).

The study met the primary endpoint, with significantly more patients treated with upadacitinib (70 [45%] of 156 patients) than placebo (35 [23%] of 157 patients) with ASAS40 at week 14 (treatment difference of 22%, 95% CI 12–32; p<0·0001; figure 3A; appendix pp 7–8). A higher proportion of patients in the upadacitinib group had ASAS40 compared with the placebo group from week 2 onwards (nominal p=0·043; appendix p 11).

Improvements from baseline were seen across the individual ASAS components with upadacitinib versus placebo from week 1 onwards for patient's global assessment of disease activity (nominal p=0·047) and from week 2 onwards for patient's assessment of total back pain (nominal p=0·0078), BASFI (nominal p=0·0022), and morning stiffness (nominal p=0·0036; appendix pp 12–13). Upadacitinib showed significantly greater improvement in total back pain (p=0·0004) and BASFI (p<0·0001) at week 14 than did placebo. Results for ASAS40 response in the prespecified per-protocol analysis were consistent with the full analysis set (appendix p 14). Subgroup analyses for ASAS40 showed consistently better responses for upadacitinib versus placebo at week 14 across the subgroups of patients who were bDMARD-naive, had an inadequate response to bDMARDs, had an inadequate response to TNF inhibitors, and had an inadequate response to IL-17 inhibitors (appendix p 15) and across the subgroups of patients based on MRI sacroiliitis and screening high-sensitivity C-reactive protein status (appendix p 16).

Upadacitinib showed significantly higher response rates versus placebo at week 14 in additional measures of disease activity, including BASDAI50 (p=0·0001), ASDAS inactive disease (p=0·0063), ASDAS low disease activity (p<0·0001), ASAS partial remission (p=0·0035), and ASAS20 (p<0·0001; appendix pp 17–19; figure 3A). A greater proportion of patients also achieved ASDAS major improvement (nominal p=0·0001) and ASDAS clinically important improvement (nominal p<0·0001) with upadacitinib than with placebo (appendix pp 17–18).

Greater improvements from baseline in ASDAS and its components (appendix pp 17–18, 20–21), and pain outcomes were consistently observed with upadacitinib versus placebo at week 14 (figure 3B, appendix p 22). Complementary to improvements in signs and symptoms based on patient-reported outcomes, greater improvements in objective signs of inflammation as measured by high-sensitivity C-reactive protein (nominal p<0·0001; appendix pp 20–21) and SPARCC MRI sacroiliac joint (p<0·0001; figure 3C) and spine inflammation (nominal p=0·021; figure 3C) scores were reported at week 14 in upadacitinib-treated than in placebo-treated patients. Cumulative probability plots show individual changes in MRI SPARCC scores (appendix p 23).

Patients' quality of life significantly improved with upadacitinib treatment versus placebo at week 14 (p<0·0001; figure 3D). Improvements from baseline in BASMI and MASES (nominal p=0·019) in patients with baseline enthesitis were not statistically significant compared with the placebo group at week 14 (figure 3B; appendix pp 7–8). Greater improvements in additional efficacy endpoints were observed among patients treated with upadacitinib versus placebo (appendix p 9).

A similar proportion of patients in each treatment group had treatment-emergent adverse events (75 [48%] of 156 with upadacitinib; 72 [46%] of 157 with placebo), including those that were COVID-19-related (eight [5%] of 156 with upadacitinib; ten [6%] of 157 with placebo; table 2). Serious treatment-emergent adverse events and adverse events leading to discontinuation of study drug were each reported in four (3%) of 156 upadacitinib-treated patients and two (1%) of 157 placebo-treated patients. Few patients had serious infections (two [1%] of 156 in the upadacitinib group; one [1%] of 157 in the placebo group). In the upadacitinib group, COVID-19 pneumonia occurred in a 55-year-old man who was a former smoker with a medical history of ischaemic heart disease, type 2 diabetes, hypertension, and a BMI of 40 mg/k². The patient was hospitalised and the investigator considered this event as having no reasonable possibility of being related to study drug; it was possible to restart study drug after resolution of the infection. Pyelonephritis occurred in a 62-year-old woman with a medical history of acute cystitis. Urine culture showed *Escherichia coli*, which resolved with antibiotic treatment. Study drug was interrupted, the event resolved, and it was possible to restart study drug; the investigator considered the event as having no reasonable possibility of being related to study drug. Three patients had herpes zoster (two [1%] of 156 in the upadacitinib group; one [1%] of 157 in the placebo group); all events were non-serious, mild, or moderate in severity, and limited to one dermatome. The two cases of herpes zoster in the upadacitinib group resolved without treatment interruption. One non-serious event of basal cell carcinoma in the nasal alar region occurred in a White patient from Australia receiving placebo (one [1%] of 157) who had a history of regular sun exposure, which did not lead to study drug discontinuation. No malignancy was reported with upadacitinib. Additionally no deaths, opportunistic infections, active tuberculosis, adjudicated major adverse cardiovascular events, adjudicated venous thromboembolic events, lymphopenia, renal dysfunction, or adjudicated gastrointestinal perforations were reported.

The proportion of patients with hepatic disorders was similar in the upadacitinib (four [3%] of 156) and placebo (five [3%] of 157) groups; all events were non-serious aminotransferase elevations and did not result in study drug discontinuation. No hepatic events fulfilling Hy's Law were reported. Anaemia (one [1%] of 156) and neutropenia (five [3%] of 156) were reported only with upadacitinib treatment. The one event of anaemia was non-serious, mild, transient, and did not lead to treatment interruption. All neutropenia events (four mild or moderate in severity and one severe) were non-serious and not related to serious infections, opportunistic infections, or herpes zoster. Most neutropenia events (four of five) resolved without study drug interruption. The event of severe neutropenia occurred at baseline before study drug initiation. Uveitis occurred in a patient on upadacitinib (one [1%] of 156) who had a history of uveitis. The patient did not receive specific treatment for uveitis, and study drug was continued; uveitis was ongoing when the patient discontinued the study prematurely because of another

	Placebo group (n=157)	Upadacitinib group (n=156)
(Continued from previous page)		
MRI-negative and hsCRP-positive§§	91 (58%)	86 (55%)
MRI-positive and hsCRP-negative§§	31 (20%)	32 (21%)
MRI-positive and hsCRP-positive§§	35 (22%)	38 (24%)
Ankylosing Spondylitis Quality of Life Score¶	11·9 (4·5)	11·9 (4·4)
ASAS Health Index¶¶	9·5 (3·7)	9·4 (3·6)
History of uveitis	11 (7%)	12 (8%)
History of inflammatory bowel disease	6 (4%)	3 (2%)
History of psoriasis||||	4 (3%)	4 (3%)

Data are n (%) or mean (SD), unless otherwise stated. ASAS=Assessment of SpondyloArthritis international Society. BASDAI=Bath Ankylosing Spondylitis Disease Activity Index. DMARDs=disease-modifying antirheumatic drugs. hsCRP=high-sensitivity C-reactive protein. MASES=Maastricht Ankylosing Spondylitis Enthesitis Score. NRS=numerical rating scale. SPARCC=Spondyloarthritis Research Consortium of Canada. *Patients from China (n=18), Japan (n=11), South Korea (n=9), and Taiwan (n=8). †Patients from Australia (n=12) and Israel (n=2). ‡Assessed in 156 participants in the placebo group and 155 participants in the upadacitinib group. §Back pain was defined on a numerical rating scale (0–10) based on the question, "What is the amount of back pain that you experienced at any time during the last week?" ¶Assessed in 155 participants in the placebo group and 154 participants in the upadacitinib group. ||Morning stiffness was defined as the mean score of questions 5 (severity of morning stiffness) and 6 (duration of morning stiffness) of the BASDAI. **Assessed in 155 participants in the upadacitinib group. ††Assessed in 125 participants in the placebo group and 125 participants in the upadacitinib group with MASES >0 at baseline. ‡‡Sacroiliac joint score assessed in 148 participants in the placebo group and 142 participants in the upadacitinib group; spine score assessed in 147 participants in the placebo group and 139 participants in the upadacitinib group; with available baseline MRI data up to 3 days after the first dose of study drug; MRI scored using the SPARCC 6-discovertebral unit method for the spine. §§MRI-positive defined as active sacroiliitis according to the ASAS/Outcome Measures in Rheumatology Clinical Trials definition;[21] hsCRP-positive defined as C-reactive protein greater than the upper limit of normal (2·87 mg/L). ¶¶Assessed in 155 participants in the placebo group and 153 participants in the upadacitinib group. ||||History of psoriasis obtained based on 12 psoriasis-related preferred terms, including psoriasis.

Table 1: **Baseline patient characteristics**

adverse event (worsening of axial spondyloarthritis). No uveitis occurred in the placebo group. No cases of inflammatory bowel disease were reported.

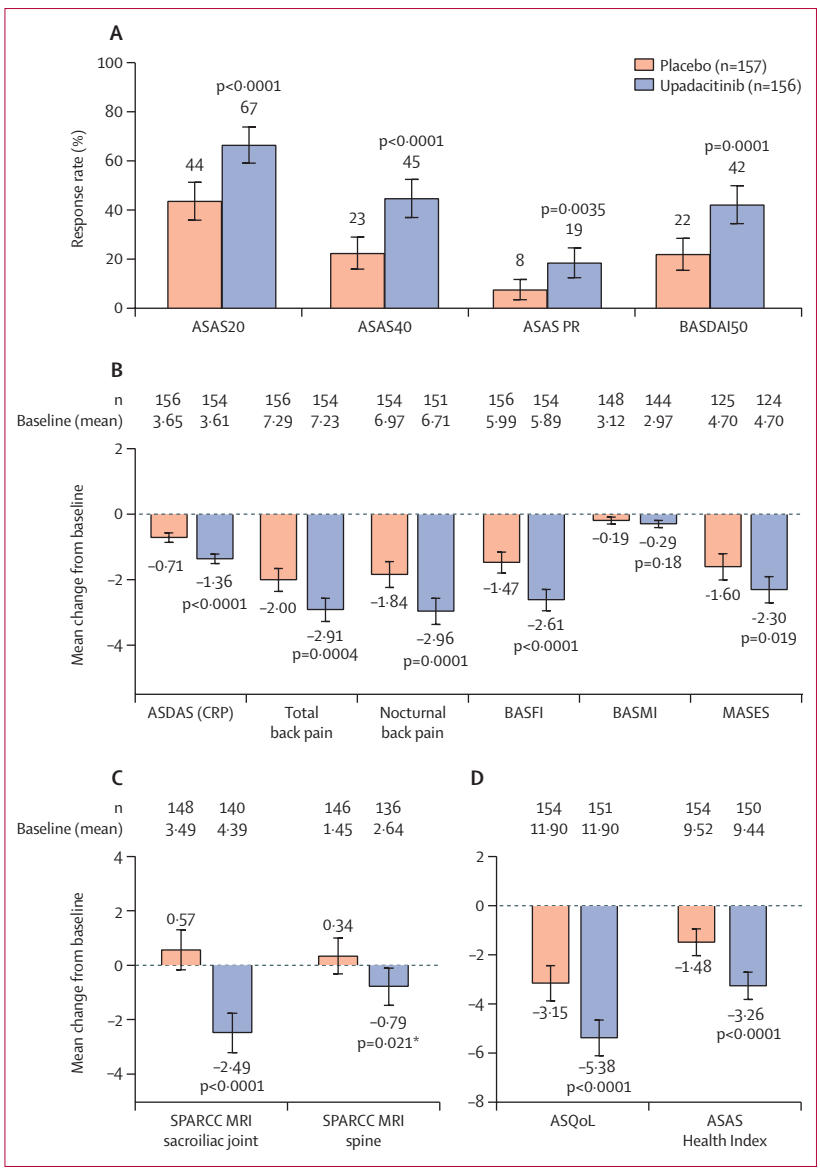

Figure 3: **Analysis of multiplicity-controlled primary and key secondary endpoints at week 14**
(A) Based on non-responder imputation incorporating multiple imputation analysis. (B) Multiplicity-controlled key secondary endpoints; ANCOVA analysis based on observed data for BASMI; MMRM analysis based on observed data for other endpoints; MASES was assessed in patients with baseline enthesitis. (C) Based on ANCOVA analysis; SPARCC MRI was assessed in patients with available baseline data up to 3 days after the first dose of study drug and available week 14 data up to the first dose of study drug in the open-label period. (D) Based on MMRM analysis. All endpoints were multiplicity controlled and sequentially tested (appendix p 10), except for SPARCC MRI spine score. Error bars show 95% CIs. MASES was not tested as part of the multiplicity-controlled test since BASMI did not meet statistical significance; only the nominal p value is presented, nominal p<0·05. ASAS20=Assessment of SpondyloArthritis international Society 20 response. ASAS40=Assessment of SpondyloArthritis international Society 40 response. ASAS PR=Assessment of SpondyloArthritis international Society partial remission. ASDAS (CRP)=Ankylosing Spondylitis Disease Activity Score C-reactive protein. ASQoL=Ankylosing Spondylitis Quality of Life Score. BASDAI50=at least 50% improvement from baseline in Bath Ankylosing Spondylitis Disease Activity Index. BASFI=Bath Ankylosing Spondylitis Functional Index. BASMI=Bath Ankylosing Spondylitis Metrology Index. MASES=Maastricht Ankylosing Spondylitis Enthesitis Score. MMRM=mixed-effect model for repeated measures. SPARCC=Spondyloarthritis Research Consortium of Canada. *Nominal p=0·021

Stable mean haemoglobin concentrations were observed up to week 14 in both treatment groups and, generally, transient changes were seen with other laboratory parameters (appendix pp 24–26). Two (1%) of 154 patients had a grade 3 decrease in lymphocyte or neutrophil counts with upadacitinib treatment; decreases were transient, and the study drug was continued.

Discussion

In this trial, the first, to our knowledge, to investigate a JAK inhibitor for the treatment of patients with active non-radiographic axial spondyloarthritis, upadacitinib met the primary endpoint of ASA40 and most of the ranked secondary endpoints (change from baseline in ASDAS [C-reactive protein], SPARCC MRI sacroiliac joint, total back pain, nocturnal back pain, BASFI, ASQoL, ASAS Health Index; and the percentage of patients achieving BASDAI50, ASDAS inactive disease, ASDAS low disease activity, ASAS partial remission, and ASAS20) at week 14 compared with placebo. Upadacitinib treatment showed clinically relevant and significant improvements in disease activity, pain, objective signs of inflammation, and quality of life compared with placebo. The rapid onset of efficacy, which was observed at week 1 or 2 and maintained up to week 14 for back pain measures, ASAS, and other components, could address an unmet medical need in this condition, which typically affects a younger, active patient population who might prefer oral therapies.[28]

The treatment framework of axial spondyloarthritis has evolved with JAK inhibitors as a new potential oral therapeutic option.[1] Evidence suggests that the JAK-STAT pathway plays a part in mediating different cytokines, including those implicated in the pathogenesis of spondyloarthritis.[13] The results seen in this study complement the treatment effects observed with upadacitinib in ankylosing spondylosis,[17–19] including both in bDMARD-naïve patients and patients with an inadequate response to bDMARDs, showing the efficacy of upadacitinib across the full spectrum of patients with axial spondyloarthritis. The SELECT-AXIS 2 non-radiographic axial spondyloarthritis trial results are in line with those observed in other phase 3 trials of TNF inhibitors and IL-17 inhibitors in patients with non-radiographic axial spondyloarthritis,[7,9,10,24] although the population enrolled here was distinct from previously conducted phase 3 trials of other compounds in patients with non-radiographic axial spondyloarthritis. The HLA-B27 positivity rate in our study was numerically lower than other studies but overall aligned with what has been reported for these populations.[5] Additionally, the proportion of MRI-positive patients in this study was lower than what has been reported in other trials.[7,9,10,29] Notably, the high-sensitivity C-reactive protein threshold for eligibility was 2·87 mg/L in this study, whereas it was higher (>5 mg/L[7,9] or 10 mg/L[10]) in other phase 3 trials. In our study, about 80% of patients had elevated high-sensitivity C-reactive protein values above the ULN

(2·87 mg/L), and 58% had values above 5 mg/L. Importantly, the SELECT-AXIS 2 trial intentionally enrolled about a third of patients who had an inadequate response to bDMARDs, representing a more treatment-refractory patient population than other phase 3 trials, which enrolled few[9,10] to no such patients.[7] Additionally, to our knowledge, this is the first non-radiographic axial spondyloarthritis study to enrol patients with an inadequate response to IL-17 inhibitors. Upadacitinib showed benefit in the subgroups of patients who were bDMARD-naive and who had an inadequate response to bDMARDs, including TNF inhibitors and IL-17 inhibitors. A higher treatment effect was seen in ASAS40 response for bDMARD-naive patients versus patients with an inadequate response to bDMARDs, which is to be expected, since patients with an inadequate response to bDMARDs have previously not responded to advanced therapy with a TNF inhibitor or IL-17 inhibitor. Additionally, the subgroup of patients with an inadequate response to bDMARDs comprised patients who are less likely to be responders (older age, longer disease duration, lower proportion of males, smokers, less objective signs of active inflammation based on high-sensitivity C-reactive protein or MRI, and higher BMI).[1]

Overall, upadacitinib was well tolerated. The rates of treatment-emergent adverse events, including serious and COVID-19-related events, were similar between treatment groups in this study. Serious adverse events for patients in the upadacitinib group included pyelonephritis, foot fracture, knee osteoarthritis, and COVID-19 pneumonia; the foot fracture occurred in the setting of a motorcycle accident, and both pyelonephritis and COVID-19 pneumonia occurred in patients with underlying risk factors. Notably, the study was conducted during the COVID-19 pandemic; however, upadacitinib treatment was not associated with increased COVID-19 infection compared with placebo. The safety data reported here might provide some insight into COVID-19-related adverse events during immunosuppressive treatment with a JAK inhibitor in those with a chronic rheumatic disease. Adverse events leading to study drug discontinuation occurred more often with upadacitinib than with placebo, mostly because of underlying active disease (other adverse events were mild to moderate non-specific events, including headache or abdominal pain). Despite the study's short-term follow-up, imbalances were observed between treatment groups, with a numerically higher proportion of patients with serious infections and herpes zoster in the upadacitinib group than the placebo group. Neutropenia events, occurring only with upadacitinib treatment, were non-serious and unrelated to infections, with most resolving without treatment interruption. Given ongoing discussions about the safety of another JAK inhibitor in patients with rheumatoid arthritis,[30] it is noteworthy that patients in our study did not experience malignancy, adjudicated major adverse cardiovascular events, or adjudicated

	Placebo group (n=157)	Upadacitinib group (n=156)
Any adverse event	72 (46%)	75 (48%)
Serious adverse events	2 (1%)*	4 (3%)†
Discontinuation of study drug due to adverse event	2 (1%)‡	4 (3%)§
COVID-19-related adverse event¶	10 (6%)	8 (5%)
Death	0	0
Infection	36 (23%)	36 (23%)
Serious infection	1 (1%)‖	2 (1%)**
Opportunistic infection	0	0
Active tuberculosis	0	0
Herpes zoster††	1 (1%)	2 (1%)
Malignancy	1 (1%)	0
Malignancy other than non-melanoma skin cancer	0	0
Non-melanoma skin cancer	1 (1%)‡‡	0
Lymphoma	0	0
Hepatic disorder§§	5 (3%)	4 (3%)
Anaemia	0	1 (1%)¶¶
Neutropenia	0	5 (3%)‖‖
Lymphopenia	0	0
Renal dysfunction	0	0
Gastrointestinal perforation (adjudicated)	0	0
Major adverse cardiovascular events (adjudicated)	0	0
Venous thromboembolic events (adjudicated)	0	0
Uveitis	0	1 (1%)***
Inflammatory bowel disease	0	0
Psoriasis†††	0	0

Data are n (%). Potential cardiovascular and arterial and venous thromboembolic events were adjudicated by a masked, independent Cardiovascular Adjudication Committee. Gastrointestinal perforations were blindly adjudicated by sponsor-employed experts. *One patient each with haemorrhagic fever with renal syndrome and pancreatitis. †One patient each with COVID-19 pneumonia, pyelonephritis, foot fracture, and knee osteoarthritis. ‡One patient each with moderate axial spondyloarthritis and mild vomiting. §Two patients with moderate axial spondyloarthritis, one patient with severe rash, moderate headache, and mild tremor, and one patient with mild abdominal pain and nausea. ¶Based on investigator assessment of adverse events associated with COVID-19 and not limited to preferred terms of COVID-19. ‖One patient with haemorrhagic fever with renal syndrome. **One patient each with COVID-19 pneumonia and pyelonephritis. ††All herpes zoster events were non-serious and mild or moderate, and limited to one dermatome; both events in the upadacitinib group resolved without study drug interruption. ‡‡One patient with basal cell carcinoma. §§All events of hepatic disorder were non-serious and mild or moderate aminotransferase elevations; one event led to interruption of study drug; none led to study drug discontinuation. ¶¶Event of anaemia was non-serious, transient, and did not lead to study drug discontinuation. ‖‖All neutropenia events were non-serious: four were mild or moderate in severity, and one was severe; the event of severe neutropenia occurred at baseline and resolved before study drug initiation. ***Event occurred in a patient with a history of uveitis. †††Adverse event of psoriasis was based on 12 psoriasis-related preferred terms, including psoriasis.

Table 2: **Safety outcomes up to week 14**

venous thromboembolic events with upadacitinib treatment for 14 weeks. Additional data will be needed to assess the long-term safety risks of upadacitinib treatment. The rates of adverse events related to extra-musculoskeletal manifestations (uveitis, inflammatory bowel disease, and psoriasis) were low, considering only few patients had a history of extra-musculoskeletal manifestations at baseline. Overall, no new safety risks were identified in this study, and the safety of upadacitinib remained consistent with previously reported data in rheumatoid arthritis,[31] psoriatic arthritis,[32] and ankylosing spondylitis.[17–19,31]

Limitations of this study include the absence of an active comparator, a small sample size of patients who had an inadequate response to IL-17 inhibitors, and the absence of longer-term data. Although upadacitinib has shown a favourable benefit–risk profile for up to 2 years in patients with ankylosing spondylitis,[19] long-term data in patients with non-radiographic axial spondyloarthritis will be generated from the ongoing extension study.

In conclusion, upadacitinib 15 mg provided rapid and significant improvements in the signs and symptoms of non-radiographic axial spondyloarthritis versus placebo after 14 weeks of treatment. The safety profile of upadacitinib was consistent with observations in other inflammatory musculoskeletal diseases, and no new risks were identified. This study shows for the first time, to our knowledge, the potential use of upadacitinib as a treatment option in patients with active non-radiographic axial spondyloarthritis.

Contributors

AD and FVdB contributed to the study design and were investigators in the study. DvdH contributed to the study design. DP, WPM, T-HK, MK, and RB were investigators in the study. YD, YL, ALP, PW, and I-HS accessed and verified the data. YD and YL conducted the statistical analyses. ALP and I-HS conceived the idea of the study concept and contributed to the study design. PW was involved in the execution of the study. All authors had access to the data, analysed and interpreted the data, and had final responsibility for the decision to submit for publication. All authors wrote the Article. All authors critically revised the Article for important intellectual content.

Declaration of interests

AD has received grant or research support from AbbVie, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Lilly, Novartis, Pfizer, and UCB; and honoraria or consultation fees from AbbVie, Amgen, Aurinia, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Lilly, MoonLake, Novartis, Pfizer, and UCB. FVdB has received speaker or consulting fees from AbbVie, Amgen, Galapagos, Janssen, Lilly, Merck, MoonLake, Novartis, Pfizer, and UCB. DP has received consulting fees, speaking fees, or honoraria from AbbVie, Biocad, Bristol Myers Squibb, Galapagos, Gilead, GlaxoSmithKline, Janssen, Lilly, MSD, Medscape, MoonLake, Novartis, Peervoice, Pfizer, Roche, Samsung Bioepis, and UCB; and research support from AbbVie, Lilly, MSD, Novartis, and Pfizer. WPM has received consulting fees from AbbVie, Boehringer Ingelheim, Celgene, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, and UCB; and grant or research support from AbbVie, Novartis, Pfizer, and UCB; and is Chief Medical Officer of CARE Arthritis. DvdH has received consulting fees from AbbVie, Bayer, Bristol Myers Squibb, Cyxone, Eisai, Galapagos, Gilead, GlaxoSmithKline, Janssen, Lilly, Novartis, Pfizer, and UCB; and is the director of Imaging Rheumatology. T-HK has received speaker fees from AbbVie, Celltrion, Kirin, Lilly, and Novartis. MK has received consulting fees or honoraria from AbbVie, Amgen, Asahi-Kasei Pharma, Astellas, Ayumi Pharma, Bristol Myers Squibb, Chugai, Daiichi Sankyo, Eisai, Gilead, Janssen, Lilly, Novartis, Ono Pharma, Pfizer, Tanabe-Mitsubishi, and UCB. RB has received grants or research support from AbbVie, MSD, and Roche; and has received consulting fees or participated in speaker's bureau from AbbVie, Bristol Myers Squibb, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, and Roche. YD, YL, PW, and I-HS are employees of AbbVie and might own stock or options. ALP is a former employee of AbbVie and might own stock or options.

Data sharing

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual, and trial-level data (analysis datasets), as well as other information (eg, protocols, clinical study reports, or analysis plans), if the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, statistical analysis plan, and execution of a data sharing agreement. Data requests can be submitted at any time after approval in the USA and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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References

1 Navarro-Compán V, Sepriano A, El-Zorkany B, van der Heijde D. Axial spondyloarthritis. *Ann Rheum Dis* 2021; **80:** 1511–21.
2 Boel A, Molto A, van der Heijde D, et al. Do patients with axial spondyloarthritis with radiographic sacroiliitis fulfil both the modified New York criteria and the ASAS axial spondyloarthritis criteria? Results from eight cohorts. *Ann Rheum Dis* 2019; **78:** 1545–49.
3 Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet* 2017; **390:** 73–84.
4 Poddubnyy D, Sieper J. Similarities and differences between nonradiographic and radiographic axial spondyloarthritis: a clinical, epidemiological and therapeutic assessment. *Curr Opin Rheumatol* 2014; **26:** 377–83.
5 López-Medina C, Ramiro S, van der Heijde D, Sieper J, Dougados M, Molto A. Characteristics and burden of disease in patients with radiographic and non-radiographic axial spondyloarthritis: a comparison by systematic literature review and meta-analysis. *RMD Open* 2019; **5:** e001108.
6 Song IH, Weiß A, Hermann KG, et al. Similar response rates in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis after 1 year of treatment with etanercept: results from the ESTHER trial. *Ann Rheum Dis* 2013; **72:** 823–25.
7 Deodhar A, van der Heijde D, Gensler LS, et al. Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial. *Lancet* 2020; **395:** 53–64.
8 Dougados M, Wei JC, Landewé R, et al. Efficacy and safety of ixekizumab through 52 weeks in two phase 3, randomised, controlled clinical trials in patients with active radiographic axial spondyloarthritis (COAST-V and COAST-W). *Ann Rheum Dis* 2020; **79:** 176–85.
9 Deodhar A, Blanco R, Dokoupilová E, et al. Improvement of signs and symptoms of nonradiographic axial spondyloarthritis in patients treated with secukinumab: primary results of a randomized, placebo-controlled phase III study. *Arthritis Rheumatol* 2021; **73:** 110–20.
10 Deodhar A, Gensler LS, Kay J, et al. A fifty-two-week, randomized, placebo-controlled trial of certolizumab pegol in nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2019; **71:** 1101–11.

11 van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017; **76:** 978–91.

12 Ward MM, Deodhar A, Gensler LS, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2019; **71:** 1599–613.

13 McInnes IB, Szekanecz Z, McGonagle D, et al. A review of JAK-STAT signalling in the pathogenesis of spondyloarthritis and the role of JAK inhibition. *Rheumatology* 2022; **61:** 1783–94.

14 Deodhar A, Sliwinska-Stanczyk P, Xu H, et al. Tofacitinib for the treatment of ankylosing spondylitis: a phase III, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 2021; **80:** 1004–13.

15 van der Heijde D, Baraliakos X, Gensler LS, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial. *Lancet* 2018; **392:** 2378–87.

16 Tanaka Y, Luo Y, O'Shea JJ, Nakayamada S. Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach. *Nat Rev Rheumatol* 2022; **18:** 133–45.

17 van der Heijde D, Song IH, Pangan AL, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. *Lancet* 2019; **394:** 2108–17.

18 Deodhar A, van der Heijde D, Sieper J, et al. Safety and efficacy of upadacitinib in patients with active ankylosing spondylitis and an inadequate response to nonsteroidal antiinflammatory drug therapy: one-year results of a double-blind, placebo-controlled study and open-label extension. *Arthritis Rheumatol* 2022; **74:** 70–80.

19 van der Heijde D, Deodhar A, Maksymowych W, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis: 2-year results from a randomized, double-blind, placebo-controlled study with open-label extension. *Arthritis Rheumatol* 2021; **73** (suppl 10): 0924 (abstr).

20 Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; **68:** 777–83.

21 Lambert RG, Bakker PA, van der Heijde D, et al. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. *Ann Rheum Dis* 2016; **75:** 1958–63.

22 Maksymowych WP, Inman RD, Salonen D, et al. Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. *Arthritis Rheum* 2005; **53:** 502–09.

23 Maksymowych WP, Inman RD, Salonen D, et al. Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. *Arthritis Rheum* 2005; **53:** 703–09.

24 Sieper J, van der Heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 2013; **72:** 815–22.

25 Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009; **68** (suppl 2): ii1–44.

26 Machado PM, Landewé R, Heijde DV. Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. *Ann Rheum Dis* 2018; **77:** 1539–40.

27 Machado P, Landewé R, Lie E, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis* 2011; **70:** 47–53.

28 Joo W, Almario CV, Ishimori M, et al. Examining treatment decision-making among patients with axial spondyloarthritis: insights from a conjoint analysis survey. *ACR Open Rheumatol* 2020; **2:** 391–400.

29 Landewé R, Sieper J, Mease P, et al. Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. *Lancet* 2018; **392:** 134–44.

30 Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med* 2022; **386:** 316–26.

31 Cohen SB, van Vollenhoven RF, Winthrop KL, et al. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. *Ann Rheum Dis* 2020; **80:** 304–11.

32 Mease PJ, Lertratanakul A, Papp KA, et al. Upadacitinib in patients with psoriatic arthritis and inadequate response to biologics: 56-week data from the randomized controlled phase 3 SELECT-PsA 2 study. *Rheumatol Ther* 2021; **8:** 903–19.