



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

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Summary

Background The JAK pathway is a potential therapeutic target in ankylosing spondylitis. This study assessed the efficacy and safety of upadacitinib, a selective JAK1 inhibitor, in patients with ankylosing spondylitis.

Methods This multicentre, randomised, double-blind, placebo-controlled, two-period, parallel-group, phase 2/3 study, SELECT-AXIS 1, enrolled adults in 62 sites in 20 countries. Eligible patients had active ankylosing spondylitis, fulfilled modified New York criteria, were previously untreated with biological disease-modifying antirheumatic drugs, and had inadequate response to at least two or intolerance or contraindication to non-steroidal anti-inflammatory drugs. Patients were randomly assigned 1:1 using interactive response technology to take oral upadacitinib 15 mg once daily or oral placebo for the 14-week period 1; only period 1 data are reported here. The primary endpoint was the composite outcome measure of the Assessment of SpondyloArthritis international Society 40 response at week 14. Analyses were done in the full analysis set of patients who were randomly assigned and received at least one dose of study drug. This study is registered with ClinicalTrials.gov, NCT03178487.

Findings Between Nov 30, 2017, and Oct 15, 2018, 187 patients were randomly assigned to upadacitinib 15 mg (93 patients) or to placebo (94 patients), and 178 (95%) patients (89 in the upadacitinib group and 89 in the placebo group) completed period 1 on study drug (by the completion date of Jan 21, 2019). Significantly more patients had an Assessment of SpondyloArthritis international Society 40 response in the upadacitinib group versus in the placebo group at week 14 (48 [52%] of 93 patients vs 24 [26%] of 94 patients; $p=0.0003$; treatment difference 26% [95% CI 13–40]). Adverse events were reported in 58 (62%) of 93 patients in the upadacitinib group versus 52 (55%) of 94 in the placebo group. The most common adverse event in the upadacitinib group was increased creatine phosphokinase (eight [9%] of 93 patients in the upadacitinib group vs two [2%] of 94 patients with placebo). No serious infections, herpes zoster, malignancy, venous thromboembolic events, or deaths were reported; one serious adverse event was reported in each group.

Interpretation Upadacitinib 15 mg was efficacious and well tolerated in patients with active ankylosing spondylitis who had an inadequate response or contraindication to non-steroidal anti-inflammatory drugs. These data support the further investigation of upadacitinib for the treatment of axial spondyloarthritis.

Funding AbbVie.

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Introduction

Axial spondyloarthritis is a chronic, progressive rheumatic disease characterised by inflammatory back pain, limited spinal mobility, enthesitis, and peripheral articular and extra-articular manifestations. Axial spondyloarthritis includes both radiographic axial spondyloarthritis in patients with sufficient evidence of radiographic sacroiliitis (also termed ankylosing spondylitis) and non-radiographic axial spondyloarthritis in patients without sufficient evidence of radiographic sacroiliitis.^{1,2} The disease typically manifests in early adulthood, with a prevalence ranging from 0.3% to 1.4%. Because of its debilitating, longstanding nature, irreversible structural damage, and negative effect on patients' quality of life, long-term pharmacological and non-pharmacological

treatments are recommended to manage the disease.³ According to the Assessment of SpondyloArthritis international Society (ASAS) and European League Against Rheumatism recommendations, non-steroidal anti-inflammatory drugs are the first-line treatment for axial spondyloarthritis, followed by biological disease-modifying antirheumatic drugs, such as TNF inhibitors, in patients who do not sufficiently respond to non-steroidal anti-inflammatory drugs.³ Unlike rheumatoid arthritis or psoriatic arthritis, therapy options for axial spondyloarthritis are limited because conventional synthetic disease-modifying antirheumatic drugs or glucocorticoids are not effective for the treatment of axial symptoms.^{2–4} Despite marketing approval of interleukin 17 (IL 17) inhibitors for ankylosing spondylitis, the unmet medical need for

Lancet 2019; 394: 2108–17

Published Online

November 12, 2019

[https://doi.org/10.1016/S0140-6736\(19\)32534-6](https://doi.org/10.1016/S0140-6736(19)32534-6)

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Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 2010, and Aug 16, 2019, using the search terms “ankylosing spondylitis” and “Janus kinase inhibitor” (JAK). Of the 23 articles retrieved, two were phase 2 clinical trials of JAK inhibitors—filgotinib and tofacitinib—in adults with ankylosing spondylitis, and one article reported post-hoc analyses from the tofacitinib study. Overall, both studies showed improved clinical efficacy and reduced active inflammation on MRI with JAK inhibitors versus placebo at week 12, suggesting a role for JAK inhibitors in the treatment of ankylosing spondylitis.

Added value of this study

SELECT-AXIS 1 is the first phase 2/3 JAK inhibitor trial in ankylosing spondylitis, to our knowledge, that has used multiplicity-controlled efficacy outcomes. The study met its primary endpoint of the Assessment of SpondyloArthritis international Society 40 (ASAS40) response at week 14 (52% for the upadacitinib group vs 26% in the placebo group; $p=0.0003$) as well as several multiplicity-controlled secondary endpoints at week 14. Overall, the findings of the study showed rapid and consistently significant results with upadacitinib compared with placebo in multiple endpoints related to disease

activity (ASAS40, 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index, ASAS partial remission, Ankylosing Spondylitis Disease Activity Score), function (Bath Ankylosing Spondylitis Functional Index), and MRI inflammation (Spondyloarthritis Research Consortium of Canada MRI spine score). Upadacitinib was well tolerated over 14 weeks of treatment, and the safety profile was consistent with findings from upadacitinib studies in patients with rheumatoid arthritis and other indications. This trial supports the role of JAK inhibitors as a targeted oral treatment option for axial spondyloarthritis.

Implications of all the available evidence

Based on the available evidence, including the results from our phase 2/3 study, JAK inhibitors appear to be well tolerated and efficacious for the treatment of patients with ankylosing spondylitis who have inadequate response to or intolerance to or contraindication for non-steroidal anti-inflammatory drugs. JAK inhibition might offer a useful oral treatment option for ankylosing spondylitis, which falls within the broader umbrella of axial spondyloarthritis. The SELECT-AXIS-1 study is ongoing to evaluate long-term safety and efficacy of upadacitinib treatment in ankylosing spondylitis.

treatment remains high, especially in patients who have an inadequate response to biological disease-modifying antirheumatic drugs,^{2,4-6} and effective oral treatment options other than non-steroidal anti-inflammatory drugs are scarce. In addition, some current biological disease-modifying antirheumatic drugs might not be appropriate treatment options in patients with axial spondyloarthritis with underlying gut inflammation.^{3,7}

Over the past 10 years, JAK inhibitors have emerged as a new therapeutic class for immune-mediated inflammatory diseases and have received marketing approval by regulatory agencies for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. Upadacitinib, a selective JAK1 inhibitor, is being investigated for several other immune-mediated inflammatory diseases, such as psoriatic arthritis, ulcerative colitis, Crohn's disease, and atopic dermatitis.⁸⁻¹¹ JAK pathways are potential therapeutic targets for axial spondyloarthritis,¹² and the benefits of JAK inhibitors (tofacitinib and filgotinib) in ankylosing spondylitis were shown in two phase 2 studies.^{13,14} Based on these findings, as well as dose-response and exposure-response analyses of the phase 2 and 3 upadacitinib rheumatoid arthritis studies,¹⁵⁻²⁰ which showed that the upadacitinib 15 mg once daily dose provided the optimal benefit to risk profile in treatment of rheumatoid arthritis, the upadacitinib 15 mg once daily dose was chosen to be investigated in ankylosing spondylitis. The objective of the SELECT-AXIS 1 study was to assess the efficacy and safety of upadacitinib 15 mg once daily versus placebo in patients with active ankylosing spondylitis and previously

untreated with biological disease-modifying antirheumatic drugs.

Methods

Study design and participants

SELECT-AXIS 1 is a multicentre, randomised, double-blind, parallel-group, placebo-controlled, phase 2/3, two-period study of upadacitinib (appendix p 3). Patients were enrolled from 62 sites in 20 countries (in North America, eastern and western Europe, Asia, and Oceania; appendix p 2). Eligible patients (≥ 18 years) met the modified New York criteria for ankylosing spondylitis based on central reading of radiographs of the sacroiliac joints, had active disease at baseline defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of 4 or more and patient's assessment of back pain score of 4 or higher (numerical rating scale 0–10) at screening and baseline visits, and had inadequate response to at least two non-steroidal anti-inflammatory drugs or intolerance to or contraindication for non-steroidal anti-inflammatory drugs. Patients receiving concomitant conventional synthetic disease-modifying antirheumatic drugs (ie, methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine, at a stable dose for ≥ 28 days before baseline) or oral glucocorticoids, non-steroidal anti-inflammatory drugs, and analgesics (stable dose for ≥ 14 days before baseline) were eligible. Patients with previous exposure to any JAK inhibitor or any biological therapy with a potential effect on spondyloarthritis were excluded. In addition, patients with

See Online for appendix

extra-articular manifestations (ie, psoriasis, uveitis, or inflammatory bowel disease) who were not clinically stable for at least 30 days before study entry were excluded. Patients with total spinal ankylosis were ineligible. Patient dosing was recorded on a dosing diary, and patients were instructed to return all drug containers (even if empty) to the study site personnel at each clinic visit. The study site personnel documented treatment adherence in the study source documents.

This study was done in accordance with International Council for Harmonisation guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles of the Declaration of Helsinki. All patients provided written informed consent, and the study protocol was approved by an institutional review board or independent ethics committee at each study site.

Randomisation and masking

At the baseline visit, all eligible patients were randomised in a 1:1 ratio using interactive response technology that assigned a unique identification number according to a randomisation schedule generated by the statistics department of the sponsor. Randomisation was stratified by screening concentrations of high-sensitivity C-reactive protein (hsCRP; $\leq$ upper limit of normal [ULN] vs $>$ ULN; ULN 2.87 mg/L) and geographical region (USA and Canada, Japan, rest of the world). All study personnel, including the sponsor, investigator, and study site personnel, and the patient were blinded to the treatment allocation. In order to maintain the blind, upadacitinib and placebo were presented as orally administered tablets that were identical in appearance.

Procedures

Patients either took oral upadacitinib 15 mg once daily or matching placebo for a 14-week period. Study visits occurred at baseline and at weeks 2, 4, 8, 12, and 14. Patients who completed period 1 were eligible to enter period 2, an ongoing 90-week, open-label extension that evaluates the long-term safety and efficacy of upadacitinib 15 mg. Data from period 1 are reported here.

Outcomes

The primary efficacy endpoint was the ASAS40 response at week 14, defined as at least 40% improvement and an absolute improvement of at least two units on a numerical rating scale of 0–10 from baseline in at least three of the following four domains, with no worsening in the remaining domain: Patient global assessment of disease activity, patient assessment of back pain, Bath Ankylosing Spondylitis Functional Index (BASFI), and inflammation defined as the mean of the BASDAI questions on severity and duration of morning stiffness.

The multiplicity-controlled key secondary endpoints (upadacitinib vs placebo at week 14) included change from baseline in Ankylosing Spondylitis Disease Activity

Score (ASDAS) based on CRP (which consists of patient-reported outcomes about back pain [BASDAI item 2], peripheral pain or swelling [BASDAI item 3], duration of morning stiffness [BASDAI item 6], the patient Global Assessment of disease activity, and hsCRP),²¹ change from baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) MRI spine score,²² proportion of patients achieving at least 50% improvement in BASDAI (BASDAI50), change from baseline in ankylosing spondylitis quality of life (ASQoL), proportion of patients achieving ASAS partial remission, and change from baseline in the following outcomes: BASFI, linear Bath Ankylosing Spondylitis Metrology Index (BASMI), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), work productivity and activity impairment (WPAI; on a scale of 0–100), and ASAS Health Index. Additional key secondary endpoints included ASAS20 response at week 14 and change from baseline in SPARCC MRI sacroiliac joint score²³ at week 14.

Additional prespecified efficacy endpoints included ASDAS inactive disease (score <1.3), ASDAS major improvement (decrease from baseline ≥ 2.0 points), and ASDAS clinically important improvement (decrease from baseline ≥ 1.1 points). ASDAS low disease activity, which was defined as less than 2.1 after the protocol and statistical analysis plan were finalised,²¹ was assessed post hoc.

Data for treatment-emergent adverse events and laboratory assessments were collected during the study. Treatment-emergent adverse events were defined as adverse events that began or worsened in severity after the first dose of study medication through 30 days after the last dose.

Statistical analysis

The planned sample size of 170 for this study (with 1:1 randomisation ratio) was determined to provide at least 90% power for detecting a 26% difference in ASAS40 response rate (assuming a placebo ASAS40 response rate of 20%).¹³ Power and sample size calculations were done at a two-sided significance level of 0.05 accounting for a 10% dropout rate.

The full analysis set included all randomly assigned patients who received at least one dose of study drug, and patients were analysed according to their assigned treatment group. Per-protocol analyses were also done, excluding patients with major protocol deviations. The safety analysis set included all patients who received at least one dose of study drug, and patients were analysed according to the actual treatment received. The SPARCC MRI assessment population was prespecified in the statistical analysis plan (baseline included MRI data ≤ 3 days after first dose of study drug, and week 14 included MRI data up to first dose of period 2 study drug; first dose in period 2 was at week 14). A supplemental post-hoc SPARCC MRI analysis was done to include all MRI data collected at nominal visits at baseline and

week 14. Cumulative probability plots were generated to illustrate SPARCC MRI score changes on a patient level.

In the full analysis set, the primary endpoint was compared between the upadacitinib and the placebo group using the Cochran-Mantel-Haenszel test, adjusting for the stratification factor of screening hsCRP concentration. Non-responder imputation was used for handling missing data. Patients who prematurely discontinued use of the study drug were considered as non-responders for all subsequent visits after discontinuation, and any patient with any missing value for binary variables at a specific visit was treated as non-responder for that visit. Similar analyses as for the primary endpoint were done for secondary efficacy binary endpoints. For continuous secondary efficacy endpoints, comparisons between the upadacitinib and the placebo groups were done using mixed-effect model for repeated measures with treatment group, visit, and treatment-by-visit interaction as fixed effects and the corresponding baseline value and the stratification factor of screening hsCRP level as the covariates. All observed longitudinal data were included in the mixed-effect model for repeated measures. To preserve the overall type I error rate at $\alpha=0.05$ level, a step-down approach was used to test the primary and multiplicity-controlled key secondary endpoints. The testing began with the primary endpoint at $\alpha=0.05$ and continued conditional on significance of higher-ranked endpoint. The testing sequence included a group of endpoints tested by the Hochberg procedure, including BASDAI50, ASQoL, ASAS partial remission, BASFI, BASMI, MASES, and WPAI; within the group, the allocated α was adjusted based on the magnitude of p values (appendix p 4).²⁴ p values without any multiplicity adjustment are indicated as nominal p values.

For the MRI analysis, each MRI was independently assessed by two primary readers blinded to the treatment arms and the sequence of the MRIs. Discrepancies between the primary readers were resolved by adjudication by a third reader. The change from baseline at week 14 was calculated using the average scores of two primary readers. For adjudicated cases, the average of the two closest scores of the three readings (two primary readers and adjudicator) was used.

This study is registered with ClinicalTrials.gov, NCT03178487.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 24, 2017, and Sept 10, 2018, 395 patients were assessed for eligibility, and 187 were enrolled into the study (figure 1). Of the 395 patients screened,

208 (53%) did not meet eligibility criteria and were excluded from the study (main reason for screening failure was not meeting the radiographic criterion of the modified New York criteria for ankylosing spondylitis). The remaining 187 patients who met eligibility criteria were randomly assigned to the placebo group (94 participants) or to the upadacitinib group (93 participants) between Nov 30, 2017, and Oct 15, 2018. Overall, 178 (95%) of these patients completed period 1 through week 14 on study drug (89 [95%] of 94 in the placebo group; 89 [96%] of 93 in the upadacitinib group). One patient in the placebo group discontinued study drug but completed period 1 visits (figure 1). The most common primary reasons for study drug discontinuation by week 14 were adverse events in the placebo group (three patients [3%]) and adverse events (two patients [2%]) and withdrawal of consent (two patients [2%]) in the upadacitinib group. Treatment adherence was 96% or higher in both treatment groups.

Mean age was 45.4 years (SD 12.5), mean duration from onset of symptoms was 14.4 years (10.8), and mean duration since diagnosis was 6.9 years (8.9). Most patients were men (132 [71%]), were HLA-B27 positive (143 [76%]), and were receiving concomitant non-steroidal anti-inflammatory drugs at baseline

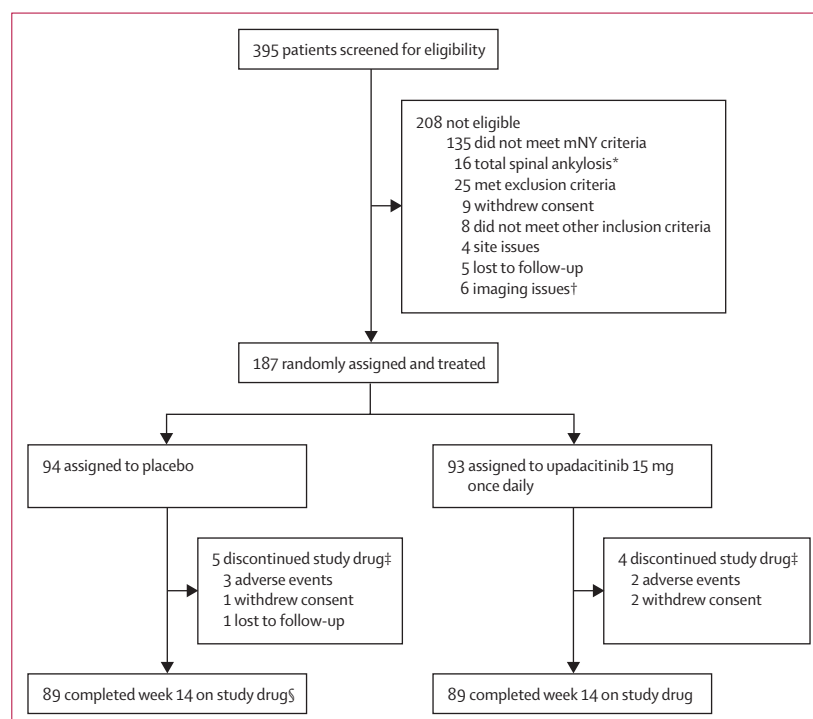


Figure 1: Patient disposition

mNY=modified New York. *Total spinal ankylosis was defined as bridging syndesmophytes (fusion) in a total sum of five or more segments of the C2-T1 or T12-S1 spine (eg, a case with two segments fused in the cervical and three segments fused in the lumbar spine would be considered positive for total spinal ankylosis). †Imaging issues included technical issues at imaging facility, delay in imaging transfer to central reading, and scheduling issues. ‡Primary reason for discontinuation given. §One patient discontinued study drug but completed period 1 visits. A patient could have more than one reason for screening failure.

	Placebo (n=94)	Upadacitinib 15 mg once daily (n=93)
Men	69 (73%)	63 (68%)
Women	25 (27%)	30 (32%)
Age, years	43.7 (12.1)	47.0 (12.8)
Body-mass index, kg/m ²	26.9 (5.1)	26.6 (4.9)
Race		
White	76 (81%)	79 (85%)
Asian	16 (17%)	13 (14%)
African American	2 (2%)	1 (1%)
Region		
USA and Canada	10 (11%)	9 (10%)
Western Europe	33 (35%)	30 (32%)
Eastern Europe	34 (36%)	36 (39%)
Asia*	14 (15%)	12 (13%)
Australia and New Zealand	3 (3%)	6 (6%)
HLA-B27 positive	73 (78%)	70 (75%)
Duration since ankylosing spondylitis diagnosis, years	6.0 (6.8)	7.8 (10.6)
Duration of ankylosing spondylitis symptoms, years	14.0 (9.9)	14.8 (11.6)
Previous NSAID use	94 (100%)	92 (99%)†
Concomitant NSAID use	81 (86%)	71 (76%)
Concomitant csDMARD use	17 (18%)	13 (14%)
Sulfasalazine	14 (15%)	8 (9%)
Mesalazine	1 (1%)	1 (1%)
Methotrexate	2 (2%)	4 (4%)
Hydroxychloroquine	0	1 (1%)
Concomitant glucocorticoid use	12 (13%)	6 (6%)
Back pain‡	6.7 (1.8)	6.8 (1.8)
Patient Global Assessment of disease activity§	6.8 (1.7)	6.6 (1.8)
Inflammation¶	6.7 (1.9)	6.5 (2.0)
ASDAS§	3.7 (0.7)	3.5 (0.8)

(Table 1 continues in next column)

(152 [81%]; table 1). Baseline disease characteristics were generally balanced between the two groups (table 1).

The study met its primary endpoint, with significantly more patients with an ASAS40 response at week 14 in the upadacitinib group versus the placebo group (48 [52%] of 93 patients vs 24 [26%] of 94 patients; $p=0.0003$) with a treatment difference of 26% (95% CI 13 to 40; figure 2A; appendix p 4). A significant difference for upadacitinib versus placebo in ASAS40 (appendix p 5) and the mean change for each of its four individual domains was observed as early as the first post-baseline visit (week 2), and this difference was maintained consistently through week 14 (appendix p 5). Results for per-protocol analyses for the primary endpoint were consistent with the full analysis set (appendix p 6). Accounting for multiplicity adjustment, change from baseline to week 14 in ASDAS, SPARCC MRI spine, and BASFI, and proportion of patients who had BASDAI50 and an ASAS partial remission were significant for

	Placebo (n=94)	Upadacitinib 15 mg once daily (n=93)
(Continued from previous column)		
BASDAI	6.5 (1.6)	6.3 (1.8)
BASFI§	5.5 (2.2)	5.4 (2.4)
BASMI	3.5 (1.5)	3.7 (1.5)
MASES**	3.7 (2.7)	3.9 (2.8)
SPARCC MRI spine score ††	11.9 (14.5)	10.4 (14.4)
SPARCC MRI sacroiliac joint score ‡‡	5.4 (8.6)	7.9 (10.9)
hsCRP, mg/L	11.7 (11.1)	9.6 (12.6)
hsCRP >ULN	68 (72%)	67 (72%)
ASQoL§	10.3 (4.7)	10.0 (5.3)
WPAI overall work impairment§§	53.3 (24.6)	54.3 (28.1)
ASAS Health Index§	8.2 (3.8)	8.6 (4.1)

Data are n (%) and mean (SD) unless noted otherwise. NSAID=non-steroidal anti-inflammatory drug. csDMARD=conventional synthetic disease-modifying antirheumatic drug. ASDAS=Ankylosing Spondylitis Disease Activity Score. BASDAI=Bath Ankylosing Spondylitis Disease Activity Index. BASFI=Bath Ankylosing Spondylitis Functional Index. BASMI=Bath Ankylosing Spondylitis Metrology Index. MASES=Maastricht Ankylosing Spondylitis Enthesitis Score. SPARCC=Spondyloarthritis Research Consortium of Canada. hsCRP=high-sensitivity C-reactive protein. ULN=upper limit of normal. ASQoL=ankylosing spondylitis quality of life score. WPAI=work productivity and activity impairment. ASAS=Assessment of SpondyloArthritis international Society. *13 patients from Japan (seven in placebo; six in upadacitinib; the other 13 patients from Asia were from South Korea. †One patient did not have previous NSAID therapy due to contraindications to NSAID therapy (warfarin use due to history of deep venous thrombosis and pulmonary embolism approximately 10 years before entering the study). ‡92 in the upadacitinib group; back pain defined on a numerical rating scale (0–10) based on the following question, "What is the amount of back pain that you experienced at any time during the last week?" §91 in the upadacitinib group. ¶92 in the upadacitinib group; inflammation defined as mean of items 5 and 6 of the BASDAI. ||92 in the upadacitinib group. **Assessed in 55 in the placebo group; and 54 in the upadacitinib group with MASES >0 at baseline. ††81 in the placebo group; 84 in the upadacitinib group. ‡‡80 in the placebo group; 84 in the upadacitinib group. §§Assessed in 66 in the placebo group and 64 in the upadacitinib group who were employed at baseline.

Table 1: Baseline demographic and disease characteristics

upadacitinib versus placebo (figure 2; appendix p 4). Mean change from baseline to week 14 for upadacitinib versus placebo was -1.45 (95% CI -1.62 to -1.28) versus -0.54 (-0.71 to -0.37 ; treatment difference -0.91 [-1.14 to -0.68 ; $p<0.0001$]) for ASDAS and -2.29 (-2.73 to -1.85) versus -1.30 (-1.74 to -0.86 ; treatment difference -1.00 [-1.60 to -0.39 ; $p=0.0013$]) for BASFI. BASDAI50 was achieved by 42 (45%) of 93 patients treated with upadacitinib versus 22 (23%) of 94 patients in the placebo group (treatment difference 22% [9 to 35; $p=0.0016$]) and ASAS partial remission was achieved by 18 (19%) of 93 patients in the upadacitinib group versus one (1%) of 94 in the placebo group (treatment difference 18% [10 to 27; $p<0.0001$]).

For the other multiplicity-controlled key efficacy endpoints, significance based on multiplicity adjustment was not met per the Hochberg procedure. Consistent improvement was observed in patients receiving upadacitinib versus placebo with nominal p values less than 0.05 for

MASES (appendix p 7), BASMI, ASQoL, and ASAS Health Index at week 14, except for WPAI (figure 2C).

The additional key secondary efficacy endpoints, ASAS20 and SPARCC MRI sacroiliac joint score, also improved with upadacitinib versus placebo based on nominal p values (figure 2A, B). ASAS20 was reached by 60 (65%) of 93 patients treated with upadacitinib versus 38 (40%) of 94 patients in the placebo group at week 14 (treatment difference 24% [10–38]; figure 2A).

For the SPARCC MRI outcomes, change from baseline to week 14 in SPARCC MRI spine was -6.93 (95% CI -8.58 to -5.28) for upadacitinib versus -0.22 (-2.01 to 1.57) for placebo (treatment difference -6.71 [-9.01 to -4.41]) and change from baseline to week 14 in SPARCC MRI sacroiliac joint was -3.91 (-5.05 to -2.77) for upadacitinib versus -0.22 (-1.47 to -1.04) for placebo (treatment difference -3.69 [-5.31 to -2.08]; figure 2B). The supplemental MRI analysis done in all patients with available data confirmed the results of the primary SPARCC MRI analysis for both the spine and sacroiliac joints (appendix p 8). The cumulative probability plots of change in SPARCC scores showed that SPARCC MRI spine and sacroiliac joint scores improved from baseline to week 14 to a greater extent in patients receiving upadacitinib compared with placebo; results for the primary and supplemental MRI analyses were consistent (appendix p 9).

The proportion of patients who had ASDAS low disease activity (46 [49%] of 93 vs ten [11%] of 94, treatment difference of 39% [95% CI 27–51]), ASDAS inactive disease (15 [16%] of 93 vs none [0%] of 94; treatment difference of 16% [9–24]), ASDAS clinically important improvement (49 [53%] of 93 vs 17 [18%] of 94; treatment difference of 35% [22–47]), and ASDAS major improvement (30 [32%] of 93 vs five [5%] of 94; treatment difference of 27% [16–38]) were greater (nominal $p<0.0001$ for all comparisons) for upadacitinib versus placebo at week 14 (figure 3A). Improvement in the mean ASDAS (figure 3B) and the individual ASDAS components (appendix p 10) was seen as early as week 2 with continued improvement up to week 14 with upadacitinib.

No serious infections, herpes zoster, malignancy, venous thromboembolic events, or deaths were reported in period 1. The proportion of patients with adverse events was higher in the upadacitinib group (58 [62%] of 93) than in the placebo group (52 [55%] of 94; table 2). One serious adverse event in each group was reported during period 1. In the placebo group, a serious adverse event was reported as circulation dysregulation in a patient who had a family history of myocardial infarction. The patient was hospitalised due to palpitations, not feeling well, and an elevated blood creatine phosphokinase (CPK). During hospitalisation, no significant findings were obtained (including normal CPK values), and the patient was discharged in good condition. In the upadacitinib group, a serious adverse event of worsening of cervical spondylosis was reported in a patient with a history of spondylosis in the cervical spine who complained about

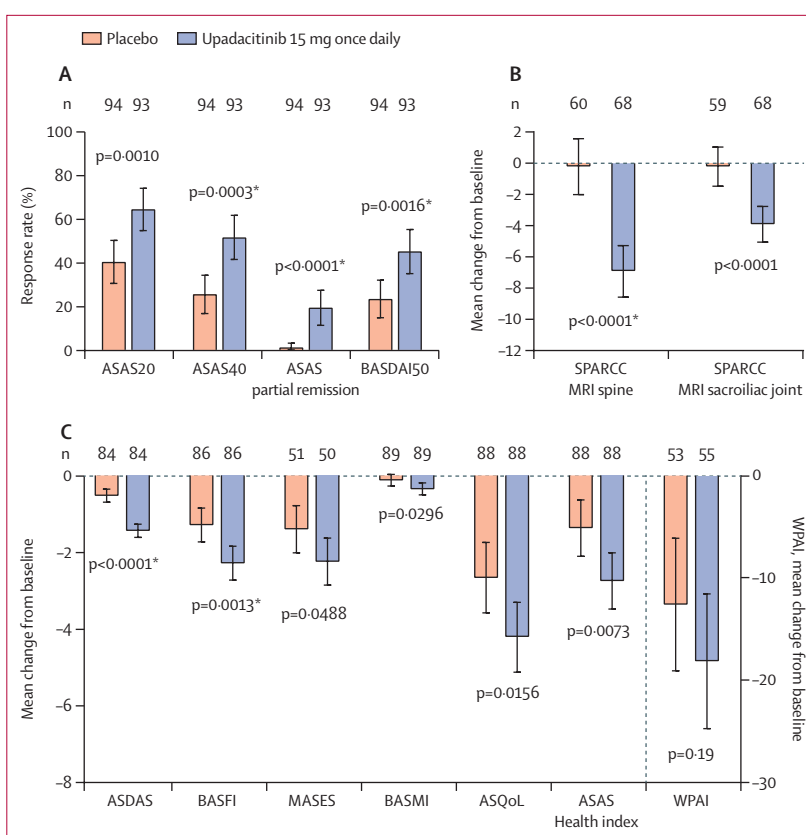


Figure 2: Multiplicity-controlled and key secondary endpoints at week 14

ASAS20, ASAS40, ASAS partial remission, and BASDAI50 responses at week 14 (A), change from baseline in SPARCC MRI spine and sacroiliac joint scores (B), and other multiplicity-controlled key secondary efficacy endpoints at week 14 (C). All endpoints were multiplicity controlled, except for ASAS20 and SPARCC MRI sacroiliac joint. The multiplicity-controlled secondary endpoints were tested in a sequential manner: ASDAS, SPARCC MRI spine, group of endpoints tested by Hochberg procedure (BASDAI50, ASQoL, ASAS partial remission, BASFI, BASMI, MASES, and WPAI), and ASAS Health Index (appendix p 4). (A) NRI analysis. (B, C) Mixed-effect model for repeated measures analysis; decreases from baseline indicate better outcome in all endpoints. (C) MASES assessment includes patients with baseline enthesitis; WPAI assessment includes patients currently employed; SPARCC MRI assessment population as prespecified in the statistical analysis plan (baseline included MRI data ≤ 3 days after first dose of study drug, and week 14 included MRI data up to first dose of period 2 study drug). Error bars show 95% CI. ASAS20=Assessment of SpondyloArthritis international Society 20 response. ASAS40=Assessment of SpondyloArthritis international Society 40 response. ASDAS=Ankylosing Spondylitis Disease Activity Score. 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. NRI=non-responder imputation. SPARCC=Spondyloarthritis Research Consortium of Canada. WPAI=work productivity and activity impairment. *Nominal p values are shown. Significant in multiplicity-controlled analysis.

swallowing problems. CT showed substantial numbers of spondylophytes in the cervical spine and a shift of the trachea and the oesophagus, which required surgical intervention. The proportion of patients with adverse events leading to discontinuation of the study drug (two [2%] of 93 in the upadacitinib group; three [3%] of 94 in the placebo group) and infections (19 [20%] of 93 in the upadacitinib group; 26 [28%] of 94 in the placebo group) was similar for both treatment groups. The most common adverse event in the upadacitinib group was increased CPK (eight [9%] of 93 patients in the upadacitinib group vs two [2%] of 94 patients in the placebo group), with four events (vs one with placebo)

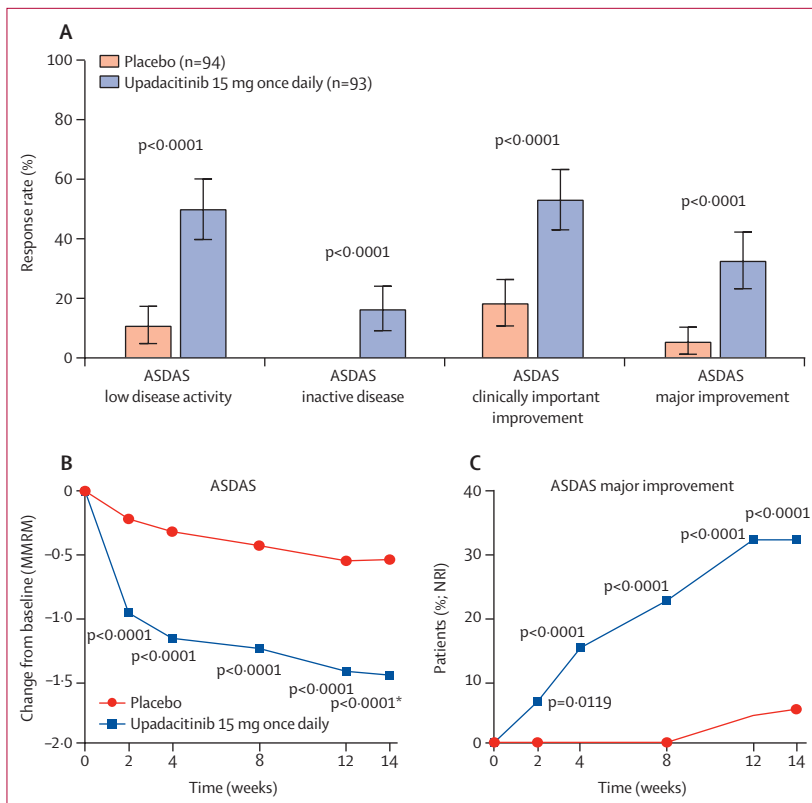


Figure 3: ASDAS responses through week 14

(A) Proportion of patients with ASDAS low disease activity, ASDAS inactive disease, ASDAS clinically important improvement, and ASDAS major improvement at week 14, (B) change from baseline in mean ASDAS over time, and (C) ASDAS major improvement over time. (A, C) NRI analysis. (B) MMRM analysis. Error bars show 95% CI. Nominal p values are shown. ASDAS=Ankylosing Spondylitis Disease Activity Score. MMRM=mixed-effect model for repeated measures. NRI=non-responder imputation. *Significant in multiplicity-controlled analysis.

assessed by the investigator to be possibly related to study drug. All patients were asymptomatic with elevations of less than $4.0 \times \text{ULN}$, except for one patient in the placebo group with muscle pain and an increase to $4.3 \times \text{ULN}$. Most of these events were reversible without study drug interruption (six of eight with upadacitinib, one of two with placebo). Other common adverse events included diarrhoea and nasopharyngitis in both groups, headache in the upadacitinib group and nausea in the placebo group. One patient in the upadacitinib group who already had grade 2 neutropenia (per Common Terminology Criteria for Adverse Events) at baseline experienced a mild adverse event of neutropenia (grade 2).

Seven patients reported adverse events relating to a hepatic disorder (five [5%] of 93 in the upadacitinib group; two [2%] of 94 in the placebo group); none resulted in study drug discontinuation, and all were asymptomatic alanine aminotransferase or aspartate aminotransferase increases, with associated elevations of less than $2.0 \times \text{ULN}$ in six of seven patients and an elevation of less than $3.0 \times \text{ULN}$ in the remaining patient (table 2). Of these seven patients, one patient in the upadacitinib

group was receiving concomitant methotrexate, and the dose of methotrexate was decreased following the adverse event. No differences in mean haemoglobin concentrations were observed throughout the 14-week period in either group (appendix p 11).

Increases from baseline to week 14 in LDL cholesterol (0.318 mmol/L) and HDL cholesterol (0.263 mmol/L) were observed in the upadacitinib group but not in the placebo group (-0.083 and 0.010 mmol/L , respectively); however, no changes in the LDL cholesterol to HDL cholesterol ratio were observed in either group (-0.153 in the upadacitinib group; -0.066 in the placebo group).

Discussion

SELECT-AXIS 1 is the first clinical trial, to our knowledge, of upadacitinib in ankylosing spondylitis and showed consistent efficacy results supported by multiplicity-controlled endpoints. The study met its primary endpoint of ASAS40 response at week 14 (52% in the upadacitinib group vs 26% in the placebo group) as well as several multiplicity-controlled secondary endpoints reflecting significant improvement in disease activity (ASAS partial remission, BASDAI50, ASDAS), function (BASFI), and MRI outcomes (SPARCC MRI spine). The other multiplicity-controlled secondary endpoints did not meet significance in the multiplicity testing but showed consistent improvements for ASQoL, BASMI, MASES, and ASAS Health Index, with upadacitinib versus placebo (nominal $p < 0.05$), with the exception of WPAI.

A rapid onset of response to upadacitinib 15 mg once daily treatment was observed for ASAS40 and ASDAS composite scores and their individual domains of disease activity, including back pain, with responses observed as early as week 2 (first post-baseline visit) and consistently maintained through week 14. The results of upadacitinib on improving the signs and symptoms of ankylosing spondylitis are further supported by a significant reduction of active inflammation on MRI for both the spine and the sacroiliac joints.

In addition, outcomes related to clinically relevant treatment goals of remission or low disease activity,²⁵ such as ASDAS inactive disease or low disease activity, were also achieved, with 50% of patients reaching ASDAS low disease activity (difference vs placebo was 39%). Of note, the placebo response rates for ASAS20 and ASAS40 in this study were similar to rates observed in other clinical studies of ankylosing spondylitis.^{13,14,26,27} In this study, differences in ASAS40 response with upadacitinib versus placebo were $p \leq 0.0002$ (based on nominal p values) as early as week 2 and maintained throughout 14 weeks.

The study results are in line with findings from two phase 2 JAK inhibitor studies in patients with active ankylosing spondylitis.^{13,14} Together with these findings, the SELECT-AXIS 1 results further support that JAK inhibitors could represent an effective treatment option for ankylosing spondylitis. Several

cytokines potentially involved in the pathogenesis of spondyloarthritis signal through the JAK1 and JAK3 or JAK1 and JAK2 combination.^{12,28} At present, only TNF- and IL-17 inhibition have been proven to be effective in axial spondyloarthritis;²⁹ however, these cytokines are not directly blocked by JAK inhibitors including upadacitinib. Nevertheless, emerging data from rheumatoid arthritis studies with upadacitinib suggest that selective inhibition of JAK1 might result in the secondary inhibition of additional pathways that do not depend on JAK1 signalling, such as TNF- α and IL-12.³⁰ Also, other JAK1-associated pathways, including IL-7 and IL-22, have been described in preclinical studies, but further research is needed to evaluate the mechanism of action of JAK inhibitors in axial spondyloarthritis.^{12,31}

The proportion of patients with adverse events was generally similar in the upadacitinib and placebo groups, and no new safety findings were observed compared with previous upadacitinib phase 3 rheumatoid arthritis studies.^{15–17,32} No serious infections, malignancies, herpes zoster, renal dysfunction, adjudicated major adverse cardiovascular events, venous thromboembolic events, or deaths were reported, and haemoglobin concentrations remained consistent throughout the study.

A higher proportion of patients in the upadacitinib group had adverse events of increased CPK, all of which were asymptomatic and most were mild and reversible without study drug interruption. One patient in the placebo group had symptoms (muscle pain) in the setting of elevated CPK and permanently discontinued study drug. In the two previous JAK inhibitor studies in ankylosing spondylitis, elevations in CPK were also observed.^{13,14} Additional data are needed to better understand the safety profile of upadacitinib in axial spondyloarthritis.

JAK inhibitors, such as upadacitinib, could help to address the unmet need in axial spondyloarthritis treatment, given that only approximately half of patients previously untreated with biological disease-modifying antirheumatic drugs reach an ASAS40 response and even fewer achieve remission with TNF or IL-17 inhibitor treatment.^{5,6,26,27,33,34} Furthermore, response rates are even lower in patients with ankylosing spondylitis who have not responded to biological disease-modifying antirheumatic drug therapy.^{2,5,6,33,34} In addition, some patients with axial spondyloarthritis might not be eligible for or might have contraindications to IL-17 and TNF inhibitor therapy, such as allergic reactions and injection site pain, or specific to TNF inhibitors, such as congestive heart failure and concomitant demyelinating disease.³⁵ The use of IL-17 inhibitors is also not recommended for patients with concomitant active inflammatory bowel disease.^{3,7} Because patients with ankylosing spondylitis are typically young and might have active lifestyles, a treatment option administered orally might be particularly important in this patient population.³⁶ Considering these unmet needs, the findings of the

	Placebo (n=94)	Upadacitinib 15 mg once daily (n=93)
Any adverse event	52 (55%)	58 (62%)
Serious adverse event	1 (1%)*	1 (1%)†
Adverse event leading to discontinuation	3 (3%)‡	2 (2%)§
Any infection	26 (28%)	19 (20%)
Infection in at least two patients		
Nasopharyngitis	4	5
Rhinitis	4	0
Upper respiratory tract infection	3	0
Pharyngitis	2	0
Urinary tract infection	2	0
Viral infection	2	0
Tonsillitis	0	2
Serious infection	0	0
Opportunistic infection	0	1 (1%)¶
Herpes zoster	0	0
Tuberculosis	0	0
Malignancy	0	0
Gastrointestinal perforation	0	0
Hepatic disorder**	2 (2%)	5 (5%)
Renal dysfunction	0	0
Anaemia	0	0
Neutropenia	0	1 (1%)
Lymphopenia	0	0
Venous thromboembolic events (adjudicated)	0	0
Cardiovascular events (adjudicated)	0	0
Death	0	0
Adverse events in ≥5% of patients in any treatment group		
Increased creatine phosphokinase††	2 (2%)	8 (9%)
Diarrhoea	5 (5%)	5 (5%)
Nasopharyngitis	4 (4%)	5 (5%)
Headache	2 (2%)	5 (5%)
Nausea	5 (5%)	1 (1%)

Data of n (%). *Cardiovascular disorder, reported as mild circulation dysregulation.

†Spinal osteoarthritis, reported as moderate worsening of cervical spondylosis 4/5.

‡Dyspepsia (n=1), blood creatine phosphokinase increased (n=1), and atlantoaxial

‡Dyspepsia (n=1), blood creatine phosphokinase increased (n=1), and ataxic axial instability (n=1). §Otitis media (n=1) and myalgia (n=1). ¶Oesophageal candidiasis

instability (n=1). *S. Oris media* (n=1) and myalgia (n=1). Oesophageal candidiasis in patient with gastro-oesophageal reflux disease: study drug continued after

in patient with gastro-oesophageal reflux disease; study drug continued after treatment with fluconazole. ||Including non-melanoma skin cancer, malignancy

treatment with fluconazole. ||Including non-melanoma skin cancer, malignancy other than non-melanoma skin cancer, and lymphoma **All seven hepatic

other than non-melanoma skin cancer, and lymphoma. ²²All seven hepatic disorders were based on asymptomatic alanine aminotransferase or aspartate

disorders were based on asymptomatic alanine aminotransferase or aspartate aminotransferase increases, and none led to premature discontinuation of study

aminotransferase increases, and none led to premature discontinuation of study drug. **All asymptomatic except for one patient in the placebo group.

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Table 2: Summary of adverse events through week 14

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other JAK inhibitors in ankylosing spondylitis,^{2,5,6,13,14,26,27} support further investigation of upadacitinib for axial spondyloarthritis.

This study is not without limitations. The focus on patients with ankylosing spondylitis who were previously untreated with biological disease-modifying antirheumatic drugs allowed for a focused evaluation of benefit and risk in a homogeneous population. However, the safety and efficacy of upadacitinib in patients with ankylosing spondylitis who have had an inadequate response to biological disease-modifying antirheumatic drugs or in patients with non-radiographic axial spondyloarthritis has not yet been evaluated, and further studies are needed in these patient populations. Furthermore, only one dose of upadacitinib was evaluated in this study; however, based on exposure-response analyses, higher doses are not expected to result in increased efficacy in ankylosing spondylitis.¹⁷ Lastly, only 14-week, short-term data are reported here, but the long-term efficacy and safety of upadacitinib will be collected in the ongoing SELECT-AXIS 1 extension period for up to 2 years.

In conclusion, oral upadacitinib 15 mg once daily significantly improved disease activity, function, and MRI-detected axial inflammation in patients with active ankylosing spondylitis after 14 weeks of treatment. The incidence of adverse events was similar with upadacitinib and placebo, and no new safety signals were observed compared with previous studies in rheumatoid arthritis. Overall, these results support the further investigation of upadacitinib for the treatment of axial spondyloarthritis.

Contributors

DvdH, AD, FvdB, WPM, JS, I-HS, and ALP conceived the idea of study concept and design. AD, FvdB, WPM, T-HK, MK, ADX, AE acquired the data. All authors analysed and interpreted the data. All authors and Maria Hovenden wrote the Article. All authors critically revised the Article for important intellectual content. YS and XW did the statistical analysis.

Declaration of interests

DvdH has received consulting fees from AbbVie, Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Cyxone, Daiichi, Eisai, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, and UCB Pharma and is the director of Imaging Rheumatology BV. AD has received research grants and consultancy fees from AbbVie, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, and UCB Pharma; consultancy fees from Amgen, Boehringer Ingelheim, Galapagos, and Janssen; and honoraria from Eli Lilly, Novartis, and Janssen. FB has received consulting fees from and is a member of the speaker's bureau of AbbVie, Celgene, Janssen, Eli Lilly, Galapagos, Merck, Novartis, Pfizer, and UCB Pharma. WPM has received grants, honoraria, and consulting fees from AbbVie, Novartis, and Pfizer; consulting and honoraria from UCB Pharma; and consulting fees from Boehringer Ingelheim, Celgene, Eli Lilly, and Galapagos. T-HK has received speaker fees from AbbVie, Eisai, Novartis, Pfizer, and Celltrion. MK has received consulting fees from AbbVie, Eli Lilly, Celgene, Pfizer, Gilead, Janssen, and UCB Pharma; and honoraria and speaker fees from AbbVie, Eisai, Celgene, Pfizer, Novartis, Eli Lilly, Tanabe-Mitsubishi, Ayumi, Janssen, Astellas, and UCB Pharma. AE is a member of advisory boards of Novartis and Eli Lilly. I-HS, ALP, YS, XW, and ADC are full-time employees of AbbVie and own AbbVie stock or stock options.

JS has received consulting and speaker fees from AbbVie, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Eli Lilly, Merck, and Novartis.

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 data sets), as well as other information (eg, protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This 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 and statistical analysis plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time and 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 AbbVie website.

Acknowledgments

AbbVie and the authors thank the patients, study sites, and investigators who participated in this clinical study. Medical writing support was provided by Maria Hovenden, Complete Publication Solutions (North Wales, PA, USA) and was funded by AbbVie.

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