Effect of Upadacitinib on Disease Activity, Pain, Fatigue, Function, Health-Related Quality of Life and Work Productivity for Biologic Refractory Ankylosing Spondylitis

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ABSTRACT

Introduction: Patients with ankylosing spondylitis (AS) have significant unmet treatment needs, despite advancements in biologic therapies. This study evaluated the impact of upadacitinib on clinically meaningful improvement in patient-reported outcomes (PROs) assessing disease activity, pain, fatigue, function, health-related quality of life (HRQoL), and work productivity in patients with AS with inadequate responses or intolerance to biologic disease-modifying antirheumatic drugs (bDMARD-IR).

Methods: Patients enrolled in the phase 3 SELECT-AXIS 2 AS bDMARD-IR study received blinded once-daily oral upadacitinib 15 mg or placebo for 14 weeks. The percentage of patients achieving improvements ≥ minimum clinically important differences (MCID) at week 14 were compared between treatment groups for disease activity (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI), patient global assessment of disease activity (PtGA), total and nocturnal back pain, fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue, FACIT-F), physical function (Bath Ankylosing Spondylitis Functional Index, BASFI), HRQoL (Assessment of SpondyloArthritis international

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Society Health Index [ASAS HI], Ankylosing Spondylitis Quality of Life [ASQoL], Short form-36 [SF-36] physical [PCS] and mental [MCS] component summary scores), and work productivity (Work Productivity and Activity Impairment [WPAI] Questionnaire). Mean changes from baseline through week 14 in fatigue and HRQoL were compared between treatment groups.

Results: A total of 420 patients with active AS who were bDMARD-IR were included. A higher proportion of patients reported MCIDs at week 14 across all PROs with upadacitinib compared with placebo (nominal $p \leq 0.05$). Greater improvements in mean change from baseline through week 14 were reported with upadacitinib compared with placebo across FACIT-F, HRQoL, and WPAI, with improvements differentiated as early as week 1 for ASAS HI, ASQoL and SF-36 PCS and week 4 for SF-36 MCS.

Conclusions: Upadacitinib 15 mg demonstrated rapid and clinically meaningful improvements in disease activity, pain, FACIT-F, function, HRQoL, and WPAI among bDMARD-IR patients with active AS.

Trial Registry: Clinical Registration number: NCT04169373, SELECT-AXIS 2.

Keywords: Ankylosing spondylitis; Axial spondyloarthritis; Patient-reported outcomes; Health-related quality of life; Upadacitinib

Key Summary Points

Why carry out this study?

In addition to reduced spinal mobility, impaired function, and presence of inflammation, patients with ankylosing spondylitis (AS) suffer from chronic back pain, fatigue, and reduced health-related quality of life (HRQoL).

Despite recent advancements in biologic therapies, there remains a significant, unmet need for the treatment of AS, highlighted by the high proportion of patients who do not achieve an adequate response to biologic disease-modifying antirheumatic drugs (bDMARDs).

This study evaluated the effect of upadacitinib versus placebo on response rates and clinically meaningful improvements in patient-reported outcomes (PROs) in patients with AS in SELECT-AXIS 2.

What has been learned from the study?

A higher proportion of patients reported clinically meaningful improvements at week 14 across PROs with upadacitinib 15 mg compared with placebo: BASDAI (73.9 vs. 47.8%), PtGA (82.9 vs. 63.2%), total back pain (80.1 vs. 65.1%), nocturnal back pain (82.9 vs. 65.1%), FACIT-F (57.7 vs. 43.0%), BASFI (74.4 vs. 53.6%), ASAS HI (46.4 vs. 23.0%), ASQoL (60.3 vs. 35.6%), SF-36 PCS (70.9 vs. 54.1%), and WPAI activity impairment (58.5 vs. 31.0%), nominal $p \leq 0.001$.

Improvements in mean change in fatigue, disease-specific and general HRQoL patient-reported measures from baseline were seen as early as week 1 or 2 and continued through week 14 in bDMARD-IR patients with active AS who received upadacitinib 15 mg compared with placebo (ASQoL, ASAS HI and SF-36 PCS and MCS; $p < 0.05$).

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that primarily involves the spine and sacroiliac joints [1]. Patients with axSpA can be differentiated by radiographic findings as having either non-radiographic axial spondyloarthritis (nr-axSpA), or ankylosing spondylitis (AS), also known as radiographic axial spondyloarthritis [2, 3].

Patients with AS experience inflammatory back pain and other symptoms leading to impaired function and reduced spinal mobility, contributing to a high burden of disease as demonstrated by diminished health-related

quality of life (HRQoL) [4]. Furthermore, fatigue and impaired function, experienced by patients with AS have been associated with a detrimental impact on work productivity [4–6]. A high disease burden as demonstrated by poor patient-reported outcome (PROs) scores at the start of treatment may be a predictor of poor treatment response and retention of first tumor necrosis factor (TNF) inhibitor treatment [7].

Treatment goals are to improve patient's HRQoL, function, and social involvement by controlling inflammation and other disease symptoms [8–10]. The American College of Rheumatology (ACR), the Spondylitis Association of America (SAA), the Spondyloarthritis Research and Treatment Network (SPARTAN) recommend non-steroidal, anti-inflammatory drugs (NSAIDs) as first-line treatment for AS, followed by biologic disease-modifying antirheumatic drugs (bDMARDs) such as TNF inhibitors (the first bDMARDs available for AS) [9]. Although the current practice is to start a TNF inhibitor or IL-17 inhibitor, the updated Assessment of SpondyloArthritis International Society (ASAS), and European League Against Rheumatism (EULAR) treatment recommendations have expanded this to also now recommend that a Janus kinase (JAK) inhibitor should be considered in patients with persistently high disease activity despite conventional therapy [8, 10]. Additionally, the updated guidance recommends switching to another biologic DMARD (TNF inhibitor or IL-17 inhibitor) or JAK inhibitor if the first biologic DMARD fails [10].

Despite recent advancements in treatments, there remains an unmet need in the treatment of AS with current therapies [11, 12]. Only 40–50% of patients achieve ASAS 40 response across different biologic studies in AS [13, 14]. In addition, approximately a third of patients do not achieve Ankylosing Spondylitis Disease Activity Score (ASDAS) low disease activity, and 65% do not achieve ASDAS inactive disease after 1 year of bDMARD therapy. In addition, there are a lack of oral agents to treat AS beyond NSAIDs, as all current biologics are injectable or infused.

Inhibition of JAK-mediated pathways may be a promising approach for the treatment of patients with AS [15, 16]. Upadacitinib, an oral and reversible JAK inhibitor, was efficacious and well tolerated in a phase 2/3 study (SELECT-AXIS 1) in patients with active AS who had an inadequate response (IR) or contraindication to NSAIDs compared with placebo. In SELECT-AXIS 2, upadacitinib has shown efficacy in patients with previous exposure to bDMARDs, including TNF inhibitors, and for the first time, also in patients with an IR to IL-17 inhibitors [17]. This analysis of the SELECT-AXIS 2 trial expands on the previously reported efficacy of upadacitinib and evaluates clinically meaningful improvements in patient-reported disease activity, pain, fatigue, function, HRQoL, and work productivity in patients with AS who had an IR to bDMARD therapy (bDMARD-IR) treated with upadacitinib 15 mg versus placebo.

METHODS

Study Design and Participants

Details of the full study design and primary results of the global, multicenter, phase 3 clinical trial, SELECT-AXIS 2 (NCT04169373) have previously been published [17]. Here we report detailed 14-week PRO results in patients with active AS who were bDMARD-IR. Briefly, this was a 14-week randomized, double-blind parallel-group, and placebo-controlled period followed by a 90-week open-label extension period. Patients were randomized 1:1 to receive upadacitinib 15 mg once daily (QD) (N = 211) or placebo QD (N = 209) for 14 weeks.

Eligible patients were ≥ 18 years of age with a clinical diagnosis of AS that fulfilled the modified New York criteria [18], with increased disease activity at study entry based on BASDAI and total back pain scores of 4 or more (numerical rating scale 0–10). Radiographic sacroiliitis (modified New York criteria) during the screening period was checked in central reading by two readers and an adjudicator if there were any discrepancies. Patients were bDMARD-IR, defined as prior exposure to one or two bDMARDs (TNF inhibitor and/or IL-17 inhibitor) with lack of efficacy or intolerance. Prior exposure to a second bDMARD was

permitted for no more than 30% of patients; lack of efficacy to one bDMARD and intolerance to another was permitted, but patients could not have lack of efficacy to two bDMARDs [17].

This study was conducted in compliance with the protocol, International Conference on Harmonisation (ICH) guidelines, local regulations and guidelines governing clinical study conduct, and the ethical principles of the Declaration of Helsinki. As per Good Clinical Practice, the protocol and consent were approved by an ethics committee or institutional review board at all study sites. All patients provided informed consent before study participation.

Outcomes

This analysis assessed multiple PROs from baseline to 14 weeks across the key domains of disease activity, pain, fatigue, function, HRQoL, and work productivity to provide a patient perspective on the benefits of upadacitinib to complement clinical measurements.

Clinically meaningful improvements in PROs were assessed by reporting the proportion of patients with improvements ≥ minimal clinically important difference (MCID) at week 14. MCIDs were defined as ≥ 1.1-point decrease for BASDAI [19], ≥ 1-point decrease for Patient Global Assessment of Disease Activity (PtGA), total and nocturnal back pain, [20] ≥ 4-point increase for Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [21], ≥ 0.6-point decrease for Bath Ankylosing Spondylitis Functional Index (BASFI) [19], and ≥ 3-point decrease for Assessment of SpondyloArthritis international Society Health Index (ASAS HI) [22], and Ankylosing Spondylitis Quality of Life (ASQoL) [23]. Short form-36 (SF-36), consisting of a Physical Component Summary (PCS) and a Mental Component Summary (MCS) score, was used to assess general HRQoL (MCID for PCS and MCS: ≥ 2.5-point increase) [24]. Work Productivity and Activity Impairment Questionnaire (WPAI) included the domains of absenteeism (work missed; MCID not available), presenteeism (impairment at work/reduced work effectiveness; MCID: ≥ 20-point decrease), overall work impairment (productivity loss; MCID: ≥ 15-point decrease), and activity impairment (MCID: ≥ 20-point decrease) [25]. The percentage of patients achieving MCID was not ranked, and was evaluated post hoc with nominal p values reported.

Mean change in PROs from baseline through 14 weeks were also assessed for fatigue (FACIT-F), HRQoL (ASAS HI, ASQoL, SF-36 MCS and PCS), and work productivity (WPAI). Mean change from baseline to 14 weeks for BASDAI, PtGA, total and nocturnal back pain, and BASFI have been published previously [17].

BASDAI, PtGA, total and nocturnal back pain, BASFI, ASAS HI, ASQoL, and SF-36 PCS and MCS were assessed at baseline and from week 1; FACIT-F was assessed at baseline and from week 2; WPAI was assessed at baseline and week 14. The WPAI domains of absenteeism, presenteeism, and overall work impairment were assessed in patients who were employed at baseline, while activity impairment was assessed in all patients.

Statistical Analyses

The full analysis set included all randomized patients who received at least one dose of the study drug and was used for all efficacy and baseline analyses. Patients were included in the analysis based on the treatment group as randomized.

Demographic and baseline characteristics were collected at the baseline visit of the study and summarized for the full analysis set by the treatment group. Categorical variables were summarized by the number and percentage of patients, and continuous variables were summarized with mean and standard deviation (SD).

MCID analyses were summarized at week 14, reporting the number and percentage of patients with improvements in PRO ≥ MCID. p values for the test of the difference between the proportion of patients achieving MCID were made between upadacitinib 15 mg and the placebo group constructed based on the multiple imputation inference. A non-responder imputation was applied incorporating multiple imputations (NRI-MI) to handle missing data

due to COVID-19. Patients who prematurely discontinued the study drug were considered non-responders for all subsequent visits after discontinuation. In addition, any patients with missing values for the PRO assessed at a specific visit were treated as non-responders for that visit to calculate the MCID.

Least squares (LS) mean change from baseline to week 14 was assessed; 95% confidence intervals and nominal p values were based on mixed-effects repeated measures model (MMRM) analysis, including stratification factors of treatment, visit, and treatment-by-visit interaction as fixed factors and baseline value as a covariate. Stratification factor high-sensitivity C-reactive protein (hsCRP) level ($\leq$ upper limit of normal [ULN] vs. > ULN) was also included in the model. All observed patient data are included in the MMRM. For WPAI domains, LS mean change, 95% CI, and nominal p value for each visit were based on analysis of covariance (ANCOVA), including treatment and main stratification factors MRI and screening hsCRP status as fixed factors and baseline value as covariate.

NNT analyses are reported, defined as the number of patients who need to be treated to achieve one additional "responder" on PRO of interest versus placebo. NNTs per MCID response were calculated for upadacitinib versus placebo and compared using the Cochran–Mantel–Haenszel test (CMH). NNTs for each PRO with an MCID were calculated as follows: 1/MCID response rate in the treatment group – MCID response rate in the placebo group.

MCID and NNT analyses were repeated in a post hoc subgroup analysis of patients with prior exposure $\geq$ 1 TNF inhibitor (TNFi-IR) at baseline to identify whether results are consistent compared with the total population (which included IL-17 IR).

RESULTS

Study Population

A total of 420 bDMARD-IR patients with active AS were included in this analysis and each was randomly assigned to either placebo (N = 209) or upadacitinib 15 mg QD (N = 211). Several key demographic and baseline disease characteristics describing the population were previously reported: 74% were male, mean age of 42.4 years (SD 7.5), with a mean disease (symptom) duration of 12.8 years (SD 9.2) [17]. Additional demographics, disease characteristics, and PRO scores at baseline reported here were balanced across study arms. Baseline PRO scores indicate that these patients have a high burden of disease (Table 1).

Outcomes

Clinically Meaningful Improvements in PROs

A higher proportion of patients reported clinically meaningful improvements at week 14 across all PROs with upadacitinib 15 mg compared with placebo: BASDAI (73.9 vs. 47.8%), PtGA (82.9 vs. 63.2%), total back pain (80.1 vs. 65.1%), nocturnal back pain (82.9 vs. 61.3%), FACIT-F (57.7 vs. 43.0%), BASFI (74.4 vs. 53.6%), ASAS HI (46.4 vs. 23.0%), ASQoL (60.3 vs. 35.6%), SF-36 PCS (70.9 vs. 54.1%), and WPAI activity impairment (57.5 vs. 31.0%), nominal $p \leq 0.001$; WPAI presenteeism (34.5 vs. 20.7%), and WPAI overall work impairment (34.8 vs. 23.0%), nominal $p \leq 0.01$; and SF-36 MCS (46.2 vs. 35.7%), nominal $p < 0.05$ (Fig. 1). The NNTs were < 10, ranging from 3.6 to 9.5 across all PROs at week 14 for upadacitinib 15 mg versus placebo (Fig. 1).

Improvements from Baseline in PROs

Improvements from baseline with upadacitinib 15 mg versus placebo were differentiated as early as week 1 for ASAS HI, ASQoL and SF-36 PCS, and week 4 for SF-36 MCS (Fig. 2), and these continued through week 14. Improvements from baseline for FACIT-F were not differentiated between upadacitinib and placebo at early visits (e.g., week 2), but were evident by week 14 (Fig. 2).

Improvement in mean change from baseline to week 14 across WPAI domains of presenteeism, overall work impairment, and activity impairment were greater with upadacitinib 15 mg compared with placebo; however,

Table 1 Baseline disease characteristics and PROs

	Placebo (N = 209)	Upadacitinib 15 mg QD (N = 211)
Male, n (%)	158 (75.6)	153 (72.5)
Age (years)	42.2 (11.8)	42.6 (12.4)
HLA-B27 positive, n (%)	168 (81.2)	180 (85.3)
Time (years) since AS diagnosis	7.5 (7.5)	7.9 (7.5)
Time (years) since AS symptoms	12.6 (9.3)	12.9 (9.1)
Baseline medication use		
NSAID, n (%)	163 (78.0)	163 (77.3)
Oral corticosteroids, n (%)	18 (8.6)	27 (12.8)
csDMARDs, n (%)	62 (29.7)	68 (32.2)
Prior bDMARD use		
One or more TNFi, n (%)	172 (82.3)	173 (82.0)
One or more IL-17i, n (%)	25 (12.0)	30 (14.2)
One TNFi and one IL-17i, n (%)	11 (5.3)	8 (3.8)
Presence of enthesitis (MASES > 0)	162 (77.9)	148 (70.1)
Tender joint count (TJC68)	4.4 (6.1)	4.6 (7.4)
Swollen joint count (SJC66)	1.8 (4.1)	1.5 (3.1)
hsCRP at screening, mg/l	14.5 (17.8)	15.8 (17.7)
hsCRP > ULN[a] at screening, n (%)	163 (78.0)	165 (78.2)
MRI spine SPARCC score	8.8 (12.5)	10.7 (15.4)
MRI-SI joints SPARCC score	5.6 (10.6)	5.0 (10.8)
BASDAI (score 0–10)	6.8 (1.3)	6.8 (1.3)
PtGA (0–10)	7.4 (1.3)	7.5 (1.4)
Total back pain (NRS score 0–10)	7.4 (1.4)	7.5 (1.5)
Nocturnal back pain (NRS score 0–10)	7.2 (1.5)	7.1 (1.8)
FACIT-F (0–52)	28.3 (9.7)	27.5 (9.6)
BASFI (0–10)	6.2 (1.9)	6.3 (2.0)
Total back pain (NRS score 0–10)	7.4 (1.4)	7.5 (1.5)
ASAS HI (0–17)	8.9 (3.7)	9.4 (3.5)
ASQoL (0–18)	11.5 (4.4)	11.6 (4.4)
SF-36 PCS (0–100)	34.6 (7.5)	34.0 (6.7)
SF-36 MCS (0–100)	45.8 (10.9)	44.8 (11.1)
WPAI—absenteeism (0–100)[b]	13.2 (26.4)	11.1 (21.3)
WPAI—presenteeism (0–100)[b]	52.9 (20.91)	55.4 (23.7)

Table 1 continued

	Placebo (N = 209)	Upadacitinib 15 mg QD (N = 211)
WPAI—overall work impairment $(0–100)^b$	57.9 (24.0)	59.2 (25.3)
WPAI—activity impairment $(0–100)^b$	60.2 (20.7)	62.0 (21.9)

Results are reported as mean (SD) unless otherwise specified

AS ankylosing spondylitis, *ASAS* HI Assessment of SpondyloArthritis international Society Health Index, *ASQoL* Ankylosing Spondylitis Quality of Life, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue, *HLA* human leukocyte antigen, *hsCRP* high-sensitivity C-reactive protein, *IL-17i* interleukin-17 inhibitor, *MASES* Maastricht Ankylosing Spondylitis Enthesitis Score, *MCS* mental component summary, *MRI* magnetic resonance imaging, *NSAIDs* non-steroidal anti-inflammatory drugs, *PCS* physical component summary, *PROs* patient-reported outcomes, *PtGA* Patient Global Assessment of Disease Activity, *QD* once daily, *SD* standard deviation, *SF-36* 36-Item Short Form Health Survey, *SI* sacroiliac, *SJC* swollen joint count, *SPARCC* Spondyloarthritis Research Consortium of Canada, *TJC* tender joint count, *TNFi* tumor necrosis factor inhibitor, *ULN* upper limit of normal, *WPAI* Work Productivity and Activity Impairment

[a]ULN = 2.87 mg/l

[b]Includes patients currently employed; PBO n = 137 (65.7%), UPA n = 132 (63.8%)

improvement in absenteeism was similar between the treatment groups (Fig. 3).

TNFi-IR Subgroup

The TNFi-IR post hoc subgroup analysis included 364 patients who had prior exposure to one or more TNFi (N = 183 for placebo and N = 181 for upadacitinib). Consistent with the full analysis set that included IL-17 inhibitor exposed patients, prior exposure to ≥ 1 TNF inhibitor at baseline also saw a notably higher proportion of patients achieving clinically meaningful improvements in PROs with upadacitinib 15 mg treatment at week 14 compared with placebo (Figure S1). NNTs at week 14 ranged from 3.8 to 9.8 with upadacitinib 15 mg compared with placebo.

DISCUSSION

This study demonstrates that a higher proportion of bDMARD-IR patients with active AS achieved clinically meaningful improvements at week 14 in patient-reported disease activity, pain, fatigue, function, HRQoL, and work productivity with upadacitinib 15 mg compared with placebo. Rapid improvements from the patients' perspective were observed, with

improvements from baseline in PROs evaluating HRQoL seen as early as week 1 (ASQoL, ASAS HI, and SF-36-PCS) and week 2 (SF-36-MCS) with upadacitinib treatment, that were sustained through week 14. Improvement in fatigue (FACIT-F) was observed by week 14, indicating that improvement in fatigue may take longer to emerge, consistent with other studies [26]. Additionally, NNTs were below the clinically meaningful threshold of 10 for all PROs at week 14, further substantiating the efficacy of upadacitinib [27]. This study supports the increasing body of evidence demonstrating that JAK inhibitors are an effective oral therapy for the treatment of active AS, including for patients with an IR to bDMARDs [14].

These findings are in line with the SELECT-AXIS 1 study, which previously demonstrated significant improvement in a bDMARD-naïve AS population in key ranked secondary endpoints of function and consistent improvements in HRQoL (ASAS HI and ASQoL), with upadacitinib versus placebo [28]. The current study in bDMARD-IR patients provides further evidence supporting upadacitinib as a promising treatment option for this treatment-refractory population, particularly given the large number of patients with AS who do not achieve
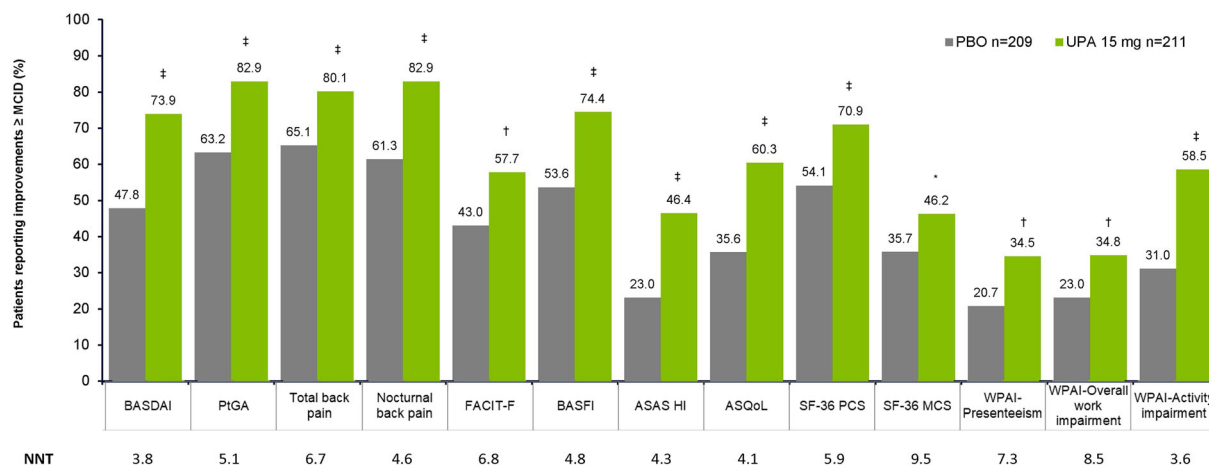
Fig. 1 Proportion of patients reporting improvements ≥ MCID and NNTs in PROs at week 14 (NRI-MI). *$p < 0.05$, †$p \leq 0.01$, and ‡$p \leq 0.001$ versus placebo. p values nominal. NRI-MI is non-responder imputation (NRI) incorporating multiple imputation (MI) to handle missing data due to COVID-19. MCID definitions: BASDAI, ≥ 1.1-point decrease; PtGA, total back pain and nocturnal back pain, ≥ 1-point decrease; FACIT-F, ≥ 4-point increase; BASFI, ≥ 0.6-point increase; ASAS HI and ASQoL, ≥ 3 points decrease; SF-36 PCS and MCS, ≥ 2.5-point increase; WPAI presenteeism and activity impairment, ≥ 20-point decrease; WPAI overall work impairment, ≥ 15-point decrease; WPAI absenteeism, MCID not available. *ASAS* HI Assessment of SpondyloArthritis international Society Health Index, *ASQoL* Ankylosing Spondylitis Quality of Life, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue, *MCID* minimal clinically important difference, *MCS* mental component summary, *NNT* number needed to treat, *NRI* non-responder imputation, *PBO* placebo, *PCS* physical component summary, *PROs* patient-reported outcomes, *PtGA* Patient Global Assessment of Disease Activity, *SF-36* 36-Item Short Form Health Survey, *UPA* upadacitinib, *WPAI* Work Productivity and Activity Impairment

desired treatment goals on current biologic therapies [13, 29].

Furthermore, real-world evidence suggests that over two-thirds of patients with AS who were treated with TNF inhibitors either discontinued or switched to a second TNF inhibitor within 2 years, highlighting the unmet need in this population [29, 30]. In a post hoc analysis, the subgroup of TNFi-IR patients showed consistent results with the full analysis set, indicating consistent improvements in PROs for patients with past use of TNF inhibitors.

There is a high burden of disease for patients with AS, with wide-ranging negative impacts across physical function and wellbeing, detrimental impact on HRQoL, loss of work productivity, and limits to daily activities [31]. Normalizing the patient's function, HRQoL, and ability to perform daily activities is an important treatment goal, highlighting the importance of improvements across a range of PROs from disease activity and function (such as BASDAI, PtGA, and BASFI), to fatigue (FACIT-F), general HRQoL (e.g. ASAS HI), and work productivity (WPAI) in the current study. Improvements observed with PROs have been linked with clinical disease activity in patients with AS, which is critical given this high burden.

Improvements in work productivity are also encouraging as this is aligned with the recommendations from ASAS-EULAR stating that work productivity loss should be taken into account in treatment decisions, as it is associated with indirect costs of economic burden in AS [8]. It has been reported that almost one in six (14.4%) patients with axSpA on biologic therapy experienced axSpA-related job loss and poor work outcomes, such as presenteeism,
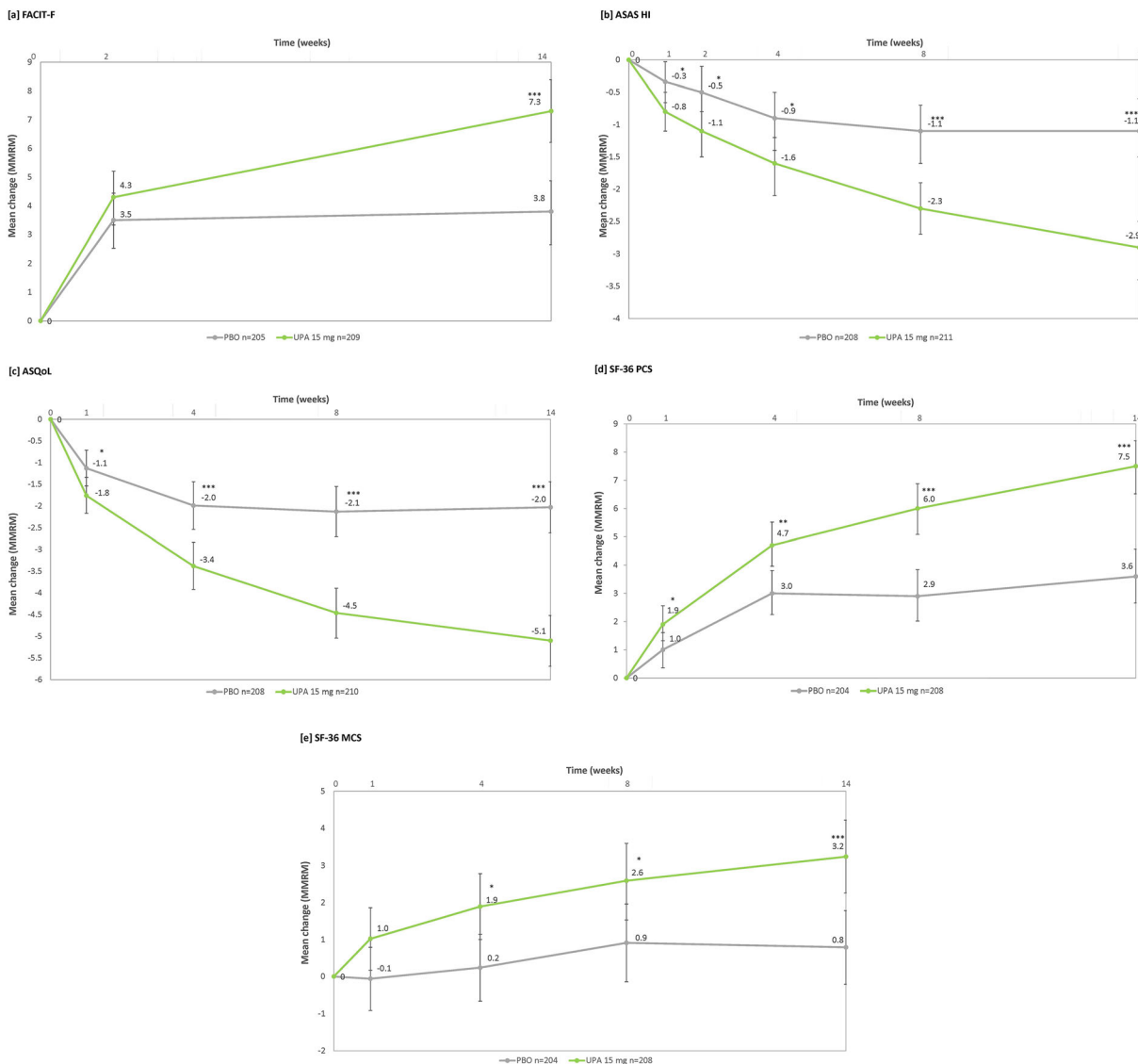
Fig. 2 Change from baseline through week 14 in **a** FACIT-F, **b** ASAS HI, **c** ASQoL, **d** SF-36 PCS, **e** SF-36 MCS (MMRM). MMRM analysis included treatment, visit and treatment-by-visit interaction as fixed factors and baseline value as covariate. Stratification factor hsCRP level (≤ ULN vs. > ULN) were also included in the model. *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$. p values nominal except for ASAS HI and ASQoL at week 14, which were ranked endpoints in the multiplicity-controlled analysis.

ASAS HI Assessment of SpondyloArthritis international Society Health Index, *ASQoL* Ankylosing Spondylitis Quality of Life, *CI* confidence interval, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue, *hsCRP* high-sensitivity C-reactive protein, *MCS* mental component summary, *MMRM* mixed effect model for repeated measures, *PBO* placebo, *PCS* physical component summary, *SF-36* 36-Item Short Form Health Survey, *ULN* upper limit of normal, *UPA* upadacitinib

were associated with poorer scores for PROs [32].

Limitations of the study include the fact that the results may not be generalizable further

than the trial population given that patients enrolled in clinical trials meet strict eligibility criteria and may differ from patients with AS in the general population. The limited sample size
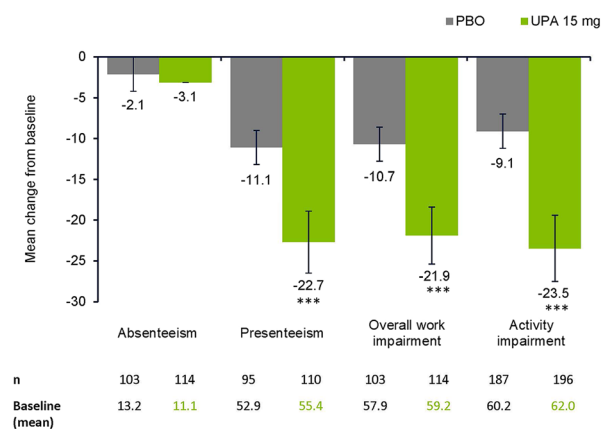
Fig. 3 Mean change (95% CI) from baseline in PRO scores at week 14 in WPAI. WPAI: change from baseline at week 14 and nominal *p* value are based on ANCOVA model including treatment and main stratification factors MRI and screening hsCRP status (MRI+/hsCRP > ULN, MRI+/hsCRP ≤ ULN, and MRI−/hsCRP > ULN) as fixed factors and baseline value as covariate. ***$p \leq 0.001$. *ANCOVA* analysis of covariance, *hsCRP* high-sensitivity C-reactive protein, *PBO* placebo, *ULN* upper limit of normal, *UPA* upadacitinib, *WPAI* Work Productivity and Activity Impairment

may also result in imprecise estimates that may limit the ability to make causal inferences. Additionally, the outcome data are provided only up to 14 weeks, therefore long-term follow-up is needed to confirm the durability of PRO improvements. Concomitant use of steroids or NSAIDs was allowed during the study period, which may have contributed to the high MCID response rates seen across both the placebo and UPA treatment groups for some outcomes e.g., PtGA and total back pain. However, higher proportions of patients achieved clinically meaningful improvements with UPA compared to placebo. This study used phase 3 clinical trial data, ensuring that patients are closely monitored and that the outcomes of interest are well-measured. The randomized study design implemented mitigates bias that may arise due to unobservable differences between cohorts. This study demonstrated improvements seen across a broad range of PROs previously not measured within other studies of JAK inhibitors. Another key strength of this study is the clinically meaningful

improvement across outcomes in TNFi-IR patients observed with upadacitinib versus placebo, supporting the current evidence base in patients with AS refractory to biological therapy.

CONCLUSIONS

In bDMARD-IR patients with active AS, upadacitinib 15 mg demonstrated clinically meaningful improvements in disease activity, pain, fatigue, function, HRQoL, and work productivity at week 14 compared with placebo. Rapid improvements from baseline were seen as early as week 1 for disease-specific and general HRQoL patient-reported measures. These data support findings from previous clinical trials evaluating the efficacy of upadacitinib in AS by further substantiating the benefit of upadacitinib in this biologic refractory population.

ACKNOWLEDGEMENTS

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