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ORIGINAL RESEARCH

Efficacy of upadacitinib in subgroups of patients with axial spondyloarthritis with early versus established disease

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ABSTRACT

Objectives Early disease activity control with targeted therapies may improve long-term outcomes in axial spondyloarthritis (axSpA). Here, we evaluated the efficacy of upadacitinib in patients with axSpA with shorter versus longer symptom durations.

Methods SELECT-AXIS 1 and 2 studies enrolled patients with radiographic axSpA (r-axSpA) and non-radiographic axSpA (nr-axSpA) naïve to biologic disease-modifying antirheumatic drugs (bDMARD-naïve) and with an intolerance or inadequate response to bDMARD therapy. Patients were stratified by symptom duration (nr-axSpA: early vs established (≤2 vs >2 years=Assessment of SpondyloArthritis international Society (ASAS) definition) and shorter vs longer (≤5 vs >5 years); r-axSpA: ≤5 vs >5 years). Efficacy endpoints assessed through week 14 included the proportion of patients achieving Axial Spondyloarthritis Disease Activity Score and ASAS40 responses, among others. Across all endpoints, the efficacy of upadacitinib versus placebo was assessed by relative risk (RR), and the placebo-adjusted effect of upadacitinib between shorter versus longer symptom duration was assessed by the RR ratio.

Results At week 14, better responses were observed in patients treated with upadacitinib in all endpoints assessed compared with placebo, regardless of symptom duration. When comparing patients with early/shorter versus established/longer symptom durations, for all measures assessed, no statistically significant differences were observed except for the change from baseline in high-sensitivity C-reactive protein in the nr-axSpA group, with a better response in early disease (difference −8.2, 95% CI −14.9 to −1.6).

Conclusion Regarding short-term outcomes, both subgroups of patients (shorter axSpA symptom duration (≤2 years) and longer symptom duration (>2 years)) achieved comparable results when treated with upadacitinib.

Trial registration number NCT03178487 (SELECT-AXIS 1) and NCT04169373 (SELECT-AXIS 2).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is limited evidence to suggest that early treatment may have a potential beneficial effect on axial spondyloarthritis (axSpA), notably among patients with shorter symptom duration.

WHAT THIS STUDY ADDS

⇒ The results from this study suggest that patients who meet the Assessment of SpondyloArthritis international Society consensus definition of early axSpA (symptom duration ≤2 years) achieve comparable short-term treatment outcomes to those with established disease (symptom duration >2 years) when treated with upadacitinib.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further studies that evaluate shorter symptom duration cut-offs, have longer-term follow-up periods and use a consistent statistical approach are required to assess whether a window of opportunity to change the long-term outcomes of patients with early axSpA disease exists.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that primarily affects the axial skeleton (ie, sacroiliac joints (SIJs) and spine). It encompasses both radiographic axSpA (r-axSpA), traditionally known as ankylosing spondylitis, and non-radiographic axSpA (nr-axSpA).[1–3] Left untreated or inadequately treated, irreversible structural damage leading to functional disability and reduced spinal mobility can occur, significantly impacting patient quality of life. Reducing the diagnostic delay in axSpA and initiating treatment earlier in the disease course may improve long-term outcomes.[4 5]

Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line recommended pharmacological treatment according to the latest Assessment of SpondyloArthritis international Society-European Alliance of Associations for Rheumatology (ASAS-EULAR)

recommendations.[6] Treatment with targeted therapies, such as tumour necrosis factor inhibitors (TNFis), interleukin-17 inhibitors (IL-17is) or Janus kinase inhibitors (JAKis) are recommended for patients with an inadequate response to NSAIDs.[6]

Early treatment with targeted therapies may slow or prevent the structural damage associated with axSpA and thus improve long-term outcomes.[4 7–10] Indeed, a recent systematic literature review conducted in the context of the ASAS-SPondyloarthritis EARly definition project, while unable to conclude a benefit of early treatment in axSpA, revealed evidence suggestive of a potential beneficial effect in patients with nr-axSpA, notably among patients with a shorter symptom duration.[11] However, across most studies included in the systematic literature review, the minimum cut-off used for symptom duration was 5 years, suggesting these patients may not have been at an early stage in their disease course. Historically, studies evaluating early axSpA have proved challenging, given the absence of a consensus definition and a lack of validated diagnostic criteria.[4 12 13] Most recently, an ASAS consensus definition of early axSpA has been developed, which consists of a duration of axial symptoms of ≤2 years.[14] This definition will help ensure a more homogenous population of patients with early axSpA across different studies, improving the robustness of evidence from cross-study comparisons.

Studies enriched for patients with early axSpA using the new ASAS definition will allow for the evaluation of whether outcomes among patients with axSpA treated with targeted therapies in the clinical trial setting are impacted by baseline characteristics such as symptom duration. More specifically, the question is whether patients with shorter symptom duration have different treatment outcomes compared with patients with longer symptom duration and to determine whether, in axSpA, a window of opportunity exists.[4]

Upadacitinib is an oral, reversible and selective JAKi that has demonstrated efficacy and an acceptable safety profile in axSpA through week 14[15–17] and maintenance of response through 2 years.[16 18] Here, we compare from the SELECT-AXIS 1 and 2 trials, baseline characteristics and the treatment effect of upadacitinib versus placebo, in patients with axSpA with shorter versus longer symptom duration.

METHODS

Study designs and treatment

SELECT-AXIS 1 (NCT03178487) and SELECT-AXIS 2 (NCT04169373) are global, placebo-controlled, multicentre, randomised trials that enrolled patients with axSpA. The methodologies for both trials have been previously described.[15–17]

This study enrolled adult patients from the SELECT-AXIS 2 study with a clinical diagnosis of nr-axSpA who met the 2009 ASAS classification criteria and had at least one objective sign of inflammation at screening based on MRI of the SIJs, high-sensitivity C-reactive protein (hsCRP) above the upper limit of normal (2.87 mg/L) or both.[15] Patients had an inadequate response (IR) to at least two NSAIDs, or intolerance or contraindication to NSAIDs. For patients who had discontinued prior biologic disease-modifying antirheumatic drugs (bDMARDs) due to lack of efficacy (after 12 weeks of treatment at an adequate dose) or intolerance (regardless of treatment duration), one bDMARD (either a TNFi or an IL-17i) was permitted for at least 20% but not exceeding 35% of enrolled patients. In the SELECT-AXIS 2 nr-axSpA study, patients were randomised to upadacitinib 15 mg once daily or placebo for a 52-week, double-blind, placebo-controlled period. Patients with active r-axSpA based on the modified New York criteria, who were naïve to bDMARDs (bDMARD-naïve) but had experienced an IR or intolerance to at least two NSAIDs, were enrolled from the SELECT-AXIS 1 study. Patients received upadacitinib 15 mg once daily or placebo during a 14-week, double-blind, placebo-controlled period.[17] Patients with active r-axSpA (based on the New York criteria) who had experienced IR to at least two NSAIDs or intolerance/contraindications to NSAIDs, as well as an IR to bDMARD therapy (bDMARD-IR, defined as discontinuation of TNFi or IL-17i therapy due to lack of efficacy after ≥12 weeks of treatment at an adequate dose, based on the investigator's assessment, or intolerance to bDMARDs irrespective of treatment duration) were enrolled from the SELECT-AXIS 2 study.[16] Prior exposure to a second bDMARD was allowed for ≤30% of patients; among patients with prior exposure to two bDMARDs, lack of efficacy to one bDMARD and intolerance to another was allowed, but lack of efficacy to two bDMARDs was not allowed. Patients in the SELECT-AXIS 2 r-axSpA bDMARD-IR study were randomised to receive upadacitinib 15 mg once daily or placebo for a 14-week, double-blind, placebo-controlled period. All three studies enrolled patients with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and patient's assessment of total back pain scores ≥4 (Numeric Rating Scale 0–10) at baseline and screening, and allowed stable concomitant doses of background medications including conventional synthetic DMARDs, oral glucocorticoids and NSAIDs.[15–17]

Subgroup analysis based on symptom duration

Each trial was evaluated separately, and within each study patients were stratified according to baseline symptom duration. Patients with nr-axSpA were stratified by early and established disease defined as ≤2 years and >2 years symptom duration, in accordance with the ASAS consensus definition.[15] Additionally, patients from both the bDMARD-naïve and bDMARD-IR r-axSpA populations were stratified based on symptom durations of ≤5 years and >5 years. Furthermore, the nr-axSpA patient population was evaluated using the same cut-off of ≤5 years and >5 years, and therefore in alignment with the cut-off applied to the r-axSpA patient populations.

Assessments

In this post hoc subgroup analysis, efficacy endpoints assessed through week 14 included the proportion of

patients achieving Axial Spondyloarthritis Disease Activity Score low disease activity (ASDAS LDA; <2.1), ASDAS inactive disease (ID; <1.3), ASDAS clinically important improvement (CII; Δ≥1.1-point decrease from baseline), ASDAS major improvement (MI; Δ≥2-point decrease from baseline) and 40% improvement in three out of the four ASAS domains without worsening in the remaining domain (ASAS40) response. Additional efficacy endpoints included ≥50% improvement from baseline in BASDAI (BASDAI50), change from baseline in patient's assessment of total back pain, hsCRP, MRI SpondyloArthritis Research Consortium of Canada (SPARCC) score (SIJs and spine), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI) and ASAS Health Index (ASAS HI).

MRI scans of the SIJs and spine were conducted at screening and week 14 and were assessed using the SPARCC score methodology. Two primary readers masked to treatment assignment and time point independently read the scans, with a third reader adjudicating if the mean absolute difference between the SPARCC change scores between readers exceeded a certain threshold. The mean of the two closest scores was used for adjudicated cases. Inter-reader reliability was determined through secondary reviews that were conducted in a blinded manner. Readers were, at a minimum, board-eligible or had an equivalent level of certification in their respective relevant areas of expertise. In addition, all readers received project-specific training before they started performing any evaluations.

Statistical analyses

For each study, baseline data were pooled by treatment group (upadacitinib and placebo), then stratified by symptom duration according to the two previously mentioned cut-offs, ≤2 years versus >2 years (only for nr-axSpA) and ≤5 years versus >5 years.

In the nr-axSpA and bDMARD-IR r-axSpA groups (SELECT-AXIS 2), response rates for binary endpoints were calculated using non-responder imputation with multiple imputation. In the bDMARD-naïve r-axSpA group (SELECT-AXIS 1), response rates were calculated using non-responder imputation. The different approaches for each group were consistent with the primary analysis of each trial. For continuous endpoints collected at multiple postbaseline visits in all groups, an as-observed mixed effect model for repeated measures including treatment, visit and treatment by visit interaction as fixed factors, baseline value as covariate, as well as main stratification factor of screening hsCRP level (and MRI status for nr-axSpA) was applied. For a change from baseline in BASMI and MRI SPARCC score (SIJs and spine), the analysis of covariance (ANCOVA) model was used as data were only collected at screening and week 14. The ANCOVA model for BASMI included treatment, main stratification factor of screening hsCRP level (and MRI status for nr-axSpA) and baseline value as covariate. The ANCOVA model for MRI SPARCC score included treatment, main stratification factor of screening hsCRP level (and MRI status for nr-axSpA), treatment and stratification interaction for nr-axSpA and baseline value as covariate. Between-group difference and associated CIs were constructed with a normal approximation for all continuous endpoints.

Across all binary endpoints, relative risk (RR) along with 95% CIs were calculated for both early/shorter (≤2 or ≤5 years) and established/longer disease (>2 or >5 years) to evaluate and compare the effect of upadacitinib versus placebo within symptom duration subgroups. RR ratio (RRR) along with 95% CIs were calculated by dividing the RR of upadacitinib (vs placebo) in early/shorter axSpA by the RR in established/longer disease to compare the placebo-adjusted effect of upadacitinib between early/shorter and established/longer disease. Rubin's rule was used to calculate the aggregated RR. The RRR and associated CIs were constructed on log-transformed RR estimates and SE. RR and SE were estimated using the Cochran–Mantel–Haenszel model with screening hsCRP level (plus MRI status for nr-axSpA) as the main stratification factor, and the construction of CIs was based on multiple imputation inference. For binary endpoints, an RRR above 1 indicated better outcomes in early/shorter disease, while an RRR below 1 indicated worse outcomes in early/shorter disease. For all continuous endpoints, except ASAS HI, a between-group difference above 0 indicated better outcomes in early/shorter disease, while a between-group difference below 0 indicated worse outcomes in early/shorter disease. For ASAS HI, a between-group difference below 0 indicated better outcomes in early/shorter disease, while a between-group difference above 0 indicated worse outcomes in early/shorter disease.

RESULTS

Patient disposition and baseline characteristics

Baseline characteristics were generally similar across nr-axSpA, bDMARD-naïve r-axSpA and bDMARD-IR r-axSpA groups and between patients with symptom durations of ≤2 years versus >2 years and ≤5 years versus >5 years within each disease subgroup (table 1). The mean age was similar across all groups; there was a higher proportion of females in the nr-axSpA group compared with the r-axSpA groups and among those with established (>2 years) versus early nr-axSpA (≤2 years). Baseline measures of disease activity and burden including ASDAS, patient's assessment of total back pain, BASFI and BASDAI were similar across all patient groups and between patients with symptom duration of ≤5 years versus >5 years for both nr-axSpA and r-axSpA groups and early versus established nr-axSpA. Baseline MRI SPARCC (SIJs) scores were lower for patients with symptom duration of >5 years versus ≤5 years across all groups, and established versus early nr-axSpA. In patients with bDMARD-naïve and bDMARD-IR r-axSpA, baseline MRI SPARCC (spine) scores were higher in patients with symptom duration of >5 years versus ≤5 years.

Table 1 Baseline demographics and disease characteristics for patients with early and established nr-axSpA, bDMARD-naïve r-axSpA and bDMARD-IR r-axSpA

	nr-axSpA				bDMARD-naïve r-axSpA		bDMARD-IR r-axSpA	
	Symptom duration ≤2 years versus >2 years		Symptom duration ≤5 years versus >5 years		Symptom duration ≤5 years versus >5 years		Symptom duration ≤5 years versus >5 years	
Characteristic*	Early disease (n=56)	Established disease (n=255)	Short symptom duration (n=115)	Long symptom duration (n=196)	Short symptom duration (n=38)	Long symptom duration (n=149)	Short symptom duration (n=92)	Long symptom duration (n=328)
Female, n (%)	28 (50.0)	153 (60.0)	62 (53.9)	119 (60.7)	14 (36.8)	41 (27.5)	29 (31.5)	80 (24.4)
Age, years	35.7 (13.4) (19 to 62)	43.4 (11.4) (21 to 79)	38.4 (12.9) (19 to 67)	44.1 (11.2) (21 to 79)	41.9 (14.6) (21 to 71)	46.2 (11.8) (22 to 74)	37.5 (12.9) (20 to 82)	43.8 (11.5) (23 to 79)
Median time since axSpA diagnosis, years	0.5 (0.1 to 4.8)	3.4 (0.1 to 32.4)	0.8 (0.1 to 4.8)	5.0 (0.1 to 32.4)	0.8 (0.1 to 4.5)	5.5 (0.1 to 40.9)	2.3 (0.2 to 4.8)	6.8 (0.2 to 44.8)
Median duration of axSpA symptoms, years	1.0 (0.2 to 2.0)	8.7 (2.0 to 41.1)	2.2 (0.2 to 5.0)	10.6 (5.0 to 41.1)	2.6 (0.5 to 5.0)	15.4 (5.0 to 51.9)	3.3 (0.6 to 4.9)	12.8 (5.1 to 46.4)
HLA-B27 positive, n (%)	37 (66.1)	146 (58.2)	71 (62.3)	112 (58.0)	25 (65.8)	118 (79.2)	78 (84.8)	270 (82.8) N/A
Concomitant csDMARD use, n (%)	18 (32.1)	72 (28.2)	36 (31.3)	54 (27.6)	N/A	N/A	30 (32.6)	100 (30.5) N/A
Concomitant oral corticosteroid use, n (%)	6 (10.7)	29 (11.4)	16 (13.9)	19 (9.7)	N/A	N/A	12 (13.0)	33 (10.1) N/A
Prior bDMARD exposure, n (%)	7 (12.5)	95 (37.3)	26 (22.6)	76 (38.8)	N/A	N/A	92 (100)	328 (100) N/A
ASDAS	3.7 (0.7) (2.3 to 5.1)	3.6 (0.7) (1.5 to 5.3)	3.7 (0.7) (2.1 to 5.1)	3.6 (0.7) (1.5 to 5.3)	3.6 (0.8)† (1.0 to 5.0)	3.6 (0.8)‡ (2.0 to 5.0)	3.8 (0.8) (2.1 to 6.1)	3.9 (0.8) (1.5 to 5.8)
Patient's assessment of total back pain (NRS score 0–10)	7.0 (1.3) (4.0 to 10.0)	7.3 (1.5) (2.0 to 10.0)	7.1 (1.4) (3.0 to 10.0)	7.3 (1.5) (2.0 to 10.0)	6.9 (1.7) (2.0 to 9.0)	6.7 (1.8)‡ (2.0 to 10.0)	7.3 (1.4) (3.0 to 10.0)	7.4 (1.5) (2.0 to 10.0)
ASAS HI	9.1 (3.4) (2.0 to 17.0)	9.6 (3.7)§ (0.0 to 17.0)	9.3 (3.6)¶ (0.0 to 17.0)	9.6 (3.6)** (0.0 to 17.0)	9.9 (3.8)† (4.0 to 17.0)	8.1 (3.9)‡ (0.0 to 17.0)	9.5 (3.7)†† (1.1 to 16.0)	9.1 (3.6) (0.0 to 17.0)
BASDAI (score 0–10)	6.7 (1.0) (4.0 to 9.1)	6.9 (1.3) (2.9 to 9.9)	6.8 (1.1) (3.8 to 9.1)	6.9 (1.3) (2.9 to 9.9)	6.6 (1.4) (3.0 to 9.0)	6.3 (1.7)‡ (1.0 to 10.0)	6.8 (1.3) (4.1 to 9.4)	6.8 (1.3) (1.7 to 9.8)
BASFI (NRS score 0–10)	5.5 (2.0) (0.1 to 9.3)	6.0 (2.1) (0.4 to 9.7)	5.71 (2.1) (0.1 to 9.4)	6.1 (2.1) (0.6 to 9.7)	5.7 (2.1)† (1.0 to 9.0)	5.4 (2.3)‡ (0.0 to 10.0)	6.0 (2.2) (0.8 to 9.3)	6.3 (1.9) (0.0 to 10.0)
BASMI	3.1 (1.6) (0.2 to 7.8)	3.0 (1.3)‡‡ (0.5 to 7.7)	3.0 (1.5)¶ (0.2 to 7.8)	3.0 (1.2) (0.6 to 7.7)	3.2 (1.5) (1.0 to 6.0)	3.7 (1.4) (1.0 to 7.0)	3.4 (1.5) (0.4 to 8.2)	4.0 (1.6) (0.6 to 8.2)
MRI SPARCC score (SIJs)	4.8 (9.2)‡‡‡ (0.0 to 42.5)	3.8 (8.0)§§§ (0.0 to 48.0)	5.1 (9.4)¶¶¶ (0.0 to 42.5)	3.3 (7.4)**** (0.0 to 48.0)	7.7 (10.3)§§ (0.0 to 33.0)	6.4 (9.8)¶¶ (0.0 to 40.0)	8.8 (13.9)*** (0.0 to 61.0)	4.4 (9.4)††† (0.0 to 58.0)

Continued

Table 1 Continued

Characteristic*	nr-axSpA				bDMARD-naïve r-axSpA		bDMARD-IR r-axSpA	
	Symptom duration ≤2 years versus >2 years		Symptom duration ≤5 years versus >5 years		Symptom duration ≤5 years versus >5 years		Symptom duration ≤5 years versus >5 years	
	Early disease (n=56)	Established disease (n=255)	Short symptom duration (n=115)	Long symptom duration (n=196)	Short symptom duration (n=38)	Long symptom duration (n=149)	Short symptom duration (n=92)	Long symptom duration (n=328)
MRI SPARCC score (spine)	2.2 (6.4)‡‡‡‡ (0.0 to 36.5)	2.0 (5.4)§§§§ (0.0 to 34.5)	2.5 (6.5)¶¶¶¶ (0.0 to 36.5)	1.8 (4.9)**** (0.0 to 25.5)	7.0 (10.6)†††† (0.0 to 36.0)	12.2 (15.1)¶¶ (0.0 to 68.0)	7.8 (13.2)*** (0.0 to 75.5)	10.3 (14.2)††† (0.0 to 75.0)

*All data are mean (SD) (min, max) unless otherwise stated.
†n=37.
‡n=148.
§n=250.
¶n=114.
**n=192.
††n=91.
‡‡n=254.
§§n=33.
¶¶n=131.
***n=87.
†††n=314.
‡‡‡n=51.
§§§n=237.
¶¶¶n=104.
****n=184.
††††n=34.
‡‡‡‡n=48.
§§§§n=236.
¶¶¶¶n=100.
ASAS HI, Assessment of SpondyloArthritis international Society Health Index; ASDAS, Axial Spondyloarthritis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; HLA-B27, human leucocyte antigen B27; N/A, not available; nr-axSpA, non-radiographic axSpA; NRS, Numeric Rating Scale; r-axSpA, radiographic axSpA; SIJ, sacroiliac joint; SPARCC, SpondyloArthritis Research Consortium of Canada.

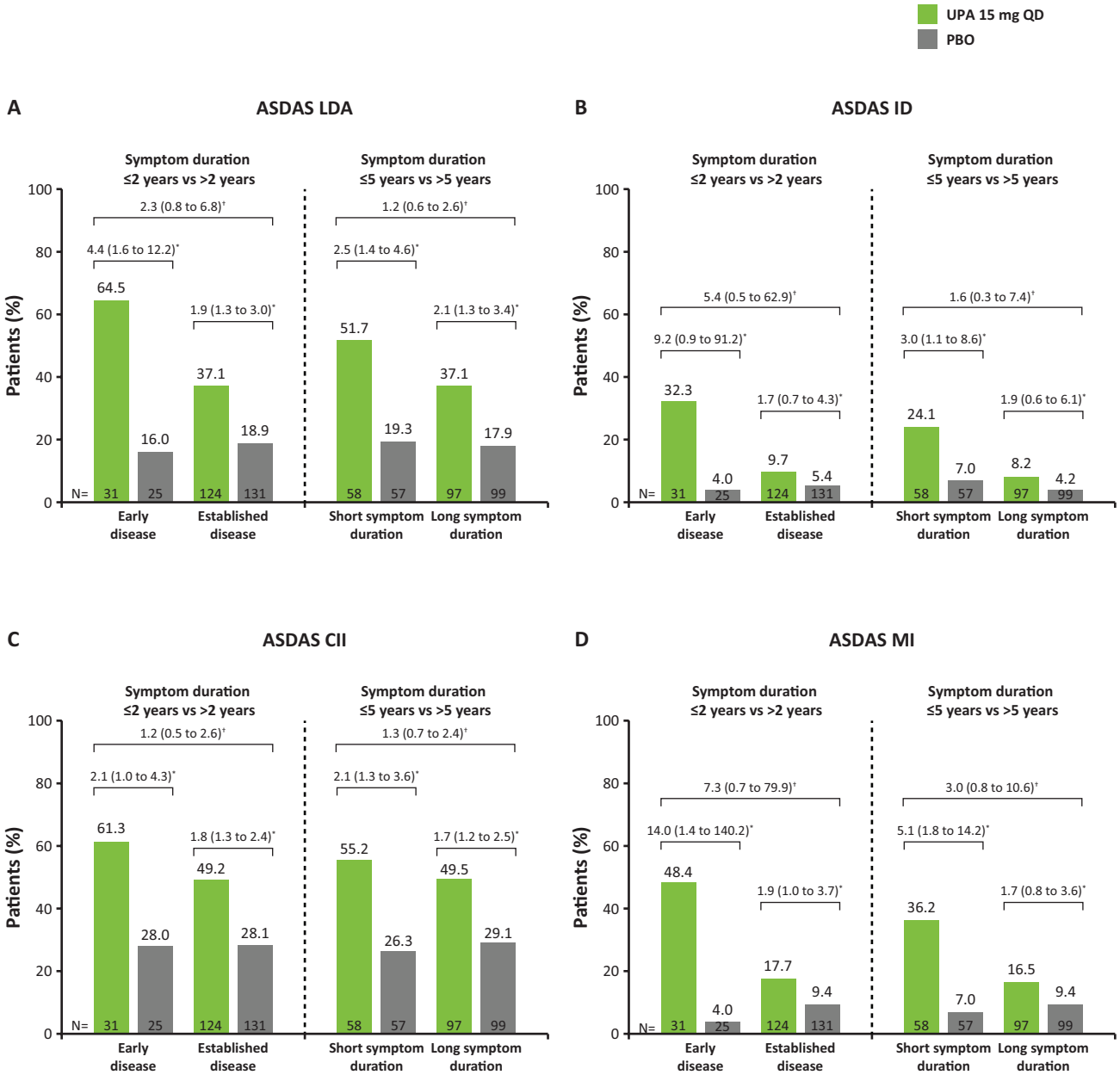


Figure 1 Proportion of patients achieving ASDAS LDA, ASDAS ID, ASDAS CII and ASDAS MI at week 14 with early versus established (≤2 years vs >2 years) nr-axSpA as defined by the ASAS consensus definition, and nr-axSpA with short versus long (≤5 years vs >5 years) symptom duration. *RR (95% CI) UPA versus PBO. †RRR (95% CI) early/short versus established/long disease/symptom duration. ASAS, Assessment of Spondyloarthritis international Society; ASDAS, Axial Spondyloarthritis Disease Activity Score; CII, clinically important improvement; ID, inactive disease; LDA, low disease activity; MI, major improvement; nr-axSpA, non-radiographic axial spondyloarthritis; PBO, placebo; QD, once daily; RR, relative risk; RRR, RR ratio; UPA, upadacitinib.

nr-axSpA

At week 14, a higher proportion of patients with nr-axSpA treated with upadacitinib achieved ASDAS LDA compared with those who received placebo among patients with early disease according to the new ASAS consensus definition (64.5% vs 16.0%, respectively (RR 4.4, 95% CI 1.6 to 12.2)), and among those with established disease (37.1% vs 18.9% (RR 1.9, 95% CI 1.3 to 3.0)) (figure 1A). A similar pattern was noted for the additional ASDAS endpoints, with a higher proportion of patients treated with upadacitinib compared with those who received placebo achieving ASDAS ID (figure 1B), ASDAS CII (figure 1C) and ASDAS MI (figure 1D). Compared with patients with established disease, patients with early disease receiving upadacitinib did not show a statistically higher achievement of ASDAS outcomes (ASDAS LDA: RRR 2.3, 95% CI 0.8 to 6.8; ASDAS ID: RRR 5.4, 95% CI 0.5 to 62.9; ASDAS CII: RRR 1.2, 95% CI 0.5 to 2.6; ASDAS MI: RRR 7.3, 95% CI 0.7 to 79.9) (figure 1). When stratified by symptom durations of ≤5 years versus >5 years, a consistent pattern of results was observed, with a numerically higher proportion of patients treated with upadacitinib achieving each ASDAS endpoint compared with those who

received placebo (figure 1). No significant differences in the achievement of ASDAS outcomes were found between the groups with shorter (≤5 years) and longer symptom duration (>5 years) (ASDAS LDA: RRR 1.2, 95% CI 0.6 to 2.6; ASDAS ID: RRR 1.6, 95% CI 0.3 to 7.4; ASDAS CII: RRR 1.3, 95% CI 0.7 to 2.4; ASDAS MI: RRR 3.0, 95% CI 0.8 to 10.6) (figure 1).

At week 14, a larger proportion of patients treated with upadacitinib achieved ASAS40 compared with those who received placebo among patients with early disease (61.3% vs 16.0%, respectively (RR 3.9, 95% CI 1.4 to 10.9)), and among those with established disease (40.3% vs 24.0% (RR 1.7, 95% CI 1.1 to 2.4)) (figure 2A). When comparing patients with shorter versus longer symptom durations, no significant differences in the proportion of patients receiving upadacitinib who achieved ASAS40 were found between the groups, regardless of which symptom duration cut-off was used (early vs established nr-axSpA: RRR 2.3, 95% CI 0.8 to 7.0; symptom duration ≤5 years vs >5 years: RRR 1.5, 95% CI 0.7 to 3.2) (figure 2A).

Mean change from baseline through week 14 in patient's assessment of total back pain, hsCRP and ASAS HI score favoured upadacitinib versus placebo among those with either early or established nr-axSpA according to the new ASAS consensus definition (figure 2B, 2C and 3D). No significant differences were found between patients with shorter versus longer symptom durations, regardless of which symptom duration cut-off was used, except for the change from baseline in hsCRP in patients with early versus established disease, in which a better response was seen in patients with early disease (difference –8.2, 95% CI –14.9 to –1.6).

At week 14, the pattern of response and improvements from baseline for the Bath Ankylosing Spondylitis endpoints (BASDAI50, BASFI and BASMI) was consistent with those reported for the other endpoints evaluated (figure 3).

A numerically larger improvement in MRI SPARCC (SIJs) from baseline to week 14 was seen with upadacitinib versus placebo among patients with early nr-axSpA (RR –3.1, 95% CI –6.3 to 0.1) and established nr-axSpA (RR –2.9, 95% CI –4.0 to –1.9) (figure 4A). No significant differences in the improvement of MRI SPARCC (SIJs) scores were observed for patients with shorter versus longer symptom durations, regardless of the symptom duration cut-off used (figure 4A). Consistent with these observations, a numerically higher improvement in MRI SPARCC (spine) from baseline to week 14 in favour of upadacitinib was seen for patients with early and established disease and for those with symptom durations ≤5 years versus >5 years (figure 4B). No significant differences in the improvement of MRI SPARCC (SIJs) scores were observed for patients with shorter versus longer symptom durations, regardless of the symptom duration cut-off used (figure 4B).

bDMARD-naïve r-axSpA

In the bDMARD-naïve r-axSpA group, a higher proportion of patients treated with upadacitinib achieved each of the ASDAS endpoints, ASAS40 and BASDAI50, at week 14 compared with those who received placebo (table 2). Compared with patients with longer symptom duration (>5 years), patients with shorter symptom duration (≤5 years) did not show a statistically higher achievement of ASDAS outcomes (ASDAS LDA: RRR 0.8, 95% CI 0.2 to 3.1; ASDAS CII: RRR 0.9, 95% CI 0.3 to 2.4; ASDAS MI: RRR 1.2, 95% CI 0.1 to 10.8); ASAS40: RRR 0.7, 95% CI 0.3 to 1.7 or BASDAI50: RRR 2.6, 95% CI 0.8 to 8.5) (table 2).

No significant difference was observed in mean change from baseline in patient's assessment of total back pain, hsCRP, ASAS HI, BASFI or BASMI between patients with symptom duration of >5 years and patients with symptom duration of ≤5 years (table 2).

For the MRI SPARCC (SIJs) and MRI (spine) scores, no significant differences in mean change from baseline in MRI SPARCC (SIJs) scores were observed for patients with shorter versus longer symptom durations, regardless of the symptom duration cut-off used (table 2).

bDMARD-IR r-axSpA

In the bDMARD-IR r-axSpA group, a higher proportion of patients treated with upadacitinib achieved each of the ASDAS endpoints, ASAS40 and BASDAI50, at week 14 compared with those who received placebo (table 3). Compared with patients with longer symptom duration (>5 years), patients with shorter symptom duration (≤5 years) did not show a statistically higher achievement of ASDAS outcomes (ASDAS LDA: RRR 0.9, 95% CI 0.4 to 2.5; ASDAS ID: RRR 1.0, 95% CI 0.1 to 10.4; ASDAS CII: RRR 0.8, 95% CI 0.4 to 1.4; ASDAS MI: RRR 0.5, 95% CI 0.1 to 1.7; ASAS40: RRR 0.8, 95% CI 0.4 to 1.7; BASDAI50: RRR 1.4, 95% CI 0.6 to 3.0) (table 3).

No significant difference was observed in mean change from baseline in patient's assessment of total back pain, hsCRP, ASAS HI, BASFI or BASMI between patients with symptom duration of >5 years and patients with symptom duration of ≤5 years (table 3).

For the MRI SPARCC (SIJs) and MRI (spine) scores, no significant differences in mean change from baseline in MRI SPARCC (SIJs) scores were observed for patients with shorter versus longer symptom durations, regardless of the symptom duration cut-off used (table 3).

DISCUSSION

This analysis of data from the SELECT-AXIS 1 and SELECT-AXIS 2 trials compared treatment response to upadacitinib versus placebo after 14 weeks stratified by symptom duration. Responses were examined in patients with short versus long symptom duration using a logistically feasible cut-off (≤5 years vs >5 years) in patients with bDMARD-naïve r-axSpA, bDMARD-IR r-axSpA and nr-axSpA and between those with early versus established nr-axSpA as defined by the ASAS consensus definition (symptom duration ≤2 years vs >2 years). Upadacitinib was associated with numerically higher improvements in clinical outcomes compared with placebo

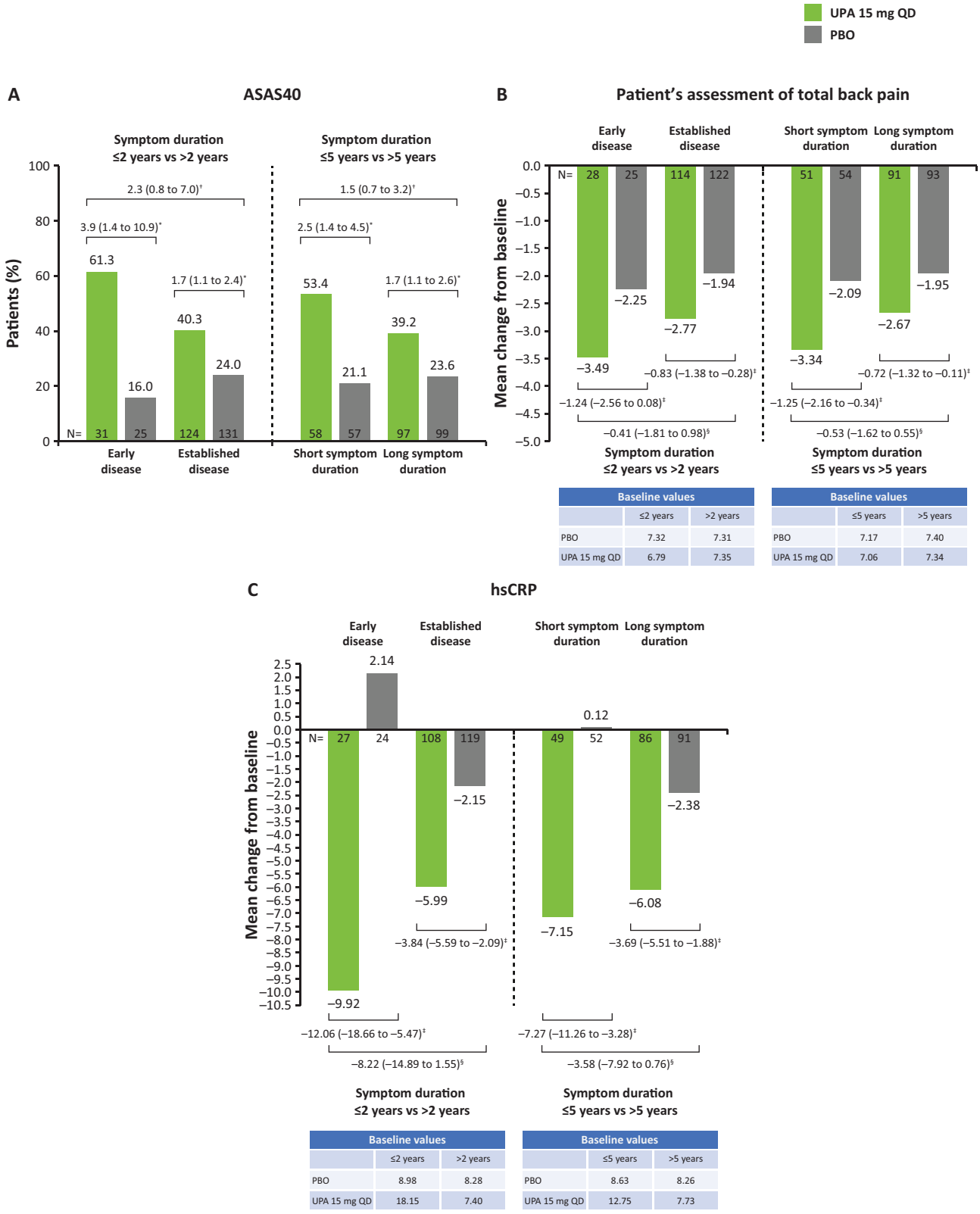


Figure 2 Proportion of patients achieving ASAS40, and mean change from baseline in patient assessment of total back pain and hsCRP at week 14 with early versus established (≤2 years vs >2 years) nr-axSpA as defined by the ASAS consensus definition, and nr-axSpA with short versus long (≤5 years vs >5 years) symptom duration. *RR (95% CI) UPA versus PBO. †RRR (95% CI) early/short versus established/long disease/symptom duration. ‡Between-group difference (95% CI) UPA versus PBO. §Between-treatment group difference (95% CI) early/short versus established/long disease. ASAS, Assessment of SpondyloArthritis international Society; ASAS40, 40% improvement in three out of the four ASAS domains without worsening in the remaining domain; hsCRP, high-sensitivity C-reactive protein; nr-axSpA, non-radiographic axial spondyloarthritis; PBO, placebo; QD, once daily; RR, relative risk; RRR, RR ratio; UPA, upadacitinib.

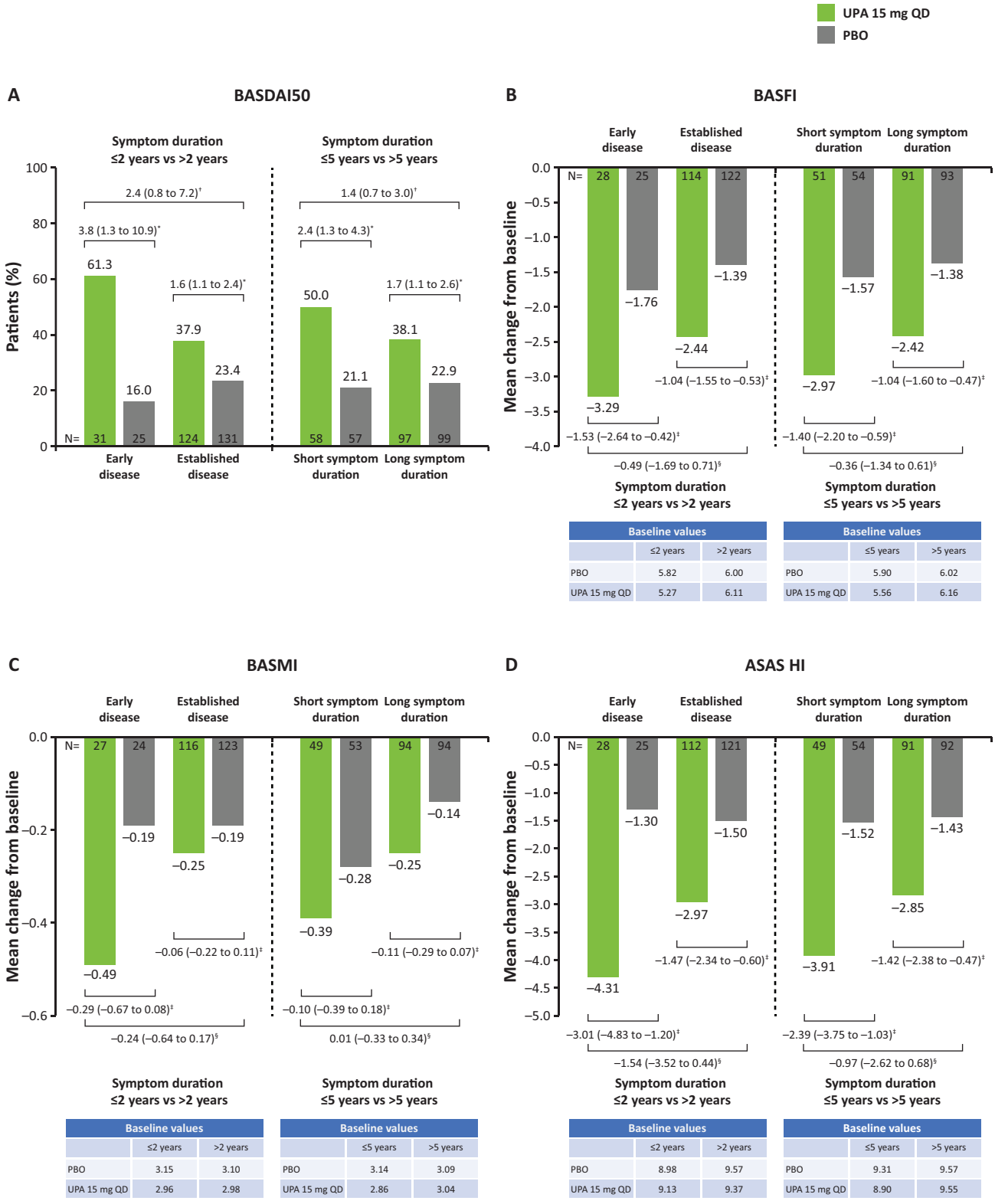
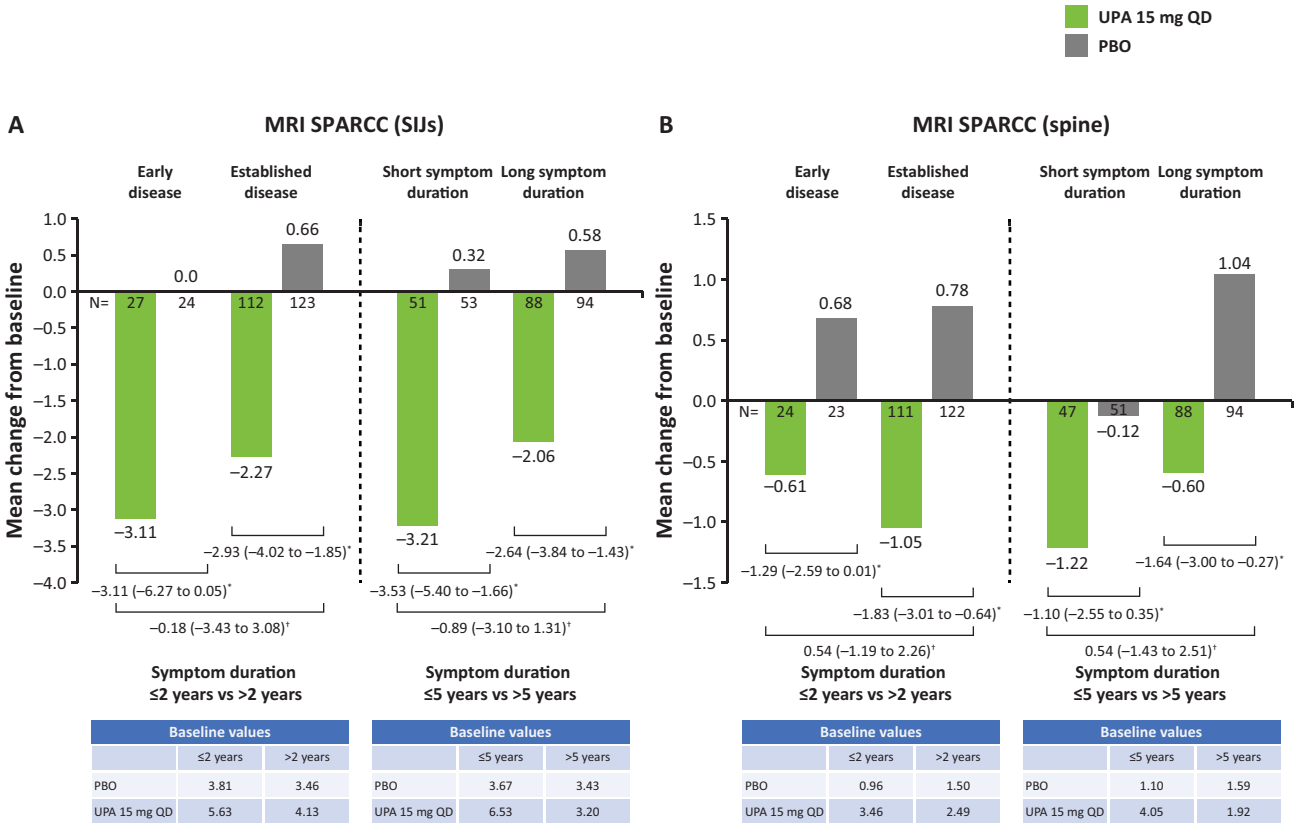


Figure 3 Proportion of patients achieving BASDAI50, and mean change from baseline in BASFI, BASMI and ASAS HI at week 14 with early versus established (≤2 years vs >2 years) nr-axSpA as defined by the ASAS consensus definition, and nr-axSpA with short versus long (≤5 years vs >5 years) symptom duration. *RR (95% CI) UPA versus PBO. †RRR (95% CI) early/short versus established/long disease/symptom duration. ‡Between-group difference (95% CI) UPA versus PBO. §Between-treatment group difference (95% CI) early/short versus established/long disease. ASAS, Assessment of SpondyloArthritis international Society; ASAS HI, ASAS Health Index; BASDAI50, ≥50% improvement in Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; nr-axSpA, non-radiographic axial spondyloarthritis; PBO, placebo; QD, once daily; RR, relative risk; RRR, RR ratio; UPA, upadacitinib.



Baseline values		
	≤2 years	>2 years
PBO	3.81	3.46
UPA 15 mg QD	5.63	4.13

Baseline values		
	≤5 years	>5 years
PBO	3.67	3.43
UPA 15 mg QD	6.53	3.20

Baseline values		
	≤2 years	>2 years
PBO	0.96	1.50
UPA 15 mg QD	3.46	2.49

Baseline values		
	≤5 years	>5 years
PBO	1.10	1.59
UPA 15 mg QD	4.05	1.92

Figure 4 Mean change from baseline in MRI SPARCC (SIJs and spine) at week 14 in patients with early versus established (≤2 years vs >2 years) nr-axSpA as defined by the ASAS consensus definition, and nr-axSpA with short versus long (≤5 years vs >5 years) symptom duration. *Between-group difference (95% CI) UPA versus PBO. †Between-treatment group difference (95% CI) early/short versus established/long disease. ASAS, Assessment of SpondyloArthritis international Society; nr-axSpA, non-radiographic axial spondyloarthritis; PBO, placebo; QD, once daily; SIJ, sacroiliac joint; SPARCC, SpondyloArthritis Research Consortium of Canada; UPA, upadacitinib.

at week 14 for patients with nr-axSpA. While there was a clear trend towards better outcomes across all assessed efficacy endpoints through week 14 (particularly for stringent outcomes, such as ASDAS MI and ASDAS ID) in patients with nr-axSpA in early disease (symptom duration ≤2 years), no significant differences in clinical outcomes were observed between patients with early (symptom duration ≤2 years) versus established (symptom duration >2 years) nr-axSpA, or for patients with either nr-axSpA or r-axSpA with short versus long symptom duration (≤5 years vs >5 years). However, it should be noted that the SELECT-AXIS 1 and 2 studies were not powered to compare the placebo-corrected efficacy of upadacitinib in these subgroups.

The RRs/between-group differences for upadacitinib versus placebo were numerically larger for patients with early versus established nr-axSpA (as defined by the ASAS consensus) for all endpoints apart from MRI SPARCC (spine). Using the ASAS-defined cut-off of early versus established nr-axSpA resulted in numerical improvements compared with using the 5-year cut-off (short vs long symptom duration) for most week 14 clinical outcomes. The RRRs/between-treatment group differences for early versus established nr-axSpA were not significantly different between short versus long symptom duration nr-axSpA across ASDAS LDA, ASDAS ID, ASDAS MI, ASAS40, ASAS HI, BASDAI50, BASFI and BASMI; change from baseline in hsCRP showed a better response in early disease.

There is limited evidence to suggest better outcomes for patients with a shorter symptom duration versus longer symptom duration in axSpA. Previous studies comparing the effect of symptom and/or disease duration in response to active treatment (eg, bDMARDs) mostly use a 5-year cut-off (<5 years vs ≥5 years), rather than the ASAS consensus definition, and only look at the difference in the effect of the active treatment, rather than the overall response with active treatment versus placebo.[11 19 20]

Patients with nr-axSpA have a relatively low rate of disease progression, which may offer a window of opportunity for effective early treatment. Indeed, elevated C-reactive protein levels have been shown to be a strong predictor of disease progression in patients with nr-axSpA who do progress, suggesting reducing active inflammation could play an important role in slowing disease progression.[21 22] In support of this, high intake of NSAIDs was shown to be associated with a slowed rate of radiographic spinal progression, although with a less evident effect in nr-axSpA.[23 24] In a separate study, when the 5-year cut-off was used to compare reductions in hsCRP, the between-treatment group difference was less than

Table 2 Efficacy outcomes at week 14 for patients with bDMARD-naïve r-axSpA with short versus long symptom duration, defined as symptom duration ≤5 years versus >5 years

Binary efficacy endpoints (% of patients)	Symptom duration (years)	PBO	UPA	RR (95% CI) UPA versus PBO	RRR (95% CI) short versus long symptom duration
ASDAS LDA*†	Short (≤5)	15.0	61.1	4.1 (1.3 to 12.3)	0.8 (0.2 to 3.1)
	Long (>5)	9.5	46.7	4.9 (2.3 to 10.4)	
ASDAS ID*†	Short (≤5)	0	11.1	N/A	N/A
	Long (>5)	0	17.3	N/A	
ASDAS CII*†	Short (≤5)	25.0	66.7	2.7 (1.2 to 6.1)	0.9 (0.3 to 2.4)
	Long (>5)	16.2	49.3	3.0 (1.7 to 5.3)	
ASDAS MI*†	Short (≤5)	5.0	33.3	6.9 (1.0 to 50.3)	1.2 (0.1 to 10.8)
	Long (>5)	5.4	32.0	5.9 (2.2 to 15.9)	
ASAS40*†	Short (≤5)	35.0	55.6	1.6 (0.8 to 3.3)	0.7 (0.3 to 1.7)
	Long (>5)	23.0	50.7	2.2 (1.4 to 3.5)	
BASDAI50*†	Short (≤5)	15.0	61.1	4.1 (1.4 to 12.4)	2.6 (0.8 to 8.5)
	Long (>5)	25.7	41.3	1.6 (1.0 to 2.6)	
Continuous efficacy endpoints (mean change from baseline)	**Symptom duration (years)**	**PBO**	**UPA**	**Difference (95% CI) UPA versus PBO**	**Difference (95% CI) short versus long symptom duration**
Patient's assessment of total back pain‡	Short (≤5)	–2.3	–4.3	–2.0 (–3.5 to –0.5)	–0.5 (–2.2 to 1.1)
	Long (>5)	–1.5	–3.0	–1.4 (–2.2 to –0.7)	
hsCRP§	Short (≤5)	2.2	–7.2	–9.4 (–20.1 to 1.4)	–1.1 (–11.8 to 9.7)
	Long (>5)	–0.1	–8.4	–8.3 (–11.2 to –5.4)	
ASAS HI¶	Short (≤5)	–2.8	–5.4	–2.6 (–5.5 to 0.2)	–1.5 (–4.4 to 1.4)
	Long (>5)	–1.1	–2.2	–1.1 (–2.1 to –0.1)	
BASFI‡	Short (≤5)	–1.3	–2.9	–1.6 (–3.2 to –0.1)	–0.8 (–2.4 to 0.8)
	Long (>5)	–1.3	–2.1	–0.8 (–1.5 to –0.2)	
BASMI**	Short (≤5)	–0.2	–0.2	–0.0 (–0.5 to 0.4)	0.3 (–0.3 to 0.8)
	Long (>5)	–0.1	–0.4	–0.3 (–0.5 to –0.0)	
MRI SPARCC (SIJs)††	Short (≤5)	0.7	–4.6	–5.3 (–9.9 to –0.6)	2.4 (–2.3 to 7.1)
	Long (>5)	–0.7	–3.6	–2.9 (–4.6 to –1.2)	
MRI SPARCC (spine)‡‡	Short (≤5)	–0.1	–5.6	–5.4 (–9.7 to –1.2)	–1.6 (–6.4 to 3.2)
	Long (>5)	–0.3	–7.3	–7.1 (–9.8 to –4.3)	

*PBO short symptom duration n=20; long symptom duration n=74.
†UPA short symptom duration n=18; long symptom duration n=75.
‡PBO short symptom duration n=18, long symptom duration n=68; UPA short symptom duration n=16, long symptom duration n=70.
§PBO short symptom duration n=17, long symptom duration n=67; UPA short symptom duration n=16, long symptom duration n=69.
¶PBO short symptom duration n=18, long symptom duration n=70; UPA short symptom duration n=16, long symptom duration n=72.
**PBO short symptom duration n=18, long symptom duration n=71; UPA short symptom duration n=16, long symptom duration n=73.
††PBO short symptom duration n=13, long symptom duration n=46; UPA short symptom duration n=11, long symptom duration n=57.
‡‡PBO short symptom duration n=14, long symptom duration n=46; UPA short symptom duration n=11, long symptom duration n=57.
ASAS, Assessment of SpondyloArthritis international Society; ASAS40, 40% improvement in three out of the four ASAS domains without worsening in the remaining domain; ASAS HI, ASAS Health Index; ASDAS, Axial Spondyloarthritis Disease Activity Score; ASDAS CII, ASDAS clinically important improvement; ASDAS ID, ASDAS inactive disease; ASDAS MI, ASDAS major improvement; BASDAI50, ≥50% improvement in Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; bDMARD, biologic disease-modifying antirheumatic drug; hsCRP, high-sensitivity C-reactive protein; LDA, low disease activity; N/A, not available; PBO, placebo; r-axSpA, radiographic axial spondyloarthritis; RR, relative risk; RRR, RR ratio; SIJ, sacroiliac joint; SPARCC, SpondyloArthritis Research Consortium of Canada; UPA, upadacitinib.

half of that observed when the 2-year cut-off was applied. This observation raises the question of whether the current ASAS cut-off for early axSpA of a symptom duration of ≤2 years is low enough. Early rheumatoid arthritis was initially defined as a symptom duration <2 years[25 26]; the current definition is a symptom duration <6 months.[27] However, evidence

Table 3 Efficacy outcomes at week 14 for patients with bDMARD-IR r-axSpA with short versus long symptom duration, defined as symptom duration ≤5 years vs >5 years

Binary efficacy endpoints (% of patients)	Symptom duration (years)	PBO	UPA	RR (95% CI) UPA versus PBO	RRR (95% CI) short versus long symptom duration
ASDAS LDA*†	Short (≤5)	12.2	48.8	4.2 (1.8 to 9.7)	0.9 (0.4 to 2.5)
	Long (>5)	9.5	42.9	4.5 (2.7 to 7.5)	
ASDAS ID*†	Short (≤5)	2.0	14.0	6.3 (0.8 to 50.1)	1.0 (0.1 to 10.4)
	Long (>5)	1.9	12.5	6.6 (2.0 to 21.7)	
ASDAS CII*†	Short (≤5)	26.5	62.8	2.3 (1.4 to 3.9)	0.8 (0.4 to 1.4)
	Long (>5)	20.1	61.3	3.1 (2.2 to 4.3)	
ASDAS MI*†	Short (≤5)	8.2	32.6	3.7 (1.3 to 10.2)	0.5 (0.1 to 1.7)
	Long (>5)	3.8	29.8	8.0 (3.5 to 18.1)	
ASAS40*†	Short (≤5)	24.5	53.5	2.2 (1.2 to 3.9)	0.8 (0.4 to 1.7)
	Long (>5)	16.3	42.3	2.6 (1.8 to 3.9)	
BASDAI50*†	Short (≤5)	16.3	53.5	3.3 (1.6 to 6.6)	1.4 (0.6 to 3.0)
	Long (>5)	16.9	40.5	2.4 (1.6 to 3.6)	
Continuous efficacy endpoints (mean change from baseline)	**Symptom duration (years)**	**PBO**	**UPA**	**Difference (95% CI) UPA versus PBO**	**Difference (95% CI) short versus long symptom duration**
Patient assessment of total back pain‡	Short (≤5)	–1.6	–3.7	–2.1 (–3.0 to –1.1)	–0.7 (–1.7 to 0.4)
	Long (>5)	–1.4	–2.8	–1.4 (–1.9 to –0.9)	
hsCRP§	Short (≤5)	–2.2	–10.2	–8.0 (–12.9 to –3.1)	4.0 (–1.6 to 9.6)
	Long (>5)	1.0	–10.9	–12.0 (–14.8 to –9.2)	
ASAS HI¶	Short (≤5)	–1.4	–3.4	–2.0 (–3.3 to –0.7)	–0.2 (–1.7 to 1.3)
	Long (>5)	–1.0	–2.8	–1.8 (–2.5 to –1.2)	
BASFI‡	Short (≤5)	–1.5	–2.8	–1.3 (–2.1 to –0.5)	–0.2 (–1.1 to 0.7)
	Long (>5)	–1.0	–2.2	–1.2 (–1.6 to –0.7)	
BASMI**	Short (≤5)	–0.4	–0.6	–0.2 (–0.4 to 0.1)	0.2 (–0.1 to 0.5)
	Long (>5)	–0.1	–0.5	–0.4 (–0.5 to –0.2)	
MRI SPARCC (SIJs)††	Short (≤5)	–0.1	–4.0	–3.9 (–6.8 to –1.0)	–0.9 (–4.0 to 2.3)
	Long (>5)	1.5	–1.6	–3.1 (–4.4 to –1.8)	
MRI SPARCC (spine)††	Short (≤5)	–0.4	–3.8	–3.4 (–6.4 to –0.4)	0.9 (–2.6 to 4.4)
	Long (>5)	0.3	–4.0	–4.3 (–6.1 to –2.4)	

*PBO short symptom duration n=49; long symptom duration n=160.
†UPA short symptom duration n=43; long symptom duration n=168.
‡PBO short symptom duration n=48, long symptom duration n=155; UPA short symptom duration n=42, long symptom duration n=164.
§PBO short symptom duration n=49, long symptom duration n=149; UPA short symptom duration n=41, long symptom duration n=161.
¶PBO short symptom duration n=47, long symptom duration n=154; UPA short symptom duration n=42, long symptom duration n=163.
**PBO short symptom duration n=49, long symptom duration n=152; UPA short symptom duration n=42, long symptom duration n=163.
††PBO short symptom duration n=47, long symptom duration n=139; UPA short symptom duration n=37, long symptom duration n=144.
ASAS, Assessment of SpondyloArthritis international Society; ASAS40, 40% improvement in three out of the four ASAS domains without worsening in the remaining domain; ASAS HI, ASAS Health Index; ASDAS, Axial Spondyloarthritis Disease Activity Score; ASDAS CII, ASDAS clinically important improvement; ASDAS ID, ASDAS inactive disease; ASDAS MI, ASDAS major improvement; BASDAI50, ≥50% improvement in Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; bDMARD, biologic disease-modifying antirheumatic drug; hsCRP, high-sensitivity C-reactive protein; IR, inadequate response; LDA, low disease activity; N/A, not available; PBO, placebo; r-axSpA, radiographic axial spondyloarthritis; RR, relative risk; RRR, RR ratio; SIJ, sacroiliac joint; SPARCC, SpondyloArthritis Research Consortium of Canada; UPA, upadacitinib.

suggests the window of opportunity to change disease course with bDMARD initiation in early rheumatoid arthritis may be between 12 and 15 weeks from symptom onset, depending on anticitrullinated protein antibody positivity.[28] Of note, very early rheumatoid arthritis has been defined as symptom duration ≤12 weeks and has been shown to be a predictor of the potential to achieve remission.[28]

For r-axSpA, patients with a shorter symptom duration (≤5 years) had a tendency towards a better treatment response to upadacitinib versus placebo at week 14 compared with patients with longer symptom duration (>5 years), for all the efficacy endpoints analysed except change from baseline in hsCRP. Patients with short symptom duration showed numerically higher

improvements from baseline in patient's assessment of total back pain, ASAS HI, BASFI, BASMI and MRI SPARCC (SIJs and spine), and were more likely to achieve ASDAS endpoints, ASAS40 and BASDAI50, compared with patients with longer symptom duration, with differences in MRI SPARCC (SIJs and spine), favouring patients with shorter symptom duration.

Similar to our findings, post hoc analyses of the COAST-V, COAST-W and COAST-X trials of the IL-17Ai ixekizumab (nr-axSpA and r-axSpA), and the C-axSpAnd trial of the TNFi certolizumab pegol (nr-axSpA), showed numerically higher improvement in signs, symptoms and quality of life in patients with <5 years versus ≥5 years symptom duration.[19 20] A post hoc analysis of patients with r-axSpA in the MEASURE phase 3 programme for the IL-17Ai secukinumab compared the effect of active treatment on health-related quality of life between patients <2 years versus ≥2 years since diagnosis and showed more prominent improvement in patients <2 years since diagnosis.[29] However, unlike our study, these analyses focused on comparing the effect of active treatment rather than the response versus placebo, which may not account for a difference in placebo response between the subgroups. A post hoc analysis of the TNFi adalimumab ABILITY-1 trial (nr-axSpA) compared treatment effect versus placebo for patients with symptom duration <5 years versus ≥5 years and showed that patients with shorter symptom duration had a statistically significant greater treatment effect in ASAS40 response at 12 weeks.[30] However, it is likely that this finding was largely driven by the low ASAS40 response rate (6%) for patients with symptom duration <5 years who received placebo.[30] Furthermore, unlike the SELECT-AXIS 1 and 2 studies, the ABILITY-1 trial did not enrol patients with previous exposure to bDMARDs and this may also have contributed to the differential findings.[30] A recent meta-analysis evaluating the efficacy of bDMARDs in early versus established axSpA also found that treating patients earlier or later in the disease course resulted in the achievement of comparable short-term clinical outcomes.[31] An analysis of the Swiss Clinical Quality Management registry using the ASAS consensus definition of early axSpA showed slightly lower treatment response at 1 year with a first TNFi in patients with early versus established disease. However, when the statistical model was adjusted for potential confounders and other exploratory variables, there was no significant difference in response between patients with early versus established disease. Of note, only the response rates on the TNFi were compared.[32] Recently, a prospective clinical trial evaluated the efficacy of golimumab monotherapy in newly diagnosed, treatment-naïve patients with axSpA, following the ASAS-EULAR disease management recommendations.[6 33] At week 52, 61.8% of patients achieved sustained clinical remission, and of these patients, 84.8% of those who were taken off treatment, experienced a disease relapse within 1 year. However, as this study lacked a control group, no definitive conclusion on the value of early treatment in this study can be made.[32] Our analysis observed similar results to an analysis of data from the Swiss Clinical Quality Management registry, and the COAST-V/-W/-X, MEASURE and C-axSpAnd studies[19 20 30 32] (ie, numerically improved outcomes in patients with shorter symptom duration). Indeed, similar to the analysis of the Swiss Clinical Quality Management registry, our analysis also found no significant difference in response between patients with early versus established disease.[32] However, the COAST-V/-W/-X, MEASURE and C-axSpAnd studies included no formal direct comparison between patients with shorter versus longer disease duration, taking both treatment arms into account, and therefore, statistical significance could not be confirmed.[19 20 29 30] Thus, there remains a need for further studies using a consistent statistical approach to compare the effect of active treatment versus placebo across subgroups with different symptom durations. Further analyses using the ASAS consensus definition for early axSpA are required, as well as analyses using more stringent cut-offs to assess whether the ASAS definition of early axSpA needs to be lowered to represent patients who are likely to have a statistically higher treatment response across multiple endpoints.

A limitation of the current analysis of clinical trial data is that the SELECT-AXIS studies were designed to assess differences in response between upadacitinib and placebo and were not designed or powered to enable statistical comparisons between subgroups of different symptom duration. No threshold lower than 2 years was evaluated, and a 5-year cut-off had to be used for patients with bDMARD-naïve and bDMARD-IR r-axSpA (rather than the ASAS consensus definition of early vs established axSpA) due to sample size constraints, partly owing to the difficulty in diagnosing r-axSpA early. This analysis also only looked at short-term outcomes at week 14; additional analyses are required to assess whether early treatment impacts longer-term outcomes for patients, indicating whether a window of opportunity exists to change the course of the disease. Also, as no formal sample size calculations were performed, CIs are wide and overlapping. Despite these limitations, this analysis used a robust methodology by comparing the RR/between-treatment group difference and RRR/between-group difference across early and established disease, taking into consideration placebo response in both groups.

CONCLUSION

In conclusion, these results suggest that, although all efficacy outcomes assessed through week 14 showed a clear trend towards better outcomes (irrespective of disease duration), patients who meet the ASAS consensus definition of early axSpA (symptom duration ≤2 years) achieve comparable short-term outcomes to those with established disease (symptom duration >2 years) when treated with upadacitinib. However, the SELECT-AXIS 1 and 2 studies were not powered for such comparisons. Future studies should, therefore, evaluate shorter symptom duration cut-offs with a longer-term follow-up in a larger patient population to further evaluate whether a window of opportunity to change the long-term outcomes of patients with early disease exists.

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Data availability statement Data are available upon reasonable request. 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, clinical study reports or analysis plans), 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. 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.abbvieclinicaltrials.com/hcp/data-sharing.

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