SUPPLEMENTAL MATERIALS

Supplemental Table 1. ASAS40 Responders and Change from Baseline in BASFI and Morning Stiffness Over Time

	ASAS40*		BASFI†		Morning Stiffness‡	
Week	**UPA**	**PBO to UPA**	**UPA**	**PBO to UPA**	**UPA**	**PBO to UPA**
W2	16.7 (15/90)	1.1 (1/90)	-0.92	-0.34	-1.74	-0.92
W4	32.2 (28/87)	7.5 (7/93)	-1.40	-0.63	-2.30	-1.24
W8	42.7 (38/89)	13.2 (12/91)	-1.78	-0.87	-2.56	-1.54
W12	52.8 (47/89)	14.6 (13/89)	-1.94	-1.07	-2.85	-1.66
W14	54.0 (47/87)	27.6 (24/87)	-2.31	-1.29	-3.22	-1.99
W16	58.1 (50/86)	42.7 (38/89)	-2.41	-1.90	-3.29	-3.13
W20	60.9 (53/87)	54.4 (49/90)	-2.47	-2.36	-3.52	-3.42
W24	73.8 (62/84)	66.7 (60/90)	-3.10	-2.92	-4.07	-4.15
W32	78.3 (65/83)	66.7 (58/87)	-3.19	-3.05	-4.33	-4.17
W40	79.0 (64/81)	78.6 (66/84)	-3.43	-3.35	-4.51	-4.44
W52	80.2 (65/81)	77.4 (65/84)	-3.49	-3.40	-4.59	-4.47
W64	84.8 (67/79)	80.5 (66/82)	-3.49	-3.38	-4.52	-4.46
W76	83.1 (64/77)	74.7 (59/79)	-3.39	-3.24	-4.50	-4.31
W88	85.7 (60/70)	85.9 (61/71)	-3.44	-3.22	-4.70	-4.51
W96	88.1 (59/67)	81.2 (56/69)	-3.52	-3.15	-4.58	-4.33
W104	85.9 (61/71)	88.7 (63/71)	-3.50	-3.26	-4.53	-4.57

ASAS, Assessment of SpondyloArthritis international Society; BASFI, Bath Ankylosing Spondylitis Functional Index; MMRM, mixed-effect model repeated measure; PBO, placebo; UPA, upadacitinib; W, week.

*Results are shown as percent of patients achieving an ASAS40 response (n/N). Data are reported as observed.

†Results are shown as mean change from baseline. Data are based on MMRM analysis; 93 patients contributed to the MMRM model for the placebo to upadacitinib switch group and 91 patients contributed to the MMRM model for the continuous upadacitinib group.

‡Results are shown as mean change from baseline for the mean of BASDAI question 5 and 6. Data are based on MMRM analysis; 93 patients contributed to the MMRM model for the placebo to upadacitinib switch group and 92 patients contributed to the MMRM model for the continuous upadacitinib group. Patients originally randomized to placebo were switched to upadacitinib at week 14.

van der Heijde D, *et al. RMD Open* 2022; 8:e002280. doi: 10.1136/rmdopen-2022-002280

Supplemental Table 2. Mean Baseline (SD) and Mean (SD) Change from Baseline to Week 14, Week 52/64 and Week 104 in Disease Activity, Function, and Quality of Life in the Continuous Upadacitinib and Placebo-to-Upadacitinib Switch Groups

	Continuous UPA 15 mg QD				PBO to UPA 15 mg QD			
Mean (SD)	Week 0	Week 14[*]	Week 52/64[†]	Week 104[‡]	Week 0	Week 14[*]	Week 52/64[†]	Week 104[‡]
BASDAI	6.3 (1.76)	–2.79 (2.03)	–4.45 (2.04)	–4.56 (1.71)	6.5 (1.56)	–1.80 (1.97)	–4.42 (1.97)	–4.58 (1.69)
BASDAI Q1 (fatigue)	6.3 (2.17)	–2.25 (2.47)	–3.96 (2.49)	–4.34 (2.25)	6.5 (1.70)	–1.60 (2.51)	–3.65 (2.33)	–4.11 (1.94)
BASDAI Q2 (back pain)	7.1 (1.83)	–3.34 (2.56)	–5.05 (2.12)	–4.83 (2.26)	7.3 (1.53)	–1.76 (2.15)	–5.06 (2.17)	–5.13 (1.87)
BASDAI Q3 (peripheral pain)	5.6 (2.32)	–2.40 (2.49)	–3.95 (2.79)	–4.23 (2.32)	5.9 (2.42)	–1.67 (2.53)	–4.20 (2.93)	–4.11 (2.74)
BASDAI Q5/6 (morning stiffness)	6.5 (1.99)	–3.22 (2.17)	–4.78 (2.02)	–4.89 (2.05)	6.7 (1.90)	–2.03 (1.96)	–4.74 (2.07)	–4.87 (1.80)
ASDAS	3.5 (0.76)	–1.44 (0.99)	–2.04 (0.92)	–2.10 (0.88)	3.7 (0.74)	–0.62 (0.76)	–2.18 (0.87)	–2.11 (0.86)
hsCRP	9.6 (12.6)	–6.80 (12.7)	–6.66 (14.0)	–8.03 (14.1)	11.7 (11.1)	0.34 (12.1)	–8.60 (11.0)	–6.79 (13.8)
Back pain	6.8 (1.77)	–3.24 (2.47)	–4.95 (2.05)	–4.79 (2.10)	6.7 (1.78)	–1.66 (2.38)	–4.46 (2.12)	–4.46 (1.95)
Nocturnal back pain	6.4 (2.29)	–3.44 (2.41)	–4.87 (2.18)	–4.70 (2.30)	6.3 (2.01)	–1.79 (2.57)	–4.62 (2.15)	–4.82 (1.92)
BASFI	5.4 (2.36)	–2.31 (2.44)	–3.75 (2.28)	–3.76 (2.34)	5.5 (2.17)	–1.44 (2.06)	–3.60 (2.00)	–3.59 (1.92)
TJC68	4.3 (8.11)	–2.00 (3.92)	–2.44 (5.23)	–2.96 (4.85)	3.5 (6.54)	–0.86 (3.92)	–1.94 (3.79)	–2.28 (3.85)
SJC66	1.1 (3.27)	–0.57 (1.67)	–0.64 (2.76)	–1.07 (3.36)	1.0 (2.27)	–0.30 (2.40)	–0.87 (2.25)	–0.94 (2.42)
FACIT-F	28.2 (11.4)	6.46 (12.1)	11.2 (11.7)[§]	13.5 (11.5)	29.6 (8.95)	3.91 (10.4)	9.47 (10.5)[§]	11.5 (9.64)
ASAS HI	8.6 (4.12)	–2.92 (4.09)	–4.76 (4.47)[§]	–5.03 (4.07)	8.2 (3.84)	–1.53 (3.30)	–3.63 (3.60)[§]	–4.32 (3.61)
ASQoL	10.0 (5.27)	–4.28 (5.04)	–6.52 (5.59)[§]	–7.22 (5.33)	10.3 (4.65)	–2.87 (4.27)	–5.88 (4.72)[§]	–6.42 (4.58)
WPAI overall work impairment	54.3 (28.1)	–20.5 (24.3)	–35.6 (26.5)[§]	–34.5 (31.7)	53.3 (24.6)	–12.3 (27.7)	–27.7 (28.2)[§]	–28.3 (28.4)

ASDAS, Ankylosing Spondylitis Disease Activity Score; ASAS, Assessment of SpondyloArthritis international Society; ASAS HI, ASAS Health Index; ASQoL, AS 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; hsCRP, high-sensitivity C-reactive protein; PBO, placebo; Q, question; QD, once daily; SJC, swollen joint count; TJC, tender joint count; UPA, upadacitinib; WPAI, Work Productivity and Activity Impairment questionnaire.

[*]Mean values are for patients with both baseline and week 14 data.

[†]Values are for patients with both baseline and week 64 data unless otherwise indicated.

[‡]Values are for patients with both baseline and week 104 data.

[§]Values are for patients with both baseline and week 52 data.

Supplemental Table 3. Change from Baseline in PtGA, Back Pain, and Nocturnal Back Pain Over Time

	PtGA*		Back Pain†		Nocturnal Back Pain‡	
Week	**UPA**	**PBO to UPA**	**UPA**	**PBO to UPA**	**UPA**	**PBO to UPA**
W2	-1.39	-0.44	-1.77	-0.52	-1.75	-0.61
W4	-2.05	-0.75	-2.05	-0.93	-2.10	-1.01
W8	-2.33	-0.79	-2.60	-1.02	-2.57	-1.27
W12	-2.97	-1.41	-3.17	-1.40	-3.06	-1.63
W14	-2.95	-1.35	-3.17	-1.67	-3.37	-1.75
W16	-3.20	-2.72	-3.33	-2.97	-3.44	-3.07
W20	-3.21	-3.18	-3.23	-3.44	-3.29	-3.47
W24	-3.79	-3.73	-4.08	-4.06	-4.23	-4.14
W32	-4.31	-3.95	-4.47	-3.98	-4.25	-4.16
W40	-4.53	-4.36	-4.53	-4.49	-4.48	-4.63
W52	-4.37	-4.15	-4.48	-4.52	-4.47	-4.64
W64	-4.36	-4.36	-4.60	-4.40	-4.60	-4.52
W76	-4.54	-4.09	-4.74	-4.13	-4.49	-4.24
W88	-4.49	-4.18	-4.54	-4.37	-4.54	-4.42
W96	-4.61	-4.15	-4.64	-4.15	-4.38	-4.13
W104	-4.37	-4.24	-4.40	-4.30	-4.32	-4.59

PtGA, Patient Global Assessment of disease activity MMRM, mixed-effect model repeated measure; PBO, placebo; UPA, upadacitinib; W, week.

*Results are shown as mean change from baseline. Data are based on MMRM analysis; 93 patients contributed to the MMRM model for the placebo to upadacitinib switch group and 91 patients contributed to the MMRM model for the continuous upadacitinib group.

†Results are shown as mean change from baseline in patient's assessment of total back pain (numeric rating scale [NRS] 0-10). Data are based on MMRM analysis; 93 patients contributed to the MMRM model for the placebo to upadacitinib switch group and 92 patients contributed to the MMRM model for the continuous upadacitinib group.

‡Results are shown as mean change from baseline in patient's assessment of nocturnal back pain (NRS 0-10). Data are based on MMRM analysis; 93 patients contributed to the MMRM model for the placebo to upadacitinib switch group and 91 patients contributed to the MMRM model for the continuous upadacitinib group.

Patients originally randomized to placebo were switched to upadacitinib at Week 14.

Supplemental Table 4. Changes From Baseline in WPAI Overall Work Impairment Score*

	Continuous Upadacitinib 15 mg QD, Mean (95% CI)		Placebo to Upadacitinib 15 mg QD, Mean (95% CI)	
	As Observed	MMRM	As Observed	MMRM
Week 14	–20.5 (–27.1 to –14.0) n=56	–18.5 (–24.5 to –12.4) n=63	–12.3 (–19.8 to –4.8) n=55	–11.5 (–17.6 to –5.5) n=64
Week 24	–31.3 (–39.5 to –23.0) n=52	–29.1 (–35.0 to –23.2) n=63	–25.1 (–31.5 to –18.7) n=61	–23.9 (–29.5 to –18.4) n=64
Week 104	–34.5 (–44.2 to –24.7) n=43	–31.1 (–38.3 to –23.9) n=63	–28.3 (–36.7 to –19.8) n=46	–28.0 (–35.0 to –21.1) n=64

MMRM, mixed-effect model repeated measure; QD, once daily; WPAI, Work Productivity and Activity Impairment.
*Assessed in 70 patients in the placebo group and 65 patients in the upadacitinib group who were employed at baseline.

Supplemental Table 5. Characteristics of the AS Patients With Highest mSASSS Progression

Treatment Arm	Baseline mSASSS	mSASSS Change From Baseline	Sex	Age at Baseline	CRP Elevated at Screening or Baseline (Higher Value)	HLA-B27	Smoker (Current/ Former)	ASAS40 Responder at Week 104
PBO/UPA	34	11	Male	40	No (<2.87 mg/L)	Positive	Current	Yes
PBO/UPA	17.5	11	Male	37	No (2.87 mg/L)	Positive	Current	Yes
PBO/UPA	12.5	10.5	Male	62	Yes (7 mg/L)	Negative	No	No
UPA/UPA	12.7	10	Female	52	Yes (14 mg/L)	Positive	No	Yes
UPA/UPA	38	9	Male	44	Yes (13 mg/L)	Positive	No	NA
UPA/UPA	32	8.5	Male	55	Yes (34 mg/L)	Positive	No	Yes
UPA/UPA	18.5	7.5	Male	38	Yes (89 mg/L)	Positive	Former	Yes
PBO/UPA	21	7	Male	45	Yes (21 mg/L)	Positive	Current	Yes
PBO/UPA	17	6.5	Male	44	Yes (32 mg/L)	Positive	No	No

ASAS, Assessment of SpondyloArthritis international Society; CRP, C-reactive protein; HLA-B27, human leukocyte antigen B27; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; NA, not available; PBO, placebo; UPA, upadacitinib.

Supplemental Table 6. Exposure-Adjusted Event Rate and Exposure-Adjusted Incidence Rate of Anterior Uveitis

	Upadacitinib 15 mg QD N=182 (308.6 PY)
Exposure-adjusted event rate	
Events (E/100 PY) [95% CI]	
With history of uveitis	15 (4.9) [2.7–8.0]
Without history of uveitis	1 (0.3) [0.0–1.8]
Total	16 (5.2) [3.0–8.4]
Exposure-adjusted incidence rate	
n/PY (n/100 PY) [95% CI]	
With history of uveitis	9/299.7 (3.0) [1.4–5.7]
Without history of uveitis	1/308.6 (0.3) [0.0–1.8]
Total	10/299.8 (3.3) [1.6–6.1]

PY; patient years; QD, once daily.

Supplemental Table 7. Grade 3 and 4 Laboratory Parameters

Parameter	Upadacitinib 15 mg QD N=182, n (%)
Creatine phosphokinase[*]	
Grade 3 (>5–10 ULN)	4 (2.2)
Grade 4 (>10 ULN)[†]	5 (2.7)
Alanine aminotransferase[‡]	
Grade 3 (>5–20 ULN)[†]	2 (1.1)
Grade 4 (>20 ULN)	0
Aspartate aminotransferase[‡]	
Grade 3 (>5–20 ULN)	1 (0.5)
Grade 4 (>20 ULN)[†]	1 (0.5)
Lymphocytes	
Grade 3 (0.2–<0.5 × 10^9/L)	0
Grade 4 (<0.2 × 10^9/L)	0
Neutrophils	
Grade 3 (0.5–<1.0 × 10^9/L)	3 (1.6)
Grade 4 (<0.5 × 10^9/L)	0
Hemoglobin	
Grade 3 (<80 g/L)	0

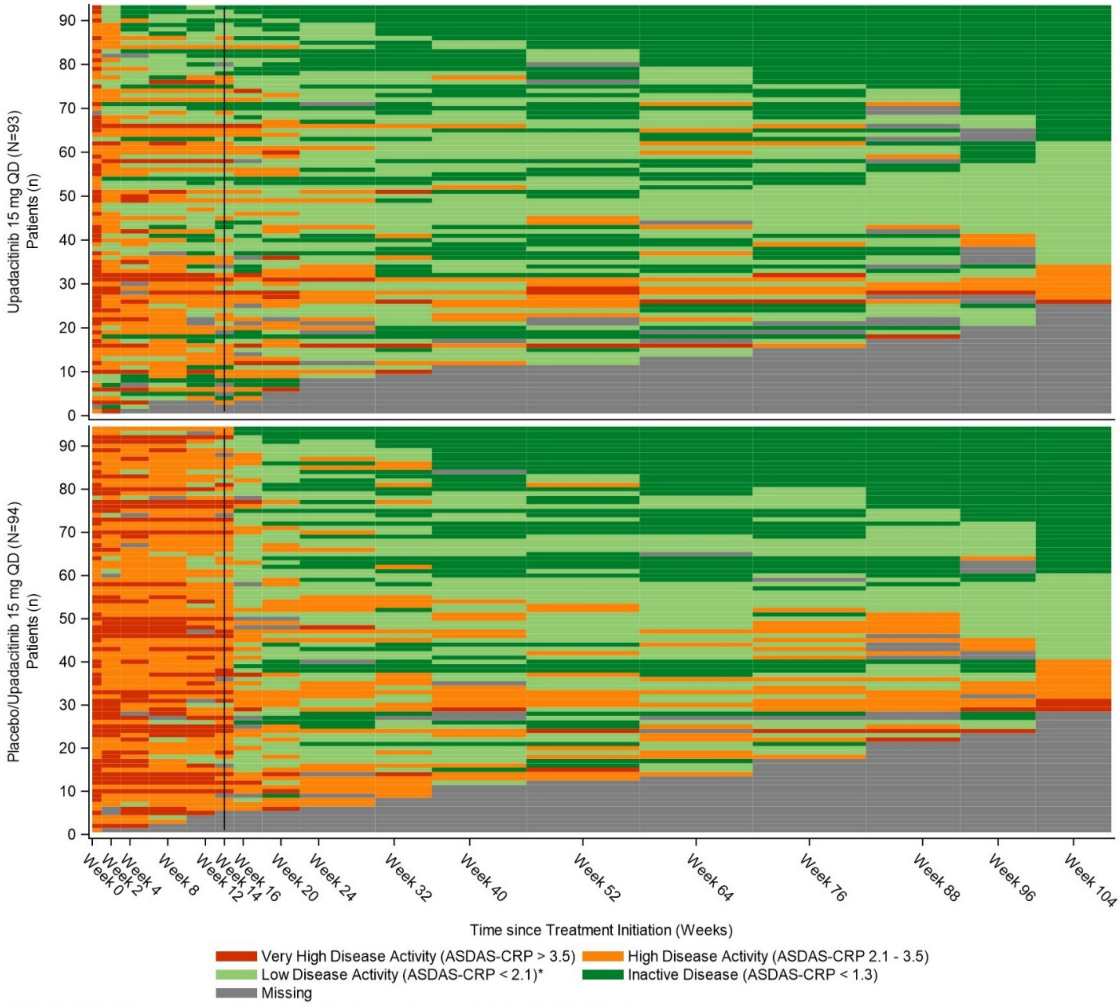
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase elevation; QD, once daily; ULN, upper limit of normal.

[*]Occurred in young male patients; none led to study drug discontinuation, none met toxicity criteria threshold (none confirmed ≥4 × ULN), and 5 were transient and normalized, including the 2 grade 4 increases.

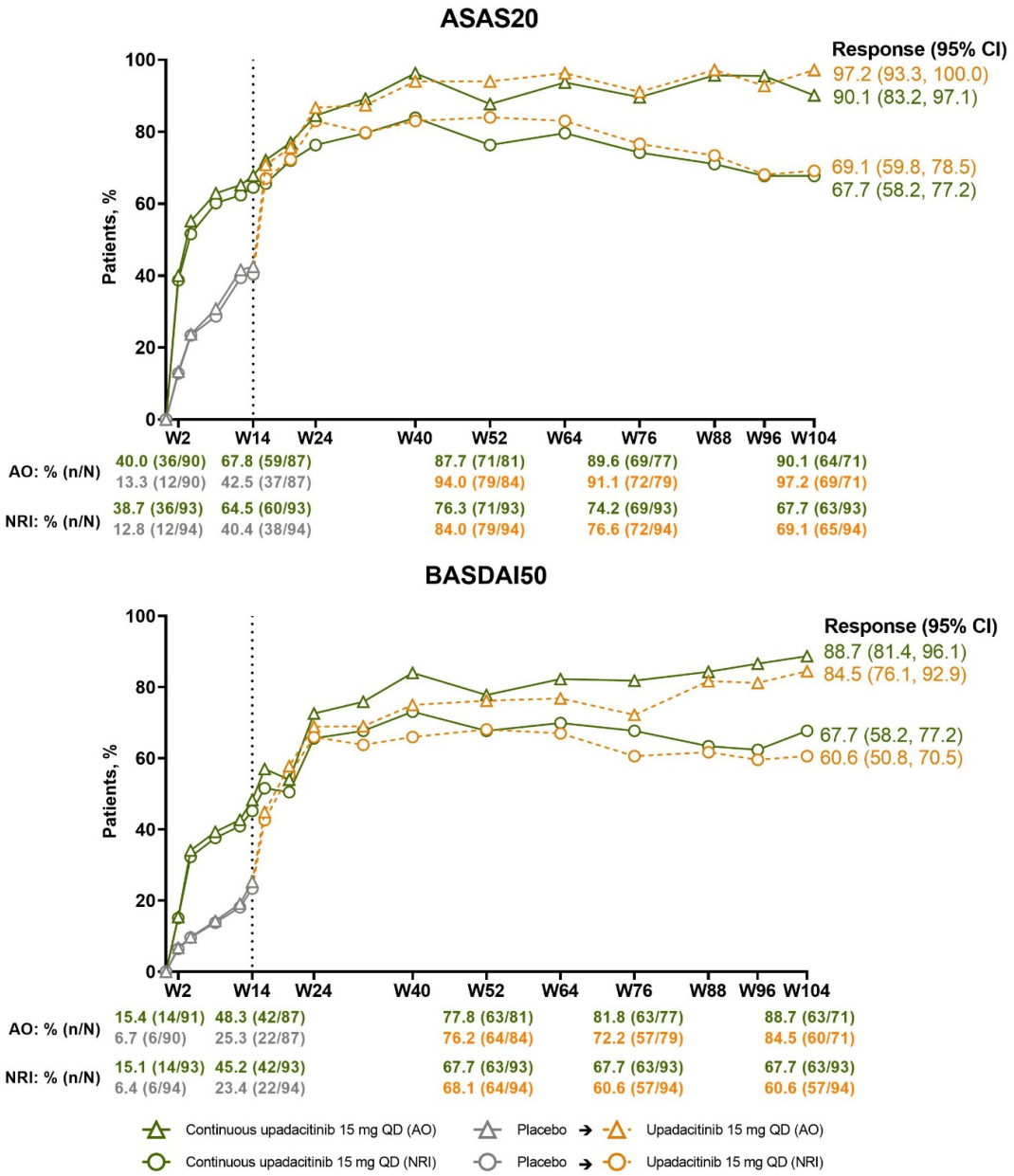
[†]A 28-year-old White male patient had a grade 4 (≥20 × ULN) AST elevation along with a grade 3 ALT elevation, which represents a case that met biochemical criteria for Hy's Law but was not judged to be a Hy's Law case because the elevated aminotransferases were associated with a concurrent grade 4 CPK elevation triggered by intense exercise (weight lifting). There were no signs/symptoms of a hepatic injury, and an alternative etiology of Gilbert syndrome (diagnosed more than 4 months prior to the occurrence of the grade 4 AST and CPK elevations) was identified for the mildly persistent predominantly unconjugated bilirubin elevations. The CPK increase led to hospitalization, and study drug was interrupted. The patient who had onset of muscle pain 3 d prior to hospitalization was free of symptoms and had normal renal function during and after hospitalization. Exercise was stopped and study drug could be resumed, and during continued treatment with study drug, ALT, AST, and CPK values normalized and remained stable.

[‡]ALT normalized after interruption of study drug; study drug was continued.

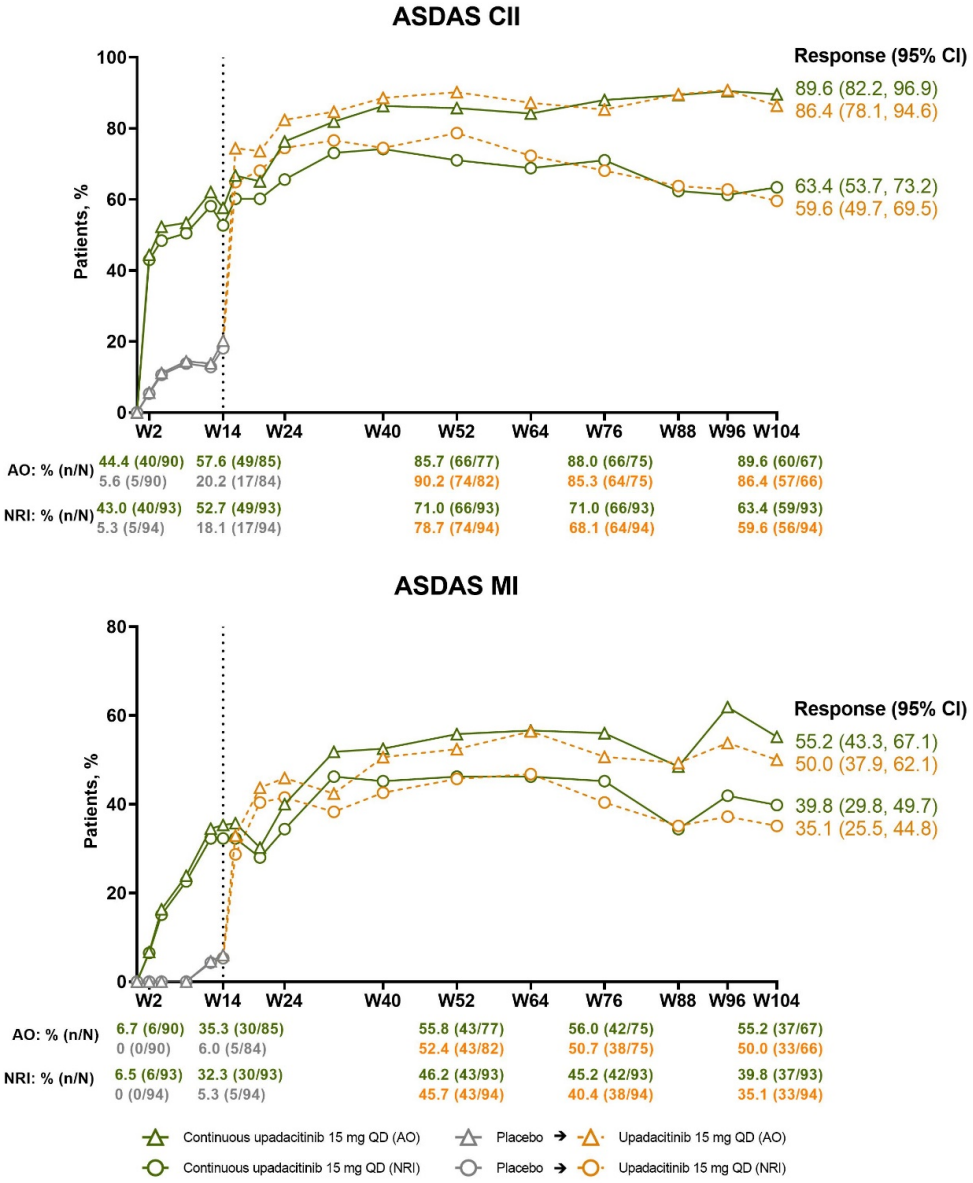
Supplemental Figure 1. ASDAS Response Statuses Over Time. ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score based on C-reactive protein; QD, once daily.



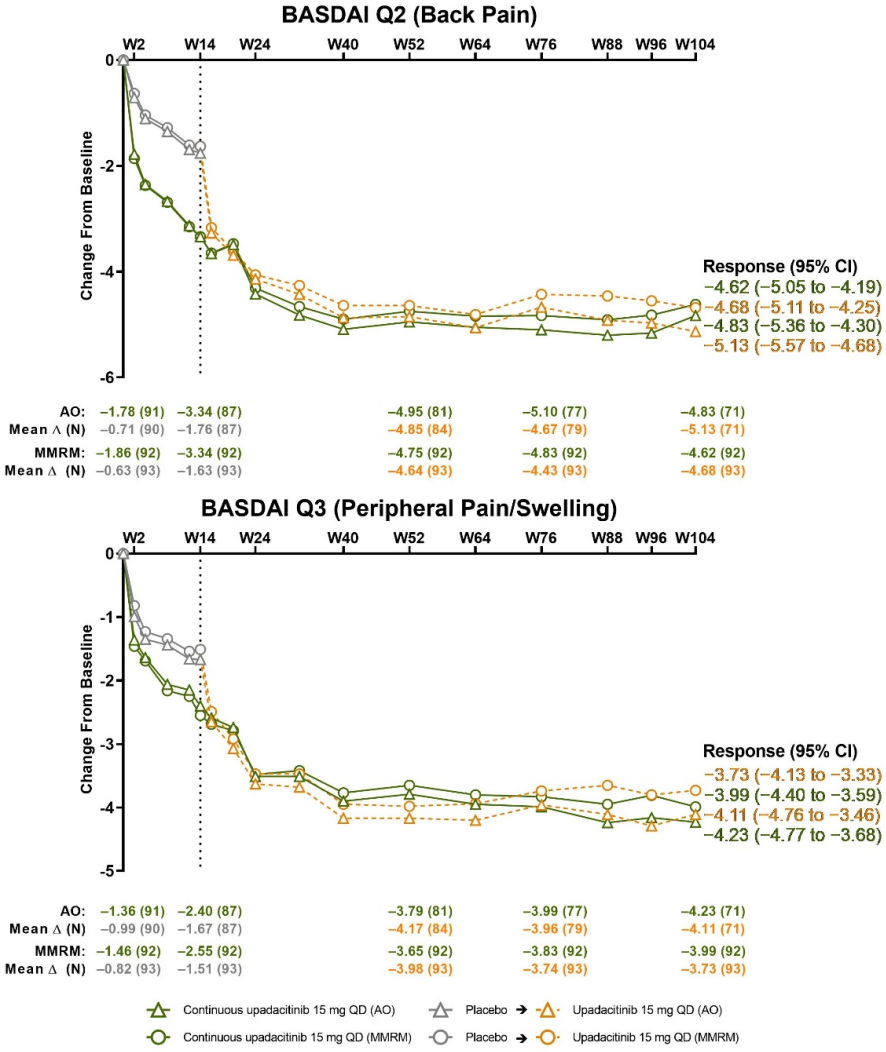
Supplemental Figure 2. **Percentages of Patients Achieving ASAS20 and BASDAI50 Over Time.** Dashed line: all patients randomized to placebo in period 1 who received open-label upadacitinib starting from week 14. Descriptive statistics are provided. AO, as observed; ASAS, Assessment of SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; NRI, non-responder imputation; QD, once daily; W, week.



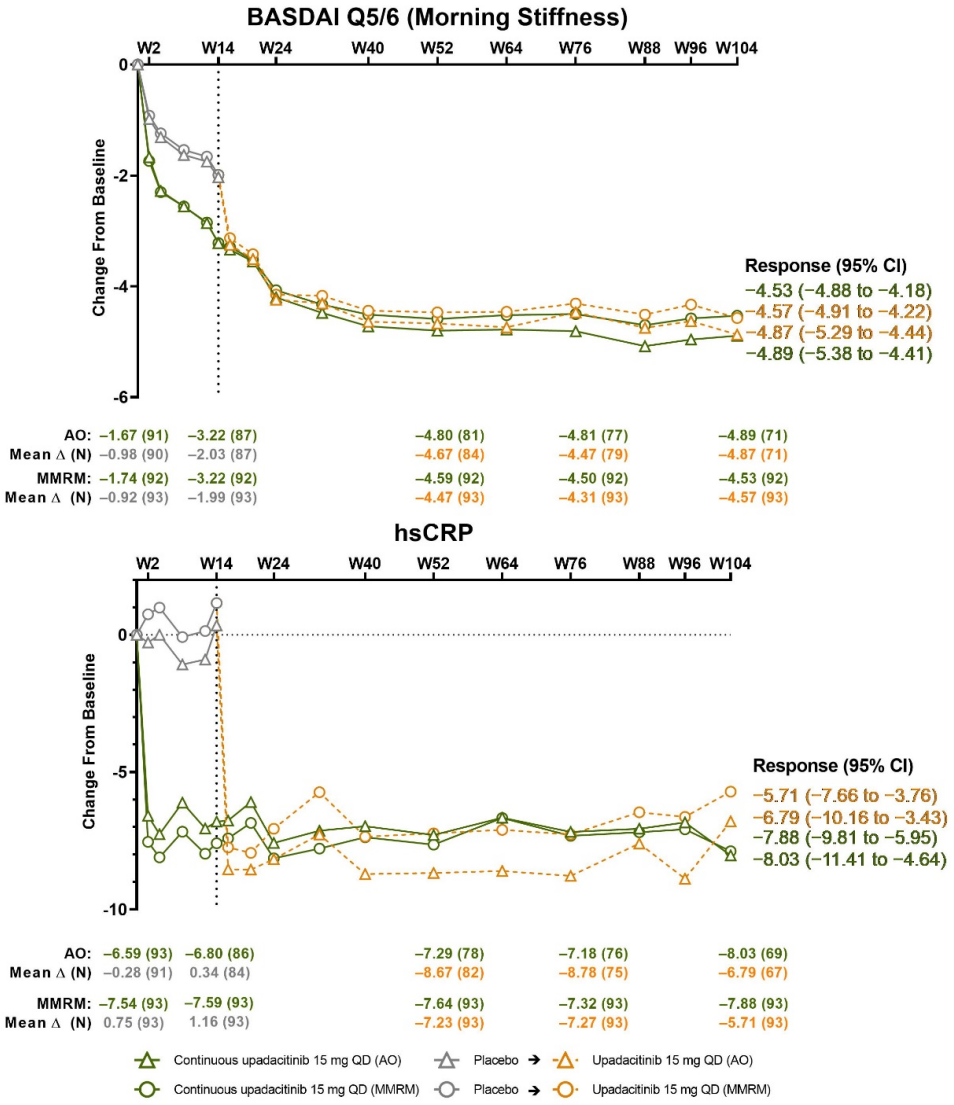
Supplemental Figure 3. Percentages of Patients Achieving ASDAS CII (Decrease From Baseline ≥1.1) and ASDAS MI (Decrease From Baseline ≥2.0) Over Time. Dashed line: all patients randomized to placebo in period 1 who received open-label upadacitinib starting from week 14. Descriptive statistics are provided. AO, as observed; ASDAS, Ankylosing Spondylitis Disease Activity Score; CII, clinically important improvement; MI, major improvement; NRI, non-responder imputation; QD, once daily; W, week.



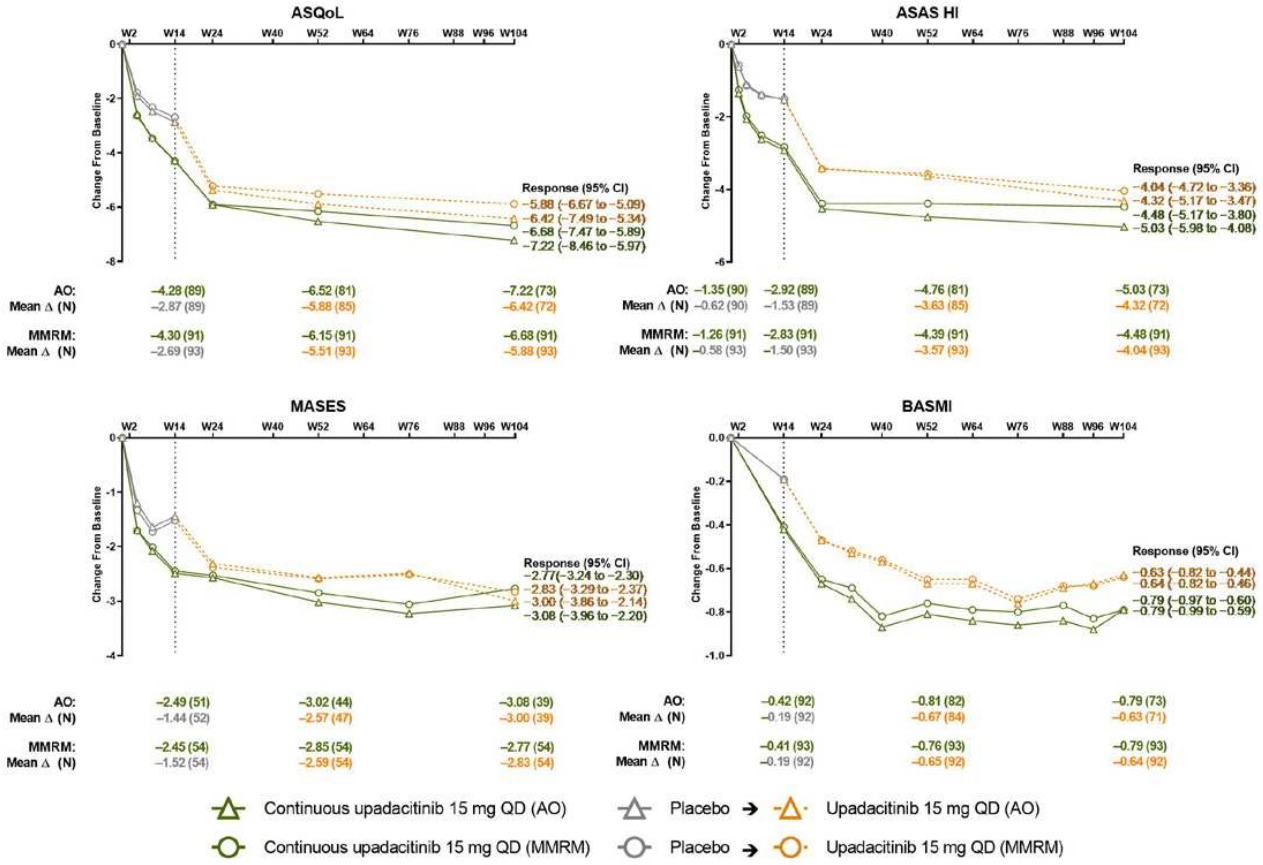
Supplemental Figure 4. Changes From Baseline in BASDAI Q2 (Back Pain) and BASDAI Q3 (Peripheral Pain/Swelling) Over Time. Dashed line: all patients randomized to placebo in period 1 who received open-label upadacitinib starting from week 14. BASDAI Q2 and Q3 are part of the BASDAI instrument based on the following questions (both referring to the previous week): Q2, "How would you describe the overall level of AS neck, back, or hip pain you have had?" and Q3, "How would you describe the overall level of pain/swelling in joints other than neck, back, or hips you have had?" AO, as observed; AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; MMRM, mixed-effect model repeated measure; Q, question; QD, once daily; W, week.



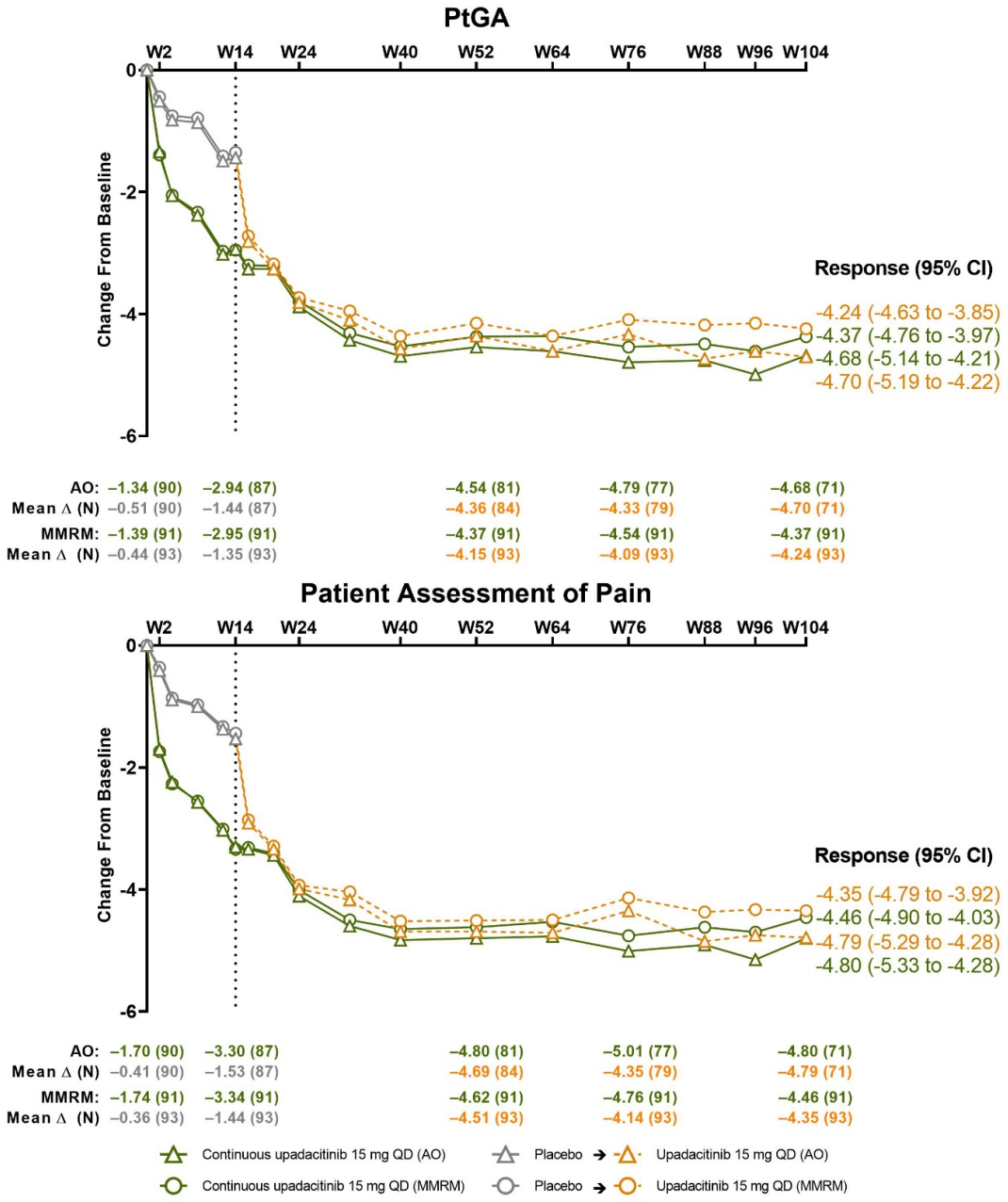
Supplemental Figure 5. Changes From Baseline in BASDAI Q5/6 (Morning Stiffness) and hsCRP Over Time. Dashed line: all patients randomized to placebo in period 1 who received open-label upadacitinib starting from week 14. BASDAI Q5/6 is the mean of Q5 and Q6, which are part of the BASDAI instrument (both referring to the previous week): Q5, "How would you describe the overall level of morning stiffness you have had from the time you wake up?" and Q6, "How long does your morning stiffness last from the time you wake up?" AO, as observed; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; hsCRP, high-sensitivity C-reactive protein; MMRM, mixed-effect model repeated measure; Q, question; QD, once daily; W, week.



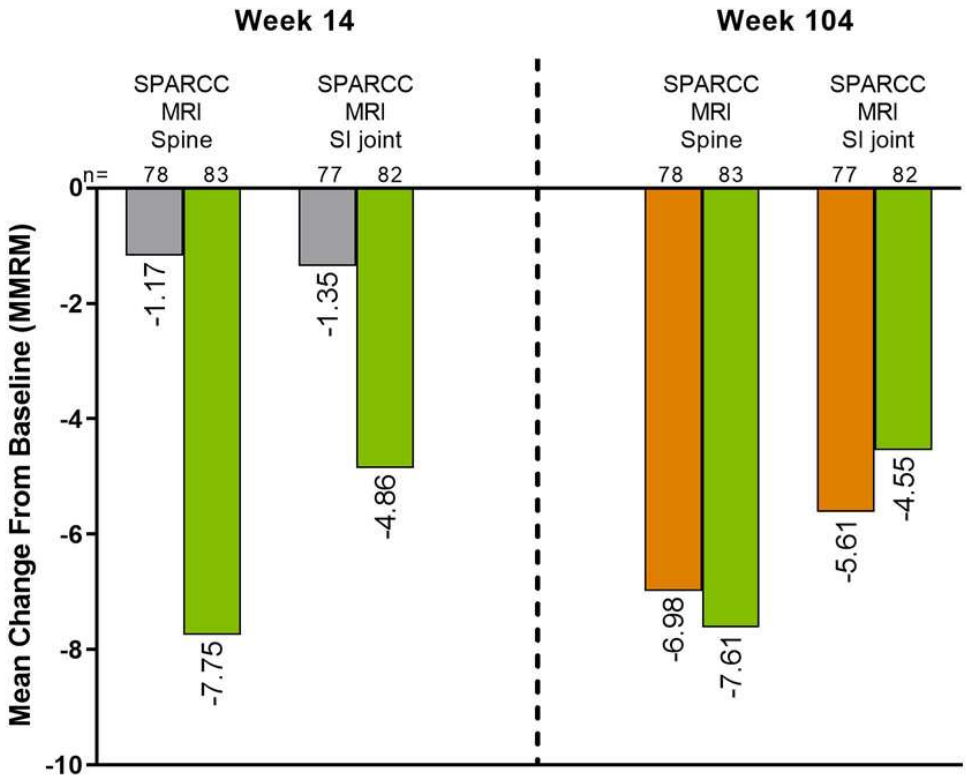
Supplemental Figure 6. Changes From Baseline in ASQoL, ASAS HI, BASMI, and MASES Over Time. Dashed line: all patients randomized to placebo in period 1 who received open-label upadacitinib starting from week 14. AO, as observed; ASAS HI, Assessment of SpondyloArthritis international Society Health Index; ASQoL, AS quality of life; BASMI, Bath Ankylosing Spondylitis Metrology Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MMRM, mixed-effect model repeated measure; QD, once daily; W, week.



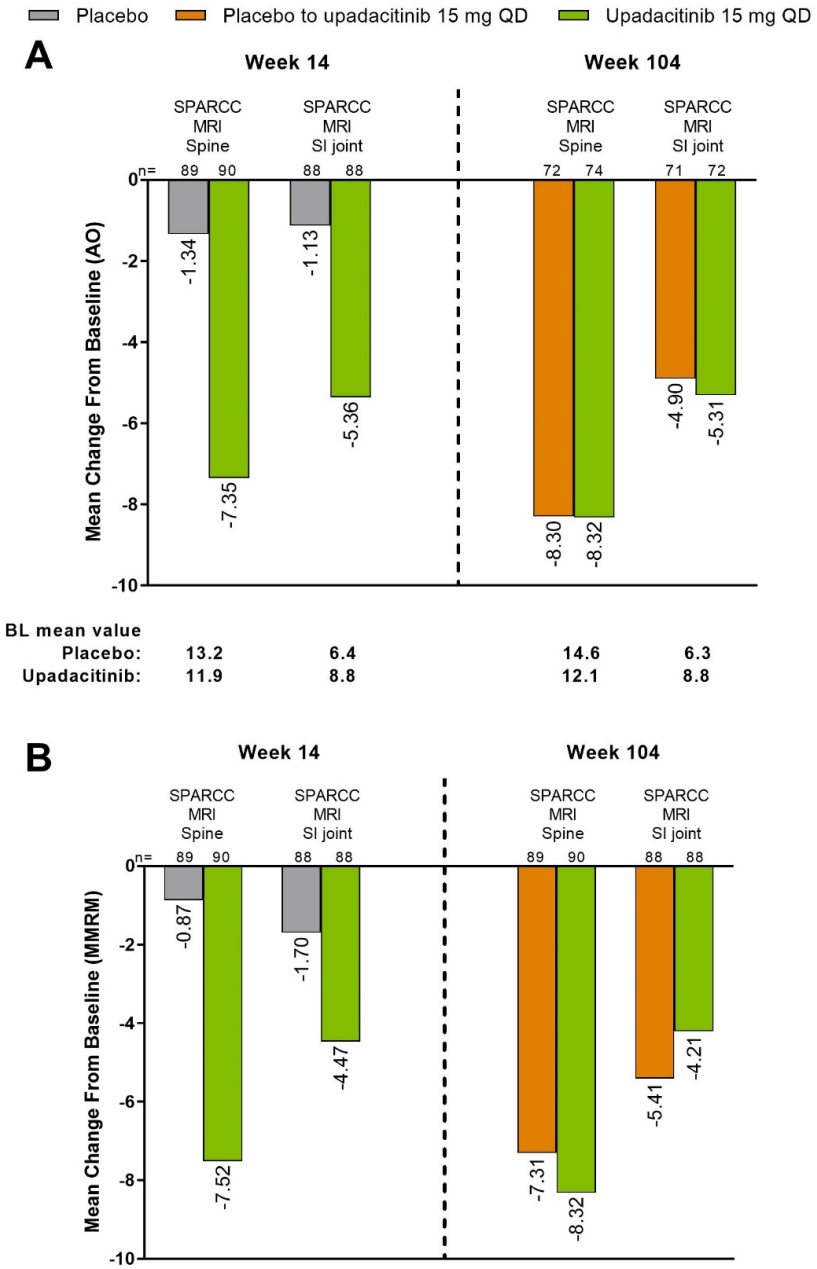
Supplemental Figure 7. Changes From Baseline in PtGA and Patient Assessment of Pain Over Time. Dashed line: all patients randomized to placebo in period 1 who received open-label upadacitinib starting from week 14. AO, as observed; MMRM, mixed-effect model repeated measure; PtGA, Patient Global Assessment of disease activity; QD, once daily; W, week.



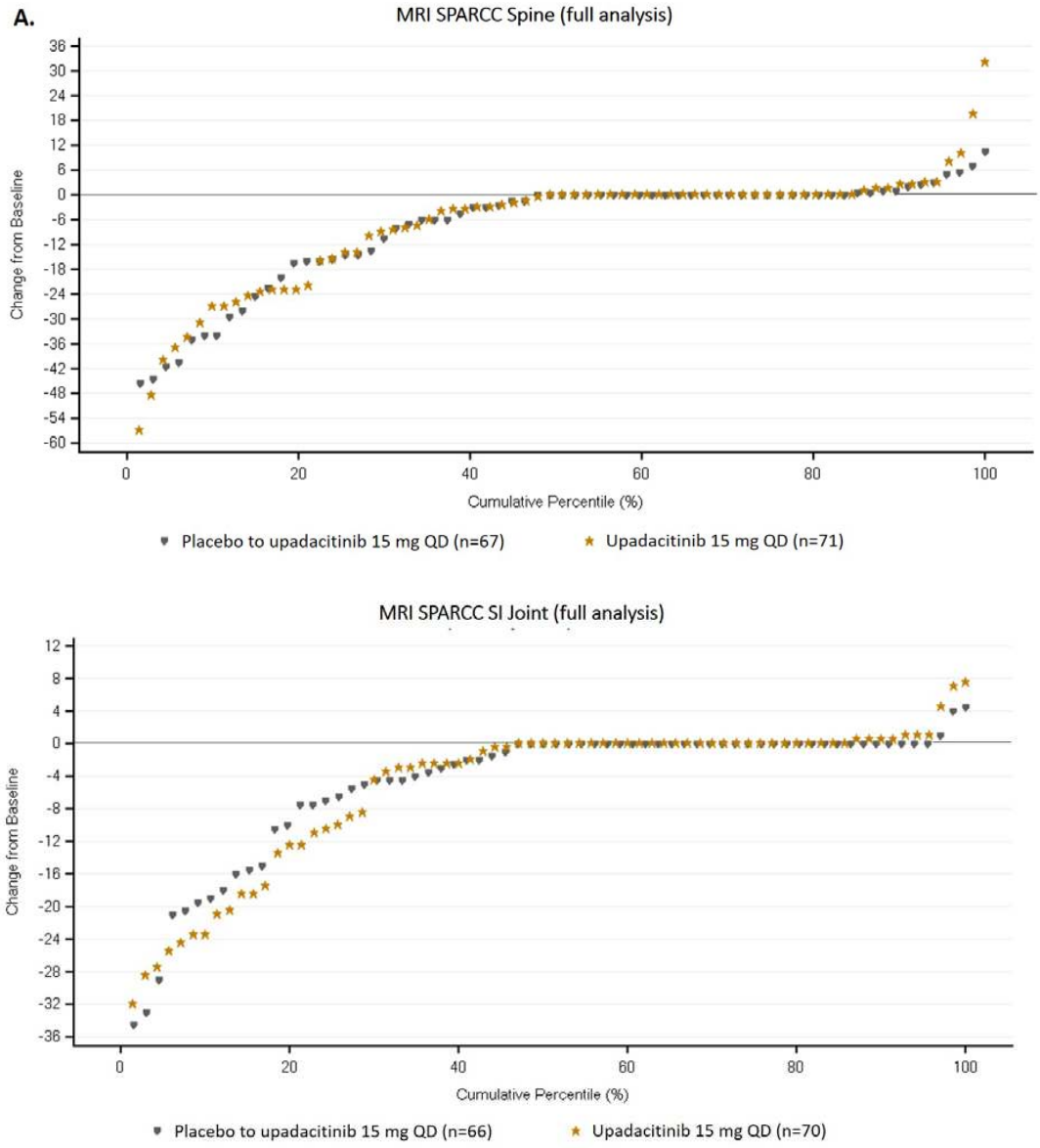
Supplemental Figure 8. Changes from Baseline in SPARCC MRI Spine and SI Joint Inflammation Scores at Weeks 14 and 104 MMRM Analysis. Results are from reading session 2. BL, baseline; MMRM, mixed-effect model repeated measure; MRI, magnetic resonance imaging; SI, sacroiliac; SPARCC, Spondyloarthritis Research Consortium of Canada.



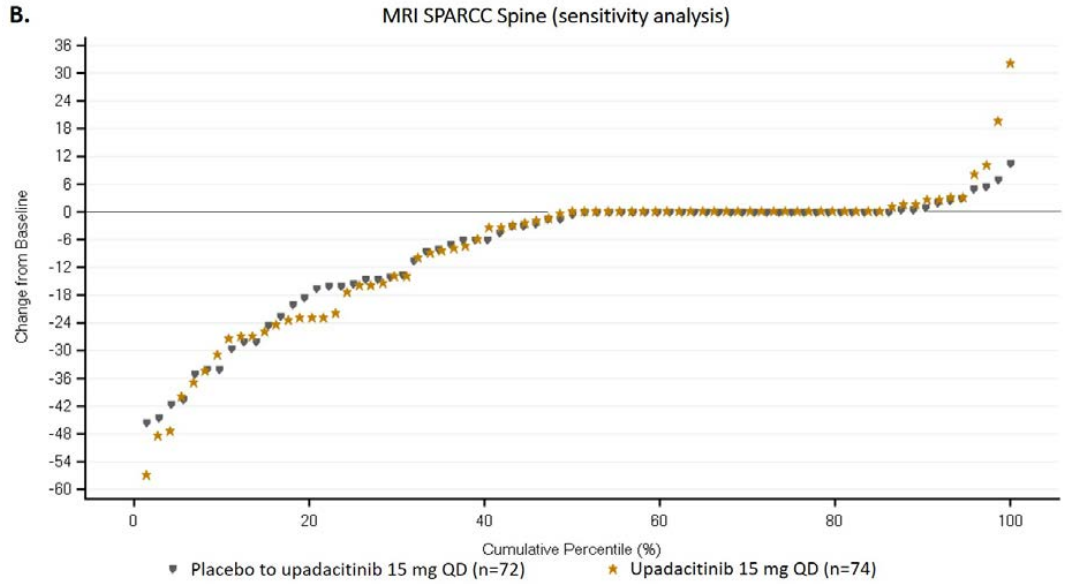
Supplemental Figure 9. Change from Baseline in MRI SPARCC Spine and SI Joint Inflammation Scores at Week 14 and Week 104 (Sensitivity Analyses) AO (A) and MMRM (B). Sensitivity analyses include patients with delayed MRIs. Results are from reading session 2. AO, as observed; BL, baseline; MMRM, mixed-effect model repeated measures; MRI, magnetic resonance imaging; SI, sacroiliac; SPARCC, Spondyloarthritis Research Consortium of Canada.

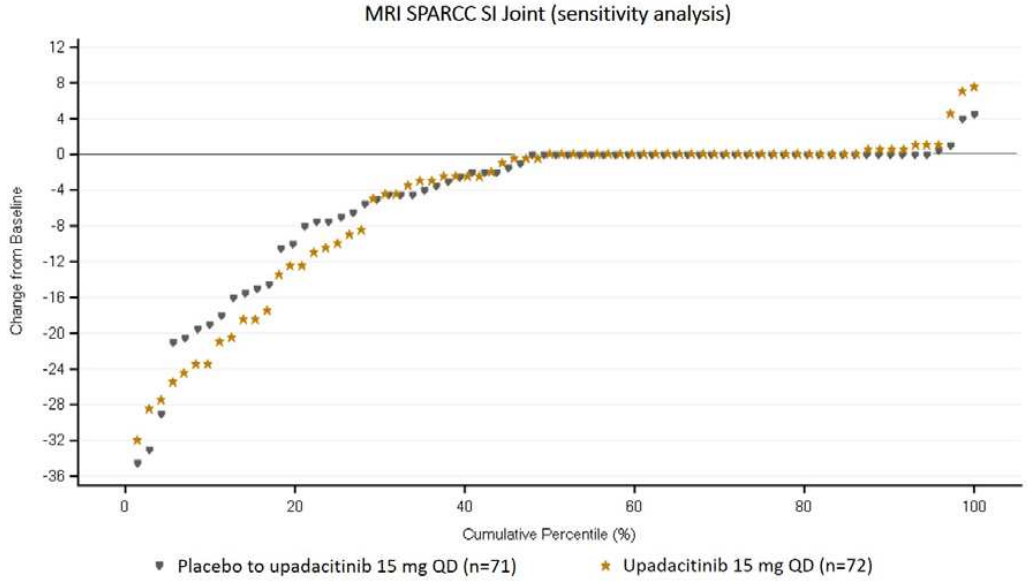


Supplemental Figure 10. Probability Plot of Changes From Baseline in SPARCC MRI Spine and SI Joint Inflammation Scores at Week 104 in Full Analysis Set (A) and Sensitivity Analysis Set (B). Data are from reading session 2. Sensitivity SPARCC MRI analyses (both spine and SI joints) included patients with delayed MRIs conducted outside of the analysis window (analysis window defined as up to 3 days after first dose for baseline reading, –7 days or +3 days for the week 14 MRI, and ±7 days for the week 104 MRI). MRI, magnetic resonance imaging; SI, sacroiliac; SPARCC, Spondyloarthritis Research Consortium of Canada.

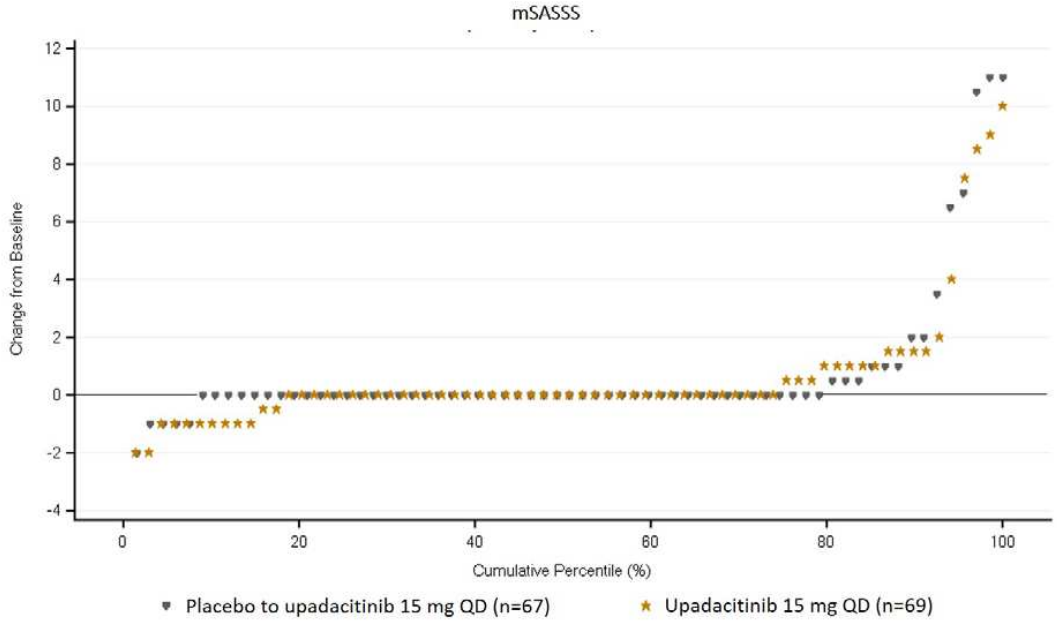


B.


MRI SPARCC Spine (sensitivity analysis)
Change from Baseline
Cumulative Percentile (%)
Placebo to upadacitinib 15 mg QD (n=72)
Upadacitinib 15 mg QD (n=74)


MRI SPARCC SI Joint (sensitivity analysis)
Change from Baseline
Cumulative Percentile (%)
Placebo to upadacitinib 15 mg QD (n=71)
Upadacitinib 15 mg QD (n=72)

Supplemental Figure 11. Probability Plot of Changes From Baseline in mSASSS at Week 104. mSASSS, modified Stoke Ankylosing Spondylitis Spine Score.



Supplemental Figure 12. Mean Hemoglobin, CPK, Lymphocyte, and Neutrophil Levels Over Time. Dashed line: all patients randomized to placebo in period 1 who received open-label upadacitinib starting from week 14. Of note, the week 104 CPK value for the patient with Gilbert syndrome who experienced a CPK increase after intense weight lifting (for more details, see footnote of Supplemental Table 5) is not included because that CPK value was an outlier (value of 100 288 U/L; >10 × ULN). After exercise was stopped, CPK and aminotransferase elevations subsequently normalized and remained stable, and study drug was restarted. CPK normalized on day 781 and in subsequent testing. AO, as observed; CPK, creatine phosphokinase; QD, once daily; ULN, upper limit of normal; W, week.