Upadacitinib in patients with psoriatic arthritis and an inadequate response to non-biologic therapy: 56-week data from the Phase 3 SELECT-PsA 1 study

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Section S1 Assessment details

Musculoskeletal outcomes assessed through week 56 included the proportion of patients achieving ≥20%/50%/70% improvement according to the American College of Rheumatology (ACR) criteria (ACR20/50/70 response); Psoriatic Arthritis Response Criteria (PsARC; improvement in two of the four criteria, one of which must be TJC68 or SJC66, without worsening in any measure: ≥30% improvement in TJC68 or SJC66, and improvement in Patient or Physician's Global Assessment of Disease Activity [range 0–10, higher scores indicating greater disease activity]); no radiographic progression (change from baseline in modified total Sharp/van der Heijde Score [mTSS] ≤0 or mTSS ≤0.5), resolution of enthesitis (Leeds Enthesitis Index [LEI]=0) for patients with baseline LEI >0, resolution of dactylitis (Leeds Dactylitis Index [LDI]=0) for patients with baseline LDI >0; minimal disease activity (MDA) (patient fulfilling five of the seven MDA criteria), changes from baseline in individual components of ACR response, mTSS (range 0–528, higher scores indicating greater damage), and in Disease Activity in Psoriatic Arthritis (DAPSA); and for patients with psoriatic spondylitis at baseline, as assessed by the investigator, change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS). Skin outcomes through week 56 included: proportion of patients achieving ≥75%/90%/100% improvement in Psoriasis Area Severity Index (PASI75/90/100 response) for patients with psoriasis affecting ≥3% of body surface area at baseline, Static Investigator Global Assessment of Psoriasis of 0 or 1 (sIGA 0/1), and at least a 2-point improvement from baseline for patients with baseline sIGA ≥2 (range 0–4, higher scores indicating severe skin involvement), and change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire (range 0–110, higher scores indicating more severe psoriasis symptoms). Patient-reported endpoints assessed through week 56 included change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI; range 0–3, higher scores indicating greater disability), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) total (range 0–52, higher scores indicating less fatigue); Short Form Health Survey

questionnaire (SF-36), Physical Component Summary (PCS) and Mental Component Summary (MCS) scores (norm-based scores were used, higher scores indicating better health-related quality of life); morning stiffness (mean of BASDAI questions 5 and 6, higher scores indicating more severe and longer duration of morning stiffness), Work Productivity and Activity Impairment (WPAI) Overall Work Impairment (range 0–100; higher scores indicating greater impairment) for patients employed at baseline, patient's assessment of pain on a numeric rating scale (range 0–10, higher scores indicating greater pain). The proportion of patients achieving ≥30% and ≥50% reduction in pain, a minimal clinically important difference (MCID) of ≥0.35-point improvement from baseline in HAQ-DI, and a normative HAQ-DI (≤0.25) was also assessed.

Section S2 Summary narratives for deaths

Treatment-emergent deaths are defined as deaths that occurred after the first dose and within 30 days of the last dose of upadacitinib or 70 days after the last dose of adalimumab. Non-treatment emergent deaths are defined as deaths that occurred more than 70 days following the last dose of study drug for patients on adalimumab, and more than 30 days following the last dose of study drug for patients on upadacitinib.

1. One treatment-emergent death was reported with placebo during the 24-week placebo-controlled period in a 58-year-old white male on day 62. The subject was driving and experienced an unspecified emergency which resulted in death. The investigator had no additional information, and a death certificate was not obtained. The investigator reported the death was due to cardiac arrest, however, the death was adjudicated by the Cardiovascular Adjudication Committee as an undetermined cause of death. The patient had confounding risk factors that may have contributed to the fatal event including diabetes, hyperlipidaemia, and hypertension.

2. One non-treatment-emergent death occurred during the study in a 71-year-old white male in the upadacitinib 15 mg group, who died due to metastatic lung cancer. The subject withdrew consent following diagnosis on day 239, and no additional information was provided. The patient died approximately 2 months later. The investigator considered the event to be related to study drug. The subject had a confounding risk factor of history of smoking (1 pack/day for 50 years) that may have contributed to the event. The period of drug exposure does not suggest a temporal relationship between the malignant event and upadacitinib therapy.

3. One non-treatment-emergent death occurred during the study in a 55-year-old male in the upadacitinib 15 mg group with medical history of diabetes mellitus and concomitant use of leflunomide. The patient died due to a lower respiratory tract infection. On day 346, the patient was admitted to the hospital with dry cough, worsening dyspnoea, and oxygen saturation of 60%. He received assisted ventilation. On day 349, the patient died. The site was unable to confirm the presence of COVID-19, and a death certificate was unavailable. The last dose of study drug was recorded on day 309 per the last entry in the patient's available study drug diary; however, the site was unable to obtain further information including an updated diary. The fatal event was captured in the database as non-treatment-emergent; however, the patient had study drug at home and the true last date of study drug administration is unknown, so the fatal event may have occurred less than 30 days after the last dose of study drug. The investigator assessed the lower respiratory tract infection as having a reasonable possibility of being related to study drug.

4. One treatment-emergent death was reported in a 46-year-old female in the upadacitinib 30 mg group with medical history of asthma, body mass index of 48.8, and concomitant use of methotrexate, due to corona-virus infection. The patient experienced corona-virus infection and pneumonia 788 days after switching from placebo to upadacitinib 30 mg. The patient was admitted to the hospital due to fever, sore throat, cough, dyspnoea, and hypoxia. She was diagnosed with

pneumonia, based on computed tomography findings of bilateral infiltrates, and found to be positive for COVID-19 via sputum testing. The patient was intubated and required vasopressor support. She was also treated with acyclovir, azithromycin, hydroxychloroquine, solumedrol, cefepime, tocilizumab, and bronchodilators. During the hospitalisation, the patient also experienced acute renal failure, thought to likely be due to a COVID-19-related embolic event, for which the patient was treated with heparin. The patient did not improve after 15 days of treatment and died. The events of corona-virus infection and pneumonia were considered by the investigator as having a reasonable possibility of being related to study drug.

5. One non-treatment-emergent death occurred during the study in a 46-year-old white female in the upadacitinib 30 mg group, due to an event of interstitial lung disease. On day 191 the patient experienced a serious adverse event of bronchitis with symptoms of fever and cough. Study drugs were discontinued, and she was treated with antibiotics with improvement noted. On day 199, the subject experienced recurrence of fever, lower extremity weakness, and erythematous skin rash on the face and thorax, and was ultimately diagnosed with dermatomyositis and interstitial lung disease based on clinical presentation, muscle oedema suggestive of myositis by magnetic resonance imaging, elevated creatine phosphokinase (CPK) (5,537 U/L), and bilateral lung infiltrates on computed tomography with evaluation for infection negative, including cultures of blood, sputum, and bronchoalveolar lavage. The patient was treated empirically with antibiotics, antifungals, and corticosteroids with partial improvement in muscle weakness, but persistent CPK elevation, lung infiltrates, shortness of breath, and hypoxaemia. On day 240, the patient received cyclophosphamide, she subsequently required mechanical ventilation due to worsening respiratory status and death occurred on day 243 (52 days after the last dose of study drugs). The cause of death was reported as unspecified interstitial pneumonitis following acute respiratory failure. The

investigator reported the events of acute bronchitis, interstitial lung disease, and dermatomyositis as having a reasonable possibility of being related to study drug.

6. One treatment-emergent death was reported in a 45-year-old male in the adalimumab group. The patient was involved in a car accident and died instantly due to multiple injuries. The cause of death was reported as road traffic accident and multiple injuries, both of which were considered by the investigator as having no reasonable possibility of being related to study drug.

Section S3 Summary narratives for major adverse cardiovascular events

1. One event of non-fatal stroke occurred during the study in a 77-year-old male with upadacitinib 15 mg once daily. The patient is a former smoker of 1.5 pack per day for 25 years with medical history of coronary artery disease, hypertension, diabetes mellitus, and high cholesterol. Study drug was temporarily interrupted, and the events of ischaemic stroke and mitral valve sclerosis were assessed by the investigator as having no reasonable possibility of being related to study drug.
2. One event of non-fatal myocardial infarction occurred during the study in a 54-year-old male with upadacitinib 15 mg once daily. The patient is a former smoker of 1 pack per day for 20 years with medical history of hypertension. There was no change in study drug administration, and the event was assessed by the investigator as having no reasonable possibility of being related to study drug.
3. One event of non-fatal stroke occurred during the study in a 61-year-old male with upadacitinib 15 mg once daily. The patient had a medical history of hypertension and high cholesterol and BMI of 37.9. Temporary interruption of the study drug was initiated, but subsequently the patient discontinued study drug. The event was assessed by the investigator as having a reasonable possibility of being related to study drug.
4. One event of non-fatal myocardial infarction occurred during the study in a 62-year-old male with upadacitinib 30 mg once daily. The patient is a former smoker of 1 pack per day for 10 years with medical history of hyperlipidaemia, sleep disorder, and family history of cardiovascular disease. There was no change in study drug administration, and the event was assessed by the investigator as having no reasonable possibility of being related to study drug.
5. One event of non-fatal myocardial infarction occurred during the study in a 55-year-old male with upadacitinib 30 mg once daily. The patient is a current smoker of 0.25 pack per day for 20 years with medical history of hypertension, hypercholesterolaemia, and incomplete right bundle branch block. Study drug was temporarily interrupted, and the events of coronary artery disease and

myocardial infarction were assessed by the investigator as having no reasonable possibility of being related to study drug.

6. One event of non-fatal myocardial infarction occurred during the study in a 45-year-old male with adalimumab. The patient had a medical history of obesity (BMI 34.4), hyperlipidaemia, family history of cardiovascular disease, and cigarette smoking.
7. One event of non-fatal myocardial infarction occurred during the study in a 56-year-old female with adalimumab. The patient had a medical history of history of hypertension and obesity (BMI 42.3).
8. One event of non-fatal myocardial infarction occurred during the study in a 67-year-old male with adalimumab. The patient had a medical history of hypertension and diabetes.

Section S4 Summary narratives for venous thromboembolic events

1. A 64-year-old female with a history of obesity (BMI 32.5), sedentary, hypertension, family history of VTE, and a former smoker for 33 years developed deep vein thrombosis, pulmonary embolism, and pulmonary hypertension on day 808 of treatment with upadacitinib 15 mg once daily. The event led to the discontinuation of study drug. The investigator assessed the event as having reasonable possibility of being related to study drug.

2. A 59-year-old female with a history of smoking 1 pack per day for 44 years developed pulmonary embolism during hospitalisation for H1N1 on day 213 of treatment with upadacitinib 15 mg once daily. The event led to the discontinuation of study drug. The investigator assessed the event as having reasonable possibility of being related to study drug.

3. A 43-year-old male with a history of hypertension and a smoker (2 packs per day for 8 years) developed deep vein thrombosis on day 240 of treatment with upadacitinib 15 mg once daily. The event led to the discontinuation of study drug. The investigator assessed the event as having reasonable possibility of being related to study drug.

4. A 59-year-old female with a history of smoking 1 pack per day for 43 years developed pulmonary embolism on day 138 of treatment with upadacitinib 30 mg once daily. The event led to the discontinuation of study drug. The investigator assessed the event as having reasonable possibility of being related to study drug.

5. A 66-year-old female with a history of obesity (BMI 39.1); sedentary, and hypertension developed pulmonary embolism on day 138 of treatment with upadacitinib 30 mg once daily. The event led to the discontinuation of study drug. The investigator assessed the event as having reasonable possibility of being related to study drug.

6. A 52-year-old male with a history of hypercholesterolaemia; obesity (BMI 33.3); former smoker 30 packs per day for 35 years developed pulmonary embolism on day 537 of treatment with upadacitinib 30 mg once daily. The event led to the discontinuation of study drug. The investigator assessed the event as having no reasonable possibility of being related to study drug.

7. A 62-year-old male with a history of hypertension; hyperlipidaemia; obesity (BMI 42.3) developed deep vein thrombosis on day 459 of treatment with upadacitinib 30 mg once daily. The event did not lead to the discontinuation of study drug. The investigator assessed the event as having no reasonable possibility of being related to study drug.

8. A 50-year-old male with a history of obesity (BMI 43.1); hypertension; arrhythmia; smoking 1 pack per day for 15 years developed deep vein thrombosis on day 112 of treatment with adalimumab. The event led to the discontinuation of study drug. The investigator assessed the event as having no reasonable possibility of being related to study drug.

9. A 46-year-old female with a history of hypercoagulation; chronic thromboembolism; obesity (BMI 44.9); use of oestrogen containing hormonal contraceptive developed deep vein thrombosis on day 55 of treatment with adalimumab. The event did not lead to the discontinuation of study drug. The investigator assessed the event as having reasonable possibility of being related to study drug.

Table S1 Demographics and characteristics at baseline

Parameter	Placebo N=423	Upadacitinib 15 mg QD N=429	Upadacitinib 30 mg QD N=423	Adalimumab 40 mg EOW N=429
Female, n (%)	211 (49.9)	238 (55.5)	236 (55.8)	222 (51.7)
Age (years)	50.4 ± 12.2	51.6 ± 12.2	49.9 ± 12.4	51.4 ± 12.0
White race, n (%)	377 (89.1)	386 (90.0)	377 (89.1)	375 (87.4)
BMI ≥25 kg/m^2, n (%)	329 (77.8)	342 (79.7)	319 (75.4)	334 (77.9)
Duration since PsA diagnosis (years)	6.2 ± 7.0	6.2 ± 7.4	5.9 ± 6.4	5.9 ± 7.1
Monotherapy, n (%)	76 (18.0)	76 (17.7)	77 (18.2)	82 (19.1)
Any non-biologic DMARD at baseline, n (%)	347 (82.0)	353 (82.3)	346 (81.8)	347 (80.9)
MTX alone	267 (63.1)	279 (65)	268 (63.4)	270 (62.9)
MTX + another non-biologic DMARD	26 (6.1)	20 (4.7)	27 (6.4)	16 (3.7)
Non-biologic DMARD other than MTX	54 (12.8)	54 (12.6)	51 (12.1)	61 (14.2)
Steroid use at baseline, n (%)	70 (16.5)	73 (17.0)	71 (16.8)	72 (16.8)
TJC68	20.0 ± 14.3	20.4 ± 14.7	19.4 ± 13.3	20.1 ± 13.8
SJC66	11.0 ± 8.2	11.6 ± 9.3	10.6 ± 7.1	11.6 ± 8.8
hs-CRP >ULN[a], n (%)	324 (76.6)	324 (75.5)	324 (76.6)	308 (71.8)
HAQ-DI	1.1 ± 0.6	1.2 ± 0.7	1.1 ± 0.6	1.1 ± 0.6
Patient's assessment of pain (NRS 0–10)	6.1 ± 2.1	6.2 ± 2.1	5.9 ± 2.1	6.0 ± 2.1
BSA-psoriasis ≥3%, n (%)	211 (49.9)	214 (49.9)	210 (49.6)	211 (49.2)
PASI (for baseline BSA-psoriasis ≥3%)	11.2 ± 11.4	9. 8 ± 10.0	9.5 ± 8.8	9.4 ± 8.5
BSA-psoriasis ≥0%, n (%)	400 (94.6)	394 (91.8)	397 (93.9)	397 (92.5)
sIGA of psoriasis score, n (%)				

0	24 (5.7)	34 (7.9)	21 (5.0)	34 (7.9)
1	86 (20.3)	73 (17.0)	78 (18.4)	65 (15.2)
2	167 (39.5)	170 (39.6)	173 (40.9)	181 (42.2)
3	119 (28.1)	133 (31.0)	128 (30.3)	132 (30.8)
4	27 (6.4)	19 (4.4)	23 (5.4)	17 (4.0)
Presence of enthesitis (defined as LEI >0), n (%)	241 (57.0)	270 (62.9)	267 (63.1)	265 (61.8)
Presence of dactylitis (defined as LDI >0), n (%)	126 (29.8)	136 (31.7)	127 (30.0)	127 (29.6)

Values are mean ± SD unless noted. [a]ULN >2.87 mg/L.

Permitted concomitant non-biologic DMARDs included: methotrexate, sulfasalazine, leflunomide, apremilast, hydroxychloroquine, bucillamine, and iguratimod.

BSA, body surface area; DMARD, disease-modifying anti-rheumatic drug; EOW, every other week; HAQ-DI, Health Assessment Questionnaire - Disability Index; hs-CRP, high-sensitivity C-reactive protein; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MTX, methotrexate; NRS, numeric rating scale; NSAID, nonsteroidal anti-inflammatory drug; PASI, psoriasis area severity index; PsA, psoriatic arthritis; QD, once daily; SD, standard deviation; ULN, upper limit normal; SD, standard deviation; sIGA, Static Investigator Global Assessment of Psoriasis; SJC, swollen joint count; TJC, tender joint count.

Table S2 Efficacy endpoints at week 56 (as observed)

Endpoint	Placebo → Upadacitinib 15 mg QD		Placebo → Upadacitinib 30 mg QD		Upadacitinib 15 mg QD		Upadacitinib 30 mg QD		Adalimumab 40 mg EOW	
	N	n (%), (95% CI)	N	n (%), (95% CI)	N	n (%), (95% CI)	N	n (%), (95% CI)	N	n (%), (95% CI)
ACR20	177	155 (87.6) (82.7, 92.4)	174	151 (86.8) (81.7, 91.8)	369	317 (85.9) (82.4, 89.5)	359	313 (87.2) (83.7, 90.6)#	356	289 (81.2) (77.1, 85.2)
ACR50	177	114 (64.4) (57.4, 71.5)	175	123 (70.3) (63.5, 77.1)	368	251 (68.2) (63.4, 73.0)*	358	252 (70.4) (65.7, 75.1)#	356	214 (60.1) (55.0, 65.2)
ACR70	178	62 (34.8) (27.8, 41.8)	175	71 (40.6) (33.3, 47.8)	371	170 (45.8) (40.8, 50.9)*	359	181 (50.4) (45.2, 55.6)#	359	131 (36.5) (31.5, 41.5)
PsARC	177	164 (92.7) (88.8, 96.5)	175	164 (93.7) (90.1, 97.3)	369	338 (91.6) (88.8, 94.4)	358	334 (93.3) (90.7, 95.9)#	357	315 (88.2) (84.9, 91.6)
PASI75[a]	88	61 (69.3) (59.7, 79.0)	87	67 (77.0) (68.2, 85.9)	187	143 (76.5) (70.4, 82.6)	183	136 (74.3) (68.0, 80.6)	178	129 (72.5) (65.9, 79.0)
PASI90[a]	88	44 (50.0) (39.6, 60.4)	87	59 (67.8) (58.0, 77.6)	187	108 (57.8) (50.7, 64.8)	183	104 (56.8) (49.7, 64.0)	178	99 (55.6) (48.3, 62.9)
PASI100[a]	88	23 (26.1) (17.0, 35.3)	87	43 (49.4) (38.9, 59.9)	187	74 (39.6) (32.6, 46.6)	183	83 (45.4) (38.1, 52.6)	178	66 (37.1) (30.0, 44.2)
sIGA 0/1	137	52 (38.0) (29.8, 46.1)	126	78 (61.9) (53.4, 70.4)	281	169 (60.1) (54.4, 65.9)	279	173 (62.0) (56.3, 67.7)	283	156 (55.1) (49.3, 60.9)
MDA	178	79 (44.4) (37.1, 51.7)	178	89 (50.0) (42.7, 57.3)	374	205 (54.8) (49.8, 59.9)*	361	200 (55.4) (50.3, 60.5)#	362	171 (47.2) (42.1, 52.4)
Resolution of enthesitis (LEI=0)[b]	102	70 (68.6) (59.6, 77.6)	99	73 (73.7) (65.1, 82.4)	234	176 (75.2) (69.7, 80.7)	226	166 (73.5) (67.7, 79.2)	218	155 (71.1) (65.1, 77.1)
Resolution of dactylitis (LDI=0)[c]	56	50 (89.3) (81.2, 97.4)	50	48 (96.0) (90.6, 100.0)	121	113 (93.4) (89.0, 97.8)	108	104 (96.3) (92.7, 99.9)	110	102 (92.7) (87.9, 97.6)
HAQ-DI (≥0.35)[d]	153	91 (59.5) (51.7, 67.3)	152	101 (66.4) (58.9, 74.0)	326	229 (70.2) (65.3, 75.2)*	311	230 (74.0) (69.1, 78.8)#	324	202 (62.3) (57.1, 67.6)

*p≤0.05, for upadacitinib 15 mg QD versus adalimumab; #p≤0.05, for upadacitinib 30 mg QD versus adalimumab. All p-values are nominal.

[a]For patients with ≥3% body surface area psoriasis at baseline. [b]For patients with baseline LEI >0. [c]For patients with baseline LDI >0. [d]For patients with baseline HAQ-DI ≥0.35.

ACR20/50/70, ≥20%/50%/70% improvement in American College of Rheumatology response criteria; AO, as observed; CI, confidence interval; EOW; every other week; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDI, Leeds Dactylitis Index; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; PASI75/90/100, ≥75%/90%/100% improvement in Psoriasis Area Severity Index; QD, once daily; sIGA 0/1, Static Investigator Global Assessment of Psoriasis of 0 or 1 and at least a 2 point improvement from baseline.

Table S3 Most frequent AEs through week 56 (≥3 events per 100 PY in any group)

MedDRA preferred term, (events/100 PY)	Upadacitinib 15 mg QD, N=617 PY=839.1	Upadacitinib 30 mg QD, N=613 PY=842.8	Adalimumab 40 mg EOW N=429 PY=631.4
Upper respiratory tract infection	124 (14.8)	152 (18.0)	73 (11.6)
Blood CPK increase	100 (11.9)	146 (17.3)	46 (7.3)
Nasopharyngitis	72 (8.6)	84 (10.0)	67 (10.6)
ALT increase	68 (8.1)	65 (7.7)	58 (9.2)
Urinary tract infection	56 (6.7)	79 (9.4)	23 (3.6)
Bronchitis	48 (5.7)	56 (6.6)	18 (2.9)
AST increase	46 (5.5)	54 (6.4)	38 (6.0)
Herpes zoster	29 (3.5)	49 (5.8)	3 (0.5)
Leukopenia	27 (3.2)	34 (4.0)	11 (1.7)
Oral herpes	20 (2.4)	57 (6.8)	17 (2.7)
Neutropenia	18 (2.1)	37 (4.4)	21 (3.3)
Injection site reaction	0	2 (0.2)	24 (3.8)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; EOW, every other week; MedDRA, Medical Dictionary for Regulatory Activities; PY, patient year; QD, once daily.

Table S4 Patients meeting criteria for potentially clinically significant values for laboratory variables up to week 56

Parameter, n/N (%)		Upadacitinib 15 mg QD, N=617	Upadacitinib 30 mg QD, N=613	Adalimumab 40 mg EOW N=429
Haemoglobin (g/dL)	Grade 3 (<80)	1/613 (0.2)	1/611 (0.2)	2/427 (0.5)
Platelets ($\times 10^9$/L)	Grade 3 (25–<50)	0	1/611 (0.2)	0
	Grade 4[a] (<25)	6/613 (1.0)	4/611 (0.7)	3/427 (0.7)
Lymphocytes ($\times 10^9$/L)	Grade 3 (0.2–<0.5)	11/613 (1.8)	25/611 (4.1)	0
	Grade 4[a] (< 0.2)	4/613 (0.7)	3/611 (0.5)	1/426 (0.2)
Neutrophils ($\times 10^9$/L)	Grade 3 (0.5–<1·0)	3/613 (0.5)	14/611 (2.3)	3/426 (0.7)
	Grade 4[a] (<0.5)	4/613 (0.7)	4/611 (0.7)	1/426 (0.2)
ALT (U/L)	Grade 3 (>5.0–20.0 × ULN)	8/613 (1.3)	12/611 (2.0)	9/427 (2.1)
	Grade 4 (>20.0 × ULN)	0	1/611 (0.2)	0
AST (U/L)	Grade 3 (>5.0–20.0 × ULN)	3/613 (0.5)	10/611 (1.6)	3/426 (0.7)
	Grade 4 (>20.0 × ULN)	0	2/611 (0.3)	0
CPK (U/L)	Grade 3 (>5.0 × ULN–10.0 × ULN)	13/613 (2.1)	22/611 (3.6)	4/426 (0.9)
	Grade 4 (>10.0 × ULN)	5/613 (0.8)	13/611 (2.1)	4/426 (0.9)
Creatinine (µMoL/L)	Grade 3 (>3.0–6.0 × ULN or >3.0 × baseline)	0	2/611 (0.3)	0
	Grade 4 (>6.0 × ULN)	0	0	1/427 (0.2)

[a]Post-database lock, all Grade 4 decreases were determined to be due to data entry errors by the site and were not considered potentially clinically significant, with the exception of one grade 4 platelet decrease in the upadacitinib 15 mg group.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; EOW, every other week; QD, once daily; ULN, upper limit of normal.

Figure S1 Patient disposition at week 56

ADA, adalimumab; AE, adverse event; EOW, every other week; QD, once daily; UPA, upadacitinib.

*1 patient did not receive study drug.

Numbers reflect completion on study drug.

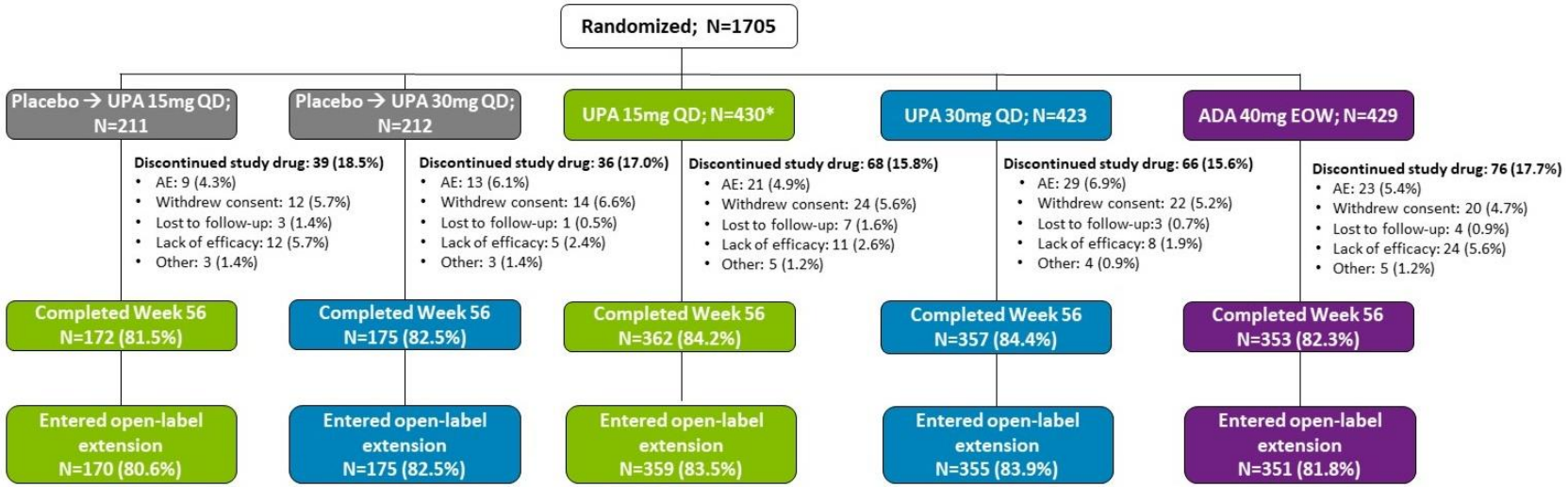
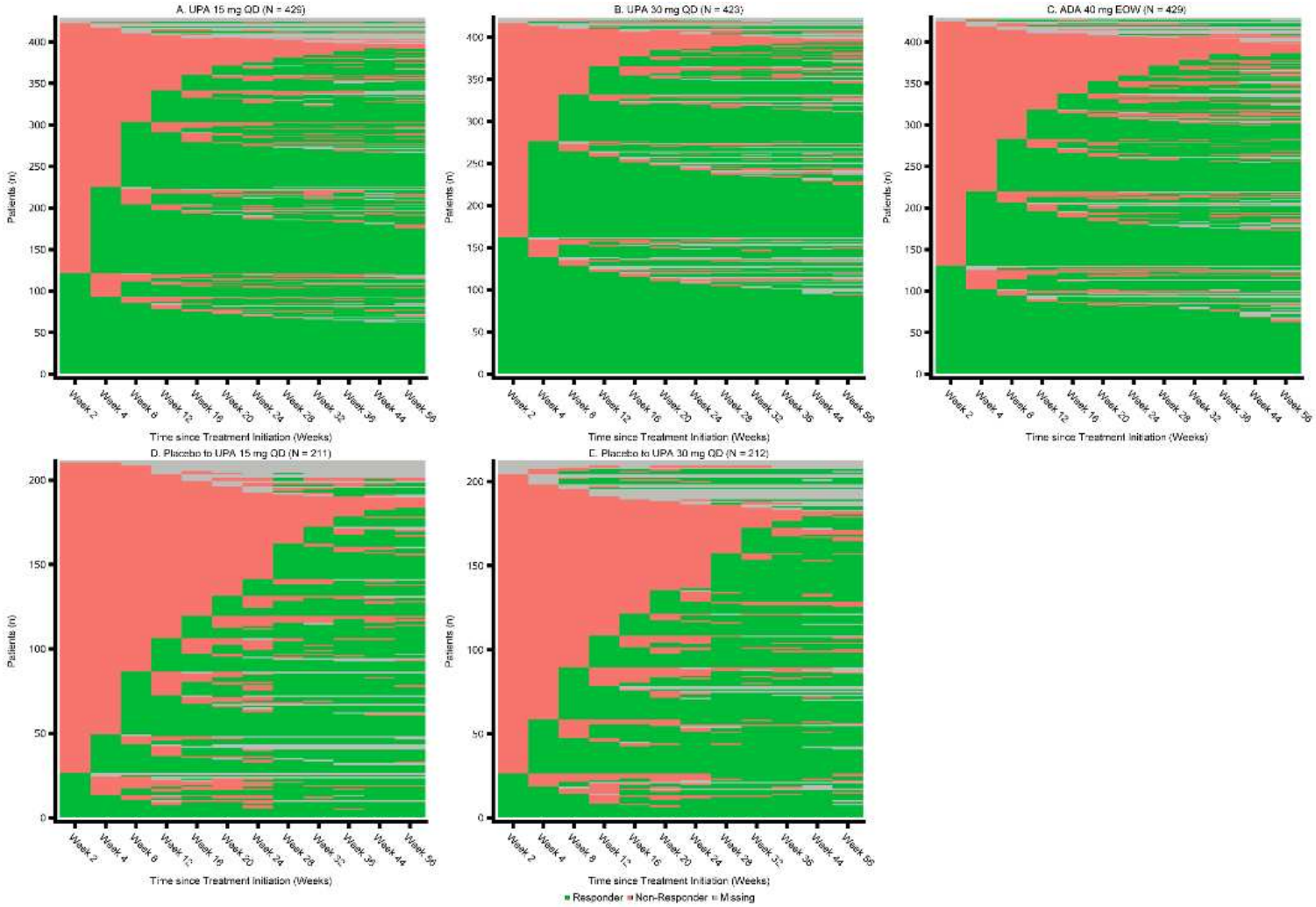


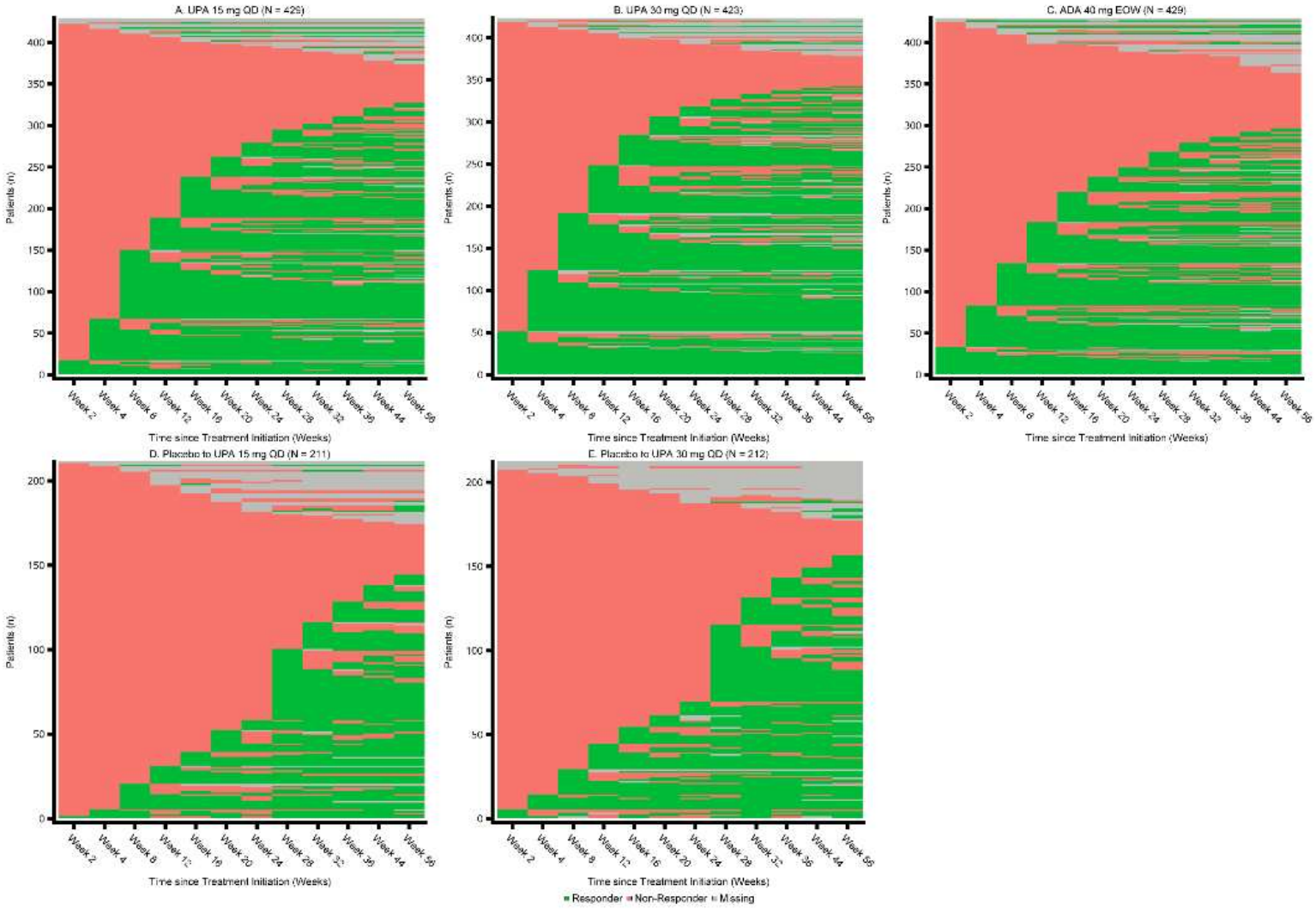
Figure S2 (A) ACR20, (B) ACR50, and (C) ACR70 responses per patient over 56 weeks (as observed)

ACR20/50/70, ≥20%/50%/70% improvement in American College of Rheumatology response criteria; ADA, adalimumab; EOW; every other week; QD, once daily; UPA, upadacitinib.

A.


A. UPA 15 mg QD (N = 429)
B. UPA 30 mg QD (N = 423)
C. ADA 40 mg EOW (N = 429)
D. Placebo to UPA 15 mg QD (N = 211)
E. Placebo to UPA 30 mg QD (N = 212)
Patients (n)
Time since Treatment Initiation (Weeks)
Week 2
Week 4
Week 8
Week 12
Week 16
Week 20
Week 24
Week 28
Week 32
Week 36
Week 44
Week 56
Responder
Non-Responder
Missing

B.


A. UPA 15 mg QD (N = 428)
B. UPA 30 mg QD (N = 423)
C. ADA 40 mg EOW (N = 429)
D. Placebo to UPA 15 mg QD (N = 211)
E. Placebo to UPA 30 mg QD (N = 212)
Patients (n)
Time since Treatment Initiation (Weeks)
Responder
Non-Responder
Missing

C.

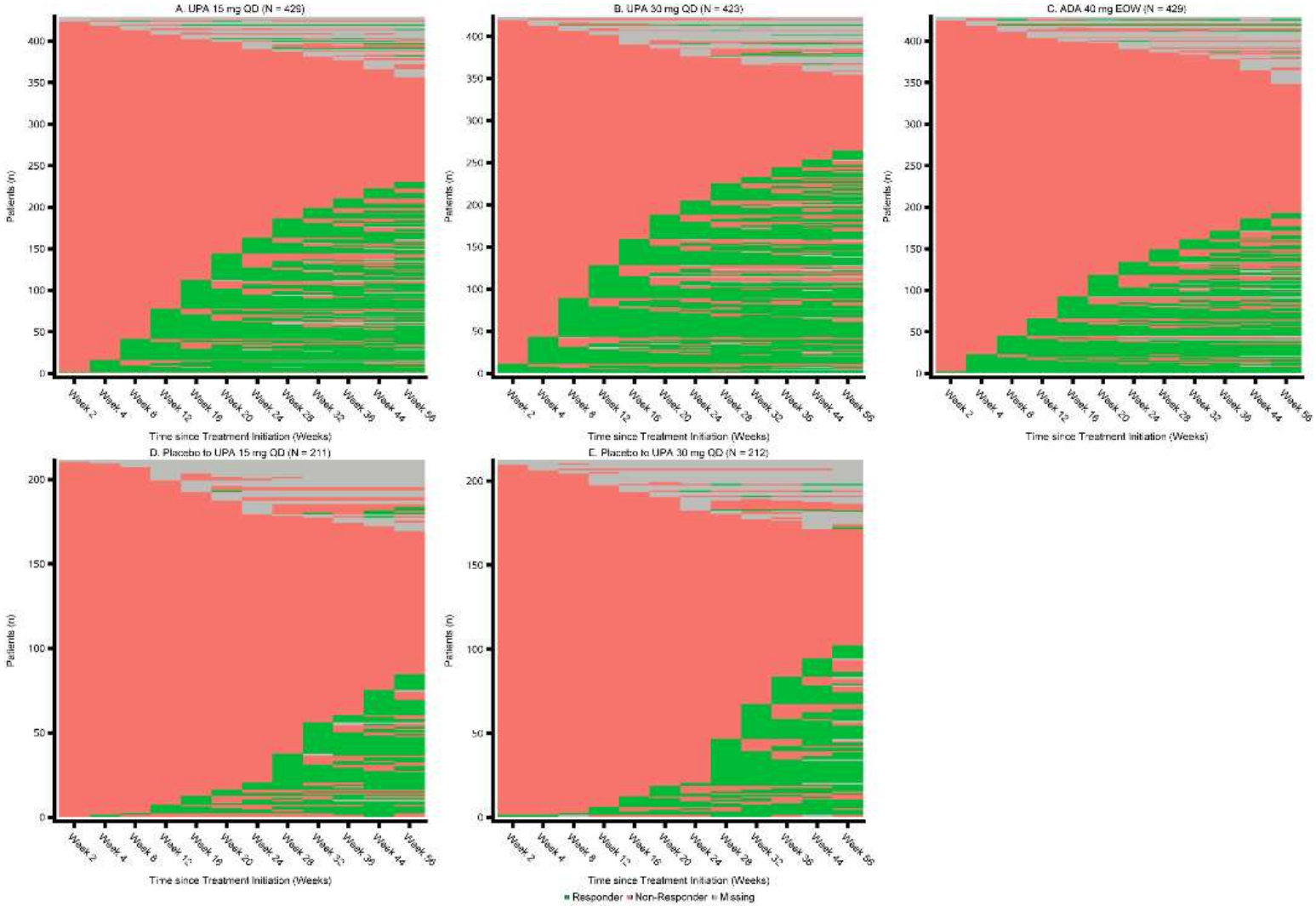

A. UPA 15 mg QD (N = 429)
B. UPA 30 mg QD (N = 423)
C. ADA 40 mg EOW (N = 429)
D. Placebo to UPA 15 mg QD (N = 211)
E. Placebo to UPA 30 mg QD (N = 212)
Patients (n)
Time since Treatment Initiation (Weeks)
Responder
Non-Responder
Missing

Figure S3 Patients achieving PsARC response over 56 weeks (NRI)

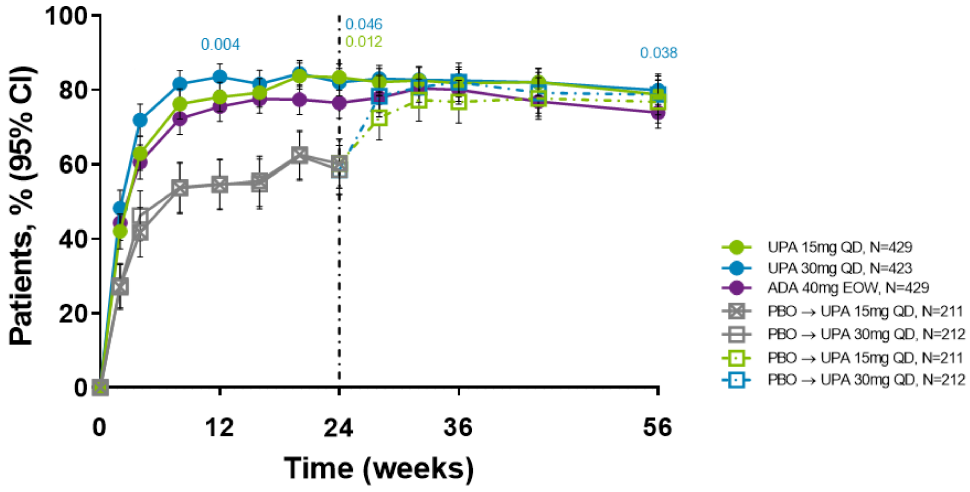
Nominal p-values are for upadacitinib versus adalimumab.

ADA, adalimumab; CI, confidence interval; EOW, every other week; NRI, non-responder imputation; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; UPA, upadacitinib; QD, once daily.

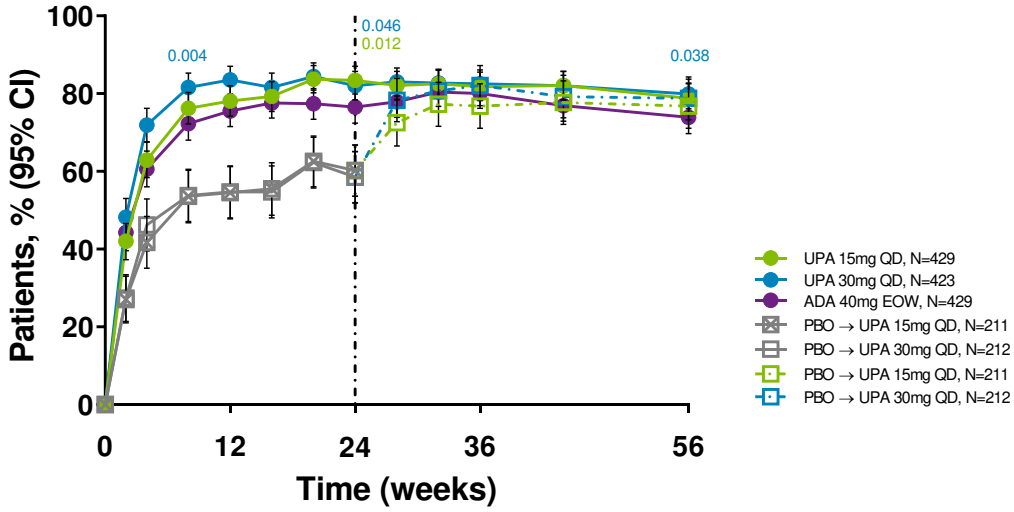
Patients originally randomised to placebo switched to either upadacitinib 15 mg QD or upadacitinib 30 mg QD (1:1) at week 24 and their data up to week 24 are under placebo exposure.

95% CIs for response rate were calculated based on normal approximation to the binominal distribution

Nominal p-value was constructed using Cochran-Mantel-Haenszel test adjusted for the main stratification factor of current DMARD use (yes/no).



	Weeks											
Patients, %	2	4	8	12	16	20	24	28	32	36	44	56
UPA 15mg QD	42.0	62.9	76.2	78.1	79.3	83.7	83.4	82.1	82.5	81.8	82.1	78.8
UPA 30mg QD	48.2	71.9	81.6	83.5	81.6	84.4	82.0	83.0	82.7	82.5	82.0	79.9
ADA 40mg EOW	44.3	60.6	72.3	75.5	77.6	77.4	76.5	77.9	80.4	80.0	76.9	73.9
PBO → UPA 15mg QD	27.0	41.7	53.6	54.5	55.5	62.6	60.2	72.5	77.3	76.8	77.7	76.8
PBO → UPA 30mg QD	27.4	46.2	53.8	54.7	54.7	62.3	58.5	78.3	80.7	82.1	79.2	78.8



	Weeks											
Patients, %	2	4	8	12	16	20	24	28	32	36	44	56
UPA 15mg QD	42.0	62.9	76.2	78.1	79.3	83.7	83.4	82.1	82.5	81.8	82.1	78.8
UPA 30mg QD	48.2	71.9	81.6	83.5	81.6	84.4	82.0	83.0	82.7	82.5	82.0	79.9
ADA 40mg EOW	44.3	60.6	72.3	75.5	77.6	77.4	76.5	77.9	80.4	80.0	76.9	73.9
PBO → UPA 15mg QD	27.0	41.7	53.6	54.5	55.5	62.6	60.2	72.5	77.3	76.8	77.7	76.8
PBO → UPA 30mg QD	27.4	46.2	53.8	54.7	54.7	62.3	58.5	78.3	80.7	82.1	79.2	78.8

Figure S4 (A) Proportion of patients with resolution of enthesis by LEI and (B) proportion of patients with resolution of dactylitis by LDI over 56 weeks (NRI)

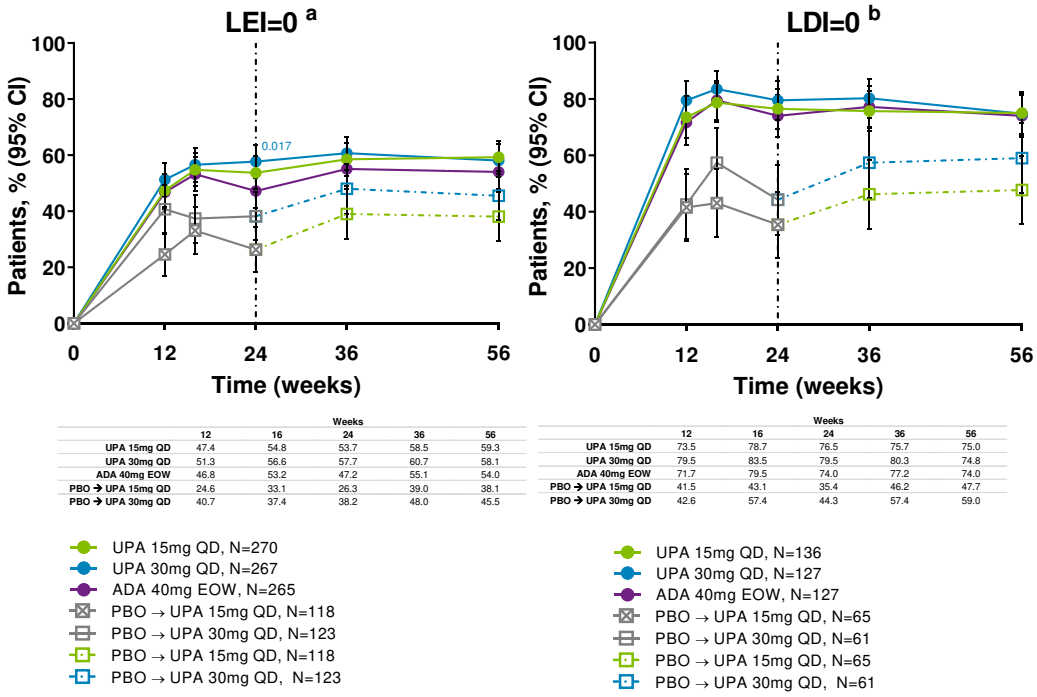
Nominal p-values are for upadacitinib versus adalimumab.

[a]Assessed in patients with LEI >0 at baseline. [b]Assessed in patients with LDI >0 at baseline.

ADA, adalimumab; CI, confidence interval; EOW, every other week; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib; QD, once daily.

Patients originally randomised to placebo switched to either upadacitinib 15 mg QD or upadacitinib 30 mg QD (1:1) at week 24 and their data up to week 24 are under placebo exposure.

Non-responder imputation with additional rescue handling was used, where patients rescued at week 16 are imputed as non-responders. 95% CIs for response rate were calculated based on normal approximation to the binominal distribution. Nominal p-value was constructed using Cochran-Mantel-Haenszel test adjusted for the main stratification factor of current DMARD use (yes/no).



Weeks	12	16	24	36	56
UPA 15mg QD	47.4	54.8	53.7	58.5	59.3
UPA 30mg QD	51.3	56.6	57.7	60.7	58.1
ADA 40mg EOW	46.8	53.2	47.2	55.1	54.0
PBO → UPA 15mg QD	24.6	33.1	26.3	39.0	38.1
PBO → UPA 30mg QD	40.7	37.4	38.2	48.0	45.5

Weeks	12	16	24	36	56
UPA 15mg QD	73.5	78.7	76.5	75.7	75.0
UPA 30mg QD	79.5	83.5	79.5	80.3	74.8
ADA 40mg EOW	71.7	79.5	74.0	77.2	74.0
PBO → UPA 15mg QD	41.5	43.1	35.4	46.2	47.7
PBO → UPA 30mg QD	42.6	57.4	44.3	57.4	59.0

Figure S5 Proportion of patients with no radiographic progression. (A) Change from baseline in mTSS ≤0.0; (B) Change from baseline in mTSS ≤0.5 at week 56 (linear extrapolation)

Nominal p-values are for upadacitinib versus placebo.

ADA, adalimumab; CI, confidence interval; EOW, every other week; JSN, joint space narrowing score; mTSS, modified total Sharp/van der Heijde Score; PBO, placebo; UPA, upadacitinib; QD, once daily.

Patients originally randomised to placebo switched to either upadacitinib 15 mg QD or upadacitinib 30 mg QD (1:1) at week 24 and their data up to week 24 are under placebo exposure.

95% CIs for response rate were calculated based on normal approximation to the binominal distribution. Nominal p-value was constructed using Cochran-Mantel-Haenszel test adjusted for the main stratification factor of current DMARD use (yes/no).

[a]Per study design, all patients in the placebo group were switched to receiving upadacitinib 15 mg QD or upadacitinib 30 mg QD at week 24. All placebo data at week 56 was derived using linear extrapolation.

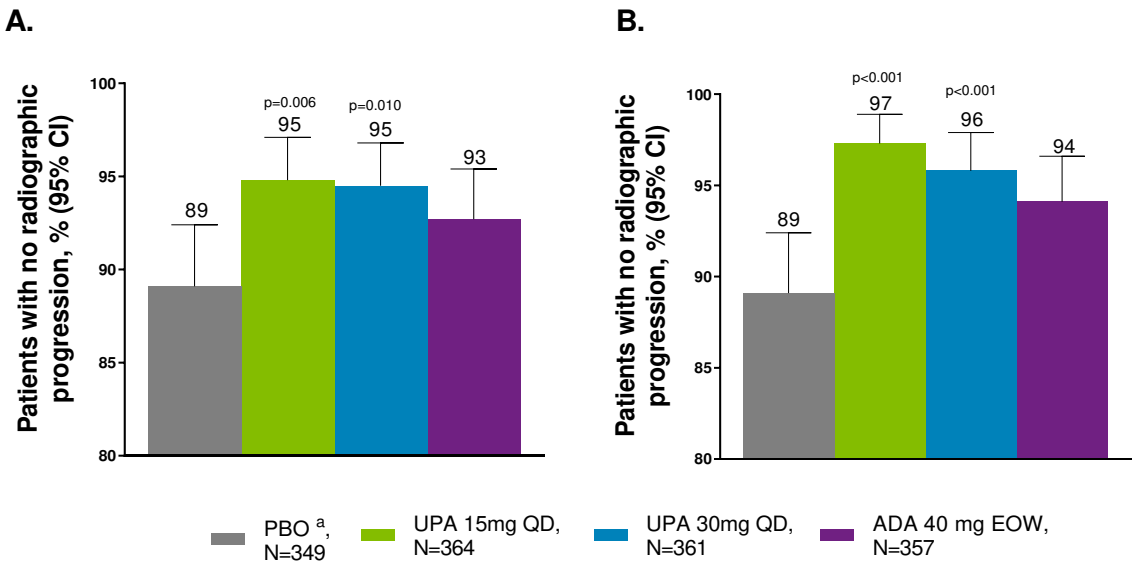


Figure S6 Minimal disease activity response per patient over 56 weeks (as observed)

ADA, adalimumab; EOW, every other week; QD, once daily; UPA, upadacitinib.

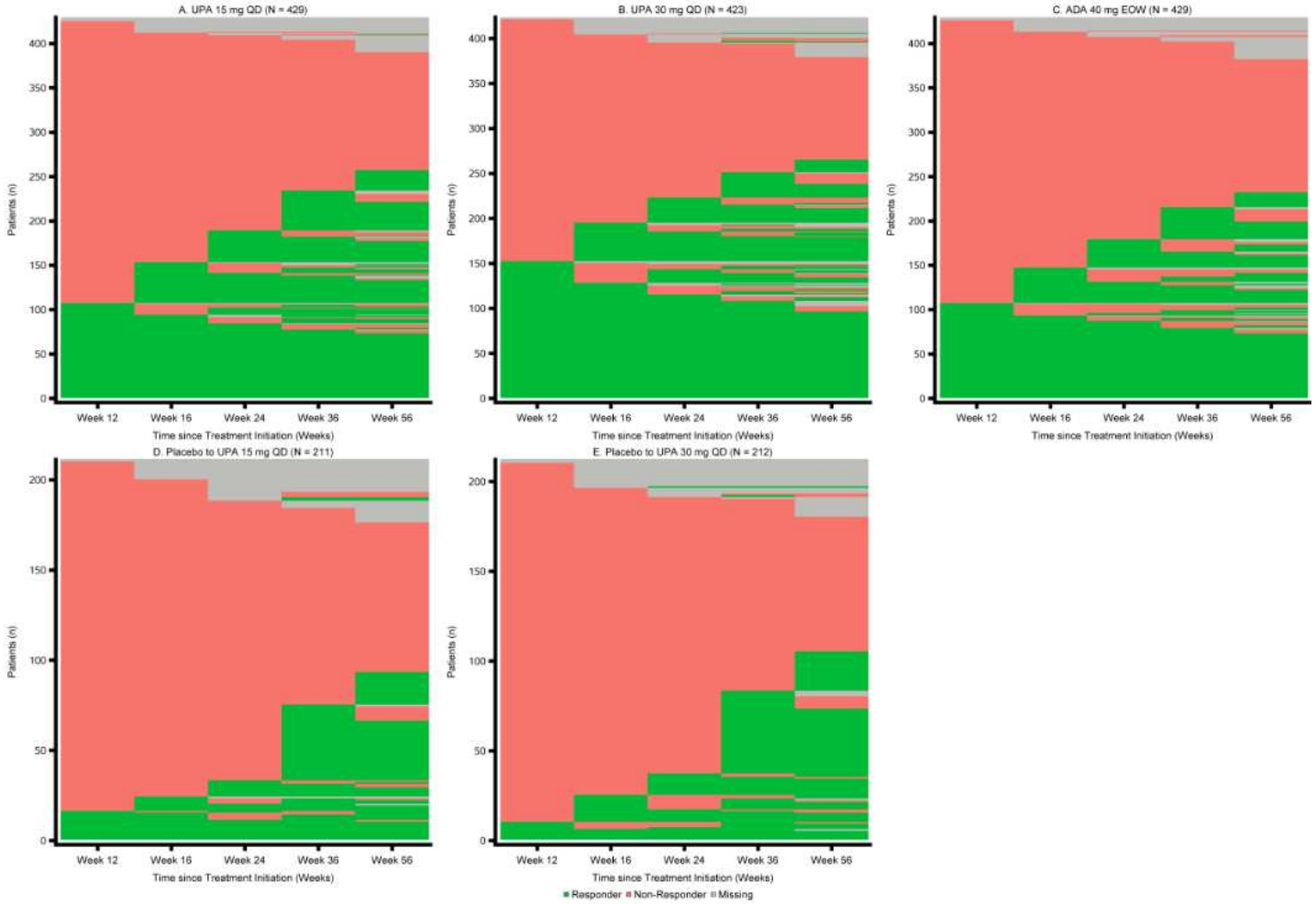
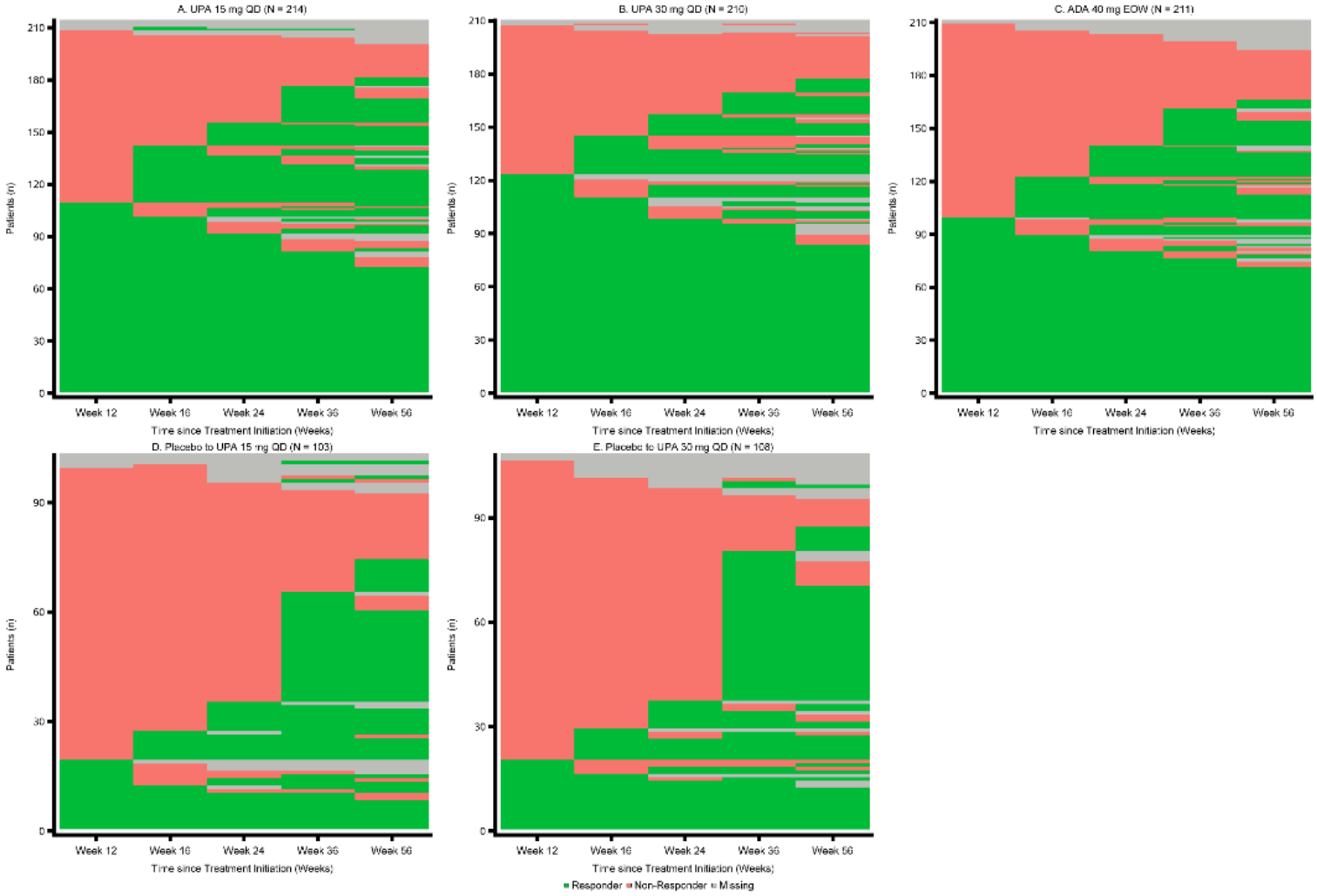


Figure S7 (A) PASI75 and (B) PASI90 responses per patient over 56 weeks (as observed)

ADA, adalimumab; CI, confidence interval; EOW, every other week; PASI75/90, ≥75%/90% improvement in Psoriasis Area Severity Index; QD, once daily; UPA, upadacitinib.

A.


A. UPA 15 mg QD (N = 214)
B. UPA 30 mg QD (N = 210)
C. ADA 40 mg EOW (N = 211)
D. Placebo to UPA 15 mg QD (N = 103)
E. Placebo to UPA 30 mg QD (N = 108)
Patients (n)
Time since Treatment Initiation (Weeks)
Week 12
Week 16
Week 24
Week 36
Week 56
Responder
Non-Responder
Missing

B.

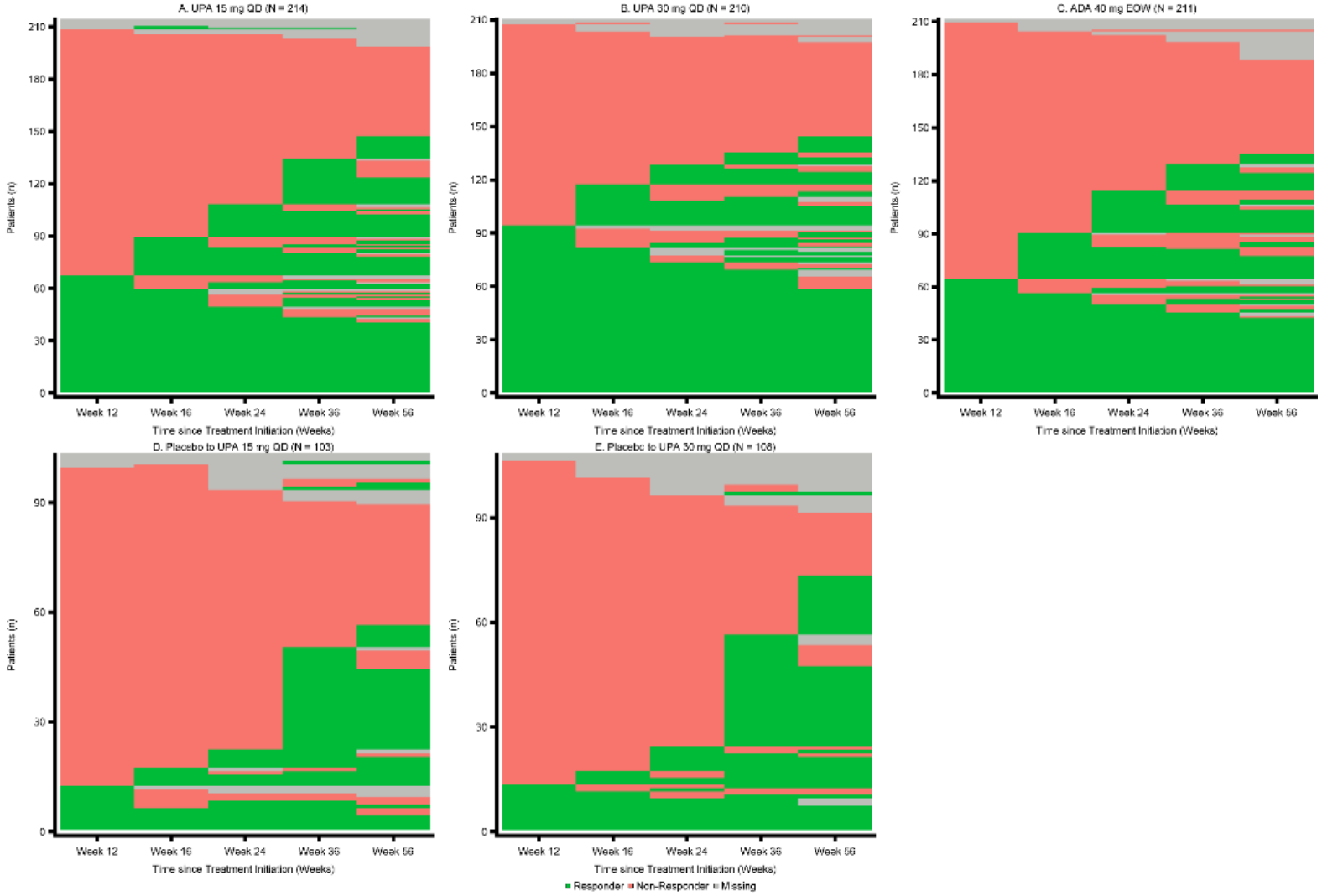

A. UPA 15 mg QD (N = 214)
B. UPA 30 mg QD (N = 210)
C. ADA 40 mg EOW (N = 211)
D. Placebo to UPA 15 mg QD (N = 103)
E. Placebo to UPA 30 mg QD (N = 108)
Patients (n)
Week 12
Week 16
Week 24
Week 36
Week 56
Time since Treatment Initiation (Weeks)
Responder
Non-Responder
Missing

Figure S8 (A) Proportion of patients with ≥30% reduction in pain and (B) proportion of patients with ≥50% reduction in pain (NRI)

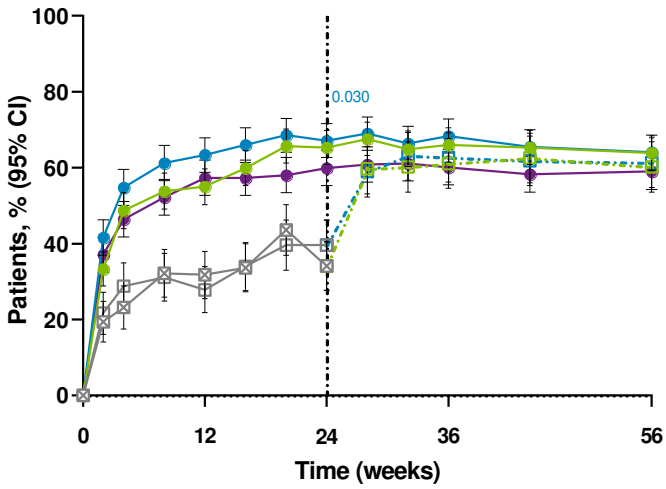
Nominal p-values are for upadacitinib versus adalimumab.

ADA, adalimumab; CI, confidence interval; EOW, every other week; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib; QD, once daily.

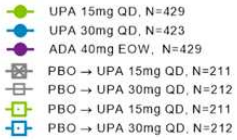
Patients originally randomised to placebo switched to either upadacitinib 15 mg QD or upadacitinib 30 mg QD (1:1) at week 24 and their data up to week 24 are under placebo exposure.

Non-responder imputation with additional rescue handling was used, where patients rescued at week 16 are imputed as non-responders. 95% CIs for response rate were calculated based on normal approximation to the binominal distribution.

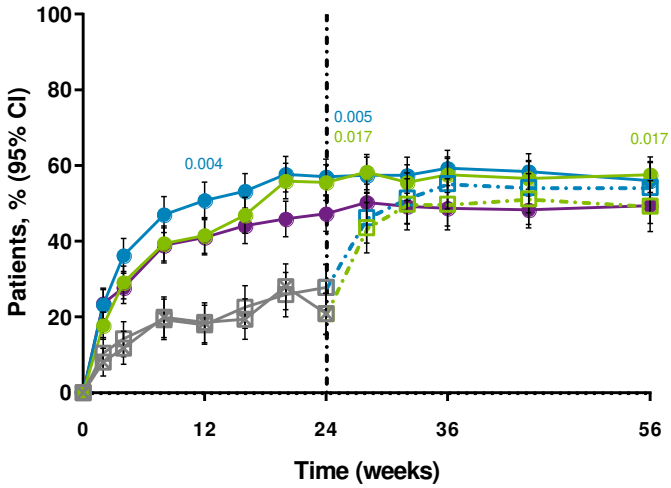
A.



Weeks												
Patients, %	2	4	8	12	16	20	24	28	32	36	44	56
UPA 15mg QD	33.3	48.7	53.8	55.0	59.9	65.7	65.3	67.6	64.8	66.0	65.3	63.9
UPA 30mg QD	41.6	54.8	61.2	63.4	66.0	68.6	67.1	69.0	66.4	68.3	65.5	64.1
ADA 40mg EOW	37.1	46.4	52.2	57.3	57.3	58.0	59.9	60.8	61.1	60.1	58.3	59.0
PBO --> UPA 15mg QD	19.4	23.2	32.2	31.8	33.6	43.6	34.1	59.7	60.2	61.1	62.6	60.2
PBO --> UPA 30mg QD	21.7	28.8	31.1	27.8	34.0	39.6	39.6	59.0	63.2	62.7	61.8	61.3



B.



Weeks												
Patients, %	2	4	8	12	16	20	24	28	32	36	44	56
UPA 15mg QD	17.7	29.1	39.4	41.5	46.9	55.9	55.5	58.3	55.5	57.6	56.6	57.6
UPA 30mg QD	23.2	36.2	47.0	50.8	53.2	57.7	57.0	57.4	57.4	59.3	58.4	56.0
ADA 40mg EOW	23.5	27.7	38.9	41.0	44.1	45.9	47.3	50.3	49.2	48.7	48.3	49.4
PBO --> UPA 15mg QD	8.1	11.8	19.9	18.5	19.4	28.0	20.9	43.6	49.8	49.8	51.2	49.3
PBO --> UPA 30mg QD	10.4	14.2	19.3	17.9	22.6	25.9	27.8	46.2	51.4	55.2	54.2	54.2

Figure S9 (A) Patients achieving HAQ-DI MCID (≥0.35) over 56 weeks (NRI) and (B) change from baseline over 56 weeks in HAQ-DI (as observed)

Nominal p-values are for upadacitinib versus adalimumab.

Assessed in patients with HAQ-DI ≥0.35 at baseline.

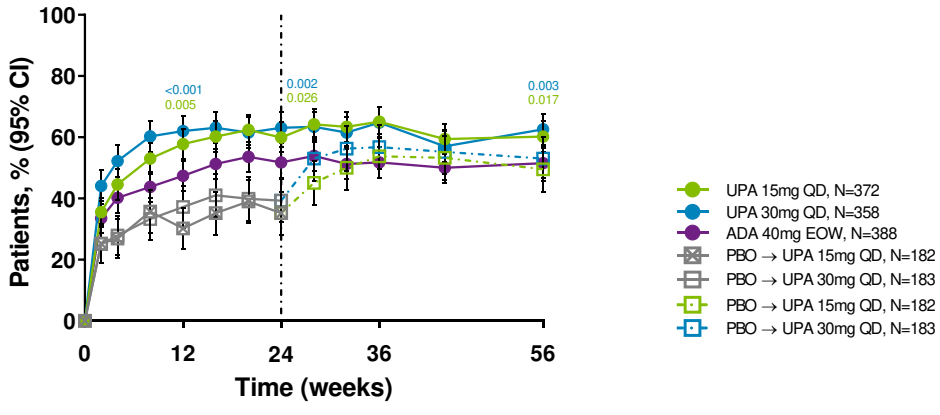
ADA, adalimumab; CI, confidence interval; EOW, every other week; HAQ-DI, Health Assessment Questionnaire-Disability Index; MCID, minimal clinically important difference; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib; QD, once daily.

Patients originally randomised to placebo switched to either upadacitinib 15 mg QD or upadacitinib 30 mg QD (1:1) at week 24 and their data up to week 24 are under placebo exposure.

(A) 95% CIs for response rate were calculated based on normal approximation to the binominal distribution Nominal p-value was constructed using Cochran-Mantel-Haenszel test adjusted for the main stratification factor of current DMARD use (yes/no).

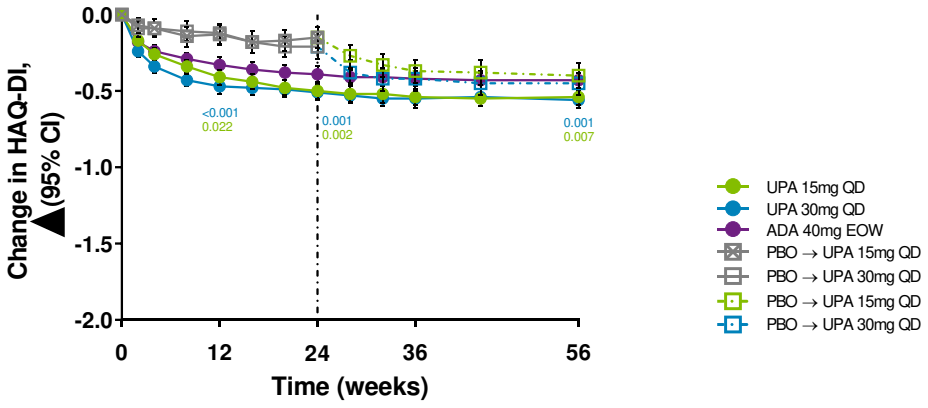
(B) Within group LS mean and 95% CI, and between group LS mean difference and 95% CI and nominal p-value are based on Mixed-Effect Model Repeated Measurement (MMRM) analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement.

A.



	Weeks											
Patients, %	2	4	8	12	16	20	24	28	32	36	44	56
UPA 15mg QD	35.5	44.6	53.0	57.8	60.2	62.4	59.9	64.2	63.4	65.1	59.4	60.2
UPA 30mg QD	44.1	52.2	60.3	62.0	63.1	61.5	63.1	63.4	61.5	64.8	57.0	62.6
ADA 40mg EOW	33.5	40.2	43.8	47.4	51.3	53.6	51.8	53.9	51.3	51.8	50.0	51.5
PBO → UPA 15mg QD	25.3	26.9	35.7	30.2	35.2	39.0	35.2	45.1	50.0	53.8	53.3	49.5
PBO → UPA 30mg QD	25.1	27.9	33.3	37.2	41.0	39.9	39.3	53.0	56.3	56.8	55.2	53.0

B.



	Weeks											
Mean Δ	2	4	8	12	16	20	24	28	32	36	44	56
UPA 15mg QD	-0.17	-0.26	-0.34	-0.41	-0.44	-0.48	-0.50	-0.52	-0.52	-0.54	-0.55	-0.54
UPA 30mg QD	-0.24	-0.34	-0.43	-0.47	-0.48	-0.49	-0.51	-0.53	-0.55	-0.55	-0.54	-0.56
ADA 40mg EOW	-0.18	-0.24	-0.29	-0.33	-0.36	-0.38	-0.39	-0.41	-0.41	-0.42	-0.43	-0.43
PBO → UPA 15mg QD	-0.07	-0.09	-0.14	-0.13	-0.18	-0.17	-0.15	-0.27	-0.33	-0.37	-0.38	-0.40
PBO → UPA 30mg QD	-0.09	-0.09	-0.11	-0.12	-0.18	-0.21	-0.21	-0.38	-0.42	-0.42	-0.45	-0.45

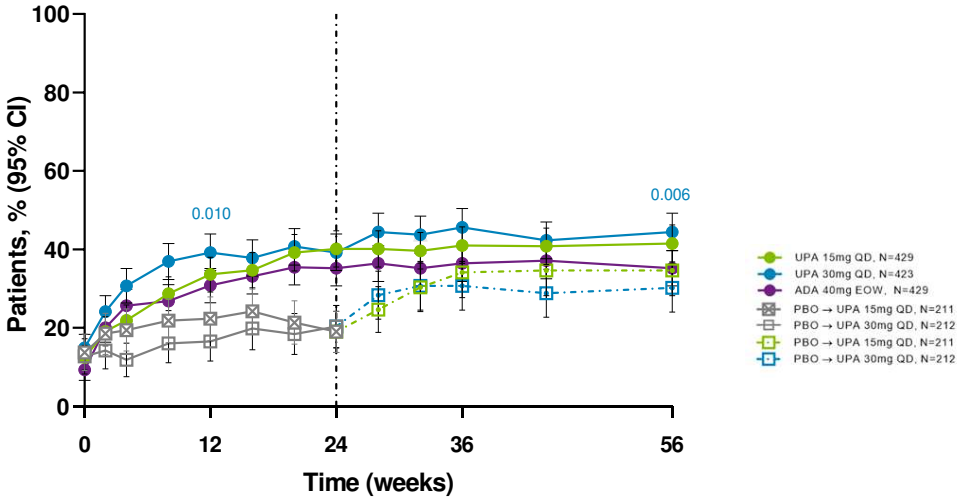
Figure S10 Patients achieving a normative HAQ-DI (≤0.25) over 56 weeks (NRI)

Nominal p-values are for upadacitinib versus adalimumab.

ADA, adalimumab; CI, confidence interval; EOW, every other week; HAQ-DI, Health Assessment Questionnaire-Disability Index; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib; QD, once daily.

Patients originally randomised to placebo switched to either upadacitinib 15 mg QD or upadacitinib 30 mg QD (1:1) at week 24 and their data up to week 24 are under placebo exposure.

95% CIs for response rate were calculated based on normal approximation to the binominal distribution.



	Weeks											
Patients, %	2	4	8	12	16	20	24	28	32	36	44	56
UPA 15mg QD	19.1	21.9	28.7	33.6	34.7	39.2	40.1	40.1	39.6	41.0	40.8	41.5
UPA 30mg QD	24.1	30.7	36.9	39.2	37.8	40.7	39.2	44.4	43.7	45.6	42.3	44.4
ADA 40mg EOW	20.0	25.6	26.8	30.8	33.1	35.4	35.2	36.4	35.2	36.4	37.1	35.2
PBO --> UPA 15mg QD	18.5	19.4	21.8	22.3	24.2	21.3	19.0	24.6	30.3	34.1	34.6	34.6
PBO --> UPA 30mg QD	14.2	11.8	16.0	16.5	19.8	18.4	20.3	28.3	30.7	30.7	28.8	30.2