SUPPLEMENTAL MATERIAL

Safety profile of upadacitinib over 15,000 patient-years across rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis

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Active tuberculosis

Active tuberculosis (TB) was reported in patients with rheumatoid arthritis (RA) (<0.1/100 patient-years [PY] for upadacitinib and 0.2/100 PY for adalimumab) and atopic dermatitis (AD) (<0.1 E/100 PY for each upadacitinib 15 mg and 30 mg). A total of five RA patients receiving upadacitinib were diagnosed with active TB including one patient with female genital tract and peritoneal TB, two with pulmonary TB, one with disseminated TB and one with non-specified TB (**supplemental table S11**). Four of these five patients had latent TB at study entry, and the remaining patient cohabitated with individuals who have had TB. Of the four patients with latent TB at study entry, one patient received adequate treatment, one started treatment 23 days prior to study entry but discontinued at study day 10 due to inability to obtain the TB treatment, one was treated but no information regarding treatment duration is available and the fourth was provided TB treatment for 2 years prior to the event of active TB occurrence. An additional two patients with AD also experienced active TB: one patient receiving upadacitinib 15 mg diagnosed with pulmonary TB and one patient receiving upadacitinib 30 mg diagnosed with non-specified TB. Travel to an endemic country was identified in one patient with AD and TB and the other lived in Russia, which has a high TB burden.

GI perforation

No events of adjudicated gastrointestinal (GI) perforation were observed in patients with ankylosing spondylitis (AS) or AD. The rate of adjudicated GI perforation in RA was <0.1/100 PY with five total events and 0.1/100 PY with two total events in patients with psoriatic arthritis (PsA). GI perforation was due to a traffic accident in one patient with RA that was conservatively included in the analysis, and risk factors (concomitant non-steroidal anti-inflammatory drugs (NSAID) use and history of diverticulosis) or other causes were reported for the majority of the remaining events.[1,2] The exposure-adjusted rate is consistent with rates reported in other clinical programs studying RA and in observational studies of patients with RA. One episode of gastric ulcer perforation attributed to concomitant NSAID use and one episode of enterovesical fistula attributed to a history of diverticulosis occurred in patients with PsA.

AEs related to laboratory parameters

Anemia was most prevalent in patients with RA taking upadacitinib (3.0 E/100 PY) compared with patients with PsA (2.4 E/100 PY), AS (1.6 E/100 PY) and AD (upadacitinib 15 mg, 1.7 E/100 PY; upadacitinib 30 mg, 2.5 E/100 PY). Rates in RA were comparable to patients receiving adalimumab (3.4 E/100 PY) or methotrexate (3.6 E/100 PY). Anemia leading to discontinuation was ≤ 0.2 E/100 PY for all diseases except AS where one event of decreased hemoglobin leading to discontinuation resulted in an event rate of 0.3 E/100 PY.

Rates of neutropenia for patients receiving upadacitinib 15 mg were 2.1 E/100 PY in RA, 1.8 E/100 PY in PsA, 2.8 E/100 PY in AS and 1.6 E/100 PY in AD, but were highest at 2.9 E/100 PY in patients with AD who were receiving upadacitinib 30 mg. Rates were 2.0 E/100 PY for adalimumab and 1.7 E/100 PY for methotrexate in RA. Neutropenia leading to discontinuation of upadacitinib was highest in upadacitinib 30 mg in AD at 0.2 E/100 PY. Lymphopenia rates for patients receiving upadacitinib 15 mg were 1.7 E/100 PY in RA, 2.4 E/100 PY in PsA, 0.9 E/100 PY in AS and 0.5 E/100 PY in AD, with 0.9 E/100 PY among patients receiving upadacitinib 30 mg in AD. No serious events were reported across all diseases. Within the RA studies, rates of lymphopenia were higher in patients receiving methotrexate (3.2 E/100 PY) compared with those receiving upadacitinib (1.7 E/100 PY) or adalimumab (0.9 E/100 PY). Lymphopenia leading to discontinuation of upadacitinib was < 0.1 E/100 PY for all diseases and no apparent association was observed between infections and neutropenia or lymphopenia.

Rates of hepatic disorder varied across diseases with PsA having the highest rates, followed by AS, RA and then AD. Hepatic disorders include liver diseases or laboratory abnormalities that are considered clinically significant and reported as adverse events by the investigator. In RA, rates of hepatic disorder were highest with the methotrexate group followed by upadacitinib then adalimumab; however, rates were higher with adalimumab than with upadacitinib for PsA. Rates of serious hepatic disorders were≤0.1 E/100 PY in patients receiving upadacitinib 15 mg in RA and PsA and patients receiving upadacitinib 30 mg in AD with no events of serious hepatic disorder in AS or patients with AD receiving upadacitinib 15 mg. Most events of hepatic disorder involved transaminase elevations. The exposure-adjusted event rates (EAERs) for hepatic disorder

were higher overall for patients receiving upadacitinib 30 mg versus upadacitinib 15 mg in the AD study. Rates of hepatic disorders leading to discontinuation were <0.1 E/100 PY in RA, 0.1 E/100 PY in AS, 0 events in AS and 0.2 E/100 PY in AD among patients receiving upadacitinib 15 mg and 0.4 E/100 PY among patients with AD receiving upadacitinib 30 mg.

Rates of elevations in creatine phosphokinase (CPK) levels were higher for upadacitinib (4.4 E/100 PY) compared with adalimumab (1.6 E/100 PY) and methotrexate (1.4 E/100PY) in RA and compared with adalimumab in PsA (7.9 E/100 PY versus 5.9 E/100 PY, respectively). Events of elevation in blood CPK levels leading to discontinuation were ≤0.1 E/100 PY in all groups except for patients with AD who were receiving upadacitinib 30 mg (0.3 E/100 PY). Upadacitinib 30 mg resulted in higher rates of elevations of CPK levels than did upadacitinib 15 mg (9.1 E/100 PY versus 6.8 E/100 PY, respectively) in AD.

References

1. Pavlidis ET, Pavlidis TE. Current Aspects on the Management of Perforated Acute Diverticulitis: A Narrative Review. *Cureus* 2022;14(8):e28446. doi: 10.7759/cureus.28446 [published Online First: 20220826]

2. Kapp JR, Muller PC, Gertsch P, et al. A systematic review of the perforated duodenal diverticula: lessons learned from the last decade. *Langenbecks Arch Surg* 2022;407(1):25-35. doi: 10.1007/s00423-021-02238-1 [published Online First: 20210623]

Online Supplemental Table S1 Summary of studies included in the safety analysis

Study	NCT number	Patients Enrolled and Received Treatment	Patient population	Treatments	Study duration
RA					
M13-549 SELECT-NEXT	NCT02675426	Period 1: 661 Period 2: 618	RA patients receiving stable dose of csDMARDs with inadequate response to csDMARDS	Period 1: PBO and UPA 15 mg QD or 30 mg QD Period 2: UPA 15 mg QD or 30 mg QD	Period 1: 12 weeks Period 2: LTE ongoing
M15-555 SELECT-MONOTHERAPY	NCT02706951	Period 1: 648 Period 2: 603	RA patients with inadequate response to MTX	Period 1: MTX, UPA 15 mg QD or 30 mg QD Period 2: UPA 15 mg QD or 30 mg QD	Period 1: 14 weeks Period 2: LTE ongoing
M13-542 SELECT-BEYOND	NCT02706847	Period 1: 498 Period 2: 428	RA patients with inadequate response or intolerance to bDMARDs and currently receiving a stable dose of csDMARDS	Period 1: PBO and UPA 15 mg QD or 30 mg QD Period 2: UPA 15 mg QD or 30 mg QD	Period 1: 24 weeks Period 2: LTE ongoing
M14-465 SELECT-COMPARE	NCT02629159	Period 1: 1629 Period 2: 1403	RA patients with inadequate response to MTX while receiving a stable MTX dose	Period 1: PBO, ADA 40 mg EOW, UPA 15 mg QD Period 2: ADA 40 mg EOW, UPA 15 mg QD	Period 1: 48 weeks Period 2: LTE ongoing

Study	NCT number	Patients Enrolled and Received Treatment	Patient population	Treatments	Study duration
M13-545 SELECT-EARLY	NCT02706873	Period 1: 945 Period 2: 844	MTX-naïve RA patients	Period 1: MTX, UPA 15 mg QD or 30 mg QD Period 2: UPA 15 mg QD or 30 mg QD	Period 1: 48 weeks Period 2: LTE, ongoing
M15-925 SELECT-CHOICE	NCT03086343	Period 1: 612 Period 2: 590	RA patients with inadequate response or intolerance to bDMARDS receiving stable csDMARDs, abatacept-naïve	Period 1: abatacept IV, UPA 15 mg QD Period 2: UPA 15 mg QD	Period 1: 24 weeks Period 2: LTE, ongoing
PsA					
M15-554 SELECT-PsA 2	NCT03104374	641	PsA patients with inadequate response or intolerance to bDMARDs	Period 1: PBO, UPA 15 mg QD or 30 mg QD Period 2: UPA 15 mg QD or 30 mg QD	Period 1: 24 weeks DB, parallel group then 32 weeks blinded treatment with PBO switched to UPA 15 mg or 30 mg Period 2: Up to 3 years, ongoing
M15-572 SELECT-PsA 1	NCT03104400	1704	PsA patients with inadequate response or intolerance to non-bDMARDs	Period 1: PBO, UPA 15 mg QD or 30 mg QD, ADA 40 mg EOW	Period 1: 24-week DB, parallel group PBO and active

Study	NCT number	Patients Enrolled and Received Treatment	Patient population	Treatments	Study duration
				Period 2: UPA 15 mg QD or 30 mg QD, ADA 40 mg EOW	comparator-controlled followed by 32-week blinded treatment with PBO switched to UPA 15 mg QD or 30 mg QD Period 2: OLE up to 5 years, ongoing
AS					
M16-098 SELECT-AXIS 1	NCT03178487	187	Patients with active AS and inadequate response to ≥2 NSAIDS or intolerance to NSAIDs, and bDMARD-naïve	Period 1: PBO, UPA 15 mg QD Period 2: UPA 15 mg QD	Period 1: 14 weeks DB, PBO-controlled Period 2: 90-Week OL LTE
AD					
M16-045 Measure UP 1	NCT03569293	847	Adolescents (up to 180 will be adolescent) and adults with moderate-to-severe AD	PBO, UPA 15 mg QD or 30 mg QD (Extension: PBO re-randomized to UPA 15 mg QD or 30 mg QD)	16-week, DB, PBO-controlled, up to 260 weeks blinded extension, ongoing
M16-047 AD Up	NCT03568318	901	Adolescents and adults with moderate-to-severe AD	PBO, UPA 15 mg QD or 30 mg QD (Extension: PBO re-randomized to UPA	16-week, DB, PBO-controlled up to 260 weeks blinded

Study	NCT number	Patients Enrolled and Received Treatment	Patient population	Treatments	Study duration
				15 mg QD or 30 mg QD)	extension, ongoing
M18-891 Measure Up 2	NCT03607422	836	Adolescents and adults with moderate-to-severe AD	PBO, UPA 15 mg QD or 30 mg QD (Extension: PBO re-randomized to UPA 15 mg QD or 30 mg QD)	16-week, DB, PBO-controlled up to 260 weeks blinded LTE

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; bDMARD, biologic disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; DB, double blind; EOW, every other week; LTE, long-term extension; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; OL, open label; OLE, open-label extension; PBO, placebo; PsA, psoriatic arthritis; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib.

Online Supplemental Table S2. Exposure and overview of TEAEs by upadacitinib monotherapy and upadacitinib combination therapy

	RA		PsA	
Parameter	**UPA 15 mg QD Monotherapy N=661**	**UPA 15 mg QD csDMARD Combination N=2548**	**UPA 15 mg QD Monotherapy N=265**	**UPA 15 mg QD csDMARD Combination N=642**
Exposure				
Total, PY	2100.1	6979.0	513.9	1358.4
Median (minimum, maximum), years*	3.91 (0.01, 5.01)	2.95 (0, 5.45)	2.25 (0, 3.75)	2.25 (0, 3.90)
Overall TEAEs, E/100 PYs (95% CI)				
Any AE	208.9 (202.8, 215.2)	204.4 (201.1, 207.8)	248.1 (234.7, 262.1)	243.6 (235.4, 252.0)
Any serious AE	12.8 (11.3, 14.4)	12.3 (11.5, 13.2)	9.9 (7.4, 13.0)	11.6 (9.8,13.5)
Any AE leading to discontinuation	5.5 (4.5, 6.6)	4.7 (4.2, 5.2)	6.6 (4.6, 9.2)	5.0 (3.9, 6.3)
Deaths†, E/100 PY (95% CI)	0.6 (0.3, 1.0)	0.9 (0.7, 1.1)	0.2 (0, 1.1)	1.0 (0.6, 1.7)

*Minimum in days are as follows: RA: UPA 15 mg monotherapy, 4 days; UPA 15 mg combination, 2 days. PsA: UPA 15 mg monotherapy, 1 day; UPA 15 mg combination, 2 days; ADA 40 mg monotherapy, 29 days; ADA 40 mg combination, 14 days.
†Non-treatment emergent deaths included.
AE, adverse event; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; E/100 PY, events/100 patient-years; PsA, psoriatic arthritis; PY, patient-years; QD, once daily; RA, rheumatoid arthritis; TEAEs, treatment-emergent adverse events; UPA, upadacitinib.

Online Supplemental Table S3. Summary of most common (≥5 E/100 PY) AEs with upadacitinib

Rheumatoid arthritis	Upper respiratory tract infection (7.9 E/100 PY), urinary tract infection (7.6 E/100 PY), nasopharyngitis (7.1 E/100 PY)
Psoriatic arthritis	Upper respiratory tract infection (10.1 E/100 PY), blood creatine phosphokinase levels increased (7.9 E/100 PY), nasopharyngitis (7.5 E/100 PY), urinary tract infection (6.9 E/100 PY), hypertension (5.2 E/100 PY), alanine aminotransferase levels increased (5.1 E/100 PY), bronchitis (5.1 E/100 PY)
Ankylosing spondylitis	Nasopharyngitis (14.7 E/100 PY), blood creatine phosphokinase levels increased (10.9 E/100 PY), upper respiratory tract infection (9.4 E/100 PY), ankylosing spondylitis (5.6 E/100 PY), headache (5.0 E/100 PY)
Atopic dermatitis	UPA 15 mg: nasopharyngitis (11.5 E/100 PY), acne (11.1 E/100 PY), upper respiratory tract infection (9.9 E/100 PY), dermatitis atopic (9.6 E/100 PY), blood creatine phosphokinase levels increased (6.8 E/100 PY), headache (6.5 E/100 PY) UPA 30 mg: acne (16.3 E/100 PY), nasopharyngitis (9.9 E/100 PY), blood creatine phosphokinase levels increased (9.1 E/100 PY), upper respiratory tract infection (8.9 E/100 PY), oral herpes (7.7 E/100 PY), headache (6.3 E/100 PY), dermatitis atopic (5.3 E/100 PY)

AEs, adverse events; E/100 PY, events/100 patient-years; UPA, upadacitinib.

Online Supplemental Table S4. Observed COVID-19 infections in patients receiving upadacitinib

	RA			PsA		AS	AD	
Parameter, n (%)	**UPA 15 mg QD N=3209**	**ADA 40 mg EOW N=579**	**MTX N=314**	**UPA 15 mg QD N=907**	**ADA 40 mg EOW N=429**	**UPA 15 mg QD N=182**	**UPA 15 mg QD N=1340**	**UPA 30 mg QD N=1353**
COVID-19 Infection	190 (5.9)	32 (5.5)	11 (3.5)	93 (10.3)	37 (8.6)	3 (1.6)	72 (5.4)	88 (6.5)
Serious	54 (28.4)	5 (15.6)	1 (9.1)	29 (31.2)	4 (10.8)	0	6 (8.3)	13 (14.8)
Fatal	8 (4.2)	0	0	6 (6.5)	0	0	0	2 (2.3)
Age at baseline (years)								
Mean (SD)	51.4 (11.75)	48.9 (10.39)	52.5 (12.35)	49.6 (9.84)	51.4 (11.41)	37.7 (12.74)	29.1 (13.05)	35.1 (16.58)
Median (min,max)	51.0 (20, 82)	49.5 (21, 63)	58.0 (29, 68)	49.0 (25, 70)	50.0 (33, 72)	44.0 (23, 46)	25.5 (12, 67)	32.0 (13, 72)
Geographic Region								
North America	39 (20.5)	6 (18.8)	2 (18.2)	11 (11.8)	6 (16.2)	0	20 (27.8)	41 (46.6)
South/Central America	53 (27.9)	8 (25.0)	6 (54.5)	24 (25.8)	3 (8.1)	0	4 (5.6)	4 (4.5)
Western Europe	11 (5.8)	0	0	3 (3.2)	2 (5.4)	3 (100)	23 (31.9)	21 (23.9)
Eastern Europe	78 (41.1)	17 (53.1)	3 (27.3)	50 (53.8)	25 (67.6)	0	23 (31.9)	21 (23.9)
Asia	0	0	0	0	0	0	0	1 (1.1)
Other	9 (4.7)	1 (3.1)	0	5 (5.4)	1 (2.7)	0	2 (2.8)	0
Severity								
Mild	77 (40.5)	9 (28.1)	4 (36.4)	22 (23.7)	12 (32.4)	1 (33.3)	40 (55.6)	42 (47.7)
Moderate	78 (41.1)	19 (59.4)	7 (63.6)	46 (49.5)	23 (62.2)	2 (66.7)	25 (34.7)	31 (35.2)
Severe	35 (18.4)	4 (12.5)	0	24 (25.8)	2 (5.4)	0	7 (9.7)	15 (17.0)
Unknown	0	0	0	1 (1.1)	0	0	0	0
Resultant hospitalization								
Yes	51 (26.8)	5 (15.6)	1 (9.1)	28 (30.1)	4 (10.8)	0	6 (8.3)	12 (13.6)
No	22 (11.6)	2 (6.3)	0	4 (4.3)	4 (10.8)	0	0	1 (1.1)
Missing	117 (61.6)	25 (78.1)	10 (90.9)	61 (65.6)	29 (78.4)	3 (100)	66 (91.7)	75 (85.2)
Action with study drug								
Dose not changed	49 (25.8)	13 (40.6)	6 (54.5)	22 (23.7)	12 (32.4)	1 (33.3)	30 (41.7)	39 (44.3)
Drug interrupted	132 (69.5)	18 (56.3)	5 (45.5)	63 (67.7)	25 (67.6)	2 (66.7)	40 (55.6)	44 (50.0)
Drug withdrawn	9 (4.7)	1 (3.1)	0	7 (7.5)	0	0	1 (1.4)	3 (3.4)
Multiple (interrupted, withdrawn)	0	0	0	0	0	0	0	0
Missing	0	0	0	1 (1.1)	0	0	1 (1.4)	2 (2.3)

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; EOW, every other week; MTX, methotrexate; PsA, psoriatic arthritis; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib.

Online Supplemental Table S5 Summary of opportunistic infections excluding tuberculosis and herpes zoster with upadacitinib by decreasing number of events

Rheumatoid arthritis	Esophageal candidiasis (8), oral fungal infection (4), oropharyngeal candidiasis (4), bronchopulmonary aspergillosis (3), coccidioidomycosis (1), cytomegalovirus infection (1), eczema herpeticum (1), fungal pharyngitis (1), gastrointestinal candidiasis (1), meningitis listeria (1), pneumocystis jiroveci pneumonia (1), pneumonia cryptococcal (1), sinusitis aspergillus (1)
Psoriatic arthritis	Esophageal candidiasis (2), oral fungal infection (2), bronchopulmonary aspergillosis (1), candida urethritis (1), coccidioidomycosis (1), oropharyngeal candidiasis (1), respiratory moniliasis (1)
Ankylosing spondylitis	Esophageal candidiasis (2)
Atopic dermatitis	UPA 15 mg: eczema herpeticum (29), Kaposi's varicelliform eruption (6), strongyloidiasis (1) UPA 30 mg: eczema herpeticum (33), Kaposi's varicelliform eruption (17), esophageal candidiasis (1), oral fungal infection (1)

UPA, upadacitinib.

Online Supplemental Table S6. Summary of extent of involvement for patients with treatment-emergent herpes zoster who are receiving upadacitinib

Characteristics	RA n=232	PsA n=61	AS n=4	AD UPA 15 mg n=59	AD UPA 30 mg n=110
Age					
Mean (SD)	57.7 (11.7)	54.7 (10.4)	52.5 (11.5)	34.2 (14.0)	35 (14.6)
≥65 years	65 (28.0)	9 (14.8)	1 (25.0)	3 (5.1)	3 (2.7)
History of HZ event	18 (7.8)	0	2 (50.0)	6 (10.2)	11 (10.0)
Previous HZ vaccination	11 (4.7)	5 (8.3)	0	3 (5.1)	7 (6.4)
Geographic region					
North America	58 (25.0)	19 (31.1)	0	17 (28.8)	23 (20.9)
South/Central America	45 (19.4)	6 (9.8)	0	0	5 (4.5)
Western Europe	21 (9.1)	7 (11.5)	0	18 (30.5)	38 (34.5)
Eastern Europe	56 (24.1)	15 (24.6)	1 (25.0)	6 (10.2)	10 (9.1)
Asia	39 (16.8)	11 (18.0)	3 (75.0)	15 (25.4)	23 (20.9)
Other	13 (5.6)	3 (4.9)	0	3 (5.1)	11 (10.0)
Extent of involvement					
One dermatome	177 (76.3)	41 (67.2)	4 (100)	46 (78.0)	74 (67.3)
Ophthalmic	15 (6.5)	3 (4.9)	0	1 (1.7)	3 (2.7)
Characteristics	**RA n=231**	**PsA n=61**	**AS n=4**	**AD UPA 15 mg n=59**	**AD UPA 30 mg n=110**

Oticus (Ramsay Hunt Syndrome)	2 (0.9)	1 (1.6)	0	0	3 (2.7)
CNS	0	0	0	0	0

Data are presented as n (%) unless otherwise specified.
AD, atopic dermatitis; AS, ankylosing spondylitis; CNS, central nervous system; HZ, herpes zoster; PsA, psoriatic arthritis; RA, rheumatoid arthritis, UPA, upadacitinib.

Online Supplemental Table S7 Summary of malignancies in patients receiving upadacitinib by decreasing number of events

Rheumatoid arthritis	**Skin – 40** (basal cell carcinoma [19], squamous cell carcinoma of the skin [12], malignant melanoma [4], Bowen's disease [1], malignant melanoma in situ [1], malignant melanoma stage III [1], sebaceous carcinoma [1], skin cancer [1]); **Gastrointestinal – 13** (rectal adenocarcinoma [2], adenocarcinoma gastric [1], adenocarcinoma of colon [1], adenocarcinoma pancreas [1], colon cancer metastatic [1], gastric cancer [1], intestinal metastasis [1], malignant palate neoplasm [1], pancreatic carcinoma stage IV [1], rectal cancer [1], squamous cell carcinoma of the oral cavity [1], tongue neoplasm malignant stage unspecified [1]); **Respiratory – 12** (lung adenocarcinoma [4], squamous cell carcinoma of lung [3], lung carcinoma cell type unspecified stage IV [2], laryngeal cancer [1], lung neoplasm malignant [1], non-small cell lung cancer [1]); **Breast – 11** (breast cancer [7], invasive ductal carcinoma [3], intraductal proliferative breast lesion [1]); **Renal and urinary tract – 6** (bladder cancer [3], bladder transitional cell carcinoma [1], clear cell renal cell carcinoma [1], renal cancer stage I [1]); **Reproductive – 6** (endometrial adenocarcinoma [2], Paget's disease of nipple [1], prostate cancer [1], squamous cell carcinoma of vulva [1], uterine carcinoma in situ [1]); **Unknown origin – 4** (adenocarcinoma [1], malignant neoplasm of unknown primary site [1], metastatic squamous cell carcinoma [1], squamous cell carcinoma [1]); **Endocrine – 3** (papillary thyroid cancer [2], neuroendocrine carcinoma of the skin [1]); **Lymphoma – 3** (cutaneous T-cell lymphoma [1], Non-Hodgkin's lymphoma [1], Non-Hodgkin's lymphoma stage IV [1]); **Blood – 1** (acute promyelocytic leukemia); **Hepatobiliary – 1** (metastasis to liver); **Musculoskeletal – 1** (myxoid liposarcoma); **Nervous system – 1** (glioblastoma)
Psoriatic arthritis	**Skin – 17** (basal cell carcinoma [8], squamous cell carcinoma of the skin [7], malignant melanoma [1], malignant melanoma stage III [1]); **Reproductive – 4** (prostate cancer [2], endometrial adenocarcinoma [1], ovarian cancer [1]); **Respiratory – 2** (lung adenocarcinoma [1], lung cancer metastatic [1]);

	Gastrointestinal – 1 (rectal cancer); **Endocrine – 1** (neuroendocrine carcinoma); **Renal and urinary tract – 1** (bladder transitional cell carcinoma)
Ankylosing spondylitis	**Gastrointestinal – 1** (Squamous cell carcinoma of the tongue)
Atopic dermatitis	UPA 15 mg: **Skin – 7** (squamous cell carcinoma of the skin [3], basal cell carcinoma [1], Bowen's disease [1], keratoacanthoma [1], skin cancer [1]); **Gastrointestinal – 3** (colon cancer [1], anal squamous cell carcinoma [1], gastric cancer [1]); **Breast – 1** (breast cancer) UPA 30 mg: **Skin – 8** (squamous cell carcinoma of the skin [5], basal cell carcinoma [1], keratoacanthoma [1], malignant melanoma in situ [1]); **Gastrointestinal – 3** (adenocarcinoma of colon [1], anal squamous cell carcinoma [1], gastric cancer [1]); **Renal and urinary tract – 2** (bladder transitional cell carcinoma [1], clear cell renal cell carcinoma [1]); **Breast – 1** (invasive ductal breast carcinoma); **Endocrine – 1** (thyroid cancer); **Lymphoma – 1** (cutaneous T-cell lymphoma stage I); **Reproductive – 1** (endometrial adenocarcinoma)

Online Supplemental Table S8. Laboratory changes in RA*

	RA		
Variable (unit) Criteria	**UPA 15 mg QD n = 3209**	**ADA 40 mg EOW n = 579**	**MTX n = 314**
Hemoglobin (G/L)			
Grade 2 (decreased 15-<21)	14.9% (478/3201)	8.3% (48/576)	13.8% (43/312)
Grade 3 (70-<80 or decreased 21-<30)	8.8% (281/3201)	6.1% (35/576)	9.3% (29/312)
Grade 4 (<70 or decreased ≥30)	4.0% (128/3201)	4.0% (23/576)	6.7% (21/312)
Platelets (10^9/L)			
Grade 2 (50-<75)	0.4% (12/3197)	0.5% (3/576)	0.3% (1/311)
Grade 3 (20-<50)	<0.1% (1/3197)	0	0
Grade 4 (<20)	0.4% (13/3197)	0.5% (3/576)	0.3% (1/311)
Leukocytes (10^9/L)			
Grade 2 (2.0-<3.0)	5.6% (180/3201)	0.7% (4/576)	5.4% (17/312)
Grade 3 (1.0-<2.0)	0.4% (12/3201)	0.5% (3/576)	0
Grade 4 (<1.0)	0.7% (23/3201)	0.5% (3/576)	0.3% (1/312)
Neutrophils (10^9/L)			
Grade 2 (1.0-<1.5)	7.7% (248/3201)	5.2% (30/576)	3.5% (11/312)
Grade 3 (0.5-<1.0)	1.5% (47/3201)	0.7% (4/576)	1.3% (4/312)
Grade 4 (<0.5)	0.5% (16/3201)	0.2% (1/576)	0.3% (1/312)
Lymphocytes (10^9/L)			
Grade 2 (1.0-<1.5)	31.2% (998/3201)	19.3% (111/576)	28.5% (89/312)
Grade 3 (0.5-<1.0)	28.5% (911/3201)	10.9% (63/576)	27.2% (85/312)
Grade 4 (<0.5)	3.2% (102/3201)	1.2% (7/576)	2.2% (7/312)
Alanine aminotransferase (U/L)			
Grade 2 (1.5-<3.0 x ULN)	18.9% (606/3199)	14.0% (81/577)	16.7% (52/312)
Grade 3 (3.0-<8.0 x ULN)	5.3% (169/3199)	2.6% (15/577)	8.3% (26/312)
Grade 4 (>8.0 x ULN)	1.0% (32/3199)	0.7% (4/577)	2.2% (7/312)
Aspartate aminotransferase (U/L)			
Grade 2 (1.5-<3.0 x ULN)	14.9% (478/3199)	9.5% (55/577)	13.1% (41/312)
Grade 3 (3.0-<8.0 x ULN)	3.5% (113/3199)	1.9% (11/577)	5.1% (16/312)
Grade 4 (>8.0 x ULN)	0.7% (22/3199)	0.9% (5/577)	0.6% (2/312)
Bilirubin (µmol/L)			
Grade 2 (1.4-<1.9 x ULN)	1.3% (42/3199)	0.7% (4/577)	1.9% (6/312)
Grade 3 (1.9-<3.0 x ULN)	0.3% (9/3199)	0.5% (3/577)	0
Grade 4 (>3.0 x ULN)	0.2% (6/3199)	0.2% (1/577)	0.6% (2/312)
Creatine kinase (U/L)			
Grade 2 (<2.5-5.0 x ULN)	9.2% (295/3199)	4.0% (23/577)	3.2% (10/312)
Grade 3 (>5.0-10.0 x ULN)	2.3% (72/3199)	0.9% (5/577)	0.6% (2/312)
Grade 4 (>10.0 x ULN)	0.8% (27/3199)	0.5% (3/577)	0
Creatinine (µmol/L)			

	RA		
Variable (unit) **Criteria**	**UPA 15 mg QD** **n = 3209**	**ADA 40 mg EOW** **n = 579**	**MTX** **n = 314**
Grade 2 (>1.5-3.0 x ULN)	0.9% (30/3199)	1.0% (6/577)	1.6% (5/312)
Grade 3 (>3.0-6.0 x ULN)	<0.1% (3/3199)	0.3% (2/577)	0
Grade 4 (>6.0 x ULN)	0.2% (5/3199)	0.2% (1/577)	0.6% (2/312)

*Toxicity grading scales are based on OMERACT criteria, with the exception of creatine kinase and creatinine, which are based on NCI CTCAE.

ADA, adalimumab; CTCAE, common terminology criteria for adverse events; EOW, every other week; MTX, methotrexate; NCI, National Cancer Institute; OMERACT, Outcome Measures in Rheumatologic Clinical Trials; QD, once daily; RA, rheumatoid arthritis, UPA, upadacitinib.

Online Supplemental Table S9. Laboratory changes in PsA, AS and AD*

	PsA		AS	AD	
Variable (unit) Criteria	**UPA 15 mg QD n = 907**	**ADA 40 mg EOW n = 429**	**UPA 15 mg n = 182**	**UPA 15 mg n = 1340**	**UPA 30 mg QD n = 1353**
Hemoglobin (G/L)					
Grade 2 (80-<100)	2.6% (23/901)	1.6% (7/427)	2.7% (5/182)	0.7% (9/1333)	1.9% (25/1349)
Grade 3 (<80)	0.4% (4/901)	0.2% (1/427)	0	<0.1% (1/1333)	0.6% (8/1349)
Platelets (10^9/L)					
Grade 2 (50-<75)	0.3% (3/901)	0	0	<0.1% (1/1333)	0.3% (4/1349)
Grade 3 (25-<50)	0.1% (1/901)	0	0	0	0.1% (2/1349)
Grade 4 (<25)	0.1% (1/901)	0	0	0	0
Leukocytes (10^9/L)					
Grade 2 (2.0-<3.0)	6.3% (57/901)	2.3% (10/427)	4.4% (8/182)	3.2% (42/1333)	5.7% (77/1349)
Grade 3 (1.0-<2.0)	0.1% (1/901)	0	0.5% (1/182)	0	0.2% (3/1349)
Grade 4 (<1.0)	0	0	0	0	<0.1% (1/1349)
Neutrophils (10^9/L)					
Grade 2 (1.0-<1.5)	6.0% (54/901)	4.9% (21/426)	6.6% (12/182)	7.9% (105/1333)	13.3% (179/1349)
Grade 3 (0.5-<1.0)	0.8% (7/901)	0.9% (4/426)	1.6% (3/182)	1.1% (14/1333)	1.9% (26/1349)
Grade 4 (<0.5)	0.1% (1/901)	0	0	<0.1% (1/1333)	0.1% (2/1349)
Lymphocytes (10^9/L)					
Grade 2 (0.5-<0.8)	13.1% (118/901)	2.1% (9/426)	4.9% (9/182)	6.6% (88/1333)	9.1% (123/1349)
Grade 3 (0.2-<0.5)	2.6% (23/901)	0	0	0.7% (9/1333)	1.6% (22/1349)
Grade 4 (<0.2)	0.2% (2/901)	0	0	0	<0.1% (1/1349)
Alanine aminotransferase (U/L)					
Grade 2 (>3.0-5.0 x ULN)	5.5% (50/901)	6.8% (29/427)	1.6% (3/182)	2.9% (39/1333)	3.8% (51/1349)
Grade 3 (>5.0-20.0 x ULN)	1.6% (14/901)	2.6% (11/427)	1.1% (2/182)	0.5% (6/1333)	0.8% (11/1349)
Grade 4 (>20.0 x ULN)	0.2% (2/901)	0	0	<0.1% (1/1333)	<0.1% (1/1349)
Aspartate aminotransferase (U/L)					
Grade 2 (>3.0-5.0 x ULN)	3.0% (27/901)	4.0% (17/426)	2.7% (5/182)	1.9% (25/1332)	3.4% (46/1349)
Grade 3 (>5.0-20.0 x ULN)	1.2% (11/901)	1.6% (7/426)	1.1% (2/182)	0.8% (10/1332)	1.3% (17/1349)
Grade 4 (>20.0 x ULN)	0	0	0.5% (1/182)	0.2% (2/1332)	0.1% (2/1349)
Bilirubin (µmol/L)					
Grade 2 (>1.5-3.0 x ULN)	1.7% (15/901)	2.3% (10/426)	2.2% (4/182)	3.8% (50/1333)	4.1% (55/1349)
Grade 3 (>3.0-10.0 x ULN)	0.1% (1/901)	0.2% (1/426)	0	0.2% (2/1333)	0.3% (4/1349)
Grade 4 (>10.0 x ULN)	0	0	0	0	0
Creatine kinase (U/L)					
Grade 2 (>2.5-5.0 x ULN)	11.5% (104/901)	5.4% (23/426)	17.6% (32/182)	14.4% (192/1333)	21.8% (294/1350)
Grade 3 (>5.0-10.0 x ULN)	2.3% (21/901)	0.9% (4/426)	4.9% (9/182)	5.5% (73/1333)	8.0% (108/1350)
Grade 4 (>10.0 x ULN)	1.1% (10/901)	1.4% (6/426)	2.7% (5/182)	2.3% (30/1333)	3.6% (49/1350)
Creatinine (µmol/L)					
Grade 2 (>1.5-3.0 x ULN or >1.5-3.0 x BL)	7.3% (66/901)	6.8% (29/427)	4.9% (9/182)	3.1% (42/1334)	4.1% (56/1350)

	PsA		AS	AD	
Variable (unit) **Criteria**	**UPA 15 mg QD** **n = 907**	**ADA 40 mg EOW** **n = 429**	**UPA 15 mg** **n = 182**	**UPA 15 mg** **n = 1340**	**UPA 30 mg QD** **n = 1353**
Grade 3 (>3.0-6.0 x ULN or >3.0 x BL)	0.3% (3/901)	0.2% (1/427)	0	0.3% (4/1334)	0.4% (5/1350)
Grade 4 (>6.0 x ULN)	0.1% (1/901)	0.2% (1/427)	0	0.2% (3/1334)	<0.1% (1/1350)

*Toxicity grading scales are based on NCI CTCAE

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; BL, baseline; CTCAE, common terminology criteria for adverse events; EOW, every other week; NCI, National Cancer Institute; PsA, psoriatic arthritis; QD, once daily; ULN, upper limit of normal; UPA, upadacitinib.

Online Supplemental Table S10 TEAEs of special interest with upadacitinib stratified by age

	RA						PsA		AS				AD			
	UPA 15 mg		ADA 40 mg		MTX		UPA 15 mg		ADA 40 mg		UPA 15 mg		UPA 15 mg		UPA 30 mg	
Event, E/100 PY (95% CI)	<65 yo n=2566 PYs= 7444.4	≥65 yo n= 643 PYs= 1634.7	<65 yo n= 473 PYs= 1093.1	≥65 yo n= 106 PYs= 214.7	<65 yo n= 256 PYs= 630.4	≥65 yo n= 58 PYs= 151.4	<65 yo n= 778 PYs= 1622.1	≥65 yo n= 129 PYs= 250.2	<65 yo n= 362 PYs= 764.1	≥65 yo n= 67 PYs= 139.6	<65 yo n= 171 PYs= 299.4	≥65 yo n= 11 PYs= 20.7	<65 yo n= 1292 PYs= 1970.2	≥65 yo n= 48 PYs= 65.6	<65 yo n= 1285 PYs= 2015.2	≥65 yo n=68 PYs= 102.7
Serious infection	3.1 (2.7, 3.5)	5.1 (4.1, 6.4)	3.4 (2.4, 4.7)	4.2 (1.9, 8.0)	1.3 (0.5, 2.5)	5.3 (2.3, 10.4)	3.6 (2.8, 4.7)	5.6 (3.1, 9.4)	1.0 (0.5, 2.1)	3.6 (1.2, 8.4)	0.0	0.0	2.5 (1.8, 3.3)	1.5 (0.0, 8.5)	2.7 (2.0, 3.5)	9.7 (4.7, 17.9)
Opportunistic infection	0.3 (0.2, 0.4)	0.4 (0.1, 0.8)	0.2 (0.0, 0.7)	0.0 (0.0, 1.7)	0.0 (0.0, 0.6)	0.7 (0.0, 3.7)	0.6 (0.3, 1.1)	0.0 (0.0, 1.5)	0.0 (0.0, 0.5)	0.0 (0.0, 2.6)	0.7 (0.1, 2.4)	0.0	1.8 (1.3, 2.5)	0.0	2.5 (1.9, 3.3)	1.0 (0.0, 5.4)
Malignancy excluding NMSC	0.5 (0.3, 0.7)	1.8 (1.2, 2.5)	0.5 (0.2, 1.2)	2.8 (1.0, 6.1)	1.0 (0.3, 2.1)	1.3 (0.2, 4.8)	0.3 (0.1, 0.7)	2.4 (0.9, 5.2)	0.3 (0.0, 0.9)	1.4 (0.2, 5.2)	0.3 (0.0, 1.9)	0.0	0.2 (0.1, 0.5)	0.0	0.3 (0.1, 0.6)	2.9 (0.6, 8.5)
NMSC	0.2 (0.1, 0.3)	1.3 (0.8, 2.0)	0.0 (0.0, 0.3)	0.5 (0.0, 2.6)	0.0 (0.0, 0.6)	0.0 (0.0, 2.4)	0.4 (0.2, 0.9)	3.2 (1.4, 6.3)	0.3 (0.0, 0.9)	0.0 (0, 2.6)	0.0	0.0	0.4 (0.1, 0.7)	0.0	0.3 (0.1, 0.7)	1.0 (0.0, 5.4)
Hepatic disorder	10.5 (9.8, 11.3)	8.5 (7.1, 10.0)	8.6 (6.9, 10.5)	2.8 (1.0, 6.1)	12.5 (9.9, 15.6)	5.9 (2.7, 11.3)	13.7 (11.9, 15.6)	9.6 (6.1, 14.3)	21.3 (18.2, 24.9)	7.2 (3.4, 13.2)	9.7 (6.5, 13.9)	14.5 (3.0, 42.4)	5.5 (4.5, 6.7)	1.5 (0.0, 8.5)	7.3 (6.2, 8.6)	4.9 (1.6, 11.4)
GI perforation (adjudicated)	<0.1 (0.0, 0.1)	<0.1 (0.0, 0.3)	0.0 (0.0, 0.3)	0.0 (0.0, 1.7)	0.0 (0.0, 0.6)	0.0 (0.0, 2.4)	0.0 (0.0, 0.2)	0.8 (0.1, 2.9)	0.0 (0.0, 0.5)	0.0 (0.0, 2.6)	0.0	0.0	0.0	0.0	0.0	0.0
Anemia	2.6 (2.2, 2.9)	5.2 (4.2, 6.4)	3.4 (2.4, 4.7)	3.3 (1.3, 6.7)	3.6 (2.3, 5.5)	3.3 (1.1, 1.7)	2.5 (1.8, 3.4)	1.6 (0.4, 4.1)	1.7 (0.9, 2.9)	5.0 (2.0, 10.3)	1.7 (0.5, 3.9)	0.0	1.5 (1.0, 2.2)	7.6 (2.5, 17.8)	1.7 (1.2, 2.4)	19.5 (11.9, 30.1)
Neutropenia	2.2 (1.9, 2.6)	1.9 (1.3, 2.7)	1.7 (1.0, 2.7)	3.3 (1.3, 6.7)	1.6 (0.8, 2.9)	2.0 (0.4, 5.8)	2.0 (1.4, 2.9)	0.4 (0.0, 2.2)	4.2 (2.9, 5.9)	1.4 (0.2, 5.2)	3.0 (1.4, 5.7)	0.0	1.6 (1.1, 2.2)	1.5 (0.0, 8.5)	2.9 (2.2, 3.8)	2.9 (0.6, 8.5)
Lymphopenia	1.6 (1.3, 1.9)	1.8 (1.2, 2.6)	0.7 (0.3, 1.4)	1.9 (0.5, 4.8)	3.6 (2.3, 5.5)	1.3 (0.2, 4.8)	2.3 (1.7, 3.2)	2.8 (1.1, 5.8)	0.3 (0.0, 0.9)	0.0 (0.0, 2.6)	0.3 (0.0, 1.9)	9.7 (1.2, 34.9)	0.6 (0.3, 1.0)	0.0	0.8 (0.5, 1.4)	1.9 (0.2, 7.0)
Herpes zoster	2.5 (2.2, 2.9)	5.1 (4.0, 6.3)	1.1 (0.6, 1.9)	2.3 (0.8, 5.4)	0.8 (0.3, 1.9)	1.3 (0.2, 4.8)	3.6 (2.7, 4.6)	4.0 (1.9, 7.4)	0.5 (0.1, 1.3)	0.0 (0.0, 2.6)	1.3 (0.4, 3.4)	4.8 (0.1, 26.9)	3.0 (2.3, 3.9)	4.6 (0.9, 13.4)	5.9 (4.8, 7.0)	2.9 (0.6, 8.5)
Elevated CPK levels	4.5 (4.1, 5.0)	4.0 (3.1, 5.1)	1.9 (1.2, 2.9)	0.0 (0.0, 1.7)	1.4 (0.7, 2.7)	1.3 (0.2, 4.8)	8.3 (6.9, 9.8)	5.6 (3.1, 9.4)	5.9 (4.3, 7.9)	5.7 (2.5, 11.3)	11.0 (7.6, 15.5)	9.7 (1.2, 34.9)	7.0 (5.8, 8.2)	3.0 (0.4, 11.0)	9.3 (8.0, 10.7)	4.9 (1.6, 11.4)
Active TB	<0.1 (0.0, 0.1)	0.1 (0.0, 0.4)	0.3 (0.1, 0.8)	0.0 (0.0, 1.7)	0.0 (0.0, 0.6)	0.0 (0.0, 2.4)	0.0 (0.0, 0.2)	0.0 (0, 1.5)	0.0 (0, 0.5)	0.0 (0, 2.6)	0.0	0.0	<0.1 (0.0, 0.3)	0.0	<0.1 (0.0, 0.3)	0.0

	RA						PsA				AS		AD			
	UPA 15 mg		ADA 40 mg		MTX		UPA 15 mg		ADA 40 mg		UPA 15 mg		UPA 15 mg		UPA 30 mg	
Event, E/100 PY (95% CI)	<65 yo n=2566 PYs= 7444.4	≥65 yo n= 643 PYs= 1634.7	<65 yo n= 473 PYs= 1093.1	≥65 yo n= 106 PYs= 214.7	<65 yo n= 256 PYs= 630.4	≥65 yo n= 58 PYs= 151.4	<65 yo n= 778 PYs= 1622.1	≥65 yo n= 129 PYs= 250.2	<65 yo n= 362 PYs= 764.1	≥65 yo n= 67 PYs= 139.6	<65 yo n= 171 PYs= 299.4	≥65 yo n= 11 PYs= 20.7	<65 yo n= 1292 PYs= 1970.2	≥65 yo n= 48 PYs= 65.6	<65 yo n= 1285 PYs= 2015.2	≥65 yo n=68 PYs= 102.7
MACE (adjudicated)	0.3 (0.2, 0.4)	1.0 (0.6, 1.7)	0.2 (0.0, 0.7)	0.9 (0.1, 3.4)	0.2 (0.0, 0.9)	0.7 (0.0, 3.7)	0.2 (0.1, 0.6)	0.4 (0.0, 2.2)	0.3 (0.0, 0.9)	0.7 (0.0, 4.0)	0.0	0.0	0.0	1.5 (0.0, 8.5)	0.0	1.0 (0.0, 5.4)
VTE (adjudicated)	0.3 (0.2, 0.5)	0.7 (0.4, 1.3)	0.4 (0.1, 0.9)	0.5 (0.0, 2.6)	0.6 (0.2, 1.6)	0.0 (0.0, 2.4)	0.2 (0.0, 0.5)	0.4 (0.0, 2.2)	0.3 (0.0, 0.9)	0.0 (0.0, 2.6)	0.3 (0.0, 1.9)	0.0	<0.1 (0.0, 0.3)	1.5 (0.0, 8.5)	0.0	1.0 (0.0, 5.4)

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CPK, creating phosphokinase; E/100 PY, events/100 patient-years; GI, gastrointestinal; MACE, major adverse cardiovascular event; MTX, methotrexate; NMSC, non-melanoma skin cancer; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TB, tuberculosis; UPA, upadacitinib; VTE, venous thromboembolism; yo, years old.

Online supplemental table S11 Summary of active tuberculosis cases

Study	Age/ sex	Country	Preferred term(s)	Status at screening	TB treatment	Risk factors
RA UPA M13-545	48/F	Tunisia	Female genital tract TB Peritoneal TB	QuantiFERON-Gold TB test negative	Rifampicin, INH, pyrazinamide, and ethambutol	Cohabitation with individuals who have had TB
RA UPA M13-549	40/F	Hungary	TB	QuantiFERON-Gold TB test positive, CXR negative	Fraxiparine, INH, rifampin	History of latent TB, early discontinuation of prophylactic INH
RA UPA M14-465	60/F	South Africa	Pulmonary TB	QuantiFERON-GOLD TB test positive; CXR negative	INH and pyridoxine from day –75 to day 255	Active TB in 2011, latent TB on study entry, living in high TB-burden region
RA UPA M14-465	72/M	Brazil	Pulmonary TB	QuantiFERON-Gold TB test positive	Rifampicin, INH, pyrazinamide, and ethambutol	History of latent TB
RA UPA M14-465	67/F	Korea	Disseminated TB		Rifampin, pyrazinamide, ethambutol, INH	History of latent TB. Patient received INH for TB prophylaxis 2 year before event of interest
RA ADA M14-465	64/F	Estonia	TB	QuantiFERON-Gold TB test negative	Amikacin, cycloserine, levofloxacin, linezolid, and ethambutol	History of latent TB
RA ADA M14-465	63/F	Argentina	Pulmonary TB	QuantiFERON-Gold TB test negative	Isoniazid, rifampicin, pyrazinamide, ethambutol	
RA ADA M14-465	62/M	Bosnia and Herzegovina	TB	QuantiFERON-Gold TB test negative	Isoniazid, pyridoxine	Positive QuantiFERON TB test 1 year before event of active TB and received INH and pyridoxine for TB prophylaxis for 6 months. Diagnosis of active TB was made 6 months after end of TB prophylaxis treatment

Study	Age/ sex	Country	Preferred term(s)	Status at screening	TB treatment	Risk factors
AD UPA 15 M16-045	27/M	Russia	Pulmonary TB	QuantiFERON-Gold TB test negative and clear CXR	Pyrazinamide and levofloxacin	Living in high TB-burden country
AD UPA 30 M18-891	29/M	Canada	TB	QuantiFERON-Gold TB test negative	Rifampin, isoniazid, ethambutol, and pyrazinamide	Trip to Korea before symptom onset (travel to endemic country); also traveled to Taiwan and Japan

AD, atopic dermatitis; ADA, adalimumab; CXR, chest radiograph; F, female; INH, isoniazid; M, male; RA, rheumatoid arthritis; TB, tuberculosis; UPA, upadacitinib

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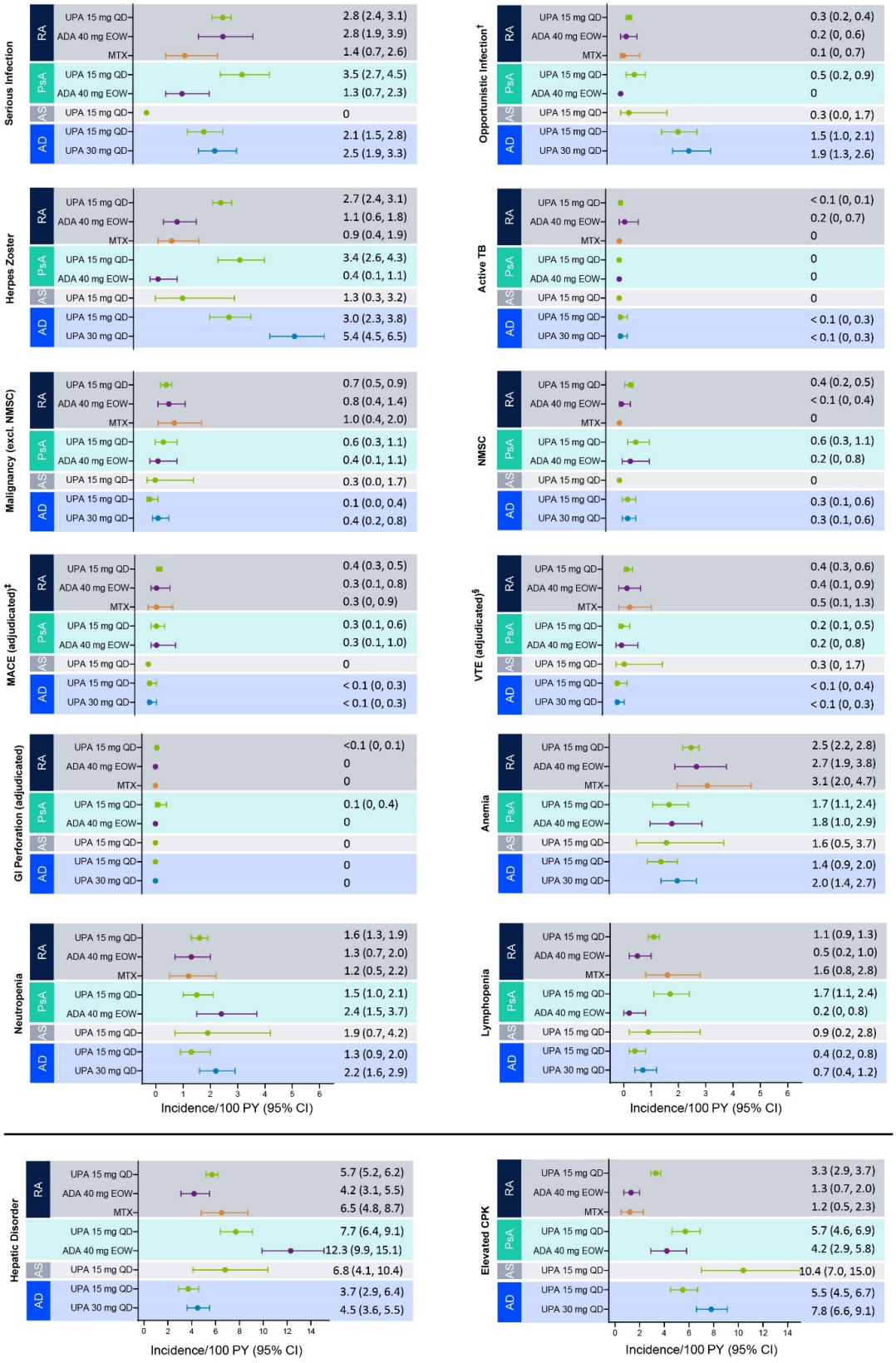
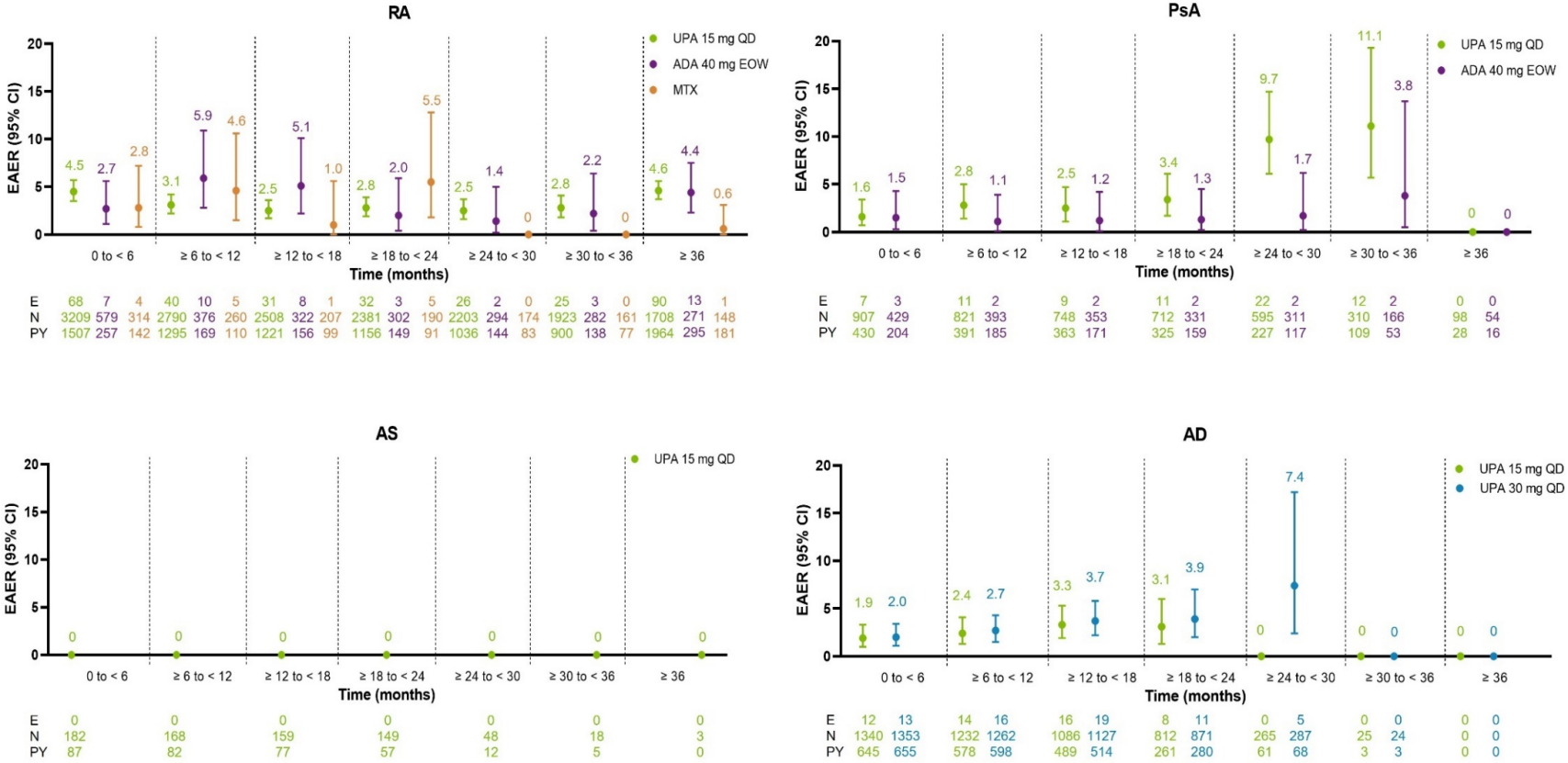
Online Supplemental Figure S1 Incidence rates for TEAEs of special interest*

*RA: UPA 15 mg QD (N = 3209), ADA 40 mg EOW (N = 579), MTX (N = 314); PsA: UPA 15 mg QD (N = 907), ADA 40 mg EOW (N = 429); AS: UPA 15 mg QD (N = 182); AD: UPA 15 mg QD (N = 1340), UPA 30 mg QD (N = 1353).
†Excluding TB, oral candidiasis, and herpes zoster.
‡Defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.
§Including deep vein thrombosis and pulmonary embolism.
AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CPK, creatine phosphokinase; E, event; EOW, every other week; GI, gastrointestinal; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; PsA, psoriatic arthritis; PY, patient years; QD, once daily; RA, rheumatoid arthritis; TB, tuberculosis; TEAE, treatment-emergent adverse event; UPA, upadacitinib; VTE, venous thromboembolic events.


Serious Infection
RA
UPA 15 mg QD 2.8 (2.4, 3.1)
ADA 40 mg EOW 2.8 (1.9, 3.9)
MTX 1.4 (0.7, 2.6)
PsA
UPA 15 mg QD 3.5 (2.7, 4.5)
ADA 40 mg EOW 1.3 (0.7, 2.3)
AS
UPA 15 mg QD 0
AD
UPA 15 mg QD 2.1 (1.5, 2.8)
UPA 30 mg QD 2.5 (1.9, 3.3)
Opportunistic Infection†
RA
UPA 15 mg QD 0.3 (0.2, 0.4)
ADA 40 mg EOW 0.2 (0, 0.6)
MTX 0.1 (0, 0.7)
PsA
UPA 15 mg QD 0.5 (0.2, 0.9)
ADA 40 mg EOW 0
AS
UPA 15 mg QD 0.3 (0.0, 1.7)
AD
UPA 15 mg QD 1.5 (1.0, 2.1)
UPA 30 mg QD 1.9 (1.3, 2.6)
Herpes Zoster
RA
UPA 15 mg QD 2.7 (2.4, 3.1)
ADA 40 mg EOW 1.1 (0.6, 1.8)
MTX 0.9 (0.4, 1.9)
PsA
UPA 15 mg QD 3.4 (2.6, 4.3)
ADA 40 mg EOW 0.4 (0.1, 1.1)
AS
UPA 15 mg QD 1.3 (0.3, 3.2)
AD
UPA 15 mg QD 3.0 (2.3, 3.8)
UPA 30 mg QD 5.4 (4.5, 6.5)
Active TB
RA
UPA 15 mg QD < 0.1 (0, 0.1)
ADA 40 mg EOW 0.2 (0, 0.7)
MTX 0
PsA
UPA 15 mg QD 0
ADA 40 mg EOW 0
AS
UPA 15 mg QD 0
AD
UPA 15 mg QD < 0.1 (0, 0.3)
UPA 30 mg QD < 0.1 (0, 0.3)
Malignancy (excl. NMSC)
RA
UPA 15 mg QD 0.7 (0.5, 0.9)
ADA 40 mg EOW 0.8 (0.4, 1.4)
MTX 1.0 (0.4, 2.0)
PsA
UPA 15 mg QD 0.6 (0.3, 1.1)
ADA 40 mg EOW 0.4 (0.1, 1.1)
AS
UPA 15 mg QD 0.3 (0.0, 1.7)
AD
UPA 15 mg QD 0.1 (0.0, 0.4)
UPA 30 mg QD 0.4 (0.2, 0.8)
NMSC
RA
UPA 15 mg QD 0.4 (0.2, 0.5)
ADA 40 mg EOW < 0.1 (0, 0.4)
MTX 0
PsA
UPA 15 mg QD 0.6 (0.3, 1.1)
ADA 40 mg EOW 0.2 (0, 0.8)
AS
UPA 15 mg QD 0
AD
UPA 15 mg QD 0.3 (0.1, 0.6)
UPA 30 mg QD 0.3 (0.1, 0.6)
MACE (adjudicated)‡
RA
UPA 15 mg QD 0.4 (0.3, 0.5)
ADA 40 mg EOW 0.3 (0.1, 0.8)
MTX 0.3 (0, 0.9)
PsA
UPA 15 mg QD 0.3 (0.1, 0.6)
ADA 40 mg EOW 0.3 (0.1, 1.0)
AS
UPA 15 mg QD 0
AD
UPA 15 mg QD < 0.1 (0, 0.3)
UPA 30 mg QD < 0.1 (0, 0.3)
VTE (adjudicated)§
RA
UPA 15 mg QD 0.4 (0.3, 0.6)
ADA 40 mg EOW 0.4 (0.1, 0.9)
MTX 0.5 (0.1, 1.3)
PsA
UPA 15 mg QD 0.2 (0.1, 0.5)
ADA 40 mg EOW 0.2 (0, 0.8)
AS
UPA 15 mg QD 0.3 (0, 1.7)
AD
UPA 15 mg QD < 0.1 (0, 0.4)
UPA 30 mg QD < 0.1 (0, 0.3)
GI Perforation (adjudicated)
RA
UPA 15 mg QD <0.1 (0, 0.1)
ADA 40 mg EOW 0
MTX 0
PsA
UPA 15 mg QD 0.1 (0, 0.4)
ADA 40 mg EOW 0
AS
UPA 15 mg QD 0
AD
UPA 15 mg QD 0
UPA 30 mg QD 0
Anemia
RA
UPA 15 mg QD 2.5 (2.2, 2.8)
ADA 40 mg EOW 2.7 (1.9, 3.8)
MTX 3.1 (2.0, 4.7)
PsA
UPA 15 mg QD 1.7 (1.1, 2.4)
ADA 40 mg EOW 1.8 (1.0, 2.9)
AS
UPA 15 mg QD 1.6 (0.5, 3.7)
AD
UPA 15 mg QD 1.4 (0.9, 2.0)
UPA 30 mg QD 2.0 (1.4, 2.7)
Neutropenia
RA
UPA 15 mg QD 1.6 (1.3, 1.9)
ADA 40 mg EOW 1.3 (0.7, 2.0)
MTX 1.2 (0.5, 2.2)
PsA
UPA 15 mg QD 1.5 (1.0, 2.1)
ADA 40 mg EOW 2.4 (1.5, 3.7)
AS
UPA 15 mg QD 1.9 (0.7, 4.2)
AD
UPA 15 mg QD 1.3 (0.9, 2.0)
UPA 30 mg QD 2.2 (1.6, 2.9)
0 1 2 3 4 5 6
Incidence/100 PY (95% CI)
Lymphopenia
RA
UPA 15 mg QD 1.1 (0.9, 1.3)
ADA 40 mg EOW 0.5 (0.2, 1.0)
MTX 1.6 (0.8, 2.8)
PsA
UPA 15 mg QD 1.7 (1.1, 2.4)
ADA 40 mg EOW 0.2 (0, 0.8)
AS
UPA 15 mg QD 0.9 (0.2, 2.8)
AD
UPA 15 mg QD 0.4 (0.2, 0.8)
UPA 30 mg QD 0.7 (0.4, 1.2)
0 1 2 3 4 5 6
Incidence/100 PY (95% CI)
Hepatic Disorder
RA
UPA 15 mg QD 5.7 (5.2, 6.2)
ADA 40 mg EOW 4.2 (3.1, 5.5)
MTX 6.5 (4.8, 8.7)
PsA
UPA 15 mg QD 7.7 (6.4, 9.1)
ADA 40 mg EOW 12.3 (9.9, 15.1)
AS
UPA 15 mg QD 6.8 (4.1, 10.4)
AD
UPA 15 mg QD 3.7 (2.9, 6.4)
UPA 30 mg QD 4.5 (3.6, 5.5)
0 2 4 6 8 10 12 14
Incidence/100 PY (95% CI)
Elevated CPK
RA
UPA 15 mg QD 3.3 (2.9, 3.7)
ADA 40 mg EOW 1.3 (0.7, 2.0)
MTX 1.2 (0.5, 2.3)
PsA
UPA 15 mg QD 5.7 (4.6, 6.9)
ADA 40 mg EOW 4.2 (2.9, 5.8)
AS
UPA 15 mg QD 10.4 (7.0, 15.0)
AD
UPA 15 mg QD 5.5 (4.5, 6.7)
UPA 30 mg QD 7.8 (6.6, 9.1)
0 2 4 6 8 10 12 14
Incidence/100 PY (95% CI)

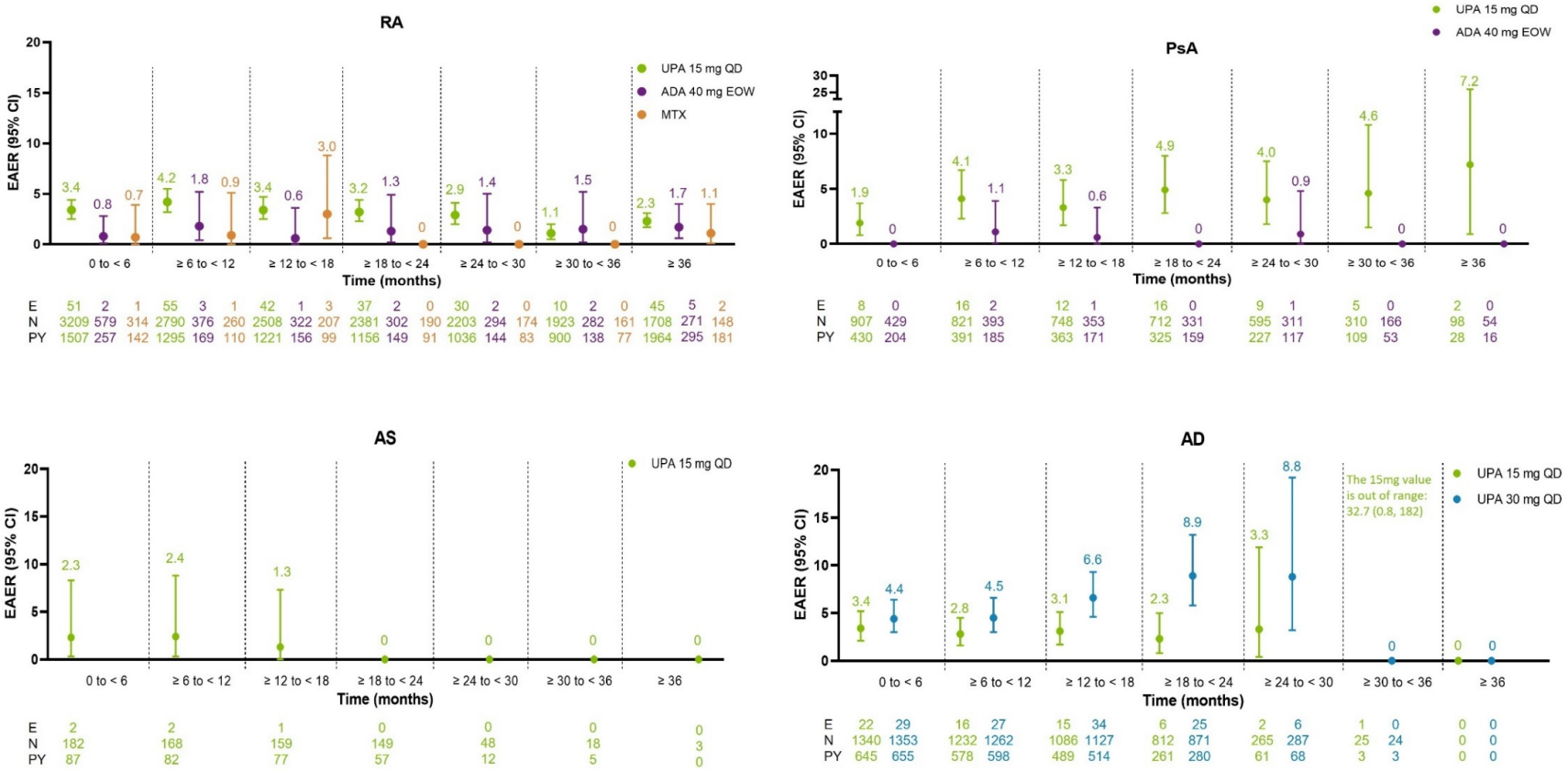
Online Supplemental Figure S2 Treatment-emergent serious infections over time

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; E, event; EOW, every other week; EAER, exposure-adjusted event rate; MTX, methotrexate; PsA, psoriatic arthritis; PY, person-years; QD. every day; RA, rheumatoid arthritis; UPA, upadacitinib.



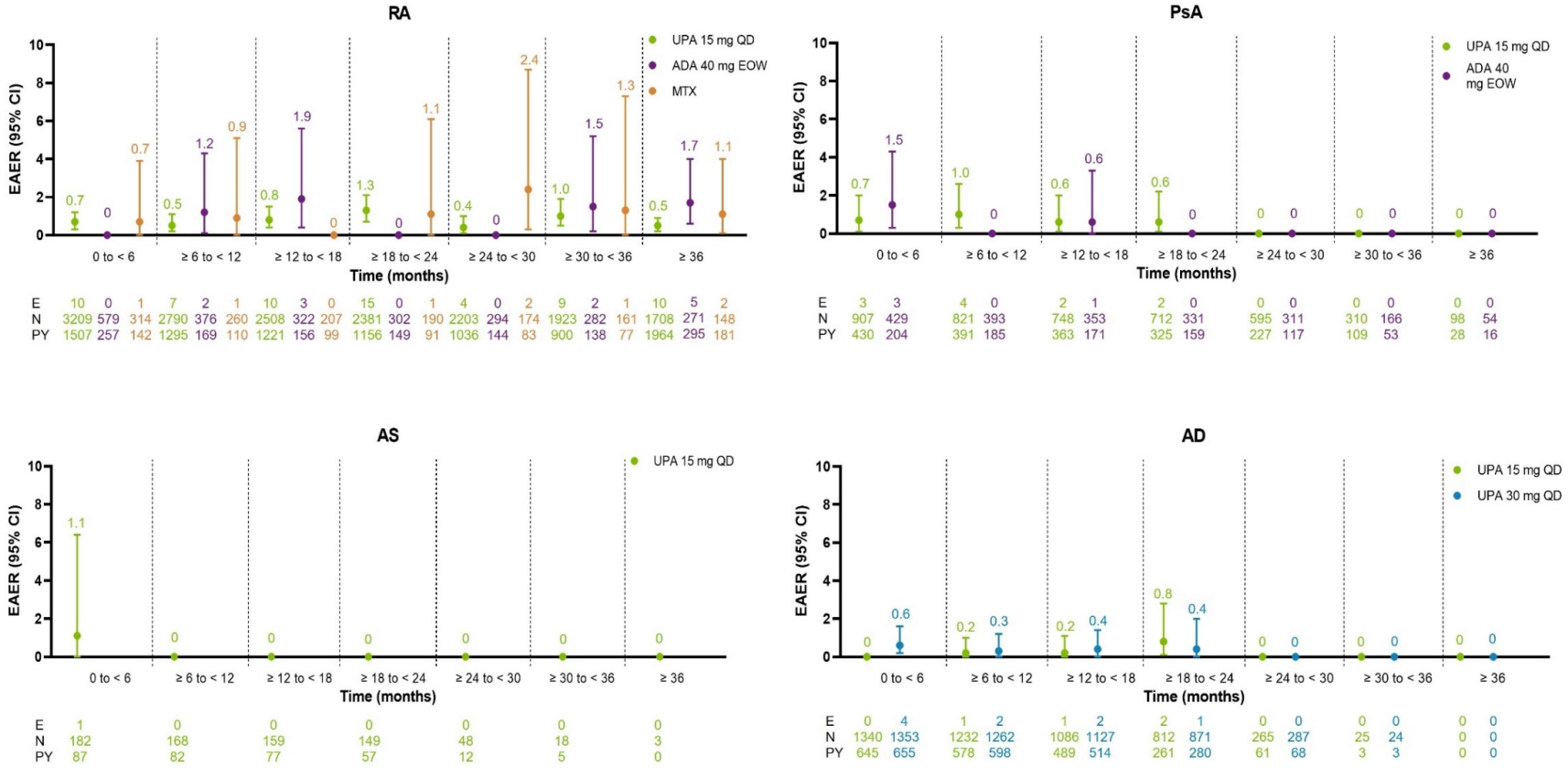
Online Supplemental Figure S3 Treatment-emergent herpes zoster over time

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; E, event; EOW, every other week; EAER, exposure-adjusted event rate; MTX, methotrexate; PsA, psoriatic arthritis; PY, person-years; QD, every day; RA, rheumatoid arthritis; UPA, upadacitinib.



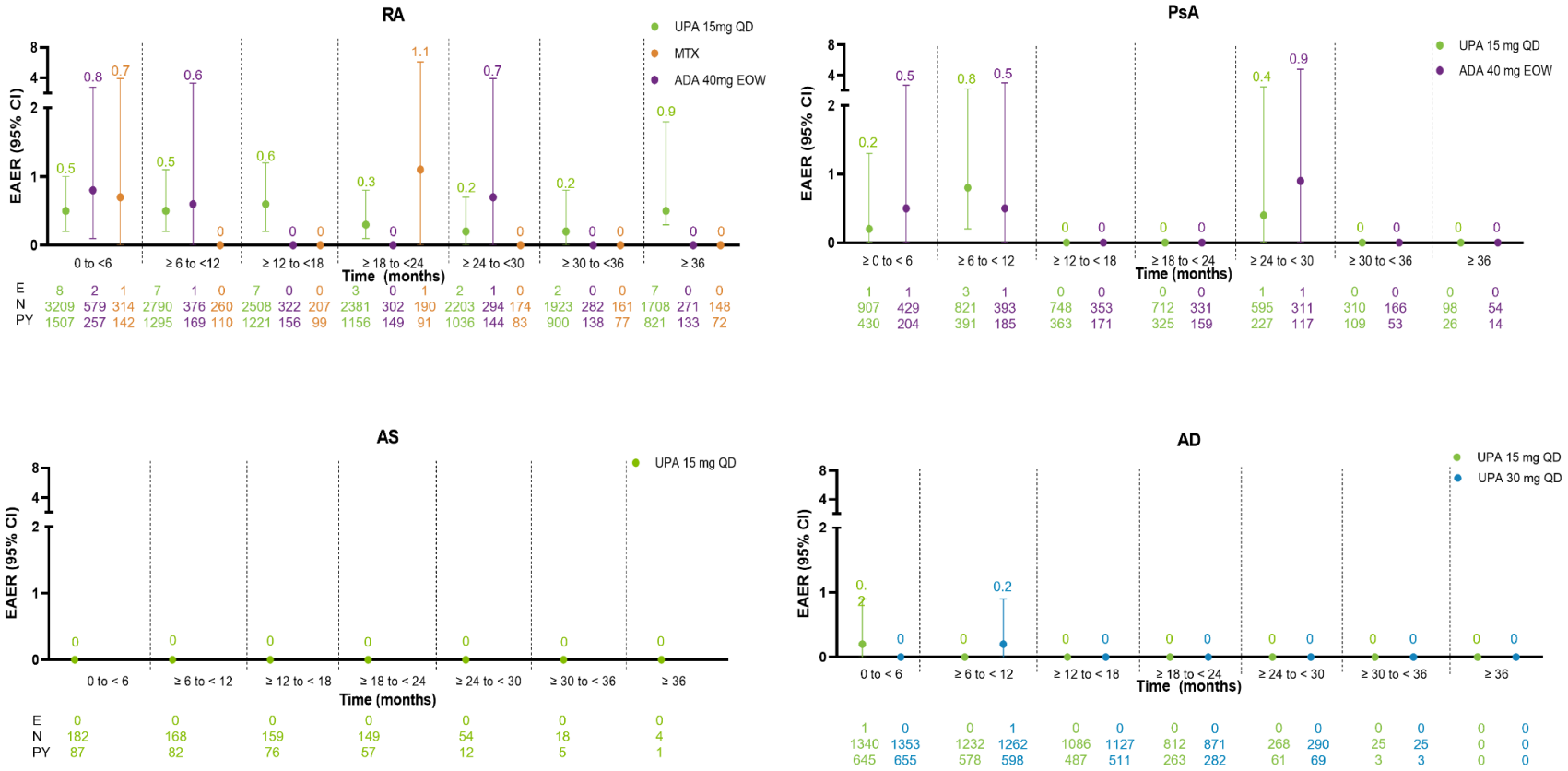
Online Supplemental Figure S4 Treatment-emergent malignancy excluding NMSC over time

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; E, event; EOW, every other week; EAER, exposure-adjusted event rate; MTX, methotrexate; NMSC, nonmelanoma skin cancer; PsA, psoriatic arthritis; PY, person-years; QD, every day; RA, rheumatoid arthritis; UPA, upadacitinib.



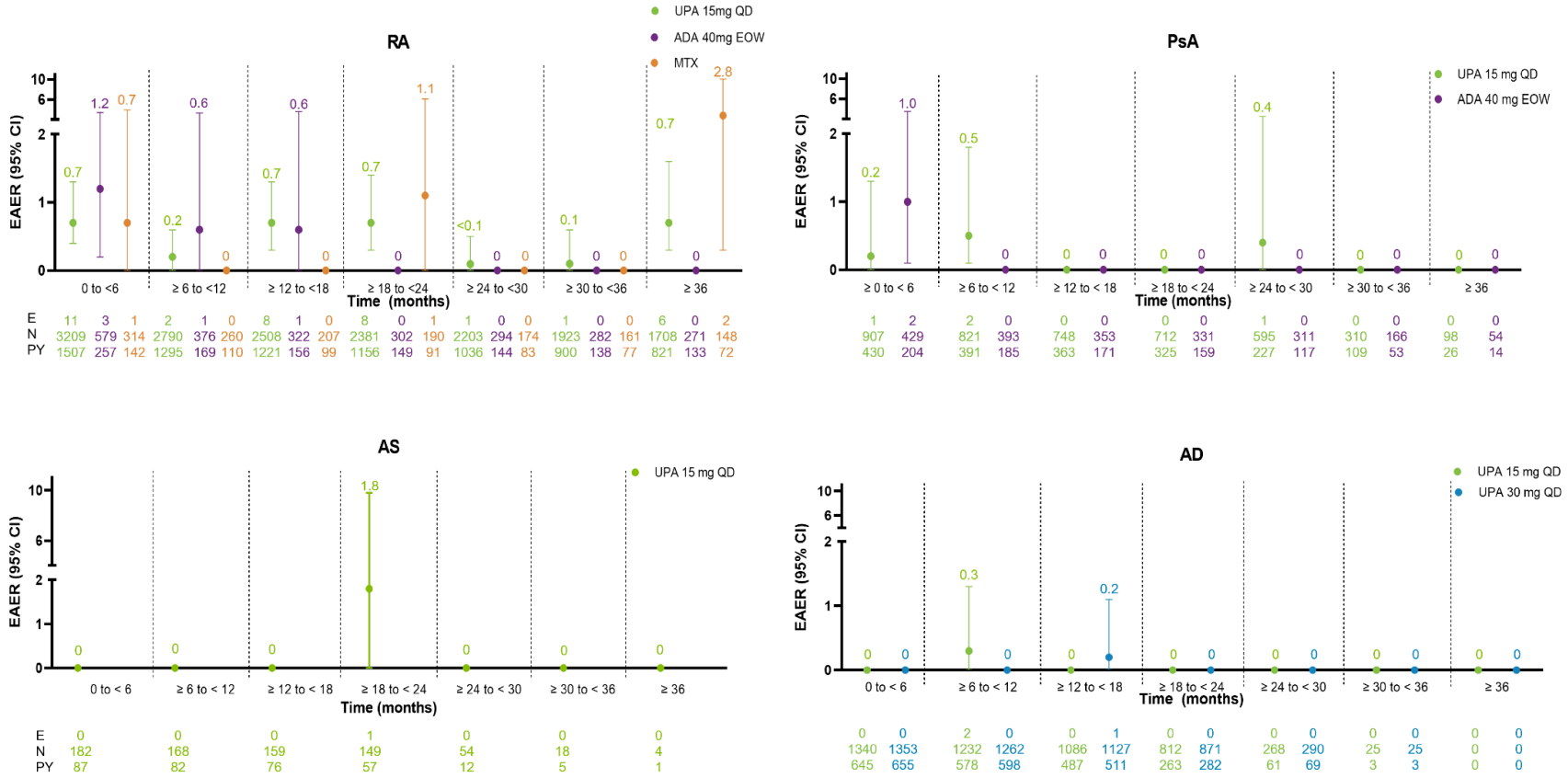
Online Supplemental Figure S5 Treatment-emergent MACE over time

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; E, event; EOW, every other week; EAER, exposure-adjusted event rate; MACE, major adverse cardiovascular event; MTX, methotrexate; PsA, psoriatic arthritis; PY, person-years; QD, every day; RA, rheumatoid arthritis; UPA, upadacitinib.



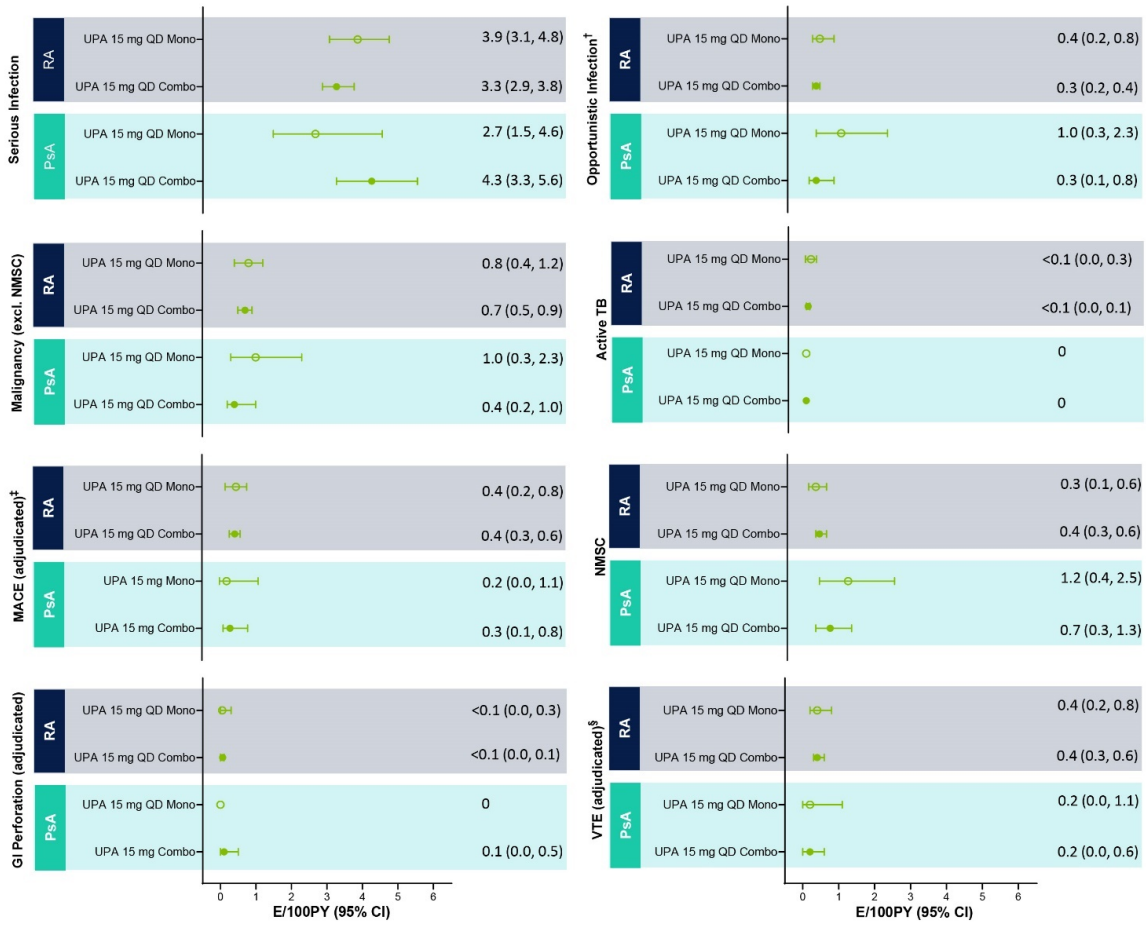
Online Supplemental Figure S6 Treatment-emergent VTE over time

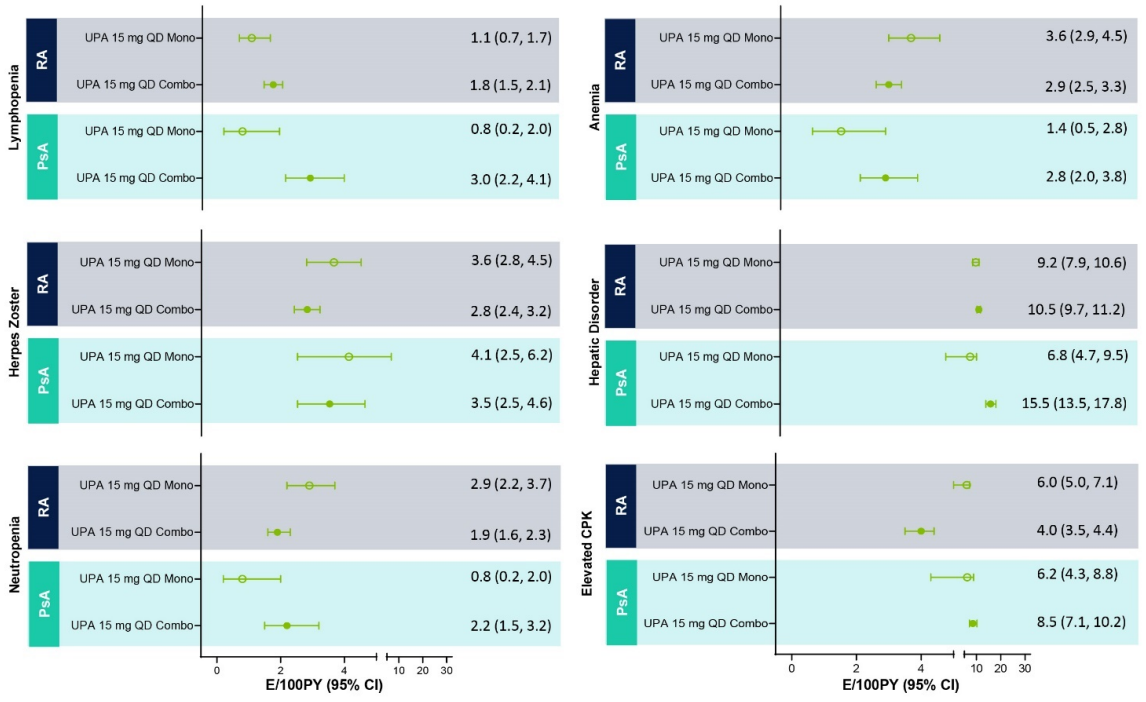
AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; E, event; EOW, every other week; EAER, exposure-adjusted event rate; MTX, methotrexate; NMSC, nonmelanoma skin cancer; PsA, psoriatic arthritis; PY, person-years; QD, every day; RA, rheumatoid arthritis; UPA, upadacitinib; VTE, venous thromboembolism.



Online Supplemental Figure S7 Exposure-adjusted rates for TEAEs of special interest by upadacitinib monotherapy and upadacitinib combination therapy*

*RA: UPA 15 mg QD Mono (N = 661), UPA 15 mg QD Combo (N = 2548); PsA: UPA 15 mg QD Mono (N = 265), UPA 15 mg QD Combo (N = 642).
†Excluding TB, oral candidiasis, and herpes zoster.
‡Defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.
§Including deep vein thrombosis and pulmonary embolism.
CPK, creatine phosphokinase; E, event; GI, gastrointestinal; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; PsA, psoriatic arthritis; PY, patient years; QD, once daily; RA, rheumatoid arthritis; TB, tuberculosis; TEAE, treatment-emergent adverse event; UPA, upadacitinib; VTE, venous thromboembolic events.


Serious Infection
RA
UPA 15 mg QD Mono 3.9 (3.1, 4.8)
UPA 15 mg QD Combo 3.3 (2.9, 3.8)
PsA
UPA 15 mg QD Mono 2.7 (1.5, 4.6)
UPA 15 mg QD Combo 4.3 (3.3, 5.6)
Opportunistic Infection†
RA
UPA 15 mg QD Mono 0.4 (0.2, 0.8)
UPA 15 mg QD Combo 0.3 (0.2, 0.4)
PsA
UPA 15 mg QD Mono 1.0 (0.3, 2.3)
UPA 15 mg QD Combo 0.3 (0.1, 0.8)
Malignancy (excl. NMSC)
RA
UPA 15 mg QD Mono 0.8 (0.4, 1.2)
UPA 15 mg QD Combo 0.7 (0.5, 0.9)
PsA
UPA 15 mg QD Mono 1.0 (0.3, 2.3)
UPA 15 mg QD Combo 0.4 (0.2, 1.0)
Active TB
RA
UPA 15 mg QD Mono <0.1 (0.0, 0.3)
UPA 15 mg QD Combo <0.1 (0.0, 0.1)
PsA
UPA 15 mg QD Mono 0
UPA 15 mg QD Combo 0
MACE (adjudicated)‡
RA
UPA 15 mg QD Mono 0.4 (0.2, 0.8)
UPA 15 mg QD Combo 0.4 (0.3, 0.6)
PsA
UPA 15 mg Mono 0.2 (0.0, 1.1)
UPA 15 mg Combo 0.3 (0.1, 0.8)
NMSC
RA
UPA 15 mg QD Mono 0.3 (0.1, 0.6)
UPA 15 mg QD Combo 0.4 (0.3, 0.6)
PsA
UPA 15 mg QD Mono 1.2 (0.4, 2.5)
UPA 15 mg QD Combo 0.7 (0.3, 1.3)
GI Perforation (adjudicated)
RA
UPA 15 mg QD Mono <0.1 (0.0, 0.3)
UPA 15 mg QD Combo <0.1 (0.0, 0.1)
PsA
UPA 15 mg QD Mono 0
UPA 15 mg Combo 0.1 (0.0, 0.5)
VTE (adjudicated)§
RA
UPA 15 mg QD Mono 0.4 (0.2, 0.8)
UPA 15 mg QD Combo 0.4 (0.3, 0.6)
PsA
UPA 15 mg QD Mono 0.2 (0.0, 1.1)
UPA 15 mg QD Combo 0.2 (0.0, 0.6)
0 1 2 3 4 5 6
E/100PY (95% CI)
0 1 2 3 4 5 6
E/100PY (95% CI)


Lymphopenia
RA
UPA 15 mg QD Mono 1.1 (0.7, 1.7)
UPA 15 mg QD Combo 1.8 (1.5, 2.1)
PsA
UPA 15 mg QD Mono 0.8 (0.2, 2.0)
UPA 15 mg QD Combo 3.0 (2.2, 4.1)
Anemia
RA
UPA 15 mg QD Mono 3.6 (2.9, 4.5)
UPA 15 mg QD Combo 2.9 (2.5, 3.3)
PsA
UPA 15 mg QD Mono 1.4 (0.5, 2.8)
UPA 15 mg QD Combo 2.8 (2.0, 3.8)
Herpes Zoster
RA
UPA 15 mg QD Mono 3.6 (2.8, 4.5)
UPA 15 mg QD Combo 2.8 (2.4, 3.2)
PsA
UPA 15 mg QD Mono 4.1 (2.5, 6.2)
UPA 15 mg QD Combo 3.5 (2.5, 4.6)
Hepatic Disorder
RA
UPA 15 mg QD Mono 9.2 (7.9, 10.6)
UPA 15 mg QD Combo 10.5 (9.7, 11.2)
PsA
UPA 15 mg QD Mono 6.8 (4.7, 9.5)
UPA 15 mg QD Combo 15.5 (13.5, 17.8)
Neutropenia
RA
UPA 15 mg QD Mono 2.9 (2.2, 3.7)
UPA 15 mg QD Combo 1.9 (1.6, 2.3)
PsA
UPA 15 mg QD Mono 0.8 (0.2, 2.0)
UPA 15 mg QD Combo 2.2 (1.5, 3.2)
Elevated CPK
RA
UPA 15 mg QD Mono 6.0 (5.0, 7.1)
UPA 15 mg QD Combo 4.0 (3.5, 4.4)
PsA
UPA 15 mg QD Mono 6.2 (4.3, 8.8)
UPA 15 mg QD Combo 8.5 (7.1, 10.2)
0 2 4 10 20 30
E/100PY (95% CI)
0 2 4 10 20 30
E/100PY (95% CI)