SUPPLEMENTARY MATERIAL

Safety Profile of Upadacitinib: Descriptive Analysis in Over 27,000 Patient-Years Across Rheumatoid Arthritis, Psoriatic Arthritis, Axial Spondyloarthritis, Atopic Dermatitis, and Inflammatory Bowel Disease

Gerd R Burmester, MD[1]; Atul Deodhar, MD[2]; Alan D Irvine, MD, DSc[3,4]; Remo Panaccione, MD[5]; Kevin L Winthrop, MD, MPH[6]; Ruth Ann Vleugels, MD, MPH, MBA[7,8]; Gweneth Levy, MD[9]; Smitha Suravaram, MD[9]; Hannah Palac, MS[9]; Lani Wegrzyn, MS, ScD[9]; Sharanya Ford, PhD[9]; Sebastian Meerwein, MD[10]; Emma Guttman-Yassky, MD, PhD[11,12]

[1]Department of Rheumatology and Clinical Immunology, Freie Universität Berlin and Humboldt-Universität zu Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany; [2]Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, Oregon, United States; [3]Department of Clinical Medicine, Trinity College Dublin, Dublin, Ireland; [4]Wellcome-HRB Clinical Research Facility, St. James' Hospital, Dublin, Ireland; [5]Inflammatory Bowel Disease Unit, Division of Gastroenterology and Hepatology, University of Calgary, Calgary, Alberta, Canada; [6]Division of Infectious Diseases, School of Medicine, School of Public Health, Oregon Health & Science University, Portland, Oregon, United States; [7]Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States; [8]Dermatology Program, Division of Immunology, Boston Children's Hospital, Boston, Massachusetts, United States; [9]AbbVie Inc., North Chicago, Illinois, United States; [10]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany; [11]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, New York, United States; [12]Laboratory for Investigative Dermatology, Rockefeller University, New York, New York, United States

Corresponding Author: Gerd R Burmester, MD; gerd.burmester@charite.de; Department of Rheumatology and Clinical Immunology, Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

Table of Contents

Supplemental Table 1. Summary of Included Phase 3 Studies

Study	NCT Number	Number of Treated Patients	Patient Population	Treatments	Study Duration
RA					
M13-549 SELECT-NEXT[1] (Completed)	NCT02675426	661	Patients with moderately to severely active RA receiving stable dose of csDMARDs who have inadequate response to csDMARDs	Period 1: PBO or UPA 15 mg or 30 mg Period 2: UPA 15 mg or 30 mg	Period 1: 12 weeks Period 2: 248-week LTE
M15-555 SELECT-MONOTHERAPY[2] (Completed)	NCT02706951	648	Patients with moderately to severely active RA who have inadequate response to MTX	Period 1: MTX or UPA 15 mg or 30 mg Period 2: UPA 15 mg or 30 mg	Period 1: 14 weeks Period 2: 246-week LTE
M13-542 SELECT-BEYOND[3] (Completed)	NCT02706847	498	Patients with moderately to severely active RA who have inadequate response or intolerance to bDMARDs and were receiving a stable dose of csDMARDs	Period 1: PBO or UPA 15 mg or 30 mg Period 2: UPA 15 mg or 30 mg	Period 1: 24 weeks Period 2: 236-week LTE
M14-465 SELECT-COMPARE[4] (Ongoing)	NCT02629159	1629	Patients with moderately to severely active RA who have inadequate response to MTX and were receiving a stable MTX dose	Period 1: PBO, ADA 40 mg, or UPA 15 mg Period 2: ADA 40 mg or UPA 15 mg	Period 1: 48 weeks Period 2: 5-year LTE

Study	NCT Number	Number of Treated Patients	Patient Population	Treatments	Study Duration
M13-545 SELECT-EARLY[5] (Completed)	NCT02706873	1000	Patients with moderately to severely active RA naive to MTX	Period 1: MTX or UPA 15 mg or 30 mg Period 2: MTX or UPA 15 mg or 30 mg	Period 1: 48 weeks Period 2: 212-week LTE
M15-925 SELECT-CHOICE[6] (Completed)	NCT03086343	656	Patients with moderately to severely active RA who have inadequate response or intolerance to bDMARDs, were receiving stable doses of csDMARDs, and were abatacept-naive	Period 1: abatacept or UPA 15 mg Period 2: UPA 15 mg	Period 1: 24 weeks Period 2: 5-year LTE
PsA					
M15-554 SELECT-PsA 2[7] (Completed)	NCT03104374	641	Patients with moderately to severely active PsA who have inadequate response or intolerance to bDMARDs	Period 1: PBO or UPA 15 mg or 30 mg Period 2: UPA 15 mg or 30 mg	Period 1: 56 weeks Period 2: 3-year LTE
M15-572 SELECT-PsA 1[8] (Completed)	NCT03104400	1704	Patients with moderately to severely active PsA who have inadequate response or intolerance to non-bDMARDs	Period 1: PBO, UPA 15 mg or 30 mg, ADA 40 mg Period 2: UPA 15 mg or 30 mg or ADA 40 mg	Period 1: 56 weeks Period 2: 5-year LTE

Study	NCT Number	Number of Treated Patients	Patient Population	Treatments	Study Duration
AS					
M16-098 SELECT-AXIS 1[9] (Completed)[a]	NCT03178487	187	Patients with active AS who have inadequate response to ≥ 2 NSAIDs or intolerance to NSAIDs and were bDMARD-naive	Period 1: PBO or UPA 15 mg Period 2: UPA 15 mg	Period 1: 14 weeks Period 2: 90-week LTE
M19-944 SELECT-AXIS 2[10] Study 1 (Ongoing)	NCT04169373	420	Patients with active AS who have inadequate response to bDMARDs	Primary period: PBO or UPA 15 mg LTE: UPA 15 mg Remission-withdrawal period: withdrawal of UPA 15 mg in those who achieved remission by week 104; patients who experience a disease flare by week 152 may receive UPA 15 mg for 24 weeks	Primary period: 14 weeks LTE: 90 weeks Remission-withdrawal period: 48 weeks
nr-axSpA					
M19-944 SELECT-AXIS 2[11] Study 2 (Ongoing)	NCT04169373	313	Patients with active nr-axSpA	Primary period: PBO or UPA 15 mg LTE: UPA 15 mg	Primary period: 52 weeks LTE: 52 weeks

Study	NCT Number	Number of Treated Patients	Patient Population	Treatments	Study Duration
				Remission-withdrawal period: withdrawal of UPA 15 mg in those who achieved remission by week 104; patients who experience a disease flare by week 152 may receive UPA 15 mg for 24 weeks	Remission-withdrawal period: 48 weeks
AD					
M16-045 Measure Up 1[12] (Ongoing)	NCT03569293	902	Adolescents and adults with moderate-to-severe AD who are candidates for systemic therapy	Primary period: PBO or UPA 15 mg or 30 mg LTE: UPA 15 mg or 30 mg	Primary period: 16 weeks LTE: 244 weeks
M16-047 AD Up (Ongoing)[13]	NCT03568318	1075	Adolescents and adults with moderate-to-severe AD who are candidates for systemic therapy	Primary period: PBO or UPA 15 mg or 30 mg LTE: UPA 15 mg or 30 mg	Primary period: 16 weeks LTE: 508 weeks

Study	NCT Number	Number of Treated Patients	Patient Population	Treatments	Study Duration
M18-891 Measure Up 2[12] (Ongoing)	NCT03607422	912	Adolescents and adults with moderate-to-severe AD who are candidates for systemic therapy	Primary period: PBO or UPA 15 mg or 30 mg LTE: UPA 15 mg or 30 mg	Primary period: 16 weeks LTE: 244 weeks
CD					
M14-430 U-ENDURE[14] (Ongoing)	NCT03345823	905	Patients with moderate-to-severe CD who achieved clinical response with UPA during the induction studies (NCT03345849, NCT03345836)	Substudy 1: PBO or UPA 15 mg or 30 mg Substudy 2 (LTE): PBO or UPA 15 or 30 mg	Substudy 1: 52 weeks Substudy 2: 240-week LTE
UC					
M14-234 U-ACHIEVE Maintenance[15] (Completed)	NCT02819635	451	Patients with moderately to severely active UC who achieved clinical response with UPA during the induction studies (NCT02819635, NCT03653026)	PBO or UPA 15 mg or 30 mg	52 weeks

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; bDMARD, biologic disease-modifying antirheumatic drug; CD, Crohn's disease; csDMARD, conventional synthetic disease-modifying antirheumatic drug; LTE, long-term extension; MTX, methotrexate; NCT, national clinical trial; nr-axSpA, non-radiographic axial spondyloarthritis; NSAID, nonsteroidal anti-inflammatory drug; PBO, placebo; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis; UPA, upadacitinib.

[a]SELECT-AXIS 1 was a phase 2/3 trial.

1. Burmester GR, Kremer JM, Van den Bosch F, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2018;391:2503–2512.

2. Smolen JS, Pangan AL, Emery P, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. *Lancet.* 2019;393:2303–2311.

3. Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet.* 2018;391:2513–2524.

4. Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. *Arthritis Rheumatol.* 2019;71:1788–1800.

5. van Vollenhoven R, Takeuchi T, Pangan AL, et al. Efficacy and safety of upadacitinib monotherapy in methotrexate-naive patients with moderately-to-severely active rheumatoid arthritis (SELECT-EARLY): a multicenter, multi-country, randomized, double-blind, active comparator-controlled trial. *Arthritis Rheumatol.* 2020;72:1607–1620.

6. Rubbert-Roth A, Enejosa J, Pangan AL, et al. Trial of upadacitinib or abatacept in rheumatoid arthritis. *N Engl J Med.* 2020;383:1511–1521.

7. Mease PJ, Lertratanakul A, Anderson JK, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. *Ann Rheum Dis.* 2021;80:312–320.

8. McInnes IB, Anderson JK, Magrey M, et al. Trial of upadacitinib and adalimumab for psoriatic arthritis. *N Engl J Med.* 2021;384:1227–1239.

9. van der Heijde D, Song IH, Pangan AL, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. *Lancet.* 2019;394:2108–2117.

10. van der Heijde D, Baraliakos X, Sieper J, et al. Efficacy and safety of upadacitinib for active ankylosing spondylitis refractory to biological therapy: a double-blind, randomised, placebo-controlled phase 3 trial. *Ann Rheum Dis.* 2022;81:1515–1523.

11. Deodhar A, Van den Bosch F, Poddubnyy D, et al. Upadacitinib for the treatment of active non-radiographic axial spondyloarthritis (SELECT-AXIS 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2022;400:369–379.

12. Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet.* 2021;397:2151–2168.

13. Reich K, Teixeira HD, de Bruin-Weller M, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2021;397:2169–2181.

14. Loftus EV, Jr, Panés J, Lacerda AP, et al. Upadacitinib induction and maintenance therapy for Crohn's disease. *N Engl J Med.* 2023;388:1966–1980.

15. Vermeire S, Danese S, Zhou W, et al. Efficacy and safety of upadacitinib maintenance therapy for moderately to severely active ulcerative colitis in patients responding to 8 week induction therapy (U-ACHIEVE Maintenance): overall results from the randomised, placebo-controlled, double-blind, phase 3 maintenance study. *Lancet Gastroenterol Hepatol.* 2023;8:976–989.

Supplemental Table 2. Summary of Most Common (≥ 5 n/100 PYs) TEAEs in Patients Treated With UPA

Indication	UPA 15 mg	UPA 30 mg
RA	Urinary tract infection (5.0 n/100 PY)	—
PsA	COVID-19 (8.6 n/100 PY), upper respiratory tract infection (6.7 n/100 PY)	—
AS	COVID-19 (9.6 n/100 PY), nasopharyngitis (6.8 n/100 PY)	—
nr-axSpA	COVID-19 (22.6 n/100 PY), nasopharyngitis (6.6 n/100 PY)	—
AD	COVID-19 (11.2 n/100 PY), acne (6.5 n/100 PY), nasopharyngitis (6.4 n/100 PY), dermatitis atopic (6.1 n/100 PY), upper respiratory tract infection (5.9 n/100 PY)	COVID-19 (12.3 n/100 PY), acne (10.0 n/100 PY), nasopharyngitis (6.2 n/100 PY), blood creatine kinase increased (5.8 n/100 PY), upper respiratory tract infection (5.7 n/100 PY)
CD	CD (13.7 n/100 PY), COVID-19 (10.8 n/100 PY), nasopharyngitis (5.5 n/100 PY), pyrexia (5.2 n/100 PY)	COVID-19 (15.6 n/100 PY), CD (8.4 n/100 PY), pyrexia (5.7 n/100 PY), herpes zoster (5.5 n/100 PY)
UC	Colitis ulcerative (16.8 n/100 PY), nasopharyngitis (12.3 n/100 PY), blood creatine kinase increased (7.9 n/100 PY), arthralgia (7.7 n/100 PY), upper respiratory tract infection (6.2 n/100 PY), herpes zoster (5.6 n/100 PY)	Nasopharyngitis (12.8 n/100 PY), colitis ulcerative (9.8 n/100 PY), blood creatine kinase increased (9.2 n/100 PY), pyrexia (7.0 n/100 PY), herpes zoster (6.6 n/100 PY), upper respiratory tract infection (5.2 n/100 PY), rash (5.2 n/100 PY)

AD, atopic dermatitis; AS, ankylosing spondylitis; CD, Crohn's disease; n/100 PY, patients with at least 1 event per 100 patient-years; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TEAE, treatment-emergent adverse event; UC, ulcerative colitis; UPA, upadacitinib.

Supplemental Table 3. Exposure and Overview of TEAEs by UPA Monotherapy and UPA Combination Therapy

Parameter	RA		PsA	
	UPA 15 mg Monotherapy n = 661	UPA 15 mg and csDMARD Combination n = 2548	UPA 15 mg Monotherapy n = 255	UPA 15 mg and csDMARD Combination n = 652
Exposure				
Total PY	2402.8	9912.9	714.2	2257.6
Weeks, median (min, max)	248.1 (0.6, 346.4)	215.9 (0.3, 441.0)	152.0 (0.1, 322.3)	235.5 (0.3, 332.9)
TEAEs, n/100 PYs (95% CI)				
Any TEAE	119.2 (109.8, 129.2)	128.9 (123.7, 134.3)	173.3 (151.5, 197.4)	137.0 (126.2, 148.4)
Any serious TEAE	8.7 (7.5, 10.1)	8.5 (7.9, 9.1)	6.2 (4.5, 8.5)	8.3 (7.0, 9.6)
Any treatment-related TEAE[a]	32.0 (28.9, 35.4)	26.7 (25.4, 28.2)	28.9 (24.1, 34.4)	29.0 (26.1, 32.2)
Any TEAE leading to treatment discontinuation	4.1 (3.3, 5.0)	3.9 (3.5, 4.3)	4.8 (3.3, 6.7)	4.1 (3.3, 5.1)
Any TEAE leading to death	0.3 (0.1, 0.7)	0.7 (0.6, 0.9)	0.6 (0.2, 1.4)	0.6 (0.3, 1.0)

csDMARD, conventional synthetic disease-modifying antirheumatic drug; max, maximum; min, minimum; n/100 PY, number of patients with at least 1 event per 100 patient-years; PsA, psoriatic arthritis; PY, patient-years; RA, rheumatoid arthritis; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

[a]As assessed by the investigator.

Supplemental Table 4. Number of Patients With Opportunistic Infections (Excluding HZ and TB)

Indication	UPA 15 mg	UPA 30 mg
RA	Esophageal candidiasis (8), oral fungal infection (4), bronchopulmonary aspergillosis (3), oropharyngeal candidiasis (2), *pneumocystis jirovecii* pneumonia (1), aspergillus infection (1), candida sepsis (1), coccidioidomycosis (1), cytomegalovirus infection (1), eczema herpeticum (1), eye infection toxoplasmal (1), fungal pharyngitis (1), gastrointestinal candidiasis (1), meningitis listeria (1), pneumonia cryptococcal (1), sinusitis aspergillus (1)	—
PsA	Esophageal candidiasis (3), oral fungal infection (2), bronchopulmonary aspergillosis (1), candida urethritis (1), coccidioidomycosis (1), oropharyngeal candidiasis (1), respiratory moniliasis (1)	—
AS	Esophageal candidiasis (1)	—
nr-axSpA	Herpes simplex meningomyelitis (1)	—
AD	Eczema herpeticum (51), strongyloidiasis (2), eczema coxsackium (1), legionella infection (1), esophageal candidiasis (1),	Eczema herpeticum (58), cytomegalovirus infection (2), disseminated herpes simplex (1), fungal pharyngitis (1), esophageal candidiasis (1), oral fungal infection (1), strongyloidiasis (1)
CD	Esophageal candidiasis (1), *pneumocystis jirovecii* pneumonia (1)	Esophageal candidiasis (1)

UC	Cytomegalovirus infection (1), esophageal candidiasis (1)	Pneumonia cryptococcal (2)

AD, atopic dermatitis; AS, ankylosing spondylitis; CD, Crohn’s disease; HZ, herpes zoster; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TB; tuberculosis; UC, ulcerative colitis; UPA, upadacitinib.

For each infection, the number of patients experiencing the event is shown.

Supplemental Table 5. Summary of HZ Involvement in Patients Receiving UPA

Characteristic	RA	PsA	AS	nr-axSpA	AD		CD		UC	
	UPA 15 mg n = 321	UPA 15 mg n = 81	UPA 15 mg n = 27	UPA 15 mg n = 10	UPA 15 mg n = 123	UPA 30 mg n = 221	UPA 15 mg n = 9	UPA 30 mg n = 24	UPA 15 mg n = 12	UPA 30 mg n = 14
Age, years, mean (SD)	56.9 (11.7)	54.2 (10.8)	48.4 (12.9)	43.0 (10.2)	33.2 (14.6)	35.4 (14.9)	44.8 (13.2)	36.1 (13.3)	50.6 (12.7)	53.9 (10.6)
Age ≥ 65 years	82 (25.5)	11 (13.6)	2 (7.4)	0	4 (3.3)	7 (3.2)	0	2 (8.3)	2 (16.7)	3 (21.4)
History of HZ	22 (6.9)	2 (2.5)	2 (7.4)	0	13 (10.6)	24 (10.9)	1 (11.1)	0	1 (8.3)	2 (14.3)
History of HZ vaccination	15 (4.7)	5 (6.2)	0	0	6 (4.9)	11 (5.0)	0	0	0	1 (7.1)
Geographic region										
North America	73 (22.7)	21 (25.9)	1 (3.7)	1 (10.0)	31 (25.2)	58 (26.2)	2 (22.2)	6 (25.0)	2 (16.7)	2 (14.3)
South/Central America[a]	74 (23.1)	8 (9.9)	1 (3.7)	0	1 (0.8)	10 (4.5)	0	1 (4.2)	1 (8.3)	0
Western Europe[b]	34 (10.6)	11 (13.6)	5 (18.5)	2 (20.0)	38 (30.9)	70 (31.7)	2 (22.2)	1 (4.2)	3 (25.0)	2 (14.3)
Eastern Europe	77 (24.0)	25 (30.9)	8 (29.6)	1 (10.0)	12 (9.8)	22 (10.0)	2 (22.2)	1 (4.2)	1 (8.3)	3 (21.4)
Asia	45 (14.0)	12 (14.8)	11 (40.7)	5 (50.0)	32 (26.0)	46 (20.8)	1 (11.1)	13 (54.2)	5 (41.7)	7 (50.0)
Other	18 (5.6)	4 (4.9)	1 (3.7)	1 (10.0)	9 (7.3)	15 (6.8)	2 (22.2)	2 (8.3)	0	0
Extent of involvement										
1 dermatome	242 (75.4)	62 (76.5)	22 (81.5)	8 (80.0)	89 (72.4)	145 (65.6)	4 (44.4)	14 (58.3)	10 (83.3)	7 (50.0)
Ophthalmic	19 (5.9)	5 (6.2)	0	0	4 (3.3)	4 (1.8)	0	1 (4.2)	0	0
Oticus (Ramsay Hunt Syndrome)	3 (0.9)	1 (1.2)	0	0	1 (0.8)	2 (0.9)	0	1 (4.2)	0	0
Central nervous system[c]	0	0	0	0	0	0	0	0	0	1 (7.1)

AD, atopic dermatitis; AS, ankylosing spondylitis; CD, Crohn's disease; HZ, herpes zoster; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis; UPA, upadacitinib.

Data are n (%) unless otherwise specified.

[a]Geographic region was Latin America for the AD and RA cohorts.

[b]Also included Oceania for the AD and RA cohorts.

[c]For the RA and UC populations, central nervous system involvement specifically indicated meningoencephalopathic involvement.

Supplemental Table 6. Number of Patients With Malignancies

Indication	UPA 15 mg	UPA 30 mg
RA	**Skin (NMSC) – 52** (basal cell carcinoma [29], squamous cell carcinoma of skin [16], Bowen's disease [2], sebaceous carcinoma [2], carcinoma in situ of skin [1], neuroendocrine carcinoma of the skin [1], skin squamous cell carcinoma metastatic [1]); **Respiratory – 18** (lung adenocarcinoma [6], squamous cell carcinoma of the lung [4], stage IV lung carcinoma [2], small cell lung cancer [2], laryngeal cancer [1], lung adenocarcinoma stage IV [1], lung neoplasm malignant [1], non-small cell lung cancer metastatic [1]); **Breast – 16** (breast cancer [8], invasive ductal breast carcinoma [6], intraductal proliferative breast lesion [1], invasive breast carcinoma [1]); **Gastrointestinal – 16** (adenocarcinoma of the colon [2], gastric cancer [2], rectal adenocarcinoma [2], adenocarcinoma gastric [1], adenocarcinoma pancreas [1], anal cancer [1], colon cancer metastatic [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]); **Reproductive – 13** (endometrial adenocarcinoma [2], prostate cancer [2], cervix carcinoma [1], ovarian endometrioid carcinoma [1], ovarian epithelial cancer metastatic [1], Paget's disease of nipple [1], squamous cell	—

	carcinoma of the cervix [1], squamous cell carcinoma of the vulva [1], uterine cancer [1], uterine carcinoma in situ [1], vulval cancer [1]); **Skin (excluding NMSC) – 8** (malignant melanoma [6], Kaposi's sarcoma [1], malignant melanoma in situ [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]); **Lymphoma – 5** (cutaneous T-cell lymphoma [1], metastases to lymph nodes [1], mantle cell lymphoma [1], non-Hodgkin's lymphoma [1], non-Hodgkin's lymphoma stage IV [1]); **Endocrine – 3** (papillary thyroid cancer [2], neuroendocrine tumor [1]); **Unknown origin – 3** (squamous cell carcinoma [2], malignant neoplasm of unknown primary site [1]); **Ophthalmic – 1** (malignant neoplasm of conjunctiva [1]); **Skin (unspecified) – 1** (skin cancer [1]); **Blood – 1** (acute promyelocytic leukemia [1]); **Hepatobiliary – 1** (metastases to liver [1]); **Musculoskeletal – 1** (myxoid liposarcoma [1]); **Nervous system – 1** (glioblastoma [1])	
PsA	**Skin (NMSC) – 22** (basal cell carcinoma [14], squamous cell carcinoma of the skin [7], Bowen's disease [1]); **Reproductive – 5** (prostate cancer [2], endometrial adenocarcinoma [1], ovarian cancer [1], squamous cell carcinoma of the cervix [1]); **Skin (excluding NMSC) – 4** (malignant melanoma [1], malignant melanoma in situ [1], malignant melanoma stage III	—

	[1], nevoid melanoma [1]); **Gastrointestinal – 3** (adenocarcinoma gastric [1], rectal cancer [1], signet-ring cell carcinoma [1]); **Renal and urinary tract – 3** (bladder transitional cell carcinoma [2], clear cell renal cell carcinoma [1]); **Respiratory – 3** (lung adenocarcinoma [1], lung adenocarcinoma stage IV [1], lung cancer metastatic [1]); **Endocrine – 2** (papillary thyroid cancer [1], poorly differentiated thyroid cancer [1]); **Unknown origin – 2** (metastatic squamous cell carcinoma [1], neoplasm malignant [1]); **Blood – 1** (chronic lymphocytic leukemia [1])	
AS	**Skin (NMSC) – 4** (basal cell carcinoma [3], squamous cell carcinoma of skin [1]); **Gastrointestinal – 2** (colorectal adenocarcinoma [1], squamous cell carcinoma of the tongue [1]); **Hepatobiliary – 1** (metastases to liver [1])	—
nr-axSpA	**Skin (NMSC) – 1** (basal cell carcinoma [1]); **Breast – 1** (invasive ductal breast carcinoma [1])	—
AD	**Skin (NMSC) – 21** (squamous cell carcinoma of the skin [8], basal cell carcinoma [8], Bowen's disease [3], keratoacanthoma [2]); **Gastrointestinal – 5** (gastric cancer [1], colon cancer [1], colon cancer metastatic [1], pancreatic carcinoma [1], squamous cell carcinoma of the oral cavity [1]); **Lymphoma – 4** (B-cell lymphoma [1], cutaneous T-cell lymphoma stage III [1], diffuse large B-cell lymphoma stage III	**Skin (NMSC) – 20** (squamous cell carcinoma of the skin [9], basal cell carcinoma [8], Bowen's disease [2], keratoacanthoma [1]); **Gastrointestinal – 6** (adenocarcinoma of colon [1], anal squamous cell carcinoma [1], gastric cancer [1], esophageal adenocarcinoma [1], esophageal squamous cell carcinoma [1], solid pseudopapillary tumor of the

	[1], metastases to lymph nodes [1]); **Skin (excluding NMSC) – 2** (malignant melanoma [2]); **Breast – 1** (breast cancer [1]); **Reproductive – 1** (seminoma [1]); **Respiratory – 1** (lung neoplasm malignant [1]); **Nervous system – 1** (medulloblastoma [1])	pancreas [1]); **Unknown origin – 4** (squamous cell carcinoma [4]); **Lymphoma – 3** (cutaneous T-cell lymphoma stage I [1], diffuse large B-cell lymphoma [1], follicular lymphoma stage II [1]); **Renal and urinary tract – 3** (clear cell renal cell carcinoma [1], neuroendocrine carcinoma of the bladder [1], transitional cell carcinoma [1]); **Skin (excluding NMSC) – 2** (malignant melanoma in situ [1], metastatic malignant melanoma [1]); **Endocrine – 2** (papillary thyroid cancer [1], thyroid cancer [1]); **Reproductive – 2** (endometrial adenocarcinoma [1], squamous cell carcinoma of the cervix [1]); **Breast – 1** (invasive ductal breast carcinoma [1]); **Respiratory – 1** (lung adenocarcinoma [1])
CD	**Skin (excluding NMSC) – 1** (malignant melanoma [1]); **Renal and urinary tract – 1** (bladder transitional cell carcinoma [1]); **Reproductive – 1** (ovarian cancer metastatic [1])	**Skin (NMSC) – 2** (squamous cell carcinoma of skin [2]); **Gastrointestinal – 1** (adenocarcinoma of colon [1]); **Breast – 1** (invasive lobular breast carcinoma [1]); **Musculoskeletal – 1** (malignant fibrous histiocytoma [1])
UC	**Breast – 1** (Invasive breast carcinoma [1])	**Skin (NMSC) – 3** (basal cell carcinoma [3]); **Gastrointestinal – 1** (adenocarcinoma of colon [1]); **Unknown origin – 1** (small cell carcinoma [1])

AD, atopic dermatitis; AS, ankylosing spondylitis; CD, Crohn's disease; NMSC, nonmelanoma skin cancer; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis; UPA, upadacitinib. For each malignancy, the number of patients that experienced the event is shown.

Supplemental Table 7. Proportion of Patients Experiencing MACE and VTE With CV Risk Factors at Baseline

	RA	PsA	AS	nr-axSpA	AD		CD		UC	
Number of Patients	**UPA 15 mg**	**UPA 15 mg**	**UPA 15 mg**	**UPA 15 mg**	**UPA 15 mg**	**UPA 30 mg**	**UPA 15 mg**	**UPA 30 mg**	**UPA 15 mg**	**UPA 30 mg**
Patients with MACE	44	11	2	2	7	2	0	1	0	1
Patients with MACE and ≥ 1 CV risk factor at baseline	43	11	1	2	7	2	0	0	0	1
Patients with VTE	47	5	3	3	5	6	0	1	2	2
Patients with VTE and ≥ 1 CV risk factor at baseline	46	5	2	3	3	6	0	1	2	2

AD, atopic dermatitis; AS, ankylosing spondylitis; CD, Crohn's disease; CV, cardiovascular; MACE, major adverse cardiovascular event; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis; UPA, upadacitinib; VTE, venous thromboembolism.

Supplemental Table 8. Grade 3/4 Laboratory Abnormalities in RA

	RA		
Parameter, n (%)	**UPA 15 mg**	**ADA 40 mg**	**MTX**
Hemoglobin (g/L)	n = 3201	n = 411	n = 37
Grade 3 (70 to < 80 or decrease of 21 to < 30)	349 (10.9)	57 (13.9)	4 (10.8)
Grade 4 (< 70 or decrease of ≥ 30)	196 (6.1)	40 (9.7)	3 (8.1)
Platelets (10^9/L)	n = 3197	n = 411	n = 37
Grade 3 (20 to < 50)	2 (< 0.1)	0	0
Grade 4 (< 20)	4 (0.1)	0	0
Leukocytes (10^9/L)	n = 3201	n = 411	n = 37
Grade 3 (1.0 to < 2.0)	17 (0.5)	4 (1.0)	1 (2.7)
Grade 4 (< 1.0)	3 (< 0.1)	0	0
Neutrophils (10^9/L)	n = 3201	n = 411	n = 37
Grade 3 (0.5 to < 1.0)	61 (1.9)	10 (2.4)	1 (2.7)
Grade 4 (< 0.5)	15 (0.5)	4 (1.0)	1 (2.7)
Lymphocytes (10^9/L)	n = 3201	n = 411	n = 37
Grade 3 (0.5 to < 1.0)	1148 (35.9)	134 (32.6)	16 (43.2)
Grade 4 (< 0.5)	157 (4.9)	19 (4.6)	2 (5.4)
Alanine aminotransferase (U/L)	n = 3199	n = 411	n = 37
Grade 3 (3.0 to < 8.0 x ULN)	216 (6.8)	26 (6.3)	5 (13.5)
Grade 4 (> 8.0 x ULN)	38 (1.2)	6 (1.5)	0
Aspartate aminotransferase (U/L)	n = 3199	n = 411	n = 37
Grade 3 (3.0 to < 8.0 x ULN)	155 (4.8)	16 (3.9)	2 (5.4)
Grade 4 (> 8.0 x ULN)	29 (0.9)	6 (1.5)	0

Parameter, n (%)	RA		
	UPA 15 mg	ADA 40 mg	MTX
Bilirubin (µmol/L)	n = 3199	n = 411	n = 37
Grade 3 (1.9 to < 3.0 x ULN)	11 (0.3)	2 (0.5)	0
Grade 4 (> 3.0 x ULN)	7 (0.2)	2 (0.5)	0
Creatine kinase (U/L)	n = 3199	n = 411	n = 37
Grade 3 (> 5.0 to 10.0 x ULN)	89 (2.8)	8 (1.9)	4 (10.8)
Grade 4 (> 10.0 x ULN)	39 (1.2)	6 (1.5)	1 (2.7)
Creatinine (µmol/L)	n = 3199	n = 411	n = 37
Grade 3 (> 3.0 x baseline or > 3.0 to 6.0 x ULN)	15 (0.5)	6 (1.5)	0
Grade 4 (> 6.0 x ULN)	6 (0.2)	0	0

ADA, adalimumab; CTCAE, common terminology criteria for adverse events; MTX, methotrexate; NCI, National Cancer Institute; RA, rheumatoid arthritis, ULN, upper limit of normal; UPA, upadacitinib.

Laboratory abnormalities were graded based on the Rheumatology Common Toxicity Criteria version 2.0, except for creatine kinase and creatinine, which were graded using the NCI CTCAE.

Supplemental Table 9. Grade 3/4 Laboratory Abnormalities in PsA, AS, nr-axSpA, AD, CD, and UC

	PsA		AS	nr-axSpA	AD		CD		UC	
Parameter, n (%)	**UPA 15 mg**	**ADA 40 mg**	**UPA 15 mg**	**UPA 15 mg**	**UPA 15 mg**	**UPA 30 mg**	**UPA 15 mg**	**UPA 30 mg**	**UPA 15 mg**	**UPA 30 mg**
Hemoglobin (g/L)	n = 901	n = 427	n = 595	n = 282	n = 1330	n = 1342	n = 219	n = 229	n = 250	n = 250
Grade 3 (< 80)	5 (0.6)	4 (0.9)	1 (0.2)	0	3 (0.2)	9 (0.7)	4 (1.8)	10 (4.4)	0	1 (0.4)
Grade 4 (urgent intervention indicated)	0	0	0	0	0	0	0	0	0	0
Platelets (10^9/L)	n = 901	n = 427	n = 595	n = 282	n = 1330	n = 1342	n = 218	n = 229	n = 250	n = 248
Grade 3 (25 to < 50)	2 (0.2)	1 (0.2)	0	0	0	4 (0.3)	0	1 (0.4)	0	0
Grade 4 (< 25)	2 (0.2)	0	0	0	0	0	0	1 (0.4)	0	0
Leukocytes (10^9/L)	n = 901	n = 427	n = 595	n = 282	n = 1330	n = 1342	n = 219	n = 229	n = 250	n = 250
Grade 3 (1.0 to < 2.0)	1 (0.1)	0	1 (0.2)	0	0	8 (0.6)	1 (0.5)	2 (0.9)	0	0
Grade 4 (< 1.0)	0	0	0	0	0	1 (< 0.1)	0	0	0	0
Neutrophils (10^9/L)	n = 901	n = 426	n = 595	n = 282	n =1330	n = 1342	n = 218	n = 229	n = 250	n = 250
Grade 3 (0.5 to < 1.0)	11 (1.2)	9 (2.1)	13 (2.2)	8 (2.8)	23 (1.7)	50 (3.7)	3 (1.4)	8 (3.5)	2 (0.8)	6 (2.4)
Grade 4 (< 0.5)	1 (0.1)	1 (0.2)	0	1 (0.4)	2 (0.2)	3 (0.2)	0	0	0	0
Lymphocytes (10^9/L)	n = 901	n = 426	n = 595	n = 282	n = 1330	n = 1342	n = 218	n = 229	n = 250	n = 250
Grade 3 (0.2 to < 0.5)	37 (4.1)	1 (0.2)	6 (1.0)	2 (0.7)	22 (1.7)	49 (3.7)	18 (8.3)	18 (7.9)	4 (1.6)	4 (1.6)
Grade 4 (< 0.2)	1 (0.1)	0	0	0	0	1 (< 0.1)	0	0	0	0
Alanine aminotransferase (U/L)	n = 901	n = 427	n = 595	n = 282	n = 1330	n = 1342	n = 218	n = 229	n = 250	n = 250
Grade 3 (> 5.0 to 20.0 x ULN)	24 (2.7)	18 (4.2)	7 (1.2)	1 (0.4)	7 (0.5)	18 (1.3)	2 (0.9)	1 (0.4)	0	2 (0.8)
Grade 4 (> 20.0 x ULN)	2 (0.2)	0	0	0	2 (0.2)	2 (0.1)	0	0	0	1 (0.4)
Aspartate aminotransferase (U/L)	n = 901	n = 426	n = 595	n = 282	n = 1329	n = 1342	n = 218	n = 229	n = 250	n = 250

Parameter, n (%)	PsA		AS	nr-axSpA	AD		CD		UC	
	UPA 15 mg	ADA 40 mg	UPA 15 mg	UPA 15 mg	UPA 15 mg	UPA 30 mg	UPA 15 mg	UPA 30 mg	UPA 15 mg	UPA 30 mg
Grade 3 (> 5.0 to 20.0 x ULN)	19 (2.1)	11 (2.6)	7 (1.2)	0	15 (1.1)	34 (2.5)	4 (1.8)	1 (0.4)	0	2 (0.8)
Grade 4 (> 20.0 x ULN)	0	0	1 (0.2)	0	2 (0.2)	4 (0.3)	1 (0.5)	0	0	0
Bilirubin (µmol/L)	n = 901	n = 426	n = 595	n = 281	n = 1330	n = 1342	n = 218	n = 229	n = 250	n = 249
Grade 3 (> 3.0 to 10.0 x ULN)	1 (0.1)	1 (0.2)	1 (0.2)	0	1 (< 0.1)	3 (0.2)	1 (0.5)	1 (0.4)	0	1 (0.4)
Grade 4 (> 10.0 x ULN)	0	0	0	0	0	0	0	0	0	0
Creatine kinase (U/L)	n = 901	n = 426	n =184	n = 2	n = 1330	n = 1343	n = 216	n = 229	n = 249	n = 250
Grade 3 (> 5.0 to 10.0 x ULN)	42 (4.7)	13 (3.1)	9 (4.9)	0	123 (9.2)	174 (13.0)	8 (3.7)	16 (7.0)	11 (4.4)	16 (6.4)
Grade 4 (> 10.0 x ULN)	14 (1.6)	7 (1.6)	5 (2.7)	0	53 (4.0)	88 (6.6)	6 (2.8)	7 (3.1)	4 (1.6)	5 (2.0)
Creatinine (µmol/L)	n = 901	n = 427	n = 595	n = 282	n = 1331	n = 1343	n = 218	n = 229	n = 250	n = 251
Grade 3 (> 3.0 to 6.0 x ULN or > 3.0 x baseline)	5 (0.6)	3 (0.7)	1 (0.2)	1 (0.4)	6 (0.5)	8 (0.6)	0	0	0	0
Grade 4 (> 6.0 x ULN)	2 (0.2)	1 (0.2)	0	0	3 (0.2)	1 (< 0.1)	0	0	0	0

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CD, Crohn's disease; CTCAE, common terminology criteria for adverse events; NCI, National Cancer Institute; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; UC, ulcerative colitis; ULN, upper limit of normal; UPA, upadacitinib.
Laboratory abnormalities were graded based on the NCI CTCAE.

Supplemental Table 10. TEAEs of Special Interest Stratified by Age in RA, PsA, AS, and nr-axSpA Cohorts

TEAE, n/100 PY (95% CI)	RA						PsA				AS		nr-axSpA	
	UPA 15 mg		ADA 40 mg		MTX		UPA 15 mg		ADA 40 mg		UPA 15 mg		UPA 15 mg	
	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y
	n = 2566	n = 643	n = 473	n = 106	n = 256	n = 58	n = 778	n = 129	n = 362	n = 67	n = 564	n = 32	n = 278	n = 8
Serious infection	2.5 (2.2, 2.8)	4.9 (4.0, 6.0)	2.3 (1.6, 3.1)	3.2 (1.5, 6.1)	0.9 (0.3, 1.9)	3.2 (1.0, 7.4)	2.7 (2.1, 3.3)	4.2 (2.3, 6.9)	0.9 (0.5, 1.6)	2.9 (1.0, 6.2)	2.0 (1.2, 3.2)	3.7 (0.4, 13.4)	1.4 (0.4, 3.2)	0 (0, 40.1)
Opportunistic infection[a]	0.2 (0.1, 0.3)	0.3 (0.1, 0.7)	0.2 (0, 0.5)	0 (0, 1.2)	0 (0, 0.5)	0.6 (0, 3.4)	0.4 (0.2, 0.7)	0 (0, 1.0)	0 (0, 0.3)	0 (0, 1.7)	0.1 (0, 0.6)	0 (0, 6.6)	0.3 (0, 1.5)	0 (0, 40.1)
HZ	2.5 (2.2, 2.8)	4.3 (3.4, 5.3)	0.7 (0.4, 1.3)	1.4 (0.4, 3.5)	0.7 (0.2, 1.7)	1.3 (0.2, 4.5)	2.9 (2.2, 3.6)	3.1 (1.5, 5.5)	0.5 (0.2, 1.1)	0.5 (0, 2.6)	2.7 (1.7, 3.9)	3.8 (0.5, 13.7)	2.8 (1.3, 1.5)	0 (0, 40.1)
Active TB	< 0.1 (0, 0.1)	< 0.1 (0, 0.3)	0.2 (0.1, 0.6)	0 (0, 1.2)	0 (0, 0.5)	0 (0, 2.2)	0 (0, 0.1)	0 (0, 1.0)	< 0.1 (0, 0.4)	0 (0, 1.7)	0 (0, 0.4)	0 (0, 6.6)	0 (0, 1.0)	0 (0, 40.1)
Malignancy (excl. NMSC)	0.5 (0.3, 0.6)	1.9 (1.3, 2.6)	0.5 (0.2, 0.9)	2.0 (0.7, 4.3)	0.9 (0.3, 1.9)	1.2 (0.1, 4.4)	0.5 (0.2, 0.8)	2.9 (1.5, 5.2)	0.2 (0, 0.6)	1.8 (0.5, 4.7)	0.2 (0, 0.8)	0 (0, 6.6)	0.3 (0, 1.5)	0 (0, 40.1)
NMSC	0.3 (0.2, 0.4)	1.1 (0.7, 1.6)	< 0.1 (0, 0.3)	0.7 (0.1, 2.4)	0 (0, 0.5)	0 (0, 2.2)	0.5 (0.2, 0.8)	2.1 (0.9, 4.3)	0.2 (0, 0.6)	0 (0, 1.7)	0.2 (0, 0.8)	1.8 (0, 9.9)	0.3 (0, 1.5)	0 (0, 40.1)
MACE	0.2 (0.1, 0.3)	1.1 (0.7, 1.6)	0.4 (0.1, 0.8)	0.7 (0.1, 2.4)	0.3 (0, 1.0)	0.6 (0, 3.4)	0.3 (0.2, 0.7)	0.5 (0.1, 1.9)	0.2 (0, 0.7)	0.5 (0, 2.5)	0.2 (0, 0.8)	0 (0, 6.6)	0.5 (0.1, 1.9)	0 (0, 40.1)
VTE	0.3 (0.2, 0.4)	0.9 (0.5, 1.4)	0.2 (0.1, 0.6)	1.0 (0.2, 2.9)	0.7 (0.2, 1.7)	0 (0, 2.2)	0.2 (0, 0.4)	0.3 (0, 1.5)	0.2 (0, 0.6)	0.5 (0, 2.5)	0.3 (0.1, 0.9)	0 (0, 6.6)	0.5 (0.1, 1.9)	10.9 (0.3, 60.6)
Anemia	2.0 (1.7, 2.3)	4.5 (3.6, 5.6)	2.5 (1.7, 3.4)	2.0 (0.7, 4.4)	3.7 (2.4, 5.5)	3.2 (1.0, 7.4)	1.8 (1.3, 2.4)	2.8 (1.3, 5.1)	1.4 (0.9, 2.3)	1.9 (0.5, 4.9)	1.3 (0.7, 2.2)	5.5 (1.1, 16.2)	1.1 (0.3, 2.8)	0 (0, 40.1)
Lymphopenia	1.1 (0.9, 1.3)	1.6 (1.1, 2.3)	0.4 (0.1, 0.8)	1.0 (0.2, 2.9)	1.7 (0.8, 3.0)	1.9 (0.4, 5.5)	1.4 (1.0, 1.9)	2.8 (1.3, 5.1)	0.2 (0, 0.6)	0 (0, 1.7)	0.3 (0.1, 0.9)	3.7 (0.4, 13.3)	0 (0, 1.0)	0 (0, 40.1)
Neutropenia	1.5 (1.3, 1.8)	1.4 (0.9, 2.0)	1.1 (0.6, 1.7)	1.7 (0.6, 4.0)	1.3 (0.6, 2.5)	1.3 (0.2, 4.6)	1.5 (1.1, 2.1)	0.8 (0.2, 2.3)	2.1 (1.3, 3.0)	0.5 (0, 2.6)	2.0 (1.2, 3.2)	1.8 (0, 10.3)	2.8 (1.3, 5.1)	0 (0, 40.1)
Elevated CK	2.8 (2.5, 3.2)	2.5 (1.8, 3.3)	1.3 (0.8, 2.0)	0 (0, 1.2)	1.3 (0.6, 2.5)	0.6 (0, 3.5)	4.9 (4.0, 5.2)	4.1 (2.2, 6.9)	3.2 (2.3, 4.5)	1.9 (0.5, 5.0)	3.0 (2.0, 4.4)	3.8 (0.5, 13.7)	0 (0, 1.0)	0 (0, 40.1)
Hepatic disorder	5.0 (4.5, 5.5)	4.9 (3.9, 6.0)	3.2 (2.4, 4.3)	1.4 (0.4, 3.6)	6.9 (5.0, 9.4)	3.9 (1.4, 8.4)	6.7 (5.7, 7.9)	5.8 (3.6, 9.0)	9.0 (7.3, 11.1)	5.7 (2.8, 10.2)	5.1 (3.7, 6.8)	7.8 (2.1, 20.0)	3.3 (1.7, 5.8)	0 (0, 40.1)
GI perforation	< 0.1 (0, 0.1)	< 0.1 (0, 0.3)	0 (0, 0.2)	0 (0, 1.2)	0 (0, 0.5)	0 (0, 2.2)	< 0.1 (0, 0.2)	0.5 (0.1, 1.9)	0 (0, 0.3)	0 (0, 1.7)	0 (0, 0.4)	0 (0, 6.6)	0 (0, 1.0)	0 (0, 40.1)
Renal dysfunction	0.1 (0.1, 0.2)	0.9 (0.5, 1.4)	0.2 (0, 0.5)	0.3 (0, 1.8)	0.4 (0.1, 1.3)	0.6 (0, 3.4)	0.2 (0, 0.4)	0.8 (0.2, 2.3)	0 (0, 0.3)	0.5 (0, 2.5)	0.1 (0, 0.6)	0 (0, 6.6)	0 (0, 1.0)	12.0 (0.3, 67.1)
Bone fracture	2.1 (1.8, 2.4)	4.4 (3.5, 5.5)	1.8 (1.2, 2.6)	3.6 (1.7, 6.7)	2.1 (1.2, 3.5)	3.8 (1.4, 8.2)	1.6 (1.1, 2.2)	5.1 (2.9, 8.1)	1.1 (0.6, 1.8)	3.5 (1.4, 7.2)	1.7 (1.0, 2.7)	3.6 (0.4, 13.2)	1.6 (0.6, 3.6)	11.5 (0.3, 64.0)

TEAE, n/100 PY (95% CI)	RA						PsA				AS		nr-axSpA	
	UPA 15 mg		ADA 40 mg		MTX		UPA 15 mg		ADA 40 mg		UPA 15 mg		UPA 15 mg	
	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y
	n = 2566	n = 643	n = 473	n = 106	n = 256	n = 58	n = 778	n = 129	n = 362	n = 67	n = 564	n = 32	n = 278	n = 8
Retinal detachment	< 0.1 (0, 0.2)	0.1 (0, 0.4)	< 0.1 (0, 0.3)	0 (0, 1.2)	0.1 (0, 0.8)	0 (0, 2.2)	< 0.1 (0, 0.3)	0 (0, 1.0)	0 (0, 0.3)	0 (0, 1.7)	0 (0, 0.4)	0 (0, 6.6)	0 (0, 1.0)	0 (0, 40.1)
Serious hypersensitivity reaction	< 0.1 (0, 0.1)	0 (0, 0.2)	0 (0, 0.2)	0 (0, 1.2)	0.1 (0, 0.8)	0 (0, 2.2)	< 0.1 (0, 0.3)	0 (0, 1.0)	0 (0, 0.3)	0 (0, 1.7)	0 (0, 0.4)	0 (0, 6.6)	0 (0, 1.0)	0 (0, 40.1)

ADA, adalimumab; AS, ankylosing spondylitis; CK, creatine kinase; excl., excluding; GI, gastrointestinal; HZ, herpes zoster; MACE, major adverse cardiovascular event; MTX, methotrexate; n/100 PY, number of patients with at least 1 event per 100 patient-years; NMSC, nonmelanoma skin cancer; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TB, tuberculosis; TEAE, treatment-emergent adverse event; UPA, upadacitinib; VTE, venous thromboembolism; y, year.

[a]Excluding HZ and TB.

Supplemental Table 11. TEAEs of Special Interest Stratified by Age in AD, CD, and UC Cohorts

TEAE, n/100 PY (95% CI)	AD				CD				UC			
	UPA 15 mg		UPA 30 mg		UPA 15 mg		UPA 30 mg		UPA 15 mg		UPA 30 mg	
	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y
	n = 1289	n = 48	n = 1278	n = 68	n = 214	n = 7	n = 221	n = 8	n = 227	n = 23	n = 230	n = 21
Serious infection	1.7 (1.4, 2.2)	1.6 (0.2, 5.7)	2.1 (1.7, 2.6)	5.5 (2.7, 9.9)	2.5 (1.1, 4.7)	10.5 (1.3, 37.9)	3.6 (2.1, 5.9)	6.7 (0.2, 37.4)	4.6 (2.0, 9.0)	4.8 (0.1, 27.0)	3.5 (1.4, 7.2)	5.7 (0.1, 32.0)
Opportunistic infection[a]	1.3 (1.0, 1.7)	0 (0, 2.9)	1.5 (1.1, 1.9)	0.5 (0, 2.7)	0.5 (0.1, 2.0)	0 (0, 19.4)	0.2 (0, 1.2)	0 (0, 24.2)	0.6 (0, 3.1)	4.8 (0.1, 26.5)	1.0 (0.1, 3.6)	0 (0, 20.2)
HZ	2.9 (2.4, 3.5)	3.4 (0.9, 8.7)	5.3 (4.6, 6.0)	3.5 (1.4, 7.1)	2.5 (1.2, 4.8)	0 (0, 19.4)	5.1 (3.2, 7.8)	20.0 (2.4, 72.4)	5.7 (2.8, 10.6)	9.8 (1.2, 35.3)	5.6 (2.8, 10.0)	17.7 (3.6, 51.7)
Active TB	< 0.1 (0, 0.2)	0 (0, 2.9)	< 0.1 (0, 0.1)	0 (0, 1.7)	0 (0, 1.0)	0 (0, 19.4)	0 (0, 0.8)	0 (0, 24.2)	0 (0, 2.1)	0 (0, 17.5)	0 (0, 1.8)	0 (0, 20.2)
Malignancy (excl. NMSC)	0.2 (0.1, 0.4)	1.6 (0.2, 5.7)	0.3 (0.2, 0.5)	3.9 (1.7, 7.7)	0.8 (0.2, 2.4)	0 (0, 19.4)	0.6 (0.1, 1.9)	0 (0, 24.2)	0.6 (0, 3.1)	0 (0, 17.5)	1.0 (0.1, 3.6)	0 (0, 20.2)
NMSC	0.4 (0.2, 0.6)	2.5 (0.5, 7.2)	0.3 (0.2, 0.5)	2.0 (0.5, 5.1)	0 (0, 1.0)	0 (0, 19.4)	0.4 (0.1, 1.5)	0 (0, 24.2)	0 (0, 2.1)	0 (0, 17.5)	0.5 (0, 2.8)	11.2 (1.4, 40.3)
MACE	< 0.1 (0, 0.2)	2.4 (0.5, 7.0)	0 (0, 0.1)	0.9 (0.1, 3.4)	0 (0, 1.0)	0 (0, 19.4)	0.2 (0, 1.2)	0 (0, 24.2)	0 (0, 2.1)	0 (0, 17.5)	0.5 (0, 2.8)	0 (0, 20.2)
VTE	< 0.1 (0, 0.2)	0.8 (0, 4.4)	< 0.1 (0, 0.2)	0.9 (0.1, 3.4)	0 (0, 1.0)	0 (0, 19.4)	0.2 (0, 1.2)	0 (0, 24.2)	1.1 (0.1, 4.1)	0 (0, 17.5)	0.5 (0, 2.8)	5.5 (0.1, 30.7)
Anemia	1.1 (0.8, 1.5)	4.5 (1.5, 10.5)	1.1 (0.8, 1.5)	10.9 (6.5, 17.2)	4.3 (2.4, 7.1)	0 (0, 19.4)	4.8 (3.0, 7.4)	0 (0, 24.2)	4.6 (2.0, 9.1)	16.3 (3.4, 47.5)	4.6 (2.1, 8.7)	5.5 (0.1, 30.6)
Lymphopenia	0.6 (0.4, 0.9)	0 (0, 2.9)	0.8 (0.6, 1.2)	1.0 (0.1, 3.5)	3.8 (2.0, 6.5)	0 (0, 19.4)	4.7 (2.9, 7.3)	0 (0, 24.2)	3.4 (1.3, 7.5)	5.0 (0.1, 27.7)	2.0 (0.5, 5.2)	5.5 (0.1, 30.5)
Neutropenia	0.9 (0.6, 1.2)	1.6 (0.2, 5.9)	1.2 (0.9, 1.6)	1.5 (0.3, 4.4)	1.4 (0.5, 3.3)	0 (0, 19.4)	2.2 (1.0, 4.0)	0 (0, 24.2)	4.6 (2.0, 9.1)	0 (0, 17.5)	7.9 (4.4, 13.0)	0 (0, 20.2)
Elevated CK	4.2 (3.6, 4.9)	2.4 (0.5, 7.2)	6.0 (5.2, 3.8)	3.2 (1.2, 6.9)	3.8 (2.0, 6.4)	0 (0, 19.4)	4.3 (2.6, 6.7)	0 (0, 24.2)	7.6 (4.0, 13.0)	10.4 (1.3, 37.6)	10.1 (6.1, 15.8)	0 (0, 20.2)
Hepatic disorder	2.8 (2.3, 3.4)	2.4 (0.5, 7.1)	3.5 (3.0, 4.2)	2.5 (0.8, 5.8)	3.8 (2.0, 6.5)	0 (0, 19.4)	5.3 (3.4, 8.0)	0 (0, 24.2)	8.8 (4.9, 14.6)	15.8 (3.2, 46.0)	6.7 (3.6, 11.5)	5.6 (0.1, 31.3)
GI perforation	0 (0, 0.1)	0 (0, 2.9)	< 0.1 (0, 0.2)	0 (0, 1.7)	0.5 (0.1, 2.0)	5.3 (0.1, 29.3)	0.4 (0.1, 1.5)	0 (0, 24.2)	0 (0, 2.1)	0 (0, 17.5)	0 (0, 1.8)	0 (0, 20.2)
Renal dysfunction	< 0.1 (0, 0.2)	0 (0, 2.9)	< 0.1 (0, 0.2)	0.9 (0.1, 3.4)	0 (0, 1.0)	0 (0, 19.4)	0.2 (0, 1.2)	0 (0, 24.2)	0.6 (0, 3.1)	0 (0, 17.5)	0 (0, 1.8)	5.5 (0.1, 30.5)

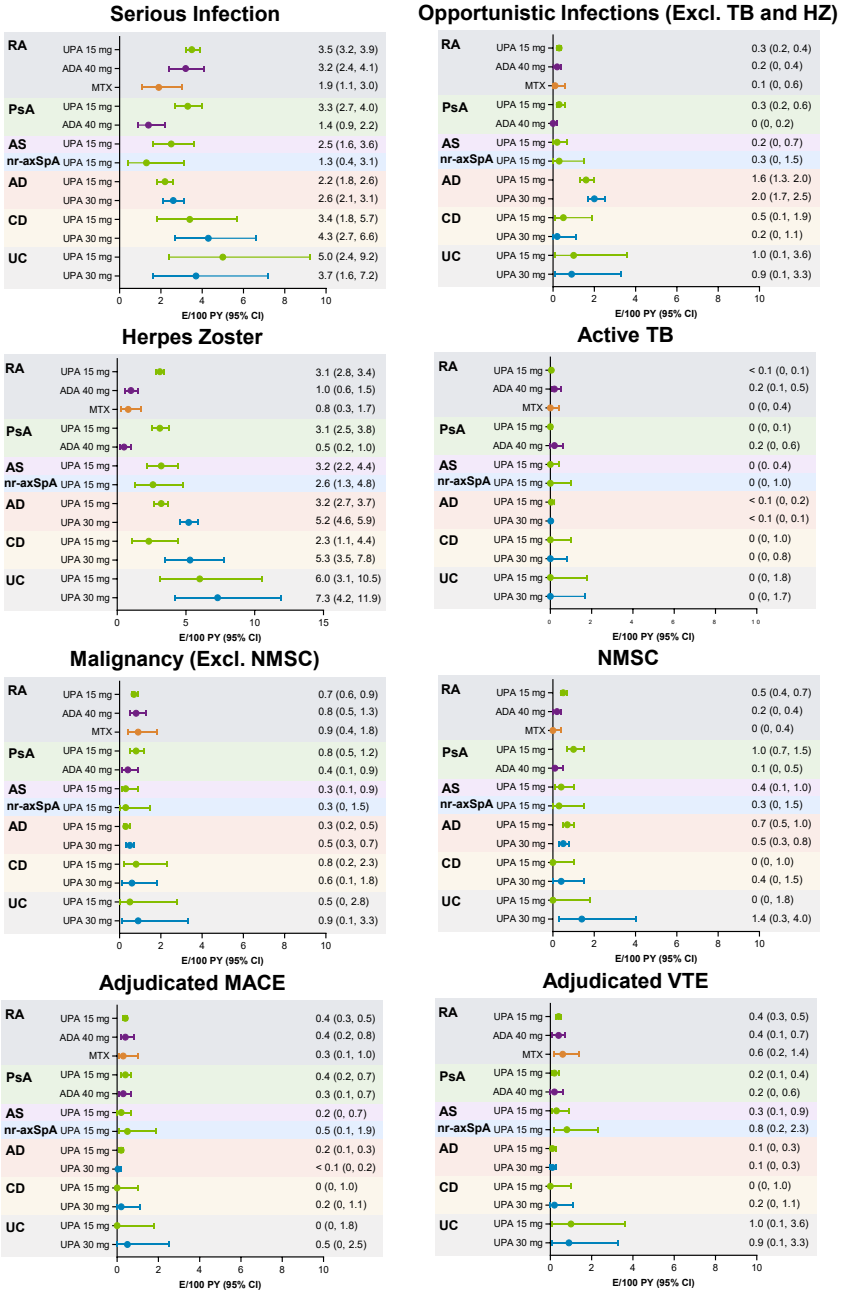
TEAE, n/100 PY (95% CI)	AD				CD				UC			
	UPA 15 mg		UPA 30 mg		UPA 15 mg		UPA 30 mg		UPA 15 mg		UPA 30 mg	
	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y	< 65 y	≥ 65 y
	n = 1289	n = 48	n = 1278	n = 68	n = 214	n = 7	n = 221	n = 8	n = 227	n = 23	n = 230	n = 21
Bone fracture	1.1 (0.8, 1.5)	2.5 (0.5, 7.4)	1.7 (1.4, 2.2)	4.1 (1.8, 8.0)	0.5 (0.1, 2.0)	6.1 (0.2, 34.1)	0.9 (0.2, 2.2)	0 (0, 24.2)	0.6 (0, 3.1)	0 (0, 17.5)	1.5 (0.3, 4.4)	11.2 (1.4, 40.3)
Retinal detachment	< 0.1 (0, 0.2)	0 (0, 2.9)	0.1 (0, 0.3)	1.0 (0.1, 3.4)	0 (0, 1.0)	0 (0, 19.4)	0 (0, 0.8)	0 (0, 24.2)	0.6 (0, 3.1)	0 (0, 17.5)	1.0 (0.1, 3.6)	0 (0, 20.2)
Serious hypersensitivity reaction	< 0.1 (0, 0.1)	0 (0, 2.9)	0.2 (0.1, 0.3)	0 (0, 1.7)	0 (0, 1.0)	0 (0, 19.4)	0 (0, 0.8)	0 (0, 24.2)	0 (0, 2.1)	0 (0, 17.5)	0 (0, 1.8)	0 (0, 20.2)

AD, atopic dermatitis; CD, Crohn's disease; CK, creatine kinase; excl., excluding; GI, gastrointestinal; HZ, herpes zoster; MACE, major adverse cardiovascular event; n/100 PY, number of patients with at least 1 event per 100 patient-years; NMSC, nonmelanoma skin cancer; TB, tuberculosis; TEAE, treatment-emergent adverse event; UC, ulcerative colitis; UPA, upadacitinib; VTE, venous thromboembolism; y, year.

[a]Excluding HZ and TB.

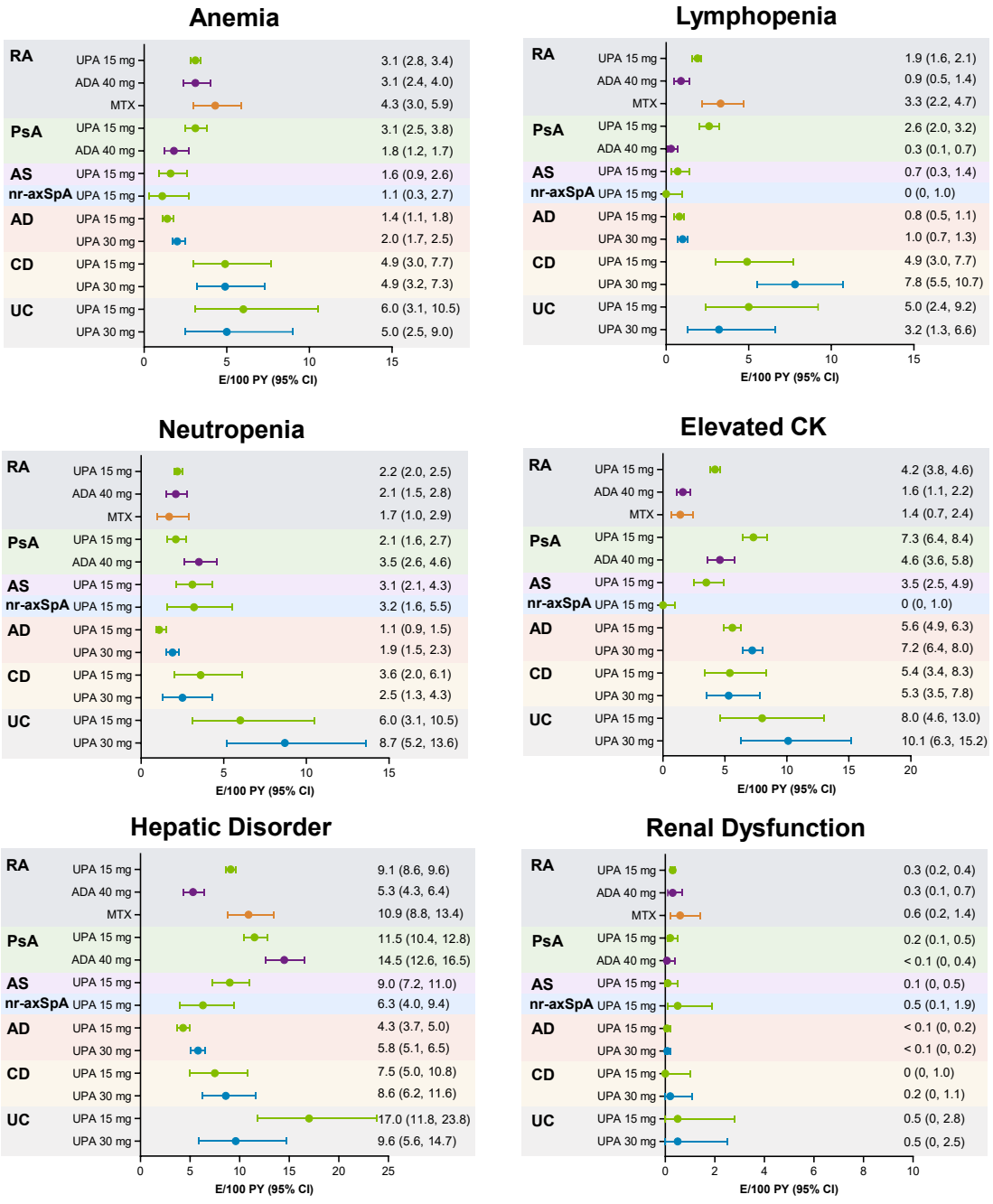
Supplemental Figure 1. Exposure-adjusted event rates of infections, malignancies, and cardiovascular events[a]

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CD, Crohn's disease; E/100 PY, events per 100 patient-years; excl., excluding; MACE, major adverse cardiovascular events; MTX, methotrexate; NMSC, nonmelanoma skin cancer; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TB, tuberculosis; UC, ulcerative colitis; UPA, upadacitinib; VTE, venous thromboembolism. [a]RA: UPA 15 mg (n = 3209), ADA 40 mg (n = 579), MTX (n = 314); PsA: UPA 15 mg (n = 907), ADA 40 mg (n = 429); AS: UPA 15 mg (n = 596); nr-axSpA: UPA 15 mg (n = 286); AD: UPA 15 mg (n = 1337), UPA 30 mg (n = 1346); CD: UPA 15 mg (n = 221), UPA 30 mg (n = 229); UC: UPA 15 mg (n = 250), UPA 30 mg (n = 251).



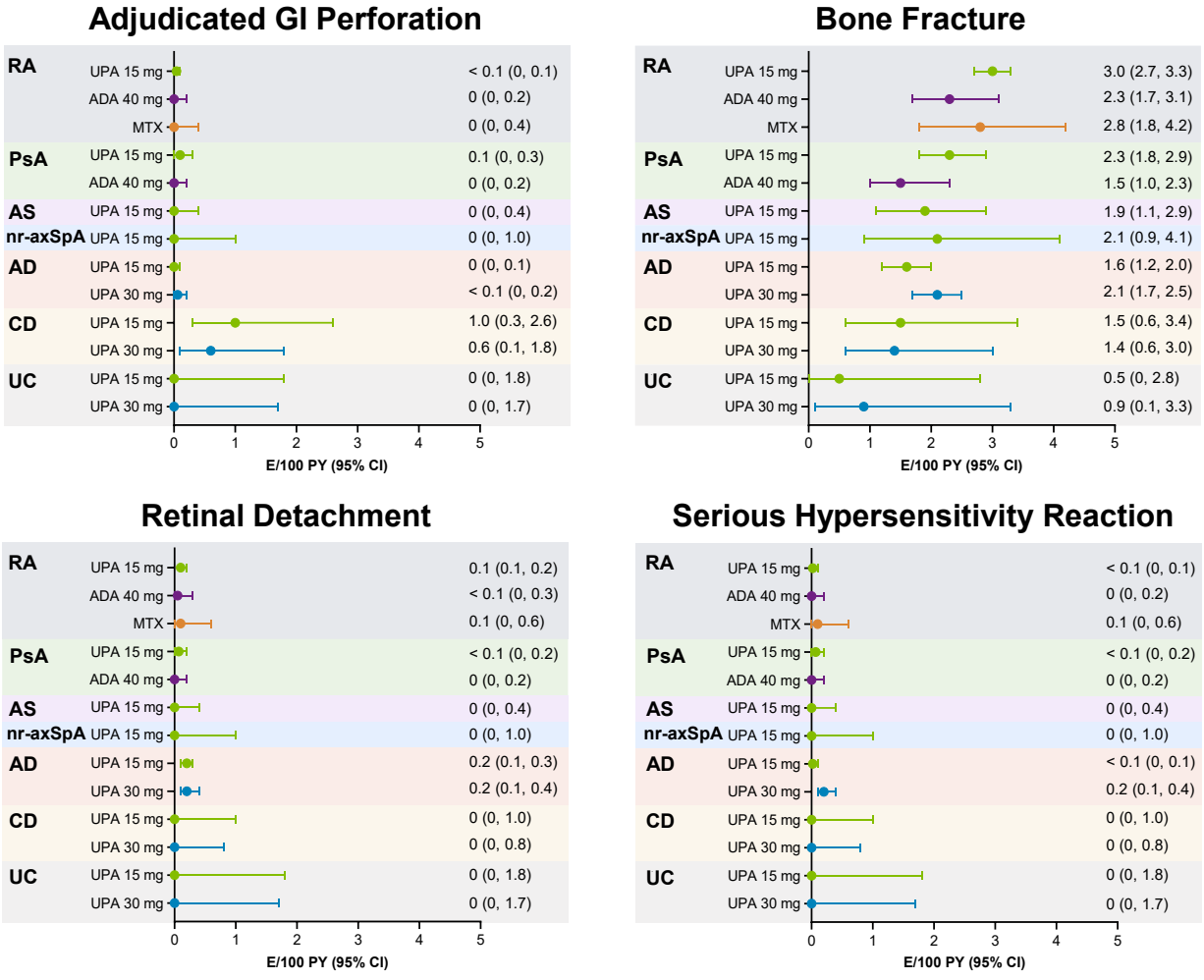
Supplemental Figure 2. Exposure-adjusted event rates of laboratory-related abnormalities[a]

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CD, Crohn's disease; CK, creatine kinase; E/100 PY, events per 100 patient-years; MTX, methotrexate; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis; UPA, upadacitinib. [a]RA: UPA 15 mg (n = 3209), ADA 40 mg (n = 579), MTX (n = 314); PsA: UPA 15 mg (n = 907), ADA 40 mg (n = 429); AS: UPA 15 mg (n = 596); nr-axSpA: UPA 15 mg (n = 286); AD: UPA 15 mg (n = 1337), UPA 30 mg (n = 1346); CD: UPA 15 mg (n = 221), UPA 30 mg (n = 229); UC: UPA 15 mg (n = 250), UPA 30 mg (n = 251).



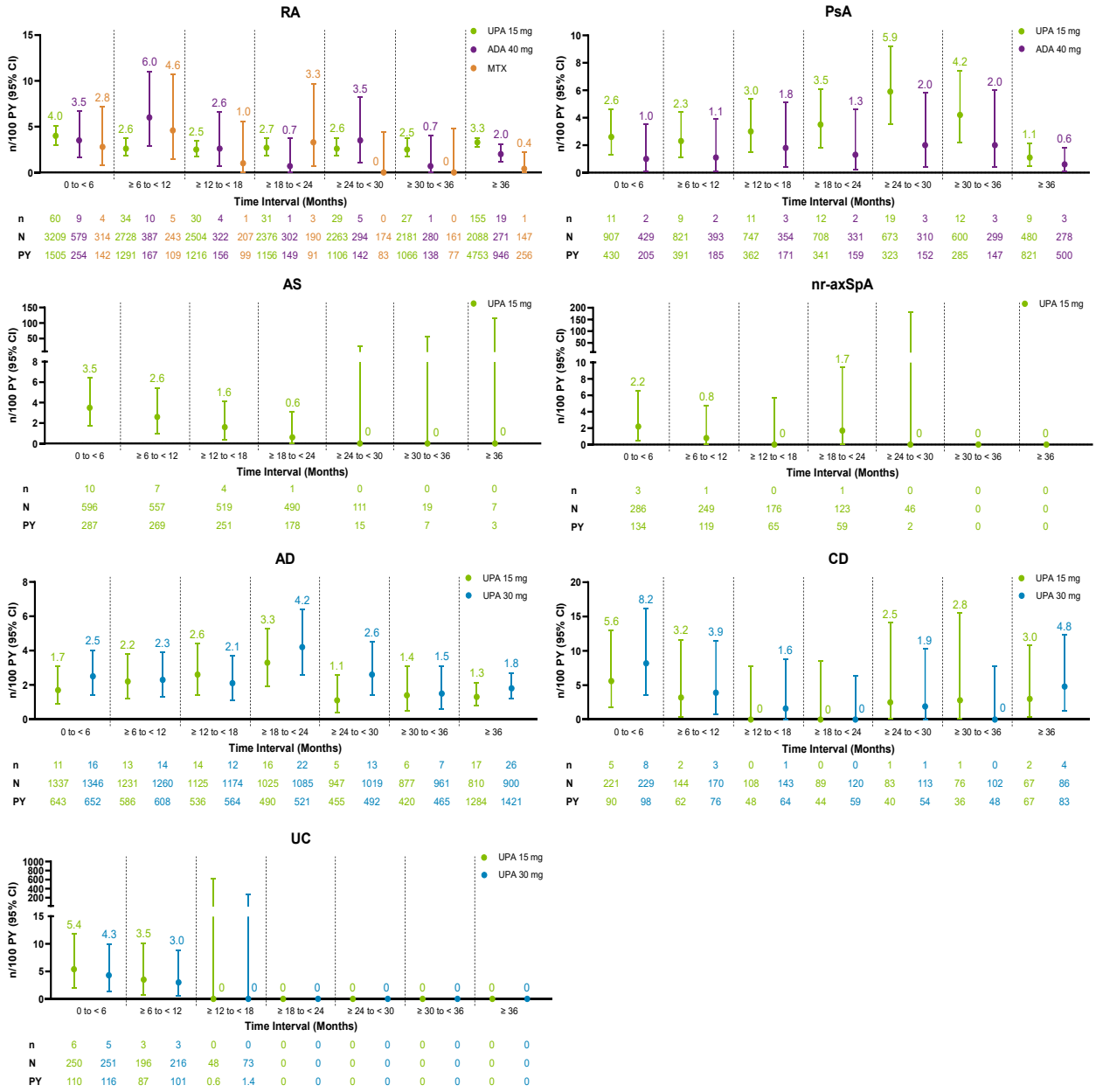
Supplemental Figure 3. Exposure-adjusted event rates of GI perforation, bone fracture, retinal detachment, and serious hypersensitivity reaction[a]

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CD, Crohn's disease; E/100 PY, events per 100 patient-years; GI, gastrointestinal; MTX, methotrexate; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis; UPA, upadacitinib. [a]RA: UPA 15 mg (n = 3209), ADA 40 mg (n = 579), MTX (n = 314); PsA: UPA 15 mg (n = 907), ADA 40 mg (n = 429); AS: UPA 15 mg (n = 596); nr-axSpA: UPA 15 mg (n = 286); AD: UPA 15 mg (n = 1337), UPA 30 mg (n = 1346); CD: UPA 15 mg (n = 221), UPA 30 mg (n = 229); UC: UPA 15 mg (n = 250), UPA 30 mg (n = 251).



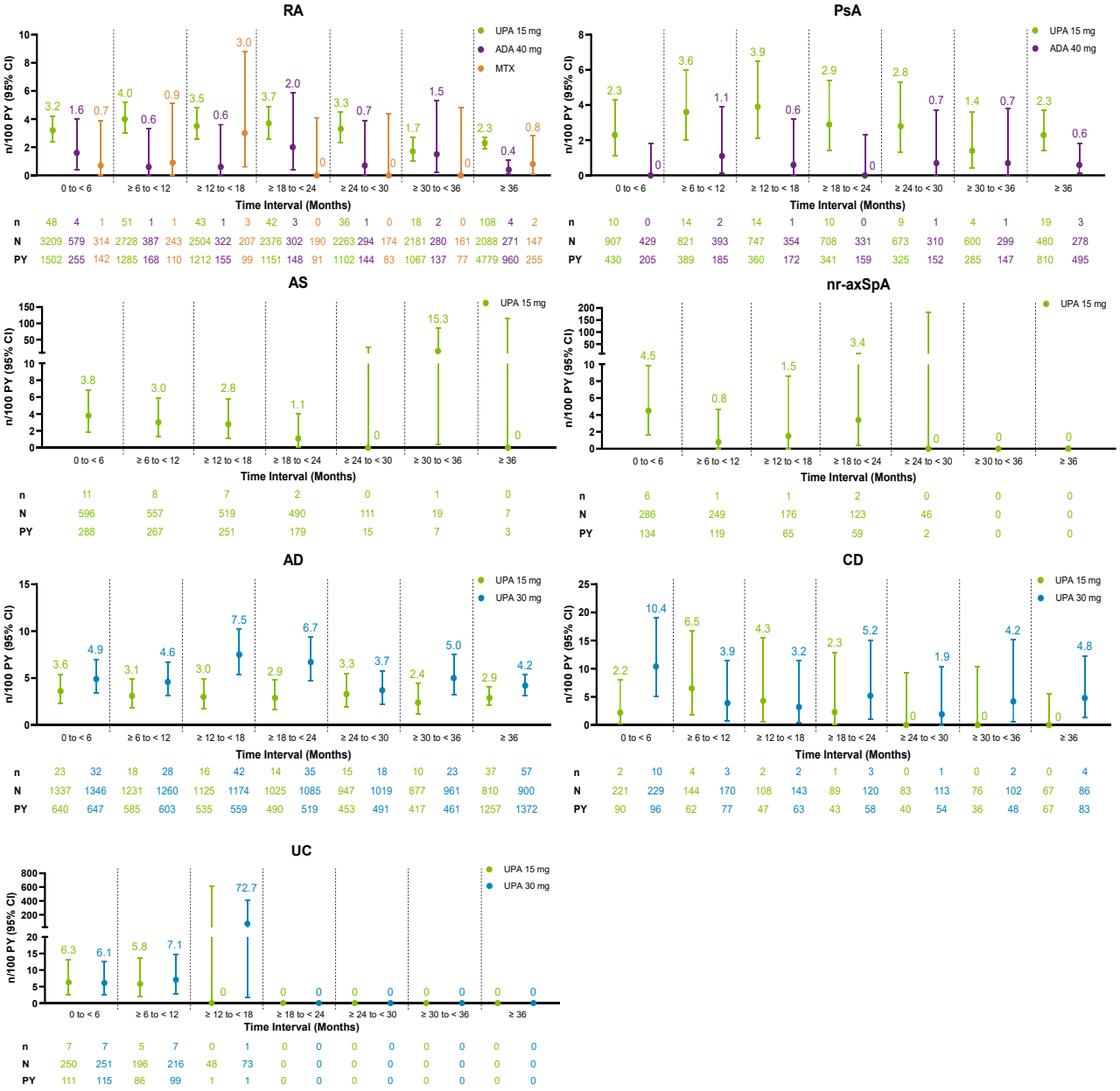
Supplemental Figure 4. Treatment-emergent serious infections over time

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CD, Crohn's disease; MTX, methotrexate; n/100 PY, patients with at least 1 event per 100 patient-years; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; PY, patient-years; RA, rheumatoid arthritis; UC, ulcerative colitis; UPA, upadacitinib.



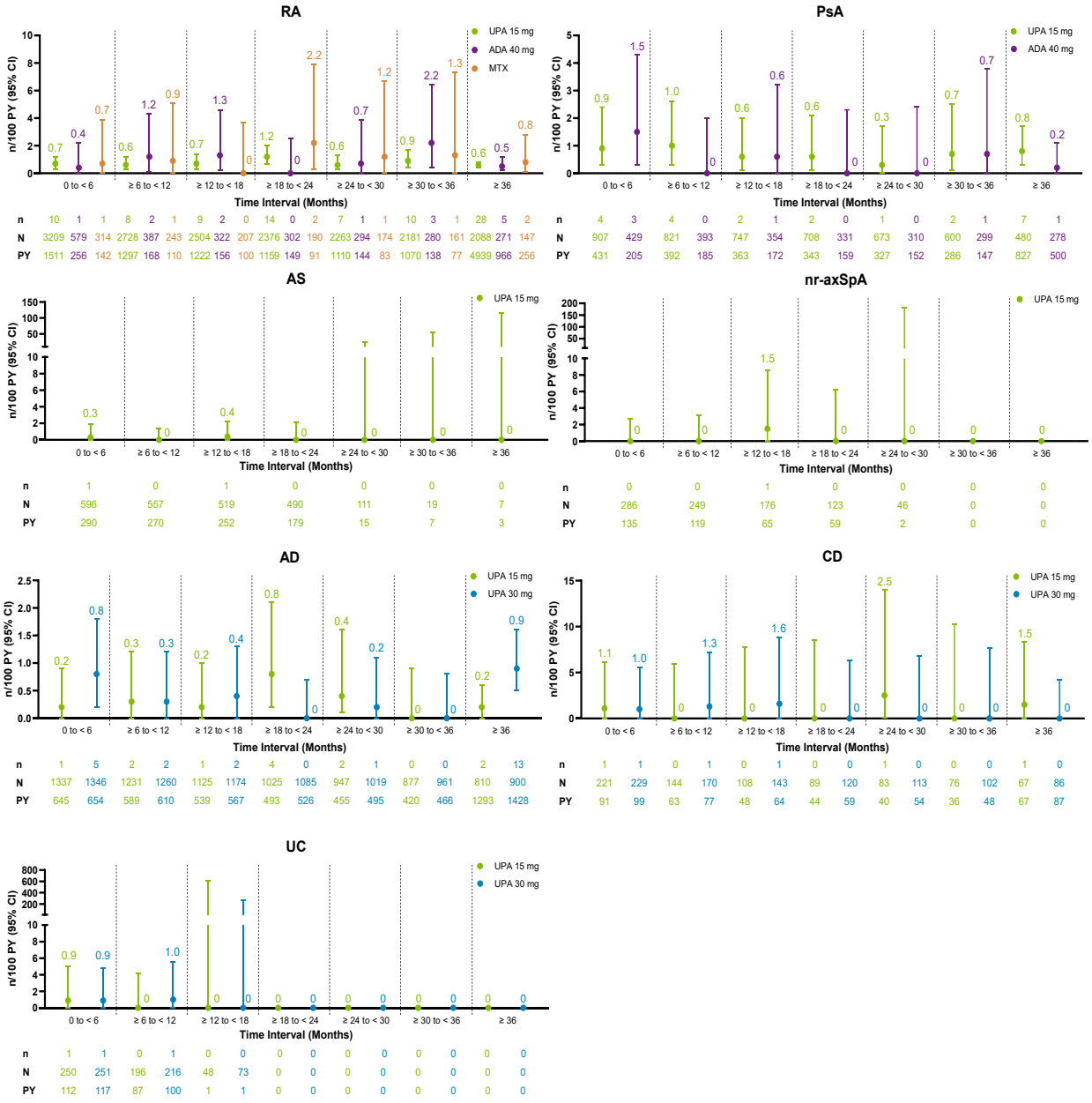
Supplemental Figure 5. Treatment-emergent herpes zoster over time

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CD, Crohn's disease; MTX, methotrexate; n/100 PY, patients with at least 1 event per 100 patient-years; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; PY, patient-years; RA, rheumatoid arthritis; UC, ulcerative colitis; UPA, upadacitinib.



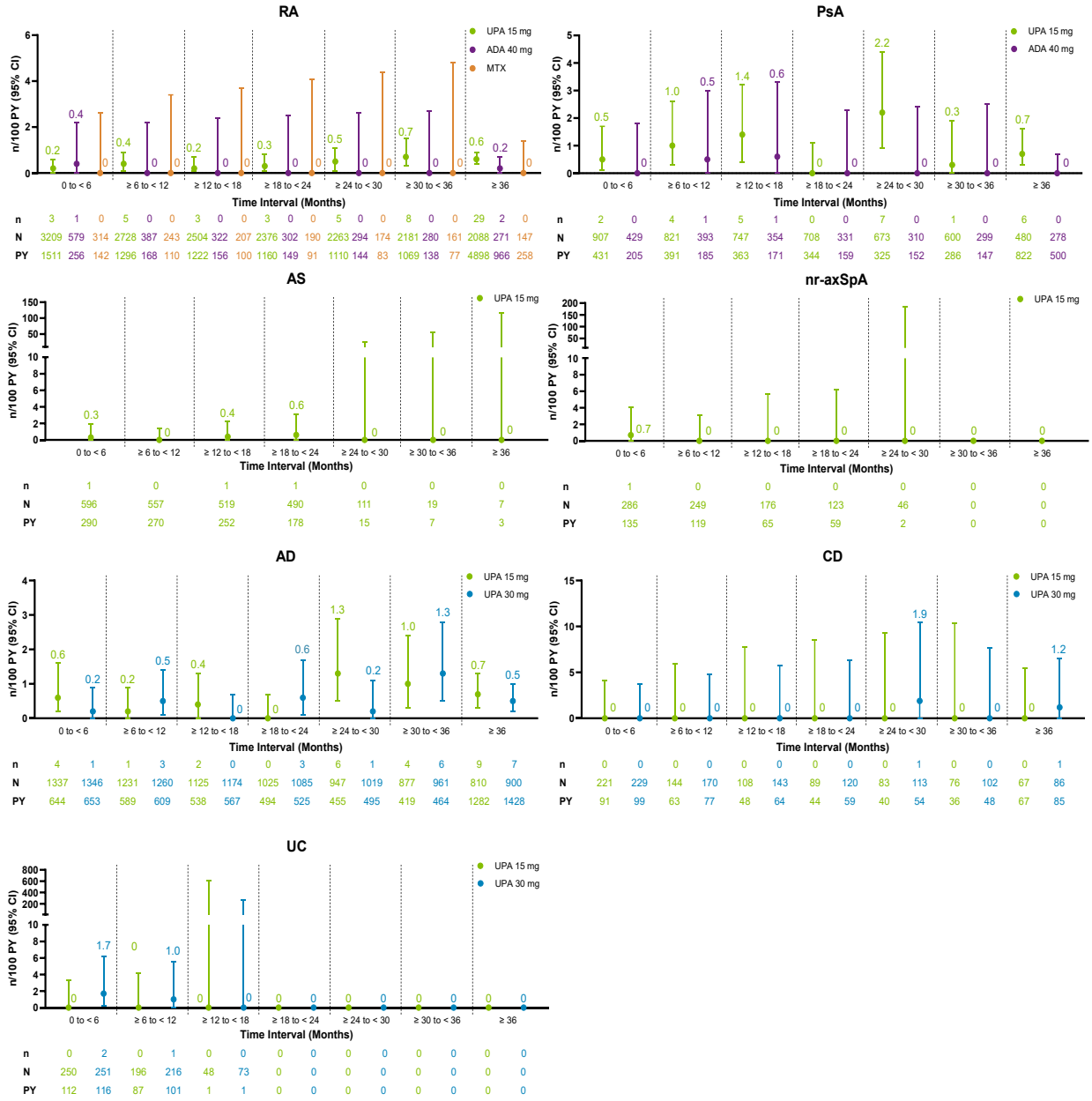
Supplemental Figure 6. Treatment-emergent malignancy (excluding NMSC) over time

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CD, Crohn's disease; MTX, methotrexate; n/100 PY, patients with at least 1 event per 100 patient-years; NMSC, nonmelanoma skin cancer; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; PY, patient-years; RA, rheumatoid arthritis; UC, ulcerative colitis; UPA, upadacitinib.



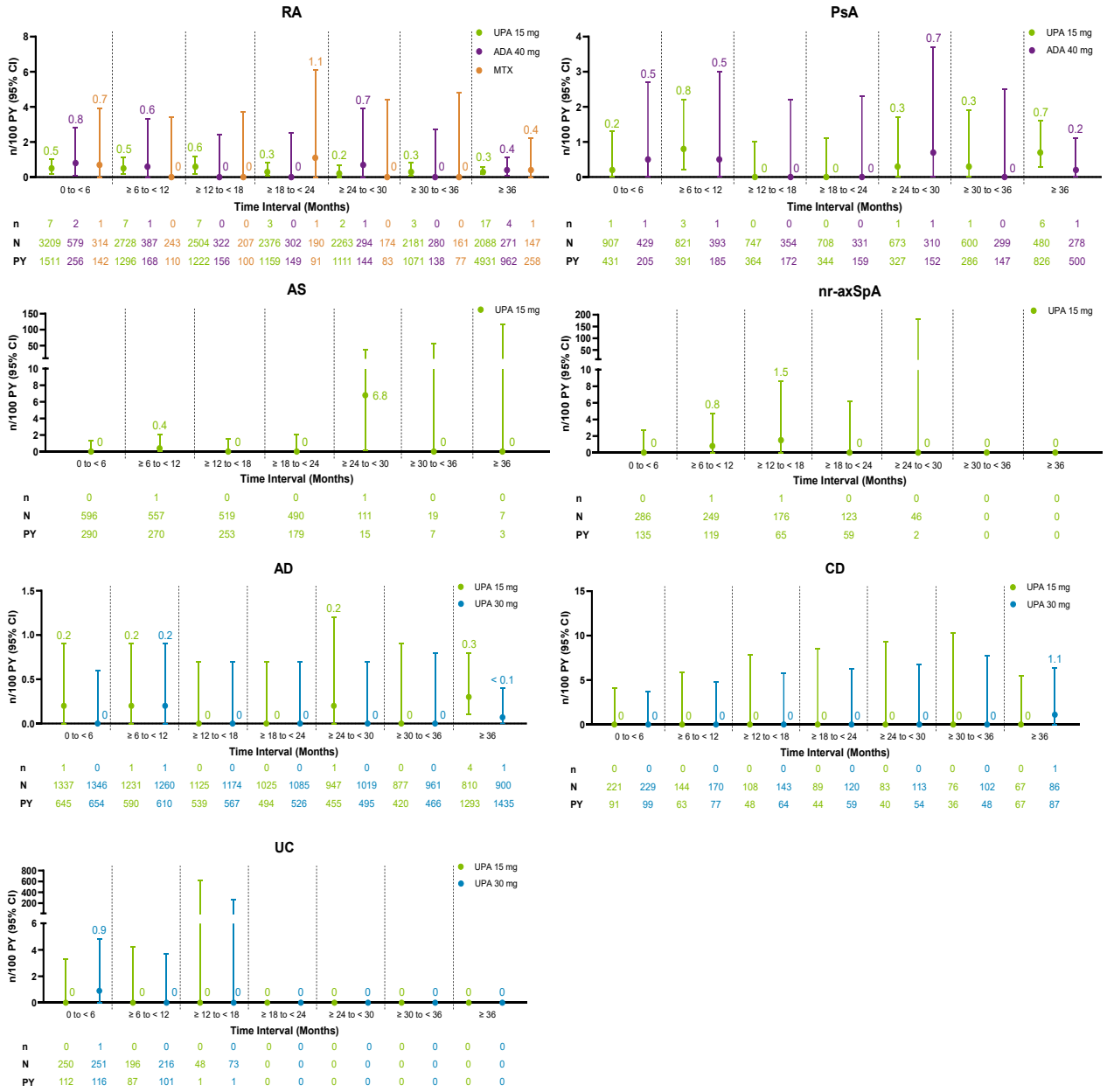
Supplemental Figure 7. Treatment-emergent NMSC over time

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CD, Crohn's disease; MTX, methotrexate; n/100 PY, patients with at least 1 event per 100 patient-years; NMSC, nonmelanoma skin cancer; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; PY, patient-years; RA, rheumatoid arthritis; UC, ulcerative colitis; UPA, upadacitinib.



Supplemental Figure 8. Treatment-emergent MACE over time

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CD, Crohn's disease; MACE, major adverse cardiovascular event; MTX, methotrexate; n/100 PY, patients with at least 1 event per 100 patient-years; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; PY, patient-years; RA, rheumatoid arthritis; UC, ulcerative colitis; UPA, upadacitinib.



Supplemental Figure 9. Treatment-emergent VTE over time

AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CD, Crohn's disease; MTX, methotrexate; n/100 PY, patients with at least 1 event per 100 patient-years; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; PY, patient-years; RA, rheumatoid arthritis; UC, ulcerative colitis; UPA, upadacitinib; VTE, venous thromboembolism.