**SUPPLEMENTARY MATERIALS**

# Malignancy in the Upadacitinib Clinical Trials for Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, and Non-radiographic Axial Spondyloarthritis

Andrea Rubbert-Roth, MD[1]; Adriana M. Kakehasi, MD, PhD[2]; Tsutomu Takeuchi, MD, PhD[3]; Marc Schmalzing, MD[4]; Hannah Palac, MS[5]; Derek Coombs, BA, MPH[5]; Jianzhong Liu, MD, MS[5*]; Samuel I. Anyanwu, PhD[5]; Ralph Lippe, PhD[6]; Jeffrey R. Curtis, MD, MS, MPH[7]

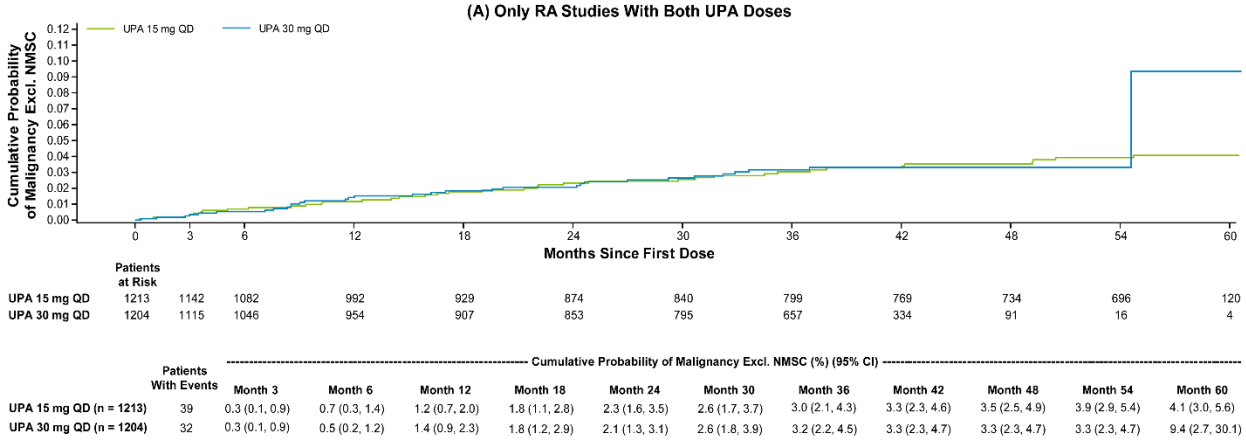
*[1]Division of Rheumatology, Cantonal Clinic St Gallen, St Gallen, Switzerland; [2]Federal University of Minas Gerais, Hospital das Clínicas, Belo Horizonte, Brazil; [3]Keio University School of Medicine, Tokyo, and Saitama Medical University, Saitama, Japan; [4]Rheumatology/Clinical Immunology, Department of Internal Medicine II, University of Würzburg, Germany; [5]AbbVie Inc., North Chicago, IL, USA; [6]AbbVie Deutschland GmbH & Co. KG, Wiesbaden, Germany; [7]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, USA*

**At time of study*

Corresponding Author: Dr. Andrea Rubbert-Roth

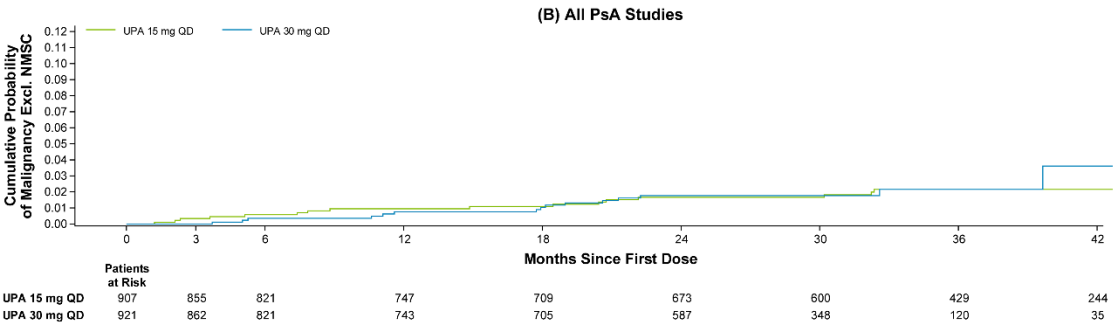
## Supplementary Figure 1. Kaplan-Meier Estimates for Time to Malignancy Excluding NMSC Events in RA and PsA With UPA 15 mg or UPA 30 mg

CI, confidence interval; NMSC, nonmelanoma skin cancer; PsA, psoriatic arthritis; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib.




| | Patients at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| UPA 15 mg QD | 1213 | 1142 | 1082 | 992 | 929 | 874 | 840 | 799 | 769 | 734 | 696 | 120 |
| UPA 30 mg QD | 1204 | 1115 | 1046 | 954 | 907 | 853 | 795 | 657 | 334 | 91 | 16 | 4 |

| | Patients With Events | Cumulative Probability of Malignancy Excl. NMSC (%) (95% CI) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Month 3 | Month 6 | Month 12 | Month 18 | Month 24 | Month 30 | Month 36 | Month 42 | Month 48 | Month 54 | Month 60 |
| UPA 15 mg QD (n = 1213) | 39 | 0.3 (0.1, 0.9) | 0.7 (0.3, 1.4) | 1.2 (0.7, 2.0) | 1.8 (1.1, 2.8) | 2.3 (1.6, 3.5) | 2.6 (1.7, 3.7) | 3.0 (2.1, 4.3) | 3.3 (2.3, 4.6) | 3.5 (2.5, 4.9) | 3.9 (2.9, 5.4) | 4.1 (3.0, 5.6) |
| UPA 30 mg QD (n = 1204) | 32 | 0.3 (0.1, 0.9) | 0.5 (0.2, 1.2) | 1.4 (0.9, 2.3) | 1.8 (1.2, 2.9) | 2.1 (1.3, 3.1) | 2.6 (1.8, 3.9) | 3.2 (2.2, 4.5) | 3.3 (2.3, 4.7) | 3.3 (2.3, 4.7) | 3.3 (2.3, 4.7) | 9.4 (2.7, 30.1) |

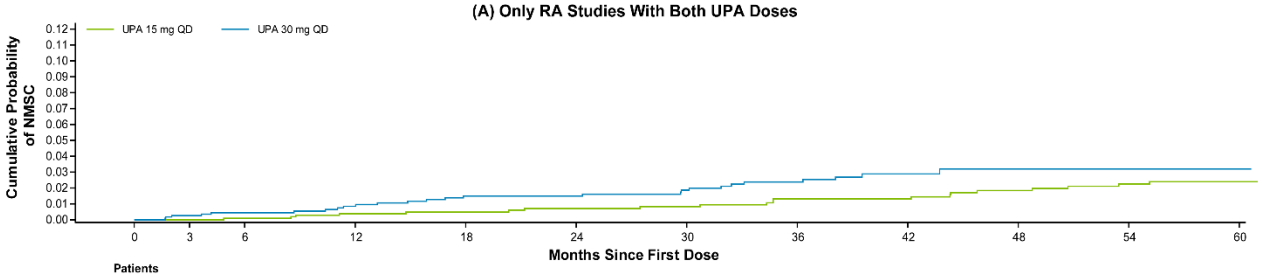



| | Patients at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| UPA 15 mg QD | 907 | 855 | 821 | 747 | 709 | 673 | 600 | 429 | 244 |
| UPA 30 mg QD | 921 | 862 | 821 | 743 | 705 | 587 | 348 | 120 | 35 |

| | Patients With Events | Cumulative Probability of Malignancy Excl. NMSC (%) (95% CI) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Month 3 | Month 6 | Month 12 | Month 18 | Month 24 | Month 30 | Month 36 | Month 42 |
| UPA 15 mg QD (n = 907) | 16 | 0.3 (0.1, 1.0) | 0.6 (0.2, 1.4) | 1.0 (0.5, 1.9) | 1.1 (0.6, 2.1) | 1.7 (1.0, 2.8) | 1.7 (1.0, 2.8) | 2.2 (1.3, 3.5) | 2.2 (1.3, 3.5) |
| UPA 30 mg QD (n = 921) | 15 | 0 | 0.4 (0.1, 1.1) | 0.8 (0.3, 1.7) | 1.0 (0.5, 2.1) | 1.8 (1.0, 3.0) | 1.8 (1.0, 3.0) | 2.2 (1.2, 3.8) | 3.6 (1.5, 8.4) |

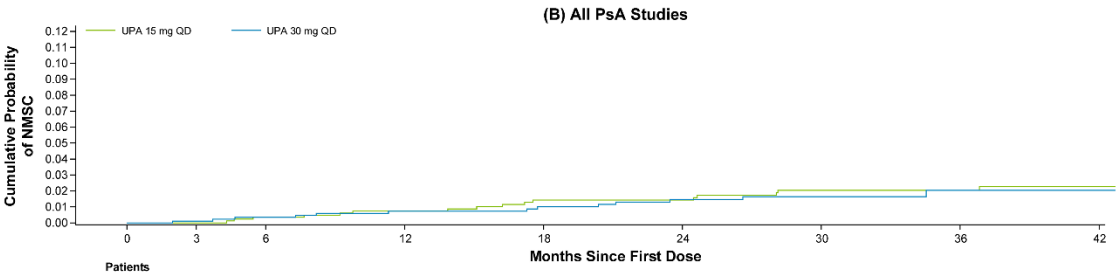
## Supplementary Figure 2. Kaplan-Meier Estimates for Time to NMSC Events in RA and PsA With UPA 15 mg or UPA 30 mg

CI, confidence interval; NMSC, nonmelanoma skin cancer; PsA, psoriatic arthritis; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib.




| Patients at Risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| UPA 15 mg QD | 1213 | 1144 | 1082 | 988 | 927 | 870 | 836 | 792 | 761 | 726 | 689 | 119 |
| UPA 30 mg QD | 1204 | 1116 | 1042 | 950 | 896 | 841 | 783 | 645 | 326 | 89 | 16 | 4 |

| | Patients With Events | Cumulative Probability of NMSC (%) (95% CI) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Month 3 | Month 6 | Month 12 | Month 18 | Month 24 | Month 30 | Month 36 | Month 42 | Month 48 | Month 54 | Month 60 |
| UPA 15 mg QD (n = 1213) | 20 | 0 | <0.1 (<0.1, 0.6) | 0.4 (0.1, 1.0) | 0.5 (0.2, 1.2) | 0.7 (0.3, 1.5) | 0.8 (0.4, 1.6) | 1.3 (0.7, 2.3) | 1.3 (0.7, 2.3) | 1.8 (1.1, 3.0) | 2.3 (1.4, 3.5) | 2.4 (1.5, 3.7) |
| UPA 30 mg QD (n = 1204) | 26 | 0.3 (<0.1, 0.8) | 0.4 (0.2, 1.1) | 0.8 (0.4, 1.6) | 1.5 (0.9, 2.5) | 1.5 (0.9, 2.5) | 1.9 (1.2, 2.9) | 2.4 (1.6, 3.6) | 2.9 (1.9, 4.3) | 3.2 (2.1, 4.8) | 3.2 (2.1, 4.8) | 3.2 (2.1, 4.8) |




| Patients at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| UPA 15 mg QD | 907 | 856 | 819 | 742 | 700 | 666 | 591 | 426 | 241 |
| UPA 30 mg QD | 921 | 861 | 819 | 739 | 703 | 583 | 345 | 118 | 35 |

| | Patients With Events | Cumulative Probability of NMSC (%) (95% CI) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Month 3 | Month 6 | Month 12 | Month 18 | Month 24 | Month 30 | Month 36 | Month 42 |
| UPA 15 mg QD (n = 907) | 16 | 0 | 0.4 (0.1, 1.1) | 0.7 (0.3, 1.6) | 1.4 (0.8, 2.6) | 1.4 (0.8, 2.6) | 2.0 (1.2, 3.4) | 2.0 (1.2, 3.4) | 2.3 (1.4, 3.7) |
| UPA 30 mg QD (n = 921) | 13 | 0.1 (<0.1, 0.8) | 0.3 (0.1, 1.1) | 0.7 (0.3, 1.6) | 1.0 (0.5, 2.0) | 1.5 (0.8, 2.6) | 1.6 (0.9, 2.9) | 2.0 (1.1, 3.7) | 2.0 (1.1, 3.7) |

## Supplementary Table 1. Overview of SELECT Clinical Trials Across RA Included in Post Hoc Analysis

| | SELECT-EARLY | SELECT-NEXT | SELECT-COMPARE | SELECT-MONOTHERAPY | SELECT-BEYOND | SELECT-CHOICE |
|---|---|---|---|---|---|---|
| NCT number | NCT02706873 | NCT02675426 | NCT02629159 | NCT02706951 | NCT02706847 | NCT03086343 |
| Patient population | MTX-naïve | csDMARD-IR | MTX-IR | MTX-IR | Biologic-IR | Biologic-IR |
| Total sample size[†] | N=947 | N=661 | N=1629 | N=648 | N=499 | N=613 |
| Treatment arms | UPA 15 mg QD (n=317) | UPA 15 mg QD (n=221) | UPA 15 mg QD (n=651) | UPA 15 mg QD (n=217) | UPA 15 mg QD (n=164) | UPA 15 mg QD (n=303) |
| | UPA 30 mg QD (n=314) | UPA 30 mg QD (n=219) | ADA 40 mg EOW (n=327) | UPA 30 mg QD (n=215) | UPA 30 mg QD (n=165) | Abatacept IV (n=309) |
| | MTX (n=314) | Placebo (n=221) | Placebo (n=651) | MTX (n=216) | Placebo (n=169) | |
| Study duration | DBPC: 48 weeks | DBPC: 12 weeks | DBPC: 48 weeks | DBPC: 14 weeks | DBPC: 24 weeks | DBPC: 24 weeks |
| | LTE: 5 years total (ongoing) | LTE: 5 years total | LTE: 10 years total (ongoing) | LTE: 5 years total | LTE: 5 years total | LTE: ~4 years (ongoing) |

ADA, adalimumab; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DBPC, double-blind placebo-controlled; EOW, every other week; IR, inadequate response; IV, intravenous; LTE, long-term extension; MTX, methotrexate; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib.

[†]For the following studies, patients underwent treatment randomization (and are included in the total sample size shown) but did not receive study drug: SELECT-EARLY (2 patients; UPA 30 mg and MTX), SELECT-BEYOND (1 patient, UPA 15 mg), and SELECT-CHOICE (1 patient, UPA 15 mg).

## Supplementary Table 2. Overview of SELECT Clinical Trials Across PsA, AS, and nr-axSpA Included in Post Hoc Analysis

| | PsA | | AS | | nr-axSpA |
|---|---|---|---|---|---|
| | SELECT-PsA 1 | SELECT-PsA 2 | SELECT-AXIS 1 | SELECT-AXIS 2 | SELECT-AXIS 2 |
| NCT number | NCT03104400 | NCT03104374 | NCT03178487 | NCT04169373 | NCT04169373 |
| Patient population | Non-bDMARD-IR | bDMARD-IR | NSAID-IR | bDMARD-IR | NSAID-IR, including bDMARD-IR |
| Total sample size[†] | N=1705 | N=642 | N=187 | N=420 | N=314 |
| Treatment arms | UPA 15 mg QD (n=429)<br>UPA 30 mg QD (n=423)<br>ADA 40 mg EOW (n=429)<br>Placebo (n=423) | UPA 15 mg QD (n=211)<br>UPA 30 mg QD (n=218)<br>Placebo (n=212) | UPA 15 mg QD (n=93)<br>Placebo (n=94) | UPA 15 mg QD (n=211)<br>Placebo (n=209) | UPA 15 mg QD (n=156)<br>Placebo (n=157) |
| Study duration | DBPC: 24 weeks<br>LTE: 5 years total (ongoing) | DBPC: 24 weeks<br>LTE: 3 years total | DBPC: 14 weeks<br>LTE: 2 years total | DBPC: 14 weeks<br>LTE: 2 years total (ongoing) | DBPC: 52 weeks<br>LTE: 2 years total (ongoing) |

AS, ankylosing spondylitis; bDMARD, biologic disease-modifying antirheumatic drug; DBPC, double-blind placebo-controlled; EOW, every other week; IR, inadequate response; LTE, long-term extension; nr-axSpA, non-radiographic axial spondyloarthritis; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; QD, once daily; UPA, upadacitinib.

[†]For the following studies, patients underwent treatment randomization (and are included in the total sample size shown) but did not receive study drug: SELECT-PsA 1 (1 patient, UPA 15 mg), SELECT-PsA 2 (1 patient, UPA 30 mg), and SELECT-AXIS 2 nr-axSpA (1 patient, placebo).

## Supplementary Table 3. Patient Baseline Characteristics Across RA, PsA, AS, and nr-axSpA by Malignancy Event Status†

| Parameter, n (%)‡ | RA | | | | PsA | | | AS | nr-axSpA |
|---|---|---|---|---|---|---|---|---|---|
| No malignancy | UPA 15 mg QD n=3093 | UPA 30 mg QD n=1147 | ADA 40 mg EOW n=568 | MTX n=306 | UPA 15 mg QD n=878 | UPA 30 mg QD n=894 | ADA 40 mg EOW n=422 | UPA 15 mg QD n=592 | UPA 15 mg QD n=284 |
| Age (years), mean (SD) | 54.0 (12.0) | 54.9 (11.8) | 53.9 (11.6) | 53.2 (12.9) | 51.1 (12.0) | 51.2 (12.2) | 51.2 (12.0) | 43.2 (12.3) | 42.2 (12.2) |
| Sex (female) | 2502 (80.9) | 911 (79.4) | 464 (81.7) | 235 (76.8) | 466 (53.1) | 485 (54.3) | 217 (51.4) | 161 (27.2) | 166 (58.5) |
| BMI (kg/m$^2$), mean (SD) | 29.1 (6.7) | 29.3 (7.0) | 29.5 (7.2) | 28.0 (6.4) | 30.6 (6.9) | 30.5 (7.0) | 30.7 (7.3) | 26.8 (5.2) | 28.1 (5.9) |
| CRP, mean (SD) | 18.0 (21.9) | 16.3 (20.0) | 19.8 (23.0) | 20.9 (21.6) | 11.2 (16.7) | 10.6 (14.6) | 10.9 (15.4) | 13.4 (17.3) | 9.1 (15.0) |
| Tobacco/nicotine use (current + former) | 1169 (37.8) | 481 (41.9) | 192 (33.8) | 115 (37.6) | 372 (42.4) | 382 (42.7) | 161 (38.2) | 261 (44.1) | 94 (33.1) |
| Alcohol use (current + former) | 1079 (34.9) | 519 (45.2) | 195 (34.3) | 100 (32.7) | 446 (50.8) | 454 (50.8) | 206 (48.8) | 316 (53.4) | 139 (48.9) |
| Previous malignancy | 30 (1.0) | 23 (2.0) | 4 (0.7) | 2 (0.7) | 9 (1.0) | 12 (1.3) | 2 (0.5) | 9 (1.5) | 0 |
| Any history of oral contraceptive/hormone replacement therapy§ | 258 (10.3) | 91 (10.0) | 48 (10.3) | 19 (8.1) | 43 (9.2) | 51 (10.5) | 19 (8.8) | 40 (24.8) | 49 (29.5) |
| Malignancy excl. NMSC | UPA 15 mg QD n=76 | UPA 30 mg QD n=32 | ADA 40 mg EOW n=10 | MTX n=8 | UPA 15 mg QD n=16 | UPA 30 mg QD n=15 | ADA 40 mg EOW n=5 | UPA 15 mg QD n=2 | UPA 15 mg QD n=1 |
| Age (years), mean (SD) | 62.2 (9.8) | 63.0 (11.5) | 66.0 (10.4) | 60.4 (9.6) | 60.9 (11.6) | 59.6 (13.6) | 64.8 (6.3) | 58.0 (2.8) | 58.0 (N/A) |
| Sex (female) | 51 (67.1) | 23 (71.9) | 5 (50.0) | 5 (62.5) | 4 (25.0) | 12 (80.0) | 3 (60.0) | 0 | 1 (100.0) |
| BMI (kg/m$^2$), mean (SD) | 28.1 (6.8) | 29.3 (8.1) | 28.5 (6.8) | 29.6 (5.2) | 32.1 (8.1) | 31.4 (6.8) | 28.7 (4.9) | 31.5 (0.2) | 31.1 (N/A) |
| CRP, mean (SD) | 14.0 (12.1) | 9.1 (8.2) | 20.1 (15.7) | 31.2 (35.3) | 8.9 (8.3) | 21.6 (42.3) | 13.7 (20.4) | 6.6 (0.4) | 5.7 (N/A) |
| Tobacco/nicotine use (current + former) | 35 (46.1) | 15 (46.9) | 7 (70.0) | 5 (62.5) | 8 (50.0) | 7 (46.7) | 2 (40.0) | 2 (100.0) | 0 |
| Alcohol use (current + former) | 34 (44.7) | 15 (46.9) | 5 (50.0) | 4 (50.0) | 12 (75.0) | 9 (60.0) | 2 (40.0) | 1 (50.0) | 0 |
| Previous malignancy | 2 (2.6) | 1 (3.1) | 0 | 0 | 1 (6.3) | 2 (13.3) | 0 | 0 | 1 (100.0) |
| Any history of oral contraceptive/hormone replacement therapy§ | 4 (7.8) | 1 (4.3) | 1 (20.0) | 0 | 0 | 3 (25.0) | 0 | 0 | 0 |
| NMSC | UPA 15 mg QD n=45 | UPA 30 mg QD n=26 | ADA 40 mg EOW n=2 | MTX n=0 | UPA 15 mg QD n=16 | UPA 30 mg QD n=13 | ADA 40 mg EOW n=2 | UPA 15 mg QD n=2 | UPA 15 mg QD n=1 |
| Age (years), mean (SD) | 63.0 (8.5) | 65.6 (10.4) | 60.5 (12.0) | N/A | 64.8 (8.4) | 59.5 (10.8) | 53.5 (5.0) | 58.0 (5.7) | 50.0 (N/A) |
| Sex (female) | 30 (66.7) | 14 (53.8) | 1 (50.0) | N/A | 8 (50.0) | 8 (61.5) | 2 (100.0) | 1 (50.0) | 0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| BMI (kg/m$^2$), mean (SD) | 27.9 (6.1) | 29.8 (7.4) | 30.5 (1.9) | N/A | 26.9 (3.6) | 30.4 (2.9) | 32.1 (0.3) | 27.2 (6.1) | 28.7 (N/A) |
| CRP, mean (SD) | 13.6 (12.0) | 12.5 (11.3) | 24.7 (26.6) | N/A | 6.1 (7.6) | 14.3 (21.9) | 0.8 (0.7) | 0.8 (0.2) | 1.7 (N/A) |
| Tobacco/nicotine use (current + former) | 22 (48.9) | 13 (50.0) | 1 (50.0) | N/A | 7 (43.8) | 6 (46.2) | 0 | 1 (50.0) | 0 |
| Alcohol use (current + former) | 21 (46.7) | 17 (65.4) | 2 (100.0) | N/A | 12 (75.0) | 9 (69.2) | 2 (100.0) | 0 | 1 (100.0) |
| Previous malignancy | 3 (6.7) | 3 (11.5) | 0 | N/A | 3 (18.8) | 3 (23.1) | 0 | 1 (50.0) | 0 |
| Any history of oral contraceptive/hormone replacement therapy[§] | 1 (3.3) | 0 | 0 | N/A | 0 | 1 (12.5) | 0 | 0 | 0 |

ADA, adalimumab; AS, ankylosing spondylitis; BMI, body mass index; CRP, C-reactive protein; EOW, every other week; MTX, methotrexate; N/A, not applicable; NMSC, nonmelanoma skin cancer; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib.

[†]Patients may have experienced more than one malignancy event; therefore, the sum of patients across all events may exceed the total number of patients in each treatment group.

[‡]Data are presented as n (%), unless indicated.

[§]The denominator is the number of female patients.

## Supplementary Table 4. Incidence Rates per 100 Patient-years for TEAEs of Malignancy in Patients Treated With UPA Across RA, PsA, AS, and nr-axSpA

| | All RA Studies | | | | Only RA Studies With Both UPA Doses | | SELECT-COMPARE (RA) Study | |
|---|---|---|---|---|---|---|---|---|
| EAIR[†] | UPA 15 mg QD n=3209 | UPA 30 mg QD n=1204 | ADA 40 mg EOW n=579 | MTX n=314 | UPA 15 mg QD n=1213 | UPA 30 mg QD n=1204 | UPA 15 mg QD n=1417 | ADA 40 mg EOW n=579 |
| Malignancy (Excl. NMSC) | 0.7 (0.6, 0.9) [76] | 1.0 (0.7, 1.4) [32] | 0.6 (0.3, 1.2) [10] | 0.9 (0.4, 1.8) [8] | 0.9 (0.6, 1.2) [39] | 1.0 (0.7, 1.4) [32] | 0.6 (0.4, 0.8) [27] | 0.6 (0.3, 1.2) [10] |
| Lymphoma[‡] | <0.1 (0.0, 0.1) [4] | <0.1 (0.0, 0.2) [2] | 0.2 (0.0, 0.6) [3] | 0.0 (0.0, 0.4) [0] | <0.1 (0.0, 0.2) [4] | <0.1 (0.0, 0.2) [2] | 0.0 (0.0, 0.1) [0] | 0.2 (0.0, 0.6) [3] |
| NMSC | 0.4 (0.3, 0.6) [45] | 0.8 (0.5, 1.2) [26] | 0.1 (0.0, 0.5) [2] | 0.0 (0.0, 0.4) [0] | 0.5 (0.3, 0.7) [20] | 0.8 (0.5, 1.2) [26] | 0.4 (0.3, 0.7) [20] | 0.1 (0.0, 0.5) [2] |
| | All PsA Studies | | | SELECT-PsA 1 Study | | | AS | nr-axSpA |
| EAIR[†] | UPA 15 mg QD n=907 | UPA 30 mg QD n=921 | ADA 40 mg EOW n=429 | UPA 15 mg QD n=617 | UPA 30 mg QD n=613 | ADA 40 mg EOW n=429 | UPA 15 mg QD n=596 | UPA 15 mg QD n=286 |
| Malignancy (Excl. NMSC) | 0.7 (0.4, 1.1) [16] | 0.8 (0.4, 1.3) [15] | 0.4 (0.1, 1.0) [5] | 0.6 (0.3, 1.0) [10] | 0.7 (0.3, 1.3) [9] | 0.4 (0.1, 1.0) [5] | 0.2 (0.0, 0.8) [2] | 0.3 (0.0, 1.7) [1] |
| Lymphoma[‡] | 0.1 (0.0, 0.4) [3] | 0.0 (0.0, 0.2) [0] | 0.0 (0.0, 0.3) [0] | <0.1 (0.0, 0.3) [1] | 0.0 (0.0, 0.3) [0] | 0.0 (0.0, 0.3) [0] | 0.1 (0.0, 0.6) [1] | 0.3 (0.0, 1.7) [1] |
| NMSC | 0.7 (0.4, 1.1) [16] | 0.7 (0.4, 1.1) [13] | 0.2 (0.0, 0.6) [2] | 0.5 (0.2, 1.0) [9] | 0.6 (0.3, 1.2) [8] | 0.2 (0.0, 0.6) [2] | 0.2 (0.0, 0.8) [2] | 0.3 (0.0, 1.7) [1] |

ADA, adalimumab; AS, ankylosing spondylitis; CI, confidence interval; EAIR, exposure-adjusted incidence rate; EOW, every other week; MTX, methotrexate; NMSC, nonmelanoma skin cancer; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; PY, patient-years; QD, once daily; RA, rheumatoid arthritis; TEAE, treatment-emergent adverse events; UPA, upadacitinib.

[†]Data are presented as EAIRs, defined as n/100 PYs (95% CIs) [number of events].

‡Cases of abnormal lymphocyte morphology are included (upadacitinib 15 mg: RA [1], PsA [3], AS [1], and nr-axSpA [1]), as this preferred term is included in the Malignant Lymphoma Standardized MedDRA Queries but were not confirmed to be true lymphomas.

## Supplementary Table 5. Summary of Malignancy Type as Incidence Rates per 100 Patient-years in Patients Treated with UPA Across RA, PsA, AS, and nr-axSpA

| | RA | | | | PsA | | | AS | nr-axSpA |
|---|---|---|---|---|---|---|---|---|---|
| EAIR[†] | UPA 15 mg QD n=3209 | UPA 30 mg QD n=1204 | ADA 40 mg EOW n=579 | MTX n=314 | UPA 15 mg QD n=907 | UPA 30 mg QD n=921 | ADA 40 mg EOW n=429 | UPA 15 mg QD n=596 | UPA 15 mg QD n=286 |
| Malignancy Excl. NMSC | | | | | | | | | |
| Breast cancer[‡] | 0.1 (0.1, 0.2) [15] | 0.2 (0.1, 0.4) [6] | <0.1 (0.0, 0.4) [1] | 0.0 (0.0, 0.4) [0] | 0.0 (0.0, 0.2) [0] | 0.2 (0.0, 0.5) [3] | 0.0 (0.0, 0.3) [0] | 0.0 (0.0, 0.4) [0] | 0.3 (0.0, 1.7) [1] |
| Colorectal cancer | <0.1 (0.0, 0.1) [5] | 0.1 (0.0, 0.3) [4] | 0.2 (0.0, 0.6) [3] | 0.1 (0.0, 0.6) [1] | <0.1 (0.0, 0.2) [1] | 0.1 (0.0, 0.4) [2] | <0.1 (0.0, 0.5) [1] | 0.0 (0.0, 0.4) [0] | 0.0 (0.0, 1.1) [0] |
| Lung cancer[§] | 0.1 (0.1, 0.2) [14] | <0.1 (0.0, 0.2) [1] | 0.1 (0.0, 0.5) [2] | 0.1 (0.0, 0.6) [1] | <0.1 (0.0, 0.3) [2] | <0.1 (0.0, 0.3) [1] | 0.0 (0.0, 0.3) [0] | 0.0 (0.0, 0.4) [0] | 0.0 (0.0, 1.1) [0] |
| Lymphoma[‖] | <0.1 (0.0, 0.1) [4] | <0.1 (0.0, 0.2) [2] | 0.2 (0.0, 0.6) [3] | 0.0 (0.0, 0.4) [0] | 0.1 (0.0, 0.4) [3] | 0.0 (0.0, 0.2) [0] | 0.0 (0.0, 0.3) [0] | 0.1 (0.0, 0.6) [1] | 0.3 (0.0, 1.7) [1] |
| Melanoma | <0.1 (0.0, 0.1) [7] | <0.1 (0.0, 0.3) [3] | <0.1 (0.0, 0.4) [1] | 0.0 (0.0, 0.4) [0] | 0.1 (0.0, 0.4) [3] | 0.2 (0.0, 0.5) [3] | 0.0 (0.0, 0.3) [0] | 0.0 (0.0, 0.4) [0] | 0.0 (0.0, 1.1) [0] |
| Pancreatic cancer | <0.1 (0.0, 0.1) [2] | 0.0 (0.0, 0.1) [0] | 0.0 (0.0, 0.2) [0] | 0.0 (0.0, 0.4) [0] | 0.0 (0.0, 0.2) [0] | 0.0 (0.0, 0.2) [0] | <0.1 (0.0, 0.5) [1] | 0.0 (0.0, 0.4) [0] | 0.0 (0.0, 1.1) [0] |
| Prostate cancer | <0.1 (0.0, 0.1) [1] | <0.1 (0.0, 0.3) [3] | 0.0 (0.0, 0.2) [0] | 0.0 (0.0, 0.4) [0] | <0.1 (0.0, 0.3) [2] | 0.0 (0.0, 0.2) [0] | <0.1 (0.0, 0.5) [1] | 0.0 (0.0, 0.4) [0] | 0.0 (0.0, 1.1) [0] |
| Other | 0.3 (0.2, 0.4) [32] | 0.5 (0.3, 0.8) [15] | <0.1 (0.0, 0.4) [1] | 0.7 (0.3, 1.5) [6] | 0.3 (0.1, 0.6) [8] | 0.3 (0.1, 0.7) [6] | 0.2 (0.0, 0.6) [2] | 0.2 (0.0, 0.8) [2] | 0.0 (0.0, 1.1) [0] |
| NMSC | | | | | | | | | |
| Basal cell carcinoma | 0.2 (0.1, 0.3) [24] | 0.5 (0.3, 0.8) 16] | <0.1 (0.0, 0.4) [1] | 0.0 (0.0, 0.4) [0] | 0.5 (0.3, 0.9) [12] | 0.4 (0.2, 0.8) [8] | 0.2 (0.0, 0.6) [2] | 0.2 (0.0, 0.8) [2] | 0.3 (0.0, 1.7) [1] |
| Cutaneous squamous cell carcinoma | 0.2 (0.1, 0.3) [17] | 0.5 (0.3, 0.8) [15] | <0.1 (0.0, 0.4) [1] | 0.0 (0.0, 0.4) [0] | 0.2 (0.1, 0.5) [6] | 0.3 (0.1, 0.7) [6] | 0.0 (0.0, 0.3) [0] | 0.0 (0.0, 0.4) [0] | 0.0 (0.0, 1.1) [0] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Other[¶] | <0.1 (0.0, 0.1) [8] | 0.0 (0.0, 0.1) [0] | 0.0 (0.0, 0.2) [0] | 0.0 (0.0, 0.4) [0] | 0.0 (0.0, 0.2) [0] | 0.0 (0.0, 0.2) [0] | 0.0 (0.0, 0.3) [0] | 0.0 (0.0, 0.4) [0] | 0.0 (0.0, 1.1) [0] |

ADA, adalimumab; AS, ankylosing spondylitis; CI, confidence interval; EAIR, exposure-adjusted incidence rate; EOW, every other week; MTX, methotrexate; NMSC, nonmelanoma skin cancer; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; PY, patient-year; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib.

[†]Data are presented as EAIRs, defined as n/100 PYs (95% CIs) [number of events].

[‡]No events of breast cancer were reported in males.

[§]Smoking status in patients with lung cancer events were as follows in RA (UPA 15 mg: 64.3% current, 28.6% former, 7.1% never; UPA 30 mg: 100.0% current; ADA 40 mg: 100.0% current; MTX: 100.0% former) and PsA (UPA 15 mg: 50.0% current, 50.0% never; UPA 30 mg: 100.0% former).

[‖]The following preferred terms were reported for events of lymphoma in RA (UPA 15 mg: 1 event each of cutaneous T-cell lymphoma, non-Hodgkin's lymphoma, non-Hodgkin's lymphoma stage IV, and lymphocyte morphology abnormal; UPA 30 mg: 1 event each of B-cell lymphoma and B-cell small lymphocytic lymphoma; ADA 40 mg: 1 event each of B-cell lymphoma, diffuse large B-cell lymphoma, and Hodgkin's disease stage IV), PsA (UPA 15 mg: 3 events of lymphocyte morphology abnormal), AS (1 event of lymphocyte morphology abnormal), and nr-axSpA (1 event of lymphocyte morphology abnormal). Cases of abnormal lymphocyte morphology are shown (upadacitinib 15 mg: RA [1], PsA [3], AS [1], and nr-axSpA [1]), as this preferred term is included in the Malignant Lymphoma Standardized MedDRA Queries but were not confirmed to be true lymphomas.

[¶]The "other" category includes malignancies not listed in the preceding categories, such as adenocarcinoma, bladder cancer, endometrial cancer, glioblastoma, and renal cancer.

## Supplementary Table 6. Incidence Rates per 100 Patient-Years for TEAEs of Malignancy in RA, PsA, AS, and nr-axSpA by Length of UPA Exposure

| | RA | | | | PsA | | | AS | nr-axSpA |
|---|---|---|---|---|---|---|---|---|---|
| EAIR[†] | UPA 15 mg QD n=3209 | UPA 30 mg QD n=1204 | ADA 40 mg EOW n=579 | MTX n=314 | UPA 15 mg QD n=907 | UPA 30 mg QD n=921 | ADA 40 mg EOW n=429 | UPA 15 mg QD n=596 | UPA 15 mg QD n=286 |
| Malignancy (Excl. NMSC) | | | | | | | | | |
| 0 to ≤ 12 months | 0.6 (0.4, 1.0) [17] | 1.4 (0.8, 2.3) [15] | 0.7 (0.1, 2.1) [3] | 0.8 (0.1, 2.9) [2] | 1.0 (0.4, 1.9) [8] | 0.7 (0.3, 1.6) [6] | 0.8 (0.2, 2.2) [3] | 0.2 (0.0, 1.0) [1] | 0.0 (0.0, 1.6) [0] |
| > 12 months | 0.7 (0.6, 1.0) [59] | 0.8 (0.5, 1.3) [17] | 0.6 (0.2, 1.3) [7] | 1.0 (0.4, 2.1) [6] | 0.5 (0.2, 1.0) [8] | 0.8 (0.4, 1.5) [9] | 0.3 (0.0, 1.0) [2] | 0.3 (0.0, 1.5) [1] | 1.1 (0.0, 6.0) [1] |
| Lymphoma[‡] | | | | | | | | | |
| 0 to ≤ 12 months | <0.1 (0.0, 0.2) [1] | <0.1 (0.0, 0.5) [1] | 0.0 (0.0, 0.9) [0] | 0.0 (0.0, 1.5) [0] | 0.2 (0.0, 0.9) [2] | 0.0 (0.0, 0.4) [0] | 0.0 (0.0, 0.9) [0] | 0.2 (0.0, 1.0) [1] | 0.4 (0.0, 2.4) [1] |
| > 12 months | <0.1 (0.0, 0.1) [3] | <0.1 (0.0, 0.3) [1] | 0.3 (0.1, 0.8) [3] | 0.0 (0.0, 0.6) [0] | <0.1 (0.0, 0.3) [1] | 0.0 (0.0, 0.3) [0] | 0.0 (0.0, 0.5) [0] | 0.0 (0.0, 1.0) [0] | 0.0 (0.0, 4.0) [0] |
| NMSC | | | | | | | | | |
| 0 to ≤ 12 months | 0.3 (0.1, 0.6) [8] | 0.8 (0.4, 1.6) [9] | 0.2 (0.0, 1.3) [1] | 0.0 (0.0, 1.5) [0] | 0.7 (0.3, 1.6) [6] | 0.7 (0.3, 1.6) [6] | 0.3 (0.0, 1.4) [1] | 0.2 (0.0, 1.0) [1] | 0.4 (0.0, 2.4) [1] |
| > 12 months | 0.5 (0.3, 0.6) [37] | 0.8 (0.5, 1.3) [17] | <0.1 (0.0, 0.5) [1] | 0.0 (0.0, 0.6) [0] | 0.6 (0.3, 1.2) [10] | 0.6 (0.3, 1.3) [7] | 0.1 (0.0, 0.7) [1] | 0.3 (0.0, 1.5) [1] | 0.0 (0.0, 3.9) [0] |

ADA, adalimumab; AS, ankylosing spondylitis; CI, confidence interval; EAIR, exposure-adjusted incidence rate; EOW, every other week; MTX, methotrexate; NMSC, nonmelanoma skin cancer; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; PY, patient-year; QD, once daily; RA, rheumatoid arthritis; TEAE, treatment-emergent adverse events; UPA, upadacitinib.

[†]Data are presented as EAIRs, defined as n/100 PYs (95% CIs) [number of events].

‡Cases of abnormal lymphocyte morphology are included (upadacitinib 15 mg: RA [1], PsA [3], AS [1], and nr-axSpA [1]), as this preferred term is included in the Malignant Lymphoma Standardized MedDRA Queries but were not confirmed to be true lymphomas.