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ORIGINAL RESEARCH

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

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ABSTRACT

Introduction: We report the long-term safety of upadacitinib (oral, selective, and reversible Janus kinase inhibitor) in rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), atopic dermatitis (AD), Crohn's disease (CD), and ulcerative colitis (UC).
Methods: Data were analyzed from 16 studies (data cutoff August 15, 2024). Each treatment group was pooled across studies within each indication. Active comparator arms included adalimumab (RA/PsA) and methotrexate (RA).

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Treatment-emergent adverse events (TEAEs) were reported as exposure-adjusted incidence rates per 100 patient-years (*n*/100 PY).

***Results*:** This analysis included 8632 (RA, *n*=3209; PsA, *n*=907; AS, *n*=596; nr-axSpA, *n*=286; AD, *n*=2683; CD, *n*=450; UC, *n*=501) upadacitinib-treated patients over 27,164.2 patient-years (range 199.4–12,315.8 PY across indications). Rates (*n*/100 PY) of any TEAEs ranged from 112.0 (AS) to 401.1 (RA). Most frequently reported TEAEs included COVID-19, upper respiratory tract infection, nasopharyngitis, herpes zoster, urinary tract infection, and acne (primarily patients with AD). Serious TEAEs ranged from 4.5 (AD) to 11.0 (UC), and those leading to discontinuation ranged from 2.9 (AS) to 8.3 (UC). TEAEs leading to death ranged from 0 (nr-axSpA, UC) to 0.7 (RA). Among upadacitinib-treated patients across indications, rates of adverse events of special interest ranged from 1.3 to 4.6 (serious infection), 2.4–6.6 (herpes zoster), 0.2–0.9 (malignancy excluding nonmelanoma skin cancer [NMSC]), 0–1.4 (NMSC), 0–0.5 (major adverse cardiovascular event [MACE]), 0–0.9 (venous thromboembolism [VTE]), and 0–9.2 (elevated creatine kinase). In RA and PsA, herpes zoster, NMSC, and elevated creatine kinase rates were numerically higher with upadacitinib vs active comparators. Serious infection, herpes zoster, malignancy (excluding NMSC), NMSC, MACE, and VTE rates remained stable over time.

***Conclusion*:** This descriptive analysis indicates a long-term safety profile of upadacitinib consistent with previous reports, further supporting long-term treatment of chronic diseases with upadacitinib. Variations in TEAE rates across indications likely reflected differences in populations and underlying comorbidities.

***Trial Registration*:** ClinicalTrials.gov identifiers NCT02675426, NCT02706951, NCT02706847, NCT02629159, NCT02706873, NCT03086343, NCT03104374, NCT03104400, NCT03178487, NCT04169373, NCT03569293, NCT03568318, NCT03607422, NCT03345823, NCT02819635.

Keywords: Arthritis; Atopic dermatitis; Axial spondyloarthritis; Infections; Inflammatory bowel diseases; Major adverse cardiovascular events; Malignancy; Rheumatoid; Safety; Upadacitinib

Key Summary Points

Why carry out this study?

Janus kinase (JAK) inhibitors have been associated with an increased risk of several adverse events, including serious infections, herpes zoster, malignancies, major adverse cardiovascular events (MACE), venous thromboembolisms (VTE), and laboratory-related abnormalities.

An integrated safety analysis characterized the safety profile of upadacitinib, an oral, reversible JAK inhibitor, across rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and atopic dermatitis; to build upon these findings, the analysis was expanded to increase follow-up duration and include additional approved indications (non-radiographic axial spondyloarthritis, Crohn's disease, and ulcerative colitis).

What was learned from the study?

Findings from this descriptive integrated safety analysis, based on over 8600 patients and 27,000 patient-years of exposure across 16 studies, indicate that upadacitinib is well tolerated over long-term follow-up; these long-term data are consistent with the known safety profile of upadacitinib.

In rheumatoid arthritis and psoriatic arthritis, malignancy (excluding nonmelanoma skin cancer, [NMSC]), MACE, and VTE occurred at similar rates between upadacitinib and active comparators (adalimumab and methotrexate), while herpes zoster, NMSC, and elevated creatine kinase occurred more frequently with upadacitinib.

Variations in rates of adverse events of special interest across indications were likely due to differences in patient populations and underlying comorbidities.

INTRODUCTION

Immune-mediated inflammatory diseases have traditionally been managed with corticosteroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and biologic

agents [1, 2]. Over the past decade, treatment for these diseases has evolved significantly, with oral small molecules—including Janus kinase (JAK) inhibitors—emerging as a rapid-acting and effective treatment option for a broad spectrum of diseases [3]. However, in select populations, JAK inhibitors have been associated with an increased risk of several adverse events, including serious infections, herpes zoster, malignancies, major adverse cardiovascular events (MACE), venous thromboembolisms (VTE), and laboratory-related abnormalities [2].

Safety concerns surrounding JAK inhibitors increased following the Oral Rheumatoid Arthritis Trial (ORAL) Surveillance study, an event-driven, randomized, postmarketing, noninferiority trial that evaluated the JAK inhibitor tofacitinib vs tumor necrosis factor inhibitors in patients with rheumatoid arthritis (RA) receiving background methotrexate [4]. Patients aged ≥ 50 years with ≥ 1 cardiovascular risk factor were enrolled to enrich the population for events of interest. Findings showed that patients treated with tofacitinib had an increased risk of MACE, malignancy (excluding nonmelanoma skin cancer, NMSC), opportunistic infections (including herpes zoster and tuberculosis), and NMSC compared to patients treated with tumor necrosis factor inhibitors. However, these findings may not be generalizable to other JAK inhibitors or disease settings, as ORAL Surveillance was conducted in a population enriched for cardiovascular and malignancy risk and does not reflect the broader population receiving JAK inhibitors in RA or other diseases. Furthermore, subsequent analyses showed that safety risks were concentrated in patients with specific characteristics at baseline, including age ≥ 65 years, smoking history, high risk of cardiovascular disease, and active RA [5–9].

Upadacitinib is an oral, selective, and reversible JAK inhibitor approved to treat multiple immune-mediated inflammatory diseases, including RA, psoriatic arthritis (PsA), atopic dermatitis (AD), ulcerative colitis (UC), Crohn's disease (CD), ankylosing spondylitis (AS), nonradiographic axial spondyloarthritis (nr-axSpA), polyarticular juvenile idiopathic arthritis, and giant cell arteritis [10]. Currently, upadacitinib is under investigation for hidradenitis suppurativa, vitiligo, alopecia areata, systemic lupus erythematosus, and Takayasu arteritis [11–15].

An analysis of integrated data from upadacitinib clinical trials, encompassing over 15,000 patient-years (PY) of exposure in RA, PsA, AS, and AD, characterized the safety profile of upadacitinib and those of active comparators (where available) [16]. Findings showed that upadacitinib had an acceptable safety profile, which was consistent with previous reports. We expanded the analysis to characterize the safety of upadacitinib over 27,000 PY of exposure, incorporating a longer follow-up period and additional approved indications (nr-axSpA, CD, and UC). This analysis aims to comprehensively characterize the safety profile of upadacitinib across multiple approved indications and offer insights into its long-term use to help inform clinical decision-making.

METHODS

Patients and Studies

This analysis included safety data from 16 upadacitinib studies (data cutoff date August 15, 2024). All studies were phase 3 studies, except for SELECT-AXIS 1, which was a phase 2/3 study. The patient populations from these studies have been described previously (Table S1 in the supplementary material) [17–31]. Patients in the RA, PsA, AS, nr-axSpA, and CD studies were aged ≥ 18 years (adolescents were also included in the AD [aged 12–17 years] and UC [aged 16–17 years] studies). Most enrolled patients had active disease and inadequate response or intolerance to ≥ 1 commonly used treatment for immune-mediated inflammatory diseases (csDMARDs, nonsteroidal anti-inflammatory drugs, or biologic therapies). All studies were conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation guidelines, and applicable local regulations. An independent ethics committee or institutional review board at each study site approved the protocol. Patients (or legal guardians of adolescents) provided written informed consent before beginning the study.

Treatment

Data for each of the following treatment groups were pooled across studies within each indication: upadacitinib 15 mg once daily (RA, PsA, AS, nr-axSpA, AD, CD, and UC), upadacitinib 30 mg once daily (AD, CD, and UC), adalimumab 40 mg every other week (RA and PsA), and methotrexate (RA). For the RA and PsA studies, patients received upadacitinib or adalimumab as monotherapy or in combination with methotrexate or another csDMARD. Data for the methotrexate group were from SELECT-EARLY and reflect methotrexate use as monotherapy in patients with methotrexate-naive RA. The methotrexate dose (7.5–20 mg/week) varied by region and patient tolerability. For the AD studies, patients received upadacitinib as monotherapy or in combination with topical corticosteroids. UC and CD study data were from patients who responded to 8 or 12 weeks (or longer for extended induction) of once-daily upadacitinib 45 mg induction therapy, respectively, and then received once-daily upadacitinib 15 mg or 30 mg maintenance treatment.

Safety Assessments

Treatment-emergent adverse events (TEAEs) were coded according to the Medical Dictionary for Regulatory Activities. TEAEs were defined as any adverse event with an onset date on or after the first dose of study drug and up to 30 days after the last dose of upadacitinib or methotrexate, or up to 70 days after the last dose of adalimumab.

Adverse events of special interest (AESIs) included serious infection, opportunistic infection (excluding herpes zoster and tuberculosis), herpes zoster, active tuberculosis, MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), VTE (deep vein thrombosis and pulmonary embolism), malignancy (excluding NMSC), NMSC, investigator-reported laboratory-related abnormalities (anemia, lymphopenia, neutropenia, elevated creatine kinase [CK]), hepatic disorder, renal dysfunction, gastrointestinal (GI) perforation, bone fracture, retinal detachment, and serious hypersensitivity reaction. An independent, external cardiovascular adjudication committee evaluated MACE and VTE in a blinded manner, and an independent, sponsor-employed committee of experts adjudicated GI perforations in a blinded manner. The proportion of patients who met criteria for potentially clinically significant changes (grade 3/4) in select laboratory parameters relevant to the JAK inhibitor class was evaluated. To grade laboratory changes for RA, the Rheumatology Common Toxicity Criteria version 2.0, developed by the Outcome Measures in Rheumatology Drug Safety Working Group [32], was used; CK and creatinine were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). NCI CTCAE was used to grade toxicity for all other indications. To assess changes over time, TEAE rates for the following AESIs were reported in 6-month intervals: serious infection, herpes zoster, malignancy (excluding NMSC), NMSC, MACE, and VTE. AESI rates were also stratified by age group (< 65 years and ≥ 65 years).

Statistical Analysis

TEAEs are reported as exposure-adjusted incidence rates (EAIR) and, in the supplemental materials, as exposure-adjusted event rates (EAER). EAIR represents the number of patients with ≥ 1 event per 100 PY (n/100 PY) over a defined period of study drug exposure; exposure time was calculated as the time to the first event. In the CD and UC studies, exposure started at the first dose in the maintenance period. For patients without an event, exposure time was censored on the date of the patient's last dose of study drug or database lock date, whichever occurred first. EAER represents the number of events occurring per 100 PY over a defined period of exposure to study drug; exposure was calculated as total study drug duration for a given dose. For EAIR and EAER, patients who switched treatments were censored at the time of treatment or dose switch; 95% CIs were calculated using the exact method for the Poisson mean. Standardized mortality ratio (SMR) was calculated using the World Health Organization age-specific, gender-specific, and country-specific death data for the general population,

and calculations included COVID-19 deaths; 95% CIs were based on the Byar's approximation. Grade 3/4 changes in laboratory parameters were summarized using numerical counts and percentages, including only patients with ≥ 1 postbaseline value for the respective parameter whose postbaseline grade was more severe than at baseline.

RESULTS

Patients and Exposure

This analysis included 8632 patients treated with upadacitinib over 27,164.2 PY. Based on data available up to the time of analysis, the median upadacitinib treatment duration was shorter in the nr-axSpA (53.8 weeks), CD (51.6 weeks), and UC (51.7 weeks) programs and longer in the RA (216.3 weeks) and AD (230.1 weeks) programs, reflecting differences in planned study durations. Adalimumab was a reference comparator arm in one RA (579 patients; 1978.0 PY) and one PsA (429 patients; 1520.0 PY) study. Methotrexate was a reference comparator arm in one RA study (314 patients; 860.1 PY).

There were notable differences in baseline characteristics, such as mean age and proportions of male and female patients across studies, which were expected on the basis of the patient populations studied in this analysis (Table 1). Patients in the RA and PsA studies were generally older (mean age range 51.4–54.3 years), whereas AD studies included younger patients (mean age range 31.9–33.1 years across upadacitinib doses). RA studies had a higher proportion of female patients (approx. 80%), while AS studies had a higher proportion of male patients (approx. 75%). For most indications, time since diagnosis was < 10 years; however, it was approximately 20 years in the AD population, reflecting an earlier age of onset compared with other conditions. Among patients receiving upadacitinib, approximately 70–80% with RA and PsA received concomitant csDMARDs, and approximately 55% with RA received concomitant corticosteroids. Approximately one-third of patients with AD received concomitant topical corticosteroids, and nearly 40% of patients with CD and UC received concomitant oral or rectal corticosteroids. Few patients (< 7.5% across all groups) were vaccinated for herpes zoster at baseline. Most patients had ≥ 1 risk factor for cardiovascular disease at baseline—including age ≥ 65 years, body mass index ≥ 30 kg/m^2, smoking history, > 4 alcoholic drinks/day, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, or a history of cardiovascular disease, diabetes, hypertension, VTE, chronic kidney disease, or dyslipidemia—with the lowest proportion in the AD population (52%) and the highest in the PsA population (86%).

General Safety Overview

EAIRs of any TEAEs with upadacitinib ranged from 112.0 *n*/100 PY (AS) to 401.1 *n*/100 PY (RA; Table 2). The most frequently reported TEAEs (≥ 5 *n*/100 PYs) included COVID-19, upper respiratory tract infection, nasopharyngitis, herpes zoster, urinary tract infection, and acne (primarily in the AD population; Table S2 in the supplementary material). Most acne cases in the AD population occurred on the face, were mild or moderate in severity, were nonserious, and did not result in treatment discontinuation; the most common risk factors for acne were family history or prior medical history of acne. In the RA and PsA populations, EAIRs of TEAEs were generally similar between upadacitinib and active comparators, though some differences were observed; in the RA population, serious TEAEs were numerically higher with upadacitinib 15 mg vs methotrexate (10.5 vs 6.8 *n*/100 PY), while treatment-related TEAEs were numerically lower with upadacitinib 15 mg vs methotrexate (36.9 vs 50.3 *n*/100 PY). EAIRs of TEAEs in the RA and PsA populations were comparable between patients who received upadacitinib as monotherapy or in combination with csDMARDs (Table S3 in the supplementary material). EAIRs of serious TEAEs among patients treated with upadacitinib were numerically lowest in the AD population (4.5 *n*/100 PY) and highest in the UC population (11.0 *n*/100 PY). In the AD population, EAIRs of any TEAEs and treatment-related TEAEs were numerically

Table 1 Baseline patient demographics and clinical characteristics

Characteristic	RA			PsA		AS	nr-axSpA	AD		CD[a]		UC[a]	
	UPA 15 mg *n* = 3209	ADA 40 mg *n* = 579	MTX *n* = 314	UPA 15 mg *n* = 907	ADA 40 mg *n* = 429	UPA 15 mg *n* = 596	UPA 15 mg *n* = 286	UPA 15 mg *n* = 1337	UPA 30 mg *n* = 1346	UPA 15 mg *n* = 221	UPA 30 mg *n* = 229	UPA 15 mg *n* = 250	UPA 30 mg *n* = 251
Age, years, mean (SD)	54.3 (12.0)	54.2 (11.7)	53.3 (12.9)	51.5 (12.1)	51.4 (12.0)	43.3 (12.3)	42.2 (12.2)	31.9 (15.2)	33.1 (15.9)	37.5 (13.4)	37.0 (13.0)	41.9 (14.2)	42.8 (14.5)
Sex													
Female	2581 (80.4)	470 (81.2)	240 (76.4)	478 (52.7)	222 (51.7)	162 (27.2)	167 (58.4)	593 (44.4)	585 (43.5)	87 (39.4)	98 (42.8)	91 (36.4)	97 (38.6)
Male	628 (19.6)	109 (18.8)	74 (23.6)	429 (47.3)	207 (48.3)	434 (72.8)	119 (41.6)	744 (55.6)	761 (56.5)	134 (60.6)	131 (57.2)	159 (63.6)	154 (61.4)
BMI, mean (SD)	29.1 (6.7)[b]	29.4 (7.1)	28.0 (6.3)	30.6 (6.9)	30.7 (7.2)	26.8 (5.2)	28.2 (5.9)	25.7 (6.0)[c]	25.8 (5.6)[d]	24.2 (5.9)	24.4 (6.3)	24.9 (5.7)	25.3 (5.9)[e]
Time since diagnosis, years, mean (SD)	8.5 (8.4)[b]	8.2 (8.0)	2.6 (5.1)	7.2 (7.8)	5.9 (7.1)	7.4 (7.9)	5.0 (5.8)	20.5 (14.2)	20.8 (14.7)[f]	10.5 (8.6)	9.4 (8.6)	8.4 (7.3)	8.2 (6.9)
Concomitant therapies													
csDMARDs	2548 (79.4)	579 (100)	0	652 (71.9)	346 (80.7)	159 (26.7)	88 (30.8)	N/A	N/A	N/A	N/A	N/A	N/A
MTX alone	2180 (67.9)	534 (92.2)	0	490 (54.0)	255 (59.4)	52 (8.7)	32 (11.2)	N/A	N/A	N/A	N/A	N/A	N/A
csDMARD other than MTX	198 (6.2)	45 (7.8)	0	126 (13.9)	74 (17.2)	102 (17.1)	52 (18.2)	N/A	N/A	N/A	N/A	N/A	N/A
Corticosteroids	1756 (54.7)	350 (60.4)	164 (52.2)	133 (14.7)	70 (16.3)	59 (9.9)	31 (10.8)	N/A	N/A	80 (36.2)	85 (37.1)	95 (38.0)	89 (35.5)
Topical corticosteroids	N/A	N/A	N/A	N/A	N/A	N/A	N/A	436 (32.6)	444 (33.0)	N/A	N/A	N/A	N/A
NSAIDs	2032 (63.3)	364 (62.9)	223 (71.0)	566 (62.4)	281 (65.5)	471 (79.0)	213 (74.5)	N/A	N/A	5 (2.3)	4 (1.7)	4 (1.6)	3 (1.2)
Aspirin	269 (8.4)	36 (6.2)	24 (7.6)	89 (9.8)	27 (6.3)	17 (2.9)	5 (1.7)	25 (1.9)	45 (3.3)	2 (0.9)	7 (3.1)	6 (2.4)	8 (3.2)
Statins	321 (10.0)	42 (7.3)	26 (8.3)	82 (9.0)	28 (6.5)	17 (2.9)	8 (2.8)	8 (0.6)	6 (0.4)	2 (0.9)	3 (1.3)	8 (3.2)	12 (4.8)
History of HZ	71 (2.2)	12 (2.1)	4 (1.3)	27 (3.0)	7 (1.6)	10 (1.7)	4 (1.4)	29 (2.2)	46 (3.4)	6 (2.7)	4 (1.7)	7 (2.8)	8 (3.2)
Prior HZ vaccination	92 (2.9)	15 (2.6)	4 (1.3)	35 (3.9)	14 (3.3)	11 (1.8)	9 (3.1)	51 (3.8)	67 (5.0)	16 (7.2)	17 (7.4)	5 (2.0)	12 (4.8)
Presence/history of CV risk factors	2610 (81.3)	467 (80.7)	240 (76.4)	783 (86.3)	359 (83.7)	436 (73.2)	200 (69.9)	711 (53.2)	694 (51.6)	138 (62.4)	137 (59.8)	141 (56.4)	156 (62.2)
Age ≥ 65 years	643 (20.0)	106 (18.3)	58 (18.5)	129 (14.2)	67 (15.6)	32 (5.4)	8 (2.8)	48 (3.6)	68 (5.1)	7 (3.2)	8 (3.5)	23 (9.2)	21 (8.4)
BMI ≥ 30 kg/m^2	1201 (37.4)	227 (39.2)	97 (30.9)	431 (47.5)	209 (48.7)	140 (23.5)	92 (32.2)	251 (18.9)	258 (19.3)	44 (19.9)	44 (19.2)	43 (17.2)	43 (17.3)

Table 1 continued

Characteristic	RA			PsA		AS	nr-axSpA	AD		CD[a]		UC[a]	
	UPA 15 mg *n* = 3209	ADA 40 mg *n* = 579	MTX *n* = 314	UPA 15 mg *n* = 907	ADA 40 mg *n* = 429	UPA 15 mg *n* = 596	UPA 15 mg *n* = 286	UPA 15 mg *n* = 1337	UPA 30 mg *n* = 1346	UPA 15 mg *n* = 221	UPA 30 mg *n* = 229	UPA 15 mg *n* = 250	UPA 30 mg *n* = 251
Current or former smoker[g]	944 (29.4)	151 (26.1)	95 (30.3)	290 (32.0)	129 (30.1)	237 (39.8)	78 (27.3)	357 (26.7)	352 (26.2)	73 (33.0)	68 (29.7)	65 (26.0)	73 (29.1)
> 4 alcoholic drinks/day	4 (0.1)	1 (0.2)	2 (0.6)	3 (0.3)	1 (0.2)	3 (0.5)	0	14 (1.0)	13 (1.0)	0	0	2 (0.8)	1 (0.4)
CV disease	344 (10.7)	48 (8.3)	22 (7.0)	98 (10.8)	31 (7.2)	27 (4.5)	15 (5.2)	33 (2.5)	39 (2.9)	6 (2.7)	8 (3.5)	13 (5.2)	14 (5.6)
Diabetes mellitus[h]	384 (12.0)	61 (10.5)	31 (9.9)	124 (13.7)	48 (11.2)	24 (4.0)	15 (5.2)	27 (2.0)	28 (2.1)	4 (1.8)	7 (3.1)	15 (6.0)	17 (6.8)
HTN[i]	1427 (44.5)	255 (44.0)	114 (36.3)	408 (45.0)	184 (42.9)	120 (20.1)	62 (21.7)	149 (11.1)	131 (9.7)	21 (9.5)	33 (14.4)	28 (11.2)	43 (17.1)
VTE	37 (1.2)	7 (1.2)	3 (1.0)	18 (2.0)	3 (0.7)	1 (0.2)	1 (0.3)	4 (0.3)	6 (0.4)	4 (1.8)	2 (0.9)	3 (1.2)	5 (2.0)
CKD	25 (0.8)	5 (0.9)	2 (0.6)	11 (1.2)	5 (1.2)	4 (0.7)	1 (0.3)	4 (0.3)	4 (0.3)	3 (1.4)	0	3 (1.2)	1 (0.4)
Dyslipidemia	650 (20.3)	98 (16.9)	51 (16.2)	225 (24.8)	96 (22.4)	72 (12.1)	42 (14.7)	95 (7.1)	91 (6.8)	8 (3.6)	16 (7.0)	21 (8.4)	26 (10.4)
Elevated LDL-C (≥ 160 mg/dL)	265 (8.3)	61 (10.5)	25 (8.0)	75 (8.5)	39 (9.3)	59 (9.9)	38 (13.4)	44 (3.3)	43 (3.2)	4 (1.8)	1 (0.4)	7 (2.9)	7 (2.9)
Lowered HDL-C (< 40 mg/dL)	354 (11.0)	53 (9.2)	39 (12.4)	176 (19.6)	95 (22.4)	135 (22.7)	51 (17.8)	177 (13.2)	168 (12.5)	51 (23.1)	46 (20.1)	30 (12.3)	42 (17.3)

Data are *n* (%) unless otherwise indicated

AD atopic dermatitis, *ADA* adalimumab, *AS* ankylosing spondylitis, *BMI* body mass index, *CD* Crohn's disease, *CKD* chronic kidney disease, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *CV* cardiovascular, *HDL-C* high-density lipoprotein cholesterol, *HTN* hypertension, *HZ* herpes zoster, *LDL-C* low-density lipoprotein cholesterol, *MTX* methotrexate, *N/A* not applicable, *nr-axSpA* non-radiographic axial spondyloarthritis, *NSAID* nonsteroidal anti-inflammatory drug, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *SD* standard deviation, *UC* ulcerative colitis, *UPA* upadacitinib, *VTE* venous thromboembolism

[a]Data reflect baseline characteristics at start of induction with UPA 45 mg

[b]*n* = 3208

[c]*n* = 1331

[d]*n* = 1338

[e]*n* = 249

[f]*n* = 1345

[g]Current or former tobacco smoker within past 15 years

[h]History of diabetes mellitus or prior use of insulins and analogues

[i]History of hypertension or prior use of antihypertensive medication or elevated blood pressure

Table 2 Summary of drug exposure and exposure-adjusted incidence rates of TEAEs

Parameter	RA			PsA		AS	nr-axSpA	AD		CD		UC	
	UPA 15 mg *n* = 3209	ADA 40 mg *n* = 579	MTX *n* = 314	UPA 15 mg *n* = 907	ADA 40 mg *n* = 429	UPA 15 mg *n* = 596	UPA 15 mg *n* = 286	UPA 15 mg *n* = 1337	UPA 30 mg *n* = 1346	UPA 15 mg *n* = 221	UPA 30 mg *n* = 229	UPA 15 mg *n* = 250	UPA 30 mg *n* = 251
Exposure													
Total PY	12,315.8	1978.0	860.1	2971.7	1520.0	1015.3	380.7	4435.2	4752.5	387.2	487.9	199.4	218.5
Weeks, median (min, max)	216.3 (0.3, 441.0)	114.3 (0.1, 446.6)	134.1 (1.0, 263.1)	190.1 (0.1, 332.9)	259.7 (2.0, 294.4)	91.0 (0.1, 198.0)	53.8 (0.1, 119.6)	214.1 (0.1, 305.4)	230.1 (0.1, 302.3)	51.6 (1.3, 295.7)	103.1 (1.1, 294.0)	51.7 (0.3, 57.0)	52.0 (1.1, 64.0)
TEAEs, *n*/100 PY (95% CI)													
Any TEAE	401.1 (386.6, 416.0)	354.2 (322.8, 387.8)	391.7 (346.3, 441.4)	145.3 (135.6, 155.6)	126.5 (114.3, 139.7)	112.0 (101.9, 122.8)	137.8 (119.9, 157.7)	138.4 (130.7, 146.5)	175.6 (166.0, 185.6)	199.0 (171.6, 229.5)	199.1 (172.8 (228.2)	241.0 (208.2, 277.5)	229.1 (198.4, 263.2)
Any serious TEAE	10.5 (9.8, 11.2)	11.0 (9.3, 12.9)	6.8 (5.1, 9.0)	7.8 (6.7, 8.9)	6.3 (5.1, 7.8)	6.7 (5.2, 8.6)	7.9 (5.3, 11.4)	4.5 (3.9, 5.2)	5.3 (4.6, 6.0)	10.5 (7.5, 14.5)	10.2 (7.4, 13.6)	11.0 (6.8, 16.8)	9.9 (6.1, 15.1)
Any treatment-related TEAE[a]	36.9 (35.2, 38.7)	28.3 (24.9, 31.9)	50.3 (43.0, 58.4)	29.0 (26.5, 31.7)	30.4 (26.7, 34.4)	29.9 (26.1, 34.2)	30.6 (24.6, 37.7)	30.1 (27.9, 32.3)	43.2 (40.4, 46.1)	33.0 (26.4, 40.7)	38.1 (31.2, 46.0)	59.0 (47.3, 72.7)	61.3 (49.7, 74.7)
Any TEAE leading to treatment discontinuation	4.3 (3.9, 4.7)	4.4 (3.5, 5.5)	5.3 (3.8, 7.1)	4.3 (3.6, 5.1)	3.4 (2.5, 4.4)	2.9 (1.9, 4.1)	4.2 (2.4, 6.8)	3.6 (3.1, 4.2)	3.9 (3.4, 4.5)	5.4 (3.4, 8.3)	4.8 (3.0, 7.1)	5.5 (2.8, 9.9)	8.3 (4.9, 13.1)

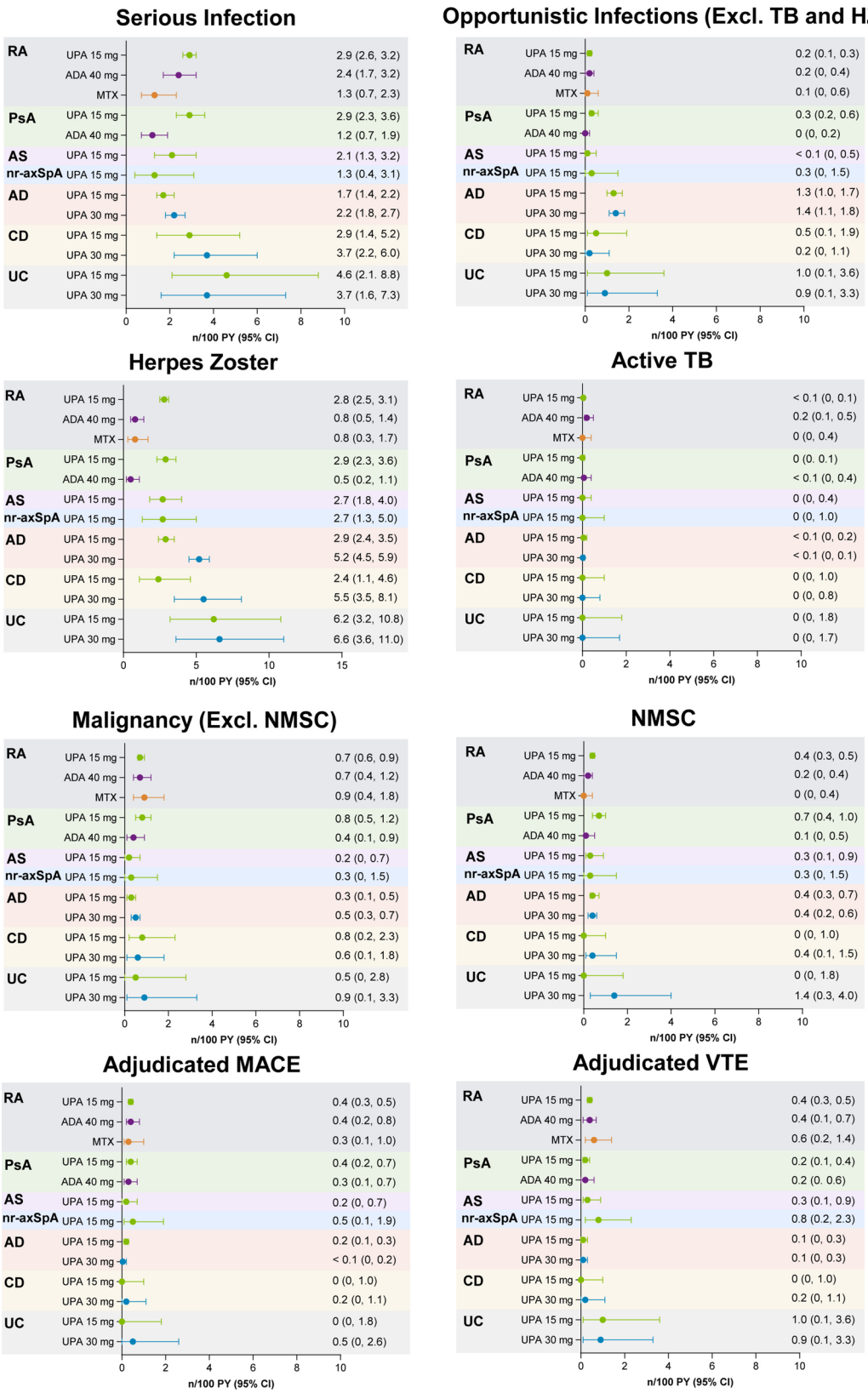
Table 2 continued

Parameter	RA			PsA		AS	nr-axSpA	AD		CD		UC	
	UPA 15 mg *n* = 3209	ADA 40 mg *n* = 579	MTX *n* = 314	UPA 15 mg *n* = 907	ADA 40 mg *n* = 429	UPA 15 mg *n* = 596	UPA 15 mg *n* = 286	UPA 15 mg *n* = 1337	UPA 30 mg *n* = 1346	UPA 15 mg *n* = 221	UPA 30 mg *n* = 229	UPA 15 mg *n* = 250	UPA 30 mg *n* = 251
Any TEAE leading to death	0.7 (0.5, 0.8)	0.7 (0.4, 1.1)	0.1 (0, 0.6)	0.6 (0.4, 1.0)	0.2 (0, 0.6)	< 0.1 (0, 0.5)	0 (0, 1.0)	< 0.1 (0, 0.2)	0.1 (0, 0.2)	0.3 (0, 1.4)	0 (0, 0.8)	0 (0, 1.8)	0 (0, 1.7)
Any death[b] *n*/100 PY (95% CI)	0.8 (0.6, 1.0)	0.9 (0.5, 1.4)	0.9 (0.4, 1.8)	0.8 (0.5, 1.2)	0.3 (0.1, 0.8)	< 0.1 (0, 0.5)	0 (0, 1.0)	0.1 (0, 0.3)	0.1 (0, 0.3)	0.3 (0, 1.4)	0 (0, 0.8)	0 (0, 1.8)	0 (0, 1.7)

AD atopic dermatitis, *ADA* adalimumab, *AS* ankylosing spondylitis, *CD* Crohn's disease, *max* maximum, *min* minimum, *CI* confidence interval, *MTX* methotrexate, *n*/100 PY number of 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, *TEAE* treatment-emergent adverse event, *UC* ulcerative colitis, *UPA* upadacitinib

[a]As assessed by the investigator

[b]Also includes deaths that were not treatment emergent


Serious Infection
RA UPA 15 mg 2.9 (2.6, 3.2)
ADA 40 mg 2.4 (1.7, 3.2)
MTX 1.3 (0.7, 2.3)
PsA UPA 15 mg 2.9 (2.3, 3.6)
ADA 40 mg 1.2 (0.7, 1.9)
AS UPA 15 mg 2.1 (1.3, 3.2)
nr-axSpA UPA 15 mg 1.3 (0.4, 3.1)
AD UPA 15 mg 1.7 (1.4, 2.2)
UPA 30 mg 2.2 (1.8, 2.7)
CD UPA 15 mg 2.9 (1.4, 5.2)
UPA 30 mg 3.7 (2.2, 6.0)
UC UPA 15 mg 4.6 (2.1. 8.8)
UPA 30 mg 3.7 (1.6, 7.3)
0 2 4 6 8 10
n/100 PY (95% CI)
Opportunistic Infections (Excl. TB and HZ)
RA UPA 15 mg 0.2 (0.1, 0.3)
ADA 40 mg 0.2 (0, 0.4)
MTX 0.1 (0, 0.6)
PsA UPA 15 mg 0.3 (0.2, 0.6)
ADA 40 mg 0 (0, 0.2)
AS UPA 15 mg < 0.1 (0, 0.5)
nr-axSpA UPA 15 mg 0.3 (0, 1.5)
AD UPA 15 mg 1.3 (1.0, 1.7)
UPA 30 mg 1.4 (1.1, 1.8)
CD UPA 15 mg 0.5 (0.1, 1.9)
UPA 30 mg 0.2 (0, 1.1)
UC UPA 15 mg 1.0 (0.1, 3.6)
UPA 30 mg 0.9 (0.1, 3.3)
0 2 4 6 8 10
n/100 PY (95% CI)
Herpes Zoster
RA UPA 15 mg 2.8 (2.5, 3.1)
ADA 40 mg 0.8 (0.5, 1.4)
MTX 0.8 (0.3, 1.7)
PsA UPA 15 mg 2.9 (2.3, 3.6)
ADA 40 mg 0.5 (0.2, 1.1)
AS UPA 15 mg 2.7 (1.8, 4.0)
nr-axSpA UPA 15 mg 2.7 (1.3, 5.0)
AD UPA 15 mg 2.9 (2.4, 3.5)
UPA 30 mg 5.2 (4.5, 5.9)
CD UPA 15 mg 2.4 (1.1, 4.6)
UPA 30 mg 5.5 (3.5, 8.1)
UC UPA 15 mg 6.2 (3.2, 10.8)
UPA 30 mg 6.6 (3.6, 11.0)
0 5 10 15
n/100 PY (95% CI)
Active TB
RA UPA 15 mg < 0.1 (0, 0.1)
ADA 40 mg 0.2 (0.1, 0.5)
MTX 0 (0, 0.4)
PsA UPA 15 mg 0 (0, 0.1)
ADA 40 mg < 0.1 (0, 0.4)
AS UPA 15 mg 0 (0, 0.4)
nr-axSpA UPA 15 mg 0 (0, 1.0)
AD UPA 15 mg < 0.1 (0, 0.2)
UPA 30 mg < 0.1 (0, 0.1)
CD UPA 15 mg 0 (0, 1.0)
UPA 30 mg 0 (0, 0.8)
UC UPA 15 mg 0 (0, 1.8)
UPA 30 mg 0 (0, 1.7)
0 2 4 6 8 10
n/100 PY (95% CI)
Malignancy (Excl. NMSC)
RA UPA 15 mg 0.7 (0.6, 0.9)
ADA 40 mg 0.7 (0.4, 1.2)
MTX 0.9 (0.4, 1.8)
PsA UPA 15 mg 0.8 (0.5, 1.2)
ADA 40 mg 0.4 (0.1, 0.9)
AS UPA 15 mg 0.2 (0, 0.7)
nr-axSpA UPA 15 mg 0.3 (0, 1.5)
AD UPA 15 mg 0.3 (0.1, 0.5)
UPA 30 mg 0.5 (0.3, 0.7)
CD UPA 15 mg 0.8 (0.2, 2.3)
UPA 30 mg 0.6 (0.1, 1.8)
UC UPA 15 mg 0.5 (0, 2.8)
UPA 30 mg 0.9 (0.1, 3.3)
0 2 4 6 8 10
n/100 PY (95% CI)
NMSC
RA UPA 15 mg 0.4 (0.3, 0.5)
ADA 40 mg 0.2 (0, 0.4)
MTX 0 (0, 0.4)
PsA UPA 15 mg 0.7 (0.4, 1.0)
ADA 40 mg 0.1 (0, 0.5)
AS UPA 15 mg 0.3 (0.1, 0.9)
nr-axSpA UPA 15 mg 0.3 (0, 1.5)
AD UPA 15 mg 0.4 (0.3, 0.7)
UPA 30 mg 0.4 (0.2, 0.6)
CD UPA 15 mg 0 (0, 1.0)
UPA 30 mg 0.4 (0.1, 1.5)
UC UPA 15 mg 0 (0, 1.8)
UPA 30 mg 1.4 (0.3, 4.0)
0 2 4 6 8 10
n/100 PY (95% CI)
Adjudicated MACE
RA UPA 15 mg 0.4 (0.3, 0.5)
ADA 40 mg 0.4 (0.2, 0.8)
MTX 0.3 (0.1, 1.0)
PsA UPA 15 mg 0.4 (0.2, 0.7)
ADA 40 mg 0.3 (0.1, 0.7)
AS UPA 15 mg 0.2 (0, 0.7)
nr-axSpA UPA 15 mg 0.5 (0.1, 1.9)
AD UPA 15 mg 0.2 (0.1, 0.3)
UPA 30 mg < 0.1 (0, 0.2)
CD UPA 15 mg 0 (0, 1.0)
UPA 30 mg 0.2 (0, 1.1)
UC UPA 15 mg 0 (0, 1.8)
UPA 30 mg 0.5 (0, 2.6)
0 2 4 6 8 10
n/100 PY (95% CI)
Adjudicated VTE
RA UPA 15 mg 0.4 (0.3, 0.5)
ADA 40 mg 0.4 (0.1, 0.7)
MTX 0.6 (0.2, 1.4)
PsA UPA 15 mg 0.2 (0.1, 0.4)
ADA 40 mg 0.2 (0. 0.6)
AS UPA 15 mg 0.3 (0.1, 0.9)
nr-axSpA UPA 15 mg 0.8 (0.2, 2.3)
AD UPA 15 mg 0.1 (0, 0.3)
UPA 30 mg 0.1 (0, 0.3)
CD UPA 15 mg 0 (0, 1.0)
UPA 30 mg 0.2 (0, 1.1)
UC UPA 15 mg 1.0 (0.1, 3.6)
UPA 30 mg 0.9 (0.1, 3.3)
0 2 4 6 8 10
n/100 PY (95% CI)

◂**Fig. 1** Exposure-adjusted incidence rates of infections, malignancies, and cardiovascular events[a]. *AD* atopic dermatitis, *ADA* adalimumab, *AS* ankylosing spondylitis, *CD* Crohn's disease, *CI* confidence interval, *excl.* excluding, *HZ* herpes zoster, *MACE* major adverse cardiovascular events, *MTX* methotrexate, *NMSC* nonmelanoma skin cancer, *n*/100 PY number of patients with at least 1 event per 100 patient-years, *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)

higher in patients receiving upadacitinib 30 mg vs upadacitinib 15 mg. EAIRs of TEAEs were comparable between upadacitinib doses in the CD and UC populations. The EAIR of TEAEs leading to death was < 1.0 *n*/100 PY across all treatment groups and populations, with the highest rate observed in patients with RA treated with upadacitinib 15 mg (0.7 *n*/100 PY) and adalimumab (0.7 *n*/100 PY). The most common causes of death, other than COVID-19, were cardiovascular related. No deaths were observed in the nr-axSpA and UC populations in the analysis sets presented. SMR estimates in patients treated with upadacitinib 15 mg were 0.63 (95% CI 0.49, 0.80) in RA and 0.66 (95% CI 0.38, 1.06) in PsA. The SMR estimate was 0.39 (95% CI 0.18, 0.74) in AD (including both doses). For the AS, nr-axSpA, CD, and UC populations, SMR estimates could not be generated because of the absence or low occurrence of treatment-emergent deaths.

AESIs

AESIs are reported as EAIR in the text and presented in Figs. 1, 2, and 3 and as EAER in the supplement (Figs. S1–S3 in the supplementary material).

Serious and Opportunistic Infections

Across indications, EAIRs of serious infections with upadacitinib treatment ranged from 1.3 *n*/100 PY (nr-axSpA) to 4.6 *n*/100 PY (UC, upadacitinib 15 mg); no clear dose-dependent relationship was observed (Fig. 1). In RA, serious infection rates were similar between upadacitinib (2.9 *n*/100 PY) and adalimumab (2.4 *n*/100 PY) and numerically lower in the methotrexate treatment group (1.3 *n*/100 PY). In the PsA population, the EAIR of serious infections was numerically higher in patients treated with upadacitinib (2.9 *n*/100 PY) vs adalimumab (1.2 *n*/100 PY).

Opportunistic infections (excluding herpes zoster and tuberculosis) were reported in all indications, with the lowest EAIR observed in rheumatological diseases (≤ 0.3 *n*/100 PY; Fig. 1). The most frequently reported opportunistic infection with upadacitinib was esophageal candidiasis in the RA, PsA, and AS populations; one patient in the RA population experienced listeria meningitis, and one patient in the nr-axSpA population experienced herpes simplex meningomyelitis (Table S4 in the supplementary material). The highest EAIR of opportunistic infections (excluding herpes zoster and tuberculosis) was observed in the AD population (1.3–1.4 *n*/100 PY across upadacitinib doses); in this indication, nearly all opportunistic infections were eczema herpeticum. Opportunistic infections (excluding herpes zoster and tuberculosis) in the CD and UC populations occurred at EAIRs of 0.2–1.0 *n*/100 PY and included esophageal candidiasis, *Pneumocystis jirovecii* pneumonia, cytomegalovirus, and pneumonia cryptococcal.

The EAIRs of herpes zoster in patients treated with upadacitinib ranged from 2.4 to 6.6 *n*/100 PY, with rates trending higher in the UC population (Fig. 1). In line with the expected safety profile of JAK inhibitors [33], the EAIR of herpes zoster was numerically higher with upadacitinib 15 mg (2.8 *n*/100 PY) vs adalimumab (0.8 *n*/100 PY) and methotrexate (0.8 *n*/100 PY) in RA and numerically higher with upadacitinib 15 mg vs adalimumab in PsA (2.9 vs 0.5 *n*/100 PY). In the AD, CD, and UC populations, EAIRs of herpes zoster were numerically higher with upadacitinib 30 mg vs upadacitinib

15 mg, suggesting a dose-dependent relationship. For most patients, herpes zoster involved a single dermatome; few patients had ophthalmic involvement (PsA, 6.2%; RA, 5.9%; other indications, ≤ 4.2%; Table S5 in the supplementary material). There was a single case of central nervous system involvement (herpes meningoencephalitis) in a patient with UC who received upadacitinib 30 mg.

Tuberculosis was rare (EAIR of < 0.1 *n*/100 PY) in patients treated with upadacitinib across all indications and doses (Fig. 1).

Malignancies

The EAIR of malignancy (excluding NMSC) was low, occurring at rates of < 1.0 *n*/100 PY across all treatment groups and indications (Fig. 1). No clear pattern of malignancies (excluding NMSC) was observed in any indication (Table S6 in the supplementary material). The EAIR of lymphoma was low in patients treated with upadacitinib (≤ 0.3 *n*/100 PY across all indications).

Across all treatment groups and indications, EAIRs of NMSC were < 1.5 *n*/100 PY, with the highest rate observed in patients with UC receiving upadacitinib 30 mg (1.4 *n*/100 PY; Fig. 1). In the RA and PsA populations, NMSC rates were numerically higher with upadacitinib 15 mg vs active comparators. NMSC was not observed in patients with RA receiving methotrexate or patients with CD and UC receiving upadacitinib 15 mg. Although EAIRs of NMSC were numerically higher with upadacitinib 30 mg vs upadacitinib 15 mg in patients with CD and UC, rates were similar between upadacitinib doses in AD.

Adjudicated MACE and VTE

The EAIR of MACE was low, occurring at rates of ≤ 0.5 *n*/100 PY across all treatment groups and indications (Fig. 1). In the RA and PsA populations, MACE rates were numerically similar between upadacitinib 15 mg and active comparators. In patients with CD and UC, MACE was not observed in patients receiving upadacitinib 15 mg and occurred at EAIRs of 0.2 *n*/100 PY and 0.5 *n*/100 PY, respectively, in patients receiving upadacitinib 30 mg.

Among patients treated with upadacitinib, VTE was observed more commonly in the nr-axSpA (0.8 *n*/100 PY) and UC (upadacitinib 15 mg, 1.0 *n*/100 PY; upadacitinib 30 mg, 0.9 *n*/100 PY) populations and occurred at EAIR of ≤ 0.4 *n*/100 PY in the other indications (Fig. 1). VTE rates were numerically similar for upadacitinib 15 mg and active comparators and between upadacitinib doses. Most patients treated with upadacitinib who experienced MACE or VTE had ≥ 1 underlying risk factor for cardiovascular disease at baseline (Table S7 in the supplementary material).

Laboratory-Related Abnormalities

EAIRs of investigator-reported anemia and lymphopenia varied across indications and trended higher in patients with CD and UC (Fig. 2). EAIRs of lymphopenia were numerically higher with upadacitinib 15 mg vs adalimumab in patients with RA (1.2 vs 0.5 *n*/100 PY) and PsA (1.6 vs 0.1 *n*/100 PY). EAIRs of neutropenia were numerically similar for upadacitinib 15 mg and active comparators and trended higher in patients with UC. In line with the known safety profile of JAK inhibitors [34–36], elevated CK levels were reported, with numerically higher EAIRs observed in patients with RA and PsA treated with upadacitinib 15 mg vs active comparators. A dose-dependent increase in elevated CK was observed with upadacitinib treatment in the AD, CD, and UC populations, though there were large overlaps of 95% CIs between doses for the CD and UC indications. Most cases of elevated CK levels were mild or moderate in severity, asymptomatic, transient, and did not result in treatment discontinuation. Rhabdomyolysis was rare, and most patients who experienced rhabdomyolysis had alternative etiologies identified (e.g., increased physical activity or infection). Hepatic disorders occurred at EAIRs of 2.8–9.5 *n*/100 PY across treatments and indications, primarily comprising transaminase elevations. Hepatic disorders rates were numerically higher in patients with RA treated with upadacitinib 15 mg (5.0 *n*/100 PY) vs adalimumab (2.9 *n*/100 PY); in PsA, rates trended higher with adalimumab vs upadacitinib (8.5 vs 6.6 *n*/100 PY). EAIRs of renal dysfunction

were low (≤0.5 *n*/100 PY across treatments and indications).

In RA, the proportion of patients with grade 3/4 laboratory abnormalities was generally comparable between upadacitinib 15 mg and adalimumab; grade 3 decreases in lymphocytes and grade 3 elevations in alanine aminotransferase, aspartate aminotransferase, and CK occurred more frequently with methotrexate than with upadacitinib 15 mg (Tables S8 and S9 in the supplementary material). In PsA, the proportion of patients with grade 3 decreases in lymphocytes was higher with upadacitinib 15 mg than with adalimumab. In the AD, CD, and UC populations, treatment with upadacitinib was associated with dose-dependent increases in grade 3 laboratory abnormalities of hemoglobin, neutrophils, and CK. In AD, dose-dependent increases in grade 3 abnormalities were observed for lymphocytes, alanine aminotransferase, and aspartate aminotransferase.

GI Perforation, Bone Fracture, Retinal Detachment, and Serious Hypersensitivity Reaction

The EAIR of GI perforation was low (≤0.1 *n*/100 PY) across treatment groups and indications, except for in the CD population, where GI perforation occurred at an incidence of 0.8 *n*/100 PY and 0.4 *n*/100 PY in the upadacitinib 15 mg and 30 mg treatment groups, respectively (Fig. 3). GI perforations in the CD population were noted to occur when patients had ongoing disease activity, deep ulcers, or complications (e.g., strictures, obstructions, or fistulas) [22]. The EAIRs of bone fracture were 0.5–2.4 *n*/100 PY across treatments and indications, with the highest rate observed in RA, in line with known background risks. In the RA and PsA populations, EAIRs of bone fracture were numerically higher with upadacitinib 15 mg vs adalimumab. Retinal detachment occurred at an EAIR of ≤0.2 *n*/100 PY across treatments and indications, with most cases primarily observed in the AD population and most frequently reported in Asian patients. The EAIR of serious hypersensitivity reaction was low (≤0.1 *n*/100 PY) across indications and treatment groups.

Rates of AESIs Over Time

Across all indications, EAIRs of serious infection, herpes zoster, malignancy (excluding NMSC), NMSC, MACE, and VTE remained stable over time (Figs. S4–S9 in the supplementary material). In the AS, nr-axSpA, and UC populations, several time intervals (≥12 to <18 months, ≥24 to <30 months, and ≥30 to <36 months) exhibited high EAIRs due to substantially reduced exposure times, as fewer patients remained toward the end of the study and long-term extension.

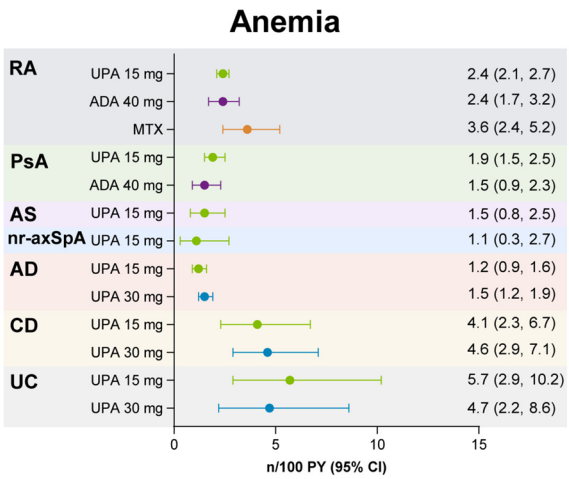
AESIs by Age

EAIRs of several AESIs were generally higher in patients aged ≥65 years vs <65 years, including serious infection, herpes zoster, malignancy, VTE, anemia, renal dysfunction, and bone fracture (Tables S10 and S11 in the supplementary material).

DISCUSSION

This descriptive integrated safety analysis, comprising data from 16 studies and over 27,000 patient-years of exposure, provides a comprehensive characterization of the long-term safety profile of upadacitinib across a broad spectrum of immune-mediated inflammatory diseases. Our analysis indicates that long-term treatment of chronic diseases with upadacitinib remains well tolerated. EAIRs of AESIs remained stable over time, suggesting no clear evidence of a cumulative increase in safety risk with longer upadacitinib exposure.

Variations in EAIRs of TEAEs among different indications likely reflect differences in patient populations and underlying background risks [37–42]. For instance, numerically higher death rates were noted in the RA and PsA populations compared with other indications, potentially attributable to a higher baseline prevalence of cardiovascular risk factors (e.g., older age [≥65 years], higher body mass index [≥30 kg/m^2], and hypertension) and these conditions being associated with multiple comorbidities [43, 44]. However, in the RA


Anemia
RA
UPA 15 mg 2.4 (2.1, 2.7)
ADA 40 mg 2.4 (1.7, 3.2)
MTX 3.6 (2.4, 5.2)
PsA
UPA 15 mg 1.9 (1.5, 2.5)
ADA 40 mg 1.5 (0.9, 2.3)
AS
UPA 15 mg 1.5 (0.8, 2.5)
nr-axSpA
UPA 15 mg 1.1 (0.3, 2.7)
AD
UPA 15 mg 1.2 (0.9, 1.6)
UPA 30 mg 1.5 (1.2, 1.9)
CD
UPA 15 mg 4.1 (2.3, 6.7)
UPA 30 mg 4.6 (2.9, 7.1)
UC
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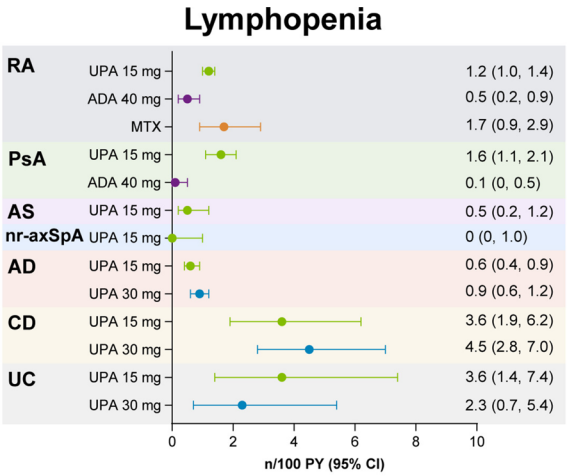
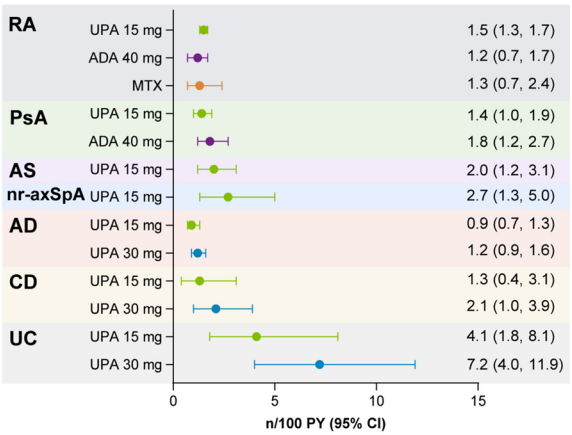
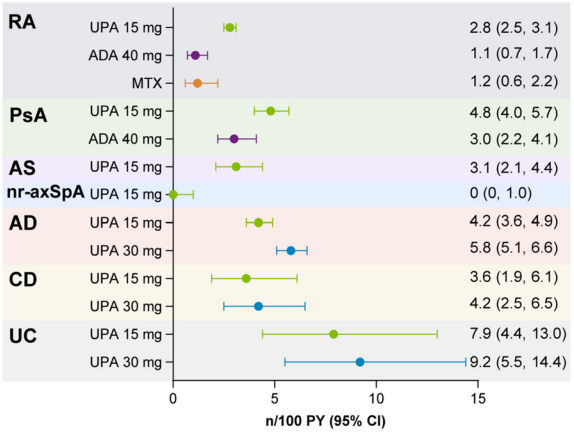
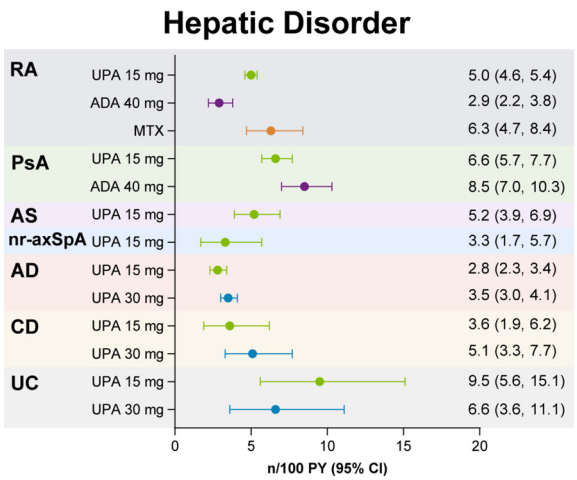
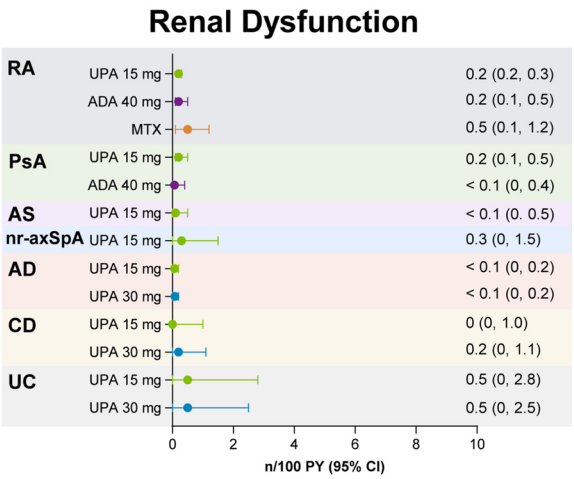
UPA 30 mg 4.7 (2.2, 8.6)
0 5 10 15
n/100 PY (95% CI)


Lymphopenia
RA
UPA 15 mg 1.2 (1.0, 1.4)
ADA 40 mg 0.5 (0.2, 0.9)
MTX 1.7 (0.9, 2.9)
PsA
UPA 15 mg 1.6 (1.1, 2.1)
ADA 40 mg 0.1 (0, 0.5)
AS
UPA 15 mg 0.5 (0.2, 1.2)
nr-axSpA
UPA 15 mg 0 (0, 1.0)
AD
UPA 15 mg 0.6 (0.4, 0.9)
UPA 30 mg 0.9 (0.6, 1.2)
CD
UPA 15 mg 3.6 (1.9, 6.2)
UPA 30 mg 4.5 (2.8, 7.0)
UC
UPA 15 mg 3.6 (1.4, 7.4)
UPA 30 mg 2.3 (0.7, 5.4)
0 2 4 6 8 10
n/100 PY (95% CI)


Neutropenia
RA
UPA 15 mg 1.5 (1.3, 1.7)
ADA 40 mg 1.2 (0.7, 1.7)
MTX 1.3 (0.7, 2.4)
PsA
UPA 15 mg 1.4 (1.0, 1.9)
ADA 40 mg 1.8 (1.2, 2.7)
AS
UPA 15 mg 2.0 (1.2, 3.1)
nr-axSpA
UPA 15 mg 2.7 (1.3, 5.0)
AD
UPA 15 mg 0.9 (0.7, 1.3)
UPA 30 mg 1.2 (0.9, 1.6)
CD
UPA 15 mg 1.3 (0.4, 3.1)
UPA 30 mg 2.1 (1.0, 3.9)
UC
UPA 15 mg 4.1 (1.8, 8.1)
UPA 30 mg 7.2 (4.0, 11.9)
0 5 10 15
n/100 PY (95% CI)


Elevated CK
RA
UPA 15 mg 2.8 (2.5, 3.1)
ADA 40 mg 1.1 (0.7, 1.7)
MTX 1.2 (0.6, 2.2)
PsA
UPA 15 mg 4.8 (4.0, 5.7)
ADA 40 mg 3.0 (2.2, 4.1)
AS
UPA 15 mg 3.1 (2.1, 4.4)
nr-axSpA
UPA 15 mg 0 (0, 1.0)
AD
UPA 15 mg 4.2 (3.6, 4.9)
UPA 30 mg 5.8 (5.1, 6.6)
CD
UPA 15 mg 3.6 (1.9, 6.1)
UPA 30 mg 4.2 (2.5, 6.5)
UC
UPA 15 mg 7.9 (4.4, 13.0)
UPA 30 mg 9.2 (5.5, 14.4)
0 5 10 15
n/100 PY (95% CI)


Hepatic Disorder
RA
UPA 15 mg 5.0 (4.6, 5.4)
ADA 40 mg 2.9 (2.2, 3.8)
MTX 6.3 (4.7, 8.4)
PsA
UPA 15 mg 6.6 (5.7, 7.7)
ADA 40 mg 8.5 (7.0, 10.3)
AS
UPA 15 mg 5.2 (3.9, 6.9)
nr-axSpA
UPA 15 mg 3.3 (1.7, 5.7)
AD
UPA 15 mg 2.8 (2.3, 3.4)
UPA 30 mg 3.5 (3.0, 4.1)
CD
UPA 15 mg 3.6 (1.9, 6.2)
UPA 30 mg 5.1 (3.3, 7.7)
UC
UPA 15 mg 9.5 (5.6, 15.1)
UPA 30 mg 6.6 (3.6, 11.1)
0 5 10 15 20
n/100 PY (95% CI)


Renal Dysfunction
RA
UPA 15 mg 0.2 (0.2, 0.3)
ADA 40 mg 0.2 (0.1, 0.5)
MTX 0.5 (0.1, 1.2)
PsA
UPA 15 mg 0.2 (0.1, 0.5)
ADA 40 mg < 0.1 (0, 0.4)
AS
UPA 15 mg < 0.1 (0. 0.5)
nr-axSpA
UPA 15 mg 0.3 (0, 1.5)
AD
UPA 15 mg < 0.1 (0, 0.2)
UPA 30 mg < 0.1 (0, 0.2)
CD
UPA 15 mg 0 (0, 1.0)
UPA 30 mg 0.2 (0, 1.1)
UC
UPA 15 mg 0.5 (0, 2.8)
UPA 30 mg 0.5 (0, 2.5)
0 2 4 6 8 10
n/100 PY (95% CI)

◂**Fig. 2** Exposure-adjusted incidence rates of investigator-reported laboratory-related abnormalities[a]. *AD* atopic dermatitis, *ADA* adalimumab, *AS* ankylosing spondylitis, *CD* Crohn's disease, *CI* confidence interval, *CK* creatine kinase, *MTX* methotrexate, *n*/100 PY number of patients with at least 1 event per 100 patient-years, *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 ($n=251$)

and PsA populations, rates of deaths were similar between upadacitinib and active comparators, and based on SMR analyses, the number of deaths in patients exposed to upadacitinib was not higher than expected for the general population. Acne was among the most frequently observed TEAEs in patients with AD but not with the other indications. These findings may be due to the younger overall patient population enrolled in the AD studies and potentially greater attention paid by dermatologists to other dermatological events. Acne has also been reported in AD studies of other JAK inhibitors [45, 46]. In a post hoc analysis characterizing acne events associated with upadacitinib treatment in three AD studies, all acne cases, except one, were mild or moderate in severity, with only two patients discontinuing treatment due to moderate acne [47]. Additionally, acne was more frequently observed in younger patients, female patients, and patients of color; most cases requiring intervention were effectively managed with topical antibiotics, retinoids, and/or benzoyl peroxide; and there was no quality of life difference in patients who developed acne vs those who did not [47]. GI perforations were primarily observed in the CD population (≤0.8 *n*/100 PY) and rarely occurred in the other indications (≤0.1 *n*/100 PY). In the CD studies, GI perforations primarily occurred in patients experiencing ongoing disease activity, deep ulcers, and/or CD complications (e.g., fistula, stricture, or obstruction) [22]. It is unclear whether GI perforations represent a safety risk associated with upadacitinib or reflect an inherent risk in patients with active inflammation and CD complications. Clinicians should closely monitor and follow up with patients presenting with severely active CD.

Data from ORAL Surveillance, a head-to-head study conducted in a RA population enriched for cardiovascular risk, showed that one or both doses of tofacitinib were associated with a higher incidence of several adverse events compared with tumor necrosis factor inhibitors [4]. On the basis of these findings, the US Food and Drug Administration and European Medicines Agency issued warnings for malignancies and serious cardiovascular events for all JAK inhibitors used to treat immune-mediated inflammatory diseases [48, 49]. However, in our analysis, the EAIR of malignancy (excluding NMSC), MACE, and VTE in patients treated with upadacitinib was low (≤1.0 *n*/100 PY) across indications, with rates comparable between upadacitinib and active comparators in the RA and PsA populations. These results are consistent with long-term safety findings of other JAK inhibitors [46, 50–52]. Furthermore, an integrated post hoc analysis of six phase 3 upadacitinib trials, which included a patient population similar to that of ORAL Surveillance, showed comparable incidence rates of malignancy (excluding NMSC), MACE, and VTE between upadacitinib, adalimumab, and methotrexate monotherapy [53]. However, no prospective safety outcomes trial similar to ORAL Surveillance has been specifically conducted for upadacitinib, and it remains unclear whether findings from ORAL Surveillance represent a JAK inhibitor class effect or can be generalized to other diseases. Consequently, clinicians should evaluate each patient's benefit-risk profile before initiating upadacitinib, particularly assessing risk factors for malignancy, serious cardiovascular events, and thrombosis [3, 10, 54]. Traditional cardiovascular and thrombotic risk factors, including age ≥ 65 years, male sex, obesity, hypertension, diabetes mellitus, tobacco/nicotine use, and history of cardiovascular events, have been associated with higher MACE and VTE rates in patients with RA treated with upadacitinib [55] and should therefore be considered in treatment decisions.

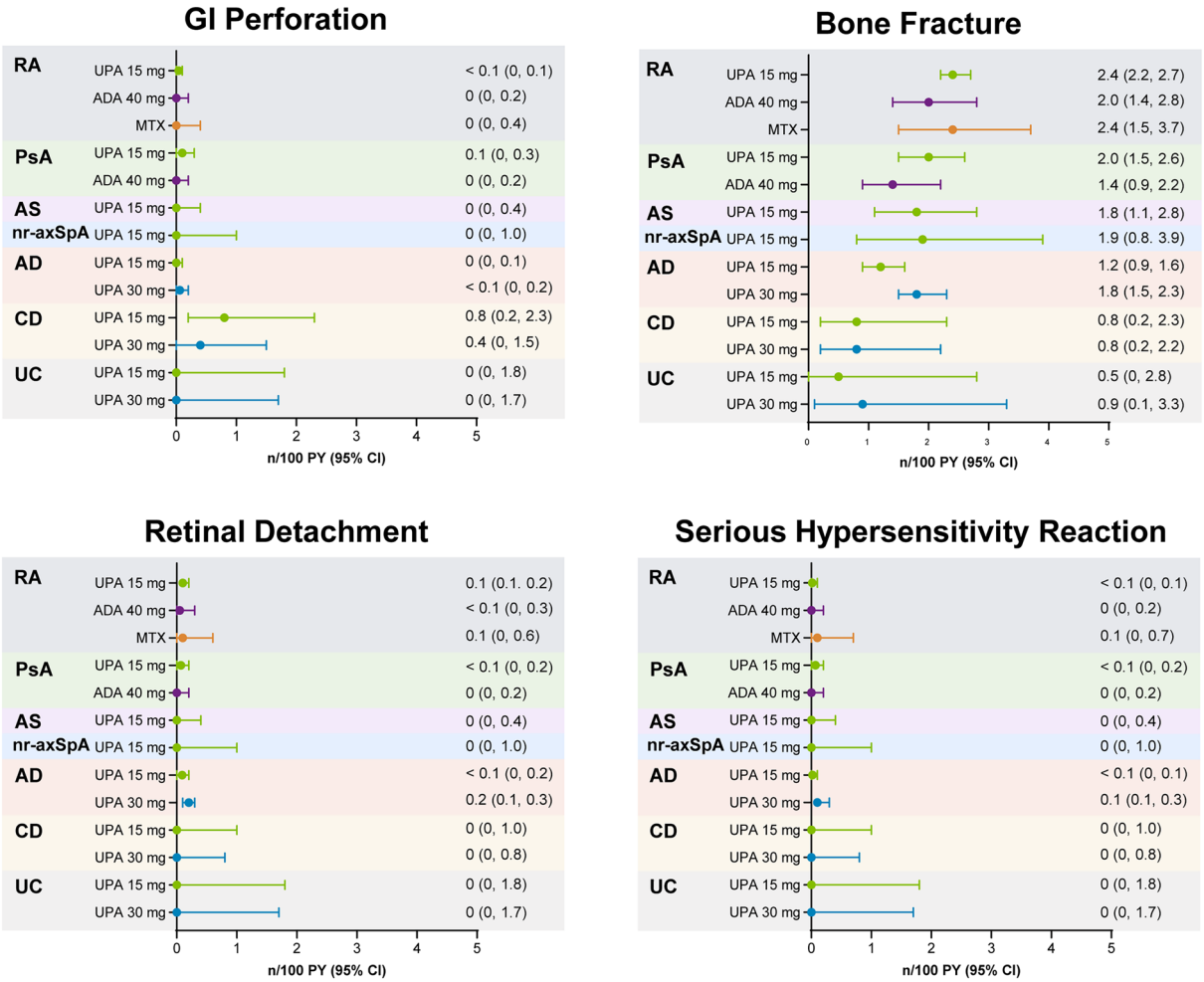


Fig. 3 Exposure-adjusted incidence rates of GI perforation, bone fracture, retinal detachment, and serious hypersensitivity reaction[a]. *AD* atopic dermatitis, *ADA* adalimumab, *AS* ankylosing spondylitis, *CD* Crohn's disease, *CI* confidence interval, *GI* gastrointestinal, *MTX* methotrexate, *n*/100 PY number of patients with at least 1 event per 100 patient-years, *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)

Other known safety risks of JAK inhibitors include herpes zoster, NMSC, and elevated CK levels [2, 56]. We observed numerically higher EAIRs of these AESIs in patients treated with upadacitinib vs active comparators in the RA and PsA populations. For most patients, herpes zoster involved a single dermatome. Ophthalmic and central nervous system involvement was rare; a single herpes meningoencephalitis case occurred in the UC population. In AD, CD, and UC, upadacitinib was associated with a dose-dependent increase in herpes zoster. As recommended by the upadacitinib label, eligible patients should be vaccinated for herpes zoster before receiving treatment [10]. Although immunogenicity may be of concern [57], data from the phase 3 SELECT-COMPARE trial showed that most patients receiving long-term upadacitinib 15 mg treatment and background methotrexate achieved satisfactory cell-mediated and humoral

immune responses to the adjuvanted recombinant zoster vaccine through week 60 [58]. We observed that NMSC primarily presented as basal or squamous cell carcinoma. Patients treated with upadacitinib should undergo regular skin examinations, especially those who may be at increased risk for NMSC (e.g., age ≥ 65 years, white, male, and body mass index ≥ 30 kg/m^2) [3, 59]. Most cases of elevated CK levels were nonserious, asymptomatic, and transient; rhabdomyolysis was rare and often associated with other factors, such as physical activity or infection. Routine CK monitoring is not necessary, as CK elevations in patients treated with JAK inhibitors have not been associated with clinical sequelae [3].

Higher EAIRs of several AESIs were observed among patients aged ≥ 65 years vs < 65 years, which may be due to factors related to advanced age, such as increased frailty, comorbidities, and concomitant medications. Although we were unable to directly compare the incidence of AESIs in the studied populations with the background incidence in older patients because of methodological challenges, other studies have also identified older age as a significant risk factor for several AESIs [4, 60–62]. These findings underscore the need for more careful monitoring and management of older patients to potentially decrease their risks of important safety events.

JAK inhibitors, including upadacitinib, have demonstrated efficacy in managing a range of immune-mediated inflammatory diseases, and their overall safety profiles are increasingly well characterized through extensive clinical trial programs and real-world experience [10, 63–71]. Although these agents are associated with certain safety risks that warrant careful monitoring, clinicians must also consider the benefits of achieving disease control. These benefits include not only alleviating debilitating symptoms and improving quality of life but also mitigating the long-term complications and morbidity associated with uncontrolled disease activity in these chronic conditions. A benefit-risk assessment and a treatment plan tailored to the individual patient's specific disease characteristics, risk factors, and therapeutic goals will guide the decision to initiate or continue treatment with upadacitinib.

Major strengths of this analysis include its large sample size, long-term follow-up, and the inclusion of data from seven indications. The use of adalimumab (RA and PsA) and methotrexate (RA only) as comparator arms in long-term treatment enabled meaningful contextualization of safety data. Our findings provide clinicians with a comprehensive and detailed understanding of the long-term safety profile of upadacitinib, minimizing the need to extrapolate safety results from other JAK inhibitors or different indications. Limitations include the lack of comparator arms in indications other than RA and PsA. Additionally, safety data for polyarticular juvenile idiopathic arthritis and giant cell arteritis were not included because of insufficient long-term data to support an assessment of long-term safety. As all safety data were reported in clinical trial settings, further research is warranted to characterize the safety profile of upadacitinib across multiple indications in real-world settings. The median observation time varied across indications; the median observation time was about 1 year in three indications and approximately 5 years in two indications. No statistical tests for significance were performed, and all analyses are descriptive. Therefore, comparisons across treatments and indications should be made with caution. Differences in patient characteristics and varying comorbidities across indications further complicate the interpretation of safety data. For an individual indication in which data were pooled from multiple studies, the populations in these studies were generally similar; however, variability in factors, such as age, sex, disease severity, and prior treatment history, may have influenced the observed safety outcomes. Lastly, the proportion of patients aged ≥ 65 years was small for several indications; however, safety findings by age were consistent with those reported in other studies characterizing JAK inhibitor safety [4, 60–62].

CONCLUSIONS

This descriptive safety analysis characterized the long-term safety profile of upadacitinib in multiple indications. Findings from this analysis

indicate that long-term treatment of chronic diseases with upadacitinib remains well tolerated across various inflammatory diseases. Variations in EAIRs of TEAEs were observed across indications, potentially reflecting differences in patient populations and underlying background risks. Findings from this analysis can provide clinicians with a comprehensive understanding of the long-term safety profile of upadacitinib, enabling more informed treatment decisions tailored to individual patient needs.

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Data Availability. AbbVie is committed to responsible data sharing regarding the studies we sponsor. This includes access to anonymized individual data, as well as other information (e.g., protocols and analysis plans). These data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, statistical analysis plan (SAP), and execution of a data sharing agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe, and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/, then select "Home."

Declarations

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Conflict of Interest. Gerd R Burmester reports consulting fees from AbbVie, Amgen, Bristol Myers Squibb, Galapagos, Lilly, Pfizer, and Sanofi; and speaker fees from AbbVie, Amgen, Bristol Myers Squibb, Chugai, Galapagos, Lilly, Pfizer, and Sanofi. Atul Deodhar has received speaker fees from Johnson & Johnson, Novartis, Pfizer, and UCB; consulting fees from Bristol Myers Squibb, Johnson & Johnson, Lilly, MoonLake, Novartis, Pfizer, and UCB; and grant/research support from Bristol Myers Squibb, Johnson & Johnson, Lilly, MoonLake, Novartis, Pfizer, and UCB. Alan D Irvine has received grants, consulting fees, and/or advisory board honoraria from AbbVie, Almirall, Arena, Benevolent AI, Connect Biopharma, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, RAPT Therapeutics, Regeneron, Sanofi, and UCB. He is on the board of directors of the International Eczema Council. Remo Panaccione has received consulting fees from AbbVie, Abbott, Abbivax, Alimentiv, Amgen, AnaptysBio, AstraZeneca, Biogen,

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Ethical Approval. All studies were conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation guidelines, and applicable local regulations. An independent ethics committee or institutional review board at each study site approved the protocol. Patients (or legal guardians of adolescents) provided written informed consent before beginning the study.

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