Safety of Upadacitinib Across Rheumatoid Arthritis, Psoriatic Arthritis, and Axial Spondyloarthritis Encompassing 15,000 Patient-Years of Clinical Trial Data

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Presented at the European Congress of Rheumatology (EULAR), June 12–15, 2024, Vienna, Austria

OBJECTIVE

- To describe the long-term integrated safety profile of upadacitinib (UPA) 15 mg across indications in rheumatology, in the context of active comparators, from the SELECT clinical program

INTRODUCTION

- UPA, an oral JAK inhibitor, has demonstrated efficacy and safety across several rheumatic diseases, including RA, PsA, AS (also called r-axSpA), and nr-axSpA
- Safety observed with JAK inhibition to date has highlighted the need to further characterize the long-term safety profile of individual JAK inhibitors across diverse patient populations and in the context of active comparators, such as adalimumab (ADA) and MTX

METHODS

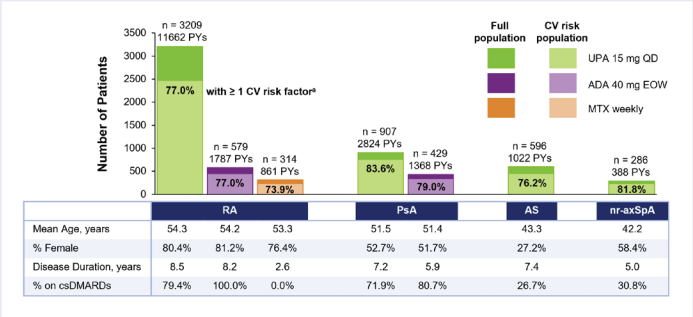
- Safety data (cutoff date: 15 August 2023) from eleven phase 3 UPA trials were compiled for RA (6), PsA (2), AS (2; one phase 2/3), and nr-axSpA (1) for this analysis[1,2]
- Treatment-emergent adverse events (TEAEs) with an onset on or after the first dose of study drug and ≤ 30 days after the last dose of study drug for UPA 15 mg and MTX, or ≤ 70 days for ADA, were coded using MedDRA version 26.0
- TEAEs were summarized for RA (pooled UPA 15 mg, ADA, and MTX [1 study each with ADA or MTX as comparator]), PsA (pooled UPA 15 mg and ADA [1 study as comparator]), AS (pooled UPA 15 mg), nr-axSpA (UPA 15 mg), and pooled axSpA (pooled UPA 15 mg from AS and nr-axSpA trials)
- TEAEs are presented as exposure-adjusted event rates (EAERs; events/100 patient-years [E/100 PY]) with 95% CIs; patients were not censored at the time of first event and multiple events in the same patient were accounted for
- Deaths (including COVID-19), MACE, VTE, and gastrointestinal perforations were adjudicated by blinded, independent committees using pre-specified definitions
- Age-gender adjusted standard incidence ratios (SIRs) using the SEER 18 database (2000-2018) and country-age-gender adjusted standardized mortality ratios (SMRs) using the World Health Organization 2016 data were calculated

RESULTS

PATIENTS

- In total, 4998 patients received ≥ 1 dose of UPA 15 mg, totaling 15,895.8 PYs of exposure **(Figure 1)**
- Baseline demographics and clinical characteristics are representative of the patient populations; most patients (range: 74%–84%) had ≥ 1 cardiovascular (CV) risk factor

Figure 1. Baseline Demographics and Clinical Characteristics



	RA			PsA		AS	nr-axSpA
Mean Age, years	54.3	54.2	53.3	51.5	51.4	43.3	42.2
% Female	80.4%	81.2%	76.4%	52.7%	51.7%	27.2%	58.4%
Disease Duration, years	8.5	8.2	2.6	7.2	5.9	7.4	5.0
% on csDMARDs	79.4%	100.0%	0.0%	71.9%	80.7%	26.7%	30.8%

ADA, adalimumab; csDMARDs, conventional synthetic DMARDs; CV, cardiovascular; EOW, every other week; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PY, patient-years; QD, once daily; UPA, upadacitinib.
[a]CV risk factors include: prior CV event, hypertension, diabetes mellitus, current and former tobacco/nicotine use, elevated LDL-C (≥ 3.36 mmol/L), and lowered HDL-C (≤ 1.034 mmol/L).

OVERVIEW OF TEAEs AND DEATHS

- The rate of adverse events (AEs) leading to discontinuation of study drug was generally similar across treatment groups and diseases **(Table 1)**
  - Types of AEs leading to discontinuation varied widely; the most frequently reported with UPA 15 mg were pneumonia (RA; n = 22/459), COVID-19 (PsA; n = 7/121), headache (AS; n = 3/42), and worsening axial spondyloarthritis and pulmonary embolism (nr-axSpA; both n = 2/20)
- Rates of treatment-emergent death were numerically higher with UPA 15 mg vs comparators in RA and PsA; rates of treatment-emergent COVID-19-related death ranged from 0.0 to 0.2 and CV death ranged from 0.0 to 0.2
- The SMR (95% CI) for treatment-emergent deaths with UPA 15 mg was 0.79 (0.63–0.98) in RA and 0.94 (0.59–1.40) in PsA; SMRs not calculated for AS or nr-axSpA (low events)

Table 1. TEAEs in Patients Treated With UPA, ADA, or MTX Across RA, PsA, AS, nr-axSpA, and Pooled axSpA

	RA			PsA		AS	nr-axSpA	Pooled axSpA
	UPA 15 mg QD n = 3209	ADA 40 mg EOW n = 579	MTX n = 314	UPA 15 mg QD n = 907	ADA 40 mg EOW n = 429	UPA 15 mg QD n = 596	UPA 15 mg QD n = 286	UPA 15 mg QD n = 882
Exposure								
Total, PY	11661.5	1787.0	860.7	2823.7	1368.0	1022.2	388.4	1410.5
Mean (SD), weeks	189.6 (112.1)	161.0 (142.0)	143.0 (105.3)	162.5 (83.1)	166.4 (84.7)	89.5 (29.4)	70.9 (34.8)	83.5 (32.4)
Median (min, max), weeks	216.3 (0.3, 394.9)	114.3 (0.1, 394.3)	134.1 (1.0, 263.1)	190.6 (0.1, 297.9)	201.0 (2.0, 264.3)	91.0 (0.1, 198.0)	53.9 (0.1, 155.0)	90.7 (0.1, 104.1)
TEAEs, E/100 PY (95% CI)								
Any AE	202.0 (199.5, 204.6)	179.2 (173.1, 185.6)	205.6 (196.2, 215.5)	227.2 (221.7, 232.8)	207.2 (199.7, 215.0)	188.4 (180.1, 197.0)	205.2 (191.2, 220.0)	193.1 (185.9, 200.4)
Any serious AE	12.6 (11.9, 13.2)	11.7 (10.2, 13.4)	9.2 (7.3, 11.4)	10.5 (9.3, 11.7)	8.2 (6.7, 9.9)	7.9 (6.3, 9.8)	8.5 (5.8, 11.9)	8.1 (6.7, 9.7)
Any AE leading to discontinuation of study drug	4.6 (4.3, 5.1)	4.5 (3.6, 5.6)	5.8 (4.3, 7.7)	5.0 (4.2, 5.9)	4.4 (3.3, 5.6)	4.1 (3.0, 5.6)	5.1 (3.1, 8.0)	4.4 (3.4, 5.6)
All deaths[a,b]	0.9 (0.7, 1.1)	0.8 (0.5, 1.4)	0.9 (0.4, 1.8)	0.8 (0.5, 1.2)	0.4 (0.1, 0.9)	< 0.1 (0.0, 0.5)	0.0 (0.0, 0.9)	0.1 (0.0, 0.4)
Treatment-emergent deaths	0.6 (0.4, 0.7)	0.4 (0.2, 0.9)	0.1 (0.0, 0.6)	0.6 (0.3, 0.9)	0.2 (0.0, 0.6)	< 0.1 (0.0, 0.5)	0.0 (0.0, 0.9)	0.1 (0.0, 0.4)
Nontreatment-emergent deaths	0.3 (0.2, 0.4)	0.4 (0.2, 0.8)	0.8 (0.3, 1.7)	0.2 (0.1, 0.5)	0.1 (0.0, 0.5)	0.0 (0.0, 0.4)	0.0 (0.0, 0.9)	0.0 (0.0, 0.3)

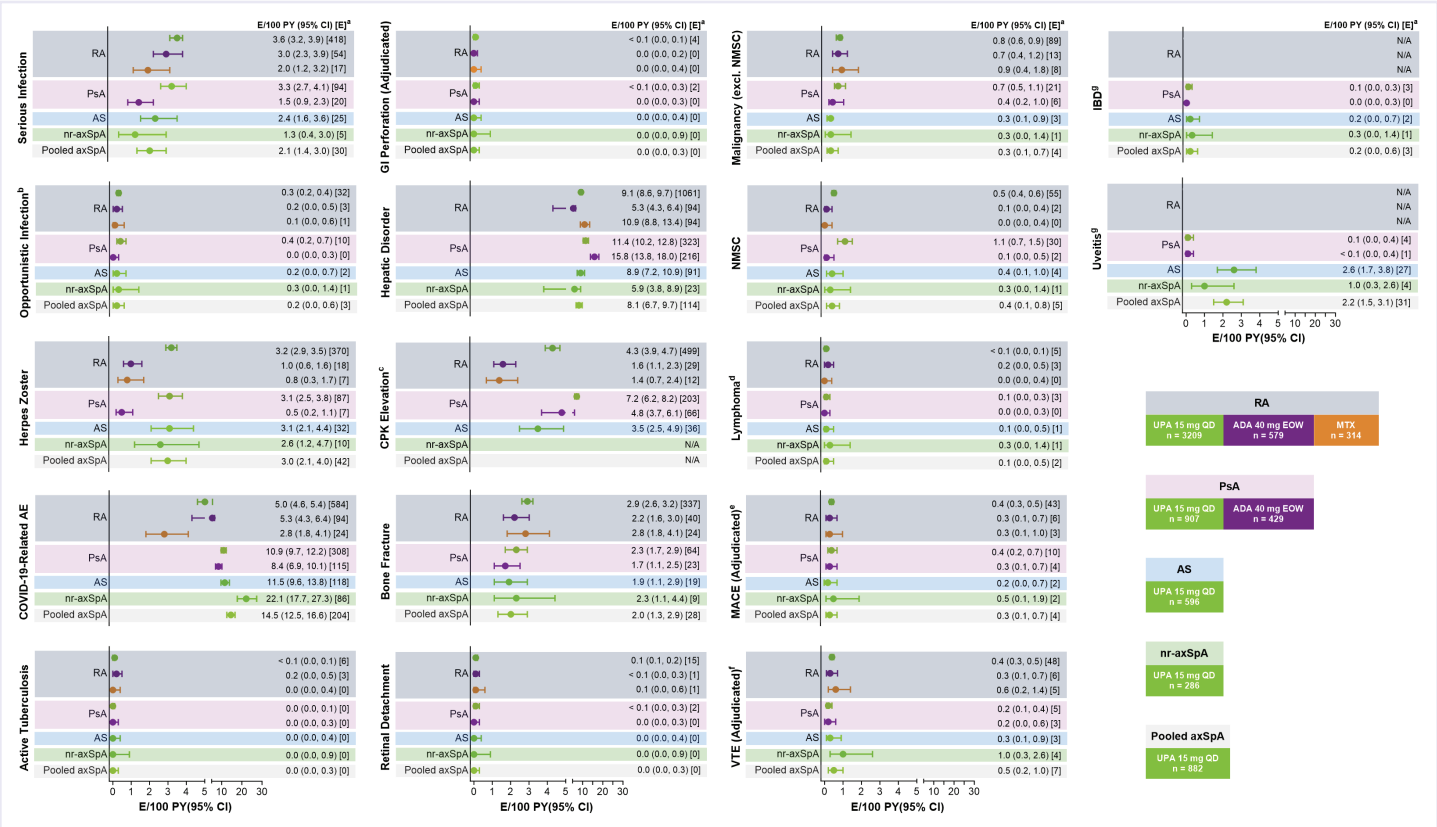
ADA, adalimumab; AE, adverse event; E, event; EOW, every other week; PY, patient-years; QD, once daily; TEAE, treatment-emergent adverse event; UPA, upadacitinib.
[a]Treatment-emergent deaths: on or after first dose of study drug and ≤ 30 days after last dose for UPA 15 mg and MTX or ≤ 70 days for ADA; Nontreatment emergent deaths: > 30 days after last dose of study drug for UPA 15 mg and MTX or > 70 days for ADA.
[b]With UPA 15 mg treatment, there were a total of 103 deaths in RA, 23 in PsA, 1 in AS, and 0 in nr-axSpA.

RESULTS (CONTINUED)

TEAEs AND AEs OF SPECIAL INTEREST (AESI)

- Rates of serious infection and opportunistic infection were generally similar across treatment groups and diseases; however, the rate of serious infection was numerically higher with UPA 15 mg vs ADA in PsA **(Figure 2)**
- COVID-19 pneumonia was both the most common serious infection and serious AE with UPA 15 mg treatment for all diseases
  - Overall, most patients with COVID-19 infection treated with UPA 15 mg had a mild or moderate case (range: 81.1%–93.2%), with 65.8% to 77.1% having study drug interrupted, but rarely withdrawn (≤ 5.5%)
- Numerically higher rates of herpes zoster (HZ) and elevated creatinine phosphokinase (CPK), which are known risks for JAK inhibitors, were reported with UPA 15 mg vs active comparators in RA and PsA
  - Most treatment-emergent events of HZ with UPA 15 mg were nonserious (RA: 96%; PsA: 98%; AS: 97%; nr-axSpA: 100%) and involved a single dermatome (RA: 76%; PsA: 74%; AS: 87%; nr-axSpA: 80%)
- Rates of malignancy excluding nonmelanoma skin cancer (NMSC) were generally similar across treatment groups and diseases; numerically higher rates of NMSC were observed with UPA 15 mg vs active comparators in RA and PsA
  - Basal cell carcinoma was the most common type of malignancy reported with UPA 15 mg treatment in RA (25 events) and PsA (14 events), with few events reported in AS (3) or nr-axSpA (1)
- The SIR (95% CI) for malignancy excluding NMSC with UPA 15 mg was 1.13 (0.94–1.36) in RA and 1.19 (0.75–1.78) in PsA
- Similar rates of MACE and VTE were observed across treatment groups and diseases; most events occurred in patients with ≥ 1 baseline CV risk factor
  - An increased risk of MACE, VTE, and malignancy excluding NMSC has been reported in RA patients with higher CV risk (aged ≥ 50 years and ≥ 1 CV risk factor) compared to the overall RA population, with risk being generally similar between UPA and ADA[5]

Figure 2. TEAEs and AEs of Special Interest in Patients Treated With UPA Across RA, PsA, AS, nr-axSpA, and Pooled axSpA[a]



AE, adverse event; ADA, adalimumab; CPK, creatine phosphokinase; E, event; EAER, exposure-adjusted event rate; EAIR, exposure-adjusted incidence rate; EMM, extra-musculoskeletal manifestation; EOW, every other week; GI, gastrointestinal; IBD, inflammatory bowel disease; NMSC, nonmelanoma skin cancer; PY, patient-years; QD, once daily; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

[a]UPA sample sizes include patients who switched from placebo and received 1 dose of upadacitinib; data are presented as EAERs, defined as E/100 PY (95% CI) [number of events] and EAER data were not censored. [b]Opportunistic infections excluding tuberculosis and herpes zoster. [c]Per the protocol, CPK elevation was not measured in the nr-axSpA study. [d]Cases of abnormal lymphocyte morphology are included (UPA 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 these events were not confirmed to be true lymphomas. [e]MACE was defined as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. [f]VTE includes deep vein thrombosis (DVT) and pulmonary embolism (PE) (fatal and non-fatal). [g]IBD includes inflammatory bowel disease, colitis ulcerative, ulcerative colitis, colitis, Crohn's disease, ulcerative proctitis, and proctitis; uveitis includes uveitis, iritis, and iridocyclitis; neither IBD or uveitis data were captured for RA.

CONCLUSIONS

- With the exception of serious infection (in PsA), HZ, elevated creatine phosphokinase, and NMSC, the rates of TEAEs were generally similar between UPA 15 mg and active comparators (ADA and MTX) in RA and PsA
- Across RA, PsA, AS, and nr-axSpA, UPA 15 mg demonstrated a generally consistent safety profile, with no new safety risks identified with long-term treatment, as shown in previous reports[1,3,4]
- Real-world data, especially for diseases with more limited clinical trial exposure (ie, AS and nr-axSpA), are needed to further contextualize and confirm these findings

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ACKNOWLEDGMENTS

AbbVie and the authors thank the participants, study sites, and investigators who participated in these clinical trials.

AbbVie funded these trials ((NCT02706873, NCT02675426, NCT02629159, NCT02706951, NCT02706847, NCT03086343, NCT03104400, NCT03104374, NCT03178487, and NCT04169373) and participated in the trial design, research, analysis, data collection, interpretation of data, and the review and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Monica R.P. Elmore, PhD of AbbVie. Editorial support was provided by Angela T. Hadsell of AbbVie.

DISCLOSURES

Financial arrangements of the authors with companies whose products may be related to the present report are listed as declared by the authors: G.R. Burmester: Speaking or consulting fees from AbbVie, Eli Lilly, Galapagos, Janssen, MSD, Pfizer, Roche, and UCB; S.B. Cohen: Consulting fees and research grants from AbbVie, Amgen, Boehringer Ingelheim, Gilead, Pfizer, Roche, and Sandoz; A. Deodhar: Received research grants, consultancy fees, speaker fees, and other support (medical writing support) from Novartis and Pfizer; research grants, consultancy fees, and other support (medical writing support) from AbbVie, Lilly, and UCB Pharma; research grants and consultancy fees from GSK; consultancy fees and other support (medical writing support) from Galapagos and Janssen; consultancy fees from Boehringer Ingelheim and Celgene; and other support (medical writing support) from Amgen; E. Mysler: Consultant of, and received grants/research support from AbbVie, AstraZeneca, BMS, GSK, Janssen, Lilly, Pfizer, Roche, and Sandoz. Hi Bio, Alpine Immunology, Novartis; A. Rubbert-Roth: Received honoraria for lectures and consulting from AbbVie, Amgen, BMS, Gilead, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, and UCB; Y. Tanaka: Received speaking fees and/or honoraria from AbbVie, Asahi-Kasei, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Gilead, GSK, Janssen, Lilly, Mitsubishi-Tanabe, Novartis, Pfizer, Sanofi, and YL Biologics, and has received research grants from AbbVie, Asahi-Kasei, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, and Takeda; K. Winthrop: Consulting fees and research grants from AbbVie, BMS, Galapagos, Gilead, Lilly, Pfizer, Roche, and UCB; P. Nakasato, D. Coombs, A. Gara, B. Kovacs, I. Lagunes, and S. Meerwein: Employees of AbbVie and may hold stock or options; J.R. Curtis: Research grants from AbbVie, Amgen, BMS, CorEvitas, Janssen, Labcorp, Lilly, Novartis, Pfizer, Sanofi/Regeneron, and UCB, consulting fees from AbbVie, Amgen, BMS, CorEvitas, Janssen, Labcorp, Lilly, Novartis, Pfizer, Sanofi/Regeneron, and UCB.