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ORIGINAL RESEARCH

MACE and VTE across upadacitinib clinical trial programmes in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis

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ABSTRACT

Objectives To provide an integrated analysis of major adverse cardiovascular events (MACEs) and events of venous thromboembolism (VTE) and associated risk factors across rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) phase 2b/3 upadacitinib clinical programmes.

Methods Data were analysed and summarised from clinical trials of RA, PsA and AS treated with upadacitinib 15 mg once daily (QD) and 30 mg QD (as of 30 June 2021). Data from adalimumab (RA and PsA) and methotrexate (RA) arms were included as comparators. Adjudicated MACEs and VTE events were presented as exposure-adjusted rates per 100 patient-years (E/100 PY). Univariable Cox proportional hazard regression analyses assessed potential associations of risk factors for MACE and VTE.

Results In total, 4298 patients received upadacitinib 15 mg (RA n=3209, PsA n=907 and AS n=182) and 2125 patients received upadacitinib 30 mg (RA n=1204 and PsA n=921). In patients with RA and PsA, rates of MACE (0.3–0.6 E/100 PY) and VTE (0.2–0.4 E/100 PY) were similar across upadacitinib doses; in patients with AS, no MACEs and one VTE event occurred. Most patients experiencing MACEs or VTE events had two or more baseline cardiovascular risk factors. Across RA and PsA groups, rates of MACEs and VTE events were similar.

Conclusions Rates of MACEs and VTE events with upadacitinib were consistent with previously reported data for patients receiving conventional synthetic and biologic disease-modifying anti-rheumatic drugs and comparable with active comparators adalimumab and methotrexate. Associated patient characteristics are known risk factors for MACEs and VTE events.

Trial registration numbers RA (SELECT-NEXT: NCT02675426; SELECT-MONOTHERAPY: NCT02706951; SELECT-BEYOND: NCT02706847; SELECT-COMPARE: NCT02629159; SELECT-EARLY: NCT02706873, SELECT-CHOICE: NCT03086343), PsA (SELECT-PsA 2: NCT03104374; SELECT-PsA 1: NCT03104400), and AS (SELECT-AXIS 1: NCT03178487).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Upadacitinib is a Janus kinase (JAK) inhibitor that has demonstrated effectiveness in treating adults with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis and ulcerative colitis. Upadacitinib is also effective in treating adults and adolescents with atopic dermatitis.

⇒ In the ORAL Surveillance trial conducted in patients with RA aged 50 years and older who had at least one cardiovascular (CV) risk factor, the combined doses of another JAK inhibitor, tofacitinib (5 and 10 mg), failed to meet non-inferiority versus tumour necrosis factor (TNF) inhibitor therapy for incidence rates of major adverse cardiovascular events (MACEs) and malignancy, excluding non-melanoma skin cancer. In a post hoc analysis from this study, the 10 mg dose of tofacitinib showed a trend for increased risk of venous thromboembolism (VTE) compared with patients who were taking TNF inhibitor therapy among patients both with and without a history of atherosclerotic CV disease. The 5 mg dose of tofacitinib also demonstrated a trend for increased risk of MACE in patients with a history (but not those without a history) of atherosclerotic CV disease.

⇒ Treatment recommendations for RA promulgated by the European Alliance of Associations for Rheumatology, as well as the European Medicines Agency and the US Food and Drug Administration, advise healthcare providers to account for pertinent risk factors for CV events, cancer and VTE when considering the use of JAK inhibitors.

INTRODUCTION

Patients with untreated immune-mediated inflammatory diseases (IMIDs) are at increased risk of major adverse cardiovascular events (MACEs) and venous thromboembolism (VTE) compared with the general population.[1–4] Patients with rheumatoid arthritis

WHAT THIS STUDY ADDS

⇒ In this integrated safety analysis of upadacitinib 15 mg once daily (QD) and 30 mg QD (across six trials in RA, two trials in PsA and one trial in AS), the observed rates of MACE and VTE were similar to those reported with the active comparators adalimumab (RA and PsA) and methotrexate (RA) and appeared consistent with the rates reported in the published literature for RA.

⇒ Potential risk factors associated with MACE and VTE in patients with RA and PsA receiving upadacitinib were identified, and the patient characteristics associated with MACE and VTE are known risk factors for these events.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Based on the results of this integrated safety analysis of events of MACE and VTE across patients with RA, PsA and AS in the upadacitinib clinical trial programme and the information regarding characteristics of those patients who experience an event of MACE or VTE, clinicians will be aided in their benefit:risk assessment to determine which patients will be appropriate candidates for upadacitinib therapy.

(RA) carry a twofold, increased risk of cardiovascular (CV) morbidity and mortality and threefold increased risk of VTE.[5 6] Psoriatic arthritis (PsA) is also associated with an increased risk of MACEs and VTE, with evidence mounting for an association in ankylosing spondylitis (AS).[1–4 7] While traditional risk factors for MACEs and VTE are more prevalent in RA, PsA and AS than in the general population, these factors alone do not fully explain IMID-associated risks.[2–4 7–10]

Systemic inflammation, a hallmark of all IMIDs, is associated with risk of CV disease.[11–15] Small-molecule Janus kinase (JAK) inhibitors are anti-inflammatory therapeutics for management of several IMIDs including RA, PsA and AS.

Recent data from the ORAL Surveillance study in patients aged 50 years and older with at least one additional CV risk factor suggest a trend for a comparative increased risk of MACE and VTE with tofacitinib (10 mg dose) versus tumour necrosis factor (TNF) inhibitor therapy.[16] In patients treated with tofacitinib 5 mg two times per day with a history of atherosclerotic CV disease, there was also a trend for increased risk for MACEs, but this potential increased risk was not detected in patients without a history of atherosclerotic CV disease.[17] Patients aged ≥65 years and past/current smokers may have been at an increased risk.[18] There have been mixed results observed with real-world data sets. Data from the overall tofacitinib development programme did not suggest increased risk. Likewise, findings from the observational STAR-RA administrative claims-based study did not identify a significantly increased risk of CV outcomes with tofacitinib compared with TNF inhibitors in a broad patient population with RA (of note, tofacitinib 5 mg is approved in the USA for RA, and this was a US claims-based study).[18 19] However, in the STAR-RA study, a numerically but not statistically significant increased risk of CV outcomes was observed in patients with RA and CV risk factors or a history of CV disease.[19] Results of a multi-database, international study suggest an increased risk of VTE and numerically increased risk of MACE with baricitinib compared with TNF inhibitors.[20] While several registries show rates of MACE or VTE are not increased with JAK inhibitors compared with TNF inhibitors, findings from one registry showed a three-times greater incidence of VTE with JAK inhibitors compared with TNF inhibitors.[21–24] In summary, analyses of longer-term clinical trials and registry data have not been consistent or definitive, and there is a need for additional data to further evaluate the risk of MACE and VTE across the JAK inhibitor class.

Upadacitinib is an oral, reversible JAK inhibitor, engineered to have greater inhibitory potency for JAK1 versus JAK2, JAK3, and TYK2 and is approved to treat RA, PsA, AS, non-radiographic axial spondyloarthritis, atopic dermatitis and ulcerative colitis.[25] Here, in this study, we report results from a long-term, integrated analysis of MACE and VTE occurring with upadacitinib 15 mg or 30 mg and active comparators across the RA, PsA and AS phase 2b/3 clinical programmes, with an emphasis on the 15 mg dose approved to treat these rheumatic diseases. Objectives of this analysis include evaluating the overall risk of MACE and VTE in patients receiving upadacitinib, comparing observed rates of MACE and VTE with upadacitinib to those of active comparators and evaluating patient characteristics for potential association with an increased risk of MACE and VTE.

METHODS

Studies

This analysis included safety data from upadacitinib phase 3 clinical trials for RA (six trials), PsA (two trials) and AS (one trial; phase 2b/3) (online supplemental table 1). All patients were aged 18 years or older.

Patient and public involvement

Patients and the public were not involved in the design, analysis or dissemination of the study results.

Treatments

Data are pooled across studies within each disease and reported for the following treatment groups: upadacitinib 15 mg once daily (QD) (RA, PsA and AS), upadacitinib 30 mg QD (RA and PsA), adalimumab 40 mg subcutaneously every other week (RA (SELECT-COMPARE) and PsA (SELECT-PsA 1)) and methotrexate monotherapy (RA (SELECT-EARLY)). Patients receiving upadacitinib did so either as monotherapy or in combination with methotrexate or other conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) therapy, depending on study protocol. All patients from the SELECT-COMPARE study receiving upadacitinib or adalimumab received background methotrexate; patients from the SELECT-PsA 1 study received adalimumab with or without concomitant background csDMARDs. All

methotrexate data reflects monotherapy use from the SELECT-EARLY study.

Safety assessments

Treatment-emergent adverse events (TEAEs) were defined as onset on or after the first dose of study drug and up to 30 days or 70 days after the last dose for upadacitinib/methotrexate or adalimumab, respectively. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes and Preferred Terms.

MACE and VTE were adjudicated by a blinded, independent CV adjudication committee. MACE included CV death, non-fatal myocardial infarction and non-fatal stroke. VTEs included pulmonary embolism (PE) only, deep vein thrombosis (DVT) only and concurrent DVT and PE. To categorise CV risk factors at baseline, the following characteristics were included: history of diabetes mellitus, previous CV event before study enrolment, hypertension, current or former tobacco/nicotine use, elevated low-density lipoprotein cholesterol levels (LDL-C; ≥3.36 mmol/L (≥130 mg/dL)) and decreased high-density lipoprotein cholesterol levels (HDL-C; <1.034 mmol/L (<40 mg/dL)).

Statistical analyses

All TEAEs are reported as exposure-adjusted event rates (EAERs; event per 100 patient-years (E/100 PY)) based on the treatment received at the time of the reported adverse event with 95% CIs calculated using the exact method for the Poisson mean; all events, including multiple events occurring in a single patient, were included in the numerator. For EAERs, exposure time was calculated as the total study drug duration. Exposure-adjusted incidence rates with 95% CIs were calculated using the exact method for the Poisson mean and calculated as the number of patients with one or more events per 100 PY. In patients who experienced an event, exposure time was calculated as the time to the first event; in patients who did not experience an event, exposure time was censored on the day of the patient's last assessment or cut-off date of database lock, whichever occurred first. Kaplan-Meier curves were generated to assess any time dependence for the events and if a differential dose effect was present. RA trials containing upadacitinib 15 mg and 30 mg arms were analysed separately for rates of total MACE and VTE and via Kaplan-Meier analysis to further assess for potential dose-effects within those trial patient populations. Univariable Cox proportional hazard regression analyses were performed using an as observed approach to determine the potential association of known risk factors on MACE and VTE in the study populations; assessed risk factors included: age (≥65 vs <65 years); sex; region (North America vs Europe); disease activity (determined using C-reactive protein (CRP)); disease duration since diagnosis; body mass index; history of VTE; history of CV events; history of hypertension; elevated LDL-C levels (≥3.36 mmol/L (≥130 mg/dL)); decreased HDL-C levels (<1.034 mmol/L (<40 mg/dL)); diabetes; current tobacco use; age plus smoking (the combined factor of being aged ≥65 years or a current or former smoker); and concomitant medication use including methotrexate, steroid, cyclooxygenase-2 inhibitor, antithrombotic, statin, aspirin and oral contraceptive/hormone replacement therapy. Change from baseline in select laboratory parameters of LDL-C, HDL-C and LDL-C:HDL-C ratio was analysed as time-varying covariates in the Cox proportional hazard models. Time-weighted average of change from baseline in disease activity to time of event (all available observations) or study end for patients without an event (Clinical Disease Activity Index (CDAI) and Disease Activity Score in 28 Joints (DAS28-CRP) were analysed for RA; Disease Activity in Psoriatic Arthritis (DAPSA) was analysed for PsA) was calculated for both MACE and VTE as area under the curve of change from baseline and standardised by length of available time duration for patients with events versus those without; analysis of covariance was used to determine the least squares mean and p value with adjudicated CV event as an outcome and baseline value as a covariate. Due to the nature in which adverse event data are collected and recorded, the absence of an adverse event for a given patient assumes that no event occurred. Medication and medical history data are collected in a similar manner. The variable of baseline disease activity (CRP) was missing 10.2% of data in the RA population. All other variables used in this component of the analysis were missing <0.1% of data.

RESULTS

Patients and exposure

Across studies, patients received at least one dose of treatment (upadacitinib 15 mg QD: for RA n=3209, for PsA n=907 and for AS n=182; upadacitinib 30 mg QD: for RA n=1204 and for PsA n=921; adalimumab 40 mg every other week: for RA n=579 and for PsA n=429; methotrexate weekly: for RA n=314). Duration of study drug exposure varied across diseases and treatments with a maximum (median) exposure in years of 5.45 (3.46) for upadacitinib 15 mg (median (range) duration 1262 (2–1988) days), 5.20 (3.98) for upadacitinib 30 mg (median (range) duration 1452 (1–1899) days), 5.44 (2.23) for adalimumab (median (range) duration 813 (14–1984) days) and 5.15 (2.57) for methotrexate (median (range) duration 939 (7–1880) days) in RA; 3.90 (2.25) for upadacitinib 15 mg (median (range) duration 820 (1–1424) days), 3.80 (2.25) for upadacitinib 30 mg (median (range) duration 820 (1–1386) days), and 3.97 (2.30) for adalimumab (median (range) duration 839

(14–1450) days) in PsA; and 3.26 (1.76) for upadacitinib 15 mg (median (range) duration 641 (6–1189) days) in AS. Irrespective of MACE and VTE outcomes, most baseline demographics and disease characteristics were relatively comparable between treatment arms and diseases, with most patients having one or more CV risk factor(s) at baseline (table 1). However, expected RA-specific differences in baseline characteristics, relative to other disease cohorts, were observed including a greater proportion of women (ranging from 76.4%–80.4% women across RA treatment groups; 51.7%–54.7% across PsA cohorts; and 29.1% in the AS cohort) and a higher use of glucocorticoids (47.4%–60.4% across RA treatment groups; 13.4%–16.8% across PsA cohorts; and 7.1% in the AS cohort). Some variability was noted in mean disease duration (ranging from 2.6–8.5 years across the RA cohorts; 5.9–7.3 years across the PsA cohorts; and 6.9 years in the AS cohort). The patient population with AS was younger than the populations with RA or PsA with only 6.0% of patients aged ≥65 years, though the proportion of patients with two or more CV risk factors (40.1%) was comparable to those of the other disease states, and the methotrexate treatment arm in RA had a shorter disease duration.

MACE

In patients with RA, a total of 36 (EAER: 0.4 E/100 PY) and 20 (0.6 E/100 PY) events of MACE were reported with upadacitinib 15 mg and upadacitinib 30 mg, respectively (figure 1). In PsA, five and six events of MACE were reported with upadacitinib 15 mg and upadacitinib 30 mg, respectively (0.3 E/100 PY each), with no events of MACE observed in AS. Among patients receiving upadacitinib 15 mg in RA, one patient experienced two non-fatal strokes, one patient had two non-fatal myocardial infarctions and one patient experienced one non-fatal myocardial infarction and CV death. Rates of MACE were generally consistent between upadacitinib 15 mg and active comparators with observed rates of 0.3 E/100 PY for both adalimumab and methotrexate in RA and 0.3 E/100 PY for adalimumab in PsA. When evaluating only those RA studies containing both upadacitinib doses, rates of MACE were 0.6 E/100 PY for both upadacitinib 15 mg and 30 mg (online supplemental figure 1). Rates of stroke, non-fatal myocardial infarction and CV death were comparable across RA and PsA treatment groups (figure 1).

Differences in baseline data between patients experiencing MACE and those who did not were consistent with known characteristics associated with increased CV risk in the general population, with more events in patients aged ≥65 years; male sex; having a previous CV event, hypertension, diabetes mellitus, history of tobacco/nicotine use; concomitant use of glucocorticoids, antithrombotics, statins and aspirin (online supplemental table 2). All but three patients experiencing MACE had CV risk factors at baseline (n=2 with RA receiving upadacitinib 15 mg; n=1 with PsA receiving adalimumab). The majority of patients experiencing MACE had two or more CV risk factors at baseline across treatments with 81.9% for upadacitinib 15 mg, 70.0% for upadacitinib 30 mg, 75.0% for adalimumab, and 100% for methotrexate in the RA study; and in the PsA study, 80.0% for upadacitinib 15 mg, 83.3% for upadacitinib 30 mg and 66.7% for adalimumab. Statistically significant ($p<0.05$) risk factors from univariable models associated with an elevated risk of MACE varied between diseases (figure 2). Factors potentially associated with MACE in patients with RA receiving upadacitinib 15 mg included male sex; age ≥65 years; hypertension; diabetes mellitus; current tobacco/nicotine use; history of a CV event; and use of aspirin, statins or antithrombotics. The combined variables of age ≥65 years or current smoker were also potentially associated with MACE in patients with RA. In patients with PsA, aspirin use was associated with increased risk of MACE.

Rates of MACE occurring during the first 12 months of exposure were numerically greater in patients with RA compared with those observed during exposures beyond 12 months (figure 3). However, there was no clear pattern of time-to-event onset of MACE by Kaplan-Meier analysis (online supplemental figure 2). Patients with RA who developed MACE (vs those who did not) tended to have less improvement in disease activity; however, this pattern was not observed among patients with PsA (table 2). Among patients who experienced a treatment-emergent MACE while receiving upadacitinib 15 mg, 24.2% (8/33) and 57.6% (19/33) with RA were in remission based on CDAI and DAS28-CRP scores, respectively; and 20.0% (1/5) with PsA were in remission (based on DAPSA scores) at the time of the event, based on last available data before the event (online supplemental table 3). There was no association identified between MACE and maximum change from baseline in LDL-C, HDL-C or LDL-C:HDL-C ratio (measured at months 3 and 6 then every 6 months thereafter) (online supplemental figures 3 and 4).

VTE

A total of 37 and 13 events of VTE were reported with upadacitinib 15 mg and upadacitinib 30 mg, respectively, in patients with RA (0.4 E/100 PY each; figure 4). In PsA, four and six events of VTE were reported with upadacitinib 15 mg (0.2 E/100 PY) and upadacitinib 30 mg (0.3 E/100 PY), respectively. Rates of VTE were comparable overall between upadacitinib and active comparators with observed rates of 0.4 E/100 PY for adalimumab, 0.5 E/100 PY for methotrexate in patients with RA and 0.2 E/100 PY for adalimumab in PsA. When evaluating only those RA studies containing both upadacitinib doses, observed response rates were 0.5 E/100 PY and 0.4 E/100 PY for upadacitinib 15 mg and upadacitinib 30 mg, respectively (online supplemental figure 1). Rates of different types of VTE (PE only, DVT only, PE and DVT) were comparable across RA and PsA, with the majority of patients experiencing either PE only or DVT only.

Table 1 Summary of demographic and baseline disease characteristics in RA, PsA and AS

Parameter	RA				PsA			AS
	UPA 15 mg n=3209 PY=9079.1	UPA 30 mg n=1204 PY=3180.4	ADA 40 mg n=579 PY=1307.7	MTX n=314 PY=781.7	UPA 15 mg n=907 PY=1872.3	UPA 30 mg n=921 PY=1867.5	ADA 40 mg n=429 PY=903.7	UPA 15 mg n=182 PY=320.1
Age (years), mean (SD)	54.3 (12.03)	55.3 (11.89)	54.1 (11.66)	53.3 (12.89)	51.5 (12.10)	51.4 (12.25)	51.4 (12.04)	45.3 (12.52)
Age ≥65 years	643 (20.0)	275 (22.8)	106 (18.3)	58 (18.5)	129 (14.2)	145 (15.7)	67 (15.6)	11 (6.0)
Female, n (%)	2581 (80.4)	948 (78.7)	470 (81.2)	240 (76.4)	478 (52.7)	504 (54.7)	222 (51.7)	53 (29.1)
Time since diagnosis (years), mean (SD)	8.5 (8.40)	7.0 (8.35)	8.2 (8.00)	2.6 (5.14)	7.2 (7.79)	7.3 (7.72)	5.9 (7.06)	6.9 (8.93)
Time since diagnosis								
<5 years	1482 (46.2)	691 (57.4)	264 (45.6)	271 (86.3)	479 (52.8)	473 (51.4)	257 (59.9)	108 (53.9)
5 to <10 years	670 (20.9)	198 (16.4)	136 (23.5)	13 (4.1)	196 (21.6)	208 (22.6)	96 (22.4)	31 (17.0)
≥10 years	1056 (32.9)	315 (26.2)	179 (30.9)	30 (9.6)	232 (25.6)	240 (26.1)	76 (17.7)	43 (23.6)
BMI (kg), mean (SD)	29.1 (6.67)	29.3 (7.01)	29.4 (7.13)	28.0 (6.34)	30.6 (6.87)	30.6 (6.91)	30.7 (7.24)	26.7 (4.99)
BMI ≥30 kg/m^2	1200 (37.4)	484 (40.4)	227 (39.2)	97 (30.9)	429 (47.3)	439 (47.7)	209 (48.7)	37 (20.3)
Disease activity (CRP), mean (SD)	5.8 (0.95)	5.7 (0.94)	5.9 (0.96)	5.9 (0.97)	5.0 (1.03)	5.0 (1.03)	4.9 (1.06)	3.6 (0.75)
CRP>ULN*	2219 (77.1)	672 (75.8)	460 (80.0)	252 (80.3)	397 (44.1)	400 (43.7)	173 (40.4)	99 (55.0)
Race								
White	2784 (86.8)	1014 (84.2)	504 (87.0)	256 (81.5)	806 (89.5)	821 (89.8)	375 (88.9)	152 (83.5)
Black or African American	170 (5.3)	56 (4.7)	39 (6.7)	12 (3.8)	12 (1.3)	11 (1.2)	2 (0.5)	3 (1.6)
American Indian/Alaska Native	22 (0.7)	17 (1.4)	1 (0.2)	2 (0.6)	4 (0.4)	2 (0.2)	2 (0.5)	0
Native Hawaiian/Other Pacific Islander	4 (0.1)	2 (0.2)	0	2 (0.6)	1 (0.1)	3 (0.3)	2 (0.5)	0
Asian	191 (6.0)	101 (8.4)	30 (5.2)	37 (11.8)	78 (8.7)	77 (8.4)	41 (9.7)	27 (14.8)
Other	38 (1.2)	14 (1.2)	5 (0.9)	5 (1.6)	0	0	0	0
Multiple	N/A	N/A	N/A	N/A	6 (0.7)	7 (0.8)	7 (1.7)	0
Region								
North America	815 (25.4)	429 (35.6)	122 (21.1)	46 (14.6)	291 (32.1)	292 (31.7)	79 (18.4)	17 (9.3)
South/Central America	725 (22.6)	153 (12.7)	126 (21.8)	90 (28.7)	98 (10.8)	108 (11.7)	53 (12.4)	0
Asia	143 (4.5)	85 (7.1)	18 (3.1)	32 (10.2)	62 (6.8)	65 (7.1)	36 (8.4)	24 (13.2)
Europe	1365 (42.5)	480 (39.9)	278 (48.0)	122 (38.9)	431 (47.5)	423 (45.9)	241 (56.2)	132 (72.5)
Other	161 (5.0)	57 (4.7)	35 (6.0)	24 (7.6)	25 (2.8)	33 (3.6)	20 (4.7)	9 (4.9)
Concomitant therapy								
Glucocorticoids	1761 (54.9)	571 (47.4)	350 (60.4)	164 (52.2)	134 (14.8)	123 (13.4)	72 (16.8)	13 (7.1)
csDMARD(s)	2548 (79.4)	561 (46.6)	579 (100)	0	642 (70.8)	639 (69.4)	338 (78.8)	28 (15.4)

Continued

Table 1 Continued

Parameter	RA				PsA			AS
	UPA 15 mg n=3209 PY=9079.1	UPA 30 mg n=1204 PY=3180.4	ADA 40 mg n=579 PY=1307.7	MTX n=314 PY=781.7	UPA 15 mg n=907 PY=1872.3	UPA 30 mg n=921 PY=1867.5	ADA 40 mg n=429 PY=903.7	UPA 15 mg n=182 PY=320.1
NSAID	2034 (63.4)	783 (65.0)	362 (62.5)	223 (71.0)	566 (62.4)	569 (61.8)	279 (65.0)	149 (81.9)
COX-2	955 (29.8)	351 (29.2)	182 (31.4)	115 (36.6)	264 (29.1)	266 (28.9)	149 (34.7)	70 (38.5)
Antithrombotic	315 (9.8)	158 (13.1)	42 (7.3)	26 (8.3)	105 (11.6)	100 (10.9)	35 (8.2)	8 (4.4)
Statin	369 (11.5)	169 (14.0)	55 (9.5)	26 (8.3)	123 (13.6)	125 (13.6)	42 (9.8)	5 (2.7)
Aspirin	269 (8.4)	131 (10.9)	36 (6.2)	24 (7.6)	89 (9.8)	74 (8.0)	27 (6.3)	N/A
Patient history								
Previous CV event	384 (12.0)	147 (12.2)	62 (10.7)	27 (8.6)	116 (12.8)	116 (12.6)	40 (9.3)	19 (10.4)
Previous VTE	53 (1.7)	21 (1.7)	9 (1.6)	3 (1.0)	23 (2.5)	15 (1.6)	3 (0.7)	1 (0.5)
Hypertension	1301 (40.5)	489 (40.6)	255 (44.0)	114 (36.3)	403 (44.4)	376 (40.8)	179 (41.7)	35 (19.2)
Diabetes mellitus	382 (11.9)	136 (11.3)	61 (10.5)	31 (9.9)	122 (13.5)	126 (13.7)	47 (11.0)	8 (4.4)
Tobacco/nicotine use†	1221 (38.0)	509 (42.3)	199 (34.4)	120 (38.2)	385 (42.4)	395 (42.9)	163 (38.0)	100 (54.9)
Elevated LDL-C (≥3.36 mmol/L)	869 (27.2)	319 (26.6)	170 (29.4)	86 (27.5)	253 (28.7)	262 (29.1)	121 (28.7)	43 (23.8)
Low HDL-C (<1.034 mmol/L)	354 (11.0)	125 (10.4)	53 (9.2)	39 (12.4)	176 (19.6)	188 (20.6)	95 (22.4)	34 (18.7)
Number of CV risk factors‡								
0	739 (23.0)	264 (21.9)	133 (23.0)	82 (26.1)	150 (16.5)	161 (17.5)	90 (21.0)	36 (19.8)
1	1073 (33.4)	411 (34.1)	199 (34.4)	103 (32.8)	308 (34.0)	310 (33.7)	140 (32.6)	73 (40.1)
2	883 (27.5)	328 (27.2)	163 (28.2)	84 (26.8)	251 (27.7)	260 (28.2)	118 (27.5)	54 (29.7)
3+	514 (16.0)	201 (16.7)	84 (14.5)	45 (14.3)	198 (21.8)	190 (20.6)	81 (18.9)	19 (10.4)

Data are presented as number of patients (%) unless otherwise noted.
*CRP>5.1 for RA and PsA, >3.5 for AS.
†Includes former and current tobacco/nicotine use.
‡Includes diabetes mellitus, previous cardiovascular event, hypertension, current or former tobacco/nicotine use, elevated LDL-C (≥3.36 mmol/L (≥130 mg/dL)), low HDL-C (<1.034 mmol/L (<40 mg/dL)).
ADA, adalimumab; AS, ankylosing spondylitis; BMI, body mass index; COX-2, cyclooxygenase-2; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; PY, patient-years; RA, rheumatoid arthritis; ULN, upper limit of normal; UPA, upadacitinib; VTE, venous thromboembolism.

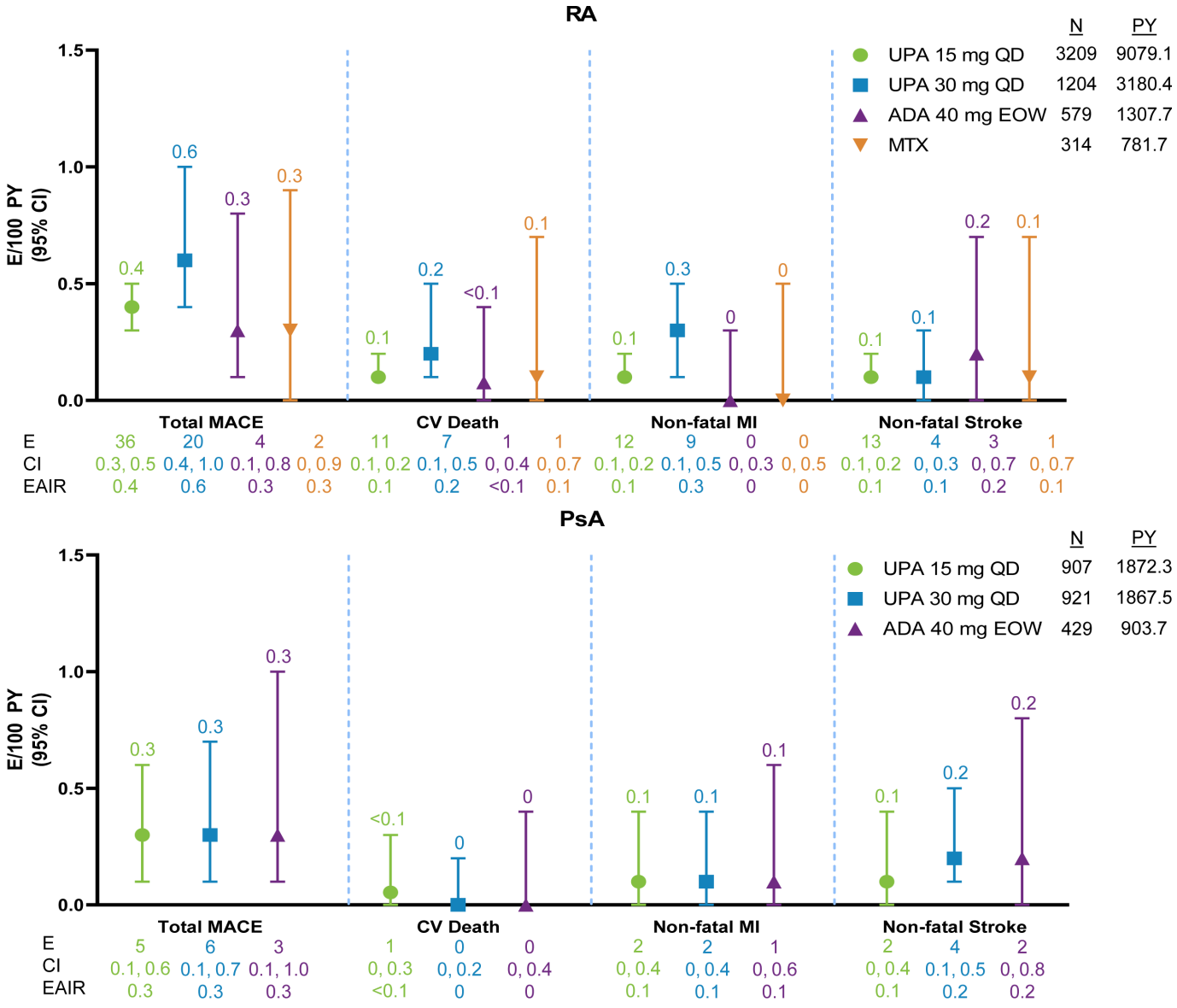

Figure 1 MACE breakdown by event type in RA and PsA. AS is not represented here as there were no MACE. ADA, adalimumab; CV, cardiovascular; E, events; E/100, events per 100; EAIR; exposure-adjusted incidence rate (n/100 PY); EOW, every other week; MACE, major adverse cardiovascular events; MI, myocardial infarction; MTX, methotrexate; PsA, psoriatic arthritis; PY, patient-years; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib.

Differences in baseline data between patients experiencing a VTE and those who did not included age ≥65 years; obesity; history of baseline hypertension; tobacco/nicotine use; and concomitant use of antithrombotics, statins and aspirin (online supplemental table 4). VTEs were observed in seven patients with no CV risks identified at baseline (n=4 in RA upadacitinib 15 mg; n=1 in RA upadacitinib 30 mg; n=1 in RA methotrexate; and n=1 in PsA adalimumab), but the majority of patients experiencing a VTE had two or more CV risk factors across treatment groups, with 59.5% for upadacitinib 15 mg, 53.8% for upadacitinib 30 mg, 60.0% for adalimumab and 50.0% for methotrexate in the RA group; and in the PsA group, 100% for upadacitinib 15 mg, 66.7% for upadacitinib 30 mg and 50.0% for adalimumab. Among patients experiencing VTE, there was a higher percentage with a previous history of a VTE event (16.2% and 15.4% in upadacitinib 15 mg and 30 mg, respectively). All patients with PsA receiving upadacitinib 15 mg or upadacitinib 30 mg and experiencing a VTE had no history of a previous VTE event. Statistically significant ($p<0.05$) risk factors associated with VTE occurrence as identified from univariable models varied between dose and disease (figure 5). Factors potentially associated with VTE in patients with RA receiving upadacitinib 15 mg included age ≥65 years; male sex; body mass index ≥30 kg/m^2; previous VTE; geographical region (North America vs Europe); use of aspirin, statins or antithrombotics; and the combined factor of being aged ≥65 years or a current or former smoker. There were no significant associations between risk factors and VTE observed in PsA.

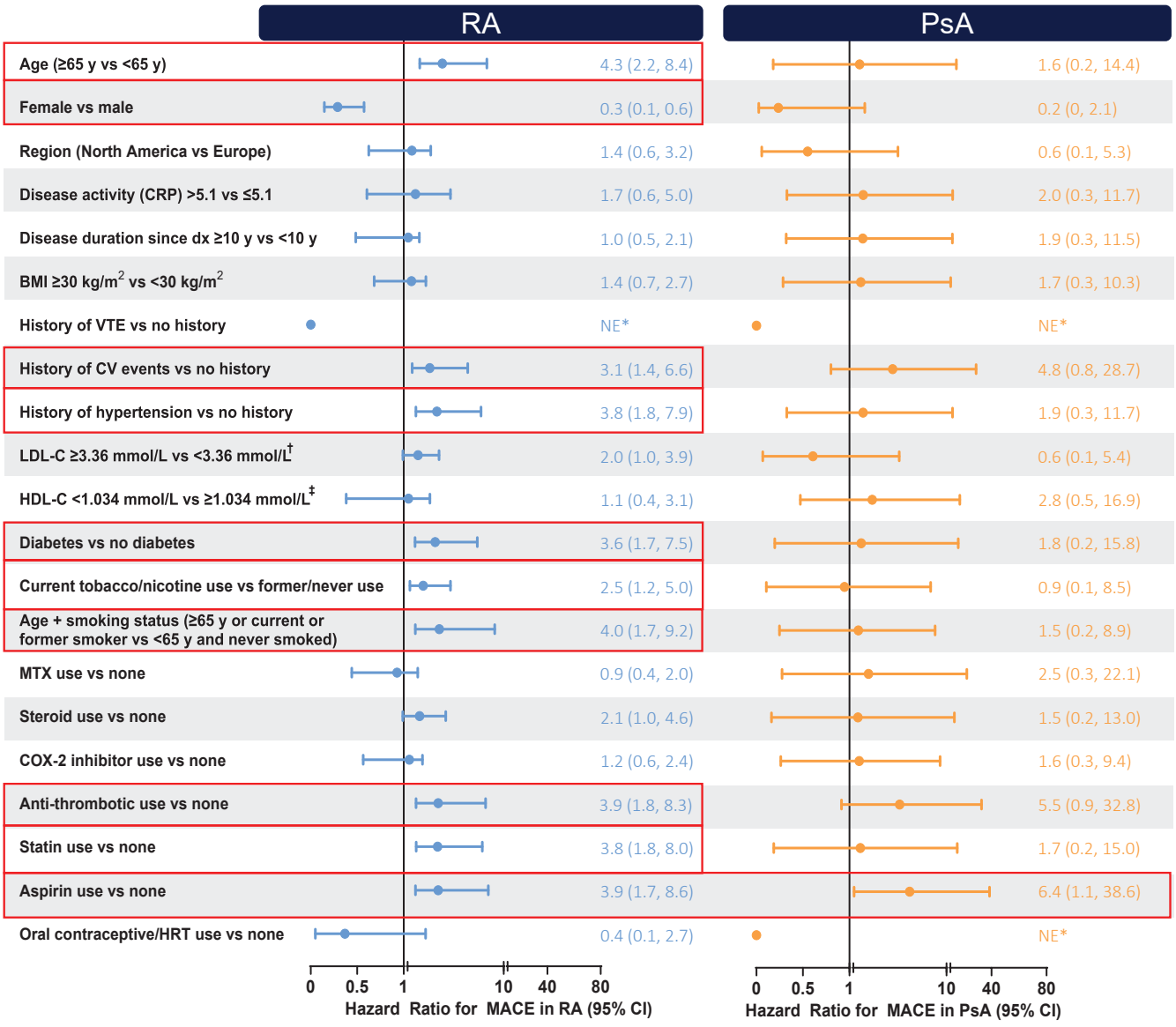

Figure 2 MACE risk factors in patients receiving UPA 15 mg (univariable analysis). Red boxes indicate statistical significance (p<0.05). *Hazard ratios not estimated due to zero events in ≥1 parameter. †Equivalent to LDL-C ≥130 mg/dL vs <130 mg/dL. ‡Equivalent to HDL-C <40 mg/dL vs ≥40 mg/dL.BMI, body mass index; COX-2, cyclooxygenase-2; CRP, C-reactive protein; CV, cardiovascular; dx, diagnosis; HDL-C, high-density lipoprotein cholesterol; HRT, hormone-replacement therapy; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MTX, methotrexate; NE, not estimable; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UPA, upadacitinib; VTE, venous thromboembolism; y, years.

Rates of VTE occurring during the first 12 months of exposure did not appear to differ from rates observed during exposures beyond 12 months (figure 6). In addition, there was no clear pattern of time to event of VTE by Kaplan-Meier analysis (online supplemental figure 5). Patients receiving upadacitinib 15 mg who did not experience a VTE event tended to have a greater improvement in disease activity (in some cases significant) compared with those who did; however, this trend was less clear or not apparent for patients receiving upadacitinib 30 mg (table 2). Among patients who experienced a treatment-emergent VTE while receiving upadacitinib 15 mg, 16.2% (6/37) and 35.1% (13/37) with RA were in remission based on CDAI and DAS28-CRP, respectively; and no patients with PsA were in remission (based on DAPSA scores) at the time of the event, based on last available data before the event (online supplemental table 3). There was no association between VTE and maximum change from baseline HDL levels or LDL:HDL ratio (online supplemental figures 6 and 7).

DISCUSSION

This long-term analysis of safety data using integrated data sets across the upadacitinib RA, PsA and AS programmes evaluated events and risk of MACE and VTE across nine clinical trials. These data demonstrate generally consistent MACE and VTE event rates for upadacitinib

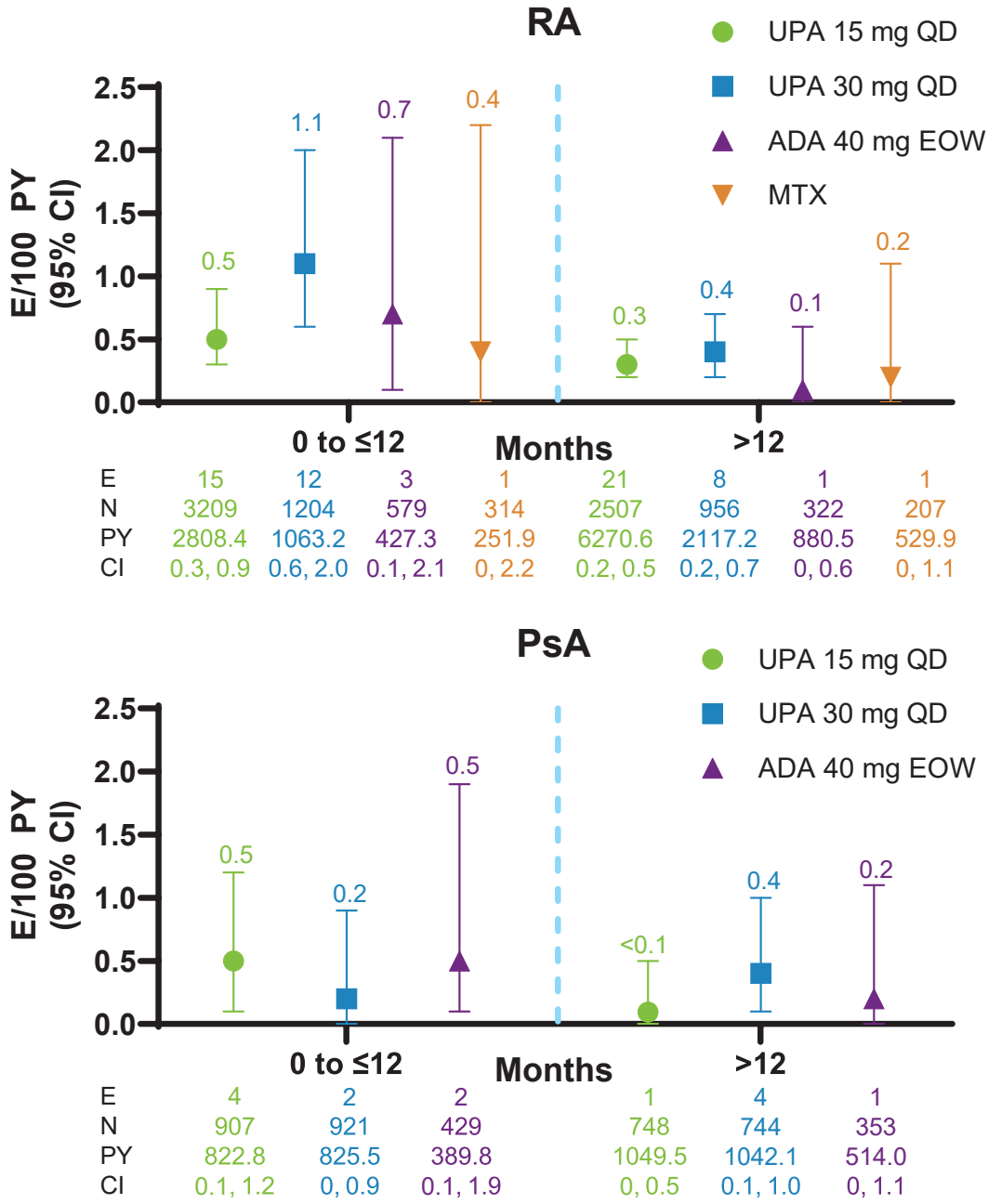

Figure 3 Events of MACE in RA and PsA by length of upadacitinib exposure in 12-month increments. ADA, adalimumab; E, event; EOW, every other week; MACE, major adverse cardiovascular event; MTX, methotrexate; PsA, psoriatic arthritis; PY, patient-years; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib.

across RA and PsA, with observed rates falling within the published ranges for these disease states.[4 26–29] Event rates appeared consistent across both upadacitinib 15 mg and 30 mg doses as well as with those observed for adalimumab and methotrexate. Within AS, a single event of VTE was reported with upadacitinib, and there were no events of MACE, which is not surprising given patients with AS were younger and less likely to have multiple CV risk factors and previous CV events, compared with RA and PsA, and there was a limited number of patients in the AS group. Although recruited patients were heterogeneous across different trial populations and disease states, more than three-fourths of patients presented with one or more traditional CV risk factors beyond their active disease at baseline, and the majority of patients experiencing events had two or more CV risk factors entering the study.

Of note, this analysis observed similar overall rates of MACEs (ranging from 0.3–0.6 E/100 PY) and VTE events (from 0.2–0.5 E/100 PY) across treatment groups and indications. While this is aligned with the previously reported safety profile of upadacitinib,[30] other published literature in rheumatological conditions described higher incidence rates of MACEs (1.57 (95% CI 1.51–1.63))

Table 2 Association between time-weighted average of change from baseline in disease activity and adjudicated MACE and VTE in RA and PsA

		TWA of patients with adjudicated event		TWA of patients without adjudicated event		LS mean difference	Percentage difference	P value
	Treatment	n	LS mean (95% CI)	n	LS mean (95% CI)			
MACE								
RA								
CDAI	UPA 15 mg	33	−23.75 (−26.98 to −20.51)	3172	−27.13 (−27.46 to −26.80)	−3.38	14	0.042
	UPA 30 mg	20	−24.06 (−28.21 to −19.91)	1184	−28.46 (−29.00 to −27.92)	−4.40	18	0.039
DAS28-CRP	UPA 15 mg	33	−2.43 (−2.80 to −2.06)	3174	−2.70 (−2.74 to −2.66)	−0.27	11	0.155
	UPA 30 mg	20	−2.56 (−3.04 to −2.09)	1184	−2.94 (−3.00 to −2.87)	−0.38	15	0.124
PsA								
DAPSA	UPA 15 mg	5	−25.70 (−39.76 to −11.63)	902	−32.81 (−33.86 to −31.75)	−7.11	28	0.323
	UPA 30 mg	6	−26.99 (−38.67 to −15.31)	915	−33.79 (−34.74 to −32.84)	−6.81	25	0.255
VTE								
RA								
CDAI	UPA 15 mg	37	−23.32 (−26.41 to −20.24)	3168	−27.15 (−27.48 to −26.82)	−3.83	16	0.016
	UPA 30 mg	13	−29.14 (−34.38 to −23.90)	1191	−28.39 (−28.93 to −27.85)	0.75	−3	0.779
DAS28-CRP	UPA 15 mg	37	−2.19 (−2.55 to −1.84)	3170	−2.70 (−2.74 to −2.67)	−0.51	23	0.005
	UPA 30 mg	13	−2.99 (−3.58 to −2.40)	1191	−2.93 (−2.99 to −2.87)	0.06	−2	0.855
PsA								
DAPSA	UPA 15 mg	4	−26.98 (−42.69 to −11.27)	903	−32.86 (−33.92 to −31.81)	−5.88	22	0.464
	UPA 30 mg	6	−32.43 (−45.21 to −19.66)	915	−33.78 (−34.72 to −32.83)	−1.34	4	0.837

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAPSA, Disease Activity in Psoriatic Arthritis; DAS28-CRP, Disease Activity Score-28 for rheumatoid arthritis with CRP; LS, least squares; MACE, major adverse cardiovascular event; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TWA, time-weighted average; UPA, upadacitinib; VTE, venous thromboembolism.

in comparison with VTE events (0.34 (95% CI 0.31–0.37)).[31] However, it is important to note the differences in data sources (real-world evidence vs post hoc analysis of randomised controlled trials). As such, we cannot rule out the possibility that rates of MACEs and VTE events reported here could differ from what may occur in real-world situations.

Heightened scrutiny has been placed on JAK inhibitor therapies for the treatment of IMIDs, in particular around CV and thrombotic events, largely stemming from the results of the tofacitinib ORAL Surveillance study. This long-term, prospective, randomised, head-to-head trial demonstrated a numerical trend for increased risk of MACE and VTE (only the 10 mg dose), among other serious adverse events, for the JAK inhibitor tofacitinib compared with TNF inhibitor therapy in a population enriched for CV risk (patients who were aged ≥50 years with at least one CV risk factor).[16] The increased relative risk of CV events observed in ORAL Surveillance of tofacitinib versus TNF inhibitor therapy appeared to be driven by those patients aged ≥65 years, smokers or those having a medical history of atherosclerotic disease.[16 17] In real-world data sources, an increased risk of CV outcomes with tofacitinib has been less definitive with a majority of analyses not identifying an increased risk in an overall population not enriched for increased CV risk.[19 21 22] A recent analysis of data from multiple registries points to an inconsistent but numerically greater risk of MACE for baricitinib relative to TNF inhibitor therapy.[20] A meta-analysis of results from the baricitinib clinical trial programmes suggests a concern for increased risk of VTE with the 4 mg dose of baricitinib.[32] Events of VTE occurred at a higher incidence at the 10 mg dose than with the 5 mg dose for tofacitinib in the ORAL Surveillance study as well.[16] To assess for a potential dose effect of MACE/VTE between the 15 mg and 30 mg upadacitinib doses, only studies including both doses of upadacitinib were pooled and analysed, and a dose effect was not apparent for either MACE or VTE.

As a result of these different safety findings for MACE and VTE, regulatory authorities have sought to mitigate the potential increased risk for these serious adverse events with JAK inhibitor therapy, either by restricting the labelled population (Food and Drug Administration) or through the inclusion of language within the warnings and precautions for those patients who may be at risk (Food and Drug Administration and European Medicines Agency).[18] Recent treatment recommendations for RA promulgated by the European Alliance of Associations for Rheumatology,[33] the European Medicines Agency[34] and the US Food and Drug Administration[35] stress the importance of a benefit:risk assessment between the healthcare professional and the patient. While some risks for CV and thrombotic events have recently been highlighted,

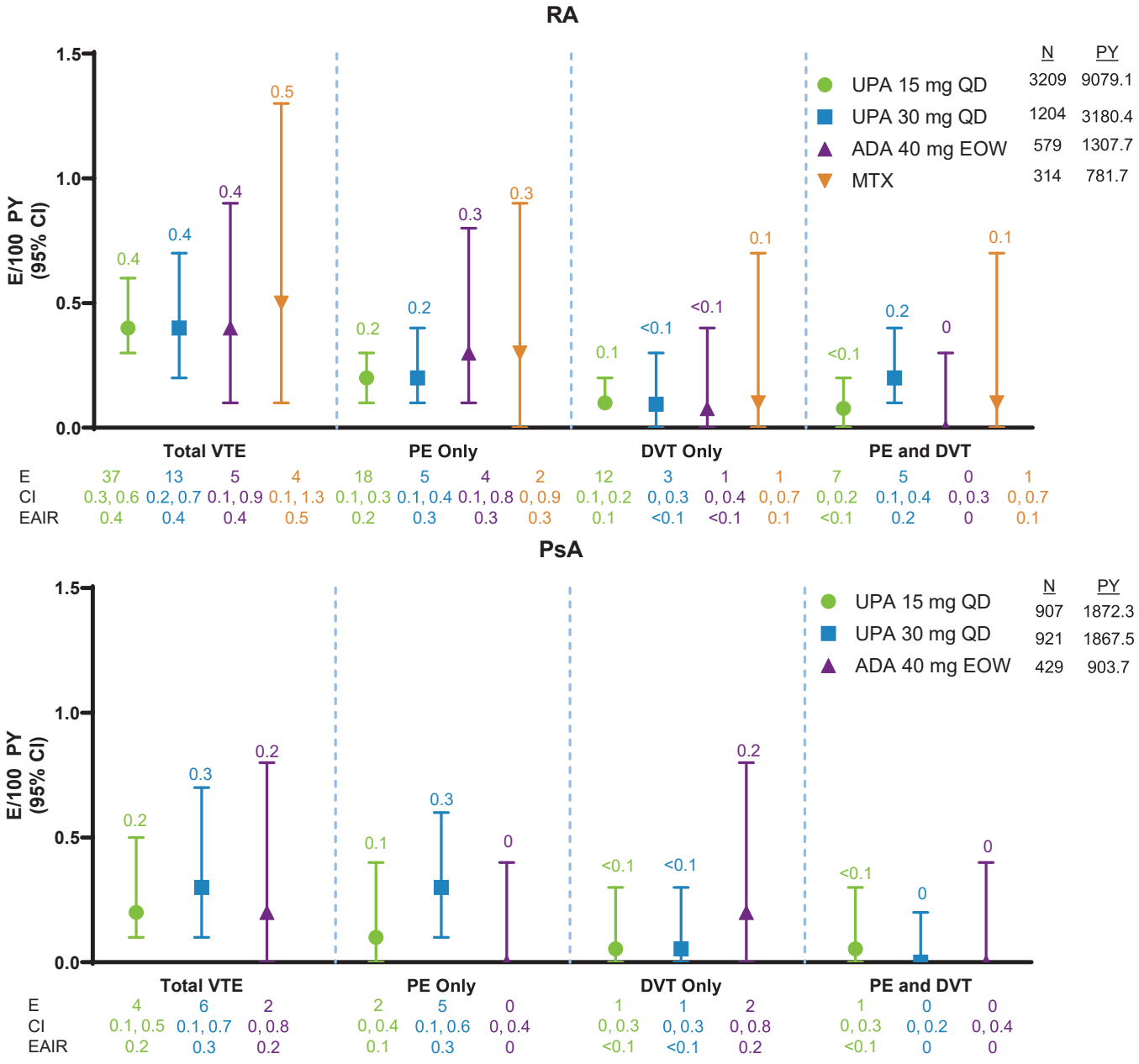

Figure 4 VTE breakdown by event type* in RA and PsA. ADA, adalimumab; DVT, deep vein thrombosis; E, event; E/100, event per 100; EAIR, exposure-adjusted incidence rate; EOW, every other week; MTX, methotrexate; PE, pulmonary embolism; PsA, psoriatic arthritis; PY, patient-years; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib; VTE, venous thromboembolism.

there remains a significant unmet need to further define those patients most at risk because notably, unresolved systemic inflammation is itself a strong contributor to the underlying risk. In particular, uncontrolled IMIDs associated with chronic inflammation are linked with increased CV risk, including heart failure, myocardial infarction and stroke, as well as associated inflammatory changes in lipid parameters, thereby increasing the risk of atherosclerotic CV disease.[9 36–38] Patients with IMIDs experience up to a twofold greater risk of CV morbidity and mortality and threefold increased risk of VTE.[5 6 39–41] Long-term evidence from a prospective cohort study with 20 years of follow-up has shown that patients with RA have a higher risk for CV disease than the general population.[42] However, in a population-based review of medical records, patients who achieved remission in RA have been shown to have comparable risk of CV disease versus people without RA, whereas the risk of CV disease was increased in patients who experience intermediate RA activity or acute flares.[43]

Results from a post hoc analysis of data from the tofacitinib ORAL Surveillance study found patients with active disease appeared to have a higher risk of MACE and VTE than did those patients who were in remission, supporting the concept that even low levels of chronic inflammation can result in adverse CV events.[44] Overall,

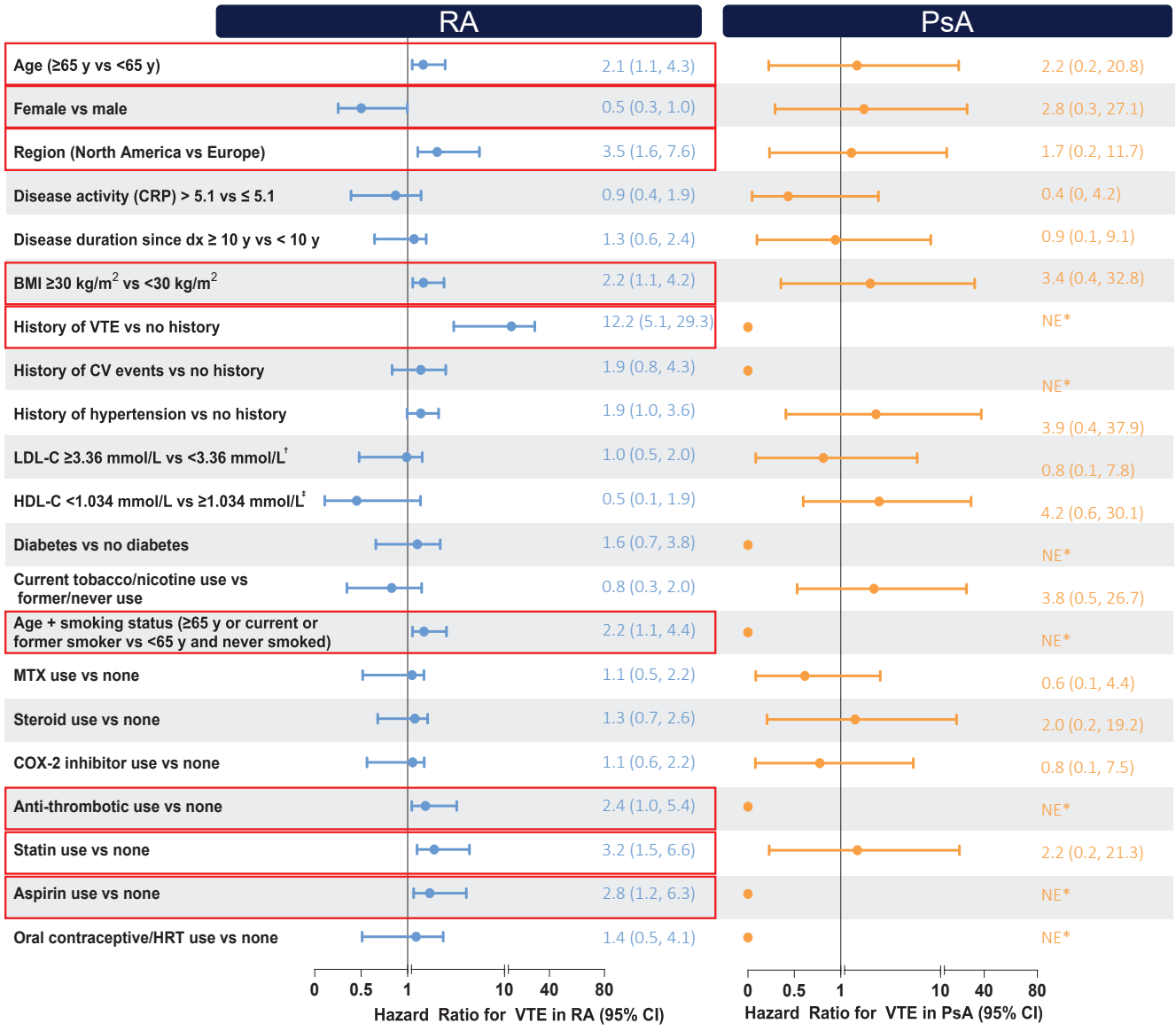

Figure 5 VTE risk factors in patients receiving UPA 15 mg (univariable analysis). Red boxes indicate statistically significant differences (p<0.05). *Hazard ratios not estimated due to zero events in ≥1 parameter. †Equivalent to LDL-C ≥130 mg/dL vs <130 mg/dL. ‡Equivalent to HDL-C <40 mg/dL vs ≥40 mg/dL. BMI, body mass index; COX-2, cyclooxygenase-2; CRP, C-reactive protein; CV, cardiovascular; dx, diagnosis; HDL-C, high-density lipoprotein cholesterol; HRT, hormone-replacement therapy; LDL-C, low-density lipoprotein cholesterol; MTX, methotrexate; NE, not estimable; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UPA, upadacitinib; VTE, venous thromboembolic event; y, years.

a greater percentage of patients experiencing a MACE or VTE had active disease at the time of the event versus those patients in remission who were receiving upadacitinib 15 mg or 30 mg. In this analysis, changes in disease activity from baseline to the time of an event or end of study were inconsistent for MACE and VTE between upadacitinib doses and diseases, underscoring the need for further investigation into the relationship between inflammatory disease control and risk of MACE or VTE with upadacitinib. Fleischmann *et al*,[45] conducted an integrated post hoc analysis of pooled safety data from six upadacitinib phase 3 RA trials (n=3209 receiving upadacitinib 15 mg; n=579 receiving adalimumab; 314 receiving methotrexate) to assess the potential risk of upadacitinib in a similar population to patients in the ORAL Surveillance study. Results of the analysis showed incidence of MACE and VTE were generally similar across treatment groups, although patients at higher risk for CV events had increased rates of MACE and VTE.[45]

In RA, up to 70% of MACE risk is explained by traditional risk factors or inflammation-specific factors, and the majority of VTE cases are associated with pre-existing risk factors.[46 47] Consistent with findings in the published literature, the majority of MACE and VTE across RA, PsA and AS occurred in patients with pre-existing risks associated with MACE and VTE or in those using concomitant antithrombotics, statins or aspirin. Of note, the association between antithrombotic, statin and aspirin use is

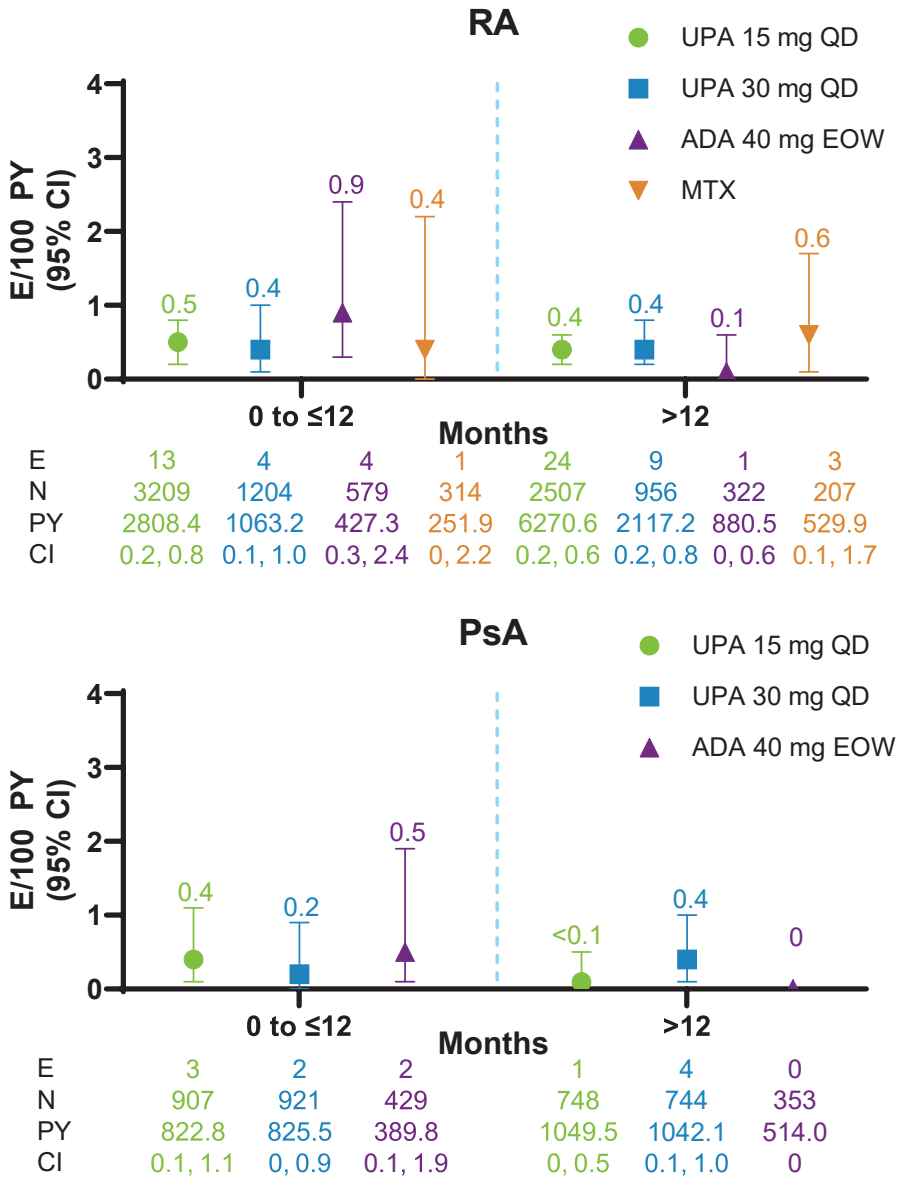

Figure 6 Events of VTE in RA and PsA by length of upadacitinib exposure in 12-month increments. ADA, adalimumab; E, event; EOW, every other week; MTX, methotrexate; PsA, psoriatic arthritis; PY, patient-years; QD, once daily; RA, rheumatoid arthritis; VTE, venous thromboembolism; UPA, upadacitinib.

likely confounded by adherence to prevention/treatment guidelines for use of these medications in patients at risk for or previously diagnosed with CV disease.[48 49] Increasing numbers of CV risk factors appeared to also be associated with an increased occurrence in events, suggesting that patients with multiple risk factors may be at particular risk. A relatively high proportion of the population had more than one risk factor; indeed, approximately 40–50% of patients with RA in this unselected population had two or more CV risk factors, which speaks to the generalisability of our results. There was no association between longer exposure to upadacitinib and rates of MACE or VTE in this analysis, which is a relevant finding given shifts in lipid parameters, and effects from those shifts are often delayed.[50] There was no significant difference observed between upadacitinib doses.

Some limitations to this study require acknowledgement. The studies included lacked a long-term placebo control arm for comparative analysis, along with a shorter duration in patient-years for the active comparator groups adalimumab and methotrexate. Comparisons between upadacitinib and adalimumab were only available within a single RA and PsA study, and not all studies included both upadacitinib 15 mg and 30 mg doses within the same study. All data were sourced from controlled clinical trials and not prospective studies designed to specifically evaluate and compare rates of MACE and VTE. All analyses were conducted post hoc. Study endpoints were not multiplicity controlled. Overall, relatively few events were observed, limiting our ability to make definitive conclusions from regression analyses and an inability to control for potential confounders. Only four events of MACE in

the adalimumab arm and two events in the methotrexate arm limit inference of MACE (and VTE) risk comparing upadacitinib to active therapies in RA. Data concerning AS were limited in comparison to RA and PsA given the patient population size and small number of events. Data from this analysis and from published data concerning background rates regarding PsA and AS are much more limited than are data for RA. It should also be noted that we discuss the findings of several observational studies in the context of the ORAL Surveillance clinical trial, and observational studies are at higher risk of bias than clinical trials.

In conclusion, this integrated analysis of upadacitinib use across the RA, PsA and AS phase 2b/3 clinical programmes found rates of MACE and VTE consistent with observed rates in the published literature and comparable to the active comparators adalimumab and methotrexate included in these programmes. Traditional CV, thrombotic and anti-inflammatory risk factors appeared associated with event occurrence in patients receiving upadacitinib. Continued follow-up is ongoing to further contextualise the risk of MACE and VTE in the upadacitinib in the RA, PsA and AS clinical trial programmes.

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Competing interests CC-S has received grant/research support from AbbVie, Bristol-Myers Squibb, CSL Behring, Alexion Pharmaceuticals, Priovant Therapeutics and Pfizer. She is a consultant for AbbVie, Priovant Therapeutics, Octapharma, Bristol-Myers Squibb, Gilead Sciences, Pfizer, Galapagos and Sanofi-Regeneron. EC has received research grants and/or has served as member of advisory boards and/or speaker bureaus for AbbVie, Amgen, Bio-Cancer, Biocon, Biogen, Bristol-Myers Squibb, Celgene, Chugai Pharma, Eli Lilly, Fresenius Kabi, Galapagos, Gilead, Inmedix, Janssen, Merck Serono, Novimmune, Novartis, ObsEva, Pfizer, Regeneron, Roche, R-Pharm, Sanofi, SynAct Pharma and UCB. IBM has received research grants and/or consulting fees from AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, EveloBio, Janssen, LEO, Lilly, Novartis, Moonlake, Pfizer and UCB. EM has received research grants and/or has served as a member of advisory boards and/or speaker bureaus for AbbVie, Amgen, AstraZeneca, Eli Lilly, BMS, Janssen, Novartis, Pfizer, Sanofi, Sandoz and Roche. PN has received research grants and/or consulting fees from and/or is a member of speakers' bureaus for AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Gilead and Janssen. KY is a member of speakers' bureaus for AbbVie, GK, Astellas, BMS, Chugai, Mitsubishi-Tanabe, Pfizer and Takeda. RL, NK, HP, AKS and JS are full-time employees of AbbVie and may hold AbbVie stock or stock options. JRC has received research grants and/or consulting fees from AbbVie, Amgen, ArthritisPower, Aqtual, Bendcare, BMS, CorEvitas, FASTER, GSK, IlluminationHealth, Janssen, Labcorp, Lilly, Myriad, Novartis, Pfizer, Sanofi, Scipher, Setpoint and UCB.

Patient consent for publication Not applicable.

Ethics approval This is an integrated analysis of a clinical trials programme. An independent ethics committee or institutional review board at each study site approved the study protocol, informed consent forms and recruitment materials before patient enrolment. The studies were conducted in accordance with the International Conference for Harmonisation guidelines, applicable regulations and the Declaration of Helsinki. Patients gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised individual and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial 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 and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the USA and Europe and after acceptance of this manuscript for publication. These 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'.

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