Patients With a Smoking History and Atopic Dermatitis: Long-Term Safety of Upadacitinib for Major Adverse Cardiovascular Events, Venous Thromboembolism, or Malignancy (Excluding Nonmelanoma Skin Cancer)

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OBJECTIVE

To evaluate long-term incidence rates of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), and malignancy (excluding nonmelanoma skin cancer [NMSC]) according to baseline smoking history among patients with moderate-to-severe atopic dermatitis who received up to 6 years of upadacitinib treatment

CONCLUSIONS

Incidence rates of MACE, VTE, and malignancy (excluding NMSC) were low among patients with moderate-to-severe atopic dermatitis who received up to 6 years of upadacitinib treatment, regardless of smoking history

MACE, VTE, and malignancy (excluding NMSC) incidence rates in upadacitinib-treated patients were similar to background rates observed in a real-world population of patients with atopic dermatitis in the United States

These findings support the favorable benefit-risk profile of upadacitinib 15 mg and upadacitinib 30 mg for the treatment of moderate-to-severe atopic dermatitis in adolescents and adults, including those with a history of smoking

BACKGROUND

- Atopic dermatitis (AD) is a chronic inflammatory disease that may be associated with multiple comorbidities, including MACE, VTE, and malignancy (excluding NMSC)[1–3]
- Upadacitinib is an oral selective JAK inhibitor approved for the treatment of moderate-to-severe AD in adolescents and adults[4]
- An integrated safety analysis of data from phase 3 studies of upadacitinib demonstrated that the incidence of MACE, VTE, and malignancy (excluding NMSC) in patients with moderate-to-severe AD treated for up to 6 years was comparable to or lower than background rates reported in the general population with AD in the United States[5]
- Smoking is a well-known modifiable and independent risk factor for developing MACE, VTE, and malignancy[6]; here, we evaluated long-term incidence rates of MACE, VTE, and malignancy (excluding NMSC) according to baseline smoking history among patients with moderate-to-severe AD with up to 6 years of upadacitinib treatment
- To contextualize long-term incidence rates among patients treated with upadacitinib, we also evaluated rates of MACE, VTE, and malignancy (excluding NMSC) by smoking history in a real-world reference cohort of patients with AD in the United States

METHODS

Study Design and Treatment

- For this 6-year interim analysis, data were pooled from the ongoing randomized, double-blind, multicenter, placebo-controlled, phase 3 Measure Up 1 (NCT03569293),[7] Measure Up 2 (NCT03607422),[7] and AD Up (NCT03568318)[8] trials
- Adolescents and adults (aged 12–75 years) with moderate-to-severe AD were randomized 1:1:1 to receive once-daily orally administered upadacitinib 15 mg, upadacitinib 30 mg, or placebo as a monotherapy (Measure Up 1 and 2) or with concomitant topical corticosteroids (AD Up) for 16 weeks
- After the 16-week double-blind treatment period, patients receiving upadacitinib continued treatment with their assigned doses in the blinded extension period, while patients treated with placebo were rerandomized (1:1) to upadacitinib 15 mg or 30 mg in the blinded extension period (patients could continue treatment up to week 524)

Assessments

- Incidence of adjudicated MACE (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), adjudicated VTE (deep vein thrombosis or pulmonary embolism [fatal and nonfatal]), and malignancy (excluding NMSC) was assessed as exposure-adjusted incidence rates per 100 patient-years (n/100 PY)
- Background rates of MACE, VTE, and malignancy (excluding NMSC) in the general US population with AD were assessed in a retrospective observational claims-based analysis from Optum's de-identified Clinformatics® Data Mart database
  - This real-world reference population included patients who had a diagnosis of AD during the study period (March 2017–September 2024) determined by International Classification of Diseases 9th or 10th edition codes (≥1 inpatient or ≥2 outpatient claims for AD)
  - Age restrictions from the upadacitinib phase 3 studies (12–75 years) were implemented for the real-world reference population, and background rates were weighted to mimic the age and sex distribution in the combined upadacitinib trial population
- Cohort stratification was based on self-reported smoking history at baseline (current/former smoker vs never smoked)

RESULTS

Patients

- A total of 2683 patients from the upadacitinib phase 3 studies were included in the analysis (upadacitinib 15 mg, n = 1337, PY = 4435.2; upadacitinib 30 mg, n = 1346, PY = 4752.5)
- Many patients from the upadacitinib phase 3 analysis had CV risk factors, with similar rates between both upadacitinib dose groups **(Table 1)**
- Rates of comorbidities and risk factors were higher among smokers than never smokers **(Table 2)**
- A total of 50,447 patients were included in the real-world reference population (current/former smoker, n = 5373; never smoked, n = 45,074)
- Relative to patients who never smoked, smokers in the real-world reference population had a higher mean age, a lower proportion of female patients, and a higher proportion with CV risk factors **(Table 3)**

Incidence of MACE, VTE, and Malignancy (Excluding NMSC) by Smoking Status

- Among patients treated with upadacitinib, long-term incidence rates in the smoker and never smoked cohorts were low for MACE (all ≤0.3 n/100 PY), VTE (all ≤0.2 n/100 PY), and malignancy ([excluding NMSC], all ≤0.7 n/100 PY; **Figure 1**)
- Incidence rates from the long-term upadacitinib phase 3 analysis were consistent with real-world incidence rates in patients with AD in the United States for smokers and never smokers

Table 1. Select Baseline Characteristics From the UPA AD Long-Term Safety Analysis (Measure Up 1, Measure Up 2, and AD Up)

Characteristic	UPA 15 mg (n = 1337)	UPA 30 mg (n = 1346)
Age, years, mean (SD)	31.9 (15.2)	33.1 (15.9)
Female, n (%)	593 (44.4)	585 (43.5)
CV risk factor, n (%)	723 (54.1)	690 (51.3)
Tobacco/nicotine use	418 (31.3)	419 (31.1)
History of hypertension	149 (11.1)	127 (9.4)
History of CV event	72 (5.4)	74 (5.5)
History of diabetes mellitus	27 (2.0)	28 (2.1)
Elevated LDL-C (≥130 mg/dL)	199 (14.9)	191 (14.2)
Low HDL-C (<40 mg/dL)	177 (13.2)	168 (12.5)
Aged ≥50 years with ≥1 CV risk factor,[a] n (%)	179 (13.4)	209 (15.5)
Number of CV risk factors,[a] n (%)		
0	614 (45.9)	656 (48.7)
1	484 (36.2)	451 (33.5)
2	175 (13.1)	176 (13.1)
3	50 (3.7)	51 (3.8)
≥4	14 (1.0)	12 (0.9)
BMI, ≥30 kg/m², n (%)	252 (18.9)	258 (19.3)
History of VTE, n (%)	4 (0.3)	6 (0.4)
Oral contraceptive use,[b] n (%)	105 (17.7)	130 (22.2)

AD, atopic dermatitis; BMI, body mass index; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UPA, upadacitinib; VTE, venous thromboembolism.

[a] CV risk factors included history of CV events, hypertension, diabetes mellitus, current or former use of tobacco/nicotine, elevated LDL-C, and low HDL-C.

[b] Evaluated among all female patients (UPA 15 mg, n = 593; UPA 30 mg, n = 585).

Table 2. Select Baseline Characteristics From the UPA AD Long-Term Safety Analysis by Smoking History

Characteristic	Current/Former Smoker[a] (n = 842)	Never Smoked[a] (n = 1841)
Age, years, mean (SD)	39.4 (15.2)	29.3 (14.8)
Female, n (%)	310 (36.8)	868 (47.1)
Race, n (%)		
White	629 (74.7)	1226 (66.6)
Asian	142 (16.9)	440 (23.9)
Black	45 (5.3)	118 (6.4)
Other	26 (3.1)	57 (3.1)
CV risk factor, n (%)		
Tobacco/nicotine use	842 (100)	17 (0.9)[b]
History of hypertension	141 (16.7)	135 (7.3)
History of CV event	61 (7.2)	85 (4.6)
History of diabetes mellitus	28 (3.3)	27 (1.5)
Elevated LDL-C (≥130 mg/dL)	163 (19.4)	227 (12.4)
Low HDL-C (<40 mg/dL)	110 (13.1)	235 (12.8)
Aged ≥50 years with ≥1 CV risk factor,[c] n (%)	242 (28.7)	147 (8.0)
Number of CV risk factors,[c] n (%)		
0	0	1253 (68.1)
1	476 (56.5)	472 (25.6)
2	255 (30.3)	99 (5.4)
3	90 (10.7)	12 (0.7)
≥4	21 (2.5)	5 (0.3)
BMI, ≥30 kg/m²	187 (22.2)	322 (17.6)
History of VTE	5 (0.6)	5 (0.3)
Oral contraceptive use[d]	76 (30.8)	222 (31.4)

AD, atopic dermatitis; BMI, body mass index; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UPA, upadacitinib; VTE, venous thromboembolism.

[a] Includes patients who received UPA 15 mg or UPA 30 mg.

[b] Some patients who used chewing tobacco were considered tobacco users but not smokers.

[c] CV risk factors included history of CV events, hypertension, diabetes mellitus, current or former use of tobacco/nicotine, elevated LDL-C, and low HDL-C.

[c] Evaluated among female patients aged 15–55 years.

Table 3. Baseline Characteristics From the US Real-World Reference Population

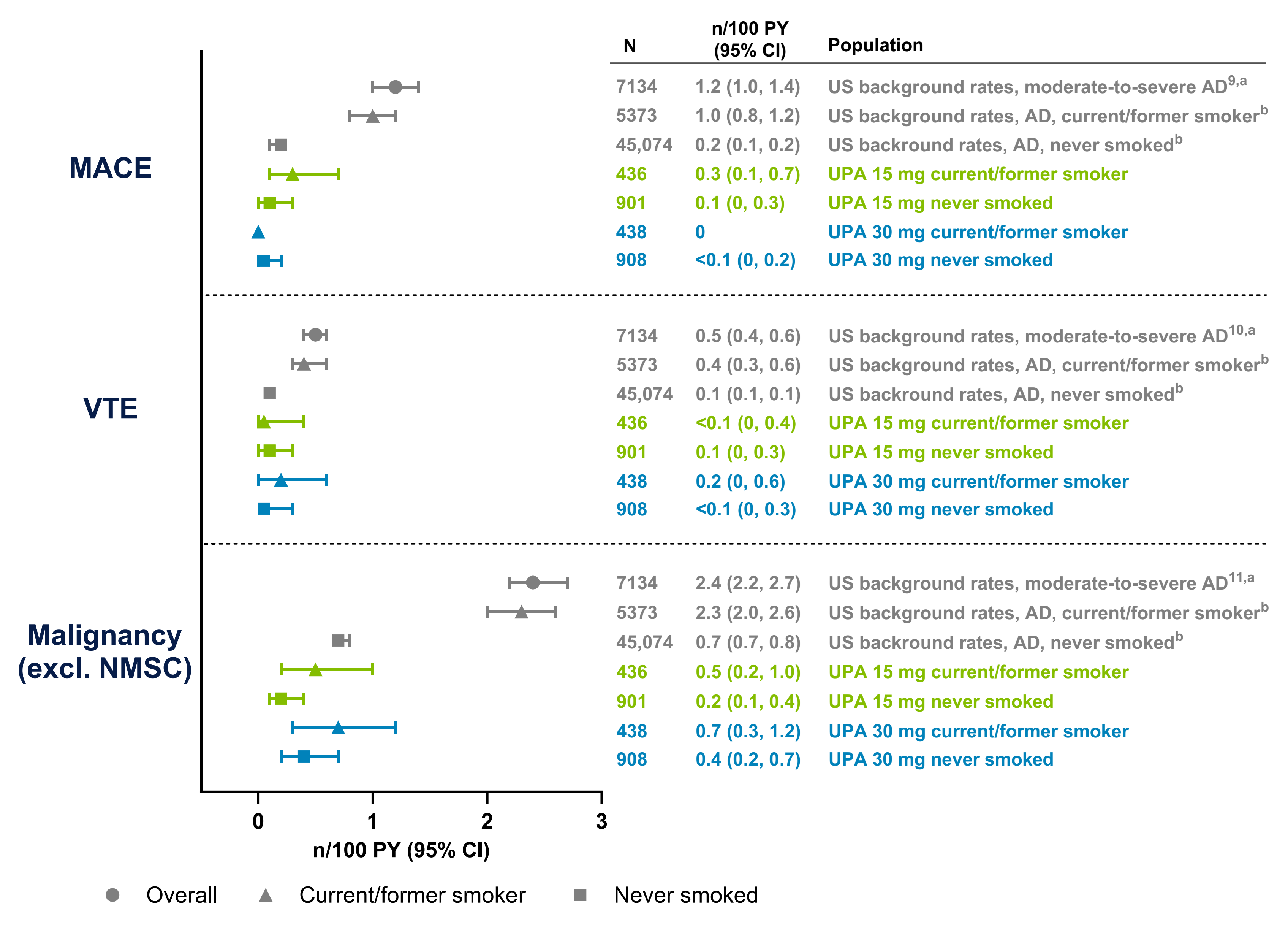
Characteristic	Current/Former Smoker[a] (n = 5373)	Never Smoked[a] (n = 45,074)
Age, years, mean (SD)	46.8 (14.9)	30.6 (15.2)
Age categories, years, n (%)		
12–17	22 (0.4)	9910 (22.0)
18–30	920 (17.1)	16,919 (37.5)
31–45	1539 (28.6)	9680 (21.5)
46–65	2278 (42.4)	7323 (16.2)
≥66	614 (11.4)	1242 (2.8)
Female, n (%)	1926 (35.8)	20,213 (44.8)
Race, n (%)		
White	2650 (49.3)	16,029 (35.6)
Asian	159 (3.0)	2812 (6.2)
Black	643 (12.0)	3474 (7.7)
Unknown	185 (3.4)	1960 (4.3)
Missing	1736 (32.3)	20,799 (46.1)
Geographic region, n (%)		
Northeast	602 (11.2)	6143 (13.6)
South	2647 (49.3)	20,716 (46.0)
Midwest	1134 (21.1)	8130 (18.0)
West	982 (18.3)	9997 (22.2)
Missing, unknown, or Puerto Rico	8 (0.1)	88 (0.2)
CV risk factor (other than smoking), n (%)		
History of hypertension	2729 (50.8)	6831 (15.2)
History of CV event[b]	273 (5.1)	192 (0.4)
History of diabetes mellitus	1118 (20.8)	2550 (5.7)
Dyslipidemia	2718 (50.6)	8736 (19.4)

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CV, cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a] To the extent observable in the data.

[b] History of MI, stroke, CABG/PCI, or ACS.

Figure 1. Incidence of MACE, VTE, and Malignancy (Excluding NMSC) by Smoking Status



	N	n/100 PY (95% CI)	Population
MACE	7134	1.2 (1.0, 1.4)	US background rates, moderate-to-severe AD[9,a]
	5373	1.0 (0.8, 1.2)	US background rates, AD, current/former smoker[b]
	45,074	0.2 (0.1, 0.2)	US backround rates, AD, never smoked[b]
	436	0.3 (0.1, 0.7)	UPA 15 mg current/former smoker
	901	0.1 (0, 0.3)	UPA 15 mg never smoked
	438	0	UPA 30 mg current/former smoker
	908	<0.1 (0, 0.2)	UPA 30 mg never smoked
VTE	7134	0.5 (0.4, 0.6)	US background rates, moderate-to-severe AD[10,a]
	5373	0.4 (0.3, 0.6)	US background rates, AD, current/former smoker[b]
	45,074	0.1 (0.1, 0.1)	US backround rates, AD, never smoked[b]
	436	<0.1 (0, 0.4)	UPA 15 mg current/former smoker
	901	0.1 (0, 0.3)	UPA 15 mg never smoked
	438	0.2 (0, 0.6)	UPA 30 mg current/former smoker
	908	<0.1 (0, 0.3)	UPA 30 mg never smoked
Malignancy (excl. NMSC)	7134	2.4 (2.2, 2.7)	US background rates, moderate-to-severe AD[11,a]
	5373	2.3 (2.0, 2.6)	US background rates, AD, current/former smoker[b]
	45,074	0.7 (0.7, 0.8)	US backround rates, AD, never smoked[b]
	436	0.5 (0.2, 1.0)	UPA 15 mg current/former smoker
	901	0.2 (0.1, 0.4)	UPA 15 mg never smoked
	438	0.7 (0.3, 1.2)	UPA 30 mg current/former smoker
	908	0.4 (0.2, 0.7)	UPA 30 mg never smoked

AD, atopic dermatitis; excl, excluding; MACE, major adverse cardiovascular event; n/100 PY, number of patients with ≥1 event per 100 patient-years; NMSC, nonmelanoma skin cancer; UPA, upadacitinib; VTE, venous thromboembolism.
MACE was defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.
VTE was defined as deep vein thrombosis or pulmonary embolism (fatal and nonfatal).

[a] In a real-world claims analysis, patients with moderate-to-severe AD were defined by dupilumab use as a proxy at any time during the follow-up period.

[b] Background rates from the claims analysis by smoking history were measured in patients who had an AD diagnosis during the study period. Age restrictions from the UPA phase 3 studies (12–75 years) were implemented for the real-world reference population, and background rates were weighted to mimic the age and sex distribution in the combined UPA trial population. Patients in the real-world population were categorized by smoking status to the extent observable in the data.

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