Patients With Cardiovascular Risk Factors 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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OBJECTIVES

To evaluate long-term incidence rates of Major adverse cardiovascular events (MACE), venous thromboembolism (VTE), and malignancy (excluding nonmelanoma skin cancer [NMSC]) by baseline cardiovascular (CV) risk category in patients with moderate-to-severe atopic dermatitis (AD) treated with upadacitinib (UPA) for up to 6 years

To contextualize these data, incidence rates by CV risk category were also assessed in a real-world population of patients with AD in the United States

CONCLUSIONS

MACE, VTE, and malignancy (excluding NMSC) incidence rates among patients with moderate-to-severe AD who received up to 6 years of UPA treatment were low, regardless of whether they had any baseline CV risk factors or the number of CV risk factors

Incidence rates of MACE, VTE, and malignancy (excluding NMSC) by CV risk category among patients treated with UPA were consistent with those observed in the real-world population of patients with atopic dermatitis in the United States

These findings support the favorable benefit-risk profile of UPA 15 mg and UPA 30 mg in adolescents and adults, including those with 1 or more CV risk factors, for the treatment of moderate-to-severe AD

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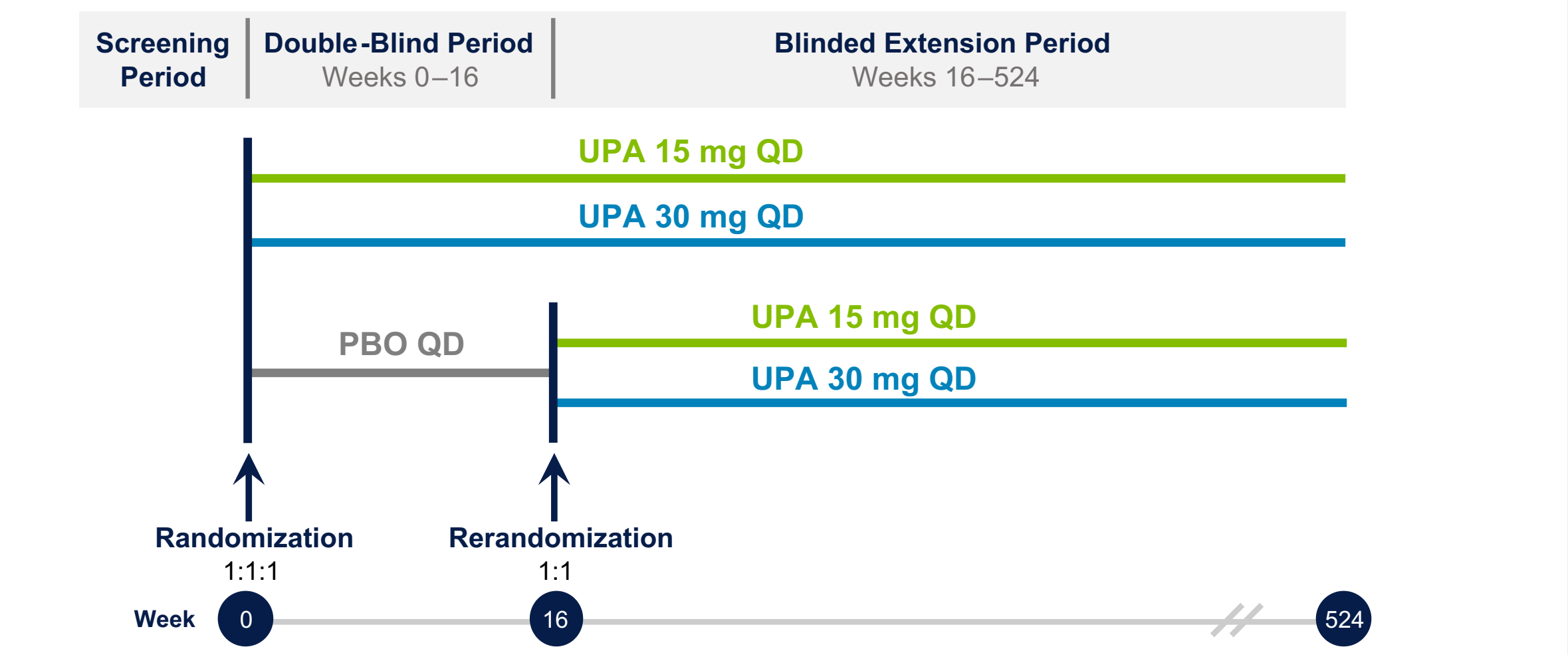
BACKGROUND

- Atopic dermatitis (AD) is a chronic inflammatory skin disease linked with comorbidities including major adverse cardiovascular events (MACE), venous thromboembolism (VTE), and malignancy (excluding [excl.] nonmelanoma skin cancer [NMSC])[1–3]
- Upadacitinib (UPA) is an oral selective Janus kinase inhibitor approved for the treatment of moderate-to-severe AD in adolescents and adults[4]
- Previous UPA phase 3 studies (≤6 years of treatment) showed incidences of MACE, VTE, and malignancy (excl. NMSC) similar to or lower than background rates in the US AD population[5]
- Patients with AD may have variable cardiovascular (CV) risk driven by baseline factors and AD severity[6]

METHODS

Data pooled from Measure Up 1 (NCT03569293),[1] Measure Up 2 (NCT03607422),[1] AD Up (NCT03568318)[2]


Screening Period | Double-Blind Period Weeks 0–16 | Blinded Extension Period Weeks 16–524

UPA 15 mg QD

UPA 30 mg QD

PBO QD

UPA 15 mg QD

UPA 30 mg QD

Randomization 1:1:1

Rerandomization 1:1

Week 0 16 524

AD, atopic dermatitis; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol MACE, major adverse cardiovascular events; NMSC, nonmelanoma skin cancer; PBO, placebo; QD, once daily; UPA, upadacitinib; VTE, venous thromboembolism.

Incidence Assessment

- MACE: CV death, nonfatal myocardial infarction, nonfatal stroke
- VTE: deep vein thrombosis or pulmonary embolism (fatal and nonfatal)
- Malignancy (excluding NMSC)

Cohort Stratification

- Presence of CV risk factors at baseline (≥1 vs 0)
  - CV risk factors included prior CV event, hypertension, diabetes mellitus, tobacco/nicotine use (current and former), elevated LDL-C, and lowered HDL-C
- 1 vs 2 CV risk factors

Real-World Reference Population

- Retrospective observational claims-based analysis
- Optum's de-identified Clinformatics® Data Mart database
- Background rates weighted to mimic the age and sex distribution in pooled UPA trial population

RESULTS

Baseline Characteristics From the UPA AD Long-Term Safety Analysis

Characteristic	UPA 15 mg (n = 1337)[a]	UPA 30 mg (n = 1346)[a]
Age, years, mean (SD)	31.9 (15.2)	33.1 (15.9)
Female, n (%)	593 (44.4)	585 (43.5)
BMI ≥30 kg/m², n (%)	252 (18.9)	258 (19.3)
Oral contraceptive use,[b] n (%)	105 (17.7)	130 (22.2)
Aged ≥50 years with ≥1 CV risk factor,[c] n (%)	179 (13.4)	209 (15.5)
History of VTE, n (%)	4 (0.3)	6 (0.4)

AD, atopic dermatitis; BMI, body mass index; CV, cardiovascular; UPA, upadacitinib; VTE, venous thromboembolism.
[a]Long-term analysis cohort of patients from the Measure Up 1, Measure Up 2, and AD Up studies.
[b]Evaluated among all female patients (UPA 15 mg, n = 593; UPA 30 mg, n = 585).
[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.

RESULTS CONTINUED

Baseline CV Risk Characteristics

Characteristic	UPA 15 mg (n = 1337)[a]	UPA 30 mg (n = 1346)[a]
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)
Number of CV risk factors,[b] 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)

CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UPA, upadacitinib.
[a]Long-term analysis cohort of patients from the Measure Up 1, Measure Up 2, and AD Up studies.
[b]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.

Select Baseline Characteristics by Number of Baseline CV Risk Factors

Characteristic	1 CV Risk Factor (n = 935)[a]	2 CV Risk Factors (n = 351)[a]
Age, years, mean (SD)	33.7 (14.7)	44.4 (15.1)
Female, n (%)	365 (39.0)	104 (29.6)
CV risk factor, n (%)		
Tobacco/nicotine use	469 (50.2)	258 (73.5)
History of hypertension	63 (6.7)	112 (31.9)
History of CV event	48 (5.1)	45 (12.8)
History of diabetes mellitus	2 (0.2)	19 (5.4)
Elevated LDL-C (≥130 mg/dL)	169 (18.2)	156 (44.6)
Low HDL-C (<40 mg/dL)	184 (19.7)	112 (31.9)
Aged ≥50 years with ≥1 CV risk factor,[b] n (%)	159 (17.0)	140 (39.9)
BMI ≥30 kg/m², n (%)	203 (21.8)	91 (26.0)
History of VTE, n (%)	4 (0.4)	2 (0.6)
Oral contraceptive use,[c] n (%)	98 (32.2)	18 (25.7)

BMI, body mass index; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VTE, venous thromboembolism.
[a]Long-term analysis cohort of patients from the Measure Up 1, Measure Up 2, and AD Up studies.
[b]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 ages 15–55 years.

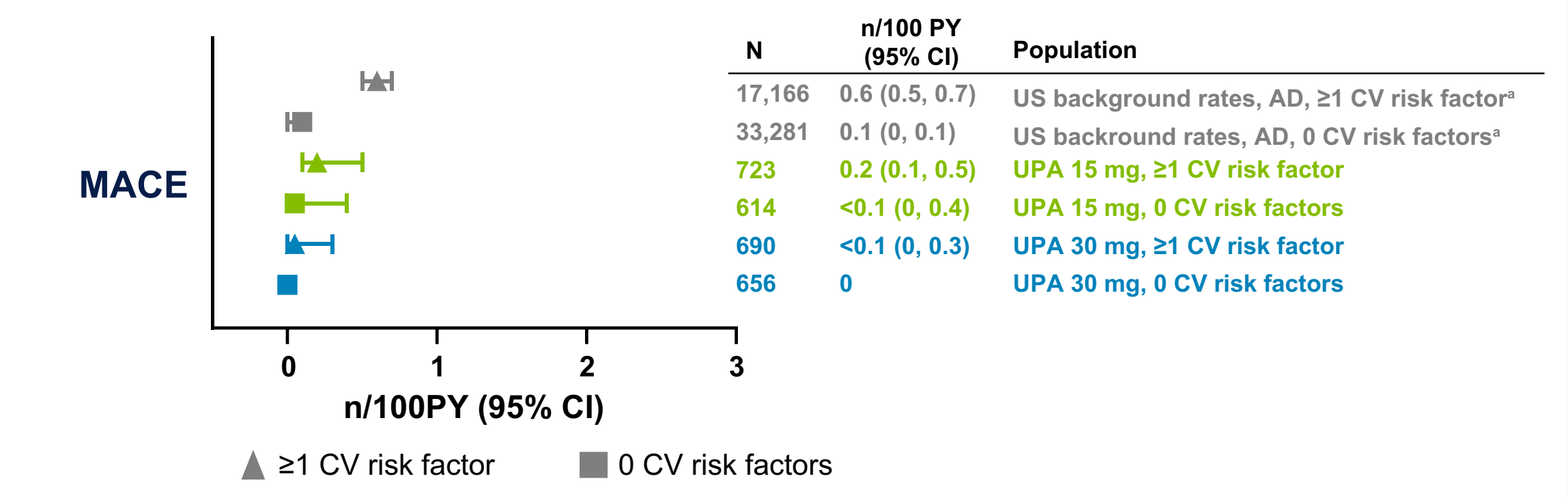
Baseline Characteristics From the US Real-World Reference Population

Characteristic	≥1 CV Risk Factor[a] (n = 17,166)	0 CV Risk Factors[a] (n = 33,281)
Age, years, mean (SD)	45.4 (15.4)	25.6 (11.5)
Female, n (%)	6748 (39.3)	15,391 (46.2)
Race, n (%)		
White	7458 (43.4)	11,221 (33.7)
Asian	955 (5.6)	2016 (6.1)
Black	1921 (11.2)	2196 (6.6)
Unknown	732 (4.3)	1413 (4.2)
Missing	6100 (35.5)	16,435 (49.4)
CV risk factor, n (%)	17,166 (100)	0
Tobacco/nicotine use	5299 (30.9)	0
History of hypertension	9560 (55.7)	0
History of CV event[b]	465 (2.7)	0
History of diabetes mellitus	3668 (21.4)	0
Dyslipidemia	11,454 (66.7)	0

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CV, cardiovascular; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention.
[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]History of MI, stroke, CABG/PCI, or ACS.

- Incidence rates of MACE in patients treated with UPA were low, and comparable for patients who had ≥1 vs 0 CV risk factor
- Rates of MACE were below or similar to incidence rates in real-world reference population

Incidence of MACE by CV Risk Category

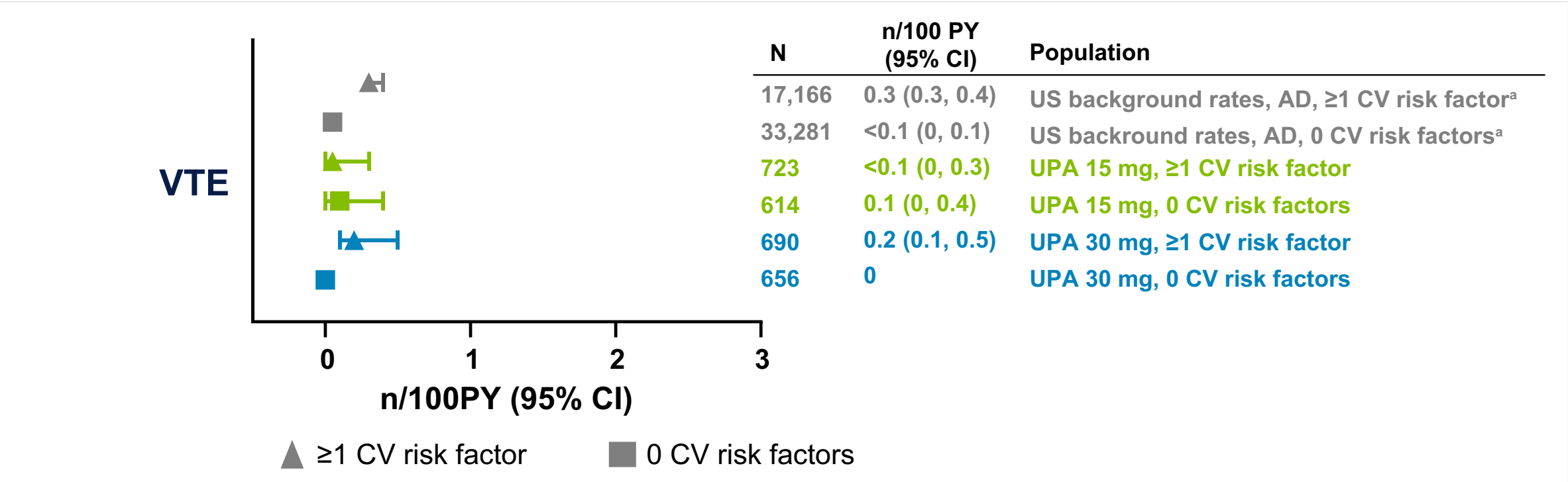


N	n/100 PY (95% CI)	Population
17,166	0.6 (0.5, 0.7)	US background rates, AD, ≥1 CV risk factor[a]
33,281	0.1 (0, 0.1)	US backround rates, AD, 0 CV risk factors[a]
723	0.2 (0.1, 0.5)	UPA 15 mg, ≥1 CV risk factor
614	<0.1 (0, 0.4)	UPA 15 mg, 0 CV risk factors
690	<0.1 (0, 0.3)	UPA 30 mg, ≥1 CV risk factor
656	0	UPA 30 mg, 0 CV risk factors

AD, atopic dermatitis; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol MACE, major adverse cardiovascular event; n/100 PY, number of patients with ≥1 event per 100 patient-years; UPA, upadacitinib.
MACE was defined as CV death, nonfatal myocardial infarction, or nonfatal stroke. 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.
[a]Background rates by CV risk category were measured in a real-world cohort of patients from the claims analysis who had a diagnosis of AD 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.

- Incidence rates of VTE in patients treated with UPA were low and comparable for patients who had 0 vs ≥1 CV risk factor
- Rates of VTE were below or similar to incidence rates in real-world reference population

Incidence of VTE by CV Risk Category

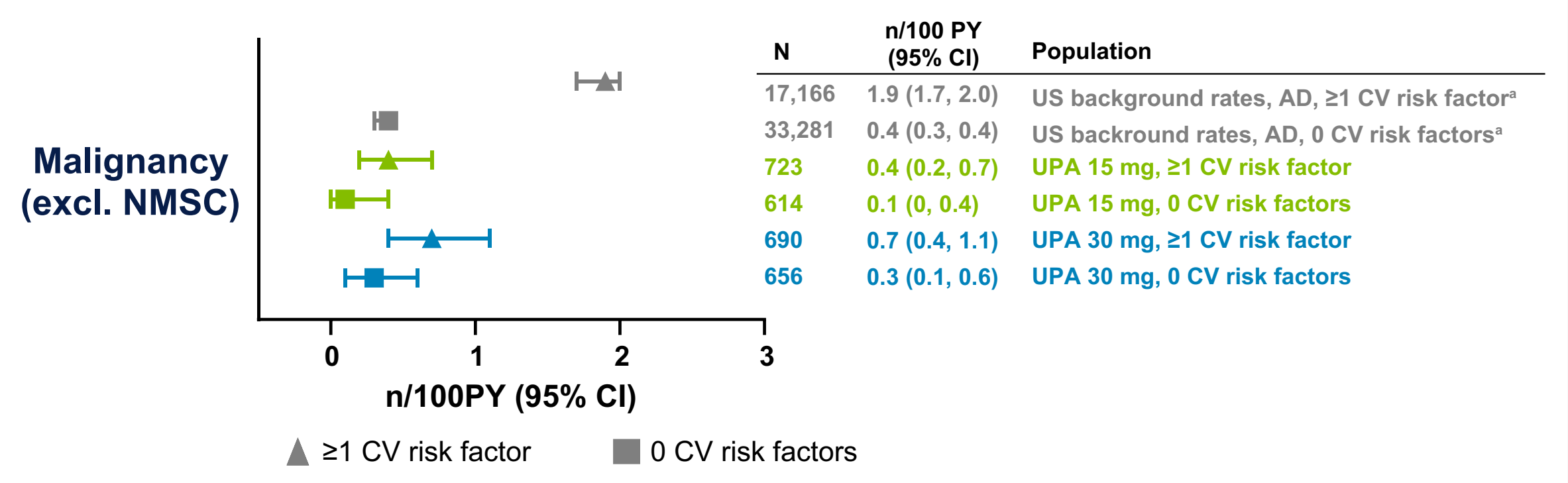


N	n/100 PY (95% CI)	Population
17,166	0.3 (0.3, 0.4)	US background rates, AD, ≥1 CV risk factor[a]
33,281	<0.1 (0, 0.1)	US backround rates, AD, 0 CV risk factors[a]
723	<0.1 (0, 0.3)	UPA 15 mg, ≥1 CV risk factor
614	0.1 (0, 0.4)	UPA 15 mg, 0 CV risk factors
690	0.2 (0.1, 0.5)	UPA 30 mg, ≥1 CV risk factor
656	0	UPA 30 mg, 0 CV risk factors

AD, atopic dermatitis; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol MACE, major adverse cardiovascular event; n/100 PY, number of patients with ≥1 event per 100 patient-years; UPA, upadacitinib.
MACE was defined as CV death, nonfatal myocardial infarction, or nonfatal stroke. 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.
[a]Background rates by CV risk category were measured in a real-world cohort of patients from the claims analysis who had a diagnosis of AD 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.

- Incidence rates of malignancy (excl. NMSC) in patients treated with UPA were low and comparable for patients who had 0 vs ≥1 CV risk factor
- Rates of malignancy (excl. NMSC) were below or similar to incidence rates in real-world reference population

Incidence of Malignancy (excl. NMSC) by CV Risk Category



N	n/100 PY (95% CI)	Population
17,166	1.9 (1.7, 2.0)	US background rates, AD, ≥1 CV risk factor[a]
33,281	0.4 (0.3, 0.4)	US backround rates, AD, 0 CV risk factors[a]
723	0.4 (0.2, 0.7)	UPA 15 mg, ≥1 CV risk factor
614	0.1 (0, 0.4)	UPA 15 mg, 0 CV risk factors
690	0.7 (0.4, 1.1)	UPA 30 mg, ≥1 CV risk factor
656	0.3 (0.1, 0.6)	UPA 30 mg, 0 CV risk factors

AD, atopic dermatitis; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol MACE, major adverse cardiovascular event; n/100 PY, number of patients with ≥1 event per 100 patient-years; UPA, upadacitinib.
MACE was defined as CV death, nonfatal myocardial infarction, or nonfatal stroke. 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.
[a]Background rates by CV risk category were measured in a real-world cohort of patients from the claims analysis who had a diagnosis of AD 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.

- Incidence rates of MACE, VTE, and malignancy (excl. NMSC) remained low when patients were stratified by 1 vs 2 CV risk factors

Incidence of MACE, VTE, and Malignancy by CV Risk Stratification

	AESI, n/100 PY (95% CI)		
CV Risk Factors[a]	**MACE[b]**	**VTE[c]**	**Malignancy (excl. NMSC)**
UPA 15 mg			
0 (n = 614)	<0.1 (0, 0.4)	0.1 (0, 0.4)	0.1 (0, 0.4)
≥1 (n = 723)	0.2 (0.1, 0.5)	<0.1 (0, 0.3)	0.4 (0.2, 0.7)
1 (n = 484)	0	<0.1 (0, 0.4)	0.2 (0, 0.6)
2 (n = 175)	0.3 (0, 1.2)	0	0.2 (0, 0.9)
UPA 30 mg			
0 (n = 656)	0	0	0.3 (0.1, 0.6)
≥1 (n = 690)	<0.1 (0, 0.3)	0.2 (0.1, 0.5)	0.7 (0.4, 1.1)
1 (n = 451)	0	0.1 (0, 0.5)	0.4 (0.2, 0.9)
2 (n = 176)	0.2 (0, 0.9)	0.5 (0.1, 1.4)	0.5 (0.1, 1.4)

AESI, adverse event of special interest; CV, cardiovascular; excl, excluding; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; 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.
[a]CV risk factors included prior CV event, hypertension, diabetes mellitus, tobacco/nicotine use (current and former), elevated LDL-C, or lowered HDL-C.
[b]MACE was defined as CV death, nonfatal myocardial infarction, or nonfatal stroke.
[c]VTE was defined as deep vein thrombosis or pulmonary embolism (fatal and nonfatal).

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