Patients With Atopic Dermatitis Using Oral Contraceptive Pills or Hormone Replacement Therapy: Long-Term Safety of Upadacitinib for Major Adverse Cardiovascular Events, Venous Thromboembolism, or Malignancy (Excluding Nonmelanoma Skin Cancer)

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OBJECTIVE

To assess long-term incidence rates of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), and malignancy (excluding nonmelanoma skin cancer [NMSC]) by baseline oral contraceptive pill (OCP) and hormone replacement therapy (HRT) use among female patients with moderate-to-severe atopic dermatitis who received up to 6 years of upadacitinib treatment

CONCLUSIONS

In female patients with moderate-to-severe atopic dermatitis who received up to 6 years of upadacitinib treatment, long-term incidence rates of MACE, VTE, and malignancy (excluding NMSC) were low, regardless of OCP or HRT use

Incidence rates of MACE, VTE, and malignancy (excluding NMSC) by OCP use in the upadacitinib phase 3 population were similar to those in the female population of patients with atopic dermatitis in the United States

Together, these results support the favorable benefit-risk profile of upadacitinib 15 mg and upadacitinib 30 mg for the treatment of moderate-to-severe atopic dermatitis in females of childbearing potential who use OCPs

BACKGROUND

- Atopic dermatitis (AD), a chronic inflammatory skin disease, can be associated with MACE, VTE, and malignancy (excluding NMSC)[1–3]
- Upadacitinib, an oral selective Janus kinase (JAK) inhibitor, is approved for the treatment of moderate-to-severe AD in adolescents and adults[4]
- An integrated analysis of up to 6 years of safety data from phase 3 studies of upadacitinib in patients with moderate-to-severe AD showed that the incidence of MACE (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), VTE (deep vein thrombosis or pulmonary embolism [fatal and nonfatal]), and malignancy (excluding NMSC) was similar to or lower than real-world background rates reported in the United States in patients with AD[5]
- Risk factors contributing to MACE, VTE, and malignancy (excluding NMSC) may include OCP or HRT use[6–8]; therefore, we evaluated long-term exposure-adjusted incidence rates of MACE, VTE, and malignancy (excluding NMSC) according to baseline OCP and HRT use among female patients with moderate-to-severe AD with up to 6 years of upadacitinib treatment

METHODS

Study Design and Treatment

- Data were pooled from the phase 3, randomized, double-blind, multicenter, placebo-controlled Measure Up 1 (NCT03569293),[9] Measure Up 2 (NCT03607422),[9] and AD Up (NCT03568318)[10] trials
- Adolescents and adults (aged 12–75 years) with moderate-to-severe AD were randomized 1:1:1 to receive either 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 rates of adjudicated MACE, adjudicated VTE, and malignancy (excluding NMSC) were evaluated among females and reported as exposure-adjusted incidence rates per 100 patient-years (n/100 PY)
- To contextualize incidence rates in the upadacitinib phase 3 trials, MACE, VTE, and malignancy (excluding NMSC) background rates in the general US AD population were assessed in a retrospective observational claims-based analysis utilizing data from Optum's de-identified Clinformatics® Data Mart database
  - This real-world reference population included female patients with an AD diagnosis 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), and age restrictions from the upadacitinib phase 3 studies (12–75 years) were implemented
  - Background rates were weighted to mimic the age and sex distribution in the combined upadacitinib trial population
- Safety analysis cohorts were stratified by OCP use (yes vs no) among females aged 15–55 years in the upadacitinib trial population and females aged 12–75 years in the real-world reference population
- Safety analysis cohorts stratified by HRT use (yes vs no) were evaluated among females aged >55 years in the upadacitinib trial population

RESULTS

Patients

- A total of 1178 females in the upadacitinib phase 3 studies were evaluated (upadacitinib 15 mg, n = 593; upadacitinib 30 mg, n = 585)
- Rates of comorbidities and risk factors were similar between females using OCPs and females not using OCPs, while baseline data among females using HRT and females not using HRT were limited by a small sample size **(Table 1)**

Table 1. Baseline Safety Characteristics Among Females in the UPA AD-Term Safety Analysis by OCP and HRT Use

Characteristic	OCP (n = 298)[a,b]	No OCP (n = 657)[a,b]	HRT (n = 5)[a,c]	No HRT (n = 126)[a,c]
Age, years, mean (SD)	27.0 (8.8)	30.0 (12.2)	68.4 (4.5)	63.2 (5.4)
Race, n (%)				
White	240 (80.5)	435 (66.2)	5 (100)	104 (82.5)
Asian	30 (10.1)	153 (23.3)	0	7 (5.6)
Black	16 (5.4)	45 (6.8)	0	14 (11.1)
Other	12 (4.0)	24 (3.7)	0	1 (0.8)
CV risk factor, n (%)				
Tobacco/nicotine use	77 (25.8)	168 (25.6)	1 (20.0)	62 (49.2)
History of hypertension	8 (2.7)	34 (5.2)	4 (80.0)	52 (41.3)
History of CV event	9 (3.0)	28 (4.3)	3 (60.0)	14 (11.1)
History of diabetes mellitus	1 (0.3)	8 (1.2)	2 (40.0)	8 (6.3)
Elevated LDL-C (≥130 mg/dL)	23 (7.7)	76 (11.6)	0	43 (34.4)
Low HDL-C (<40 mg/dL)	25 (8.4)	52 (7.9)	1 (20.0)	4 (3.2)
Aged ≥50 years with ≥1 CV risk factor,[d] n (%)	6 (2.0)	40 (6.1)	4 (80.0)	105 (83.3)
Number of CV risk factors,[d] n (%)				
0	179 (60.1)	381 (58.0)	1 (20.0)	21 (16.7)
1	98 (32.9)	206 (31.4)	0	52 (41.3)
2	18 (6.0)	52 (7.9)	1 (20.0)	33 (26.2)
3	3 (1.0)	16 (2.4)	3 (60.0)	16 (12.7)
≥4	0	2 (0.3)	0	4 (3.2)
BMI, ≥30 kg/m², n (%)	63 (21.4)	136 (20.8)	2 (40.0)	34 (27.2)
History of VTE, n (%)	0	2 (0.3)	0	4 (3.2)

AD, atopic dermatitis; BMI, body mass index; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HRT, hormone replacement therapy; LDL-C, low-density lipoprotein cholesterol; OCP, oral contraceptive pill; UPA, upadacitinib; VTE, venous thromboembolism.

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

[b] OCP use was evaluated among female patients aged 15–55 years.

[c] HRT use was evaluated among female patients aged >55 years.

[d] 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.

Table 2. Baseline Characteristics From the US Real-World Reference Population

Characteristic	OCP (n = 5137)	No OCP (n = 17,002)
Age, years, mean (SD)	26.8 (8.6)	33.1 (17.4)
Age categories, years, n (%)		
12–17	505 (9.8)	4516 (26.6)
18–30	3268 (63.6)	4452 (26.2)
31–45	1121 (21.8)	3294 (19.4)
46–65	242 (4.7)	4024 (23.7)
≥66	1 (<0.1)	716 (4.2)
Race, n (%)		
White	2097 (40.8)	6291 (37.0)
Asian	255 (5.0)	905 (5.3)
Black	391 (7.6)	1831 (10.8)
Unknown	226 (4.4)	698 (4.1)
Missing	2168 (42.2)	7277 (42.8)
Geographic region, n (%)		
Northeast	775 (15.1)	2017 (11.9)
South	2414 (47.0)	8226 (48.4)
Midwest	939 (18.3)	3075 (18.1)
West	1005 (19.6)	3650 (21.5)
Missing, unknown, or Puerto Rico	4 (0.1)	34 (0.2)
CV risk factor, n (%)	1076 (20.9)	5672 (33.4)
Tobacco/nicotine use	247 (4.8)	1617 (9.5)
History of hypertension	390 (7.6)	3200 (18.8)
History of CV event[a]	5 (0.1)	124 (0.7)
Diabetes mellitus	148 (2.9)	1340 (7.9)
Dyslipidemia	615 (12.0)	3783 (22.3)

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

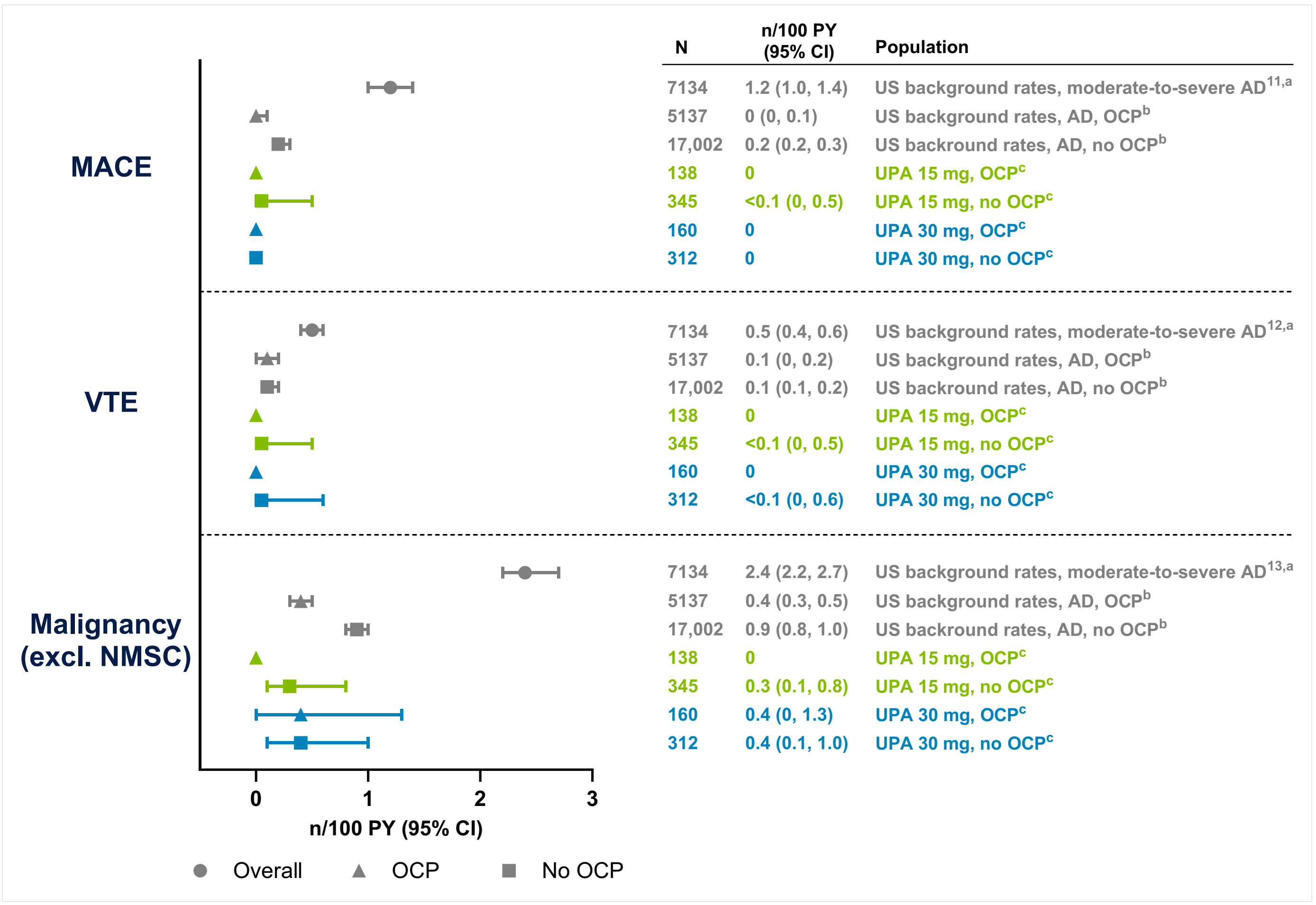
[a] History of MI, stroke, CABG/PCI, or ACS.

- A total of 22,139 females were included in the real-world reference population; of these, 5137 were using OCPs, and 17,002 were not using OCPs
- Among females using OCPs in the real-world reference population compared with those who weren't using OCPs, mean age and the proportion of patients with CV risk factors was lower **(Table 2)**

Incidence of MACE, VTE, and Malignancy (Excluding NMSC) by OCP Use

- Long-term incidence rates were low for MACE and VTE (all <0.1 n/100PY) and malignancy (excluding NMSC; all ≤0.4 n/100PY) among females treated with upadacitinib, regardless of OCP use **(Figure 1)**
- There were no MACE or VTE events in female patients using OCP or HRT and no malignancy (excluding NMSC) events in the HRT group; however, HRT results are limited by a small sample size (n = 5)
- While upadacitinib-treated patients using OCPs had no events of MACE or VTE, incidence rates for malignancy (excluding NMSC) from upadacitinib phase 3 studies were consistent with real-world incidence rates in patients with AD in the United States

Figure 1. Incidence of MACE, VTE, and Malignancy (Excluding NMSC) by OCP Use



	N	n/100 PY (95% CI)	Population
MACE	7134	1.2 (1.0, 1.4)	US background rates, moderate-to-severe AD[11,a]
	5137	0 (0, 0.1)	US background rates, AD, OCP[b]
	17,002	0.2 (0.2, 0.3)	US backround rates, AD, no OCP[b]
	138	0	UPA 15 mg, OCP[c]
	345	<0.1 (0, 0.5)	UPA 15 mg, no OCP[c]
	160	0	UPA 30 mg, OCP[c]
	312	0	UPA 30 mg, no OCP[c]
VTE	7134	0.5 (0.4, 0.6)	US background rates, moderate-to-severe AD[12,a]
	5137	0.1 (0, 0.2)	US background rates, AD, OCP[b]
	17,002	0.1 (0.1, 0.2)	US backround rates, AD, no OCP[b]
	138	0	UPA 15 mg, OCP[c]
	345	<0.1 (0, 0.5)	UPA 15 mg, no OCP[c]
	160	0	UPA 30 mg, OCP[c]
	312	<0.1 (0, 0.6)	UPA 30 mg, no OCP[c]
Malignancy (excl. NMSC)	7134	2.4 (2.2, 2.7)	US background rates, moderate-to-severe AD[13,a]
	5137	0.4 (0.3, 0.5)	US background rates, AD, OCP[b]
	17,002	0.9 (0.8, 1.0)	US backround rates, AD, no OCP[b]
	138	0	UPA 15 mg, OCP[c]
	345	0.3 (0.1, 0.8)	UPA 15 mg, no OCP[c]
	160	0.4 (0, 1.3)	UPA 30 mg, OCP[c]
	312	0.4 (0.1, 1.0)	UPA 30 mg, no OCP[c]

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; OCP, oral contraceptive pill; 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 by OCP use in the real-world reference population were measured in females who had a diagnosis of AD during the study period. Age restrictions from the UPA phase 3 studies (12–75 years) were implemented, and background rates were weighted to mimic the age and sex distribution in the combined UPA trial population.

[c] Incidence rates from the UPA long-term studies by OCP use were evaluated in females aged 15–55 years.

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