Long-Term Upadacitinib Safety in Moderate-to-Severe Atopic Dermatitis up to 7 Years: An Integrated Analysis With Over 9600 Patient-Years of Exposure

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OBJECTIVE

To evaluate the long-term safety of treatment with upadacitinib 15 mg and 30 mg for up to 7 years in adolescents and adults with moderate-to-severe atopic dermatitis from three pivotal, ongoing, phase 3 studies

CONCLUSIONS

This integrated analysis of three phase 3 trials with over 9600 patient-years demonstrates consistently low rates of adverse events of special interest throughout 7 years of upadacitinib treatment

Rates were generally similar between doses and did not exceed background incidence rates in the atopic dermatitis population, supporting the established benefit-risk profile of upadacitinib for moderate-to-severe atopic dermatitis

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BACKGROUND

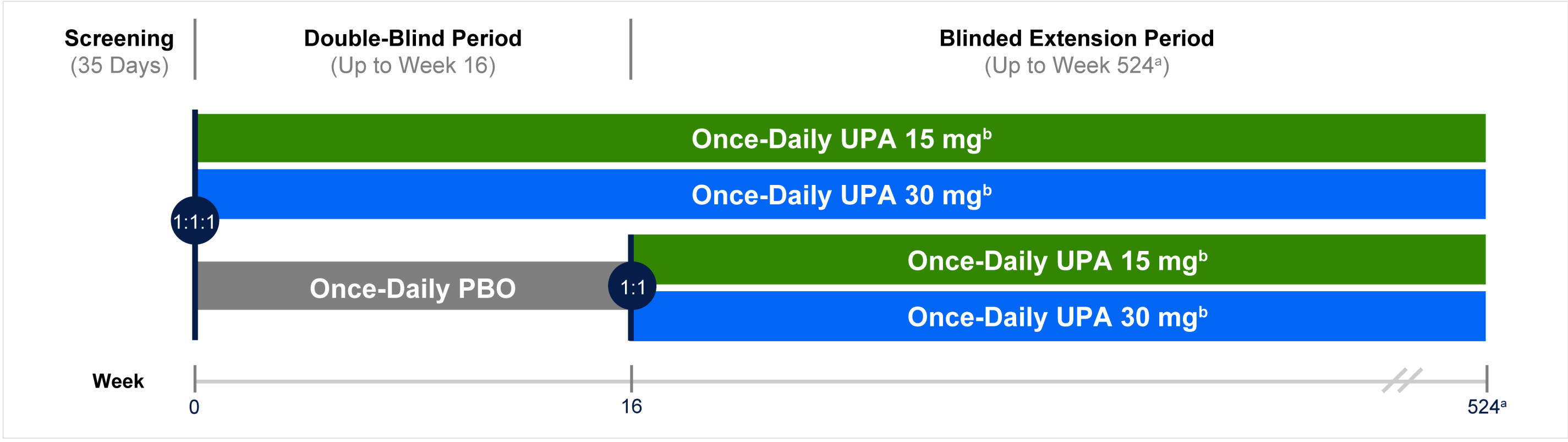
- Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense itching and skin lesions that significantly impact quality of life, sleep, and daily functioning[1,2]
- AD often begins in early childhood,[1] meaning there is a need for therapies that can provide skin clearance and relief for itch symptoms while also demonstrating long-term safety
- Upadacitinib (UPA) is a reversible, oral, selective Janus kinase inhibitor that is approved in multiple countries for the treatment of moderate-to-severe AD in adolescents and adults[3,4]
- In the phase 3 Measure Up 1 (NCT03569293), Measure Up 2 (NCT03607422), and AD Up (NCT03568318) trials, UPA demonstrated superior efficacy compared with placebo (PBO) and showed a positive benefit-risk profile in adolescents and adults with AD[3,5]
  - Treatment with UPA resulted in sustained improvements in itch, skin pain, and clearance through 188 weeks[6] and an established safety profile for up to 6 years of treatment[7]

METHODS

Study Design and Treatment

- This analysis utilized pooled data from the randomized, double-blind, multicenter, PBO-controlled, phase 3 Measure Up 1, Measure Up 2, and AD Up trials **(Figure 1)**
- The trials included adolescents (aged 12−17 years) and adults (aged 18−75 years) with moderate-to-severe AD (≥10% of body surface area, Eczema Area and Severity Index score ≥16, validated Investigator's Global Assessment for AD score ≥3, and weekly average Worst Pruritus Numerical Rating Scale ≥4)
- Following an initial screening period, patients were randomized 1:1:1 to receive once-daily double-blinded orally administered UPA 15 mg, UPA 30 mg, or PBO without (Measure Up 1 and Measure Up 2) or with (AD Up) concomitant topical corticosteroids
- After the 16-week double-blind treatment period, patients receiving UPA continued treatment with their assigned doses in the blinded extension period, while patients treated with PBO were rerandomized (1:1) to UPA 15 mg or UPA 30 mg for the blinded extension period (patients could continue treatment up to study week 524)

Figure 1. Study Design for the Measure Up 1, Measure Up 2, and AD Up Trials



PBO, placebo; UPA, upadacitinib

[a]Patients who reached study week 260 in the Measure Up 1 and Measure Up 2 trials had the opportunity to roll over into the AD Up trial and could continue their assigned treatment until study week 524

[b]Patients treated with UPA in the AD Up trial also received concomitant topical corticosteroid therapy, while patients in the Measure Up 1 and Measure Up 2 trials were treated with UPA without topical corticosteroid therapy.

RESULTS

Patients

- This integrated analysis included 2683 patients who received at least 1 dose of UPA 15 mg (n = 1337) or UPA 30 mg (n = 1346)
- Many patients included in these clinical trials had comorbidities and baseline risk factors **(Table 1)**
  - Approximately half of patients (UPA 15 mg, 54.1%; UPA 30 mg, 51.3%) had a cardiovascular risk factor, and approximately one-fifth (UPA 15 mg, 18.9%; UPA 30 mg, 19.3%) were obese (BMI ≥30 kg/m²)
- Overall, ≤5% of patients in each treatment group had prior vaccines for herpes zoster (UPA 15 mg, 3.8%; UPA 30 mg, 4.5%)

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

Characteristic, n (%)	UPA 15 mg (n = 1337)	UPA 30 mg (n = 1346)
CV risk factor[a]	723 (54.1)	691 (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)	76 (5.6)
Diabetes mellitus	27 (2.0)	27 (2.0)
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]	179 (13.4)	209 (15.5)
Number of CV risk factors[a]		
0	614 (45.9)	655 (48.7)
1	484 (36.2)	451 (33.5)
2	175 (13.1)	178 (13.2)
3	50 (3.7)	50 (3.7)
≥4	14 (1.0)	12 (0.9)
BMI ≥30 kg/m²	252 (18.9)	258 (19.3)
History of VTE	4 (0.3)	6 (0.4)
Oral contraceptive use[b]	105 (17.7)	132 (22.6)

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

Safety Overview

- With up to 7 years of treatment with UPA, overall rates of treatment-emergent adverse events (TEAEs), serious adverse events (AEs), and AEs leading to discontinuation were similar between the UPA 15 mg and UPA 30 mg treatment groups **(Table 2)**
- Rates of TEAEs leading to death were low in both UPA groups (0.1 events per 100 patient-years [E/100PY] for both groups)

Table 2. TEAE Overview in the AD Long-Term Safety Analysis

Exposure-Adjusted Event Rate, E/100PY	UPA 15 mg (n = 1337) PY = 4640.5	UPA 30 mg (n = 1346) PY = 4983.2
Any AE	212.4	237.7
Serious AE	6.7	7.6
Any AE leading to discontinuation of study drug	4.2	4.8
AEs leading to death	0.1	0.1

AD, atopic dermatitis; AE, adverse event; E/100PY, events per 100PY; PY, patient-years; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

Adverse Events of Special Interest

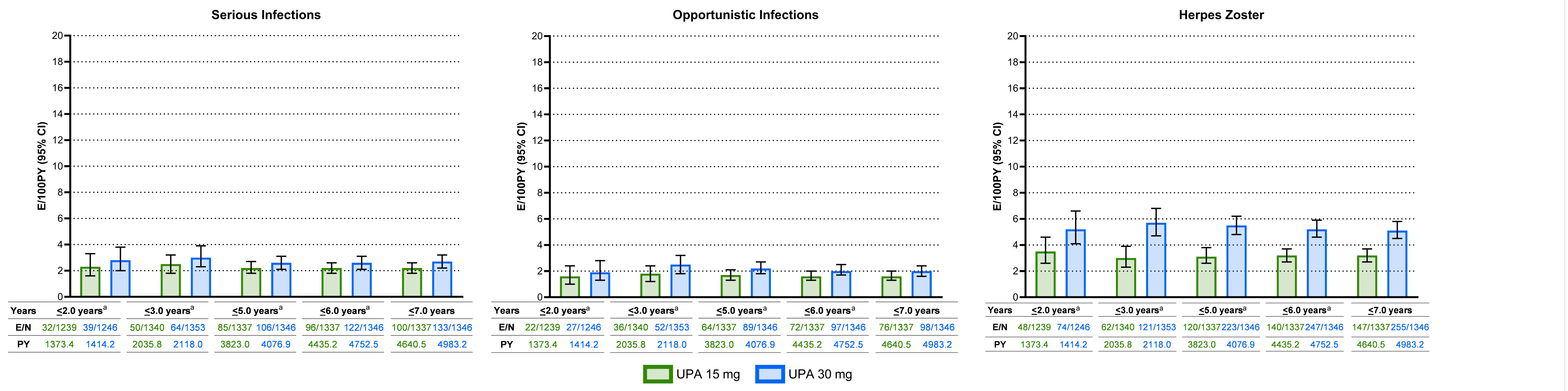
- Overall rates for TEAEs were higher with UPA 30 mg than UPA 15 mg with serious AE, and AE leading to discontinuation were generally similar between UPA 15 mg and 30 mg **(Table 3; Figures 2** and **3)**
- Up to 7 years, rates of most AESIs were similar between UPA 15 mg and UPA 30 mg, except for herpes zoster (which is known to be dose-dependent; **Table 3**)
  - Slightly higher rates of serious infections and opportunistic infections were observed with UPA 30 mg vs UPA 15 mg
  - The majority of opportunistic infections were eczema herpeticum
  - Incidence rates for malignancy excluding nonmelanoma skin cancer (NMSC), NMSC, adjudicated major adverse cardiovascular events (MACE), and adjudicated venous thromboembolism (VTE) remained low with up to 7 years of UPA treatment (≤0.5 patients per 100PY [n/100PY])
- Incidence rates of malignancy (excluding NMSC), MACE, and VTE did not exceed background incidence rates reported in the atopic dermatitis population[11-21] **(Figure 4)**

Table 3. Treatment-Emergent AESIs in Adolescents and Adults Treated With UPA for ~1 Year and up to 7 Years

Exposure Adjusted Treatment-Emergent AESIs,[b] E/100PY	~1 Year[a]		Up to 7 Years	
	UPA 15 mg (n = 1239) PY = 1373.4	UPA 30 mg (n = 1246) PY = 1414.2	UPA 15 mg (n = 1337) PY = 4640.5	UPA 30 mg (n = 1346) PY = 4983.2
Serious infections	2.3	2.8	2.2	2.7
Opportunistic infections[c]	1.6	1.9	1.6	2.0
Eczema herpeticum	1.6	1.8	1.5	1.8
Active tuberculosis	<0.1	<0.1	<0.1	<0.1
Herpes zoster	3.5	5.2	3.2	5.1
Gastrointestinal perforations[d,e]	0	0	<0.1	<0.1
NMSC[f]	0.3	0.4	0.4	0.5
Malignancy excluding NMSC[f]	0.1	0.5	0.3	0.4
Lymphoma[f]	0	<0.1	<0.1	<0.1
MACE[d,f,g]	0.1	<0.1	0.2	<0.1
VTE[d,f,h]	<0.1	<0.1	0.1	0.2

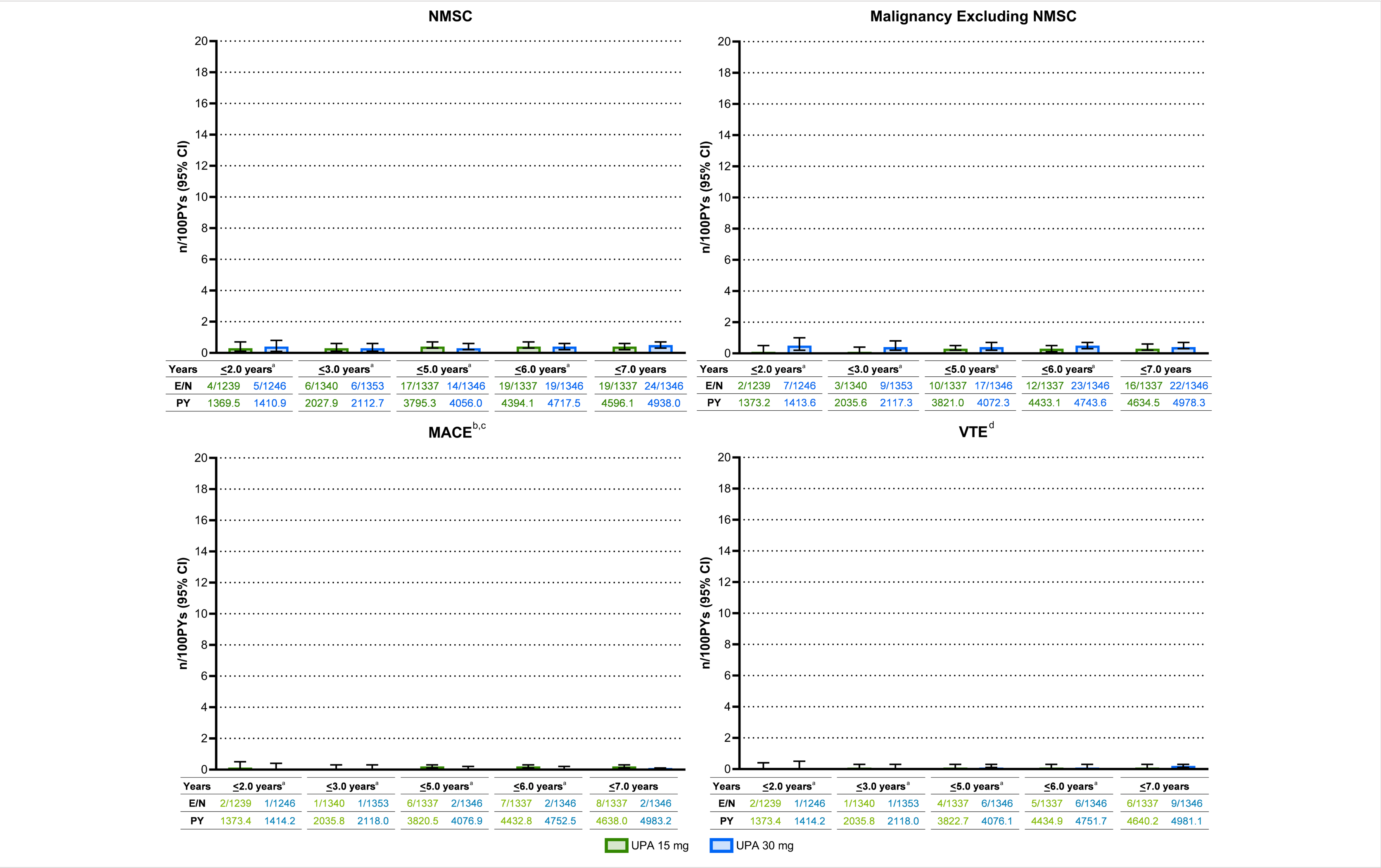
[a]Data have been previously presented.[8,9,10] [b]Lab-related AESIs are not included. [c]Excluding tuberculosis/herpes zoster. [d]Adjudicated. [e]Exposure-adjusted incidence rate. [f]n/100PY. [g]MACE was defined as CV death, nonfatal myocardial infarction, and nonfatal stroke. [h]VTE was defined as deep vein thrombosis and pulmonary embolism.
AESI, adverse events of special interest; CV, cardiovascular; E/100PY, events per 100PY; MACE, major adverse cardiovascular events; n/100PY, the number of patients with at least 1 event per 100PY; NMSC, nonmelanoma skin cancer; PY, patient-years; UPA, upadacitinib; VTE, venous thromboembolism.

Figure 2. Event Rates for Serious Infection, Opportunistic Infection, and Herpes Zoster in the AD Long-Term Safety Analysis



[a]Adapted from previously published data[8,9,10,16]
AD, atopic dermatitis; E, events; E/100PY, E per 100PY; PY, patient-years; UPA, upadacitinib.

Figure 3. Incidence Rates for NMSC, Malignancy, MACE, and VTE in the AD Long-Term Safety Analysis



[a]Adapted from previously published data[8,9,10,16] [b]Adjudicated. [c]MACE was defined as CV death, nonfatal myocardial infarction, and nonfatal stroke. [d]VTE was defined as deep vein thrombosis and pulmonary embolism.
AD, atopic dermatitis; CV, cardiovascular; E, events; MACE, major adverse cardiovascular events; n/100PY, the number of patients with at least 1 event per 100PY; NMSC, nonmelanoma skin cancer; PY, patient-years; UPA, upadacitinib; VTE, venous thromboembolism.

Figure 4. Long-Term Incidence Rates for Malignancy, MACE, and VTE for Patients Treated With UPA Relative to the Background Incidence in the AD Population

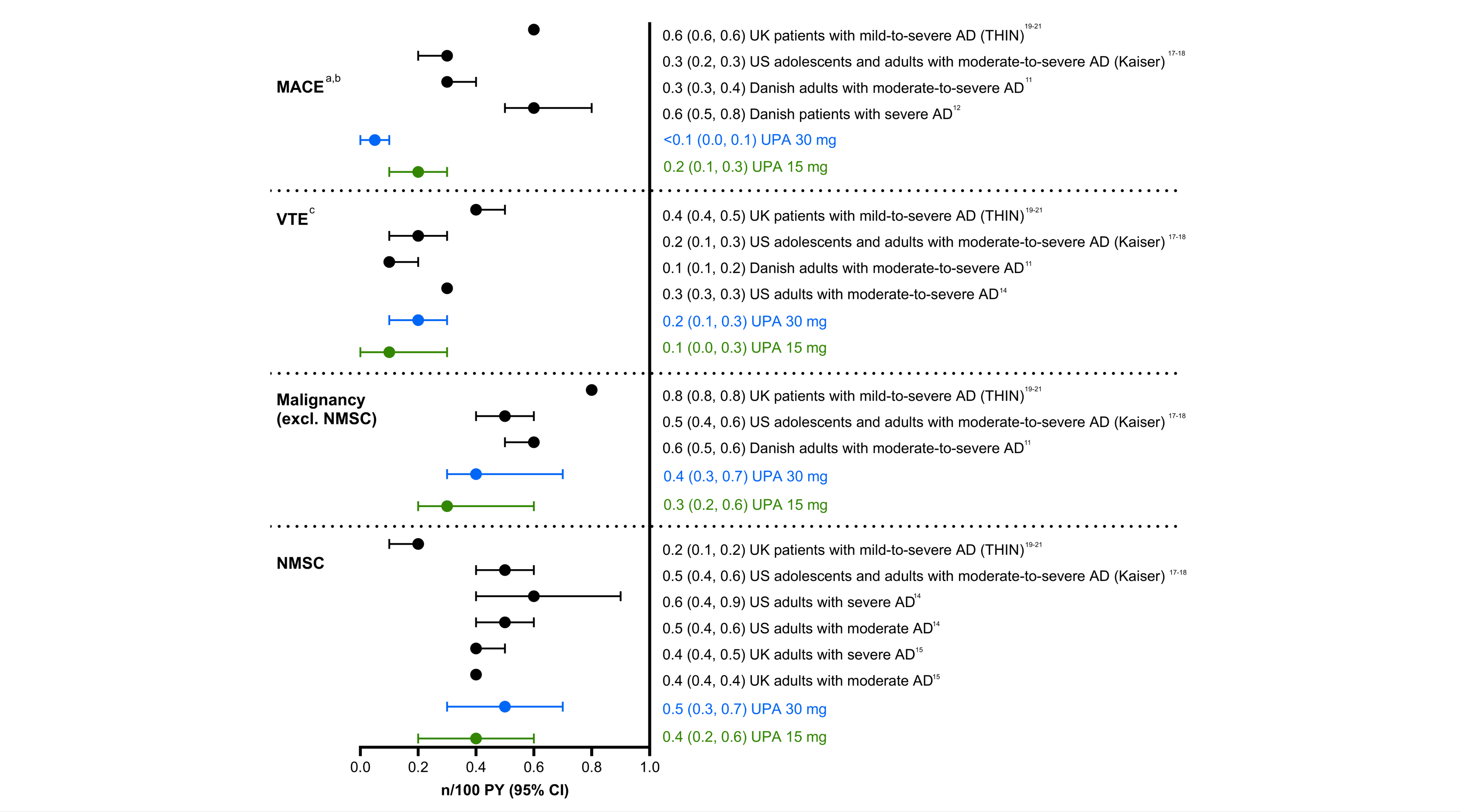


Figure adapted from previously published data[10]
[a]Adjudicated. [b]MACE was defined as CV death, nonfatal myocardial infarction, and nonfatal stroke. [c]VTE was defined as deep vein thrombosis and pulmonary embolism.
AD, atopic dermatitis; CV, cardiovascular; MACE, major adverse cardiovascular events; n/100PY, the number of patients with at least 1 event per 100 patient-years; NMSC, nonmelanoma skin cancer; UPA, upadacitinib; VTE, venous thromboembolism.
These comparisons are limited by the variability across data sources and the potential for bias in observational data.