Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for ≥156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2)

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Background: Randomized, controlled trials demonstrated efficacy and safety of apremilast for moderate-to-severe plaque psoriasis and psoriatic arthritis.

Objective: Assess long-term safety of oral apremilast in psoriasis patients.

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Methods: Safety findings are reported for 0 to ≥156 weeks from the Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) 1 and 2.

Results: The 0 to ≥156−week apremilast-exposure period included 1184 patients treated twice daily with apremilast 30 mg (1902.2 patient-years). During 0 to ≤52 weeks, the adverse events (AEs) that occurred in ≥5% of patients included diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, tension headache, and headache. From 0 to ≥156 weeks, no new AEs (affecting ≥5% of the population) were reported. AEs, serious AEs, and study drug discontinuations caused by AEs did not increase with long-term exposure. During the 0 to ≥156−week period, the rates of major cardiac events (exposure-adjusted incidence rate [EAIR] 0.5/100 patient-years), malignancies (EAIR 1.2/100 patient-years), depression (EAIR 1.8/100 patient-years), or suicide attempts (EAIR 0.1/100 patient-years) did not increase in comparison with the rates found during the 0 to ≤52−week period. No serious opportunistic infections, reactivation of tuberculosis, or clinically meaningful effects on laboratory measurements were reported.

Limitations: This study had a high dropout rate (21% of patients ongoing >156 weeks); most were unrelated to safety concerns.

Conclusions: Apremilast demonstrated an acceptable safety profile and was generally well tolerated for ≥156 weeks. (J Am Acad Dermatol 2017;77:310-7.)

Key words: apremilast; clinical trial; ESTEEM; phosphodiesterase 4 inhibitor; psoriasis; psoriatic arthritis; safety.

CAPSULE SUMMARY

- Efficacy and safety of apremilast for moderate-to-severe plaque psoriasis and psoriatic arthritis have been previously reported up to 52 weeks.
- We report long-term (3-year) safety of apremilast in patients with psoriasis.
- This information supports the favorable benefit-risk profile of apremilast for patients with psoriasis requiring long-term systemic therapy.

Psoriasis is a chronic, systemic inflammatory disease that affects 1%-3% of the world population and requires long-term management with agents that are both effective and safe.[1-3] Available therapies are often compromised by safety and tolerability issues, route of administration (injection or infusion vs oral), and the inconvenience of frequent laboratory testing and regular office visits for monitoring patients during treatment.[4-6] Safety of psoriasis treatments is particularly important in light of rates of comorbidities among patients with psoriasis, including history of major depression (16.5%), diabetes mellitus (16.5%), coronary artery disease (8.4%), and myocardial infarction (7.5%).[7]

Apremilast, approved in both the United States and Europe for the treatment of psoriasis and psoriatic arthritis, is an oral phosphodiesterase 4 (PDE4) inhibitor that works within immune cells to regulate inflammatory mediators.[8] The Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) phase 3 clinical trial program consisted of 2 randomized, placebo-controlled studies evaluating efficacy, safety, and tolerability of apremilast for the treatment of moderate-to-severe plaque psoriasis. Apremilast significantly reduced signs and symptoms and had an acceptable safety profile through week 52.[9,10] Apremilast also improves nail, scalp, and palmoplantar psoriasis; pruritus and skin discomfort; and psoriatic arthritis.[11-15] Longer-term safety of apremilast has not yet been reported. We therefore assessed the overall safety and tolerability of apremilast 30 mg twice daily for ≥156 weeks (data as of February 14, 2015) in a pooled analysis of patients with moderate-to-severe psoriasis in ESTEEM 1 (NCT01194219) and ESTEEM 2 (NCT01232283).

METHODS

Study design

ESTEEM 1 and ESTEEM 2 were similarly designed phase 3, multicenter, randomized, double-blind, placebo-controlled studies. Full details of the study designs have been previously reported.[9,10] At the end of the week 52 visit, patients were eligible to continue apremilast for up to 4 additional years. Patients provided written informed consent before study-related procedures were performed, and the protocols and consent were approved by institutional review boards or ethics committees at all investigational sites. The studies were conducted in

Abbreviations used:

AE:	adverse event
EAIR:	exposure-adjusted incidence rate
ESTEEM:	Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis
GI:	gastrointestinal
PDE4:	phosphodiesterase 4
TB:	tuberculosis

accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

Patients

Both studies enrolled adults aged ≥18 years with moderate-to-severe plaque psoriasis who were candidates for phototherapy or systemic therapy. Key exclusion criteria included other clinically significant or major uncontrolled disease, significant infection, and active or history of incompletely treated tuberculosis (TB).

Safety analysis

Safety assessments involved collection of data on adverse events (AEs), clinical laboratory tests, physical examination, and vital signs at each visit and were analyzed among the safety population (all randomized patients who received ≥1 dose of study medication). Safety outcomes were summarized descriptively. Exposure-adjusted incidence rates (EAIR) were used to assess major cardiac events, malignancies, and serious infections. EAIR per 100 patient-years is defined as 100 times the number of patients (n) reporting the event divided by patient-years (up to the first event start date for each patient reporting the event).

RESULTS

Patients

The pooled ESTEEM safety population included 1250 patients (week 0 patients treated with placebo [n = 418] or apremilast [n = 832]). A total of 1184 patients were treated with apremilast beginning at week 0 or week 16 and 249 patients (21.0%) received apremilast for ≥156 weeks. The most common reasons for study discontinuation during 0 to ≥156 weeks were lack of efficacy (34.7%) and withdrawal by patient (18.8%); 11.2% of patients discontinued because of AEs. Other reasons (each <10.0%) included loss to follow-up, noncompliance with study drug, protocol violation, other, and death. Patients in the safety population were comparable across treatment arms (Table I). Most (89.9%) had a history of ≥1 comorbid illness at baseline. Of note, >50% of patients were defined as clinically obese (baseline body mass index ≥30 kg/m^2).

There was no requirement for latent TB testing before enrollment. Patients with active TB or a history of incompletely treated TB were excluded. Seven (0.6%) patients previously treated for TB were enrolled in the ESTEEM trials. Their medical histories included latent TB (n = 4), pulmonary TB (n = 1), disseminated TB (n = 1), and TB (n = 1). Of these, 1 patient received placebo, and 1 patient with disseminated TB received placebo with subsequent apremilast. The remaining 5 patients received apremilast from baseline.

Overview of adverse events

The most common AEs were diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, tension headache, and headache (Table II). Rates for overall AEs and most common AEs (particularly diarrhea and nausea) decreased over time. Most cases of diarrhea and nausea were mild-to-moderate in severity, occurred most frequently during the first 2 weeks of apremilast treatment, and generally resolved within 4 weeks.

Rates of serious AEs were comparable across exposure periods (0 to ≤52 weeks, >52 to ≤104 weeks, >104 to ≤156 weeks, and 0 to ≥156 weeks) and did not increase with long-term apremilast exposure. Serious AEs occurring in ≥2 patients in any exposure period (0 to ≥156 weeks) included coronary artery disease (n = 6), acute myocardial infarction (n = 4), osteoarthritis (n = 4), and nephrolithiasis (n = 4). Discontinuations for AEs were few (<2% for any AE) and occurred primarily during the first few weeks of treatment. A total of 3 deaths occurred in patients receiving apremilast (1 during each year of exposure; Table II), due to cardiac failure, cerebrovascular accident, and severe mitral stenosis with congestive heart failure.

Adverse events of interest

Major cardiac events were uncommon and occurred at similar EAIRs across the 0 to ≤52–week and 0 to ≥156–week apremilast-exposure periods (0.4/100 patient-years and 0.5/100 patient-years, respectively; Table III). EAIRs for malignancies were 1.6/100 patient-years and 1.2/100 patient-years in the 0 to ≤52–week and 0 to ≥156–week apremilast-exposure periods, respectively; these included nonmelanoma skin cancers. Incidence of basal cell carcinoma was greater than that of squamous cell carcinoma, similar to what is expected in the general population.[16] EAIRs for serious infections were 0.5/100 patient-years and 0.9/100 patient-years

Table I. Baseline demographics and clinical characteristics of patients from ESTEEM 1 and 2*

Characteristic	Placebo n = 418	Apremilast 30 mg bid n = 832*	Total† N = 1184*
Age, mean (SD), years	46.3 (12.9)	45.6 (13.1)	45.9 (13.0)
Male, n (%)	294 (70.3)	553 (66.5)	805 (68.0)
White, n (%)	377 (90.2)	753 (90.5)	1071 (90.5)
Weight, mean (SD), kg	92.7 (23.0)	92.5 (21.9)	92.3 (21.8)
Body mass index, mean (SD), kg/m^2	31.1 (7.3)	31.1 (6.7)	31.0 (6.7)
Psoriasis duration, mean (SD), years	18.7 (12.3)	19.2 (12.6)	19.1 (12.5)
History of psoriatic arthritis, n (%)	63 (15.1)	164 (19.7)	215 (18.2)
Prior use of psoriasis medications			
Phototherapy, n (%)	118 (28.2)	257 (30.9)	361 (30.5)
Conventional systemic therapy, n (%)	154 (36.8)	315 (37.9)	443 (37.4)
Biologic therapy, n (%)	124 (29.7)	251 (30.2)	345 (29.1)
Comorbidities, n (%)			
Hypertension	134 (32.1)	257 (30.9)	376 (31.8)
Obesity‡	61 (14.6)	130 (15.6)	182 (15.4)
Depression	56 (13.4)	114 (13.7)	155 (13.1)
Hyperlipidemia	53 (12.7)	105 (12.6)	156 (13.2)
Type 2 diabetes	39 (9.3)	87 (10.5)	122 (10.3)

Bid, Twice a day; *BMI*, body mass index; *ESTEEM*, Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; *SD*, standard deviation.

*N indicates the total number of apremilast patients as treated, and n indicates the number of patients initially treated at week 0; actual number of patients at each end point varies.

†In total, 1184 patients were treated with apremilast beginning at week 0 or week 16. A total of 249 patients (21.0%) received apremilast for ≥156 weeks.

‡Patients with obesity who reported awareness of their obesity or had a prior clinical diagnosis of obesity from a health care professional. Obesity was not defined as a BMI of ≥30 kg/m^2.

during the 0 to ≤52–week and 0 to ≥156–week apremilast-exposure periods, respectively; these included urinary tract infection (n = 2), appendicitis (n = 3), and pneumonia (n = 2; Table III). No case of serious opportunistic infection, including clinical reactivation of TB, was reported with long-term apremilast exposure, despite inclusion of 7 patients with medical histories of TB.

At baseline, 178 (14.2%) patients reported a history of depression, and 156 (12.4%) were taking an antidepressant medication. During the placebo-controlled phase, patient-reported depression (ie, as spontaneously reported by patients and not a clinical diagnosis by a health care professional) occurred in 1.4% (12/832) of patients treated with apremilast versus 0.5% (2/418) of those receiving placebo. AEs of depression with apremilast treatment did not increase over time, with depression reported in 24 (2.0%; EAIR 2.7/100 patient-years) patients during the 0 to ≤52–week period and in 33 (2.8%; EAIR 1.8/100 patient-years) patients during the 0 to ≥156–week period. There was 1 suicide attempt with apremilast treatment (0 to ≤52 weeks), and no completed suicides in patients treated with apremilast. One patient receiving placebo in ESTEEM 1 committed suicide.

Weight change

Over the 0 to ≥156–week apremilast-exposure period, mean percent change from baseline body weight was −1.53 (Fig 1, *A*). Most patients taking apremilast for ≥156 weeks maintained body weight within 5% of baseline weight; 21.9% of patients lost >5% of their baseline body weight. The proportion of patients reporting weight loss tended to be higher among patients with higher baseline body mass index; this weight loss occurred primarily in the first year of apremilast treatment (Fig 1, *B*). The weight loss did not lead to any overt medical sequelae. Two (0.2%) patients discontinued treatment due to weight decrease. Analysis of the relationship between gastrointestinal (GI) AEs and weight loss in apremilast-treated patients revealed no association between weight loss and diarrhea, nausea, or vomiting.[10]

Laboratory parameters

Marked abnormalities and shifts outside of the normal range in clinical chemistry and hematology laboratory parameters were infrequent, reversible, and comparable across treatment groups. No clinically meaningful effects on renal function parameters were reported for 0 to ≥156 weeks.

Table II. Overview of adverse events in ESTEEM 1 and 2

	Apremilast-exposure period*					
	0 to ≤52 weeks		>52 to ≤104 weeks	>104 to ≤156 weeks	0 to ≥156 weeks	
	Apremilast 30 mg bid n = 1184; pt-yrs = 915.7		Apremilast 30 mg bid n = 654; pt-yrs = 514.6	Apremilast 30 mg bid n = 401; pt-yrs = 339.0	Apremilast 30 mg bid n = 1184; pt-yrs = 1902.2	
Patients	**n (%)**	**EAIR/100 pt-yrs**	**n (%)**	**n (%)**	**n (%)**	**EAIR/100 pt-yrs**
≥1 AE	939 (79.3)	316.9	380 (58.1)	230 (57.4)	985 (83.2)	237.5
≥1 severe AE	86 (7.3)	9.7	33 (5.0)	17 (4.2)	126 (10.6)	7.0
≥1 serious AE	58 (4.9)	6.4	36 (5.5)	18 (4.5)	106 (9.0)	5.9
AE leading to drug withdrawal	93 (7.9)	10.2	20 (3.1)	14 (3.5)	132 (11.1)	7.0
Any AE leading to death†	1‡ (0.1)	0.1	1§ (0.2)	1‖ (0.2)	3 (0.3)	0.2
AEs occurring in >5% of patients, n (%)						
Diarrhea	205 (17.3)		15 (2.3)	7 (1.7)	221 (18.7)	
Nausea	186 (15.7)		5 (0.8)	6 (1.5)	195 (16.5)	
URTI	184 (15.5)		58 (8.9)	27 (6.7)	227 (19.2)	
Nasopharyngitis	167 (14.1)		43 (6.6)	24 (6.0)	196 (16.6)	
Tension headache	106 (9.0)		8 (1.2)	5 (1.2)	115 (9.7)	
Headache	75 (6.3)		6 (0.9)	7 (1.7)	86 (7.3)	

AE, Adverse event; *bid*, twice daily; *EAIR*, exposure-adjusted incidence rate; *ESTEEM*, Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; *pt-yrs*, patient-years; *URTI*, upper respiratory tract infection.

*The data on apremilast-exposure periods (0 to ≤52 weeks, >52 to ≤104 weeks, >104 to ≤156 weeks, and 0 to ≥156 weeks [ie, beyond 3 years]) included all patients who received apremilast, regardless of when apremilast use started (week 0 or week 16).

†A 51-year-old white female patient died on day 354 from an intracranial hemorrhage, 130 days after her last dose of apremilast while in period C (weeks 32-52). This patient was considered to not be on apremilast at the time of death because of the long length of time she was off treatment, and so, this is not included herein.

‡A 30-year-old woman with a history of depression and obesity had a fatal cardiac failure on day 111.

§A 69-year-old man with a history of diabetes, hypertension, and hyperlipidemia had a fatal cerebrovascular accident on day 666 of apremilast exposure.

‖A 57-year-old woman with a history of congestive heart failure, hypertension, and coronary artery disease died of severe mitral stenosis with congestive heart failure on day 979 of apremilast exposure. EAIR per 100 patient-years is defined as 100 times the number of patients (n) reporting the event divided by patient-years (up to the first event start date for each patient reporting the event). EAIR cannot be calculated for exposure durations that do not start at week 0.

DISCUSSION

Analysis of data pooled from ESTEEM 1 and 2 allowed for a thorough characterization of apremilast safety for >3 years in patients with moderate-to-severe plaque psoriasis, many of whom had comorbid conditions typical of the general psoriasis patient population, including hypertension, obesity, and depression.[1]

In the ESTEEM studies, most AEs were mild or moderate in severity and did not lead to treatment discontinuation. Rates of AEs reported with apremilast treatment decreased with longer-term (>52 weeks) exposure. Diarrhea and nausea, which are among the most common AEs associated with oral PDE4 inhibitors,[17] were predominantly mild or moderate in severity, occurred early, and resolved within the first month. Diarrhea induced by PDE4 inhibitors is thought to be secretory. PDE4 inhibition increases intracellular levels of cyclic adenosine monophosphate, which in turn activates chloride channels in small-bowel crypts, resulting in chloride ion secretion.[18] Caffeine causes diarrhea by a similar mechanism.[19]

The nausea and vomiting induced by PDE4 inhibition is believed to arise from peripheral and central mechanisms.[20,21] Counseling patients and setting expectations before treatment initiation might increase the likelihood of treatment success, and having patients take apremilast with food could help reduce the nausea. If GI AEs require intervention, a number of nonpharmacologic and pharmacologic measures are available to manage these symptoms in the short-term, with the goal of optimizing long-term treatment outcomes. The few patients who required treatment for GI AEs in ESTEEM most commonly used loperamide or bismuth subsalicylate for diarrhea and ondansetron or prochlorperazine for nausea.[22]

Incidences of major cardiac events, malignancies, and depression did not increase with long-term apremilast exposure based on EAIR. Rates of serious infections remained low with long-term apremilast

Table III. Adverse events of interest in ESTEEM 1 and 2

	Apremilast-exposure period*			
	0 to ≤52 weeks		0 to ≥156 weeks	
	Apremilast 30 mg bid n = 1184; pt-yrs = 915.7		Apremilast 30 mg bid n = 1184; pt-yrs = 1902.2	
Patients	**n (%)**	**EAIR/100 pt-yrs**	**n (%)**	**EAIR/100 pt-yrs**
Major cardiac events	4 (0.3)	0.4	10 (0.8)	0.5
Malignancies†	15 (1.3)	1.6	23 (1.9)	1.2
Serious infections	5 (0.4)	0.5	17 (1.4)	0.9
Serious opportunistic infection	0 (0)	0	0 (0)	0
Psychiatric serious AEs				
Depression	1 (0.1)	0.1	2 (0.2)	0.1
Suicide attempts	1 (0.1)	0.1	1 (0.1)	0.1

EAIR per 100 patient-years is defined as 100 times the number of patients (n) reporting the event divided by patient-years (up to the first event start date for each patient reporting the event). EAIR cannot be calculated for exposure durations that do not start at week 0.
AE, Adverse event; *bid*, twice a day; *EAIR*, exposure-adjusted incidence rate; *ESTEEM*, Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; *pt-yrs*, patient-years.
*The apremilast-exposure periods (0 to ≤52 weeks, >52 to ≤104 weeks, >104 to ≤156 weeks, and 0 to ≥156 weeks [ie, beyond 3 years] include all patients who received apremilast regardless of when apremilast exposure started [week 0 or week 16]). Apremilast exposure is defined as the total amount of time each patient used apremilast, which includes the day of the first dose and the day of the last dose of apremilast.
†Including nonmelanoma skin cancer.

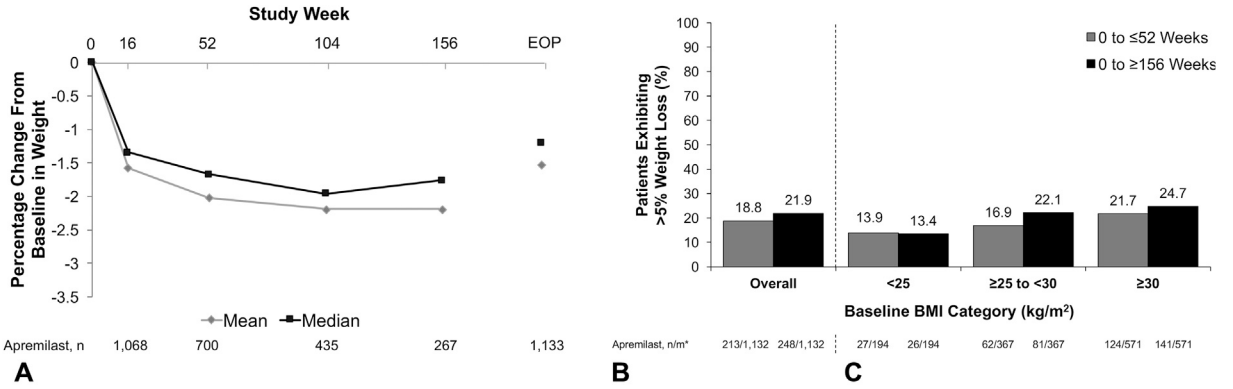

Fig 1. A, Percentage of weight change from baseline over time. **B**, Percentage of patients exhibiting >5% weight loss by apremilast-exposure period (0 to ≤52 weeks and 0 to ≥156 weeks). **C**, Percentage of patients exhibiting >5% weight loss from baseline by body mass index category (overall, <25, ≥25 to <30, and ≥30). *EOP*, End of phase; *n/m*, number of patients with weight change divided by number of patients with sufficient data. *m includes all patients who received apremilast 30 mg twice daily regardless of when apremilast exposure started (week 0 or week 16). Represents all patients who experienced weight loss at anytime during the study; some patients experienced weight loss during both study periods.

exposure with no clustering of events; there were no serious opportunistic infections or reactivations of TB infection and no clinically meaningful changes in laboratory measurements. Routine laboratory monitoring is not required during apremilast treatment, as indicated by the label.[23]

A warning for depression is included on the apremilast label because an imbalance in AEs (as spontaneously reported by patients) was noted at week 16. However, the incidence of depression did not increase with longer apremilast use. One patient receiving placebo committed suicide whereas no suicides were completed with patients on apremilast; one patient on apremilast attempted suicide. The rate of depression as an AE with apremilast is lower than the background rate in the psoriasis population (≥10%), as noted in recent reviews.[24,25]

Incidences of major cardiac events, malignancies, and infections observed with apremilast were within ranges expected for the psoriasis patient

population based on findings from other recent reports, including the international Psoriasis Longitudinal Assessment and Registry database 6-year analysis[26,27] and the US claims database 5-year analysis[28] (Supplemental Table I, available at http://jaad.org). These long-term safety analyses included patients with psoriasis receiving long-term treatment with nonbiologic systemic therapies, biologics, or phototherapy.[28] The lack of impact of apremilast on blood cell counts, serious opportunistic infections, serious infections, and malignancies suggests that apremilast does not appear to have immunosuppressive effects such as those associated with cyclosporine or tofacitinib.[29,30]

An important limitation of our study was a relatively high dropout rate (21% of patients were still ongoing at the 182-week data cutoff). Because only 11.2% of patients discontinued because of AEs, the high dropout rate does not appear to be driven by safety concerns.

Conclusions

Apremilast, an oral PDE4 inhibitor, demonstrated an acceptable safety profile and was generally well tolerated for ≥156 weeks. No new safety concerns were identified with long-term exposure in this psoriasis patient population with several comorbidities. The benefit-risk profile of apremilast, including the oral route of administration, lack of laboratory monitoring requirements during treatment, and lack of cumulative, specific organ toxicity, makes apremilast an attractive option for patients with psoriasis requiring long-term systemic therapy.

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Supplemental Table I. AEs of interest across long-term psoriasis studies

AE of interest	PSOLAR 6-year analysis,[S1] rate per 100 patient-years*	US claims 5-year analysis,[S2] rate per 100 patient-years*
MACE, total	0.36	
Infliximab	0.38	
Ustekinumab	0.33	
Other biologics	0.33	
Nonbiologics	0.45	
Malignancies (excluding NMSC), total	0.68	1.42
Infliximab	0.58	2.30
Ustekinumab	0.53	
Other biologics	0.74	0.78-1.14
Nonbiologics	0.81	1.53
Serious infection, total	1.50	
Infliximab	2.73	5.21
Ustekinumab	1.00	
Other biologics	1.80	2.88-3.25
Nonbiologics	1.26	3.32

AE, Adverse event; *MACE*, major adverse cardiovascular events; *NMSC*, nonmelanoma skin cancer; *PSOLAR*, Psoriasis Longitudinal Assessment and Registry.

*These events (reported as per 100 patient-years) were calculated by using different methods than those used to calculate the exposure-adjusted incidence rate per 100 patient-years.

[S1]Gottlieb AB, Kalb RE, Langley RG, et al. Safety observations in 12,095 patients with psoriasis enrolled in an international registry (PSOLAR): experience with infliximab and other systemic and biologic therapies. *J Drugs Dermatol*. 2014;13:1441-1448.

[S2]Kimball AB, Schenfeld J, Accortt NA, Anthony MS, Rothman KJ, Pariser D. Cohort study of malignancies and hospitalized infectious events in treated and untreated patients with psoriasis and a general population in the United States. *Br J Dermatol*. 2015;173:1183-1190.