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Long-Term Safety and Tolerability of Apremilast Versus Placebo in Psoriatic Arthritis: A Pooled Safety Analysis of Three Phase III, Randomized, Controlled Trials

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Objective. Psoriatic arthritis (PsA) requires long-term treatment, yet safety concerns and monitoring requirements make maintenance a challenge. This analysis of pooled Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) 1, 2, and 3 data describes 3-year apremilast safety and tolerability in PsA.

Methods. Patients with active PsA were randomized (1:1:1) to placebo, apremilast 30 mg twice daily, or apremilast 20 mg twice daily. Placebo patients were re-randomized to apremilast 30 mg twice daily or 20 mg twice daily at week 16 (early escape) or 24. Double-blind treatment continued to week 52; patients could continue apremilast during an open-label, long-term treatment phase.

Results. In total, 1493 patients received at least one dose of study medication and were included in the safety population (placebo: n = 495; apremilast 30 mg: n = 497; apremilast 20 mg: n = 501). Among patients receiving apremilast, 53.2% (767/1441) completed 3 years of treatment. Greater rates of adverse events (AEs) were reported with apremilast (61.1%; exposure-adjusted incidence rate [EAIR]/100 patient-years, 265.1) versus placebo (47.5%; EAIR/100 patient-years, 200.7) in the placebo-controlled period. During weeks 0 to ≤52, the most common AEs occurring in apremilast-exposed patients were diarrhea (13.9%; EAIR/100 patient-years, 18.6), nausea (12.3%; EAIR/100 patient-years, 16.0), headache (9.4%; EAIR/100 patient-years, 12.1), upper respiratory tract infection (9.1%; EAIR/100 patient-years, 11.5), and nasopharyngitis (6.2%; EAIR/100 patient-years, 7.7). Most AEs were mild/moderate with apremilast exposure ≤156 weeks. Rates of depression remained low (EAIR/100 patient-years, 1.8). Major adverse cardiac events (EAIR/100 patient-years, 0.5), malignancies (EAIR/100 patient-years, 0.9), and serious opportunistic infections (EAIR/100 patient-years, 0.0) were infrequent over the 3-year exposure period. Discontinuation rates due to AEs were low (<7.5%) across all apremilast-exposure periods. Incidences of clinically meaningful abnormalities in postbaseline laboratory values was low; most values returned to baseline levels with continued treatment and without intervention.

Conclusion. Apremilast demonstrated a favorable safety profile and was well tolerated up to 156 weeks.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic disease requiring long-term treatment to achieve continuous control of systemic inflammation and to minimize joint damage and physical disability (1–3). Rheumatologists and patients report difficulties in choosing and adhering to a treatment regimen for active PsA because of safety concerns (4,5). Many patients discontinue a prescribed conventional or biologic disease-modifying antirheumatic drug (DMARD) within 12 months in part because of adverse events (AEs) (6,7),

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and treatment is limited by concerns about long-term safety and tolerability and ongoing safety monitoring requirements due to laboratory abnormalities (4,5) as well as loss of response due to immunogenicity with biologics (8,9).

In addition, PsA has been linked to an increased risk of certain comorbidities, including cardiovascular events such as myocardial infarction (MI) and stroke (10,11), gastrointestinal (GI) diseases such as Crohn disease, ulcerative colitis, peptic ulcer disease, and irritable bowel syndrome (12), and depression (13), making cardiovascular and GI safety and risk of depression with PsA treatments important considerations when choosing treatment. Findings on the underlying risk of malignancy in PsA are limited and mixed, with comparisons of general population cohorts revealing a similar (14) or greater (15) incidence of malignancy in patients with PsA.

Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor that works within immune cells to modulate the production of multiple inflammatory mediators implicated in the pathogenesis of PsA (16). Apremilast has demonstrated efficacy and safety in the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) 1, 2, and 3 phase III studies in patients with active PsA despite prior conventional DMARDs and/or biologics, including biologic failures (limited to ≤10%) (17–19). These studies are continuing to evaluate the efficacy and safety of apremilast treatment for up to 5 years.

The current report describes the long-term safety of apremilast treatment for up to 3 years, based on a large pooled database of patients from the PALACE 1, 2, and 3 studies.

METHODS

Study design. PALACE 1 (NCT01172938), PALACE 2 (NCT01212757), and PALACE 3 (NCT01212770) are phase III, multicenter, randomized, double-blind, placebo-controlled studies with similar designs. Full details of the study designs and methods have been previously published (18–20). After the placebo-controlled period (weeks 0 to 24), all patients received apremilast 30 or 20 mg twice daily and continued double-blind treatment through week 52. Upon completion of the 52-week, double-blind period, patients were eligible to enter a long-term, open-label extension phase, for a total follow-up of up to 5 years.

Institutional review boards at each investigation site approved the study protocols in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guideline E6: Good Clinical Practice. All patients provided written informed consent before any study-related procedures were done.

Key inclusion/exclusion criteria. Adult patients (≥18 years of age) with a documented diagnosis of PsA for ≥6 months who met the Classification Criteria for Psoriatic Arthritis (CASPAR) at study entry were eligible to participate if they had at least three swollen and at least three tender joints despite past or current DMARDs. Patients with prior use of conventional DMARDs and/or biologics, including failures, were permitted, and tumor necrosis factor blocker efficacy failures were limited to 10% or fewer patients. Patients were not allowed to have therapeutic failure of more than three agents for PsA (conventional DMARDs or biologics) or more than one tumor necrosis factor blocker. Patients in PALACE 3 were required to have at least one plaque psoriasis lesion 2 cm or larger. Patients were excluded from the study if they had tuberculosis, HIV, hepatitis B or C infection, malignancies (with some exceptions), any other significant comorbidities or laboratory abnormalities, or past exposure to certain medications.

Concomitant medications. Patients taking concurrent DMARDs at baseline were allowed to continue stable doses of methotrexate (≤25 mg/wk), leflunomide (≤20 mg/d), sulfasalazine (≤2 g/d), or a combination thereof; other DMARDs or immunosuppressive systemic therapies were prohibited. A single reduction in DMARD dose was allowed after week 24. Low potency topical corticosteroids were allowed within specific parameters. Stable doses of nonsteroidal anti-inflammatory drugs (NSAIDs), narcotic analgesics, or oral corticosteroids (prednisone ≤10 mg/d or an equivalent) were permitted. After week 52, if a patient had worsening of PsA activity, the investigator could adjust or add concomitant treatment with an NSAID (change type and/or dose), conventional DMARD (add or increase dose or change route of administration [methotrexate]), or corticosteroid (intramuscular injections or short courses of oral tablets), within specific parameters. Topical therapy or phototherapy was permitted for patients with worsening skin psoriasis after week 52.

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Safety analysis. Safety outcomes were analyzed among the safety population, which included all patients who received at least one dose of study medication. Patient disposition relative to the start of apremilast treatment was provided by apremilast-exposure period, and retention rates were presented by Kaplan-Meier plots. Safety outcomes were summarized descriptively. Safety assessments included collection of AEs, clinical laboratory testing, physical examination findings, and vital signs at each visit and 12-lead electrocardiogram at screening; baseline; weeks 16, 24, and 52; and at 52-week intervals during the long-term, open-label extension phase as well as in the event of early withdrawal. Clinically meaningful changes in hematology and clinical chemistry postbaseline laboratory values were predefined and included alanine aminotransferase more than three times the upper limit of normal (ULN), aspartate aminotransferase more than three times the ULN, creatinine >1.7 × ULN, leukocytes <1.5 × 10^9/l, neutrophils <1 × 10^9/l, platelets <75 × 10^9/l, and hemoglobin <10.5 g/dl for men and <8.5 g/dl for women.

Safety data were assessed by actual exposure to placebo, apremilast 30 mg twice daily, and apremilast 20 mg twice daily. Placebo-exposure data included data through 16 weeks of exposure for placebo patients who escaped and data through 24 weeks for patients who continued on placebo until 24 weeks. Apremilast exposure data included all available apremilast treatment data for all patients who received at least one dose of apremilast. These data were assessed by length of exposure (0 to ≤52 weeks, >52 to ≤104 weeks, and >104 to ≤156 weeks). When no long-term placebo-exposure data were available for comparison, exposure-adjusted incidence rates (EAIRs) were used to assess rare instances, such as major adverse cardiac events (MACEs), malignancies, and serious infections, during 0 to ≤52, 0 to ≤104, and 0 to ≤156 weeks of exposure. EAIR/100 patient-years is defined as 100 times the number of patients (n) reporting the event divided by patients' total exposure, up to the first event start date for patients reporting the event, in years.

RESULTS

Patients. A total of 1493 patients received at least one dose of study medication and were included in the safety population (placebo: n = 495; apremilast 30 mg: n = 497; apremilast 20 mg: n = 501). Of those who were treated with apremilast, 53.2% (767/1441) completed 3 years of apremilast treatment (Figures 1 and 2). The most commonly reported reasons for discontinuation of apremilast treatment during the apremilast-exposure periods are shown in Figure 1. The five most common AEs reported as leading to discontinuation of apremilast throughout the three exposure periods were nausea (n = 24), diarrhea (n = 22), headache (n = 16), upper abdominal pain (n = 7), and vomiting (n = 7). In the weeks 0 to ≤52 period, 1441 patients received apremilast twice daily (30 mg: n = 721, patient-years = 608.7; 20 mg: n = 720, patient-years = 600.6). In the weeks >52 to ≤104 period, 1028 patients received apremilast twice daily (30 mg: n = 520, patient-years = 477.9; 20 mg: n = 508, patient-years = 459.9). During weeks >104 to ≤156 of the apremilast-exposure period, 865 patients received apremilast twice daily (30 mg: n = 443, patient-years = 424.4; 20 mg: n = 422, patient-years = 395.1).

Baseline patient demographics, disease characteristics, and prior and concurrent therapy were comparable across treatment groups (Table 1). In the overall study population, most patients (92.4%) had a history of at least one comorbid illness at baseline. The most common comorbid conditions were hypertension (40.1%), hypercholesterolemia (15.1%), depression (14.5%), gastroesophageal reflux disorder (13.0%), and obesity (11.9). In line with this pattern of comorbidities, some of the most frequently used concurrent medications were for acid-related disorders (29.8%), renin-angiotensin system antagonists (28.1%), lipid-modifying agents (20.9%), psychoanaleptics (14.7%), beta-blocking agents (13.9%), calcium channel blockers (11.1%), and medications for diabetes control (10.3%).

AE overview. During the placebo-controlled phase, 47.5% (EAIR/100 patient-years, 200.7) of patients receiving placebo, 60.8% (EAIR/100 patient-years, 272.0) of patients receiving apremilast 30 mg twice daily, and 61.5% (EAIR/100 patient-years, 258.8) receiving apremilast 20 mg twice daily reported an AE. Across all exposure periods examined, most AEs were mild to moderate in severity. During the placebo-controlled period, similar rates of serious AEs (SAEs) were observed among patients receiving either dose of apremilast compared with placebo. During weeks 0 to ≤52, 6.5% (EAIR/100 patient-years, 7.9) of patients receiving apremilast 30 mg twice daily and 5.6% (EAIR/100 patient-years, 6.8) receiving 20 mg twice daily reported an SAE; the incidence of SAEs during the longer-term apremilast-exposure periods was generally similar (Table 2).

The most common AEs occurring in 5% or more of patients in any treatment group during the placebo-controlled period were diarrhea (placebo, 2.8%; apremilast 30 mg, 16.5%; apremilast 20 mg, 12.6%), nausea (placebo, 4.6%; apremilast 30 mg, 16.1%; apremilast 20 mg, 10.0%), upper respiratory tract infection (placebo, 3.0%; apremilast 30 mg, 6.0%; apremilast 20 mg, 7.0%), and headache (placebo, 4.6%; apremilast 30 mg, 11.5%; apremilast 20 mg, 8.4%), with greater AE rates reported with apremilast treatment compared with placebo (Table 2). During weeks 0 to ≤52, AEs occurring in 5% or more of apremilast-exposed patients were diarrhea (13.9%; EAIR/100 patient-years, 18.6), nausea (12.3%; EAIR/100 patient-years, 16.0), headache (9.4%; EAIR/100 patient-years, 12.1), upper respiratory tract infection (9.1%; EAIR/100 patient-years, 11.5), and nasopharyngitis (6.2%; EAIR/100 patient-years, 7.7). Lower rates of diarrhea, nausea, and headache were observed during weeks >52 to ≤104 and >104 to ≤156 than was observed during weeks 0 to ≤52.

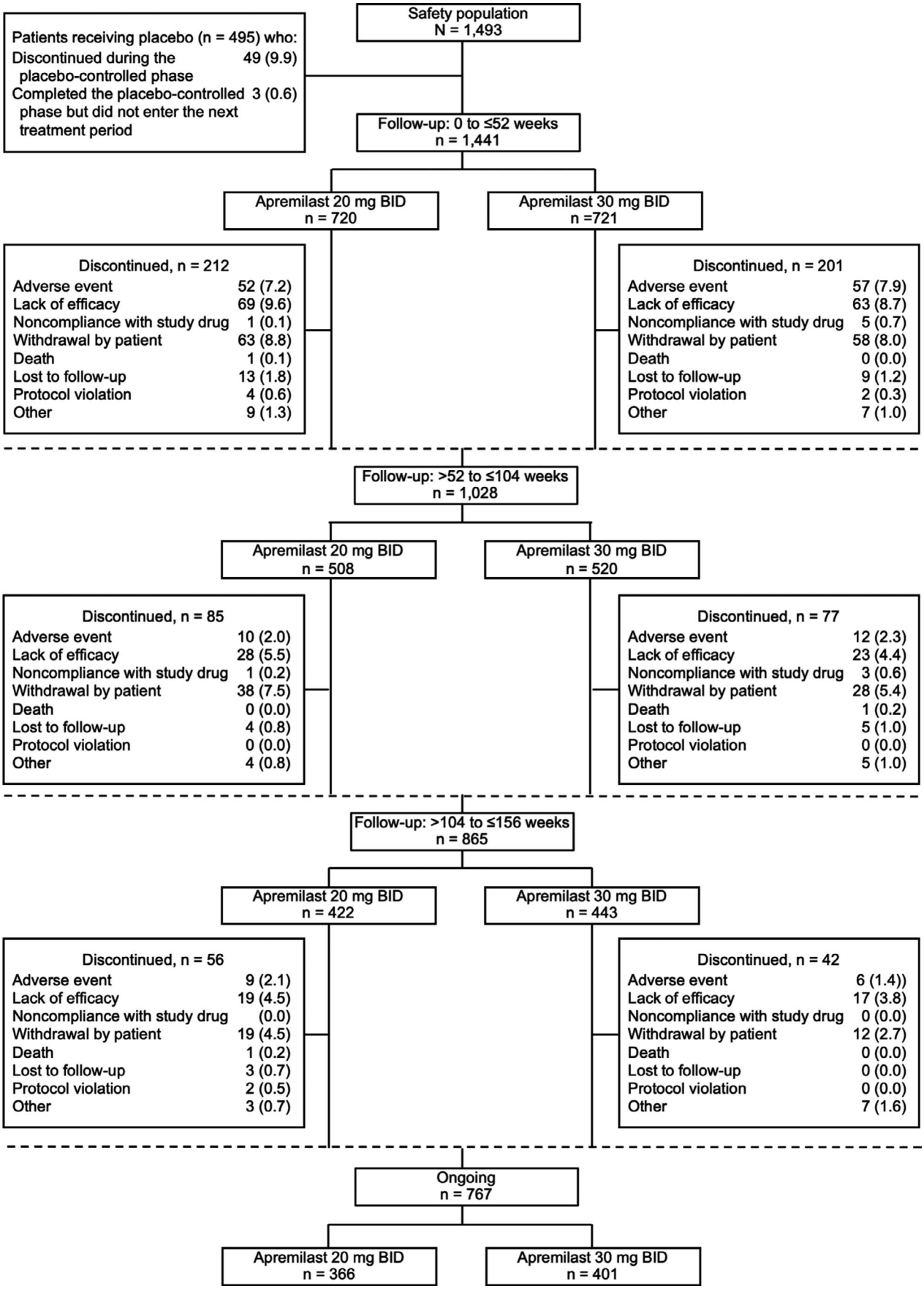
Safety population
N = 1,493
Patients receiving placebo (n = 495) who:
Discontinued during the placebo-controlled phase 49 (9.9)
Completed the placebo-controlled phase but did not enter the next treatment period 3 (0.6)
Follow-up: 0 to ≤52 weeks
n = 1,441
Apremilast 20 mg BID
n = 720
Apremilast 30 mg BID
n =721
Discontinued, n = 212
Adverse event 52 (7.2)
Lack of efficacy 69 (9.6)
Noncompliance with study drug 1 (0.1)
Withdrawal by patient 63 (8.8)
Death 1 (0.1)
Lost to follow-up 13 (1.8)
Protocol violation 4 (0.6)
Other 9 (1.3)
Discontinued, n = 201
Adverse event 57 (7.9)
Lack of efficacy 63 (8.7)
Noncompliance with study drug 5 (0.7)
Withdrawal by patient 58 (8.0)
Death 0 (0.0)
Lost to follow-up 9 (1.2)
Protocol violation 2 (0.3)
Other 7 (1.0)
Follow-up: >52 to ≤104 weeks
n = 1,028
Apremilast 20 mg BID
n = 508
Apremilast 30 mg BID
n = 520
Discontinued, n = 85
Adverse event 10 (2.0)
Lack of efficacy 28 (5.5)
Noncompliance with study drug 1 (0.2)
Withdrawal by patient 38 (7.5)
Death 0 (0.0)
Lost to follow-up 4 (0.8)
Protocol violation 0 (0.0)
Other 4 (0.8)
Discontinued, n = 77
Adverse event 12 (2.3)
Lack of efficacy 23 (4.4)
Noncompliance with study drug 3 (0.6)
Withdrawal by patient 28 (5.4)
Death 1 (0.2)
Lost to follow-up 5 (1.0)
Protocol violation 0 (0.0)
Other 5 (1.0)
Follow-up: >104 to ≤156 weeks
n = 865
Apremilast 20 mg BID
n = 422
Apremilast 30 mg BID
n = 443
Discontinued, n = 56
Adverse event 9 (2.1)
Lack of efficacy 19 (4.5)
Noncompliance with study drug (0.0)
Withdrawal by patient 19 (4.5)
Death 1 (0.2)
Lost to follow-up 3 (0.7)
Protocol violation 2 (0.5)
Other 3 (0.7)
Discontinued, n = 42
Adverse event 6 (1.4))
Lack of efficacy 17 (3.8)
Noncompliance with study drug 0 (0.0)
Withdrawal by patient 12 (2.7)
Death 0 (0.0)
Lost to follow-up 0 (0.0)
Protocol violation 0 (0.0)
Other 7 (1.6)
Ongoing
n = 767
Apremilast 20 mg BID
n = 366
Apremilast 30 mg BID
n = 401

Figure 1. Patient disposition through week 156 in apremilast patients, as treated. All patients exposed to apremilast are included, regardless of when the apremilast exposure started. For follow-up, 0 to 52 weeks or less is defined as 364 days or less, more than 52 to 104 weeks or less is defined as 365 to 728 days, and more than 104 to 156 weeks or less is defined as 729 to 1092 days. Abbreviation: BID, twice daily.

Discontinuations due to AEs during the placebo-controlled phase occurred in 4.2% of patients receiving placebo, 7.2% receiving apremilast 30 mg twice daily, and 5.6% receiving 20 mg twice daily; during weeks 0 to ≤52, 7.8% receiving apremilast 30 mg twice daily and 7.2% receiving apremilast 20 mg twice daily discontinued use because of AEs. During weeks >52 to ≤104 and >104 to ≤156, fewer patients discontinued because of AEs (Table 2).

The majority of diarrhea and nausea events occurred during the first 2 weeks of apremilast treatment (Figure 3) and resolved within 30 days. Diarrhea and nausea events were predominantly mild or moderate in severity across all apremilast-exposure periods examined. The incidence of these GI AEs was low with longer-term apremilast exposure (Table 2).

Likewise, GI AEs leading to discontinuation in more than two patients in any treatment group were infrequent with longer-term apremilast exposure (Table 3). Discontinuations due to diarrhea and nausea were low and most occurred among apremilast-treated patients during the placebo-controlled period. Among patients receiving apremilast 30 mg twice daily, one patient discontinued use because of diarrhea during weeks >52 to ≤104, and none discontinued due to diarrhea or nausea during weeks

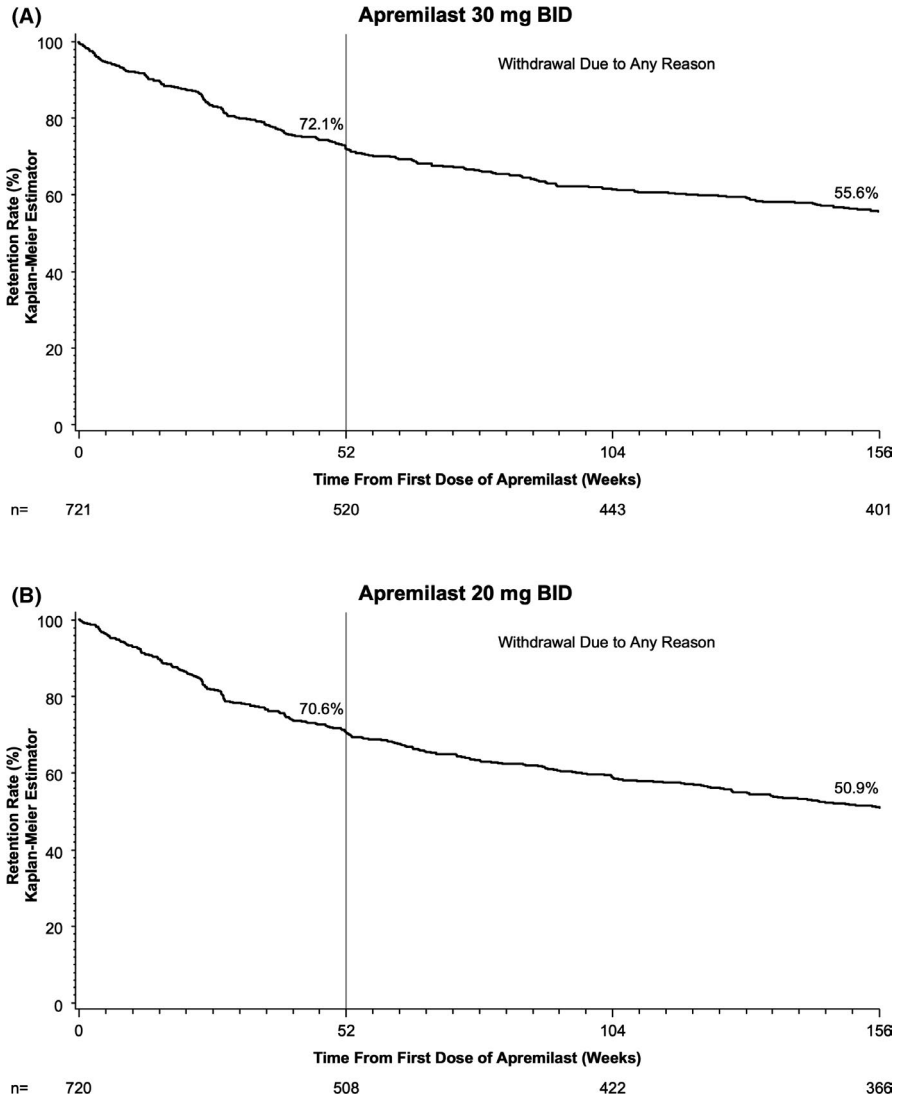

Figure 2. Withdrawal due to any reason from start of apremilast 30 mg twice daily (**A**) and apremilast 20 mg twice daily (**B**). Patients' day of withdrawal is defined as the day after their last day on apremilast. Patients who took at least one dose of apremilast and did not discontinue by week 156 are censored. The n values represent the number of patients available at the time point. Abbreviation: BID, twice daily.

Table 1. Baseline patient demographics and clinical characteristics[a]

	Placebo n = 495	Apremilast 30 mg BID n = 497	Apremilast 20 mg BID n = 501
Age, mean (SD), y	50.5 (11.6)	50.6 (11.4)	49.8 (11.7)
Female, n (%)	255 (51.5)	275 (55.3)	269 (53.7)
Race, n (%)			
White	462 (93.3)	472 (95.0)	463 (92.4)
Black	4 (0.8)	1 (0.2)	3 (0.6)
Asian	18 (3.6)	11 (2.2)	23 (4.6)
Native American, Alaskan, Hawaiian, Pacific Islander	3 (0.6)	1 (0.2)	3 (0.6)
Other	7 (1.4)	12 (2.4)	9 (1.8)
Region, n (%)			
North America	164 (33.1)	170 (34.2)	169 (33.7)
Europe	220 (44.4)	221 (44.5)	223 (44.5)
Rest of world	111 (22.4)	106 (21.3)	109 (21.8)
Weight, mean (SD), kg	86.4 (21.1)	84.5 (19.6)	86.1 (21.2)
Body mass index, mean (SD), kg/m^2	30.0 (6.5)	29.7 (6.2)	30.1 (6.8)
PsA clinical features, mean (SD)			
PsA duration, years	7.3 (7.3)	7.5 (7.8)	7.6 (7.7)
SJC (0-76)	11.0 (8.0)	11.6 (8.2)	11.4 (8.9)
TJC (0-78)	19.9 (14.8)	21.9 (15.2)	21.1 (16.4)
MASES (0-13)	3.1 (3.5)	3.0 (3.4)	2.9 (3.4)
Dactylitis severity score (0-20)	1.4 (2.7)	1.5 (2.7)	1.4 (2.8)
CDAI score (0-76)	26.6 (11.8)	27.6 (11.5)	26.7 (12.0)
DAS-28 (CRP)	4.7 (1.1)	4.7 (1.0)	4.6 (1.1)
CRP, mg/dl	1.03 (1.43)	0.96 (1.40)	0.98 (1.73)
Psoriasis duration, years	17.1 (13.4)	17.4 (13.0)	17.2 (13.5)
PASI score (0-72)[b]	8.4 (8.8)	8.3 (7.9)	7.5 (6.9)
Psoriasis-involved BSA, %	7.8 (15.5)	7.3 (13.3)	6.8 (11.9)
PsA treatment patterns, n (%)			
Prior use of conventional DMARDs only	375 (75.8)	382 (76.9)	383 (76.4)
Prior use of biologics	112 (22.6)	107 (21.5)	115 (23.0)
TNF inhibitor	104 (21.0)	98 (19.7)	108 (21.6)
Prior biologic therapeutic failures	39 (7.9)	35 (7.0)	42 (8.4)
Baseline conventional DMARD use	325 (65.7)	319 (64.2)	329 (65.7)
Methotrexate (mean dose, 15.4 mg/wk)	276 (55.8)	261 (52.5)	277 (55.3)
Leflunomide (mean dose, 18.1 mg/d)	33 (6.7)	38 (7.6)	39 (7.8)
Sulfasalazine (mean dose, 1.96 g/d)	45 (9.1)	46 (9.3)	44 (8.8)
Baseline corticosteroid use	48 (9.7)	64 (12.9)	95 (19.0)
Baseline NSAID use	340 (68.7)	355 (71.4)	360 (71.9)

Abbreviations: BID, twice daily; BSA, psoriasis-involved body surface area; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS-28, 28-item Disease Activity Score; DMARD, disease-modifying antirheumatic drug; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; NSAID, nonsteroidal anti-inflammatory drug; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count; TNF, tumor necrosis factor.
[a] The n reflects the number of patients who received at least one dose of the study medication; actual number of patients with data available for each parameter may vary.
[b] Examined among patients with psoriasis involvement of the BSA of at least 3% at baseline who had data at baseline.

>104 to ≤156. Among patients receiving apremilast 20 mg twice daily, none discontinued because of diarrhea or nausea during weeks >52 to ≤104, and one discontinued due to diarrhea during weeks >104 to ≤156.

Fewer than 2% of patients experienced an AE of weight decrease during the apremilast-exposure periods (apremilast 30 mg: weeks 0 to ≤52, 13/721 [1.8%], weeks >52 to ≤104, 1/520 [0.2%], weeks >104 to ≤156, 1/443 [0.2%]; apremilast 20 mg: weeks 0 to ≤52, 9/720 [1.3%], weeks >52 to ≤104, 2/508 [0.4%], weeks >104 to ≤156, 0/422 [0.0%]). During the placebo-controlled period, 22.1% of patients treated with apremilast with weight loss greater than 5% experienced AEs of diarrhea, 14.5% experienced nausea, and 2.3% experienced vomiting.

During weeks 0 to ≤52, the mean percent change from baseline weight (kg) was –1.03% in patients receiving apremilast 30 mg twice daily, with similar weight change observed with apremilast 20 mg twice daily; weight change was generally similar for the apremilast-exposure periods (weeks >52 to ≤104 and weeks >104 to ≤156) (Table 4). Most patients maintained their weight within 5% of baseline during each of the three long-term apremilast-exposure periods. Results with apremilast 20 mg twice daily were similar (Table 4).

Table 2. Overview of adverse events

AE Overview, n (%)	Placebo n = 495	EAIR/ 100 pt-yrs	Placebo-Controlled Period[a] Weeks 0 to 24 Apremilast 30 mg BID n = 497	EAIR/ 100 pt-yrs	Apremilast 20 mg BID n = 501	EAIR/ 100 pt-yrs	Apremilast-Exposure Period[b] Weeks 0 to ≤52 Apremilast 30 mg BID n = 721	EAIR/ 100 pt-yrs	Apremilast 20 mg BID n = 720	EAIR/ 100 pt-yrs	Weeks >52 to ≤104 Apremilast 30 mg BID n = 520	EAIR/ 100 pt-yrs	Apremilast 20 mg BID n = 508	EAIR/ 100 pt-yrs	Weeks >104 to ≤156 Apremilast 30 mg BID n = 443	EAIR/ 100 pt-yrs	Apremilast 20 mg BID n = 422	EAIR/ 100 pt-yrs
Any AE	235 (47.5)	200.7	302 (60.8)	272.0	308 (61.5)	258.8	524 (72.7)	194.9	507 (70.4)	178.5	316 (60.8)	109.1	325 (64.0)	120.2	284 (64.1)	112.6	272 (64.5)	114.2
Any SAE	19 (3.8)	11.5	19 (3.8)	9.2	17 (3.4)	8.0	47 (6.5)	7.9	40 (5.6)	6.8	35 (6.7)	7.5	39 (7.7)	8.8	40 (9.0)	9.8	33 (7.8)	8.6
Any AE leading to study drug withdrawal	21 (4.2)	12.5	36 (7.2)	17.4	28 (5.6)	13.3	56 (7.8)	9.3	52 (7.2)	8.7	13 (2.5)	2.7	11 (2.2)	2.4	7 (1.6)	1.7	9 (2.1)	2.3
Any AE leading to death	0 (0.0)	0.0	0 (0.0)	0.0	1[c] (0.2)	0.5	0 (0.0)	0.0	1[c] (0.1)	0.2	1[d] (0.2)	0.2	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
AEs reported by ≥5% of patients in any treatment group, n (%)																		
Diarrhea	14 (2.8)	8.5	82 (16.5)	45.0	63 (12.6)	32.8	112 (15.5)	20.9	88 (12.2)	16.2	20 (3.8)	4.3	10 (2.0)	2.2	12 (2.7)	2.9	13 (3.1)	3.3
Nausea	23 (4.6)	14.0	80 (16.1)	43.3	50 (10.0)	25.5	108 (15.0)	19.8	69 (9.6)	12.3	11 (2.1)	2.3	8 (1.6)	1.8	10 (2.3)	2.4	4 (0.9)	1.0
URTI	15 (3.0)	9.1	30 (6.0)	14.8	35 (7.0)	17.1	60 (8.3)	10.4	71 (9.9)	12.7	27 (5.2)	5.8	40 (7.9)	9.1	24 (5.4)	5.8	30 (7.1)	7.9
Headache	23 (4.6)	14.1	57 (11.5)	29.5	42 (8.4)	21.2	75 (10.4)	13.3	61 (8.5)	10.8	17 (3.3)	3.6	14 (2.8)	3.1	12 (2.7)	2.9	11 (2.6)	2.8
Nasopharyngitis	13 (2.6)	7.8	20 (4.0)	9.8	2 (4.4)	10.6	41 (5.7)	7.0	48 (6.7)	8.3	31 (6.0)	6.7	29 (5.7)	6.5	20 (4.5)	4.8	30 (7.1)	7.9

Abbreviations: AE, adverse event; BID, twice daily; EAIR, exposure-adjusted incidence rate; pt-yrs, patient-years; SAE, serious adverse event; URTI, upper respiratory tract infection.
[a] Includes data up to week 16 for early escaped placebo patients and up to week 24 for all other patients.
[b] Includes all patients who received apremilast during the exposure interval, relative to the start of apremilast administration.
[c] Multiorgan failure not suspected to be treatment related.
[d] Motor vehicle accident on study day 489.

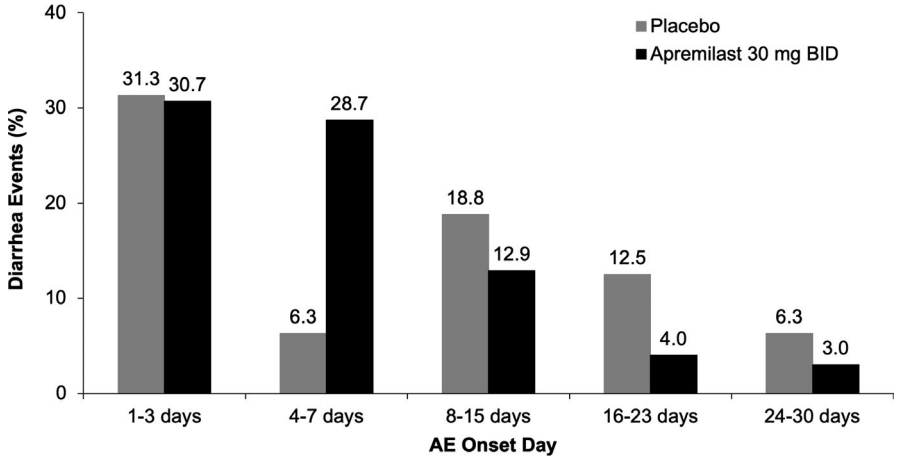

Figure 3. Time to onset of diarrhea with apremilast 30 mg twice daily (versus placebo). Percentages in each category of onset are based on the total number of events in each treatment group. Patients who received placebo and then switched to apremilast could contribute events to both treatment groups. Data after day 30 are not displayed. Abbreviations: AE, adverse event; BID, twice daily.

Other AEs of interest. Overall, serious infection rates during the placebo-controlled phase were low among patients receiving apremilast 30 mg twice daily (0.6%) and placebo (0.4%). No patients receiving apremilast 20 mg twice daily reported a serious infection during the placebo-controlled period. During each of the three apremilast-exposure periods, rates of serious infections remained low (≤1.6%) in patients receiving either dose of apremilast.

A serious opportunistic infection (cause unknown) occurred in one patient receiving placebo (ie, suppurative tenosynovitis) during weeks 0 to 24. No serious opportunistic infections were experienced with apremilast 30 mg twice daily up to 156 weeks. One (0.2%) patient, a 60-year-old female who received 20 mg of apremilast twice daily, experienced a serious opportunistic infection (*Herpes zoster* limited to one dermatome) during weeks >104 to ≤156. The event was rated as mild in severity.

No cases of tuberculosis (new or reactivation) were reported with either apremilast dose, despite study sites in areas with endemic tuberculosis, such as South Korea, South Africa, and the Russian Federation (21), and also despite enrollment of patients with a tuberculosis-related medical history (terms reported: latent tuberculosis, n = 12; pulmonary tuberculosis, n = 5; and other tuberculosis, n = 6).

AEs of depressed mood and depression during the placebo-controlled period were reported in zero (0.0%) and four (0.8%) patients receiving placebo, one (0.2%) and four (0.8%) receiving apremilast 30 mg twice daily, and one (0.2%) and eight (1.6%) receiving apremilast 20 mg twice daily, respectively.

During weeks 0 to ≤52, AEs of depressed mood and depression were reported in 4 (0.6%) and 7 (1.0%) patients receiving apremilast 30 mg twice daily, and 2 (0.3%) and 17 (2.4%) patients receiving apremilast 20 mg twice daily, respectively. A history of depression and/or bipolar disorder was present among patients receiving apremilast 30 mg twice daily (n = 73 [14.7%]) and 20 mg twice daily (n = 84 [16.8%]). No increase in the rates of depression or depressed mood was observed with longer-term apremilast exposure.

Table 3. GI AEs leading to discontinuation in more than two patients

	Placebo-Controlled Period[a]			Apremilast-Exposure Period[b]					
	Weeks 0 to 24			Weeks 0 to ≤52		Weeks >52 to ≤104		Weeks >104 to ≤156	
		Apremilast		Apremilast		Apremilast		Apremilast	
Patients[c], n (%)	Placebo n = 495	30 mg BID n = 497	20 mg BID n = 501	30 mg BID n = 721	20 mg BID n = 720	30 mg BID n = 520	20 mg BID n = 508	30 mg BID n = 443	20 mg BID n = 422
Any GI AE	6 (1.2)	25 (5.0)	13 (2.6)	35 (4.9)	19 (2.6)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Diarrhea	3 (0.6)	11 (2.2)	5 (1.0)	14 (1.9)	6 (0.8)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Nausea	3 (0.6)	13 (2.6)	7 (1.4)	16 (2.2)	8 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	3 (0.6)	1 (0.2)	6 (0.8)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upperabdominal pain	0 (0.0)	2 (0.4)	1 (0.2)	3 (0.4)	4 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE, adverse event; BID, twice daily; GI, gastrointestinal.
[a] Includes data up to week 16 for early escaped placebo patients and up to week 24 for all other patients.
[b] Includes all patients who received apremilast during the exposure interval, relative to the start of apremilast administration.
[c] Patients are counted under each AE that led to apremilast discontinuation.

Table 4. Weight change from baseline in the apremilast-exposure period[a]

	Apremilast					
	Weeks 0 to ≤52		Weeks >52 to ≤104		Weeks >104 to ≤156	
	30 mg BID n = 721	20 mg BID n = 720	30 mg BID n = 520	20 mg BID n = 508	30 mg BID n = 443	20 mg BID n = 422
Weight change from baseline, mean, kg[b]	−0.92	−1.20	−1.32	−1.36	−1.31	−1.14
Percent weight change from baseline, mean, kg[b]	−1.03	−1.26	−1.44	−1.30	−1.37	−1.09
Patients with ≥5% change in weight from baseline, n/m[c] (%)[b]						
>5% loss from baseline	99/711 (13.9)	103/708 (14.5)	123/517 (23.8)	117/501 (23.4)	99/441 (22.4)	100/419 (23.9)
>5% gain from baseline	36/711 (5.1)	27/708 (3.8)	44/517 (8.5)	58/501 (11.6)	46/441 (10.4)	57/419 (13.6)

Abbreviation: BID, twice daily.
[a] Includes all patients who received apremilast during the exposure interval, relative to the start of apremilast administration.
[b] Data include the last postbaseline value during the exposure interval, including data up to 28 days after the last dose of apremilast (including the observational follow-up visit).
[c] n/m indicates the number of patients with 5% or greater change (loss or gain) in weight from baseline/number of patients with postbaseline weight data available during the exposure interval, including data up to 28 days after the last dose of apremilast (including the observational follow-up visit).

No patients receiving placebo (0/495) or apremilast 30 mg twice daily (0/497) experienced suicidal ideation or suicide attempt during the placebo-controlled period; instances of suicidal ideation (n = 1) and suicide attempt (n = 1) were observed in 0.4% (2/501) of patients receiving apremilast 20 mg twice daily. No additional AEs of suicidal ideation or suicide attempt occurred in patients receiving apremilast 20 mg twice weekly during weeks 0 to ≤52, and neither of these AEs was reported in any patient receiving apremilast 30 mg twice daily during this apremilast treatment period.

During weeks >52 to ≤104, a patient receiving apremilast 30 mg twice daily with a history of depression, bipolar affective disorder, and physical/emotional abuse attempted suicide (1/520 [0.2%]), and a patient receiving apremilast 20 mg twice daily experienced suicidal ideation (1/508 [0.2%]). Neither of these AEs was observed in any patient during weeks >104 to ≤156.

Rates (EAIRs/100 patient-years of apremilast exposure) of malignancies were low across the apremilast dose groups throughout the 156-week exposure period (weeks 0 to ≤52: 0.6; weeks 0 to ≤104: 0.7; weeks 0 to ≤156: 0.9) (Supplementary Table 1).

MACEs were defined to include sudden unwitnessed death, cardiovascular death (ie, sudden cardiac death, death due to MI, heart failure, stroke, or other cardiovascular death), MI, and stroke. Overall, across both apremilast dose groups, EAIRs per 100 patient-years of apremilast exposure for adjudicated MACEs were low and remained consistent through weeks 0 to ≤52 (0.2), weeks 0 to ≤104 (0.4), and weeks 0 to ≤156 (0.5). MI and acute MI were the most frequently reported events over 156 weeks (n = 9), with five occurring in patients 65 years of age and older; relevant medical history for cardiac disorders included coronary artery disease. Other MACEs that occurred during the 156 weeks of apremilast exposure were ischemic stroke (n = 2; 0.1 EAIR/100 patient-years), cerebrovascular accident (n = 1; 0.0 EAIR/100 patient-years), cerebral infarction (n = 1; 0.0 EAIR/100 patient-years), and brain stem stroke (n = 1; 0.0 EAIR/100 patient-years) (Supplementary Table 1).

Table 5. Clinically meaningful abnormalities in select clinical laboratory variables in the apremilast-exposure period[a]

	Apremilast					
	Weeks 0 to ≤52		Weeks >52 to ≤104		Weeks >104 to ≤156	
Patients, n/m[b] (%)	30 mg BID n = 721	20 mg BID n = 720	30 mg BID n = 520	20 mg BID n = 508	30 mg BID n = 443	20 mg BID n = 422
ALT >3x ULN	9/713 (1.3)	8/713 (1.1)	2/518 (0.4)	1/502 (0.2)	2/442 (0.5)	2/419 (0.5)
AST >3x ULN	4/713 (0.6)	4/713 (0.6)	1/518 (0.2)	1/502 (0.2)	3/442 (0.7)	3/419 (0.7)
Creatinine >1.7x ULN	1/713 (0.1)	1/713 (0.1)	0/518 (0.0)	0/502 (0.0)	0/442 (0.0)	1/419 (0.2)
Leukocytes <1.5, 10^9/l	0/713 (0.0)	0/712 (0.0)	0/517 (0.0)	0/503 (0.0)	0/442 (0.0)	0/419 (0.0)
Neutrophils <1, 10^9/l	2/713 (0.3)	4/712 (0.6)	3/517 (0.6)	2/502 (0.4)	2/442 (0.5)	1/419 (0.2)
Platelets <75, 10^9/l	0/713 (0.0)	0/712 (0.0)	0/517 (0.0)	1/503 (0.2)	1/441 (0.2)	1/419 (0.2)
Hemoglobin <10.5 g/dl male, <8.5 g/d female	5/713 (0.7)	5/712 (0.7)	4/517 (0.8)	0/503 (0.0)	5/442 (1.1)	2/419 (0.5)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily.
[a] Represents all patients who received apremilast during the exposure interval, relative to the start of apremilast administration.
[b] Represents the number of patients with one or more occurrences of the abnormality at any time point/number of patients with one or more postbaseline values.

During all three apremilast-exposure periods, few patients experienced clinically meaningful abnormalities in hematology and clinical chemistry postbaseline laboratory values, and most values returned to baseline with continued treatment. Additionally, observed clinically meaningful abnormalities in laboratory values had no meaningful treatment or dose effect (Table 5). Most patients exhibited values within the normal range at baseline for all laboratory parameters evaluated, including neutrophils, leukocytes, and platelets, and the majority of patients continued to maintain values within the normal range for all parameters throughout longer-term apremilast exposure to 156 weeks or fewer. Clinically important shifts in patients with normal baseline laboratory values were infrequent (Supplementary Table 2). Longer-term apremilast exposure lacked new safety signals and was consistent with previously reported safety results up to week 52 (17–19).

DISCUSSION

Based on the analysis of clinical trial cohorts of patients with active PsA (N = 1493), apremilast demonstrated an acceptable safety profile and was generally well tolerated for up to 156 weeks in the PALACE 1, 2, and 3 studies.

As with other PDE4 inhibitors, apremilast was associated with GI AEs of predominantly mild or moderate diarrhea and nausea among patients in the PALACE safety population. The events tended to occur within the first 2 weeks of treatment and, with continued treatment, resolved within 30 days. The mechanism of diarrhea is thought to be related to PDE4 inhibition and increased cyclic adenosine monophosphate levels, which lead to the activation of membrane chloride channels (22) and subsequent fluid secretion in the gut, resulting in diluted digested products and watery diarrhea (23). Similarly, increases in cyclic adenosine monophosphate occurring centrally in neurons of the area postrema within the central nervous system, which controls emesis (24), and peripherally in gastric mucosal parietal cells, which subsequently increase gastric acid secretion, are thought to contribute to the mechanism of nausea related to PDE4 inhibition (25). If patients develop severe diarrhea, nausea, or vomiting with apremilast use, a dose reduction or suspension of apremilast should be considered, as noted in package labeling.

During the placebo-controlled period, 4.6% of patients receiving placebo, 12.3% receiving apremilast 30 mg twice daily, and 14.0% receiving apremilast 20 mg twice daily experienced weight loss greater than 5%. Of these patients, 4.3%, 24.6%, and 20.0% experienced diarrhea, 4.3%, 9.8%, and 18.6% experienced nausea, and 0.0%, 3.3%, and 1.4% experienced vomiting, respectively. During the long-term apremilast-exposure period, approximately 20% of patients experienced weight loss greater than 5%. Weight loss was not associated with GI AEs of diarrhea or nausea and was not linked to major consequences typically associated with abnormal or severe weight loss. Weight loss observed with apremilast in the current analyses was consistent with that observed in the ESTEEM phase III studies in patients with moderate to severe plaque psoriasis. Inhibition of PDE4 increases plasma levels of glucagon-like peptide-1 (GLP-1) (26), which stimulates insulin secretion and inhibits glucagon secretion (27). GLP-1 mimetics are used in the treatment of type 2 diabetes and are associated with weight loss (28), and a GLP-1–related mechanism may account for the weight loss documented with PDE4 inhibitors, including apremilast. As per guidance in apremilast package labeling, if unexplained or clinically significant weight loss occurs, weight loss should be evaluated and discontinuation of apremilast should be considered.

Although depression has been reported as an AE with PDE4 inhibitors (29), rates of depression in this analysis were not elevated when compared with rates seen in patients with PsA (13). Attempted suicide and suicidal ideation during the long-term exposure period were rare. According to data from the 2008 National Survey on Drug Use and Health, 3.7% of individuals 18 years of age or older in the United States had thoughts of suicide, 1.0% had made plans to commit suicide, and 0.5% had attempted suicide (30).

Concerns with long-term treatment options for PsA include serious opportunistic infections, MACEs, and malignancies. In this analysis, rates for these events were low, with no increase over long-term exposure. MACEs and malignancy rates were aligned with those in the general PsA population (31). Background incidence rates per 100 patient-years of 0.39 for acute MI and 0.32 for stroke have been reported in a cohort of PsA patients in a large US claims database analysis (31).

Rates of overall malignancy reported in the literature vary depending on the approach used in capturing and verifying such events. An incidence of 0.56 per 100 patient-years in PsA patients was reported in an analysis of the CORRONA database (32), and a 0.98 standardized incidence rate was reported in a cohort from the University of Toronto Psoriatic Arthritis Clinic (14).

Breast cancer and nonmelanoma skin cancer were reported in 3 and 11 patients, respectively, with EAIRs in the expected range; background incidence rates per 100 patient-years of 0.20 for breast cancer and 0.21 for nonmelanoma skin cancer have been reported in the CORRONA analysis (32). Most other cancer types were reported in one patient each in the current analysis. Also consistent with the CORRONA analysis (32), patients 65 years of age or older in the current analysis had slightly higher rates of malignancy overall, but there were a limited number of events (n = 5) and only one case for each of the cancer types encountered.

Despite the availability of DMARD and biologic treatments for patients with active PsA, a desire still exists for long-term therapy that does not require routine laboratory monitoring or temporary or permanent discontinuation due to laboratory abnormalities or tolerability issues. The current analysis further demonstrates that discontinuations of apremilast treatment due to AEs remains low over time and routine laboratory monitoring may not be required; clinically meaningful abnormalities were infrequent and transient,

and most patients maintained laboratory parameters within the normal range across all three apremilast-exposure periods.

The studies discussed in the current analysis did not include a long-term placebo-controlled arm; therefore, it is not possible to assess the long-term rates of AEs within this study for patients not on apremilast. Because of the controlled setting associated with clinical trials, and the limited comorbidities and biologic failures in the PALACE population, results from our analyses may not be easily interpreted to PsA patients in the general community. Data on the efficacy and safety of apremilast in the real-world setting are providing insight into the use of apremilast in the general population (33,34).

In conclusion, this pooled safety analysis of patients with active PsA demonstrates that long-term treatment with apremilast is generally safe and well tolerated, with no need for routine laboratory monitoring; no new safety concerns were identified with long-term treatment.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual contact, and all authors approved the final version to be published. Dr. Mease had full access to all of the data in the pooled study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Mease, Gladman.

Acquisition of data. Mease, Gladman, Gomez-Reino, Hall, Kavanaugh, Lespessailles, Schett, Paris, Delev, Teng, Wollenhaupt.

Analysis and interpretation of data. Mease, Gladman, Gomez-Reino, Hall, Kavanaugh, Lespessailles, Schett, Paris, Delev, Teng, Wollenhaupt.

REFERENCES

1. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med 2017;376:957–70.
2. Gladman D, Antoni C, Mease P, Clegg D, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis 2005;64 Suppl 2:ii14-17.
3. Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Acsta-Felquer ML, Armstrong AW, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis: treatment recommendations for psoriatic arthritis 2015. Arthritis Rheumatol 2016;68:1060–71.
4. Lebwohl MG, Kavanaugh A, Armstrong AW, Van Voorhees AS. US perspectives in the management of psoriasis and psoriatic arthritis: patient and physician results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey. Am J Clin Dermatol 2016;17:87–97.
5. Van de Kerkhof PC, Reich K, Kavanaugh A, Bachelez H, Barker J, Girolomoni G, et al. Physician perspectives in the managment of psoriasis and psoriatic arthritis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis survey. J Eur Acad Dermatol Venereol 2015;29:2002–10.
6. Saad AA, Ashcroft DM, Watson KD, Hyrich KL, Noyce PR, Symmons DP. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. Arthritis Res Ther 2009;11:R52.
7. Nikiphorou E, Negoescu A, Fitzpatrick JD, Goudie CT, Badcock A, Östör AJ, et al. Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: a retrospective review of discontinuation rates from a large UK cohort. Clin Rheumatol 2014;33:609–14.
8. Merola JF, Lockshin B, Mody EA. Switching biologics in the treatment of psoriatic arthritis. Semin Arthritis Rheum 2017;47:29–37.
9. Sozzani S, Abbracchio MP, Annese V, Danese S, De Pità O, De Sarro G, et al. Chronic inflammatory diseases: do immunological patterns drive the choice of biotechnology drugs? A critical review. Autoimmunity 2014;47:287–306.
10. Ogdie A, Schwartzman S, Husni ME. Recognizing and managing comorbidities in psoriatic arthritis. Curr Opin Rheumatol 2015;27:118–26.
11. Eder L, Wu Y, Chandran V, Cook R, Gladman DD. Incidence and predictors for cardiovascular events in patients with psoriatic arthritis. Ann Rheum Dis 2016;75:1680–6.
12. Zohar A, Cohen AD, Bitterman H, Feldhamer I, Greenberg-Dotan S, Lavi I, et al. Gastrointestinal comorbidities in patients with psoriatic arthritis. Clin Rheumatol 2016;35:2679–84.
13. McDonough E, Ayearst R, Eder L, Chandran V, Rosen CF, Thavaneswaran A, et al. Depression and anxiety in psoriatic disease: prevalence and associated factors. J Rheumatol 2014;41:887–96.
14. Rohekar S, Tom BD, Hassa A, Schentag CT, Farewell VT, Gladman DD. Prevalence of malignancy in psoriatic arthritis. Arthritis Rheum 2008;58:82–7.
15. Wilton KM, Crowson CS, Matteson EL. Malignancy incidence in patients with psoriatic arthritis: a comparison cohort-based incidence study. Clin Rheumatol 2016;35:2603–7.
16. Schafer PH, Parton A, Capone L, Cedzik D, Brady H, Evans JF, et al. Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. Cell Signal 2014;26:2016–29.
17. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo A, Wollenhaupt J, Gladman DD, et al. Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. J Rheumatol 2015;42:479–88.
18. Cutolo M, Myerson GE, Fleischmann R, Lioté F, Díaz-González F, Van den Bosch F, et al. A phase III, randomized, controlled trial of apremilast in patients with psoriatic arthritis: results of the PALACE 2 trial. J Rheumatol 2016;43:1724–34.
19. Edwards CJ, Blanco FJ, Crowley J, Birbara CA, Jaworski J, Aelion J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). Ann Rheum Dis 2016;75:1065–73.
20. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis 2014;73:1020–6.
21. New South Wales Government Health. List of countries with a tuberculosis incidence of 40 cases per 100,000 persons or greater. October 2019. URL: https://www.health.nsw.gov.au/Infectious/tuberculosis/Pages/high-incidence-countries.aspx.
22. Lambert JA, Raju SV, Tang LP, McNicholas CM, Li Y, Courville CA, et al. Cystic fibrosis transmembrane conductance regulator activation by roflumilast contributes to therapeutic benefit in chronic bronchitis. Am J Respir Cell Mol Biol 2014;50:549–58.

23. Langley A, Beecker J. Management of common side effects of apremilast. J Cutan Med Surg 2018;22:415–21.
24. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. Biochem Pharmacol 2012;83:1583–90.
25. Mori F, Pérez-Torres S, De Caro R, Porzionato A, Macchi V, Beleta J, et al. The human area postrema and other nuclei related to the emetic reflex express cAMP phosphodiesterases 4B and 4D. J Chem Neuroanat 2010;40:36–42.
26. Vollert S, Kaessner N, Heuser A, Hanauer G, Dieckmann A, Knaack D, et al. The glucose-lowering effects of the PDE4 inhibitors roflumilast and roflumilast-N-oxide in Db/Db mice. Diabetologia 2012;55:2779–88.
27. Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev 2007;87:1409–39.
28. Sun F, Chai S, Li L, Yu K, Yang Z, Wu S, et al. Effects of glucagon-like peptide-1 receptor agonists on weight loss in patients with type 2 diabetes: a systematic review and network meta-analysis. J Diabetes Res 2015;2015:157201.
29. Daliresp [package insert]. Wilmington (DE): AstraZeneca Pharmaceuticals; 2020.
30. National Institute of Mental Health. Thoughts of suicide and made suicide plans. 2019. URL: http://www.nimh.nih.gov/health/statistics/suicide/thoughts-of-suicide-and-made-suicide-plans.shtml.
31. Shah K, Paris M, Mellars L, Changolkar A, Mease PJ. Real-world burden of comorbidities in US patients with psoriatic arthritis. RMD Open 2017;3:e000588.
32. Gross RL, Schwartzman-Morris JS, Krathen M, Reed G, Chang H, Saunders KC, et al. A comparison of the malignancy incidence among patients with psoriatic arthritis and patients with rheumatoid arthritis in a large US cohort. Arthritis Rheumatol 2014;66:1472–81.
33. Orbai AM, Krueger K, Behrens F, Kiltz U, Guerette B, Mellars L, et al. AB0773. Psoriatic arthritis impact of disease questionnaire scores are correlated with disease activity, as measured by CDAPSA, in patients with psoriatic arthritis [abstract]. Ann Rheum Dis 2019;78:1856.
34. Kleyn CE. Apremilast real-world treatment outcomes in psoriasis patients with comorbid psoriatic arthritis: an analysis of the APPRECIATE study [abstract]. European Academy of Dermatology and Venereology: Abstracts from the 28th Congress, Madrid, Spain, October 9-13, 2019.