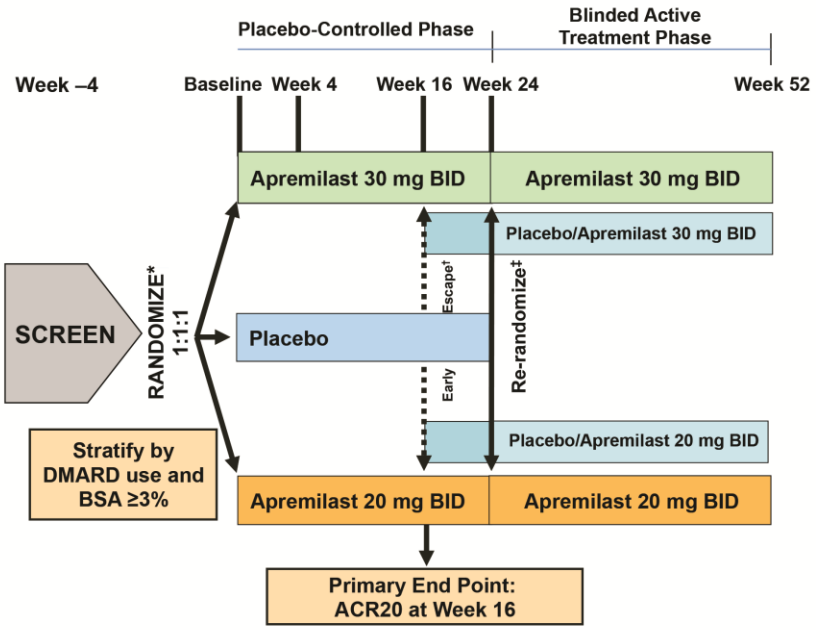
Online Supplementary Material

SUPPLEMENTARY FIG. S1 PALACE 3 study design



*All doses were titrated over the first week of treatment. †Patients whose swollen and tender joint counts had not improved by ≥20% at week 16 were considered non-responders and were required to be re-randomized (1:1) to apremilast 20 mg BID or 30 mg BID if they were initially randomized to placebo. Apremilast-treated patients continued on their initial apremilast dose. ‡At week 24, all remaining placebo patients were re-randomized to apremilast 20 mg BID or 30 mg BID. DMARD=disease-modifying antirheumatic drug; BSA=body surface area; ACR=American College of Rheumatology.

Supplementary Table S1. Subgroup analysis of ACR20 response at week 16* by concomitant and prior treatment experience

	Week 16 (ITT Population)		
	Placebo n=169	Apremilast 20 mg BID n=169	Apremilast 30 mg BID n=167
Concomitant conventional DMARD use			
Yes	22/101 (22)	33/104 (32)	42/101 (42)‡
No	9/68 (13)	15/65 (23)	26/66 (39)§
Prior biologic exposure			
Biologic naive	25/121 (21)	37/118 (31)	53/124 (43)§
Prior biologic use	6/48 (13)	11/50 (22)	15/43 (35)†
Biologic therapeutic failure	1/12 (8)	5/18 (28)	3/14 (21)

*****Patients who discontinued or did not have sufficient data were counted as non-responders. †P=0.0192; ‡P=0.0026; §P≤0.0005 versus placebo.

Supplementary Table S2. ACR response at week 52

	Placebo/ Apremilast 20 mg BID	Placebo/ Apremilast 30 mg BID	Apremilast 20 mg BID	Apremilast 30 mg BID
ACR20 (%)	34/72 (47)	39/75 (52)	73/169 (43)	87/167 (52)
ACR50 (%)	16/72 (22)	21/75 (28)	31/169 (18)	41/167 (25)
ACR70 (%)	11/72 (15)	10/75 (13)	11/169 (7)	13/167 (8)

Apremilast last observation carried forward for missing values at Week 52.

Supplementary Table S3. Common AEs (≥5% any treatment group), by concomitant conventional DMARD use

	Weeks 0 to 24*				Weeks 0 to 52†	
	Placebo		Apremilast (overall)		Apremilast (overall)	
Concomitant Conventional DMARD Use n(%)	No n=66	Yes n=102	No n=133	Yes n=204	No n=186	Yes n=297
Any AE	36 (55)	47 (46)	92 (69)	112 (55)	140 (75)	185 (62)
Diarrhea	0 (0)	3 (3)	22 (17)	30 (15)	24 (13)	41 (14)
Nausea	3 (5)	6 (6)	19 (14)	23 (11)	27 (15)	33 (11)
Headache	3 (5)	5 (5)	20 (15)	16 (8)	26 (14)	26 (9)
URTI	2 (3)	1 (1)	10 (8)	13 (6)	15 (8)	26 (9)
Fatigue	0 (0)	2 (2)	6 (5)	5 (3)	7 (4)	7 (2)
Nasopharyngitis	1 (2)	1 (1)	4 (3)	7 (3)	9 (5)	13 (4)
Vomiting	0 (0)	1 (1)	5 (4)	8 (4)	6 (3)	14 (5)

*Placebo-controlled phase includes data through week 16 for patients initially receiving placebo who escaped, and data through week 24 for all other patients. †Includes all patients who received ≥1 dose of apremilast regardless of when apremilast was started (week 0, 16, or 24).