Common Drug Review
Clinical Review Report

December 2015

Drug	Apremilast (Otezla)
Indication	For use alone, or in combination with methotrexate, for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response, intolerance, or contraindication to a prior DMARD.
Listing request	As per indication
Dosage form(s)	10 mg, 20 mg, and 30 mg tablets for oral administration
NOC date	10 June 2015
Manufacturer	Celgene Inc.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

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ABBREVIATIONS

AE	adverse event
ACR	American College of Rheumatology
ANCOVA	analysis of covariance
APR	apremilast
b.i.d.	twice-daily
BSA	body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CDAI	Clinical Disease Activity Index
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
CRP	C-reactive protein
DAS28	28-joint Disease Activity Score
DB	double-blind
DMARD	disease-modifying anti-rheumatic drug
EE	early escape
ESR	erythrocyte sedimentation rate
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FAS	full analysis set
HAQ-DI	Health Assessment Questionnaire–Disability Index
LOCF	last observation carried forward
LS mean	least squares mean
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCID	minimal clinically important difference
MTX	methotrexate
NSAID	nonsteroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PP	per-protocol
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-36	Short Form (36) Health Survey

SF-36v2	Short Form (36) Health Survey, version 2
SJC	swollen joint count
TJC	tender joint count
TNF alpha	tumour necrosis factor alpha
VAS	visual analogue scale
WDAE	withdrawal due to adverse event
WLQ-25	25-Item Work Limitations Questionnaire

EXECUTIVE SUMMARY

Introduction

Psoriatic arthritis (PsA) is a heterogeneous disease associated with multiple and variable clinical features. Patients suffer from chronic inflammatory peripheral arthritis and may also suffer from skin and nail disease, axial disease, dactylitis, and enthesitis, highlighting how this disease impacts on more than just the joints of the patient.[1,2] The prevalence of PsA is suggested to be similar to that of rheumatoid arthritis[3] and it is estimated to vary from 0.3% to 1% of the population.[1] Nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs; i.e., methotrexate [MTX], sulfasalazine, leflunomide), immunosuppressives (cyclosporine), and tumour necrosis factor alpha (TNF alpha) inhibitors (i.e., etanercept, infliximab, golimumab, adalimumab, certolizumab) are the typical drug therapies use to treat PsA.[2]

Apremilast is an orally administered small-molecule inhibitor of phosphodiesterase-4 (PDE4) for the treatment of PsA.[4] The Health Canada Notice of Compliance (NOC) is to be used alone or in combination with MTX, for the treatment of active PsA in adult patients who have had an inadequate response, intolerance, or contraindication to a prior DMARD. Apremilast is also approved for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.[4] The Health Canada–recommended dose for adult patients is 30 mg twice daily, and an initial titration schedule is required.[4]

The objective of this review is to perform a systematic review of the beneficial and harmful effects of apremilast for the treatment of active PsA in adult patients who have had an inadequate response, intolerance, or contraindication to a prior DMARD.

Results and Interpretation

Included Studies

Three manufacturer-sponsored, phase 3, multi-centre, randomized, double-blind, placebo-controlled trials, which were almost identical in design (PALACE-1 [N = 504], PALACE-2 [N = 484], and PALACE-3 [N = 505]), met the inclusion criteria for this systematic review. The trials included adults with a diagnosis of PsA of at least six months' duration. In addition, patients were required to have active PsA at time of screening. PALACE-3 also included patients with at least one ≥ 2 cm plaque psoriasis lesion in addition to active PsA. All three trials were three-arm superiority studies evaluating the efficacy and safety of apremilast 20 mg orally twice daily (b.i.d.), or apremilast 30 mg orally b.i.d. compared with identically appearing placebo over a double-blinded duration of 24 weeks. The primary efficacy end point in all three included studies was the proportion of patients in each treatment group who achieved an ACR20 response at week 16. Patients are considered ACR20 responders if they had at least 20% improvement from baseline in swollen and tender joint counts as well as for any three of the five ACR criteria. At week 16, all patients whose tender joint count (TJC) and swollen joint count (SJC) had not improved by ≥ 20% were required to enter early escape (EE) to blinded active treatment. Patients in the placebo group who met EE criteria were to be re-randomized in a 1:1 ratio in a blinded fashion to receive either apremilast 20 mg b.i.d. or apremilast 30 mg b.i.d., with the dose of apremilast being titrated during the first week of active treatment from week 16 onwards. All trials included a dose-blind active treatment period (weeks 24 to 52), and an ongoing open-label, long-term safety phase. Only apremilast 30 mg orally b.i.d. is the Health Canada–approved dose for the treatment of active PsA, and therefore only data for this dose are included in the current report.

No trials directly comparing apremilast with DMARDs or with biologic response modifiers were found in the scientific literature. All three trials had an appropriate randomization strategy, with generally similar treatment groups at baseline. By week 24, a large proportion of the patients in each study had discontinued initially assigned treatments, either by meeting the escape criteria at week 16, or because of lack of efficacy, adverse events, or patient withdrawal. This means that a substantial proportion of the outcome data at week 24 had to be imputed based on an intention-to-treat (ITT) analysis. Therefore, this limits the ability to make assertions about the results beyond the week 16 time point. Statistical significance of outcomes was assessed according to a hierarchical analysis plan and the Hochberg procedure for multiple testing. Instances where the higher order comparison failed to reach the pre-specified threshold for statistical significance, the subsequent comparisons were also deemed not statistically significant. Outcomes not included in the hierarchical analysis plan were considered exploratory in the review and the results should be interpreted with caution because of the increased risk of type 1 error.

Efficacy

The primary efficacy outcome in all three trials was ACR20 response at week 16. In all three trials, apremilast was associated with statistically significant improvements (compared with placebo) for the primary outcome of ACR20 response at week 16. However, the size of the treatment benefit was modest, with primary outcome of ACR20 being achieved by 38%, 32%, and 41% of patients on apremilast in PALACE-1, PALACE-2, and PALACE-3, respectively, compared with 19%, 19%, and 18% on placebo in PALACE-1, PALACE-2, and PALACE-3, respectively. Hence, the between-group difference in the proportion of patients achieving ACR20 response at week 16 was 19%, 13%, and 23%, respectively, across the three studies. At week 24, the between-group difference in the proportion of patients achieving ACR20 response was statistically significantly in favour of apremilast 30 mg versus placebo, with absolute differences of 22%, 9%, and 16%, respectively, across the three studies. However, given the high proportion of patients meeting EE criteria and generally discontinuing treatment, there is a high degree of uncertainty in the findings at week 24. The proportion of apremilast patients achieving an ACR50 response at week 16 was quite low (16%, 11%, and 15% for apremilast versus 6.0%, 5.0%, and 8.3% for placebo in PALACE-1, PALACE-2, and PALACE-3, respectively) and the differences between groups were not statistically significant. (Note that although the 95% confidence interval [CI] for the adjusted difference in proportions of ACR50 responders with apremilast versus placebo did not cross 0, the difference could not be declared statistically significant because a higher order comparison test failed to reach statistical significance in the step-down analysis plan.) ACR50 response is likely to be a more clinically important outcome for patients than ACR20. As would be expected, the proportion of patients achieving an ACR50 response with apremilast was higher at week 24, but only slightly. As with the analysis at week 16, the statistical significance of between-group comparisons could not be interpreted because of failure of the step-down analysis at a higher order comparison. No statistically significant difference was shown between apremilast and placebo for ACR70 response in any of the studies.

Other clinical response outcomes (Psoriatic Arthritis Response Criteria [PsARC] and Health Assessment Questionnaire–Disability Index [HAQ-DI] for all studies, and Psoriasis Area and Severity Index [PASI] 75 for PALACE-3) also demonstrated a statistically significant difference favouring apremilast treatment groups compared with placebo at week 16. There were greater reductions in Clinical Disease Activity Index (CDAI) score and Disease Activity Score C-reactive Protein (DAS-CRP) 28 score in the apremilast 30 mg b.i.d. treatment group compared with placebo at week 16. However, claims regarding statistical significance cannot be made because the hierarchical testing was stopped before testing these outcomes. In addition, there were no statistically significant differences in the change from baseline in

Dactylitis Severity Score and in the change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) scores at week 16.

Results for health-related quality of life, measured using the Short Form (36) Health Survey (SF-36), indicated that in all three trials, there were statistically significantly greater changes from baseline in the SF-36 physical functioning domain score with apremilast 30 mg versus placebo at week 16. The proportions of patients achieving an improvement ≥ 2.5 points on the SF-36 version 2 (SF-36v2) physical functioning domain (estimated minimal clinically important difference [MCID] range, 2.5 to 5 points) at weeks 16 and 24 [redacted]; however, these findings are considered exploratory because the analysis was not adjusted for multiple testing and is potentially subject to inflated type 1 error. Likewise, exploratory analyses of the proportion of patients achieving an improvement of ≥ 2.5 points in the physical component summary (PCS) of the SF-36 at weeks 16 and 24 [redacted].

Arthritis pain in patients was assessed using patient's assessment of pain. The apremilast 30 mg b.i.d. treatment group was statistically significantly improved relative to placebo for mean score change at week 16 in studies PALACE-1 and PALACE-3. The mean differences between groups ranged from –4.9 to –7.9 mm across the three studies; the MCID has been reported as 10 mm.

In all three trials, the apremilast 30 mg b.i.d. treatment group showed reduced fatigue relative to placebo for mean score change at weeks 16 and 24 on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale. However, claims of statistical significance could not be made because the hierarchical testing was stopped before testing this outcome.

In all three trials, a pre-planned subgroup analysis was carried out for the ACR20 response rate at week 16. These results demonstrated a consistent treatment effect in favour of apremilast compared with placebo regardless of concomitant treatments (whether receiving DMARDs and type of DMARD received) or prior treatments (including the number of conventional DMARDs received and whether people had received previous TNF alpha inhibitor therapies).

The longer-term phases of the trials, after 24 weeks, had limited clinical value for the following reasons: there were no control groups; there was no blinding because all people received apremilast at this time point in the trials; data were analyzed as observed, with nonresponders not contributing to the analyses; and there was a lack of stopping criteria, where early escapers at week 16 who were initially randomized to apremilast were allowed to remain on apremilast during the long-term phases — it is likely that in clinical practice, such nonresponders would no longer continue to receive apremilast.

In the absence of adequate head-to-head trial data for apremilast with other PsA treatment, the manufacturer conducted an indirect treatment comparison (IDC) based on a systematic review of RCTs to compare the efficacy of apremilast with adalimumab, certolizumab, etanercept, golimumab, infliximab, and ustekinumab. The results of the IDC showed that [redacted]. However, these outcomes were not consistently statistically significant. In addition, non-statistically significant results should be interpreted with caution because the absence of statistical significance does not indicate that there is an evidence of similarity or equivalence, as no formal test for equivalence or non-inferiority was completed by the manufacturer.

Harms

No deaths occurred in the double-blind period in any of the trials. Over 24 weeks, the overall frequency of serious adverse events (SAEs) was 5.4%, 2.5%, and 3.6% in the apremilast treatment group and 4.2%, 1.9%, and 5.4% of placebo patients in PALACE-1, PALACE-2, and PALACE-3, respectively. The overall frequency of withdrawals due to adverse events (WDAEs) was [redacted] of apremilast patients and [redacted] of placebo patients in PALACE-1, PALACE-2, and PALACE-3, respectively.

The overall frequency of treatment-emergent adverse events (TEAEs) was 61.3%, [redacted] in the apremilast treatment group and 48.2%, [redacted] of placebo patients in PALACE-1, PALACE-2, and PALACE-3, respectively. The most common adverse events (AEs) were diarrhea (19%, 14.8%, and 15.6% of apremilast patients versus 2.4%, 5.0%, and 1.8% for placebo in PALACE-1, PALACE-2, and PALACE-3, respectively) and nausea (18.5%, 16.0%, and 13.8% of apremilast patients versus 6.5%, 1.9%, and 5.4% for placebo in PALACE-1, PALACE-2, and PALACE-3, respectively). Aside from gastrointestinal AEs, weight loss was a notable harm for this review; the proportion of patients with clinically significant weight loss (i.e., weight decreases of > 5% of baseline body weight), not specified as an AE, and was [redacted] for apremilast versus [redacted] for placebo in PALACE-1, PALACE-2, and PALACE-3, respectively. Apremilast 30 mg b.i.d. was well tolerated over a 52-week period with generally mild or moderate TEAEs in most patients, which did not necessitate dose interruption or discontinuation. Gastrointestinal disorders were the most common TEAEs, with diarrhea and nausea the most frequently reported and the most common cause for drug interruptions or discontinuation.

Harms were not analyzed in the IDC, and the comparative safety between apremilast and biologics is unknown. On the other hand, there is no evidence that apremilast is better tolerated than biologic therapies, and longer-term safety data for apremilast are required.

Potential Place in Therapy[1]

Apremilast may be an alternative therapy for patients with mild to moderate disease or patients with more severe disease who refuse parenteral therapies. Most patients prefer oral to injectable drugs. Patients taking apremilast would also not need laboratory follow-up (less intrusive and costly) and probably require fewer physician visits and monitoring of laboratory tests. Apremilast does not require tuberculosis screening, and also does not lead to infections.

These decisions depend on the clinical evaluation of the patients. Poor prognostic factors, such as baseline erosive disease or severe functional impairment, might result in a decision to bypass apremilast.

Conclusions

Based on three double-blind RCTs (PALACE-1, PALACE-2, and PALACE-3) in patients with active PsA, treatment with apremilast 30 mg b.i.d. resulted in statistically significant improvements in clinical response (ACR20, PsARC, HAQ-DI, PASI75 for PALACE-3) at week 16 when compared with placebo. Although improvements in health-related quality of life were observed, they were inconsistent across studies or measures. In all three studies, a very large proportion of placebo patients discontinued randomized treatment before week 24 (either because of EE or treatment discontinuation), so claims of efficacy at week 24 are uncertain.

[1] Based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

The most common AEs with apremilast were gastrointestinal-related — nausea and diarrhea — and these were also the most common reasons for WDAEs. There were no clear indications of any serious harms issues with apremilast, although interpretation of this finding is limited by the relatively short 24-week follow-up in the double-blind comparative phase and the large proportion of patients who discontinued randomized treatment (either because of EE or treatment discontinuation).

A manufacturer-submitted network meta-analysis suggested [redacted] Harms, health-related quality of life, and patient-reported outcomes were not analyzed in the IDC, and the comparative safety between apremilast and biologics is unknown.

TABLE 1: SUMMARY OF RESULTS

Outcome	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
ACR20 at Week 16[a]						
n (%)	32 (19.0)	64 (38.1)	30 (18.9)	52 (32.1)	31 (18.3)	68 (40.7)
Adjusted % difference in proportions (95% CI)[b]	19.0 (9.7, 28.3)		13.4 (4.0, 22.7)		22.3 (13.0, 31.6)	
P value[c]	**0.0001**		**0.0060**		**< 0.0001**	
ACR20 at Week 24[a]						
n (%)	22 (13.1)	59 (35.1)	25 (15.7)	40 (24.7)	26 (15.4)	52 (31.1)
Adjusted % difference in proportions (95% CI)[b]	22.2 (13.4 to 30.9)		9.2 (0.5 to 17.8)		15.5 (6.7 to 24.3)	
P value[c]	**< 0.0001**		**0.0394**		**0.0007**	
HAQ-DI Change From Baseline at Week 16[d]						
Baseline mean (SD)	1.206 (0.6039)	1.231 (0.6093)	1.147 (0.5998)	1.222 (0.6288)	1.160 (0.6326)	1.160 (0.6535)
Change from baseline at week 16 LS mean (SE)[e]	–0.086 (0.0360)	–0.244 (0.0364)	–0.053 (0.0358)	–0.193 (0.0354)	–0.065 (0.0335)	–0.192 (0.0339)
LS mean difference to placebo difference (2-sided 95% CI)[e]	–0.159 (–0.258 to –0.060)		–0.140 (–0.236 to –0.045)		–0.127 (–0.220 to –0.034)	
P value[e]	**0.0017**		**0.0042**		**0.0073**	
HAQ-DI Change From Baseline at Weeks 24[d]						
Change from baseline at week 24 LS mean (SE)[e]	–0.076 (0.0369)	–0.258 (0.0371)	–0.085 (0.0377)	–0.206 (0.0372)	–0.053 (0.0350)	–0.192 (0.0353)
LS mean difference to placebo (2-sided 95% CI)[e]	–0.182 (–0.283 to –0.080)		–0.121 (–0.222 to –0.020)		–0.139 (–0.236 to –0.042)	
P value[e]	**0.0005**		**0.0191**		**0.0050**	
PsARC Response at Week 16[a]						
n (%)	50 (29.8)	78 (46.4)	53 (33.3)	78 (48.1)	46 (27.2)	88 (52.7)
Adjusted % difference in proportions (95% CI)	16.7 (6.6 to 26.8)[f]		14.9 (4.3 to 25.5)[f]		25.4 (15.5 to 35.3)[h]	
P value	**0.0017**[g]		**0.0065**[g]		**< 0.0001**[i]	
Change From Baseline in SF-36v2 Physical Functioning Domain at Week 16[a]						
Baseline mean (SD)	33.84 (10.516)	33.09 (10.291)	34.73 (9.873)	33.44 (10.515)	34.32 (11.029)	34.43 (10.468)
Change from baseline at week 16 LS mean (SE)	1.81 (0.621)[e]	4.23 (0.625)[e]	0.81 (0.678)[e]	2.91 (0.671)[e]	1.14 (0.589)[j]	3.47 (0.594)[j]
LS mean difference (2-sided 95% CI)	2.42 (0.71 to 4.13)[e]		2.10 (0.28 to 3.92)[e]		2.32 (0.69 to 3.95)[j]	
P value	**0.0056**[e]		**0.0237**[e]		**0.0053**[j]	

Outcome	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	**APR 30 mg b.i.d., N = 168**	**Placebo N = 159**	**APR 30 mg b.i.d., N = 162**	**Placebo N = 169**	**APR 30 mg b.i.d., N = 167**
Change From Baseline in Patient's Assessment of Pain at Week 16[a]						
Baseline mean (SD)	61.0 (20.27)	58.4 (20.13)	55.5 (19.21)	56.4 (20.68)	55.6 (21.06)	56.2 (22.94)
Change from baseline at week 16 LS mean (SE)	–5.7 (1.83)[e]	–13.5 (1.85)[e]	–7.0 (1.93)[e]	–11.9 (1.90)[e]	–4.9 (1.79)[j]	–12.7 (1.81)[j]
LS mean difference (2-sided 95% CI)	–7.9 (–12.9 to –2.8)[e]		–4.9 (–10.0 to 0.3)[e]		–7.8 (–12.8 to –2.9)[j]	
P value	**0.0023**[e]		[redacted]		**0.0021**[j]	
Change From Baseline in MASES at Week 16[a]						
n (%)[k]	95 (56.5)	108 (64.3)	100 (62.9)	97 (59.9)	106 (62.7)	107 (64.1)
Baseline mean (SD)	5.4 (3.44)	4.4 (2.91)	[redacted]	[redacted]	4.4 (3.34)	4.4 (3.23)
Change from baseline at week 16 LS mean (SE)	–0.9 (0.30)[e]	–1.3 (0.28)[e]	–1.0 (0.29)[e]	–1.4 (0.29)[e]	–0.7 (0.27)[j]	–1.0 (0.27)[j]
LS mean difference to placebo (2-sided 95% CI)	-0.4 (-1.2, 0.4)[e]		-0.4 (-1.2, 0.4)[e]		-0.2 (-1.0, 0.5)[j]	
P value	0.3605[e]				0.5349[j]	
Change from Baseline in Dactylitis Severity Score at Week 16[a]						
n (%)[l]	63 (37.5)	66 (39.3)	63 (39.6)	70 (43.2)	67 (39.6)	76 (45.5)
Baseline mean (SD)	3.3 (3.30)	2.9 (2.38)	[redacted]	[redacted]	3.9 (4.04)	4.1 (4.27)
Change from baseline at week 16 LS mean (SE)[e]	–1.4 (0.28)	–1.7 (0.28)	–1.1 (0.28)	–1.3 (0.26)	–1.3 (0.34)	–2.1 (0.32)
LS mean difference to placebo (2-sided 95% CI)[e]	–0.3 (–1.1 to 0.4)		–0.2 (–1.0 to 0.5)		–0.8 (–1.7 to 0.1)	
Harms						
N	168	168	159	162	169	167
Deaths	0	0	0	0	0	0
SAEs, n (%)	7 (4.2)	9 (5.4)	3 (1.9)	4 (2.5)	9 (5.4)	6 (3.6)
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

Outcome	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
[redacted]						
[redacted]						
[redacted]						
[redacted]						

ANCOVA = analysis of covariance; ACR20 = American College of Rheumatology 20% response; APR = apremilast; b.i.d. = twice daily; BSA = body surface area; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; DMARD = disease-modifying anti-rheumatic drug; EE = early escape; HAQ-DI = Health Assessment Questionnaire – Disability Index; LS = least squares; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; PsARC = Psoriatic Arthritis Response Criteria; SAE = serious adverse event; SD = standard deviation; SE = standard error; SF-36v2 = Short Form (36) Health Survey, version 2.

[a] Patients who discontinued early, prior to week 16, and patients who did not have sufficient data for a definitive determination of response status at week 16 were counted as nonresponders. Joints temporarily or permanently not assessable at baseline were excluded from joint count. For other unassessed joints at baseline, the joint assessment at the screening visit, if assessed, was used as the baseline assessment; otherwise, the joint was excluded from joint count. The last observed joint assessment (at baseline or post-baseline) was used for joints unassessed at week 16. There was no imputation for other missing ACR component scores.

[b] Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[c] 2-sided *P* value is based on the CMH test adjusting for baseline DMARD use. *P* values in bold are considered statistically significant.

[d] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question.

[e] LS mean (SE) and *P* value based on an ANCOVA model for the change from baseline at the respective time point, with treatment group and baseline DMARD use as factors, and the baseline value as a covariate. *P* values in bold are considered statistically significant.

[f] Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[g] 2-sided *P* value is based on the CMH test adjusting for baseline DMARD use. *P* values in bold are considered statistically significant.

[h] Adjusted difference in proportions is the weighted average of the treatment differences across the 4 strata of baseline DMARD use by involvement of ≥ 3% BSA with psoriasis at baseline with the CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average.

[i] 2-sided *P* value is based on the CMH test adjusting for baseline DMARD use and involvement of ≥ 3% BSA with psoriasis at baseline. *P* values in bold are considered statistically significant.

[j] LS mean (SE) and *P* value based on an ANCOVA model for the change from baseline at the respective time point, with treatment group, baseline DMARD use, and involvement of ≥ 3% BSA with psoriasis at baseline as factors, and the baseline value as a covariate. *P* values in bold are considered statistically significant.

[k] Patients with a baseline MASES > 0 (i.e., pre-existing enthesopathy) and at least 1 post-baseline value at or prior to the respective visits are included.

[l] Patients with a baseline Dactylitis Severity Score > 0 (i.e., pre-existing dactylitis) and at least 1 post-baseline value at or prior to the respective visits are included.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Psoriatic arthritis (PsA) is a heterogeneous disease associated with multiple and variable clinical features. Patients suffer from chronic inflammatory peripheral arthritis and, in addition to this, may suffer from skin and nail disease, axial disease, dactylitis, and enthesitis, highlighting how this disease has an impact on more than just the joints of the patient.[1,2] It results in significant disease burden, functional impairment, increased comorbidity and mortality, and reduced health-related quality of life.[2,5,6] The prevalence of PsA is suggested to be similar to that of rheumatoid arthritis[3] and it is estimated to vary from 0.3% to 1% of the population.[1] With effective treatment, functional disabilities and quality of life can be improved;[7] however, there is no one treatment regimen that works on every person anddifferent treatment options are therefore required.

1.2 Standards of Therapy

Clinical practice guidelines provide definitions of mild, moderate, and severe PsA, but these definitions vary with the symptoms being considered.[2] For example, with respect to peripheral arthritis, mild disease is considered to consist of involvement of less than five joints with no damage revealed by X-ray; moderate disease is considered to consist of five or more joints with damage revealed by X-ray and moderate impact on function and quality of life; severe disease is considered to consist of involvement of five or more joints with severe damage revealed by X-ray and a severe impact on function and quality of life. With respect to psoriasis, body surface area (BSA) involvement < 5% and a Psoriasis Area and Severity Index (PASI) > 5 is considered mild disease; non-response to topical treatments and a PASI < 10 is considered moderate disease; BSA involvement > 10% and a PASI > 10 is considered severe disease. With respect to enthesitis, mild disease is considered to consist of involvement of one or two sites with no loss of function; moderate disease is considered to consist of involvement of two or more sites or loss of function; severe disease is considered to consist of loss of function or involvement of two or more sites and failure of response. Other symptoms that should be assessed for severity include spinal disease and dactylitis. Therefore, severity of disease in PsA is difficult to classify and can depend on how the disease manifests itself in each person and the severity of different symptoms.

Several drug classes are employed in the treatment of PsA, including nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs; i.e., methotrexate, sulfasalazine, leflunomide), immunosuppressives (cyclosporine), tumour necrosis factor alpha (TNF alpha) inhibitors (i.e., etanercept, infliximab, golimumab, adalimumab, certolizumab), and ustekinumab (a fully human IgG1 kappa monoclonal antibody). Even though there were only two small controlled trials of inadequate power that evaluated methotrexate for PsA, it remains the primary treatment post-NSAIDs.[8] The next line of treatment is the biologic TNF alpha inhibitors, should the DMARDs fail or there are contraindications. If the first TNF alpha inhibitor fails, then another TNF alpha inhibitor can be offered.[2]

Although there is no Canadian treatment guideline aimed specifically at the management of PsA, the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada Treatment Recommendations for the Management of Spondyloarthritis[9] include the following recommendations: (1) Sulfasalazine, methotrexate (MTX), and leflunomide may be considered in patients with peripheral spondyloarthritis; however, these treatments have only minimal to moderate evidence of efficacy. (2) Combination therapy with DMARDs should be considered in peripheral spondyloarthritis, particularly in patients with moderate to high disease activity and poor prognostic features, and in patients with recent-onset disease, and that combination therapy should also be considered in patients with

inadequate response to monotherapy. (3) TNF alpha inhibitors should be offered to those with persistent inflammation despite a trial of NSAID and one DMARD in patients with predominantly peripheral spondyloarthritis. (4) TNF alpha inhibitors should be offered to patients with refractory enthesitis or dactylitis accompanied by persistent inflammation. The recommendations on DMARD use in peripheral spondyloarthritis were based upon PsA data, and the recommendation on TNF alpha inhibitors use was derived from PsA literature.

1.3 Drug

Apremilast is an orally administered small-molecule inhibitor of phosphodiesterase-4 (PDE4), which works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. In Canada, apremilast is indicated: alone or in combination with MTX, for the treatment of active PsA in adult patients who have had an inadequate response, intolerance, or contraindication to a prior DMARD; and for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. The Health Canada–recommended dose for adult patients is 30 mg twice daily. An initial titration schedule is required, starting with 10 mg once daily at day 1; 10 mg twice daily at day 2; 10 mg once daily and 20 mg once daily at day 3; 20 mg twice daily at day 4; 20 mg once daily and 30 mg once daily at day 5; and 30 mg twice daily at day 6 and thereafter.[4] In addition to apremilast, five anti-TNF alpha agents — etanercept, infliximab, golimumab, adalimumab, and certolizumab pegol — and a fully human IgG1 kappa monoclonal antibody (ustekinumab) are currently approved in Canada for the treatment of PsA patients (Table 2).

Indication under review
For use alone, or in combination with methotrexate, for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response, intolerance, or contraindication to a prior DMARD.
Listing criteria requested by sponsor
As per indication

TABLE 2: KEY CHARACTERISTICS OF APREMILAST, ADALIMUMAB, CERTOLIZUMAB, ETANERCEPT, GOLIMUMAB, INFLIXIMAB, AND USTEKINUMAB

	Apremilast	Adalimumab	Certolizumab Pegol	Etanercept	Golimumab	Infliximab	Ustekinumab
Mechanism of Action	PDE4 inhibitor	A recombinant human IgG1 monoclonal antibody that inhibits binding of TNF to TNF receptors	A recombinant, humanized antibody Fab' fragment inhibits binding of TNF to TNF receptors	A dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) TNF receptor linked to the Fc portion of human IgG1. Etanercept inhibits binding of TNF to TNF receptors	A human IgG1 monoclonal antibody inhibits binding of TNF to TNF receptors	A chimeric IgG1 monoclonal antibody that inhibits binding of TNF to TNF receptors	A fully human IgG1 kappa monoclonal antibody that binds to the shared p40 subunit of human cytokines IL-12 and IL-23, preventing their binding to the IL-12R beta1 receptor protein on surface immune cells.
Indication[a]	Treating active PsA in adult patients who have had an inadequate response, intolerance, or contraindication to a prior DMARD.	Reducing the signs and symptoms of active arthritis and inhibiting the progression of structural damage and improving the physical function in adult PsA patients. It can be used in combination with MTX in patients who do not respond	Reducing signs and symptoms and inhibiting the progression of structural damage as assessed by X-ray, in adult patients with moderately to severely active PsA who have failed one or more DMARDs. It can be used alone, or in combination with MTX.	Reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in adult patients with PsA. It can be used in combination with MTX in adult patients who do not respond	Reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active PsA. It can be used in combination with MTX in	Reducing signs and symptoms, inducing major clinical response, and inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with PsA.	Treating adult patients with active PsA. It can be used alone or in combination with MTX.

	Apremilast	Adalimumab	Certolizumab Pegol	Etanercept	Golimumab	Infliximab	Ustekinumab
		adequately to MTX alone.		adequately to MTX alone.	patients who do not respond adequately to MTX alone.		
Route of Administration	Oral	SC				IV	SC
Recommended Dose	30 mg twice daily	40 mg administered every other week as a SC injection	Loading dose of 400 mg (given as 2 SC injections of 200 mg each) initially (week 0) and at weeks 2 and 4 followed by a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks.	50 mg per week in one SC injection or as two 25 mg SC injections on the same day once weekly, or 3 or 4 days apart.	50 mg SC once a month on same date each month.	5 mg/kg given as an IV infusion, followed with additional similar doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.	45 mg administered at weeks 0 and 4, then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg.
Serious Side Effects / Safety Issues	Clinically significant: weight loss. Common adverse events: nausea and diarrhea	Infections, particularly opportunistic ones and TB Malignancies Allergic reactions Injection or infusion site reactions					Infections and reactivated latent infections, injection site reactions, malignancies, RPLS

DMARD = disease-modifying anti-rheumatic drug; IgG1 = immunoglobulin G1; IV = intravenous injection; MTX = methotrexate; PDE4 = phosphodiesterase-4; PsA = psoriatic arthritis; RPLS = Reversible Posterior Leukoencephalopathy Syndrome; SC = subcutaneous injection; TB = tuberculosis; TNF = tumour necrosis factor.

[a] Health Canada indication.

Source: Health Canada product monographs.[4,10-15]

2. OBJECTIVES AND METHODS

2.1 Objectives

To evaluate the beneficial and harmful effects of apremilast (Otezla) at recommended doses alone or in combination with MTX in adult patients with active PsA who have had an inadequate response, intolerance, or contraindication to a prior DMARD.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with active PsA who have had an inadequate response, intolerance, or contraindication to a prior DMARD **Subgroups of interest:** • Body weight at baseline (< 100 kg vs. > 100 kg) • Number of prior DMARDs and/or biologic response modifiers • Disease severity (based on DAS28)
Intervention	Apremilast 30 mg twice daily alone or in combination with MTX
Comparators	Individual or combination therapy with: • Biological response modifiers (e.g., infliximab, etanercept, adalimumab, golimumab, ustekinumab, certolizumab pegol) Other DMARDs, including MTX
Outcomes	**Key efficacy outcomes:** Outcome measures of PsA symptoms (e.g., DAS28, ACR20/50/70, PsARC, MDA) Health-related quality of life (e.g., HAQ-DI, SF-36, PsAQoL, EQ-5D)[a] Work productivity[a] **Other efficacy outcomes:** Psoriatic outcome measures (e.g., PASI, NAPSI, BSA)[a] Radiographic changes MASES, Dactylitis Severity Score, FACIT–F[a] **Harms outcomes:** Mortality, SAEs, AEs, WDAEs Notable harms: serious infections (including tuberculosis), neuropsychiatric effects, weight loss, gastrointestinal
Study Design	Published and unpublished phase 3 RCTs

ACR = American College of Rheumatology; AE = adverse event; BSA = body surface area; DAS28 = 28-joint Disease Activity Score; DB = double-blind; DMARD = disease-modifying anti-rheumatic drug; EQ-5D = EuroQoL Health Status Questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MDA = minimal disease activity; MTX = methotrexate; NAPSI = Nail Psoriasis Severity Index; NSAIDs = nonsteroidal anti-inflammatory drugs; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PsAQoL = Psoriatic Arthritis Quality of Life; PsARC = Psoriatic Arthritis Response Criteria; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Outcomes that were considered important by the patients groups (see Appendix 1: Patient Input Summary).

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Otezla (apremilast) and psoriatic arthritis.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on July 3, 2015. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on November 18, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases (free), Internet search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings From the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in section 3.2. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

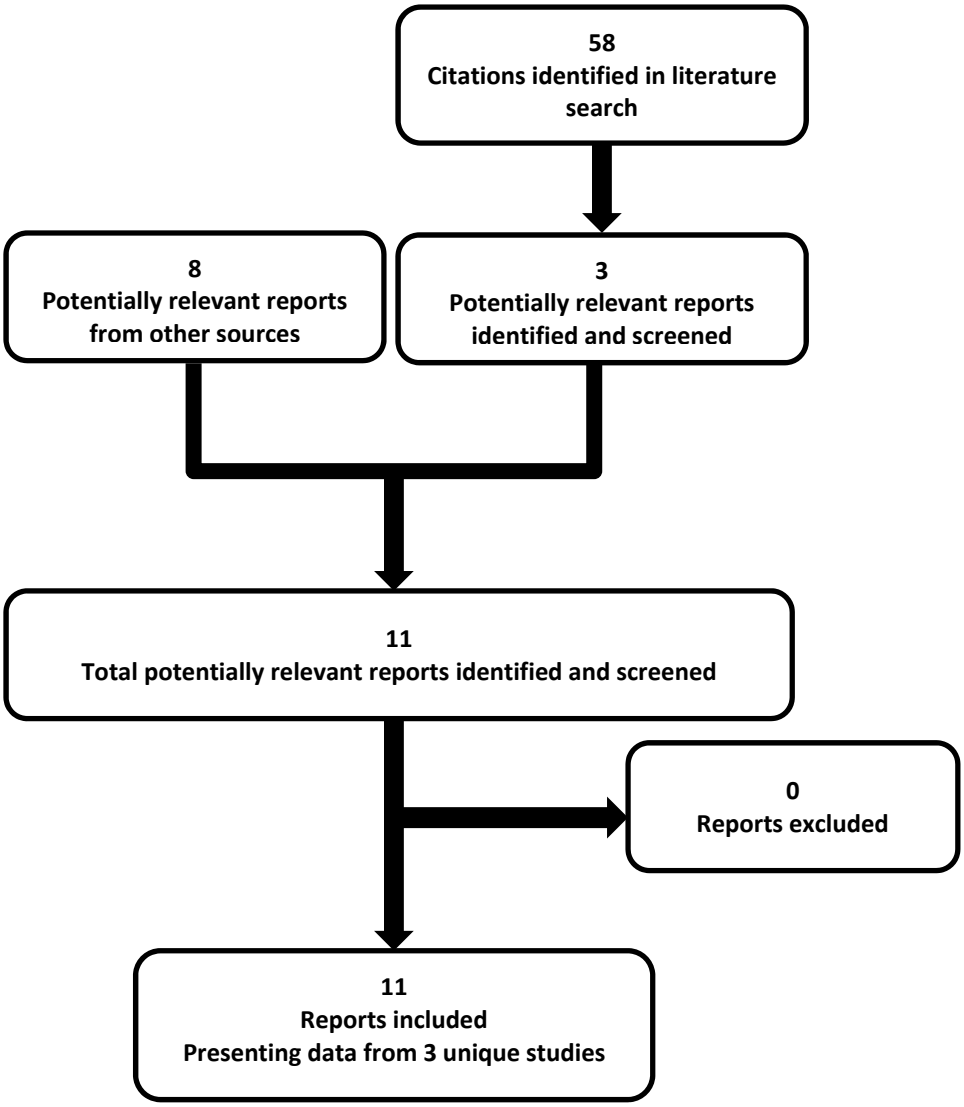


TABLE 4: DETAILS OF INCLUDED STUDIES

		PALACE-1	PALACE-2	PALACE-3
DESIGNS & POPULATIONS	**Study Design**	Phase 3, placebo-controlled, DB, multi-centre RCT		
	Locations	83 study centres — Canada, USA, Europe, Australia, New Zealand, Russia, and South Africa	84 study centres — Canada, USA, Europe, Russian Federation, South Africa, and Taiwan, Province of China.	78 study centres — Canada, USA, Europe, Australia, Republic of Korea, and the Russian Federation
	Randomized (N)	504 (168 to each of the study arms: placebo, apremilast orally 20 mg twice daily or 30 mg twice daily)	484 (159 to placebo, 163 to apremilast orally 20 mg twice daily, and 162 to apremilast 30 mg twice daily)	505 (169 to placebo, 169 to apremilast orally 20 mg twice daily, and 167 to apremilast 30 mg twice daily)
	Inclusion Criteria	Adults (aged ≥ 18 years) with a diagnosis of PsA of at least 6 months' duration, met the CASPAR criteria at time of screening and have a minimum of both ≥ 3 tender and ≥ 3 swollen joints despite prior or current treatment with DMARDs. Up to 10% of patients were permitted to enrol after having experienced a therapeutic failure with biologic TNF blockers. Patients in PALACE-3 had to have at least one ≥ 2 cm plaque psoriasis lesion.		
	Exclusion Criteria	Therapeutic failure of > 3 agents for PsA (small molecules or biologics), or > 1 biologic TNF blocker. Rheumatic autoimmune disease other than PsA, functional class IV as defined by the ACR Classification of Functional Status in Rheumatoid Arthritis, in patients who had a prior history of or current inflammatory joint disease other than PsA, had used phototherapy or DMARDs other than methotrexate, leflunomide, or sulfasalazine within 4 weeks of randomization. Use of adalimumab, etanercept, golimumab, infliximab, certolizumab pegol, or tocilizumab within 12 weeks of randomization or alefacept or ustekinumab within 24 weeks of randomization, prior treatment with apremilast. Active TB or a history of incompletely treated TB.		
DRUGS	**Intervention**	Apremilast orally 20 mg twice daily or 30 mg twice daily		
	Comparator(s)	Identically appearing 10 mg, 20 mg, or 30 mg placebo tablets		
DURATION	**Phase**			
	Early escape permitted	16 weeks		
	Double-blind, placebo-controlled	24 weeks (week 0 to 24)		
	Double-blind, active treatment phase	28 weeks (week 24 to 52)		
	Active treatment, open-label, long-term safety phase	Up to 4 years' duration		
OUTCOMES	**Primary End Point**	% patients with ACR20 at week 16		
	Other End Points	Change from baseline in physical function (HAQ-DI) at weeks 16 and 24 % patients with ACR20 at week 24 % patients who achieved a modified PsARC response at weeks 16 and 24 % patients with ACR50 at weeks 16 and 24 % patients with ACR70 at weeks 16 and 24		

		PALACE-1	PALACE-2	PALACE-3
		Change from baseline in CDAI score at weeks 16 and 24 Change from baseline in DAS28(CRP) at weeks 16 and 24 Proportion of patients with a good or moderate EULAR response at weeks 16 and 24 Change from baseline in patient's assessment of pain after 16 weeks and at week 24 Change from baseline in SF-36v2 Physical Function domain score at weeks 16 and 24 ≥ 2.5-point improvement in SF-36 physical functioning domain score and SF-36v2 PCS at weeks 16 and 24 ≥ 0.13-point and ≥ 0.30-point reductions in HAQ-DI at weeks 16 and 24 Change in EQ-5D score in each treatment group after at weeks 16 and 24 Change in WLQ-25 score in each treatment group at weeks 16 and 24 Change from baseline in MASES score in patients with pre-existing enthesopathy at weeks 16 and 24 Proportion of patients with pre-existing enthesopathy whose MASES improved by ≥ 20% at weeks 16 and 24 Change from baseline in the Dactylitis Severity Score in patients with pre-existing dactylitis at week 16 and week 24 Proportion of patients with pre-existing dactylitis whose Dactylitis Severity Score improved by ≥ 1 at weeks 16 and 24 Change from baseline in FACIT-F score at weeks 16 and 24 Proportion of patients in each treatment group whose psoriasis BSA at baseline was ≥ 3%, who achieved PASI-75 at week 16 and week 24 in PALACE-3 trial		
NOTES	**Publications**	Kavanaugh et al.[16]	None	None

ACR = American College of Rheumatology; BSA = body surface area; CASPAR = Classification Criteria for Psoriatic Arthritis; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS = Disease Activity Score; DB = double-blind; DMARDs = disease modifying anti-rheumatic drugs; EQ-5D = EuroQoL 5-Dimensions Health Status Questionnaire; EULAR = European League Against Rheumatism; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; PASI = Psoriasis Area and Severity Index; PCS = physical component summary; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; RCT = randomized controlled trial; SF-36 = Short Form (36) Health Survey; SF-36v2 = Short Form (36) Health Survey, version 2; TB = tuberculosis; TNF = tumor necrosis factor; WLQ-25 = 25-Item Work Limitations Questionnaire.
Source: Kavanaugh et al.,[16] Clinical Study Report for PALACE-1,[17] Clinical Study Report for PALACE-2,[18] Clinical Study Report for PALACE-3.[19]
Note: 7 additional reports were included.[20-26]

3.2 Included Studies

3.2.1 Description of Studies

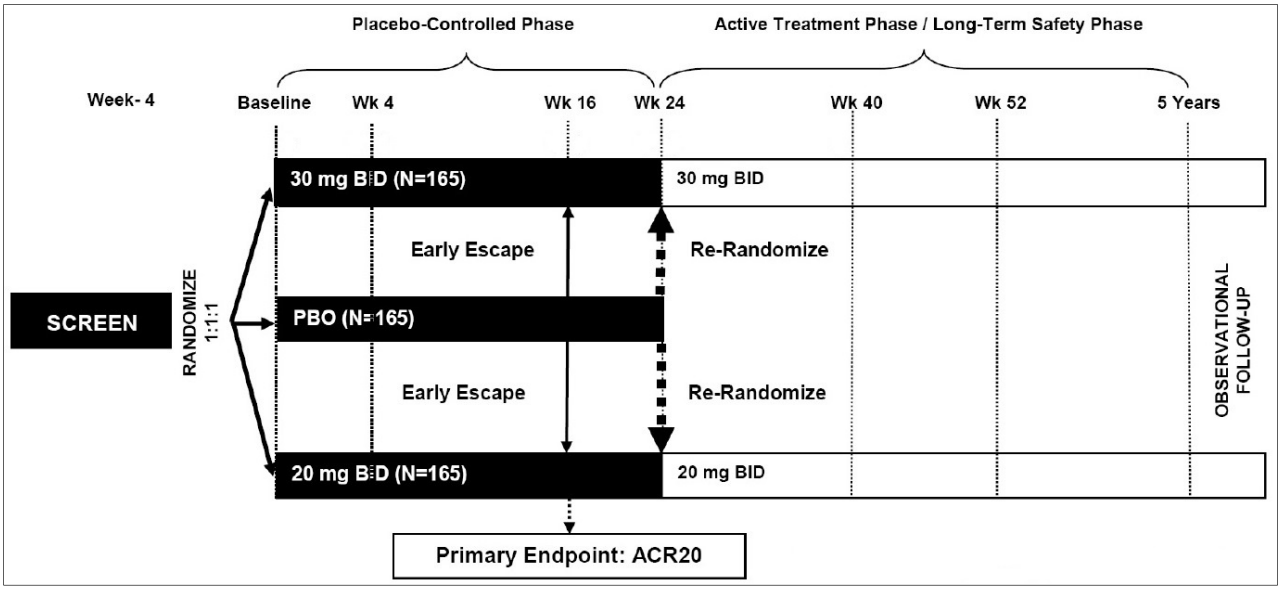
Three trials — PSA-002 (also known as PALACE-1), PSA-003 (also known as PALACE-2), and PSA-004 (also known as PALACE-3) — met the inclusion criteria for this review. All three trials were phase 3, multi-centre, randomized placebo-controlled, double-blind trials. All three trials (PALACE-1 [N = 504], PALACE-2 [N = 484], and PALACE-3 [N = 505]) were three-arm superiority studies, which evaluated the efficacy and safety of apremilast 20 mg orally twice daily (b.i.d.), or apremilast 30 mg orally b.i.d. compared with identically appearing placebo over a double-blinded duration of 24 weeks. Apremilast was dose-titrated in 10 mg daily increments over the first week of treatment. Patients in the apremilast 20 mg and apremilast 30 mg treatment groups reached their targeted dose on study days 4 and 6, respectively. At week 16, all patients whose tender joint count (TJC) and swollen joint count (SJC) had not improved by ≥

20% were required to enter early escape (EE) to blinded active treatment. Patients in the placebo group who met EE criteria were to be re-randomized in a 1:1 ratio in a blinded fashion to receive either apremilast 20 mg b.i.d. or apremilast 30 mg b.i.d. with the dose of apremilast being titrated during the first week of active treatment from week 16 onward. Patients on active treatment who met EE criteria were to continue to receive, in a blinded fashion, the same dosage of apremilast to which they had originally been assigned.

Randomization was stratified according to whether the participant was using small-molecule DMARDs. In PALACE-3, randomization was also stratified according to the involvement of ≥ 3% BSA with psoriasis and ensured that at least 60% of patients enrolled in the study had ≥ 3% BSA involved with psoriasis at baseline. Because apremilast 30 mg orally b.i.d.is the Health Canada–approved dose for the treatment of active PsA, only data for this dose from studies PALACE-1, PALACE-2, and PALACE-3 are included in the current report.

During the dose-blinded active treatment period (weeks 24 to 52), patients originally randomized to placebo and not re-randomized to escape treatment on week 16 were re-randomized in a 1:1 ratio to receive either apremilast 20 mg b.i.d. or apremilast 30 mg b.i.d. with the dose of apremilast being titrated during the first week of active treatment. All three trials include an ongoing open-label, long-term safety phase of up to four years' duration. A schematic of the study design of PALACE-1, PALACE-2, and PALACE-3 trials can be found in Figure 2. Data from the dose-blind active treatment period are summarized in APPENDIX 6.

FIGURE 2: STUDY DESIGN SCHEMATIC (PALACE-1, PALACE-2, AND PALACE-3 STUDIES)



ACR = American College of Rheumatology; BID = twice-daily; PBO = placebo; Wk = week.
Source: Clinical Study Report (CSR) for PALACE-1,[17] CSR for PALACE-2,[18] CSR for PALACE-3. [19]

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The inclusion criteria in PALACE-1, PALACE-2, and PALACE-3 were patients aged 18 years or older with a diagnosis of PsA (by any criteria) of at least six months' duration. In addition, patients were required to meet the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria at time of screening and have

active disease as evidenced by a minimum of both ≥ 3 tender and ≥ 3 swollen joints despite prior or current treatment with DMARDs (where inadequate control by DMARDs applies to therapeutic failure, loss of insurance, intolerance, adverse effects, or other reasons for discontinuation). Up to 10% of patients were permitted to enroll after having experienced a therapeutic failure with biologic TNF blockers. Patients in PALACE-3 had to have at least one ≥ 2 cm plaque psoriasis lesion in addition to active PsA. Patients were excluded if they had therapeutic failure of three or more agents for PsA (small molecules or biologics), or one or more biologic TNF blocker. Patients were also excluded if they had rheumatic autoimmune disease other than PsA, functional class IV as defined by the ACR Classification of Functional Status in Rheumatoid Arthritis; had a prior history of or current inflammatory joint disease other than PsA; had used phototherapy or DMARDs other than MTX, leflunomide, or sulfasalazine within four weeks of randomization; used adalimumab, etanercept, golimumab, infliximab, certolizumab pegol, or tocilizumab within 12 weeks of randomization, or alefacept or ustekinumab within 24 weeks of randomization; had prior treatment with apremilast; or had active tuberculosis or a history of incompletely treated tuberculosis.

b) Baseline Characteristics

The treatment groups in all three trials were generally balanced with respect to demographics between treatment arms and individual studies. Across the three trials, the patients' mean age ranged from 49.5 to 51.4 years, almost equal proportions were male and female patients, and the majority of patients were white. Patients' baseline disease characteristics and background PsA-related therapy were similar between individual treatment arms and studies. Across the three trials, mean PsA duration ranged from 6.8 to 8.1 years; mean SJC from 9.2 to 12.8; mean TJC from 18.0 to 23.3; mean PASI score from 7.6 to 9.2; mean Health Assessment Questionnaire – Disability Index (HAQ-DI) from 1.16 to 1.25; prior biologic use from 14.2% to 28.4%; concomitant DMARD use from 60% to 70%; and concomitant MTX use from 49.7% to 59.1%. In the PALACE-1 trial, the proportion of patients with psoriasis BSA ≥ 3% was higher in the apremilast 30 mg treatment groups (48.8%) than in the placebo group (40.5%) (Table 5).

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Characteristics	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
Demographic Characteristics						
Age, mean (SD)	51.1 (12.13)	51.4 (11.72)	51.2 (10.97)	50.5 (11.20)	49.5 (11.64)	49.9 (11.38)
Female, n (%)	80 (47.6)	92 (54.8)	85 (53.5)	95 (58.6)	91 (53.8)	88 (52.7)
Weight, kg, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, white, n (%)	153 (91.1)	152 (90.5)	[redacted]	[redacted]	[redacted]	[redacted]
Disease Characteristics						
PsA duration in years, mean (SD)	7.31 (7.12)	8.09 (8.09)	7.76 (8.25)	6.82 (7.59)	6.78 (6.46)	7.48 (7.65)
History of psoriasis (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of psoriasis in years, mean (SD)	15.7 (13.0)	16.50 (12.3)	[redacted]	[redacted]	[redacted]	[redacted]
Psoriasis BSA ≥ 3%, n	68 (40.5)	82 (48.8)	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
(%)						
Nail psoriasis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scalp psoriasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Plaque-type psoriasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI (range 0 to 72), mean (SD)[a]	9.1 (9.5)	9.2 (9.7)	[redacted]	[redacted]	[redacted]	[redacted]
CRP (mg/L), mean (SD)	1.1 (1.436)	0.84 (1.024)	[redacted]	[redacted]	[redacted]	[redacted]
Tender joint count (range 0 to 78 joints), mean (SD)	23.3 (15.2)	23.1 (14.5)	[redacted]	[redacted]	[redacted]	[redacted]
Swollen joint count (range 0 to 76 joints), mean (SD)	12.8 (8.8)	12.8 (7.8)	[redacted]	[redacted]	[redacted]	[redacted]
DAS28(CRP), mean (SD)	4.92 (1.0)	4.87 (1.0)	[redacted]	[redacted]	[redacted]	[redacted]
CDAI (range 0 to 76, mean [SD])	29.7 (12.0)	29.4 (11.5)	[redacted]	[redacted]	[redacted]	[redacted]
Patient's assessment of pain (range 0 mm to 100 mm VAS), mean (SD)	61.2 (20.2)	57.9 (20.2)	[redacted]	[redacted]	[redacted]	[redacted]
Patient's global assessment of disease activity (range 0 mm to 100 mm VAS), mean (SD)	58.8 (22.3)	55.9 (21.5)	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI (range 0 to 3), mean (SD)	1.2 (0.6)	1.2 (0.6)	[redacted]	[redacted]	[redacted]	[redacted]
Dactylitis Severity Score (range 0 to 20)[b]						
n	68 (40.5)	68 (40.5)	[redacted]	[redacted]	[redacted]	[redacted]
mean (SD)	3.3 (3.3)	2.9 (2.4)	[redacted]	[redacted]	[redacted]	[redacted]
MASES (range 0 to 13)[c]						
n	98 (58.3)	114 (67.9)	[redacted]	[redacted]	[redacted]	[redacted]
mean (SD)	5.4 (3.5)	4.4 (3.1)	[redacted]	[redacted]	[redacted]	[redacted]
Prior and Concomitant Medication Use						
Prior use of DMARDs (biologic-naive), n (%)	120 (71.4)	124 (73.8)	[redacted]	[redacted]	[redacted]	[redacted]
Prior use of biologics, n (%)	41 (24.4)	41 (24.4)	[redacted]	[redacted]	[redacted]	[redacted]
Prior biologic failures, n (%)	19 (11.3)	14 (8.3)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline DMARD use, n (%)	110 (65.5)	106 (63.1)	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
Baseline MTX use, n (%)	90 (53.6)	88 (52.4)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline corticosteroids use, n (%)	12 (7.1)	16 (9.5)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline use of NSAIDs, n (%)	118 (70.2)	120 (71.4)	[redacted]	[redacted]	[redacted]	[redacted]

ACR = American College of Rheumatology; APR = apremilast; b.i.d. = twice daily; BSA = body surface area; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS28 = 28-joint Disease Activity Score; DMARD = disease-modifying anti-rheumatic drug; HAQ-DI = Health Assessment Questionnaire – Disability Index; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; SD = standard deviation; VAS = visual analogue scale.

[a] Examined among patients who had BSA ≥ 3% affected at baseline.

[b] Examined among patients with pre-existing dactylitis at baseline.

[c] Examined among patients with pre-existing enthesopathy at baseline.

Source: Kavanaugh et al.,[16] Clinical Study Report (CSR) for PALACE-1,[17] CSR for PALACE-2,[18] CSR for PALACE-3.[19]

3.2.3 Interventions

Apremilast was administered orally, at a dose of 30 mg twice daily and dose-titrated in 10 mg daily increments during the first week of treatment. The regimen in the placebo group was the same, and placebo tablets were described as being identical in appearance to apremilast.

NSAIDs, narcotic analgesics, oral corticosteroids, and DMARDs (sulfasalazine, MTX, or leflunomide) were permitted during the study. DMARDs were permitted only if they had been administered for at least 16 weeks and on a stable dose for at least four weeks prior to screening and through week 24 of the study.

3.2.4 Outcomes

The primary efficacy end point in all three included studies was the proportion of patients in each treatment group who achieved ACR20 response at week 16.

a) American College of Rheumatology (ACR20/ACR50/ACR70

The ACR criteria[27] for assessing joint status (originally developed for rheumatoid arthritis [RA] patients) provide a composite measure of ≥ 20%, ≥ 50%, or ≥ 70% improvement in both swollen and tender joint counts and at least three of five additional disease criteria, including Patient or Physician Global Assessment of disease activity (10 cm visual analogue scale [VAS]), HAQ-DI, patient assessment of pain intensity, and levels of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). The ACR20 is generally accepted as the minimally clinically important difference (MCID) indicating a response to treatment, while the ACR50 and ACR70 more likely reflect truly important change for the long-term management of arthropathy. The ACR is a general measure of clinical response of peripheral joint disease and does not include assessment of enthesitis, dactylitis, the spine, or the skin. ACR20 at week 16 was the primary outcome. ACR20 at week 24, and ACR50, and ACR70 at weeks 16 and 24 were additional secondary end points.

b) Health Assessment Questionnaire – Disability Index

The HAQ-DI was developed to assess physical disability and pain in RA[28] and has been used extensively in arthritis randomized controlled trials (RCTs), including for PsA. Through a self-assessed questionnaire of eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities), the difficulty patients experience in performing these activities is scored from 0 (without any difficulty) to 3 (unable to do). The MCID for the HAQ-DI ranges from 0.3 to 0.35.[29,30] Change from baseline in the HAQ-DI score at week 16 was a key secondary end point. Change from baseline in the HAQ-DI score at week 24 was an additional secondary end point. The proportion of patients with ≥ 0.13-point and ≥ 0.30-point improvements in HAQ-DI at weeks 16 and 24 were other efficacy variables that were not included in the hierarchical testing.

c) Psoriatic Arthritis Response Criteria

The Psoriatic Arthritis Response Criteria (PsARC)[31] measures signs and symptoms of PsA assessed by TJC and/or SJC, Physician Global Assessment (0 to 5 Likert scale), and Patient Global Assessment (0 to 5 Likert scale). For the Patient Global Self-Assessment and the Physician Global Assessment, improvement or worsening is defined by a decrease or increase, respectively, by one category on the Likert scale.[32] The PsARC was modified in all three studies by the use of tender and swollen joint counts, rather than joint scores, and the assessment of improvement or worsening in patient self-assessment and physician assessment using a 20 mm change on a 100 mm VAS, rather than a one-category change on a Likert scale. A modified PsARC treatment response was defined as improvement in at least two of the four measures, one of which had to be TJC or SJC, and no worsening in any of the four measures.[33] Modified PsARC responses at weeks 16 and 24 were additional secondary end points.

d) Clinical Disease Activity Index

The Clinical Disease Activity Index (CDAI) is a composite index that includes a 28 tender and swollen joint assessment along with a Patients' Global Assessment, and Evaluator's Global Assessment. The CDAI score ranges from 0 to 76, with a score of ≤ 2.8 designating remission, while > 2.8 and ≤ 10 represent low disease activity. Moderate and high disease activities are designated by scores of > 10 and ≤ 22, and > 22, respectively.[34] Change from baseline in the CDAI score at weeks 16 and 24 were additional secondary end points.

e) Disease Activity Score 28 and C-reactive Protein

The Disease Activity Score (DAS) includes a 28 tender and swollen joint assessment along with a Patient Global Assessment of well-being to evaluate a patient's response to treatment and C-reactive protein (CRP).[35,36] The score ranges from 0 to 9.4, with higher scores indicating greater disease activity.

The threshold values are 2.6, 3.2, and 5.1 for remission, low disease activity, and high disease activity, respectively.[27] The European League Against Rheumatism (EULAR) response criteria classify patients as good or moderate responders, or as nonresponders to treatment based on the individual patient's disease severity as measured on the current DAS28 score, and changes in DAS28 from baseline at the time of assessment.[37] Patients were considered DAS responders if they had a good or moderate response, defined according to baseline DAS values:[38]

TABLE 6: CHANGE FROM BASELINE IN DAS28 SCORE

Current DAS 28	Improvement in DAS 28 from Baseline		
	> 1.2	**> 0.6 to ≤ 1.2**	**≤ 0.6**
≤ 3.2	Good	Moderate	None
> 3.2 to ≤ 5.1	Moderate	Moderate	None
> 5.1	Moderate	None	None

DAS = Disease Activity Score.

Change from baseline in the DAS28 score at weeks 16 and 24 were additional secondary end points.

f) Psoriasis Area and Severity Index

The PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It produces a numeric score ranging from 0 to 72. In general, a PASI score of 5 to 10 is considered moderate disease, and a score higher than 10 is considered severe. A 75% reduction in the PASI score (PASI 75) is the current benchmark for most clinical trials in psoriasis and the criterion for efficacy of new psoriasis treatments approved by the FDA.[39] PASI 75 at weeks 16 and 24 was considered as a secondary end point in the PALACE-3 trial, while it was considered only as an exploratory end point in the PALACE-1 and PALACE-2 trials.

g) Medical Outcomes Study Short Form-36

The Short Form (36) Health Survey (SF-36) is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[40] The SF-36 consists of eight health domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH).[41] The eight domains are aggregated to create two component summaries: the physical component summary (PCS) and the mental component summary (MCS), with scores ranging from 0 to 100; higher scores indicate better health status. The MCID for either the PCS or MCS of the SF-36 for the change from baseline is typically between 2.5 and 5 points.[42-44] Leung and colleagues[45] reported MCIDs of change scores of 3.74 and 1.77 in PsA patients treated with anti-TNF alpha drugs for the PCS and MCS subsections, respectively. Change from baseline in the PF scale score (norm-based) of the SF-36v2 at weeks 16 and 24 were additional secondary end points.

h) EuroQol 5-Dimensions Questionnaire

The EuroQol 5-Dimensions Questionnaire (EQ-5D) measures the patient's general health status using a composite of a five-dimensional multiple choice questionnaire and a vertical VAS. The five dimensions of health status are mobility, self-care, usual activities (work, study, housework, and family/leisure activities), pain/discomfort, and anxiety/depression. For each dimension, a patient's response could be one of three levels: no problems, some problems, and extreme problems. The VAS component comprises a 20 cm vertical VAS on which a patient provides a self-rated health state, ranging from "the best imaginable health state" to "the worst imaginable health state."[46] The EQ-5D has shown discrimination and responsiveness in PsA trials.[47] No MCID for improvement in the EQ-5D for PsA patients was found in the literature. No statistical test was undertaken for EQ-5D comparison.

i) Work Limitations Questionnaire

The Work Limitations Questionnaire (WLQ-25) is a validated, self-reported, 25-item instrument for measuring the degree to which chronic health problems interfere with ability to perform job roles. The WLQ has four dimensions of on-the-job disability (limitations handling time, physical, mental-interpersonal, and output demands) with a total score range of 0 (limited none of the time) to 100

(limited all of the time) for the reported amount of time in the prior two weeks the respondents were limited on the job. The instrument was validated in a population of adults working 20 or more hours per week, and thus possibly excluded individuals with severe work limitations. The WLQ is context specific and focused on job demand performance and therefore can be used to identify both the magnitude and type of impact that health problems are having on people in the workplace.[48,49] No MCID for improvement in the WLQ-25 for PsA patients was found in the literature. No statistical test was undertaken for WLQ-25 comparison.

j) Maastricht Ankylosing Spondylitis Enthesitis Score

The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) is a validated enthesitis index for ankylosing spondylitis developed by assessing measures of disease activity, including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Mander Enthesitis Index (MEI). Enthesitis is defined as inflammation at the site of tendons, ligaments, or joint capsule fibre insertion into bone.[47] The MASES aims to provide a more practical and less time-consuming alternative to the MEI. The score for MASES index ranges from 0 to 13, correlating with the number of painful entheses out of the total of 13 assessed. MASES has not been assessed specifically for PsA.[47] No MCID for improvement in the MASES for PsA patients was found in the literature. Change from baseline in the MASES at weeks 16 and 24 in patients with pre-existing enthesopathy were additional secondary end points.

k) Dactylitis Severity Score

Dactylitis is characterized by swelling of the entire digit (finger or toe) and represents a combination of synovitis and inflammation of tendon and ligament insertions.[47] It is a hallmark feature of PsA, occurring in 16% to 48% of reported cases.[47] The Dactylitis Severity Score is the sum of the individual scores for each digit, and ranges from 0 to 20: 0 for no dactylitis or 1 for dactylitis present in each digit. The results from each digit with dactylitis are then summed to produce a final score. No MCID for improvement in the Dactylitis Severity Score for PsA patients was found in the literature. Change from baseline in the Dactylitis Severity Score at weeks 16 and 24 in patients with pre-existing dactylitis were additional secondary end points.

l) Functional Assessment of Chronic Illness Therapy – Fatigue

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale is a self-administered questionnaire that assesses both the physical and functional consequences of fatigue.[50] The FACIT-F was validated in a Toronto PsA cohort study and was found to be well correlated with the modified Fatigue Severity Scale (FSS), showing high internal consistency and test–retest reliability, as well as criterion and construct validity.[47] It is a 13-item questionnaire with each question scored from 0 to 4, for a total score range of 0 to 52. Higher scores denote lower levels of fatigue. Therefore, higher FACIT-F scores are expected with greater improvements in a patient's PsA.[50] A validated MCID for improvement in the FACIT-F is not currently available in PsA patients. The clinical trials included in this review used 3.56, which is the validated FACIT-F MCID in RA patients.[51] Change from baseline in the FACIT-F scale score at weeks 16 and 24 were additional secondary end points. A post hoc analysis was conducted for the proportion of patients with ≥ 3.56-point improvement in FACIT- F score at weeks 16 and 24.

Patient's Assessment of Pain

Patients' assessment of pain was scored on a 0 mm to 100 mm horizontal line, on which 0 represents "no pain" and the 100-mm mark represents "pain as severe as can be imagined."[52] Patients were asked to place a vertical line on the horizontal line to indicate the level of their arthritis pain on the day of the visit.[52] The MCID of patient's assessment of pain was defined as an improvement (reduction) in pain of 10 mm or more from baseline.[52] Patients' assessment of pain is part of the ACR core set of measures in

arthritis.[53] Change from baseline in the patient assessment of pain at weeks 16 and 24 were additional secondary end points. A post hoc analysis was conducted for the proportion of patients with ≥ 10 mm reduction in patient's assessment of pain VAS at weeks 16 and 24.

Adverse Events

An adverse event (AE) was any noxious, unintended, or untoward medical occurrence that may appear or worsen in a patient during the course of the study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patient's health, including laboratory test values, regardless of etiology.

3.2.5 Statistical Analysis

All three studies had more than 95% power to demonstrate the superiority of one dose of apremilast over placebo with respect to the proportion of patients achieving ACR20 response at a two-sided significance level of 0.05 (0.025 per side). It was estimated that approximately 165 patients were needed to be randomized into each of the placebo, apremilast 20 mg b.i.d., and apremilast 30 mg b.i.d. treatment groups in order to achieve that power. Sample size estimations were based on the results of the phase 2 Study CC-10004-PSA-001, which reported an underlying response rate of 20% for placebo, and an underlying treatment difference of 20 percentage points (in favour of apremilast) between one dose of apremilast and placebo as measured by the proportion of patients achieving ACR20 response.

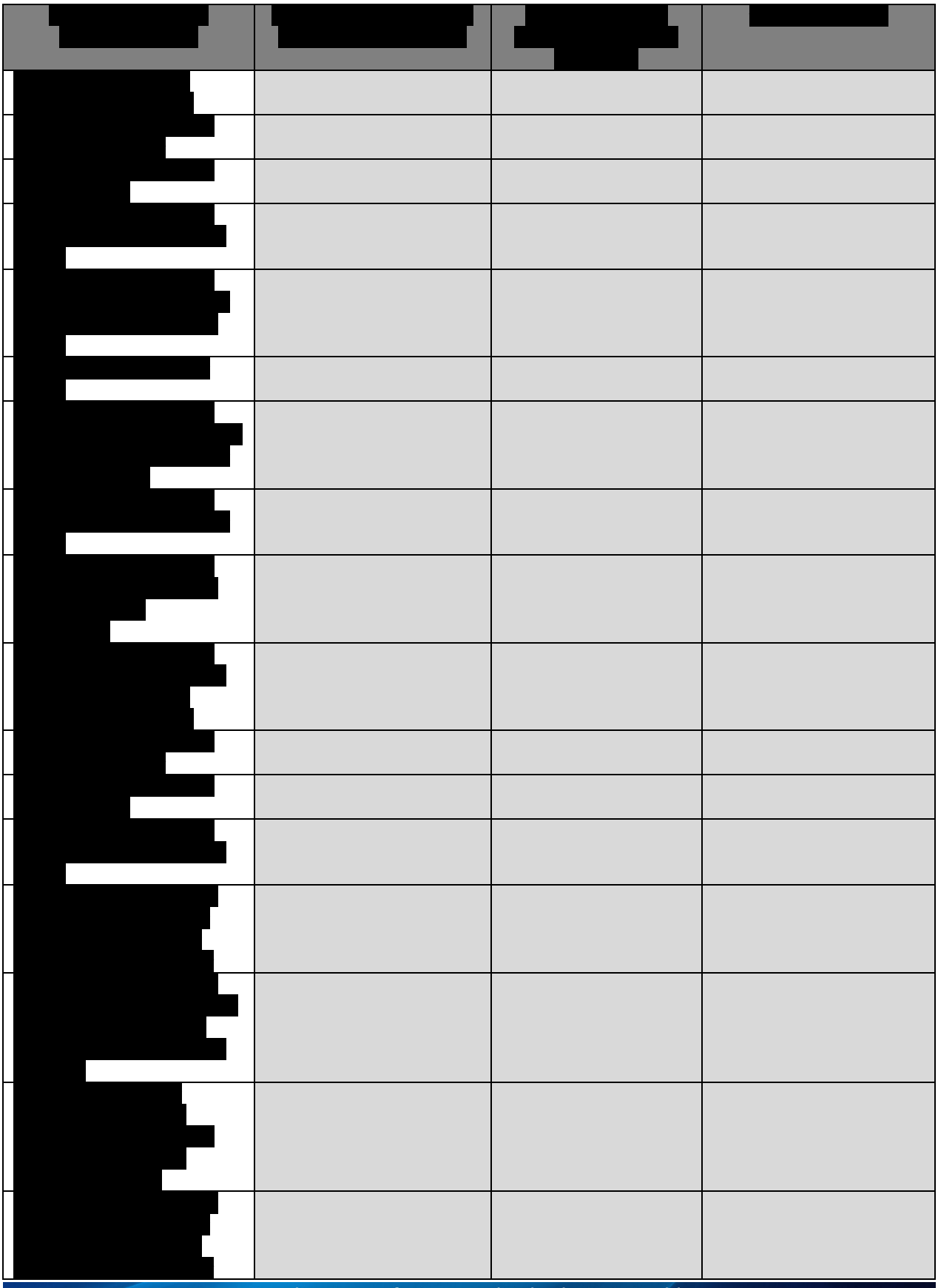
The full analysis set (FAS) was the primary population for the efficacy analyses for the placebo-controlled period. The Cochran–Mantel–Haenszel (CMH) test was used for discrete end point, and an analysis of covariance (ANCOVA) model was used for continuous outcomes. The CMH test adjusted for strata of baseline DMARD use (yes/no). This ANCOVA model used the change from baseline as the response variable, and included treatment group and baseline DMARD use, as factors and the baseline value as a covariate. In PALACE-3, the statistical analyses additionally controlled for ≥ 3% BSA with psoriasis at baseline. The analyses of the primary and secondary end points evaluated at weeks 16 or 24 were performed by treatment group (placebo, apremilast 20 mg b.i.d., and apremilast 30 mg b.i.d.). Treatment differences were evaluated only between each apremilast dose and placebo and calculated as apremilast minus placebo. Efficacy results were considered statistically significant after consideration of the strategy for controlling the type I error rate as described below. All statistical tests were conducted at the alpha = 0.050 (two-sided) level, and two-sided *P* values and confidence intervals (CIs) were reported. The primary efficacy end point in all three included studies was the proportion of patients in each treatment group who achieved ACR20 response at week 16.

Statistical tests were conducted between each apremilast dose and placebo for the primary end point and secondary end points evaluated at week 16 or 24. To control the experiment-wise type I error rate, formal statistical tests were carried out sequentially for these end points, starting with the primary end point and then the secondary end points evaluated at weeks 16 or 24 in the order presented below. The pair-wise comparisons (apremilast 30 mg b.i.d. versus placebo, and apremilast 20 mg b.i.d. versus placebo) for each end point were performed using the Hochberg procedure. Specifically, for the primary end point (ACR 20 response at week 16), if the two-sided *P* values from both of the pair-wise comparisons were ≤ 0.050, then both test results were considered statistically significant and both apremilast doses were declared efficacious. If the two-sided *P* value from one of the two pair-wise comparisons was > 0.050, but the two-sided *P* value from the other comparison was ≤ 0.025, then the latter test result was considered statistically significant and the corresponding apremilast dose tested was declared efficacious. In other situations, neither of the apremilast doses was declared efficacious.

Formal pair-wise comparisons with respect to the first secondary end point (change from baseline in the HAQ-DI score at week 16) were conducted conditional on the test results for ACR20 response at week 16. If the test results of ACR20 response for both apremilast doses were statistically significant, then the two pair-wise comparisons for the HAQ-DI score were performed using the Hochberg procedure at the alpha = 0.05 level, as described above for ACR20 response. If only the test result of ACR20 response for one apremilast dose was statistically significant, then only the comparison between that apremilast dose and placebo was conducted for the HAQ-DI score, at the alpha = 0.025 level. If neither test result of ACR 20 response was statistically significant, then formal statistical tests were not performed for the HAQ-DI score and the remaining secondary end points evaluated at weeks 16 or 24. Formal statistical tests for the remaining secondary end points evaluated at weeks 16 or 24 (in the order presented below) were carried out in the same manner as described above.

Order of statistical testing in the hierarchical analysis plan for secondary outcomes, as well as the outcomes not included in the hierarchy, are presented in Table 7.

TABLE 7: SUMMARY OF SECONDARY OUTCOMES ANALYZED IN PALACE-1, PALACE-2, AND PALACE-3



[redacted]	[redacted]	[redacted]	[redacted]
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ACR20/50/70 = American College of Rheumatology 20%/50%/70% response; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS = Disease Activity Score; EQ-5D = EuroQol-5 Dimensions; EULAR = European League Against Rheumatism; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; PCS = physical component summary; PASI-50/75 = 50%/75% or greater improvement in the Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; SF-36v2 = Short Form (36) Health Survey, version 2; WLQ-25 = 25-Item Work Limitations Questionnaire.

[a] Hierarchical testing failed for the analysis (change from baseline in the patient assessment of pain) at week 16 in PALACE-2.

[b] Hierarchical testing failed for the analysis (change from baseline in the MASES at week 16 in patients with pre-existing enthesopathy) in PALACE-1 and PALACE-3.

[redacted]

[redacted]

[redacted]

For ACR response end points, patients who discontinued early — prior to week 16 — and those who did not have sufficient data for a definitive determination of response status at week 16 were counted as nonresponders. Joints temporarily or permanently not assessable at baseline were excluded from joint count. For other unassessed joints at baseline, the joint assessment at the screening visit, if assessed, was used as the baseline assessment; otherwise, the joint was excluded from joint count. The last observed joint assessment (at baseline or post-baseline) was used for joints unassessed at week 16. There was no imputation for other missing ACR component scores. Patients who escaped early at week 16, patients who discontinued early — prior to week 24 — and patients who did not have sufficient data for a definitive determination of response status at week 24 were counted as nonresponders. Same imputation rules were applied to the other binary end points. For continuous end points, missing data at weeks 16 and 24 were imputed using last observation carried forward (LOCF).

Subgroup analyses by number of prior DMARDs and/or biologic response modifiers and by body weight at baseline were performed for ACR20. The CDR review protocol included subgroup by disease severity (based on DAS28) at baseline; however, such subgroup analyses were not undertaken.

a) Analysis Populations

The safety population dataset consisted of all patients who were randomized and received at least one dose of investigational product.

The FAS consisted of all patients who were randomized as specified in the protocol.

The per-protocol analysis dataset (PPS) consisted of all patients included in the safety population who had at least one post-treatment ACR evaluation and no major protocol deviations.

3.3 Patient Disposition

Patient disposition is summarized in Table 8. Approximately equal numbers of patients were enrolled in the three studies, with similar proportions of patients discontinued within treatment arms. At week 16, a greater proportion of placebo-treated patients entered EE (range 55% to 64%) compared with patients treated with apremilast 30 mg b.i.d. (range 31.7% to 40%). Within the 16-week treatment duration, a slightly higher number of patients treated with apremilast 30 mg b.i.d.in the PALACE-1 and PALACE-2 studies discontinued due to AEs, compared with placebo-treated patients. Discontinuation due to lack of efficacy was similar among treatment arms. At week 24, a slightly higher number of patients treated with apremilast 30 mg b.i.d. in study [redacted] discontinued due to AEs, compared with placebo-treated patients. Discontinuation due to lack of efficacy remained similar between treatment arms.

TABLE 8: PATIENT DISPOSITION

	PALACE-1		PALACE-2		PALACE-3	
	Placebo	APR 30 mg b.i.d.	Placebo	APR 30 mg b.i.d.	Placebo	APR 30 mg b.i.d.
Screened, N	615		611		612	
Randomized, N	168	168	159	162	169	167
Discontinued through week 16, N (%)	10 (6)	14 (8)	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	5 (3)	9 (5)	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	3 (2)	2 (1)	[redacted]	[redacted]	[redacted]	[redacted]
Protocol violation	1 (1)	0 (0)	[redacted]	[redacted]	[redacted]	[redacted]
Non-compliance with study drug	0 (0)	1 (1)	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by patient	1 (1)	2 (1)	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	0 (0)	0 (0)	[redacted]	[redacted]	[redacted]	[redacted]
Other	0 (0)	0 (0)	[redacted]	[redacted]	[redacted]	[redacted]
Early escape	107 (64)	58 (35)	88 (55)	64 (40)	97 (57.4)	53 (31.7)
Early escape to 20 mg b.i.d.	54 (32)	NA	44 (28)	NA	47 (28)	NA
Early escape to 30 mg b.i.d.	53(32)	NA	44(28)	NA	50 (30)	NA
Discontinued through week 24, N (%)	18 (10.7)	20 (11.9)	16 (10)	20 (12)	23 (13.6)	22 (13.2)
Adverse event	11 (6.5)	10 (6.0)	4 (3)	12 (7)	10 (5.9)	8 (4.8)
Lack of efficacy	4 (2.4)	4 (2.4)	3 (2)	2 (1)	6 (3.6)	7 (4.2)
Protocol violation	1 (0.6)	0 (0.0)	0 (0)	1 (1)	0 (0.0)	1 (0.6)
Non-compliance with study drug	0 (0.0)	2 (1.2)	0 (0)	0 (0)	0 (0.0)	0 (0.0)
Withdrawal by participant	2 (1.2)	3 (1.8)	7 (4)	3 (2)	3 (1.8)	1 (0.6)
Lost to follow-up	0 (0)	0 (0)	1 (1)	2 (1)	1 (0.6)	3 (1.8)
Other	0 (0.0)	1 (0.6)	1 (1)	0 (0)	3 (1.8)	2 (1.2)
Full analysis set, N (%)[a]	168 (100.0)	168 (100.0)	159 (100)	162 (100)	169 (100.0)	167 (100.0)
Per-protocol, N (%)[b]	165 (98.2)	161 (95.8)	[redacted]	[redacted]	[redacted]	[redacted]
Safety, N (%)[c]	168 (100.0)	168 (100.0)	159 (100)	162 (100)	168 (99.4)	167 (100.0)

APR = apremilast; b.i.d. = twice daily; NA = not applicable.
[a] Includes patients who were randomized as specified in the protocol.
[b] Includes patients who were randomized, received at least 1 dose of investigational product, had at least 1 change from baseline in tender joint count, swollen joint count, and at least 3 of the other 5 American College of Rheumatology components, and had no protocol violations that might substantially affect the efficacy results through week 24.
[c] Includes patients who were randomized and received at least 1 dose of investigational product.
Source: Kavanaugh et al.,[16] Clinical Study Report (CSR) for PALACE-1,[17] CSR for PALACE-2,[18] CSR for PALACE-3.[19]

3.4 Exposure to Study Treatments

In all three studies, the mean exposure in the apremilast 30 mg b.i.d. treatment group was approximately 22.0 (standard deviation [SD] approximately 6) weeks, whereas in the placebo group of PALACE-1, in which the majority of patients (63.7%) entered EE, the mean exposure to placebo was approximately [redacted]; in the placebo group of PALACE-2, in which approximately half the patients (55.3%) entered EE, the mean exposure to placebo was approximately [redacted]; in the placebo group of PALACE-3, in which more than half the patients (57.4%) entered EE, the mean exposure to placebo was approximately [redacted].

In the PALACE-1 trial, during the placebo-controlled period, concomitant medications used were mainly DMARDs (64.9%), which included MTX (54.2%) at a mean dose of [redacted] mg/week. In addition, the majority of patients (71.6%) were taking NSAIDs at baseline, with approximately [redacted] of patients in each treatment group taking narcotics or other analgesics. In the PALACE-2 trial, during the placebo-controlled period, the concomitant medications used were mainly DMARDs [redacted], which included MTX ([redacted]) at a mean dose of [redacted] mg/week. In addition, the majority of patients (69.6%) were taking NSAIDs at baseline, with approximately [redacted] of patients in each treatment group taking narcotics or other analgesics. In the PALACE-3 trial, during the placebo-controlled period, the concomitant medications used were mainly DMARDs ([redacted]), which included MTX ([redacted]) at a mean dose of [redacted] mg/week. In addition, the majority of patients (70.7%) were taking NSAIDs at baseline, with approximately [redacted] of patients in each treatment group taking narcotics or other analgesics.

3.5 Critical Appraisal

3.5.1 Internal Validity

Randomization was performed using an interactive voice response system and appropriate measures appear to have been taken to ensure allocation concealment. All three studies were double-blinded and the placebo intervention was described by the manufacturer as matched in appearance to apremilast. Apremilast is associated with gastrointestinal adverse effects and it is possible that this may have led to unblinding in some instances, as patients who experienced these adverse effects may have speculated that they were on apremilast. It is not known what the precise impact of unblinding would be on investigator-assessed outcomes, and the effectiveness of the blinding does not appear to have been tested.

The manufacturer accounted for multiplicity in its secondary outcomes by using a hierarchical testing procedure, which is considered an acceptable strategy for controlling for multiple comparisons. In this procedure, statistical testing is continued on subsequent outcomes only for as long as testing reveals statistical significance on the previous outcome. The comparisons of the outcomes after the statistical testing was stopped due to the hierarchy procedure could not be interpreted.

Outcomes (either exploratory, quality of life, or post hoc) were also tested that fell outside the hierarchy, although those that were key efficacy outcomes in this review were PASI 75 (for PALACE-1 and PALACE-2 trials), the EQ-5D, and the WLQ-25. Because these outcomes fell outside the hierarchy, their results must be interpreted with caution because of the risk of inflated type 1 error.

Subgroup analyses by number of prior DMARDs and/or biologic response modifiers and by body weight at baseline were performed for ACR20. Results should be interpreted with caution as they are likely not adequately powered, given the small sample sizes and that they were not adjusted for multiplicity; moreover, randomization is not maintained in these subgroup analyses. In PALACE-1, PALACE-2, and

PALACE-3, 74%, 65%, and 71% of placebo patients discontinued randomized treatment before week 24 (either due to EE or because of treatment discontinuation), respectively. This means that a substantial proportion of the outcome data at week 24 had to be imputed based on an ITT analysis. Therefore, there is a very high degree of uncertainty with respect to the findings of the studies beyond the week 16 time point.

PsA is a condition with a variable and heterogeneous course. It is possible that the patients in the placebo group who met EE criteria were experiencing a flare at 16 weeks. The impact of disease flare on EE, especially in the placebo group, is not clear.

Inclusion criteria for the trials specified active PsA despite current or previous DMARDs. Inadequate control by DMARDs applies to therapeutic failure, loss of insurance, intolerance, adverse effects, or other reasons for discontinuation. Therapeutic failure and intolerance were not defined, and who reported it (i.e., was it the patient or the physician?) it is not clear. The manufacturer clarified that the reason patients discontinued prior DMARDs was captured on the case report form by patient or investigator. The manufacturer also suggested that the definition of treatment failure is implicit, as patients had to present with active disease at screening to be eligible for study inclusion. However, this definition of treatment failure could include patients who responded to prior treatment but still have active disease, hence were misclassified as treatment failure. In the absence of a formal record of treatment failure, there remains uncertainty as to whether these patients were true treatment failures.

3.5.2 External Validity

Several outcomes measured in the trials have limitations, including lack of clearly defined minimally important difference in score change in PsA patients (see APPENDIX 5).

Approximately 1.6% of patients had never received treatments with DMARDs and these patients do not reflect the product indication. Although it was a small proportion of patients in the trials and might not have an impact on overall results, these patients may have had less severe disease than patients who had responded inadequately to DMARDs. In addition, no information was provided as to why these patients never received DMARDs.

Patients were excluded from the trials if they had a history of clinically significant cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, other major uncontrolled disease, or significant infection. While this is a prudent approach, it limits generalizability of harms results to clinical practice, where patients who are at higher risk may be prescribed the drug.

PsA is a chronic disease with the expectation that patients will be on treatment for many years. Although long-term harms data were reported for up to 52 weeks in all three studies, the only placebo-controlled data that exist for apremilast are from week 24; however, these data are likely limited in their utility, given the aforementioned high proportion of patients who discontinued randomized treatment (either due to EE or because of treatment discontinuation) during the studies.

High-quality evidence for the use of MTX in PsA is lacking, although it is generally accepted in clinical practice as a therapeutic option. With the lack of evidence, appropriate dosing of MTX is unclear. In all three studies, the median dose at baseline ranged from 15 mg/week to 16 mg/kg across studies and between treatment arms, which is lower than recommended MTX doses used in RA (approximately 25 mg/week).

There is a lack of direct, head-to-head comparisons of apremilast versus another active control, such as MTX or one of the biologics.

Limitations on concomitant medications, allowable doses of these, and treatment history may have compromised external validity to some degree. Patients were allowed to receive stable, sub-maximal doses of concomitant MTX, sulfasalazine, and leflunomide; low-dose oral corticosteroids; and/or nonsteroidal anti-inflammatory drugs. However, concomitant treatment with potent immunosuppressants, including all biologic DMARDs or cyclosporine, was not permitted. Patients who had therapeutic failures of three or more agents for PsA (DMARDs), or one or more biologic TNF blocker, were excluded. Previous treatment with a biologic, including TNF blockers, was allowed, but only up to 10% could be TNF blocker therapeutic failures, which might limit the generalizability of the results.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (section 2.2, Table 3). See APPENDIX 4 for detailed efficacy data. Only apremilast 30 mg orally b.i.d. is the Health Canada–approved dose for the treatment of active PsA, and only data for this dose are included in the Efficacy section.

The following end points were formally assessed for statistical significance according to the Hochberg procedure for multiple testing: ACR20 response at weeks 16 and 24, change from baseline in the HAQ-DI score at weeks 16 and 24, change from baseline in the PF scale score (norm-based) of the SF-36v2 at week 16, modified PsARC response at week 16, and change from baseline in the patient assessment of pain at week 16 for all three trials, and change from baseline in the MASES at week 16 in patients with pre-existing enthesopathy in PALACE-1 and PALACE-2 trials, and PASI-75 response at week 16 among patients whose psoriasis BSA at baseline was ≥ 3% in the PALACE-3 trial. All other end points are exploratory in nature and should be interpreted with caution.

3.6.1 Outcomes Related to Psoriatic Arthritis

a) ACR20, 50, 70

In all three studies, a statistically significantly greater proportion of patients in the apremilast 30 mg b.i.d. treatment group achieved an ACR20 response at week 16 compared with placebo (38.1% versus 19.0%, $P = 0.0001$ in PALACE-1; 32.1% versus 18.9%, $P = 0.0060$, in PALACE-2; and 40.7% versus 18.3%, $P < 0.0001$ in PALACE-3). Similarly, a statistically significantly greater proportion of patients in the apremilast 30 mg b.i.d. treatment group achieved an ACR20 response at week 24 compared with placebo (Table 9).

TABLE 9: PROPORTION OF PATIENTS WITH ACR20 RESPONSES AT WEEK 16 (FULL ANALYSIS SET)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d, N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
ACR20 at week 16[a]						
n (%)	32 (19.0)	64 (38.1)	30 (18.9)	52 (32.1)	31 (18.3)	68 (40.7)
Adjusted % difference in proportions (95% CI)[b]	19.0 (9.7 to 28.3)		13.4 (4.0 to 22.7)		22.3 (13.0 to 31.6)	
P value[c]	**0.0001**		**0.0060**		**< 0.0001**	
ACR20 at week 24[a]						
n (%)	22 (13.1)	59 (35.1)	25 (15.7)	40 (24.7)	26 (15.4)	52 (31.1)
Adjusted % difference in proportions (95% CI)[b]	22.2 (13.4 to 30.9)		9.2 (0.5 to 17.8)		15.5 (6.7 to 24.3)	
P value[c]	**< 0.0001**		**0.0394**		**0.0007**	

ACR20 = American College of Rheumatology 20% response; APR = apremilast; b.i.d.= twice daily; CI = confidence interval; CMH = Cochran–Mantel–Haenszel.

[a] Patients who discontinued early — prior to week 16 — and patients who did not have sufficient data for a definitive determination of response status at week 16 were counted as nonresponders. Joints temporarily or permanently not assessable at baseline were excluded from joint count. For other unassessed joints at baseline, the joint assessment at the screening visit, if assessed, was used as the baseline assessment; otherwise, the joint was excluded from joint count. The last observed joint assessment (at baseline or post-baseline) was used for joints unassessed at week 16. There was no imputation for other missing ACR component scores.

[b] Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[c] 2-sided *P* value is based on the CMH test adjusting for baseline DMARD use. *P* values in bold are considered statistically significant.

A higher proportion of patients in the apremilast 30 mg b.i.d. group achieved ACR50 and ACR70 response at weeks 16 and 24 compared with placebo in all three trials. However, claims of statistical significance could not be made because the hierarchical testing was stopped before testing these outcomes (Table 11, Table 12).

b) Health Assessment Questionnaire – Disability Index

In all three studies, a statistically significantly greater reduction from baseline in HAQ-DI score was achieved in patients in the apremilast 30 mg b.i.d. treatment group at weeks 16 and 24 compared with placebo; however, the average change from baseline in the apremilast 30 mg b.i.d. treatment group at week 16 was –0.244 (0.0364), –0.193 (0.0354), and –0.192 (0.0339) in PALACE-1, PALACE-2, and PALACE-3, respectively, and it was respectively –0.258 (0.0371), –0.206 (0.0372), and –0.192 (0.0353) at week 24. The MCID for the HAQ-DI has been estimated to range from 0.13 to 0.35 (Table 14).

The proportion of patients achieving HAQ-DI improvements of at least 0.13 points at week 16 was statistically significant in favour of the apremilast 30 mg b.i.d. treatment group in comparison with the placebo treatment group in the PALACE-2 study only, while there were no significant differences in PALACE-1 and PALACE-3. The difference in per cent HAQ-DI response ranged from 7.6% to 12.4% across the studies. At week 24, all three studies achieved statistical significance in favour of the apremilast 30 mg b.i.d. treatment group in comparison with the placebo treatment group. The difference in per cent HAQ-DI response ranged from 12.9% to 15.4% across the studies. However, this outcome assessment (at

both weeks 16 and 24) was not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type 1 error (Table 14).

The proportion of patients achieving HAQ-DI improvements of at least 0.3 points at week 16 was statistically significant in favour of the apremilast 30 mg b.i.d. treatment group in comparison with the placebo treatment group in the PALACE-1 and PALACE-2 studies, while there were no significant differences in PALACE-3. The difference in per cent HAQ-DI response ranged from 6.9% to 13.2% across the studies. Similar results were seen at week 24. However, this outcome assessment (at both weeks 16 and 24) was not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type 1 error (Table 14).

c) Psoriatic Arthritis Response Criteria

In all three trials, there were statistically significantly greater proportions of PsARC responders in the apremilast 30 mg b.i.d. treatment group compared with placebo at week 16, with differences between the apremilast 30 mg b.i.d. treatment group and placebo treatment group of 16.7%, 14.9%, and 25.4% in PALACE-1, PALACE-2, and PALACE-3, respectively. While at week 24 there were greater proportions of PsARC responders in the apremilast 30 mg b.i.d. treatment group compared with placebo, claims of statistical significance could not be made because the hierarchical testing was stopped before testing this outcome (Table 15).

d) Clinical Disease Activity Index

In all three trials, there was a greater reduction in CDAI score from baseline in the apremilast 30 mg b.i.d. treatment group compared with placebo at weeks 16 and 24; however, claims of statistical significance could not be made because the hierarchical testing was stopped before testing these outcomes (Table 16).

e) DAS28

In all three trials, there was a greater reduction in DAS28 score in the apremilast 30 mg b.i.d. treatment group compared with placebo at weeks 16 and 24; however, claims of statistical significance could not be made because the hierarchical testing was stopped before testing these outcomes (Table 17).

The proportion of patients achieving a DAS28 EULAR response of good or moderate was higher in the apremilast 30 mg b.i.d. treatment group compared with placebo at weeks 16 and 24; however, claims of statistical significance could not be made because the hierarchical testing was stopped before testing these outcomes (Table 18).

f) Enthesitis (MASES)

In all three trials in patients with pre-existing enthesopathy, there were no statistically significant differences in the change from baseline in MASES scores at week 16 (Table 24). Claims of statistical significance could not be made for the comparison at week 24 because the hierarchical testing was stopped before testing at that time point. In addition, in all three trials in patients with pre-existing enthesopathy, there were no differences in the proportion of patients achieving at least 20% MASES improvement at weeks 16 and 24; however, claims of statistical significance could not be made because the hierarchical testing was stopped before testing these outcomes (Table 25).

g) Dactylitis

In all three trials in patients with pre-existing dactylitis, there were no differences in the change from baseline in Dactylitis Severity Score at week 16. There were greater reductions in Dactylitis Severity

Score from baseline in the apremilast 30 mg b.i.d. treatment group compared with placebo at week 24 in the PALACE-3 trial only (Table 26). In all three trials in patients with pre-existing dactylitis, there were no differences in the proportion of participants achieving a Dactylitis Severity Score of 0 at weeks 16 and 24 (Table 27). However, inferences about statistical significance for the results of the dactylitis analyses could not be made because the hierarchical testing was stopped before testing these outcomes.

3.6.2 Outcomes Related to Psoriasis

a) Psoriasis Area and Severity Index

Only patients with a BSA involvement ≥ 3% at baseline had a PASI assessment. The proportion of patients achieving PASI75 response in the apremilast 30 mg b.i.d. treatment group compared with placebo was statistically significantly higher in PALACE-3. In addition, in PALACE-1 and PALACE-2, the proportion of patients achieving PASI75 response in the apremilast 30 mg b.i.d. treatment group was higher than placebo group at week 16 and it was higher in all three studies at week 24; however, claims of statistical significance for these analyses could not be made because the hierarchical testing was stopped before testing these outcomes.

A post hoc analysis was conducted on the proportion of patients achieving PASI50 response, and it was found that patients in the apremilast 30 mg b.i.d. treatment group had higher response compared with placebo at weeks 16 and 24 for all three studies (Table 30). However, these analyses were post hoc in nature and any result reported should be interpreted with caution.

3.6.3 Health-Related Quality of Life and Other Patient-Reported Outcomes

a) Short Form (36) Health Survey

Results for the mean change from baseline in SF-36 PF domain score at weeks 16 and 24 are presented in Table 20. In the three trials, the mean change from baseline at week 16 for SF-36 PF domain score ranged from 2.91 to 4.23 in the apremilast 30 mg b.i.d. treatment group and ranged from 0.81 to 1.81 in the placebo treatment group, and the difference between apremilast 30 mg b.i.d. treatment group and placebo ranged from 2.10 to 2.42. In all three trials there was statistically significantly greater change from baseline in the SF-36 PF domain score in the apremilast 30 mg b.i.d. treatment group than in the placebo group at week 16.

At week 24, there was greater change from baseline in SF-36 PF domain score in the apremilast 30 mg b.i.d. treatment group than in the placebo group in all three studies. However, claims of statistical significance could not be made because the hierarchical testing was stopped before testing this outcome.

The proportion of patients achieving an improvement ≥ 2.5 points in SF-36 PF domain at weeks 16 and 24 was statistically significantly greater in the apremilast 30 mg b.i.d. treatment group than in the placebo group in the PALACE-1 study only. However, this outcome assessment was not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type 1 error.

Results for the SF-36 PCS at weeks 16 and 24 are presented in Table 21. The proportion of patients achieving an improvement ≥ 2.5 points in SF-36 PCS at weeks 16 and 24 was statistically significantly greater in the apremilast 30 mg b.i.d. treatment group than in the placebo group in PALACE-1 and PALACE-3 studies only. However, this outcome assessment was not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type 1 error.

b) Patient's Assessment of Pain

At weeks 16 and 24, the mean change in scores decreased (improved) from baseline for all treatment arms, including placebo. The apremilast 30 mg b.i.d. treatment group was statistically significantly improved relative to placebo for mean score change at week 16 in the PALACE-1 and PALACE-3 studies. The average (SD) change from baseline in the apremilast 30 mg b.i.d. treatment group at week 16 was –13.5 (1.85), –11.9 (1.90), and –12.7 (1.81) in PALACE-1, PALACE-2, and PALACE-3, respectively, and it was respectively –5.7 (1.83), –7.0 (1.93), and –4.9 (1.79) in the placebo treatment group. The MCID has been reported as 10 mm; the mean differences between groups ranged from –4.9 to –7.9 mm across the three studies.

The apremilast 30 mg b.i.d. treatment group was improved relative to placebo for mean score change at week 24 in all three studies; however, claims of statistical significance for these analyses could not be made because the hierarchical testing was stopped before testing these outcomes (Table 19).

A post hoc analysis was conducted on the proportion of patients achieving a ≥ 10 mm reduction in patient assessment of pain at weeks 16 and 24, and it was found that a greater proportion of patients in the apremilast 30 mg b.i.d. treatment group achieved an improvement of ≥ 10 mm than in the placebo group in all three studies at weeks 16 and 24 with a difference between treatment groups of 8.9%, 12.2%, and 14.0% in PALACE-1, PALACE-2, and PALACE-3, respectively (Table 29). However, these analyses were post hoc in nature and any result reported should be interpreted with caution.

c) EuroQol 5-Dimensions

In all three trials, there was more improvement in EQ-5D index value and EQ-5D VAS in the apremilast 30 mg b.i.d. treatment group when compared with placebo at weeks 16 and 24; however, there was no statistical test applied to compare treatment groups (Table 22).

d) FACIT-F

At weeks 16 and 24, the mean change in scores increased (improved) from baseline for all treatment arms, including placebo. In all three trials, the apremilast 30 mg b.i.d. treatment group was improved relative to placebo for mean score change at weeks 16 and 24. However, claims of statistical significance could not be made because the hierarchical testing was stopped before testing this outcome (Table 28).

A post hoc analysis was conducted on the proportion of patients achieving an improvement ≥ 3.56 points in FACIT-F, and it was found that a greater proportion of patients in the apremilast 30 mg b.i.d. treatment group achieved an improvement of ≥ 3.56 than in the placebo group in all three studies at weeks 16 and 24, with a difference between treatment groups of 9.3%, 10.0%, and 11.0% in PALACE-1, PALACE-2, and PALACE-3, respectively (Table 29). However, these analyses were post hoc in nature and any result reported should be interpreted with caution

3.6.4 Work Productivity

a) 25-Item Work Limitations Questionnaire Productivity Loss Score

In all three trials, there were greater reductions (improvement) in WLQ-25 Productivity Loss Score in the apremilast 30 mg b.i.d. treatment group when compared with placebo at weeks 16 and 24; however, there was no statistical test applied to compare treatment groups (Table 23).

3.6.5 Subgroup Analyses

Subgroup analyses by body weight at baseline and by number of prior DMARDs and/or biologic response modifiers at week 16 were performed for ACR20 and are presented in Table 13. The percentage of

ACR20 responders was higher for the apremilast 30 mg b.i.d. treatment group than those in the placebo group for all subgroups in all three studies, [redacted] In most of the subgroup analyses, there were no statistically significant differences between treatment groups, potentially due to the small sample size in some subgroups.

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See APPENDIX 4 for detailed harms data. Harms data for placebo patients included data from weeks 0 to 24 for patients who did not enter EE at week 16, and data from weeks 0 to 16 for patients who did enter EE. However, for apremilast harms data included data from weeks 0 to 24 for all patients randomized to apremilast 30 b.i.d., irrespective of EE.

3.7.1 Adverse Events

In PALACE-1, 61.3% of apremilast and 48.2% of placebo patients reported an AE after 24 weeks of therapy, while in PALACE-2, 59.3% of apremilast and 45.3% of placebo patients experienced an AE, and in PALACE-3, 62.3% of apremilast and 49.4% of placebo patients experienced an AE (Table 10). The most common AEs were diarrhea (19%, 14.8%, and 15.6% of apremilast versus 2.4%, 5.0%, and 1.8% for placebo in PALACE-1, PALACE-2, and PALACE-3, respectively) and nausea (18.5%, 16.0%, and 13.8% of apremilast patients versus 6.5%, 1.9%, and 5.4% for placebo in PALACE-1, PALACE-2, and PALACE-3, respectively). In all three trials, findings after 16 weeks of therapy were consistent with what was observed during weeks 0 to 24, with the most common AEs being diarrhea (19%, 14.8%, and 15.6% of apremilast versus 2.4%, 4.4%, and 1.8% for placebo in PALACE-1, PALACE-2, and PALACE-3, respectively), nausea (16.7%, 16.0%, and 12.0% of apremilast patients versus 6.5%, 1.9%, and 5.4% for placebo in PALACE-1, PALACE-2, and PALACE-3, respectively), and headache (10.7%, 9.9%, and 10.2% of apremilast patients versus 3.6%, 3.8%, and 4.8% for placebo in PALACE-1, PALACE-2, and PALACE-3, respectively).

3.7.2 Serious Adverse Events

SAEs were reported in 5.4% of apremilast and 4.2% of placebo patients after 24 weeks of therapy in PALACE-1, in 2.5% of apremilast and 1.9% of placebo patients after 24 weeks in PALACE-2, and in 3.6% of apremilast and 5.4% of placebo patients after 24 weeks in PALACE-3 (Table 10). No single SAE occurred in more than a single patient in PALACE-1 and PALACE-2, while in PALACE-3, acute pancreatitis occurred in [redacted] patients in the placebo group, and psoriatic arthropathy occurred in [redacted] patients in placebo group and in [redacted] patients in apremilast group. [redacted].

3.7.3 Withdrawals due to Adverse Events

WDAEs occurred in [redacted] of apremilast patients and [redacted] of placebo patients after 24 weeks of therapy in PALACE-1, in [redacted] of apremilast patients and [redacted] of placebo patients after 24 weeks in PALACE-2, and in PALACE-3 [redacted] and [redacted] of patients, respectively (Table 10). The most common reason for withdrawal across groups was diarrhea in PALACE-1 and nausea in PALACE-2 and PALACE-3. After 16 weeks of therapy, WDAEs occurred in [redacted] of apremilast patients and [redacted] of placebo patients in PALACE-1, in [redacted] of apremilast patients and [redacted] of placebo patients in PALACE-2, and in [redacted] of apremilast patients and [redacted] of placebo patients in PALACE-3.

3.7.4 Mortality

There were no deaths in any of the studies after 24 weeks of therapy (Table 10).

3.7.5 Notable Harms

Aside from gastrointestinal AEs, weight loss was a notable harm for this review, and the proportion of patients with clinically significant weight loss (i.e., weight decreases of > 5% of baseline body weight), not specified as an AE, was [redacted] for apremilast versus [redacted] for placebo in PALACE-1, [redacted] for apremilast versus [redacted] for placebo in PALACE-2, and [redacted] versus [redacted], respectively, in PALACE-3. Weight decrease recorded as an AE in [redacted] of apremilast versus [redacted] for placebo in PALACE-1, PALACE-2, and PALACE-3 (Table 10).

TABLE 10: HARMS AT WEEK 24

	PALACE-1		PALACE-2		PALACE-3	
AEs	**Placebo[a] N = 168**	**APR 30 mg b.i.d.,[b] N = 168**	**Placebo[a] N = 159**	**APR 30 mg b.i.d.,[b] N = 162**	**Placebo[a] N = 169**	**APR 30 mg b.i.d.,[b] N = 167**
Patients with > 0 TEAEs, N (%)	81 (48.2)	103 (61.3)	72 (45.3)	96 (59.3)	83 (49.4)	104 (62.3)
Most common AEs						
Diarrhea	4 (2.4)	32 (19.0)	8 (5.0)	24 (14.8)	3 (1.8)	26 (15.6)
Nausea	11 (6.5)	31 (18.5)	3 (1.9)	26 (16.0)	9 (5.4)	23 (13.8)
Headache	8 (4.8)	18 (10.7)	7 (4.4)	19 (11.7)	8 (4.8)	20 (12.0)
SAEs						
Patients with > 0 SAEs, N (%)	7 (4.2)	9 (5.4)	3 (1.9)	4 (2.5)	9 (5.4)	6 (3.6)
Most common reasons[c]						
Pancreatitis, acute					2 (1.2)	0
Psoriatic arthropathy					2 (1.2)	1 (0.6)
WDAEs						
WDAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common reasons[c]						
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]			
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]		
[redacted]					[redacted]	[redacted]
[redacted]					[redacted]	[redacted]
Deaths						
Number of deaths, N (%)	0	0	0	0	0	0
Notable harms						
Gastrointestinal Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

	PALACE-1		PALACE-2		PALACE-3	
AEs	**Placebo[a] N = 168**	**APR 30 mg b.i.d.,[b] N = 168**	**Placebo[a] N = 159**	**APR 30 mg b.i.d.,[b] N = 162**	**Placebo[a] N = 169**	**APR 30 mg b.i.d.,[b] N = 167**
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

AE = adverse event; APR = apremilast; b.i.d.= twice daily; EE = early escape; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Includes data from weeks 0 to 24 for patients who did not enter EE at week 16, and data from weeks 0 to 16 for patients who did enter EE.

[b] Includes data from weeks 0 to 24 for all patients randomized to APR 30 b.i.d., irrespective of EE.

[c] Occurred in more than 1 person.

4. DISCUSSION

4.1 Summary of Available Evidence

Three manufacturer-sponsored, phase 3, multi-centre, randomized, double-blind, placebo-controlled trials, which were almost identical in design (PALACE-1, PALACE-2, and PALACE-3), met the inclusion criteria for this systematic review. The trials included adults with active PsA who had previously had treatment with DMARDs or TNF alpha inhibitors (up to 10% of enrolled). PALACE-3 also included patients with at least one ≥ 2 cm plaque psoriasis lesion in addition to active PsA. All three trials — PALACE 1 (N = 504), PALACE 2 (N = 484), and PALACE 3 (N = 505) — were three-arm superiority studies, and evaluated the efficacy and safety of apremilast 20 mg orally twice daily (b.i.d.), or apremilast 30 mg orally b.i.d. compared with identically appearing placebo over a double-blinded duration of 24 weeks. No trials directly comparing apremilast with DMARDs or with biologic response modifiers were found in the scientific literature. All three trials had an appropriate randomization strategy, with generally similar treatment groups at baseline. In PALACE-1, PALACE-2, and PALACE-3, 74%, 65%, and 71% of placebo patients discontinued randomized treatment before week 24 (either because of EE or treatment discontinuation), respectively. This means that a substantial proportion of the outcome data at week 24 had to be imputed based on an ITT analysis. Therefore, there is a very high degree of uncertainty with respect to the findings of the studies beyond the week 16 time point.

4.2 Interpretation of Results

4.2.1 Efficacy

The primary efficacy outcome in all three trials was ACR20 response at week 16 (defined as an improvement of at least 20% in both swollen and tender joint counts and at least three of five additional disease criteria). In all three trials, apremilast 30 mg orally b.i.d. was associated with statistically significant improvements (compared with placebo) for the primary outcome of ACR20 response at week 16. However, the size of the treatment benefit versus placebo was modest, with the primary outcome of ACR20 being achieved by 38%, 32%, and 41% of patients on apremilast in PALACE-1, PALACE-2, and PALACE-3, respectively, compared with 19%, 19%, and 18% on placebo in PALACE-1, PALACE-2, and PALACE-3, respectively. Hence, between-group differences in proportions ranged from 13.4% to 22.3%, which is less than that seen for the biologic response modifier trials in PsA of approximately 30% between groups at a similar time point. In all three trials, a pre-planned subgroup analysis was carried out for the ACR20 response rate at week 16. These results demonstrated a consistent treatment effect in favour of apremilast compared with placebo regardless of concomitant treatments (whether receiving DMARDs and type of DMARD received) or prior treatments (including the number of conventional DMARDs received and whether people had received previous TNF alpha inhibitor therapies). In addition, the proportion of apremilast patients achieving an ACR50 response at week 16 was quite low (16%, 11%, and 15% for apremilast versus 6.0%, 5.0% and 8.3% for placebo in PALACE-1, PALACE-2, and PALACE-3, respectively). However, it is typical for trials of interventions in PsA to accrue more ACR50 responses at later time points; this occurred in the PALACE studies as well, although the increase in the proportion of ACR50 responders at week 24 was small in the apremilast groups. ACR70 responders were also minimal at weeks 16 and 24, although this is a much harder outcome to achieve over a study of a relatively short duration. ACR50 (and ACR70) response is likely to be a more clinically important outcome for patients than ACR20. Yet, in the PALACE studies, the pre-specified hierarchical testing failed at a higher order comparison, and therefore claims with respect to statistical significance for apremilast versus placebo for ACR50 and ACR70 response could not be made. Furthermore, although EE is a common design feature for trials of interventions in rheumatologic conditions such as PsA, it has an impact on the interpretation of outcomes at subsequent time points, often with uncertainty with respect to magnitude

and direction of potential bias. Given that ACR50 and ACR70 outcomes require longer durations to achieve and a large proportion of patients discontinued treatment (due to EE and other reasons) in all three studies, coupled with the ACR20 responses observed, the clinical benefit with apremilast for ACR response truly seems modest at best. The Health Canada reviewer also considered the response to be modest for ACR20 at weeks 16 and 24.[23]

Other clinical response outcomes (PsARC, HAQ-DI, PASI75 for PALACE-3) also demonstrated a statistically significant difference favouring apremilast treatment groups compared with placebo at week 16.

There were greater improvements in CDAI score and DAS28 score in the apremilast 30 mg b.i.d. treatment group compared with placebo at week 16. However, the results cannot be interpreted because the hierarchical statistical comparisons stopped at a higher order than these outcomes.

There were no significant differences in the change from baseline in Dactylitis Severity Score and in the change from baseline in MASES scores at week 16 in any of the trials. Although there were statistically significant improvements in physical functioning, as measured by change from baseline in HAQ-DI, the clinical significance of this finding is uncertain. The MCID for HAQ-DI in PsA has been estimated to range between 0.13 and 0.35 points.[29,30,54] The least squares mean differences between treatments for HAD-DI ranged from 0.127 to 0.159 at week 16, and 0.121 to 0.182 at week 24, in favour of apremilast. Hence, the HAQ-DI mean changes were around the lower estimate for the MCID. Moreover, at week 16, in PALACE-2 a statistically significantly larger proportion of patients in the apremilast 30 mg treatment group when compared with the placebo group achieved HAQ-DI improvements of –0.13 points, but there was no statistically significant difference in PALACE-1 and PALACE-3. Also at week 16, in PALACE-1 and PALACE-2, a statistically significantly larger proportion of patients in the apremilast 30 mg treatment group when compared with the placebo group achieved HAQ-DI improvements of –0.30 points, with no significant difference in PALACE-3. However, these analyses were considered exploratory in nature because they were not part of the hierarchical analysis plan and there is a risk of inflated type 1 error.

A common theme, seen as important in the patient group input, was improvement in quality of life (APPENDIX 1). In all three trials, SF-36 was used to assess health-related quality of life. In all three trials, there was a statistically significantly greater change from baseline in the SF-36 PF domain score in the apremilast 30 mg b.i.d. treatment group than the placebo group at week 16. In exploratory analyses, it was found that the proportion of patients achieving an improvement ≥ 2.5 points in the SF-36v2 PF domain at weeks 16 and 24 was significantly greater in the apremilast 30 mg b.i.d. treatment group than in the placebo group in the PALACE-1 study only; in addition, the proportion of patients achieving an improvement ≥ 2.5 points in SF-36 PCS at weeks 16 and 24 was significantly greater in the apremilast 30 mg b.i.d. treatment group than in the placebo group in the PALACE-1 and PALACE-3 studies only. However, because these analyses were exploratory in nature, any significant result reported should be interpreted with caution. EQ-5D results were reported as well, but no statistical testing was conducted, and it seemed that results were inconsistent between the studies.

Arthritis pain in patients was assessed using patient's assessment of pain. In all three studies, the average change from baseline in the apremilast 30 mg b.i.d. treatment group at week 16 exceeded the MCID, which is typically 10 points, while patients on placebo did not. In addition, the mean change in score from baseline at week 16 was statistically significantly improved in the apremilast 30 mg b.i.d. treatment group relative to placebo in the PALACE-1 and PALACE-3 studies only. A post hoc analysis was conducted on the proportion of patients achieving a ≥ 10 mm reduction in patient assessment of pain at

weeks 16 and 24, and it was found that a greater proportion of patients in the apremilast 30 mg b.i.d. treatment group achieved an improvement of ≥ 10 mm than in the placebo group in all three studies at weeks 16 and 24, with a difference between treatment groups of 8.9%, 12.2%, and 14.0% in PALACE-1, PALACE-2, and PALACE-3, respectively. However, these analyses were post hoc in nature and any result reported should be interpreted with caution. In addition, a post hoc analysis was conducted on the proportion of patients achieving an improvement ≥ 3.56 points in FACIT-F, and it was found that a greater proportion of patients in the apremilast 30 mg b.i.d. treatment group achieved an improvement ≥ 3.56 than in the placebo group in all three studies at weeks 16 and 24, with a difference between treatment groups of 9.3%, 10.0%, and 11.0% in PALACE-1, PALACE-2, and PALACE-3, respectively. However, these analyses were post hoc in nature and any result reported should be interpreted with caution.

The improvements observed at week 24 were maintained or continued to improve through week 52 among patients in the apremilast 30 mg b.i.d. treatment group. Improvements over week 24 outcomes generally occurred in ACR and PsARC responses, as well as PASI and Dactylitis Severity Scores across all studies. Results for DAS28 remission (< 2.6 score), HAQ-DI, SF-36, MASES, and FACIT-F scores also suggested the effects were maintained at week 52. However, the longer-term phases of the trials, after 24 weeks, had limited clinical value, for the following reasons: there were no control groups; there was no blinding, because all patients received apremilast at this time point in the trials; data were analyzed as observed, with nonresponders not contributing to the analyses; there was a lack of stopping criteria, where early escapers at week 16 who were initially randomized to apremilast were allowed to remain on apremilast during the long-term phases — it is likely that in clinical practice, such nonresponders would no longer continue to receive apremilast.

No radiographic assessments were performed in the apremilast trials. This absence of any evidence that apremilast slows radiographic progression is important, given the evidence for anti-TNF alpha drugs, which do have evidence for reduced rates of radiographic progression of joint damage.

In the absence of adequate head-to-head trial data for apremilast with other PsA treatment, the manufacturer conducted an IDC based on a systematic review of RCTs, to compare the efficacy of apremilast with adalimumab, certolizumab, etanercept, golimumab, infliximab, and ustekinumab. The results of the IDC showed that [redacted]. However, these outcomes were not consistently statistically significant; where biologics [redacted] In addition, some of the biologics were significantly better than apremilast for [redacted] outcomes. Any statistically significant results should be interpreted with caution because the absence of statistical significance does not indicate that there is evidence of [redacted].

4.2.2 Harms

In their input submitted to CDR, it is clear that adverse effects are a significant concern for patients being treated for PsA. The most common AEs with apremilast were gastrointestinal in nature — nausea and diarrhea — and these are also noted in the product monograph. There were no notable differences in risk of serious gastrointestinal AEs with apremilast in the three included studies. SAEs that occurred in more than one patient occurred only in the placebo treatment group in the PALACE-3 study. Aside from gastrointestinal AEs, weight loss was a notable harm for this review, and clinically significant weight loss

is noted in the apremilast product monograph. The proportion of patients with clinically significant weight loss (i.e., weight decreases of > 5% of baseline body weight) ranged from [redacted] for the apremilast group, while in the placebo group, it ranged from [redacted] across the studies.

The long-term safety of apremilast is less clear. The placebo-controlled phase of all three trials only lasted 24 weeks, and this is likely not of sufficient duration to reveal any long-term safety issues, if any exist. Apremilast 30 mg b.i.d. was well tolerated over the 52-week period with generally mild or moderate TEAEs in most patients, which did not necessitate dose interruption or discontinuation. Gastrointestinal disorders were the most common TEAEs, with diarrhea and nausea the most frequently reported and the most common cause for drug interruptions or discontinuation.

Harms were not analyzed in the IDC, and the comparative safety between apremilast and biologics is unknown. Conversely, there is no evidence that apremilast is better tolerated than biologic therapies, and longer-term safety data for apremilast are required. As noted above, there do not appear to be any clear efficacy advantages of using apremilast versus biologics; thus, it is important that any potential safety advantages be fully characterized. However, one advantage for apremilast would be the oral formulation, which is of importance to patients.

4.3 Potential Place in Therapy[2]

The goals of treating PsA are symptom relief, inhibition of damage, maintenance of function and management of comorbidities. The current standard of care for PsA is based on the domain(s) most severely affected in the specific patient. These domains include arthritis, dactylitis, enthesitis, and spondylitis.

Initial medical treatment of arthritis rests on NSAIDs and DMARDs, the most frequently used being MTX, followed by sulfasalazine. Patients with inadequate response to DMARDs are next offered a biologic agent, most often an anti-TNF alpha drug, and less often, ustekinumab. Because there is limited evidence of efficacy of DMARDs for the three other domains, anti-TNF medication is offered if there is an inadequate response to NSAIDs with or without local steroid injections. Biologics would be taken with or without concomitant methotrexate.

Apremilast may be an alternative therapy for patients with mild to moderate disease or for patients with more severe disease who refuse parenteral therapies. Most patients prefer oral to injectable drugs. Patients taking apremilast would also not need laboratory follow-up (less intrusive and costly) and probably require fewer physician visits and monitoring of laboratory tests. Apremilast does not require tuberculosis screening, and also does not lead to infections.

These decisions depend on the clinical evaluation of the patients. Poor prognostic factors, such as baseline erosive disease or severe functional impairment, might result in a decision to bypass apremilast.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

5. CONCLUSIONS

Based on three double-blind RCTs (PALACE-1, PALACE-2, and PALACE-3) in patients with active PsA, treatment with apremilast 30 mg b.i.d. resulted in statistically significant improvements in clinical response (ACR20, PsARC, HAQ-DI, and PASI75 for PALACE-3) at week 16 when compared with placebo. Although improvements in health-related quality of life were observed, they were inconsistent across studies or measures. In all three studies, a very large proportion of placebo patients discontinued randomized treatment before week 24 (either because of EE or treatment discontinuation), so claims of efficacy at week 24 are uncertain.

The most common AEs with apremilast were gastrointestinal-related — nausea and diarrhea — and these were also the most common reasons for WDAEs. There were no clear indications of any serious harms issues with apremilast, although interpretation of this finding is limited by the relatively short 24-week follow-up in the double-blind comparative phase, and the large proportion of patients who discontinued randomized treatment (either because of EE or treatment discontinuation).

A manufacturer-submitted NMA suggested that [redacted]. Harms, health-related quality of life, and patient-reported outcomes were not analyzed in the IDC, and the comparative safety between apremilast and biologics is unknown.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Two patient groups submitted patient input.

The Arthritis Consumer Experts (ACE) group provides science-based information, education, and support programs in both official languages to help people with arthritis take control of their disease and improve their quality of life. The ACE group receives unrestricted grants-in-aid from AbbVie Corporation, Amgen Canada, BIOTECanada, Celgene Inc., Hoffmann-La Roche Canada Ltd., Janssen Inc., Pfizer Canada, Purdue Pharma L.P., and UCB Canada Inc., as well as from public sector organizations. According to the group, solely the staff and advisory board of ACE aided in the compilation of the patient input the group submitted and there is no conflict of interest with respect to compiling the patient input information.

The Canadian Arthritis Patients Alliance (CAPA) provides education and creates links between Canadians with arthritis to assist them to become more effective advocates and to improve their quality of life. In the last year, CAPA received grants and support from AbbVie, Amgen Canada, Hoffmann-La Roche, Janssen, Novartis, Pfizer Canada, Rx&D, and UCB Pharma. In addition, it received support from several public sector non-pharmaceutical industry sources. In the past, CAPA received support from Schering Canada, as well as from public sector organizations. CAPA declared there was no conflict of interest with respect to compiling the patient input information it submitted.

2. Condition-Related Information

The patient groups compiled information from responses to requests for patient input sent via email or posted on the JointHealth website, Facebook, and Twitter. One group reported information from personal experiences and many years of communicating with its membership, and the other provided comments to augment the individual pieces of information from the group.

Psoriatic arthritis (PsA) is an autoimmune disease characterized by inflammation in the joints that destroys the lining of the joint and ultimately the surrounding bone, and which causes a scaly rash on the body, which usually occurs on the elbows, knees, and scalp. The disease affects patients' day-to-day life tremendously, causing them to constantly consider their ability to cope, think of ways of doing what they need to do, and assess how much help they need. Therefore, PsA patients pace and prioritize routine activities that are taken for granted by non-patients.

PsA patients experience joint pain, stiffness, fatigue, and loss of function. Some patients have difficulty sitting, using the stairs, bending to pick up objects, and getting in and out of the bathtub. Daily living activities such as vacuuming, cleaning, doing the dishes, and grocery shopping become challenging for some patients, causing them to require help from caregivers. Patients also experience skin sensitivity, redness, flaking, and pain from the plaque psoriasis. One patient group reported that PsA is "linked to the skin disease psoriasis, which causes a scaly-type rash usually occurring on the elbows, knees, and scalp. Psoriasis is considered a significant risk factor for developing PsA — up to 30% of people diagnosed with psoriasis go on to develop psoriatic arthritis." The group reported that a patient developed ischial bursitis, in which her tendons and ligaments are also affected. The group provided the following quote from another patient: "I'm a patient suffering from rheumatoid arthritis and I take methotrexate injections, which caused plaque psoriasis to appear on my body, my scalp, and my ears."

The impact of the disease goes beyond physical well-being, with some patients likely to stop social and creative activities due to limited time and energy and increased pain. Furthermore, the acute awareness of skin lesions has a psychological impact. A patient group reported that as a result of the symptoms of PsA, anxiety and depression are prominent among people in this disease group. According to a patient group, PsA patients whose conditions are not well controlled find it difficult to participate in post-secondary education and to become employed and stay employed.

3. Current Therapy-Related Information

Current therapy includes biologic response modifiers, disease-modifying anti-rheumatic drugs (DMARDs), and nonsteroidal anti-inflammatory drugs (NSAIDs). There is a high degree of variability of disease, and there are currently no methods by which physicians can predict which patients will respond best to which therapies. Therefore, while some patients respond well to a drug for long periods, others will need to try many different drugs before they find the best treatment for their PsA. Even while responding well to their medication(s), PsA patients are aware of the potential for the drug to become ineffective over time. Therefore, patients believe that the more options there are available, the better, as more options mean better access to medication and a backup plan in case the current therapy treatment stops working.

PsA patients have concerns regarding adverse effects over a prolonged period of drug use (which may include heartburn, dizziness, and increased blood sugar levels), cost, scheduling issues for infusions, and the need to take time off work or find someone to deal with family commitments. Commonly mentioned adverse events are gastrointestinal side effects associated with DMARDs and NSAIDs. One patient group mentioned that DMARDs and biologic response modifiers suppress the patients' immune systems, predisposing them to serious infections. Other adverse events include vein scarring and scar tissue from numerous infusions and injections.

Caregiver experiences cited include having to give the patients their injections, and taking on more family responsibilities while patients are receiving their infusions or when patients' conditions are so severe that they are prevented them participating in daily activity. Caregiver burdens include inadequate time, as they need to arrange and plan their schedule to accommodate for sudden and emergency requests from the person living with PsA. For some, caring for the patient deprives them of time to engage in gainful employment, recreational activities, and socializing with friends.

4. Expectations About the Drug Being Reviewed

Sources of information for this section are identical to those described in section 2.

None of the patients from either group providing input had experience with using Otezla to treat their PsA. One patient group expects that as an oral drug, Otezla would eliminate vein scarring and scar tissue for patients who need to receive medication in the form of injections or transfusions. It was also expected that the use of Otezla would reduce the amount of time patients and families spend on injections and infusions, "allowing them increased independence, and decreased time spent 'as a patient'." Furthermore, patients expected that oral medications would be easy to take, and that coming from a different class of drugs, Otezla would provide them with an effective alternative when other drugs are ineffective. The patients hoped that Otezla would lessen their PsA pain so that they can manage to do day-to-day activities. One patient group stated that the use of Otezla lowers a patient's risk of serious infection, because the medication suppresses the immune system to a lesser degree. A patient in one group said they would not be willing to experience serious adverse effects with Otezla, while another was willing to experience adverse effects related to Otezla if there was at least a 50% improvement in her condition and the side effects were not life-threatening.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 3, 2015
Alerts:	Biweekly (twice monthly) search updates until November 18, 2015
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
.kw	Keyword heading
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	608141-41-9.rn,nm.
2	(Otezla or apremilast* or otezia or cc 10004 or cc10004 or UP7QBP99PN).ti,ab,rn,nm,sh,hw,ot,kw.
3	or/1-2
4	3 use pmez
5	Arthritis, Psoriatic/
6	((psorias* or psoriatic*) adj5 (arthrit* or arthropath* or polyarthrit*)).ti,ab.
7	Alibert bazin disease*.ti,ab.
8	PsA.ti,ab.
9	or/5-8
10	4 and 9
11	*Apremilast/
12	(Otezla or apremilast* or otezia or cc 10004 or cc10004).ti,ab.
13	or/11-12
14	13 use oemezd
15	psoriatic arthritis/
16	((psorias* or psoriatic*) adj5 (arthrit* or arthropath* or polyarthrit*)).ti,ab.
17	Alibert bazin disease*.ti,ab.
18	PsA.ti,ab.
19	or/15-18
20	14 and 19
21	conference abstract.pt.
22	20 not 21
23	10 or 22
24	remove duplicates from 23

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	July 2015
Keywords:	Otezla (apremilast), psoriatic arthritis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

No studies excluded.

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 11: PROPORTION OF PATIENTS WITH ACR20, ACR50 AND ACR 70 RESPONSES AT WEEK 16 (FULL ANALYSIS SET)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	**APR 30 mg b.i.d., N = 168**	**Placebo N = 159**	**APR 30 mg b.i.d., N = 162**	**Placebo N = 169**	**APR 30 mg b.i.d., N = 167**
ACR20[a]						
n (%)	32 (19.0)	64 (38.1)	30 (18.9)	52 (32.1)	31 (18.3)	68 (40.7)
Adjusted % difference in proportions (95% CI)[b]	19.0 (9.7 to 28.3)		13.4 (4.0 to 22.7)		22.3 (13.0 to 31.6)	
P value[c]	**0.0001**		**0.0060**		**< 0.0001**	
ACR50						
n (%)	10 (6.0)	27 (16.1)	8 (5.0)	17 (10.5)	14 (8.3)	25 (15.0)
Adjusted % difference in proportions (95% CI)[b]	10.3 (3.7 to 16.8)		5.6 (–0.2 to 11.3)		6.8 (0.0 to 13.5)	
ACR70						
n (%)	2 (1.2)	7 (4.2)	1 (0.6)	2 (1.2)	4 (2.4)	6 (3.6)
Adjusted % difference in proportions (95% CI)[b]	3.1 (–0.4 to 6.5)		0.6 (–1.5, 2.7)		1.2 (–2.4 to 4.8)	

ACR20 = American College of Rheumatology 20% response; APR = apremilast; b.i.d.= twice daily; BSA = body surface area; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; DMARD = disease-modifying anti-rheumatic drug.

[a] Patients who discontinued early — prior to week 16 — and patients who did not have sufficient data for a definitive determination of response status at week 16 were counted as nonresponders. Joints temporarily or permanently not assessable at baseline were excluded from joint count. For other unassessed joints at baseline, the joint assessment at the screening visit, if assessed, was used as the baseline assessment; otherwise, the joint was excluded from joint count. The last observed joint assessment (at baseline or post-baseline) was used for joints unassessed at week 16. There was no imputation for other missing ACR component scores.

[b] Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average. PALACE-3 was additionally adjusted for ≥ 3% BSA with psoriasis at baseline.

[c] 2-sided *P* value is based on the CMH test adjusting for baseline DMARD use. PALACE-3 was additionally adjusted for ≥ 3% BSA with psoriasis at baseline. *P* values in bold are considered statistically significant.

TABLE 12: PROPORTION OF PATIENTS WITH ACR20, ACR50 AND ACR70 RESPONSES AT WEEK 24 (FULL ANALYSIS SET)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
ACR20[a]						
n (%)	22 (13.1)	59 (35.1)	25 (15.7)	40 (24.7)	26 (15.4)	52 (31.1)
Adjusted % difference in proportions (95% CI)[b]	22.2 (13.4 to 30.9)		9.2 (0.5 to 17.8)		15.5 (6.7 to 24.3)	
P value[c]	**< 0.0001**		**0.0394**		**0.0007**	
ACR50						
n (%)	7 (4.2)	32 (19.0)	14 (8.8)	19 (11.7)	13 (7.7)	27 (16.2)
Adjusted % difference in proportions (95% CI)[b]	14.9 (8.3 to 21.5)		3.1 (–3.5 to 9.6)		8.3 (1.6 to 15.1)	
ACR70						
n (%)	1 (0.6)	17 (10.1)	5 (3.1)	4 (2.5)	6 (3.6)	9 (5.4)
Adjusted % difference in proportions (95% CI)[b]	9.5 (4.8 to 14.2)		–0.6 (–4.3 to 3.0)		1.8 (–2.6 to 6.2)	

ACR20 = American College of Rheumatology 20% response; APR = apremilast; b.i.d.= twice daily; BSA = body surface area; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; DMARD = disease-modifying anti-rheumatic drug.

[a] Patients who discontinued early — prior to week 16 — and patients who did not have sufficient data for a definitive determination of response status at week 16 were counted as nonresponders. Joints temporarily or permanently not assessable at baseline were excluded from joint count. For other unassessed joints at baseline, the joint assessment at the screening visit, if assessed, was used as the baseline assessment; otherwise, the joint was excluded from joint count. The last observed joint assessment (at baseline or post-baseline) was used for joints unassessed at week 16. There was no imputation for other missing ACR component scores.

[b] Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. PALACE-3 was additionally adjusted for ≥ 3% BSA with psoriasis at baseline. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[c] 2-sided *P* value is based on the CMH test adjusting for baseline DMARD use. PALACE-3 was additionally adjusted for ≥ 3% BSA with psoriasis at baseline. *P* values in bold are considered statistically significant.

TABLE 13: SUBGROUP ANALYSIS OF PROPORTION OF PATIENTS WITH ACR20 RESPONSES AT WEEK 16 (FULL ANALYSIS SET)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
Body weight at baseline						
< 70 KG						
n/N, (%)	6/26 (23.1)	15/34 (44.1)	9/41 (22.0)	13/47 (27.7)	7/40 (17.5)	16/40 (40.0)
Adjusted % difference in proportions (95% CI)[a]	21.1 (–2.1 to 44.2)		6.7 (–11.2 to 24.5)		20.4 (2.4 to 38.4)	
70 KG TO < 85 KG						
n/N, (%)	11/55 (20.0)	17/46 (37.0)	8/40 (20.0)	16/49 (32.7)	13/56 (23.2)	20/58 (34.5)
Adjusted % difference	16.5 (–0.6 to 33.7)		12.4 (–5.7 to 30.5)		10.5 (–5.8 to 26.8)	

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	**APR 30 mg b.i.d., N = 168**	**Placebo N = 159**	**APR 30 mg b.i.d., N = 162**	**Placebo N = 169**	**APR 30 mg b.i.d., N = 167**
in proportions (95% CI)[a]						
85 KG TO < 100 KG						
n/N, (%)	8/43 (18.6)	22/53 (41.5)	8/47 (17.0)	12/39 (30.8)	6/39 (15.4)	14/37 (37.8)
Adjusted % difference in proportions (95% CI)[a]	21.6 (4.3 to 39.0)		12.5 (–5.0 to 30.0)		21.8 (2.1 to 41.5)	
> 100 KG						
n/N, (%)	7/44 (15.9)	10/35 (28.6)	5/31 (16.1)	11/27 (40.7)	5/34 (14.7)	18/32 (56.3)
Adjusted % difference in proportions (95% CI)[a]	12.7 (–5.6 to 31.0)		24.6 (2.1 to 47.2)		38.5 (18.6 to 58.3)	
Prior use of small-molecule DMARDs						
1, n/N, (%)	20/81 (24.7)	23/77 (29.9)	18/77 (23.4)	31/73 (42.5)	20/84 (23.8)	35/79 (44.3)
Adjusted % difference in proportions (95% CI)[b]	5.2 (–8.6 to 19.0)		19.3 (4.5 to 34.0)		19.6 (5.8 to 33.5)	
2, n/N, (%)	7/29 (24.1)	14/38 (36.8)	8/44 (18.2)	13/43 (30.2)	5/25 (20.0)	15/37 (40.5)
Adjusted % difference in proportions (95% CI)[b]	13.6 (–7.6 to 34.8)		10.3 (–7.0 to 27.5)		21.1 (–0.3 to 42.6)	
≥3, n/N, (%)	1/10 (10.0)	2/14 (14.3)	2/14 (14.3)	2/18 (11.1)	0/12 (0.0)	3/8 (37.5)
Adjusted % difference in proportions (95% CI)[b]	5.8 (–20.2 to 31.7)		–3.6 (–26.8 to 19.6)		33.6 (6.7 to 60.5)	
Prior use of biologics						
n/N, (%)	2/41 (4.9)	11/37 (29.7)	2/23 (8.7)	5/23 (21.7)	6/48 (12.5)	15/43 (34.9)
Adjusted % difference in proportions (95% CI)[b]	24.5 (8.9 to 40.1)		13.0 (–7.0 to 33.1)		21.9 (4.0 to 39.8)	
Prior use of biologics excluding biologic failure						
n/N, (%)	1/22 (4.5)	8/23 (34.8)	2/15 (13.3)	4/16 (25.0)	5/36 (13.9)	12/29 (41.4)
Adjusted % difference in proportions (95% CI)[b]	28.5 (6.4 to 50.5)		12.1 (–14.2 to 38.4)		27.1 (5.9 to 48.2)	
Prior biologic failure						
n/N, (%)	1/19 (5.3)	3/14 (21.4)	0/8 (0.0)	1/7 (14.3)	1/12 (8.3)	3/14 (21.4)
Adjusted % difference in proportions (95% CI)[b]	17.4 (–7.6 to 42.5)		13.5 (–9.4 to 36.3)		13.7 (–2.7 to 30.2)	
Baseline DMARD use						
Only 1 DMARD, n/N, (%)	24/100 (24.0)	30/94 (31.9)	21/97 (21.6)	37/99 (37.4)	22/96 (22.9)	42/97 (43.3)
% difference in	7.9 (–4.7 to 20.5)		15.7 (3.2 to 28.3)		19.6 (6.8 to 32.4)	

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	**APR 30 mg b.i.d., N = 168**	**Placebo N = 159**	**APR 30 mg b.i.d., N = 162**	**Placebo N = 169**	**APR 30 mg b.i.d., N = 167**
proportions (95% CI)[b]						
> 1 DMARD, n/N, (%)	2/10 (20.0)	5/12 (41.7)	2/16 (12.5)	4/14 (28.6)	0/5 (0.0)	0/4 (0.0)
% difference in proportions (95% CI)[b]	21.7 (–15.7 to 59.0)		16.1 (–12.6 to 44.8)		0.0	
0 DMARD, n/N, (%)	6/58 (10.3)	29/62 (46.8)	7/46 (15.2)	11/49 (22.4)	9/68 (13.2)	26/66 (39.4)
% difference in proportions (95% CI)[b]	36.4 (21.7 to 51.1)		7.2 (–8.4 to 22.9)		26.6 (12.3 to 40.8)	

ACR20 = American College of Rheumatology 20% response; APR = apremilast; b.i.d. = twice daily; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; DMARD = disease-modifying anti-rheumatic drug.

[a] For all subgroup factors except for baseline DMARD use, adjusted difference in proportions is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights and 2-sided 95% CI is based on a normal approximation to the weighted average. For baseline DMARD use, or if 1 of the 2 treatment groups being compared has no subject in a stratum, adjusted difference is not calculated and 2-sided 95% CI is based on a normal approximation to unadjusted difference. PALACE-3 was additionally adjusted for ≥ 3% body surface area with psoriasis at baseline.

TABLE 14: HAQ-DI SCORE (FULL ANALYSIS SET; LAST OBSERVATION CARRIED FORWARD)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	**APR 30 mg b.i.d., N = 168**	**Placebo N = 159**	**APR 30 mg b.i.d., N = 162**	**Placebo N = 169**	**APR 30 mg b.i.d., N = 167**
HAQ-DI Change from Baseline at Weeks 16 and 24[a]						
N[b]	[redacted]					
Baseline mean (SD)	[redacted]					
Change from baseline at week 16 LS mean (SE)[c]	–0.086 (0.0360)	–0.244 (0.0364)	–0.053 (0.0358)	–0.193 (0.0354)	–0.065 (0.0335)	–0.192 (0.0339)
Difference with placebo at week 16						
LS mean difference (2-sided 95% CI)[c]	–0.159 (–0.258 to –0.060)		–0.140 (–0.236 to –0.045)		–0.127 (–0.220 to –0.034)	
P value[c]	**0.0017**		**0.0042**		**0.0073**	
Change from baseline at week 24 LS mean (SE)[c]	–0.076 (0.0369)	–0.258 (0.0371)	–0.085 (0.0377)	–0.206 (0.0372)	–0.053 (0.0350)	–0.192 (0.0353)
Difference with placebo at week 24						
LS mean difference (2-sided 95% CI)[c]	–0.182 (–0.283 to –0.080)		–0.121 (–0.222 to –0.020)		–0.139 (–0.236 to –0.042)	
P value[c]	**0.0005**		**0.0191**		**0.0050**	
Proportion of Patients Achieving HAQ-DI Improvements of at Least 0.13 Points at Weeks 16 and 24[d]						
[redacted]						

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
[redacted]						

ANCOVA = analysis of covariance; APR = apremilast; b.i.d. = twice daily; BSA = body surface area; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; DMARD = disease-modifying anti-rheumatic drug; EE = early escape; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire – Disability Index; LOCF = last observation carried forward; LS = least squares; min – max = minimum to maximum; SD = standard deviation; SE = standard error.

[a] For patients who discontinued from the study — prior to week 16 — the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question.

[b] Patients with a baseline value and at least 1 post-baseline value at or prior to the respective visits are included.

[c] LS mean (SE) and *P* value based on an ANCOVA model for the change from baseline at the respective time point, with treatment group and baseline DMARD use as factors, and the baseline value as a covariate. PALACE-3 was additionally adjusted for ≥ 3% BSA with psoriasis at baseline. *P* values in bold are considered statistically significant.

[d] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question. Patients who did not have sufficient data (observed or imputed) for a determination of response status at the respective visits were counted as nonresponders.

[e] Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. PALACE-3 was additionally adjusted for ≥ 3% BSA with psoriasis at baseline. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[f] 2-sided *P* value is based on the CMH test adjusting for baseline DMARD use. PALACE-3 was additionally adjusted for ≥ 3% BSA with psoriasis at baseline. *P* values in italics are ≤ 0.050 and considered based on exploratory analyses, as there was no adjustment for multiplicity based on hierarchical testing.

TABLE 15: PROPORTION OF PATIENTS ACHIEVING MODIFIED PSARC RESPONSE AT WEEKS 16 AND 24 (FULL ANALYSIS SET)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	**APR 30 mg b.i.d., N = 168**	**Placebo N = 159**	**APR 30 mg b.i.d., N = 162**	**Placebo N = 169**	**APR 30 mg b.i.d., N = 167**
At Week 16[a]						
n (%)	50 (29.8)	78 (46.4)	53 (33.3)	78 (48.1)	46 (27.2)	88 (52.7)
Adjusted % difference in proportions (95% CI)	16.7 (6.6 to 26.8)[b]		14.9 (4.3 to 25.5)[b]		25.4 (15.5 to 35.3)[d]	
P value	**0.0017**[c]		**0.0065**[c]		**< 0.0001**[e]	
At Week 24[a]						
n (%)	31 (18.5)	72 (42.9)	39 (24.5)	52 (32.1)	39 (23.1)	74 (44.3)
Adjusted % difference in proportions (95% CI)	24.6 (15.2 to 34.0)[b]		7.8 (–1.9 to 17.5)[b]		21.2 (11.5 to 30.9)[d]	

APR = apremilast; b.i.d.= twice daily; BSA = body surface area; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; DMARD = disease-modifying anti-rheumatic drug; FAS = full analysis set; PsARC = Psoriatic Arthritis Response Criteria.

[a] Patients who discontinued early, prior to the respective visits; patients who escaped early, at week 16 (for the week 24 analyses), and patients who did not have sufficient data for a definitive determination of response status at the respective visits were counted as nonresponders. Joints temporarily or permanently not assessable at baseline were excluded from joint count. For other unassessed joints at baseline, the joint assessment at the screening visit, if assessed, was used as the baseline assessment; otherwise, the joint was excluded from joint count. The last observed joint assessment (at baseline or post-baseline) was used for joints unassessed at the respective visits. There was no imputation for other missing PsARC component scores.

[b] Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[c] 2-sided *P* value is based on the CMH test adjusting for baseline DMARD use. *P* values in bold are considered statistically significant.

[d] Adjusted difference in proportions is the weighted average of the treatment differences across the 4 strata of baseline DMARD use by involvement of ≥ 3% BSA with psoriasis at baseline with the CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average.

[e] Two-sided *P* value is based on the CMH test adjusting for baseline DMARD use and involvement of ≥ 3% BSA with psoriasis at baseline. *P* values in bold are considered statistically significant.

TABLE 16: CDAI CHANGE FROM BASELINE AT WEEKS 16 AND 24 (FULL ANALYSIS SET; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	**APR 30 mg b.i.d., N = 168**	**Placebo N = 159**	**APR 30 mg b.i.d., N = 162**	**Placebo N = 169**	**APR 30 mg b.i.d., N = 167**
N (%)[a]	158 (94.0)	158 (94.0)	149 (93.7)	146 (90.1)	159 (94.1)	156 (93.4)
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At Week 16[b]						
Change from baseline at week 16 LS Mean (SE)[c]	–3.84 (0.929)	–8.72 (0.923)	–3.30 (0.871)	–6.81 (0.869)	–2.76 (0.869)	–7.70 (0.881)
Difference with placebo at week 16						
LS mean difference (2-sided 95% CI)[c]	–4.88 (–7.41 to –2.34)		–3.51 (–5.86 to –1.16)		–4.94 (–7.34 to –2.53)	

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	**APR 30 mg b.i.d., N = 168**	**Placebo N = 159**	**APR 30 mg b.i.d., N = 162**	**Placebo N = 169**	**APR 30 mg b.i.d., N = 167**
At Week 24[b]						
Change from baseline at week 24 LS mean (SE)[c]	–3.14 (0.965)	–9.52 (0.949)	–3.21 (0.884)	–6.35 (0.878)	–2.53 (0.889)	–7.81 (0.895)
Difference with placebo at week 24						
LS mean difference (2-sided 95% CI)[c]	–6.38 (–9.00 to –3.75)		–3.14 (–5.52 to –0.76)		–5.27 (–7.73 to –2.82)	

ANCOVA = analysis of covariance; APR = apremilast; b.i.d.= twice daily; BSA = body surface area; CDAI = Clinical Disease Activity Index; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; EE = early escape; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; min – max = minimum to maximum; SD = standard deviation; SE = standard error;.

[a] Patients with a baseline value and at least 1 post-baseline value at or prior to the respective visits are included.

[b] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question.

[c] LS mean (SE) and *P* value based on an ANCOVA model for the change from baseline at the respective time point, with treatment group and baseline DMARD use as factors, and the baseline value as a covariate. PALACE-3 was additionally adjusted for ≥ 3% BSA with psoriasis at baseline.

TABLE 17: DAS28(CRP) CHANGE FROM BASELINE AT WEEKS 16 AND 24 (FULL ANALYSIS SET; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	**APR 30 mg b.i.d., N = 168**	**Placebo N = 159**	**APR 30 mg b.i.d., N = 162**	**Placebo N = 169**	**APR 30 mg b.i.d., N = 167**
At Week 16[a]						
N (%)[b]	159 (94.6)	154 (91.7)	150 (94.3)	151 (93.2)	163 (96.4)	160 (95.8)
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 16 LS mean (SE)	–0.26 (0.082)[c]	–0.79 (0.083)[c]	–0.27 (0.082)[c]	–0.67 (0.080)[c]	–0.28 (0.084)[d]	–0.74 (0.085)[d]
Difference with placebo at week 16						
LS mean difference (2-sided 95% CI)	–0.53 (–0.76 to –0.31)[c]		–0.40 (–0.61 to –0.18)[c]		–0.47 (–0.70 to –0.24)[d]	
At Week 24[a]						
N (%)[b]	161 (95.8)	159 (94.6)	150 (94.3)	152 (93.8)	163 (96.4)	161 (96.4)
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 24 LS mean (SE)	–0.20 (0.087)[c]	–0.90 (0.087)[c]	–0.27 (0.084)[c]	–0.65 (0.083)[c]	–0.27 (0.087)[d]	–0.75 (0.087)[d]

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	**APR 30 mg b.i.d., N = 168**	**Placebo N = 159**	**APR 30 mg b.i.d., N = 162**	**Placebo N = 169**	**APR 30 mg b.i.d., N = 167**
Difference with placebo at week 24						
LS mean difference (2-sided 95% CI)	–0.70 (–0.94 to –0.46)[c]		–0.38 (–0.60 to –0.15)[c]		–0.48 (–0.72 to –0.24)[d]	

ANCOVA = analysis of covariance; APR = apremilast; b.i.d. = twice daily; BSA = body surface area; CI = confidence interval; DAS28(CRP) = Disease Activity Score (28-joint) using C-reactive protein as acute phase reactant; DMARD = disease-modifying anti-rheumatic drug; EE = early escape; LOCF = last observation carried forward; LS mean = least squares mean; min – max = minimum to maximum; SD = standard deviation SE = standard error.

[a] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question.

[b] Patients with a baseline value and at least 1 post-baseline value at or prior to the respective visits are included.

[c] LS mean (SE) and *P* value based on an ANCOVA model for the change from baseline at the respective time point, with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

[d] LS mean (SE) and *P* value based on an ANCOVA model for the change from baseline at the respective time point, with treatment group, baseline DMARD use, and involvement of ≥ 3% BSA with psoriasis at baseline as factors, and the baseline value as a covariate.

TABLE 18: PROPORTION OF PATIENTS ACHIEVING GOOD OR MODERATE EULAR RESPONSE AT WEEKS 16 AND 24 (FULL ANALYSIS SET)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
At Week 16[a]						
n (%)	50 (29.8)	82 (48.8)	50 (31.4)	79 (48.8)	49 (29.0)	86 (51.5)
Adjusted % difference in proportions (95% CI)	19.2 (9.0 to 29.3)[b]		17.5 (7.0 to 27.9)[b]		22.5 (12.4 to 32.6)[c]	
At Week 24[a]						
n (%)	27 (16.1)	71 (42.3)	34 (21.4)	54 (33.3)	34 (20.1)	71 (42.5)
Adjusted % difference in proportions (95% CI)	26.3 (17.1 to 35.5)[b]		12.1 (2.6 to 21.7)[b]		22.5 (13.0 to 32.1)[c]	

APR = apremilast; b.i.d.= twice daily; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; DAS28(CRP) = Disease Activity Score (28-joint) using C-reactive protein as acute phase reactant; DMARD = disease-modifying anti-rheumatic drug; EULAR = European League Against Rheumatism.

[a] Patients who discontinued early, prior to the respective visits; patients who escaped early, at week 16 (for the week 24 analyses); and patients who did not have sufficient data for a definitive determination of response status at the respective visits were counted as nonresponders. Joints temporarily or permanently not assessable at baseline were excluded from joint count. For other unassessed joints at baseline, the joint assessment at the screening visit, if assessed, was used as the baseline assessment; otherwise, the joint was excluded from joint count. The last observed joint assessment (at baseline or post-baseline) was used for joints unassessed at the respective visits. There was no imputation for other missing DAS28(CRP) component scores.

[b] Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[c] Adjusted difference in proportions is the weighted average of the treatment differences across the 4 strata of baseline DMARD use by involvement of ≥ 3% BSA with psoriasis at baseline with the CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average.

TABLE 19: PATIENT'S ASSESSMENT OF PAIN: CHANGE FROM BASELINE AT WEEKS 16 AND 24 (FULL ANALYSIS SET; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
At Week 16[a]						
N (%)[b]	165 (98.2)	159 (94.6)	151 (95.0)	152 (93.8)	164 (97.0)	161 (96.4)
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 16 LS mean (SE)[c]	–5.7 (1.83)	–13.5 (1.85)	–7.0 (1.93)	–11.9 (1.90)	–4.9 (1.79)	–12.7 (1.81)
Difference with placebo at week 16						
LS mean difference (2-sided 95% CI)[c]	–7.9 (–12.9 to –2.8)		–4.9 (–10.0 to 0.3)		–7.8 (–12.8 to –2.9)	
P value[c]	**0.0023**		[redacted]		**0.0021**	
At Week 24[a]						
N (%)[b]	165 (98.2)	162 (96.4)	152 (95.6)	153 (94.4)	164 (97.0)	162 (97.0)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	**APR 30 mg b.i.d., N = 168**	**Placebo N = 159**	**APR 30 mg b.i.d., N = 162**	**Placebo N = 169**	**APR 30 mg b.i.d., N = 167**
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 24 LS mean (SE)[c]						
Difference with placebo at week 24	–4.2 (1.78)	–14.7 (1.77)	–8.0 (1.90)	–9.7 (1.88)	–4.4 (1.75)	–10.9 (1.77)
LS mean difference (2-sided 95% CI)[c]	–10.6 (–15.4 to –5.7)		–1.7 (–6.8 to 3.4)		–6.6 (–11.4 to –1.7)	
Proportion of Patients with ≥ 10 mm Reduction in Patient Assessment of Pain at Weeks 16 and 24[d]						
At Week 16						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted % difference in proportions (95% CI)[e]	[redacted]		[redacted]		[redacted]	
At Week 24						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted % difference in proportions (95% CI)[e]	[redacted]		[redacted]		[redacted]	

ANCOVA = analysis of covariance; APR = apremilast; b.i.d. = twice daily; BSA = body surface area; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; EE = early escape; LOCF = last observation carried forward; LS = least squares; min – max = minimum to maximum; SD = standard deviation; SE = standard error.

[a] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question.

[b] Patients with a baseline value and at least 1 post-baseline value at or prior to the respective visits are included.

[c] LS mean (SE) and *P* value based on an ANCOVA model for the change from baseline at the respective time point, with treatment group and baseline DMARD use as factors, and the baseline value as a covariate. PALACE-3 was additionally adjusted for ≥ 3% BSA with psoriasis at baseline. *P* values in bold are considered statistically significant.

[d] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question. Patients who did not have sufficient data (observed or imputed) for a determination of response status at the respective visits were counted as nonresponders.

[e] Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. PALACE-3 was additionally adjusted for ≥ 3% BSA with psoriasis at baseline. The 2-sided 95% CI is based on a normal approximation to the weighted average.

TABLE 20: SF-36V2 PHYSICAL FUNCTIONING DOMAIN AT WEEKS 16 AND 24 (FULL ANALYSIS SET; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
Change from Baseline at Weeks 16[a]						
N (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 16 LS mean (SE)	1.81 (0.621)[c]	4.23 (0.625)[c]	0.81 (0.678)[c]	2.91 (0.671)[c]	1.14 (0.589)[d]	3.47 (0.594)[d]
Difference with placebo at week 16						
LS mean difference (2-sided 95% CI)	2.42 (0.71, 4.13)[c]		2.10 (0.28, 3.92)[c]		2.32 (0.69, 3.95)[d]	
P value	**0.0056**[c]		**0.0237**[c]		**0.0053**[d]	
Change from Baseline at Weeks 24[a]						
N (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 24 LS mean (SE)	1.45 (0.671)[c]	5.01 (0.671)[c]	1.44 (0.688)[c]	3.30 (0.679)[c]	1.03 (0.581)	3.37 (0.585)[d]
Difference with placebo at week 24						
LS mean difference (2-sided 95% CI)	3.56 (1.72, 5.40)[c]		1.86 (0.02, 3.70)[c]		2.34 (0.74, 3.94)[d]	
SF-36v2 Physical Functioning Domain Score Improvement ≥ 2.5 Points at Week 16[e]						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted % difference in proportions (95% CI)	[redacted]		[redacted]		[redacted]	
P value	[redacted]		[redacted]		[redacted]	
SF-36v2 Physical Functioning Domain Score Improvement ≥ 2.5 Points at Week 24[e]						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted % difference in	[redacted]		[redacted]		[redacted]	

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
proportions (95% CI)						
P value	[redacted]		[redacted]		[redacted]	

ANCOVA = analysis of covariance; APR = apremilast; b.i.d.= twice daily; BSA = body surface area; CMH = Cochran–Mantel–Haenszel; DMARD = disease-modifying anti-rheumatic drug; EE = early escape; LOCF = last observation carried forward; LS = least squares; min – max = minimum to maximum; SD = standard deviation; SE = standard error; SF-36v2 = Short Form (36) Health Survey, version 2.

[a] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question.

[b] Patients with a baseline value and at least 1 post-baseline value at or prior to the respective visits are included.

[c] LS mean (SE) and *P* value based on an ANCOVA model for the change from baseline at the respective time point, with treatment group and baseline DMARD use as factors, and the baseline value as a covariate. *P* values in bold are considered statistically significant.

[d] LS mean (SE) and *P* value based on an ANCOVA model for the change from baseline at the respective time point, with treatment group, baseline DMARD use, and involvement of ≥ 3% BSA with psoriasis at baseline as factors, and the baseline value as a covariate. *P* values in bold are considered statistically significant.

[e] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question. Patients who did not have sufficient data (observed or imputed) for a determination of response status at the respective visits were counted as nonresponders.

[redacted]

TABLE 21: SF-36V2 PHYSICAL COMPONENT SUMMARY AT WEEKS 16 AND 24 (FULL ANALYSIS SET; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
SF-36v2 PCS Improvement ≥ 2.5 points at week 16[d]						
n (%)	[redacted]		[redacted]		[redacted]	
Adjusted % difference in proportions (95% CI)	[redacted]		[redacted]		[redacted]	
P value	[redacted]		[redacted]		[redacted]	
SF-36v2 PCS improvement ≥ 2.5 points at week 24[d]						
n (%)	[redacted]		[redacted]		[redacted]	
Adjusted % difference	[redacted]		[redacted]		[redacted]	

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
in proportions (95% CI)						
P value	[redacted]		[redacted]		[redacted]	

ANCOVA = analysis of covariance; APR = apremilast; b.i.d.= twice daily; BSA = body surface area; CMH = Cochran–Mantel–Haenszel; DMARD = disease-modifying anti-rheumatic drug; LOCF = last observation carried forward; LS = least squares; min – max = minimum to maximum; PCS = physical component summary; SF-36v2 = 36-item Short Form Health Survey, version 2.

[a] Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[b] 2-sided *P* value is based on the CMH test adjusting for baseline DMARD use. *P* values in italics are ≤ 0.050 and considered based on exploratory analyses, as there was no adjustment for multiplicity based on hierarchical testing.

[c] Adjusted difference in proportions is the weighted average of the treatment differences across the 4 strata of baseline DMARD use by involvement of ≥ 3% BSA with psoriasis at baseline with the CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average.

[d] 2-sided *P* value is based on the CMH test adjusting for baseline DMARD use. *P* values in italics are ≤ 0.050 and considered based on exploratory analyses, as there was no adjustment for multiplicity based on hierarchical testing.

TABLE 22: EQ-5D INDEX VALUE AND VAS SCORE (0 MM TO 100 MM) AT WEEKS 16 AND 24 (FULL ANALYSIS SET; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
EQ-5D Index Value at Week 16[a]						
N (%)	[redacted]					
Baseline mean (SD)						
Change from baseline at week 16 mean (SD)						
EQ-5D Index Value at Week 24[ab]						
N (%)	[redacted]					
Baseline mean (SD)						
Change from baseline at week 16 mean (SD)						
VAS Score at Week 16[a]						
N (%)	[redacted]					
Baseline mean (SD)						
Change from baseline at week 16 mean (SD)						
VAS Score at Week 24[a]						
N (%)	[redacted]					
Baseline mean (SD)						

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
Change from baseline at week 16 mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b.i.d. = twice daily; EQ-5D = EuroQol-5 Dimensions Questionnaire; LOCF = last observation carried forward; SD = standard deviation; VAS = visual analogue score.
[a] A higher score indicates a better health state, and a positive change from baseline indicates improvement. Index values are calculated using the US (time trade-off) value set.
[b] Data obtained after early escape at week 16 are excluded. For week 24 (LOCF), for patients who escaped early at week 16, the week 16 value is carried forward; for other patients, the last post-baseline value is carried forward for a missing value at week 24. For week 24 (observed data), patients who escaped early at week 16 are excluded.

TABLE 23: WLQ-25 PRODUCTIVITY LOSS SCORE AT WEEKS 16 AND 24 (FULL ANALYSIS SET; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
WLQ-25 Productivity Loss Score at Week 16[a]						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 16 mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WLQ-25 Productivity Loss Score at Week 24[a,b]						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 16 mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b.i.d. = twice-daily; LOCF = last observation carried forward; SD = standard deviation; WLQ-25 = 25-Item Work Limitations Questionnaire.
[a] Higher scores indicate greater work limitations or productivity loss, and negative changes from baseline indicate improvement.
[b] Data obtained after early escape at week 16 are excluded: For week 24 (LOCF), for patients who escaped early at week 16, the week 16 value is carried forward; for other patients, the last post-baseline value is carried forward for a missing value at week 24. For week 24 (observed data), patients who escaped early at week 16 are excluded.

TABLE 24: CHANGE FROM BASELINE IN MASES AT WEEKS 16 AND 24 (PATIENTS WITH PRE-EXISTING ENTHESOPATHY; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	**APR 30 mg b.i.d., N = 168**	**Placebo N = 159**	**APR 30 mg b.i.d., N = 162**	**Placebo N = 169**	**APR 30 mg b.i.d., N = 167**
Change from Baseline at Week 16[a]						
N (%)[b]	95 (56.5)	108 (64.3)	100 (62.9)	97 (59.9)	106 (62.7)	107 (64.1)
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 16 LS mean (SE)	-0.9 (0.30)[c]	-1.3 (0.28)[c]	-1.0 (0.29)[c]	-1.4 (0.29)[c]	-0.7 (0.27)[d]	-1.0 (0.27)[d]
Difference with placebo at week 16						
LS mean difference (2-sided 95% CI)	–0.4 (–1.2 to 0.4)[c]		–0.4 (–1.2 to 0.4)[c]		–0.2 (–1.0 to 0.5)[d]	
P value	0.3605[c]				0.5349[d]	
Change from Baseline at Weeks 24[a]						
N (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 24 LS mean (SE)	–0.8 (0.31)[c]	–1.6 (0.29)[c]	–0.9 (0.29)[c]	–1.3 (0.29)[c]	–0.7 (0.29)[d]	–1.1 (0.29)[d]
Difference with placebo at week 24						
LS mean difference (2-sided 95% CI)	–0.8 (–1.6 to 0.0)[c]		–0.4 (–1.2 to 0.3)[c]		–0.4 (–1.3 to 0.4)[d]	

ANCOVA = analysis of covariance; APR = apremilast; b.i.d.= twice daily; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; EE = early escape; LOCF = last observation carried forward; LS = least squares; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; SD = standard deviation; SE = standard error.

[a] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question.

[b] Patients with a baseline MASES > 0 (i.e., pre-existing enthesopathy) and at least 1 post-baseline value at or prior to the respective visits are included.

[c] LS mean (SE) and *P* value based on an ANCOVA model for the change from baseline at the respective time point, with treatment group and baseline DMARD use as factors, and the baseline value as a covariate.

[d] LS mean (SE) and *P* value based on an ANCOVA model for the change from baseline at the respective time point, with treatment group, baseline DMARD use, and involvement of ≥ 3% BSA with psoriasis at baseline as factors, and the baseline value as a covariate.

TABLE 25: PROPORTION OF PATIENTS ACHIEVING AT LEAST 20% MASES IMPROVEMENT AT WEEKS 16 AND 24 (PATIENTS WITH PRE-EXISTING ENTHESOPATHY; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 98	APR 30 mg b.i.d., N = 114	Placebo N = 104	APR 30 mg b.i.d., N = 101	Placebo N = 109	APR 30 mg b.i.d., N = 112
At Week 16[a]						
n (%)	48 (49.0)	60 (52.6)	55 (52.9)	57 (56.4)	58 (53.2)	61 (54.5)
Adjusted % difference in proportions (95% CI)	3.3 (–10.1 to 16.7)[b]		3.6 (–9.9 to 17.2)[b]		2.1 (–10.9 to 15.0)[c]	
At Week 24[a]						
n (%)	46 (46.9)	69 (60.5)	53 (51.0)	58 (57.4)	56 (51.4)	61 (54.5)
Adjusted % difference in proportions (95% CI)	13.2 (–0.1 to 26.5)[b]		6.6 (–6.8 to 20.0)[b]		3.8 (–9.1 to 16.7)[c]	

APR = apremilast; b.i.d. = twice daily; BSA = body surface area; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; DMARD = disease-modifying anti-rheumatic drug; EE = early escape; LOCF = last observation carried forward; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score.

[a] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question. Patients who did not have sufficient data (observed or imputed) for a determination of response status at the respective visits were counted as nonresponders. Entheses unassessed at baseline were excluded; the last observed enthesis assessment (at baseline or post-baseline) was used for entheses unassessed at week 16.

[b] Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[c] Adjusted difference in proportions is the weighted average of the treatment differences across the 4 strata of baseline DMARD use by involvement of ≥ 3% BSA with psoriasis at baseline with the CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average.

TABLE 26: CHANGE FROM BASELINE IN DACTYLITIS SEVERITY SCORE AT WEEKS 16 AND 24 (PATIENTS WITH PRE-EXISTING DACTYLITIS; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
Change from Baseline at Week 16[a]						
N (%)[b]	63 (37.5)	66 (39.3)	63 (39.6)	70 (43.2)	67 (39.6)	76 (45.5)
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 16 LS mean (SE)[c]	–1.4 (0.28)	–1.7 (0.28)	–1.1 (0.28)	–1.3 (0.26)	–1.3 (0.34)	–2.1 (0.32)
Difference with placebo at week 16						
LS mean difference (2-sided 95% CI)[c]	–0.3 (–1.1 to 0.4)		–0.2 (–1.0 to 0.5)		–0.8 (–1.7 to 0.1)	
Change from Baseline at Week 24[a]						
N (%)[b]	64 (38.1)	66 (39.3)	63 (39.6)	71 (43.8)	67 (39.6)	77 (46.1)
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 24 LS mean (SE)[c]	–1.3 (0.27)	–1.8 (0.27)	–1.1 (0.27)	–1.4 (0.26)	–1.3 (0.35)	–2.3 (0.32)
Difference with placebo at week 24						
LS mean difference (2-sided 95% CI)[c]	–0.5 (–1.2 to 0.3)		–0.3 (–1.0 to 0.4)		–1.0 (–1.9 to –0.0)	

ANCOVA = analysis of covariance; APR = apremilast; b.i.d.= twice daily; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; EE = early escape; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error.

[a] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question.

[b] Patients with a baseline Dactylitis Severity Score > 0 (i.e., pre-existing dactylitis) and at least 1 post-baseline value at or prior to the respective visits are included.

[c] LS mean (SE) and *P* value based on an ANCOVA model for the change from baseline at the respective visit, with treatment group and baseline DMARD use as factors and the baseline value as a covariate. PALACE-3 was additionally adjusted for ≥ 3% body surface area with psoriasis at baseline.

TABLE 27: PROPORTION OF PATIENTS ACHIEVING A DACTYLITIS SEVERITY SCORE OF 0 AT WEEKS 16 AND 24 (PATIENTS WITH PRE-EXISTING DACTYLITIS; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 68	APR 30 mg b.i.d., N = 68	Placebo N = 66	APR 30 mg b.i.d., N = 73	Placebo N = 71	APR 30 mg b.i.d., N = 80
At Week 16[a]						
n (%)	27 (39.7)	26 (38.2)	27 (40.9)	30 (41.1)	25 (35.2)	33 (41.3)
Adjusted % difference in proportions (95% CI)[b]		-1.4 (-17.7, 14.8)		0.3 (-16.0, 16.6)		6.6 (-8.6, 21.8)
At Week 24[a]						
n (%)	27 (39.7)	31 (45.6)	27 (40.9)	34 (46.6)	29 (36.6)	37 (46.3)
Adjusted % difference in proportions (95% CI)[b]		5.8 (-10.7, 22.4)		5.9 (-10.3, 22.1)		9.8 (-5.8, 25.4)

APR = apremilast; b.i.d.= twice daily; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; LOCF = last observation carried forward.

[a] Pre-existing dactylitis is defined as baseline Dactylitis Severity Score > 0. For patients who escaped early at week 16, the week 16 value (if missing, the last pre-escape/post-baseline value) is carried forward at week 24; for other patients, the last post-baseline value is carried forward for a missing value at week 24. Patients who did not have sufficient data (observed or imputed) for a definitive determination of response status at week 24 are counted as nonresponders. Digits unassessed at baseline are excluded; the last observed digit assessment (at baseline or post-baseline) is used for digits unassessed at week 24.

[b] Adjusted difference in proportions is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average.

[c] 2-sided *P* value is based on the CMH test adjusting for baseline DMARD use. PALACE-3 was additionally adjusted for ≥ 3% body surface area with psoriasis at baseline.

TABLE 28: FACIT-F SCORE: CHANGE FROM BASELINE AT WEEKS 16 AND 24 (FAS; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
Change from Baseline at Week 16[a]						
N (%)[b]	162 (96.4)	159 (94.6)	153 (96.2)	154 (95.1)	160 (94.7)	160 (95.8)
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 16 LS mean (SE)[c]	1.55 (0.693)	3.88 (0.695)	0.63 (0.724)	2.75 (0.715)	1.18 (0.640)	3.72 (0.641)
Difference with placebo at week 16						
LS mean difference (2-sided 95% CI)[c]	2.33 (0.43 to 4.23)		2.12 (0.19 to 4.06)		2.54 (0.77 to 4.30)	
Change from Baseline at Week 24[a]						
N (%)[b]	163 (97)	161 (95.8)	153 (96.2)	154 (95.1)	161 (95.3)	161 (96.4)
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	**APR 30 mg b.i.d., N = 168**	**Placebo N = 159**	**APR 30 mg b.i.d., N = 162**	**Placebo N = 169**	**APR 30 mg b.i.d., N = 167**
Change from baseline at week 24 LS mean (SE)[c]	1.12 (0.691)	3.33 (0.690)	0.52 (0.721)	2.65 (0.713)	0.83 (0.652)	3.27 (0.654)
Difference with placebo at week 24						
LS mean difference (2-sided 95% CI)[c]	2.21 (0.32 to 4.10)		2.14 (0.20 to 4.07)		2.44 (0.64 to 4.24)	

ANCOVA = analysis of covariance; APR = apremilast; b.i.d.= twice daily; DMARD = disease-modifying anti-rheumatic drug; EE = early escape; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue Subscale; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error.

[a] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question.

[b] Patients with a baseline value and at least 1 post-baseline value at or prior to the respective visits are included.

[c] LS mean (SE) and *P* value based on an ANCOVA model for the change from baseline at the respective time point, with treatment group and baseline DMARD use as factors, and the baseline value as a covariate. PALACE-3 was additionally adjusted for ≥ 3% body surface area with psoriasis at baseline.

TABLE 29: PROPORTION OF PATIENTS ACHIEVING AT LEAST A 3.56-POINT IMPROVEMENT IN FACIT-F SCORE AT WEEKS 16 AND 24 (FAS; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 168	APR 30 mg b.i.d., N = 168	Placebo N = 159	APR 30 mg b.i.d., N = 162	Placebo N = 169	APR 30 mg b.i.d., N = 167
At week 16[a]						
n (%)	[redacted]		[redacted]		[redacted]	
Adjusted % difference in proportions (95% CI)[b]	[redacted]		[redacted]		[redacted]	
At week 24[a]						
n (%)	[redacted]		[redacted]		[redacted]	
Adjusted % difference in proportions (95% CI)[b]	[redacted]		[redacted]		[redacted]	

APR = apremilast; b.i.d.= twice daily; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; EE = early escape; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue Subscale; FAS = full analysis set; LOCF = last observation carried forward.

[a] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question. Patients who did not have sufficient data (observed or imputed) for a determination of response status at the respective visits were counted as nonresponders.

[b] Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the Cochran–Mantel–Haenszel weights. PALACE-3 was additionally adjusted for ≥ 3% body surface area with psoriasis at baseline. The 2-sided 95% CI is based on a normal approximation to the weighted average.

TABLE 30: PROPORTION OF PATIENTS ACHIEVING PASI-75 AND PASI-50 RESPONSES AT WEEKS 16 AND 24 (FAS; LOCF)

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 68	APR 30 mg b.i.d., N = 77	Placebo N = 74	APR 30 mg b.i.d., N = 80	Placebo N = 89	APR 30 mg b.i.d., N = 91
PASI-75						
At week 16[ab]						
n (%)	[redacted]		[redacted]		7 (7.9)	20 (22.2)
Adjusted % difference in proportions (95% CI)[c]	[redacted]		[redacted]		14.6 (4.5 to 24.8)	
P value[d]	[redacted]		[redacted]		**0.0062**	
At week 24[ab]						
n (%)	[redacted]		[redacted]		10 (11.2)	23 (25.6)
Adjusted % difference in proportions (95% CI)[c]	[redacted]			[redacted]		14.8 (3.8 to 25.7)
P value[d]	[redacted]		[redacted]			

	PALACE-1		PALACE-2		PALACE-3	
	Placebo N = 68	APR 30 mg b.i.d., N = 77	Placebo N = 74	APR 30 mg b.i.d., N = 80	Placebo N = 89	APR 30 mg b.i.d., N = 91
PASI-50						
At week 16[ab]						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted % difference in proportions (95% CI)[c]	[redacted]		[redacted]		[redacted]	
At week 24[ab]						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted % difference in proportions (95% CI)[c]	[redacted]		[redacted]		[redacted]	

APR = apremilast; b.i.d.= twice daily; BSA = body surface area; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; DMARD = disease-modifying anti-rheumatic drug; EE = early escape; FAS = full analysis set; LOCF = last observation carried forward; PASI-50/75 = 50%/75% or greater improvement in the Psoriasis Area and Severity Index.

[a] Among patients with baseline psoriasis skin involvement of ≥ 3% BSA who were evaluated for a PASI response.

[b] For patients who discontinued from the study prior to week 16, the last available post-baseline value observed prior to discontinuation was carried forward to weeks 16 and 24. For patients who entered EE at week 16 or who did not enter EE but discontinued from the study between weeks 16 and 24, the last available post-baseline value observed prior to EE or discontinuation, respectively, was carried forward to week 24. Missing values for patients who did not discontinue or enter EE were imputed using the latest available post-baseline value prior to the visit in question. Patients who did not have sufficient data (observed or imputed) for a determination of response status at the respective visits were counted as nonresponders.

[c] Adjusted difference is the weighted average of the treatment differences across the 2 strata of baseline DMARD use with the CMH weights. PALACE-3 was additionally adjusted for ≥ 3% BSA with psoriasis at baseline. The 2-sided 95% CI is based on a normal approximation to the weighted average.

[d] 2-sided *P* value is based on the CMH test adjusting for baseline DMARD use. *P* values in italics are ≤ 0.050 and considered based on exploratory analyses, as there was no adjustment for multiplicity based on hierarchical testing.

TABLE 31: INCIDENCE OF TEAES REPORTED IN AT LEAST 2% OF PATIENTS IN ANY TREATMENT GROUP DURING THE PLACEBO-CONTROLLED PERIOD (WEEKS 0-24) (SAFETY POPULATION)

AE[a]	PALACE-1		PALACE-2		PALACE-3	
	Placebo[b] N = 168	APR 30 mg b.i.d.,[c] N = 168	Placebo[b] N = 159	APR 30 mg b.i.d.,[c] N = 162	Placebo[b] N = 168	APR 30 mg b.i.d.,[c] N = 167
[redacted]						

AE[a]	PALACE-1		PALACE-2		PALACE-3	
	Placebo[b] N = 168	APR 30 mg b.i.d.,[c] N = 168	Placebo[b] N = 159	APR 30 mg b.i.d.,[c] N = 162	Placebo[b] N = 168	APR 30 mg b.i.d.,[c] N = 167
[redacted]						

APR = apremilast; b.i.d.= twice daily; EE = early escape; TEAE = treatment-emergent adverse event.
[a] A patient with multiple occurrences of an adverse event is counted only once in the preferred term category.
[b] Includes data from weeks 0 to 24 for patients who did not enter EE at week 16, and data from weeks 0 to 16 for patients who did enter EE.
[c] Includes data from weeks 0 to 24 for all patients randomized to APR 30 b.i.d., irrespective of EE.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Objective

To provide information on the characteristics of the scales and instruments of outcome measures, including their validity and clinically important differences, employed in the clinical trials included in the review by the CADTH Common Drug Review (CDR).

Findings

Currently available outcome measures in psoriatic arthritis (PsA) have largely been adopted from other conditions, such as rheumatoid arthritis (RA) and psoriasis. Hence, validity and reliability data specific to PsA are sparse. Furthermore, there are many different parameters of disease activity in PsA and no single evaluation tool assesses all components of PsA. Therefore, clinical trials use multiple outcome measures to evaluate response to interventions. Characteristics of measures of outcomes reported in this review are summarized below.

American College of Rheumatology 20/50/70

The American College of Rheumatology (ACR) criteria for assessing joint status were originally developed for RA patients, and provide a composite measure of ≥ 20%, ≥ 50%, or ≥ 70% (ACR20, ACR50, and ACR70, respectively) improvement in both swollen and tender joint counts and at least three of five additional disease criteria, including Patient or Physician Global Assessment of disease activity (10 cm visual analogue scale [VAS]), Health Assessment Questionnaire (HAQ), patient assessment of pain intensity, and levels of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR).[27] The ACR joint count assesses 68 joints for tenderness and 66 joints for swelling. Assessment of the proximal interphalangeal and distal interphalangeal joints of the hands and feet (i.e., 78 joints for tenderness and 76 for swelling) is not typically included for PsA because of difficulty distinguishing proximal and distal interphalangeal joint inflammation in the toes.[55] The ACR has been shown to have good inter- and intra-observer reliability in PsA, [56,57] and was shown to be a valid outcome measure in RCTs.[32] The ACR20 is generally accepted as the minimally clinically important difference (MCID) indicating a response to treatment, while the ACR50 and ACR70 more likely reflect truly important change for the long-term management of arthropathy. The ACR is a general measure of clinical response of peripheral joint disease and does not include assessment of enthesitis, dactylitis, the spine, or the skin. Consequently, it represents only part of the clinical features of PsA; therefore, the use of additional assessment instruments to assess other clinical features is necessary.

Health Assessment Questionnaire

The HAQ was developed to assess physical disability and pain in RA[28] and has been used extensively in randomized controlled trials (RCTs) in arthritis, including for PsA. Patients assess and score their difficulty in performing activities in eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities) using a self-assessed questionnaire. The performance scores range from 0 (without any difficulty) to 3 (unable to do), and are adjusted for use of aids, devices, or persons who help with the activity. The summed score is then divided by the number answered questions and reported. Scores are evaluated based on change from baseline. The MCID for the Health Assessment Questionnaire – Disability Index (HAQ-DI) has been estimated from a phase 3 trial of etanercept in PsA[29] to be 0.3 (unlike 0.22 for RA). Mease and colleagues[30] have determined that the MCID for the HAQ-DI is 0.35, while the MCID has been estimated to be 0.13 (equal bidirectional magnitudes for improvement and worsening) by Kwok and Pope.[54] Blackmore et al. have shown that the HAQ-DI adequately captures clinically important changes in functional status and pain.[28,29] However, the HAQ-DI focuses on physical

disability and may not adequately capture disability in patients with predominantly skin disease.[58] Modified versions of the HAQ to include spinal domains (HAQ-S) or skin disease assessment (HAQ-SK) have not proven to be significantly better in assessing health status in PsA than the original HAQ-DI.[38,58] The HAQ-SK has poor correlation with the Psoriasis Area and Severity Index (PASI), and does correlate with patient-assessed or physician-assessed severity of psoriasis.[38]

Psoriatic Arthritis Response Criteria

Patients are classified as Psoriatic Arthritis Response Criteria (PsARC) responder or non-responder based on four criteria of clinical improvement — a joint pain/tenderness score, joint swelling score, patient global self-assessment (0 to 5 Likert scale), and Physician Global Assessment (0 to 5 Likert scale).[31] For the Patient Global Self-Assessment and the Physician Global Assessment, improvement or worsening is defined by a decrease or increase, respectively, by one category on the Likert scale.[32] A PsARC responder should have a ≥ 30% reduction in tender or swollen joint count, a 1-point reduction on the 5-point Patient and/or Physician Global Assessment scales, without worsening on any score.[32,33] A modified PsARC treatment response was defined as improvement in at least two of the four measures, one of which must be tender joint count (TJC) or swollen joint count (SJC), and no worsening in any of the four measures.[33] The PsARC assesses general clinical status and does not account for psoriasis severity. PsARC has been shown to be a responsive and discriminate outcome instrument in RCTs in PsA.[32] However, the PsARC tends to have a higher percentage response than the ACR20, which may be explained by the fact that unlike the ACR, PsARC is based on changes in either tender or swollen joint (not both), and possibly because it does not require the HAQ score and measurement of ESR or CRP.[59]

Clinical Disease Activity Index

The Clinical Disease Activity Index (CDAI) is a composite index defined by the following formula:

CDAI = SJC28 + TJC28 + PGA + EGA.[34]

Where SJC28 and TJC28 are the 28-joint swollen and tender joint counts, respectively, as described by the Disease Activity Score (DAS) 28 and CRP (DAS28[CRP]), PGA is Patients' Global Assessment, and EGA is Evaluator's (physician's) Global Assessment. Both PGA and EGA are expressed as a 10 cm VAS score

The CDAI score ranges from 0 to 76 with a score of ≤ 2.8 designating remission while > 2.8 and ≤ 10 represents low disease activity. Moderate and high disease activities are designated by scores of > 10 and ≤ 22, and > 22, respectively.[34] The CDAI is not dependent on the results of acute phase reactant testing such as CRP or ESR.

Disease Activity Score 28 and C-reactive Protein

The DAS28 score evaluates a patient's response to treatment based on assessment of 28 each of tender and swollen joints, along with a Patient Global Assessment of well-being [35,36] The score ranges from 0 to 9.4 and is calculated using either clinical values of ESR or CRP. DAS28 can be expressed as:

$$DAS28 = 0.56(\sqrt{TJC28}) + 0.28(\sqrt{SJC28}) + 0.36Ln(CRP + 1) + 0.014(PGA).$$[35]

where TJC28 and SJC28 are the tender and swollen joint counts, respectively, and PGA is Patient's Global Assessment.

The threshold values for DAS28 are 2.6, 3.2, and 5.1, corresponding with remission, low disease activity, and high disease activity, respectively.[27] As with the ACR and PsARC, the DAS28 is only a general assessment of clinical response.

The DAS components correlate well with each other and with the ACR,[35,60-62] and have been shown to be discriminant and responsive in trials.[63] However, the DAS 28 does not include assessment of distal interphalangeal or lower extremity disease and, thus, may not describe the full extent of a patient's disease status. The DAS28 using ESR is better established compared with DAS28 using CRP, and it has been validated for use as an outcome measure in several RA trials.[27,32,35,64] Although DAS 28-ESR has shown the ability to discriminate between placebo and active treatment in PsA trials,[63] a formal validation in PsA has not yet been conducted. The DAS 28-CRP, which was used in trials included in this review, shows general agreement with the ESR equation in RA trials, and tends to yield better response criteria results than the DAS 28-ESR when disagreements occur between the two.[65-67] The CRP may be a more desirable clinical measurement than ESR because CRP levels are sensitive to short-term changes in disease activity, whereas ESR can be influenced by such factors as age, gender, or plasma proteins.[68]

European League Against Rheumatism Response

The European League Against Rheumatism (EULAR) response criteria classify patients as good or moderate responders, or as nonresponders to treatment based on the individual patient's disease severity as measured on the current DAS28 score, and changes in DAS28 from baseline at the time of assessment.[37] The definition of a good or moderate EULAR response is presented in Table 32.

TABLE 32: EULAR RESPONDER CLASSIFICATION

Current DAS 28	Improvement in DAS 28 From Baseline		
	> 1.2	**> 0.6 to ≤ 1.2**	**≤ 0.6**
≤ 3.2	Good	Moderate	None
> 3.2 to ≤ 5.1	Moderate	Moderate	None
> 5.1	Moderate	None	None

DAS = Disease Activity Score.

Patient's Assessment of Pain

Patients' assessment of pain was scored on a 0 mm to 100 mm horizontal line, on which 0 represents "no pain" and the 100 mm mark represents "pain as severe as can be imagined." [52] Patients were asked to place a vertical line on the horizontal line to indicate the level of their arthritis pain on the day of the visit.[52] The MCID of patient's assessment of pain was defined as an improvement (reduction) in pain of 10 mm or more from baseline.[52] Patients' assessment of pain is part of the ACR core set of measures in arthritis.[53]

Medical Outcomes Study Short Form (36)

The Short Form (36) Health Survey (SF-36) is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[40] The SF-36 consists of eight health domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH).[41] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries, the physical component summaries (PCS) and the mental component summary (MCS), derived from aggregating the eight domains according to a scoring algorithm. The PCS and MCS scores range from 0 to 100, with higher scores indicating better health status. The summary scales are scored using norm-based

methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a standard deviation (SD) of 10 in the general US population. Therefore, all scores above or below 50 are considered above or below average for the general US population. Husted et al.[69] and Leung et al.[45] reported that the SF-36 is reliable and valid for assessment of patients with PsA, and could be used to distinguish PsA patients from patients without PsA. In addition, the PCS and MCS scores support the SF-36 validity.[45] The SF-36 is at least equally responsive as the HAQ instrument to short-term changes in perceived health status and inflammatory disease activity in patients with PsA.[70]

The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 and 5 points.[42-44] Leung and colleagues[45] reported MCIDs of 3.74 and 1.77 for the PCS and MCS subsections, respectively, in PsA patients treated with anti-TNF alpha drugs. The MCS was observed in a phase 3 trial[45] to be weaker in differentiating drug and placebo effects. However, the trial was limited by its small sample size (n = 17).[45]

EuroQol 5-Dimensions Questionnaire

The EuroQol 5-Dimensions Questionnaire (EQ-5D) measures the patient's general health status using a descriptive system of five-dimensional multiple choice questionnaire and a vertical VAS. The five dimensions of health status are mobility, self-care, usual activities (work, study, housework, and family/leisure activities), pain/discomfort, and anxiety/depression. For each dimension, patient's response could be one of three levels: no problems, some problems, and severe problems. The respondent indicates their health state by selecting the most appropriate statement in each of the five dimensions, resulting in a one-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a five-digit number that describes the respondent's health state.[46] For example, a respondent's health state scored as 12231 indicates no problems with mobility, some problems with self-care and performing usual activities, severe pain or discomfort, and no problems with anxiety or depression. The five EQ-5D descriptive system score may be converted into a single summary index using a formula that applies weights to each of the levels in each dimension.[46] The VAS component comprises a 20 cm vertical VAS on which a patient provides a self-rated health state, ranging from "the best imaginable health state" to "the worst imaginable health status."[46] The EQ-5D has shown discrimination and responsiveness in PsA trials.[47] A literature search for this supplemental issue did not find an MCID for improvement in the EQ-5D for PsA patients.

Work Limitations Questionnaire

The Work Limitations Questionnaire (WLQ-25) is a validated, self-reported, 25-item instrument for measuring the degree to which chronic health problems interfere with ability to perform job roles. The WLQ has four dimensions of on-the-job disability (limitations handling time, physical, mental-interpersonal, and output demands) with a total score range of zero (limited none of the time) to 100 (limited all of the time) for the reported amount of time in the prior two weeks the respondents were limited on-the-job. The instrument was validated in a population of adults working ≥20 hours per week, and thus possibly excluded individuals with severe work limitations. Literature search for this supplemental issue did not find an MCID for improvement in the WLQ-25 for PsA patients. The WLQ is context specific and focused on job demand performance, and can therefore be used to identify both the magnitude and type of impact that health problems are having in the workplace.[48,49]

Maastricht Ankylosing Spondylitis Enthesitis Score

The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) is a validated enthesis index for ankylosing spondylitis developed by assessing measures of disease activity, including the Bath

Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Mander enthesis index (MEI). Enthesitis is defined as inflammation at the site of tendons, ligaments, or joint capsule fibre insertion into bone.[47] The MASES aims to provide a more practical and less time-consuming alternative to the MEI. The index assesses 13 enthesis points compared with 66 on the MEI index, and replaces the 0 to 3 grading of tenderness score in MEI with a dichotomous (0/1 for no/yes) score for tenderness to reduce confounding in assessment. Thus, the score for MASES index ranges from 0 to 13, correlating with the number of painful entheses out of the total of 13 assessed. A literature search for this supplemental issue did not find an MCID for improvement in the MASES index for PsA patients. MASES is a more feasible alternative to the MEI[71] with a good correlation between the two indexes (Spearman correlation coefficient of 0.90). However, MASES has not been assessed specifically for PsA.[47]

Dactylitis Severity Score

Dactylitis is characterized by swelling of the entire digit (finger or toe) and represents a combination of synovitis and inflammation of tendon and ligament insertions.[47] It is a hallmark feature of PsA, occurring in 16% to 48% of reported cases.[47] The Dactylitis Severity Score is the sum of the individual scores for each digit, and ranges from 0 to 20 — 0 for no dactylitis or 1 for dactylitis present in each digit. The results from each digit with dactylitis are then summed to produce a final score.

Functional Assessment of Chronic Illness Therapy – Fatigue

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale is a self-administered questionnaire that assesses both the physical and functional consequences of fatigue.[50] The FACIT-F was validated in a Toronto PsA cohort study and was found to be well correlated with the modified Fatigue Severity Scale (FSS), showing high internal consistency, and test–retest reliability, as well as criterion, and construct validity.[47] It is a 13-item questionnaire with each question scored from 0 to 4 for a total score range of 0 to 52. Higher scores denote lower levels of fatigue. Therefore, higher FACIT-F scores are expected with greater improvements in a patient's PsA.[50] A validated MCID for improvement in the FACIT-F is not currently available in PsA patients. The clinical trials included in this review used 3.56, which is the validated FACIT-F MCID in RA patients.[51]

Psoriasis Area and Severity Index

The PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It produces a numeric score ranging from 0 to 72. In general, a PASI score of 5 to 10 is considered moderate disease and a score higher than 10 is considered severe. A 75% reduction in the PASI score (PASI 75) is the current benchmark for most clinical trials in psoriasis and the criterion for efficacy of new psoriasis treatments approved by the FDA.[39] PASI 75 is a dichotomous (yes/no) scale that indicates whether a patient achieved ≥ 75% improvement from baseline PASI score.

In calculating the PASI, severity is determined by dividing the body into four regions: head (h), upper extremities (u), trunk (t), and lower extremities (l), and these account for 10%, 20%, 30%, and 40% of the total body surface area (BSA), respectively.[72] Each of these areas is assessed separately for erythema, induration, and scaling, which is rated on a scale of 0 (none) to 4 (very severe). The extent of psoriatic involvement is graded as follows: 0 = no involvement; 1 = 1% to 9%; 2 = 10% to 29%; 3 = 30% to 49%; 4 = 50% to 69%; 5 = 70% to 89%; and 6 = 90% to 100%. The following formula is used to calculate the PASI score:

PASI = 0.1 (Eh + lh + Sh) Ah + 0.2 (Eu + lu + Su) Au + 0.3 (Et +lt + St) At + 0.4 (El +ll +Sl) Al.[72]

where E = erythema, I = induration, S = scaling, A = area, h = head score, t = trunk score, u = upper extremities, and l = lower extremities score.

A number of limitations of the PASI have been identified:

- The PASI has been criticized as not correlating the clinical extent of the disease with quality of life and the psychological stress caused by psoriasis. The patient's measure of quality of life is often worse than the physician-rated clinical severity.[73]
- There are significant inter-rater reliability issues regarding the measurement of BSA.[74,75]
- It often fails to predict severity as seen from the patient's perspective.[74,75]
- Improvements in PASI score are not linearly related to severity or improvements in psoriasis.[74,75] The extent of psoriatic involvement is measured using a scale of 1 to 6, and the areas corresponding to each score are nonlinear.
- Some severe disease (clinically) may be scored low. For example, scores as low as 3 (on palms and soles) may represent psoriasis that affects a patient's ability to work and conduct other life activities.
- Most patients fall into a narrow band of scores, thereby decreasing the usefulness of the full range of scores (i.e., scores higher than 40 are rare).[74]
- There is little research on the reliability of the assessments for erythema, desquamation, and induration, together with overall PASI scores.[74]
- Criterion validity is restricted by the lack of a "gold standard" measure of psoriatic severity.[76]
- The PASI lacks sensitivity, as erythema, desquamation, and induration are scored with equal weight within each of the four body regions. Thus, a reduction in scaling with a concomitant increase in skin erythema could be recorded with the same PASI score.
- Improvement of the histological phenotype of psoriasis can be underestimated by the per cent improvement in PASI (e.g., reduction of T cells, loss of K16 expression, and reduction in epidermal thickness).[39]
- Little work has been done to determine the clinical relevance of derived PASI scores.[74]

APPENDIX 6: SUMMARY OF FINDINGS AT 52 WEEKS OF INCLUDED STUDIES

Aim

To summarize the efficacy and safety findings at 52 weeks in psoriatic arthritis (PsA) patients treated with apremilast 30 mg twice daily as provided in the manufacturer-submitted clinical studies (PALACE -1 -2, and -3).[17-19]

Findings

Study and Baseline Disease Characteristics

PALACE-1,[17] PALACE-2,[18] and PALACE-3[19] are randomized phase 3, double-blind, placebo-controlled studies, which enrolled patients with active PsA with three or more swollen and three or more tender joints, whose disease was inadequately controlled by DMARDs (small molecules and/or biologics). Eligible patients were randomized to receive apremilast 20 mg twice daily (b.i.d.), apremilast 30 mg b.i.d., or identical appearing placebo on 1:1:1 bases during a 24-week, placebo-controlled phase. All patients who did not have at least a 20% reduction in tender joint count (TJC) and swollen joint count (SJC) at week 16 entered early escape (EE), and were re-randomized 1:1 in a blinded fashion to either the apremilast 20 mg b.i.d. treatment group or the apremilast 30 mg b.i.d. treatment group. A second phase began at week 24, with all remaining patients in the placebo group re-randomized 1:1 in a blinded manner to either the apremilast 20 mg b.i.d. or apremilast 30 mg b.i.d. treatment group for an additional 28 weeks, bringing the total duration to 52 weeks.

The primary efficacy end point was the proportion of patients achieving a 20% reduction in American College of Rheumatology 20% (ACR20) response at week 16. The key secondary end point was the change from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) scores at week 16. Other secondary end points included ACR20/50/70 scores, and indices of disease activity such as Disease Activity Score 28 (DAS28), Psoriasis Area and Severity Index (PASI), Psoriatic Arthritis Response Criteria (PsARC), dactylitis severity, and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) scores; as well as patients' health-related quality of life as determined by the Short Form (36) Health Survey (SF-36) and EuroQol 5-Dimensions (EQ-5D) at all end points. Other efficacy outcomes included Functional Assessment of Chronic Illness Therapy – Fatigue Subscale (FACIT-F), and lost productivity score as determined by 25-Item Work Limitations Questionnaire (WLQ-25) scale. Reported safety outcomes included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events (AEs) leading to dose interruptions or discontinuation of the study drug. This summary focuses on the week 52 efficacy and safety data for apremilast 30 mg b.i.d., which is the only dose with current Health Canada approval for the treatment of PsA.

Patient Disposition

Of the patients randomized in the placebo-controlled phase of PALACE-1 (N = 504),[17] PALACE-2 (N = 484),[18] and PALACE-3 (N = 505),[19] 88.1%, 88.4% and 86.7%, respectively, completed week 24. Overall, the completion rates from baseline (week 0) to week 52 ranged from 70.4 to 77.4 in the apremilast 30 b.i.d. treatment group. Among patients initially randomized to placebo, the proportion who completed 52 weeks of study ranged from 70.8% to 76.7%. This included patients who escaped early at week 16 to apremilast 20 mg b.i.d. (placebo [PBO]/20 EE) or to apremilast 30 mg b.i.d. (PBO/30 EE), as well as those who crossed over at week 24 to apremilast 20 mg b.i.d. (PBO/20 XO) or to apremilast 30 mg b.i.d.

(PBO/30 XO). The most frequently reported reasons for discontinuation were withdrawal by patients (0.7% to 5.2%), lack of efficacy (2.9% and 5.2%), and AEs (1.5% and 4.3%).

Results

Efficacy Outcomes

In general, the improvements observed at week 24 were maintained or continued to improve through week 52 among patients in the apremilast 30 b.i.d. treatment group.

ACR Response

Response rates for all ACR measures (ACR 20/50/70) were numerically higher at week 52 than at week 24 in all the studies (Table 33). The proportion of patients in the apremilast 30 b.i.d. group who achieved ACR20, ACR50, and ACR70 responses at week 52 ranged from 52.6% to 63.0%, 18.6% to 30.3% and 6.8% to 13.8%, respectively. Response rates were lowest in the PALACE-2 [18] study for all the ACR outcomes (Table 33).

DAS-28 Response

Among patients in the apremilast 30 b.i.d. treatment group, the proportion who achieved DAS28 C-reactive protein (DAS28[CRP]) < 2.6 remission ranged from 17.8% to 29.9% at weeks 52. The percentage of patients who achieved DAS28 remission at week 52 was similar to week 24, although week 52 rates were slightly lower in PALACE-1,[17] and PALACE-2,[18] and slightly higher in PALACE-3[19] (Table 33).

PsARC Response

The proportion of patients in the apremilast 30 b.i.d. group who had PsARC response ranged from 73.6% to 79.0%. The PsARC response rates were consistently higher at week 52 than week 24 in all the studies (Table 33).

HAQ-DI

Mean improvements from baseline in physical disability was higher at week 52 (mean [standard deviation (SD)] –0.32 [0.55] to –0.35 [0.51]) than at week 24 (–0.20 [0.54] to –0.34 [0.53]) among patients in the apremilast 30 b.i.d. group. In addition, the improvements continued to increase from week 24 with a numerically higher percentage of patients reaching the minimal clinically important difference (MCID) of ≥ 0.3 for PsA in at week 52 (Table 33).

SF-36

Mean improvements in both the physical function domain and the physical component summary score of the SF-36 scale was maintained at week 52 among patients in the apremilast 30 mg b.i.d. group in all the studies (Table 33). The percentage of patients in the apremilast 30 b.i.d. treatment group with improvements that reached or exceeded the MCID of 2.5 points was similar at both weeks 24 and 52 in all the studies. No notable trends in the mental domain scores were observed.

PASI Scores

Patients in the apremilast 30 b.i.d. treatment group had similar mean improvements from baseline in severity of psoriatic lesions at weeks 24 and 52, with a trend favouring week 52 scores in all studies (Table 33). Furthermore, a numerically higher proportion of the patients had a 50% (PASI50) and 75% (PASI75) reduction in psoriatic lesion at week 52 (range: 54.7% to 60.3% and 36.8% to 39.3%, respectively) than week 24 (range: 48.6% to 53.4% and 20.5% to 31.3%, respectively).

Changes MASES

The mean (SD) reductions in pre-existing enthesopathy at baseline and measured by MASES score were numerically greater for the apremilast 30 b.i.d. treatment group at week 52, ranging from –1.9 (2.93) to –2.1 (2.82) compared with week 24 (–1.5 [3.26] to –1.9 [2.93]). In general, a higher percentage of patients had ≥ 20% improvement or complete resolution of their baseline enthesopathy at week 52 than at week 24 (Table 33).

Dactylitis Severity Score

Patients in the apremilast 30 b.i.d. treatment group had numerically higher reductions in the baseline severity of dactylitis at week 52 (–1.8 (2.06] to –3.6 [4.30] points) compared with week 24 (–1.5 [1.92] to –2.9 [4.08] points). Furthermore, a higher proportion of the patients had dactylitis severity reduced to the minimum (score of 0) or had ≥ 1 point improvements at week 52 (Table 33).

FACIT-F

The mean (SD) change from baseline in FACIT-F score was similar at weeks 24 and 52 for all studies (Table 33). The proportion of patients who achieved a ≥ 3.56 improvement in score was also generally maintained at week 52 compared with week 24 (45.25 to 57.5% versus 42.1% to 53.7%, respectively) in all studies.

TABLE 33: EFFICACY OUTCOMES FOR APREMILAST 30 MG TWICE DAILY IN THE EXTENDED STUDIES

Outcomes	PALACE-1[17] (N = 168)		PALACE-2[18] N = 162		PALACE-3[19] N = 167	
	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52
DAS28(CRP)	N = 144	N = 129	N = 139	N = 117	N = 145	N = 127
Change from baseline, mean (SD)	–1.25 (1.16)	–1.31 (1.11)	–0.98 (0.96)	–1.30 (1.03)	–0.99 (1.07)	–1.41 (1.20)
Remission < 2.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR Response						
ACR20, n/N (%)	73/145 (50.3)	71/130 (54.6)	60/138 (43.5)	61/116 (52.6)	63/145 (43.4)	80/127 (63.0)
ACR50, n/N (%)	35/146 (24.0)	32/130 (24.6)	25/140 (17.9)	22/118 (18.6)	33/146 (22.6)	38/126 (30.2)
ACR70, n/N (%)	19/146 (13.0)	18/130 (13.8)	5/141 (3.5)	8/118 (6.8)	9/145 (6.2)	13/125 (10.4)
Psoriatic Arthritis Response Criteria Response, n (%)	98/142 (69.0)	95/129 (73.6)	85/136 (62.5)	85/114 (74.6)	94/144 (65.3)	98/124 (79.0)
HAQ-DI						
• Mean (SD) change from BL	–0.34 (0.53)	–0.32 (0.55)	–0.20 (0.54)	–0.33 (0.51)	–0.27 (0.48)	–0.35 (0.51)
• Improvement ≥ 0.13, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Outcomes	PALACE-1[17] (N = 168)		PALACE-2[18] N = 162		PALACE-3[19] N = 167	
	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52
Short Form (36) Health Survey						
• PCS change from BL, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• PCS ≥ 2.5 points, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriasis Area and Severity Index Score						
• Change from BL, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• PASI-50, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• PASI-75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maastricht Ankylosing Spondylitis Enthesitis Score						
• Change from BL, mean (SD)	–1.7 (2.98)	–1.9 (2.93)	–1.9 (2.68)	–2.1 (2.82)	–1.5 (3.26)	–1.9 (2.99)
• Improvement ≥ 20%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dactylitis Severity Score						
• Change from BL, mean (SD)	–1.7 (2.16)	–1.8 (3.23)	–1.5 (1.92)	–1.8 (2.06)	–2.9 (4.08)	–3.6 (4.30)
• Improvement ≥ 1 point, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACIT-F						
• Change from BL, mean (SD)	4.65 (9.61)	3.67 (9.08)	2.94 (10.00)	4.38 (9.85)	4.76 (8.22)	6.20 (8.68)
• Improvement ≥ 3.56, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ACR = American College of Rheumatology; APR30 = patients originally randomized to apremilast 30 mg twice daily; BL = baseline; DAS28(CRP) = 28-joint Disease Activity Score using C-reactive protein as the acute phase reactant; EE = early escape (non-responder placebo patients, re-randomized to APR at week 16; APR patients continue treatment as randomized); FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; NEE = no early escape; PBO = placebo; PCS = physical component summary; SD = standard deviation; XO-30 = crossover (re-randomized to APR 30 mg at week 24).

Safety and Tolerability

Apremilast, at the 30 mg b.i.d. dose, was generally well tolerated, as demonstrated by the low incidence of serious TEAEs and TEAEs leading to discontinuation of study drug during the 52 weeks' exposure. In

most patients, TEAEs were generally mild or moderate and did not necessitate dose interruption or discontinuation.

Mortality

There was no death reported in the apremilast 30 b.i.d. treatment group in the second phase (24 to 25 weeks) of any of the studies.

Serious Treatment-Emergent Adverse Events

The incidence of TEAEs ranged from 4.1% to 7.8% in the apremilast 30 b.i.d. treatment group across all the studies. There was no serious TEAE with more than one (0.4%) incidence in the apremilast 30 b.i.d. treatment group at week 52 in any of the studies.

Any Treatment-Emergent Adverse Event

More than two-third of patients in the apremilast 30 b.i.d. treatment group across all the three studies reported incidence of TEAEs at week 52 (Table 34). The most common TEAEs were gastrointestinal (GI)-related, with diarrhea and nausea the most frequently reported. Other common TEAEs were headache (9.8% to 10.7%), upper respiratory tract infections (5.7% to 8.3%), and nasopharyngitis (4.1% to 6.5%)

Withdrawal Due to TEAEs

The incidence of TEAEs leading to discontinuation of study drug in the apremilast 30 b.i.d. treatment group was low (< 10%) across all the studies (Table 34). GI events were the leading TEAEs that resulted in discontinuation, with diarrhea and nausea the most frequently reported (1.7% to 2.4% and 1.6% to 2.6%, respectively). At week 52, the reported incidence of TEAEs leading to drug interruptions in the apremilast 30 b.i.d. treatment group ranged from 10.7% to 20.9% (Table 34)

Notable Harms

Serious Infections

The incidence of serious infections in the apremilast 30 b.i.d. treatment group was rare; with 1.2%, 0%, and < 1% occurrence in PALACE-1,[17] PALACE-2,[18] and PALACE-3,[19] respectively (Table 34). There was no report of reactivation or de novo tuberculosis during the apremilast exposure period in any of the studies.

Weight Loss

Across the three studies, the mean percentage weight loss in the apremilast 30 b.i.d. treatment group ranged from [redacted] at the end of the 52-week exposure. The majority of patients maintained their weight within ± 5% of baseline. However, weight loss > 5% to ≤ 10% was observed in 11.8 to 14.3% of patients in the apremilast 30 b.i.d. treatment group, with no patient experiencing weight loss > 20% in any of the studies (Table 34).

Gastrointestinal Disorders

GI disorders were reported at week 52 in more than a third of patients in the apremilast 30 b.i.d. treatment groups across all three studies (Table 34). Although GI events included diarrhea, nausea, vomiting, abdominal pain and discomfort, dyspepsia, and gastroesophageal reflux disease, the most frequently reported GI disorders at week 52 were diarrhea (13.6% to 19.2 5) and nausea (13.7% to 14.9%).

TABLE 34: TREATMENT-EMERGENT ADVERSE EVENTS THROUGH 52 WEEKS[A]

	PALACE-1[17] N = 245	PALACE-2[18] N = 234	PALACE-3[19] N = 242
Serious TEAEs, n (%)	19 (7.8)	12 (5.1)	10 (4.1)
Any TEAE, n (%)	174 (71.0)	163 (69.7)	165 (68.2)
Common (≥ 5% Incidence) TEAEs			
• Diarrhea, n (%)	47 (19.2)	32 (13.7)	33 (13.6)
• Nausea, n (%)	35 (14.3)	32 (13.7)	36 (14.9)
• Headache, n (%)	24 (9.8)	23 (9.8)	26 (10.7)
• Nasopharyngitis, n (%)	16 (6.5)	10 (4.3)	10 (4.1)
• Upper respiratory tract infection, n (%)	14 (5.7)	22 (9.4)	20 (8.3)
Drug interruption due to TEAE, n (%)	[redacted]	[redacted]	[redacted]
Withdrawal due to TEAEs, n (%)	23 (9.4)	[redacted]	14 (5.8)
Common (≥ 1% incidence) TEAEs Leading to Withdrawal, n (%)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Notable Harms			
Serious infections, n (%)	3 (1.2)	0 (0.0)	1 (0.4)
• Pneumonia	[redacted]	[redacted]	[redacted]
• Anal abscess	[redacted]	[redacted]	[redacted]
• [redacted]	[redacted]	[redacted]	[redacted]
• [redacted]	[redacted]	[redacted]	[redacted]
Weight loss			
Mean (SD) loss from baseline, kg	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation; TEAE = treatment-emergent adverse event.

[a] Includes all apremilast 30 mg b.i.d. exposure data; patients could have started receiving apremilast at baseline, week 16, or week 24.

[b] Gastrointestinal events included diarrhea, nausea, vomiting, abdominal pain and discomfort, dyspepsia, and gastroesophageal reflux disease.

Limitation

Although patients were re-randomized in a blinded manner in the second phase (24 to 52 weeks), the placebo arm was dropped for this section in all the studies. Therefore, a comparison of outcomes at week 52 was not possible between patients in the apremilast 30 mg treatment group and patients in the placebo group who were not classified as nonresponders at week 24. However, because treatment with apremilast demonstrated superior efficacy to placebo in a dose-dependent fashion in the first phase, with many patients in the placebo group escaping early to receive apremilast treatment at 16 weeks, it is reasonable to expect that the efficacy trend to continue in favour apremilast 30 mg b.i.d. in the second phase.

Furthermore, outcomes in the 24- to 52-week study were considered secondary and exploratory end points and were reported as descriptive summary statistics or proportion without rigorous analysis. Therefore, findings from this phase of the study are limited in the extent to which they can be used to draw a firm conclusion. In addition, although the safety and tolerability profile of apremilast 30 mg b.i.d. in PsA patients was acceptable after 52 weeks' exposure, it is worth noting that the duration is not enough to assess long-term safety issues. However, 52 weeks seem to be a reasonable duration for a randomized controlled trial, and is consistent with another study in PsA patients.[77]

Summary

In general, the improvements observed at week 24 were maintained or continued to improve through week 52 among patients in the apremilast 30 b.i.d. treatment group. Improvements over week 24 outcomes generally occurred in ACR and PsARC responses, as well as PASI and Dactylitis Severity Scores across all studies. DAS28 remission (< 2.6 score), HAQ-DI, SF-36, MASES, and FACIT-F scores generally showed a trend toward continuous improvement at week 52, although there were instances where the week 24 scores were maintained or were slightly higher. Apremilast 30 mg b.i.d. was well tolerated with generally mild or moderate TEAEs in most patients, which did not necessitate dose interruption or discontinuation. GI disorders were the most common TEAEs, with diarrhea and nausea the most frequently reported and the most common cause for drug interruptions or discontinuation.

APPENDIX 7: SUMMARY OF INDIRECT COMPARISONS

1. Introduction

1.1 Background

The included clinical trials in this review did not provide direct evidence about the comparative efficacy and safety of apremilast relative to disease-modifying anti-rheumatic drugs (DMARDs) or biological response modifiers (biologics). The objective of this section is to summarize and critically appraise published and unpublished indirect evidence available for assessment of comparative efficacy and harms of apremilast versus DMARDs and biologics. This summary will inform the pharmacoeconomic evaluation.

1.2 Methods

One indirect treatment comparison (IDC) submitted by the manufacturer was reviewed in this section. An information specialist conducted an independent literature search for published IDCs that compared apremilast with other available agents (adalimumab, certolizumab, etanercept, golimumab, infliximab, and ustekinumab) when used for the treatment of psoriatic arthritis (PsA), but were unable to identify any additional published indirect evidence.

2. Review and Appraisal of the Manufacturer-Submitted Indirect Treatment Comparison

2.1 Review of the Indirect Treatment Comparison

Objectives and Rationale for the Indirect Treatment Comparison

The objective of the IDC was to compare the efficacy of apremilast relative to biologics when used for the treatment of patients with active PsA. The manufacturer used this information to support the submitted pharmacoeconomic evaluation of apremilast.

Study Eligibility and Selection Process

A systematic literature search was conducted by the authors using PubMed/MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and clinicaltrials.gov databases. Studies published in full texts were eligible for inclusion in the network meta-analysis (NMA) if they included PsA patients aged 18 years or older. Active and placebo-controlled randomized controlled trials were eligible for inclusion if at least one PsA treatment was evaluated as monotherapy; treatments of interest were apremilast and six biologics — adalimumab, certolizumab, etanercept, golimumab, infliximab, and ustekinumab. Outcomes of interest were the Psoriasis Area and Severity Index (PASI), American College of Rheumatology (ACR), Health Assessment Questionnaire – Disability Index (HAQ-DI), Psoriatic Arthritis Response Criteria (PsARC), and HAQ-DI upon PsARC. Study selection and data extraction were conducted by at least two reviewers. The authors used intention-to-treat (ITT) datasets from the included studies.

Study/Population Characteristics

The authors included 14 placebo-controlled studies that included adult PsA patients. Patients' characteristics are summarized in Table 35. Female patients were predominant in studies for apremilast (46.4%) and certolizumab (44.7%), while male patients were in the majority in studies for adalimumab (54.8%), etanercept (54.1%), golimumab (60.3%), infliximab (59.4%), and ustekinumab (50.1%). The average age of patients ranged from 45.2 to 57.4 years, and PsA duration ranged from 3.6 to 9.8 years. The percentage of patients who have normal or negative rheumatoid factor was not systematically reported, and it was 92.4% in apremilast studies, 89.5% in adalimumab studies, 94% in one etanercept study, and 100% in infliximab studies. Mean tender joints at baseline ranged from 16.0 to 25.8, and

mean swollen joints ranged from 7.0 to 18.4. Ustekinumab studies reported the highest percentage of previous biologic use (42.7%); this was 22.3% of patients in apremilast studies and 19.5% in certolizumab study, and all other biologic studies either had no prior biologic use or this information was not reported. Concomitant use of small molecular DMARDs ranged from 20.6% and 71.2%, while that of methotrexate ranged from 20.6% to 63.8%.

Interventions and Comparators

Three studies compared twice-daily apremilast 20 mg and 30 mg with placebo; other studies compared placebo with adalimumab 40 mg every two weeks, certolizumab 200 mg and 400 mg every two weeks, etanercept 25 mg twice weekly, golimumab 50 mg and 100 mg every four weeks, infliximab 5 mg/kg weekly, and ustekinumab 45 mg and 90 mg at weeks 0 and 4 and every 12 weeks thereafter. A summary of the included studies is provided in Table 36. Outcome data measured at weeks 12 to 16 were used for the analysis if outcomes were reported at multiple time points; hence, only data used prior to study crossover or the early escape period were considered for the IDC analysis.

Outcomes

The reported outcomes included ACR, PASI, HAQ-DI, PsARC, and HAQ-DI upon PsARC, but not all studies included the totality of these measures. Table 36 provides a summary of the evaluated outcomes and the time points of outcome assessment. If outcomes were reported at multiple time points, data measured at weeks 10 to 16 were mainly used. The IDC did not include any safety or harm outcomes, nor did it include health-related quality of life data other than HAQ-DI.

TABLE 35: PATIENTS' CHARACTERISTICS IN THE INCLUDED STUDIES

Direct Comparisons	Studies	N	Male %	Age[a] (Years)	PsA Duration[a] (Years)	Normal or Negative Rh Factor (%)	Mean Baseline Tender Joints Count[a]	Mean Baseline Swollen Joints Count[a]	Prior Biologic Use (%)	Concomitant Use of		
										Biologics (%)	Small Molecular DMARD (%)	MTX (%)
Apremilast vs. placebo	PALACE-1	504	49.4%	48.7 to 51.1	7.2 to 8.1	92.7%	22.2 to 23.3	12.5 to 12.8	23.7%	0%	64.9%	54.2%
	PALACE-2	484	43.2%	50.5 to 51.2	6.8 to 7.8	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	PALACE-3	505	46.7%	46.2 to 47.3	6.8 to 7.7	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Adalimumab vs. placebo	ADEPT	313	55.6%	48.6 to 49.2	9.2 to 9.8	89.8%	23.9 to 25.8	14.3	0%		50.5%	50.5%
	Genovese et al. 2007	100	54.0%	47.7 to 56.9	7.2 to 7.5	89.2%	25.3 to 29.3	18.2 to 18.4	0%		66.0%	47.0%
Certolizumab vs. placebo	RAPID-PsA	409	44.7%	47.1 to 48.2	7.9 to 9.6	NR	19.6 to 21.5	10.4 to 11.0	19.5%		70.2%	63.8%
Etanercept vs. placebo	Mease et al. 2000	60	57%	46.5 to 46.0	9.0 to 9.5	NR	19.8 to 20.5	14.2 to 15.4	NR		46.7%	46.7%
	Mease et al. 2004	205	51.3%	45.2 to 57.4	9.0 to 9.2	94%	NR	NR	NR		41.5%	41.5%
Golimumab vs. placebo	GO-REVEAL	405	60.3%	45.7 to 48.2	7.2 to 7.6	NR	21.9 to 24.0	12.0 to 14.1	0%		NR	49.9%
Infliximab vs. placebo	IMPACT	104	57.7%	45.2 to 45.7	11.0 to 11.7	100%	20.4 to 23.7	14.6 to 14.7	NR		71.2%	55.8%
	IMPACT 2	200	61%	46.5 to 47.1	7.5 to 8.4	100%	25.1 to 24.6	13.9 to 14.4	0%		46%	46%
Ustekinumab vs. placebo	PSUMMT 1	615	53.7%	47.0 to 48.0	3.6 to 4.9	NR	18.0 to 22.0	10.0 to 12.0	NR		NR	48.1%
	PSUMMT 2	312	47.8%	47.6 to 48.0	7.2 to 8.5	NR	23.4 to 27.2	13.5 to 15.0	57.7%		NR	NR
	Gottlieb et al.	146	48.8%	47.5 to 50.0	4.9 to 6.2	NR	16.0 to 19.5	7.0 to 10.0	27.6%		20.6%	20.6%

DMARD = disease-modifying anti-rheumatic drug; MTX = methotrexate; NR = not reported; PsA = psoriatic arthritis; Q2W = every 2 weeks; Q4W = every 4 weeks; q.d. = every day; vs. = versus.

[a] Range of study arms means.

Source: Manufacturer's submission.[22]

TABLE 36: STUDY CHARACTERISTICS

Direct Comparisons	Studies	N	Intervention and Comparators	Outcomes	Outcome Assessment
Apremilast vs. placebo	PALACE-1	504	• Apremilast 20 mg b.i.d. (N = 168) • Apremilast 30 mg b.i.d. (N = 168) • Placebo (N = 168)	• ACR (20, 50, 70) • PASI (50, 75, 90) • HAQ-DI, PsARC, & HAQ-DI/PsARC	16 weeks
	PALACE-2	484	• Apremilast 20 mg b.i.d. (N = 162) • Apremilast 30 mg b.i.d. (N = 163) • Placebo (N = 159)		
	PALACE-3	505	• Apremilast 20 mg b.i.d. (N = 169) • Apremilast 30 mg b.i.d. (N = 167) • Placebo (N = 169)		
Adalimumab vs. placebo	ADEPT	313	• Adalimumab 40 mg Q2W (N = 151) • Placebo (N = 162)	• ACR (20, 50, 70) • PASI (50, 75, 90) • HAQ-DI, PsARC, & HAQ-DI/PsARC	12[b, c] & 24 weeks
	Genovese et al. 2007	100	• Adalimumab 40 mg Q2W (N = 51) • Placebo (N = 49)	• ACR (20, 50, 70) • HAQ-DI, PsARC, & HAQ-DI/PsARC	12 weeks
Certolizumab vs. placebo	RAPID-PsA	409	• Certolizumab 200 mg Q2W (N = 138) • Certolizumab 400 mg Q2W (N = 135) • Placebo (N = 136)	• ACR (20, 50, 70) • PASI (50, 75, 90) • HAQ-DI, PsARC	12 weeks
Etanercept vs. placebo	Mease et al. 2000	60	• Etanercept 25 mg twice weekly (N = 30) • Placebo (N = 30)	• ACR (20, 50, 70) • PASI (50, 75) • HAQ-DI, PsARC	4, 8, & 12[b, c] weeks
	Mease et al. 2004	205	• Etanercept 25 mg twice weekly (N = 101) • Placebo (N = 104)	• ACR (20, 50, 70) • PASI (50, 75, 90) • HAQ-DI, PsARC, & HAQ-DI/PsARC	4, 12[b], & 24[c] weeks
Golimumab vs. placebo	GO-REVEAL	405	• Golimumab 50 mg Q4W (N = 146) • Golimumab 100 mg Q4W (N = 146) • Placebo (N = 113)	• ACR (20) • PASI (50, 75, 90) • PsARC	14 weeks
Infliximab vs. placebo	IMPACT	104	• Infliximab 5 mg/kg wk 0, 2, 6, 14 (N = 52) • Placebo (N = 52)	• ACR (20, 50, 70) • PASI (50, 75, 90) • HAQ-DI, PsARC, & HAQ-DI/PsARC	16 weeks
	IMPACT 2	200	• Infliximab 5 mg/kg wk 0, 2, 6, 14 (N = 100) • Placebo (N = 100)		14 weeks
Ustekinumab vs placebo	PSUMMT 1	615	• Ustekinumab 45 mg[a] (N = 205) • Ustekinumab 90 mg[a] (N = 204) • Placebo (N = 206)	• ACR (20, 50, 70) • PASI (75, 90) • HAQ-DI	12 weeks
	PSUMMT 2	312	• Ustekinumab 45 mg[a] (N = 103) • Ustekinumab 90 mg[a] (N = 105) • Placebo (N = 104)	• PASI (75, 90) • PsARC	12 weeks
	Gottlieb et al. 2009	146	• Ustekinumab 45 mg[a] (N = 76) • Placebo (N =70)		12 weeks

ACR = American College of Rheumatology; b.i.d. = twice daily; HAQ = Health Assessment Questionnaire; NR = not reported; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; Q2W = every 2 weeks; Q4W = every 4 weeks; vs. = versus; wk = week.

[a] At weeks 0 and 4, and every 12 weeks thereafter.

[b] Time point of ACR, PsARC, HAQ-DI, and HAQ-DI upon PsARC assessment.

[c] Time point of PASI assessment.

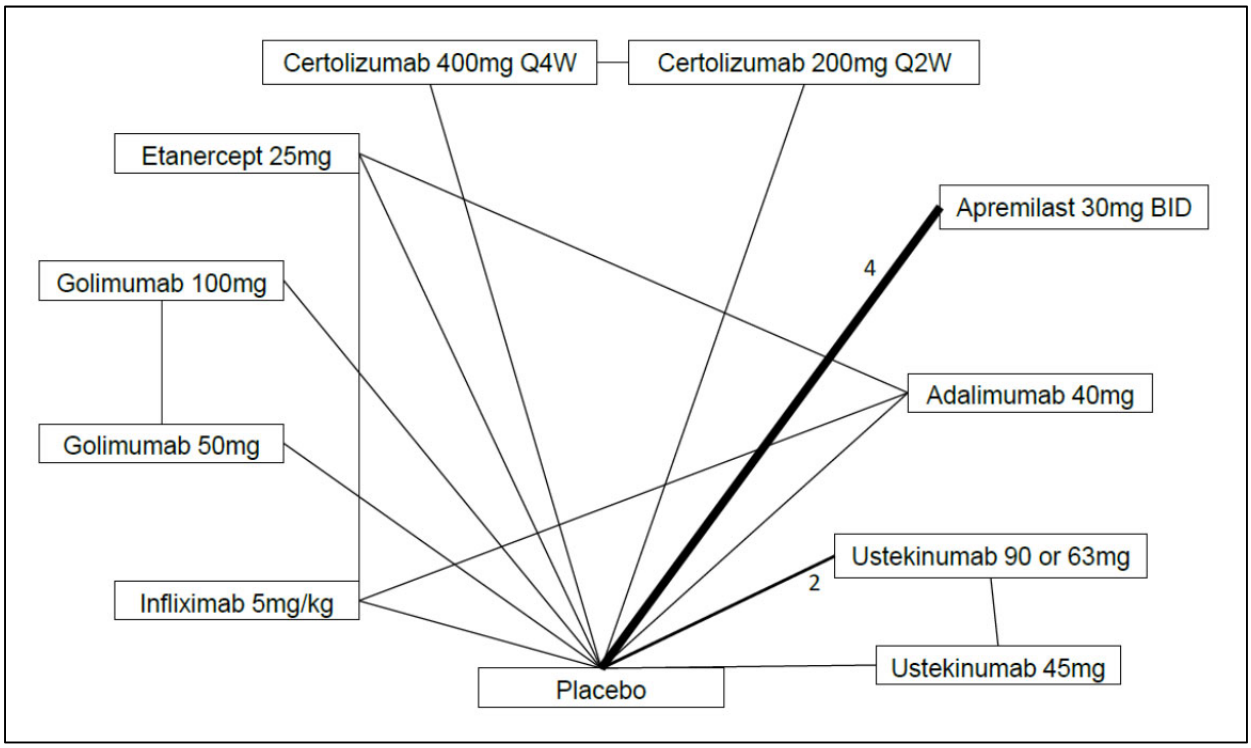
Source: Manufacturer's submission.[22]

Quality Assessment of Included Studies

The quality of individual studies was evaluated using an 18-item questionnaire. The questionnaire targeted the reporting quality of studies rather than study design and risk of bias. Based on the questionnaire answers, the reviewer attributed a global ordinal rating for each study, ranging from excellent, good, satisfactory, to poor. The authors reported that all studies had good global rating and that study quality was not associated with size of treatment effect in the included studies.

Evidence Network

FIGURE 3: EVIDENCE NETWORK



b.i.d. = twice daily; Q2W = every 2 weeks; Q4W = every 4 weeks.
Source: Manufacturer's submission.[22]

2.2 Indirect Comparison Methods

The submitted IDC did not include any description of the analysis model or the analysis methodology. The deviance information criterion (DIC) was reported in the provided material, which might indicate the use of a Bayesian analysis approach. DIC value is an indicator for model fit; smaller values indicate better fit. In the context of Bayesian-IDC, DIC are generally used to choose between fixed and random effect models. DIC values for fixed and random effect models were reported for PsARC, HAQ-DI, and HAQ-DI upon PsARC. However, ACR20/ACR50/ACR70 and PASI50/PASI75/PASI90 were all analyzed simultaneously within one single model; thus, only one DIC value was generated. This method prevented the appraisal of DIC for each separate outcome. Residual deviance values were also reported for the aforementioned outcomes.

The manufacturer used the Q statistic to evaluate the heterogeneity among apremilast studies for ACR, PASI, PsARC, and HAQ-DI outcomes, and the authors reported that there was no statistically significant heterogeneity in these studies. Clinical and statistical heterogeneity of other studies were not evaluated. Furthermore, the manufacturer did not evaluate the consistency of IDC findings with direct evidence; direct evidence was available to compare certolizumab 400 mg versus certolizumab 200 mg, etanercept 25 mg versus adalimumab and infliximab, adalimumab versus infliximab, golimumab 100 mg versus golimumab 50 mg, and ustekinumab 45 mg versus ustekinumab 90.

2.3 Results

[redacted]

ACR

[redacted]

PsARC

[redacted]

PASI

[redacted]

HAQ-DI

[redacted]

TABLE 37: INDIRECT DRUG COMPARISON RESULTS: ALL-POPULATION ANALYSIS

	ACR 20	PsARC	PASI-50	HAQ-DI	HAQ-DI/PsARC Response	HAQ-DI/PsARC Non-response
	Median odd ratio versus apremilast30 mg b.i.d. (95% credible interval)[a]			Median difference versus apremilast (95% credible interval)[a]		
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

ACR = American College of Rheumatology; b.i.d. = twice daily; DIC = deviance information criterion; HAQ = Health Assessment Questionnaire; NR = not reported; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria.

[a] Random effect results. Differences in DIC values between random and fixed effect model were less than 3 points; residual deviance values were smaller for the random effect models.[78]

Source: Manufacturer's submission.[22]

TABLE 38: INDIRECT DRUG COMPARISON RESULTS: BIOLOGIC-NAIVE POPULATION ANALYSIS

	ACR 20	PsARC	PASI-50	HAQ-DI	HAQ-DI/PsARC response	HAQ-DI/PsARC non-response
	Median odds ratio versus apremilast (95% credible interval)[a]			Median difference versus apremilast (95% credible interval)[a]		
[redacted]						

ACR = American College of Rheumatology; b.i.d. = twice daily; DIC = deviance information criterion; HAQ = Health Assessment Questionnaire; NR = not reported; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria.

[a] Random effect results. Differences in DIC values between random- and fixed- effect model were less 3 points; residual deviance values were smaller for the random effect models.[78]

Source: Manufacturer's submission.[22]

2.4 Critical Appraisal and Discussion

The included studies had similar patient population in terms of baseline characteristics. According to a clinical expert consulted by the CADTH Common Drug Review, the patient characteristics for the included studies reflect the profile of Canadian PsA patients. Apremilast and biologic dosing strategies are in line with the Health Canada–approved labels for these products.

ACR20/ACR50/ACR70 and PASI50/PASI75/PASI90 were all analyzed simultaneously within one single model; thus, only one DIC value was generated. This method prevented the appraisal of DIC for each separate outcome.

Consistency was not evaluated in the submitted IDC; consistency testing is useful to validate the indirect comparison results by comparing them with the available direct evidence. Direct comparative evidence was available for certolizumab 400 mg versus certolizumab 200 mg, etanercept 25 mg versus adalimumab and infliximab, adalimumab versus infliximab, golimumab 100 mg versus golimumab 50 mg, and for ustekinumab 45 mg versus ustekinumab 90. No direct evidence was available for apremilast. Furthermore, the manufacturer did not conduct a formal evaluation of clinical and statistical heterogeneity of all included studies. Only apremilast studies were evaluated for heterogeneity between each other, but without cross-evaluating them relative to the other studies. However, the included studies had similar patient populations in terms of baseline characteristics and that the baseline DMARD use in the placebo arms was relatively consistent across trials; except the two trials with notably high (79%) and low (21%) baseline DMARD use were comparatively small trials and expected to exert a lesser influence on the estimates of comparative efficacy. Therefore, the trials were likely homogeneous enough to be included in the IDC.

PsA is a lifelong disease, and it is therefore not clear how meaningful the comparisons are, given the short duration of the studies.

The Q statistic did not find heterogeneity, but that could be because the number of studies for the end points was small; hence, there was no power to find heterogeneity. Conversely, it would have been nice to also observe the I^2 statistic, which is less sensitive to the number of studies included, like the Q statistic.

It was not reported how PsARC was defined across the studies, and hence whether different definitions used across the studies would lead to different results, which would make the results of the IDC on PsARC unreliable. The manufacturer indicated that it was unable to identify the PsARC definition from the published articles of biologics trials, but it was noted that studies frequently referenced trial by Clegg et al.,[31] which is the original study in which PsARC was used.

There is no evidence of similarity or equivalence for any comparison, as no formal test for equivalence or non-inferiority was completed by the manufacturer.

The CDR reviewers conducted an independent literature search for published IDCs that compared apremilast with other available agents when used for the treatment of PsA, but were unable to identify any published alternatives to IDC provided by the manufacturer.

3. Conclusion

The results of the IDC provided by the manufacturer of apremilast that compared apremilast with biologics showed that [redacted]. However, these outcomes were not consistently statistically significant. There is no evidence of [redacted]. Harms were not analyzed in the IDC, and the comparative safety between apremilast and biologics is unknown.

REFERENCES

1. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis [Internet]. 2005 Mar [cited 2015 Oct 28];64 Suppl 2:ii14-ii17. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1766874/pdf/v064p0ii14.pdf
2. Ritchlin CT, Kavanaugh A, Gladman DD, Mease PJ, Helliwell P, Boehncke WH, et al. Treatment recommendations for psoriatic arthritis. Ann Rheum Dis [Internet]. 2009 Sep [cited 2015 Oct 28];68(9):1387-94. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719080/pdf/ARD-68-09-1387.pdf
3. Dandorfer SW, Rech J, Manger B, Schett G, Englbrecht M. Differences in the patient's and the physician's perspective of disease in psoriatic arthritis. Semin Arthritis Rheum. 2012 Aug;42(1):32-41.
4. Otezla® (apremilast): 10 mg, 20 mg, and 30 mg tablets [product monograph]. Mississauga (ON): Celgene Inc.; 2015 May 29.
5. Rosen CF, Mussani F, Chandran V, Eder L, Thavaneswaran A, Gladman DD. Patients with psoriatic arthritis have worse quality of life than those with psoriasis alone. Rheumatology (Oxford) [Internet]. 2012 Mar [cited 2015 Oct 28];51(3):571-6. Available from: http://rheumatology.oxfordjournals.org/content/51/3/571.full.pdf+html
6. Husted JA, Tom BD, Farewell VT, Schentag CT, Gladman DD. A longitudinal study of the effect of disease activity and clinical damage on physical function over the course of psoriatic arthritis: does the effect change over time? Arthritis Rheum [Internet]. 2007 Mar [cited 2015 Oct 28];56(3):840-9. Available from: http://onlinelibrary.wiley.com/doi/10.1002/art.22443/pdf
7. Diagnosis and management of psoriasis and psoriatic arthritis in adults [Internet]. Edinburgh: Scottish Intercollegiate Guidelines Network; 2010 Oct. [cited 2015 Oct 28]. Available from: http://www.sign.ac.uk/pdf/sign121.pdf
8. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol. 2009 Sep;61(3):451-85.
9. Rohekar S, Chan J, Tse SM, Haroon N, Chandran V, Bessette L, et al. 2014 update of the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada treatment recommendations for the management of spondyloarthritis. Part II: specific management recommendations. J Rheumatol. 2015 Apr;42(4):665-81.
10. Cimzia® (certolizumab pegol): solution for injection in a single-use pre-filled glass syringe, 200mg/mL [product monograph]. Oakville (ON): UCB Canada, Inc.; 2014 Jan 15.
11. Simponi (golimumab): solution for injection 50 mg/0.5mL, 100mg/1.0mL [product monograph] [Internet]. Toronto (ON): Janssen Inc.; 2014 Nov 25. [cited 2015 Oct 28]. Available from: http://www.janssen.ca/product/187
12. Enbrel (etanercept): solution for injection in a prefilled syringe 50 mg/mL and lyophilized powder for reconstitution in a vial 25 mg/vial [product monograph] [Internet]. Thousand Oaks (CA): Immunex Corporation; 2013 Sep 13. [cited 2015 Oct 28]. Available from: https://www.amgen.ca/Enbrel_PM.pdf

13. Humira (adalimumab): 40 mg in 0.8 mL sterile solution (50 mg/mL) subcutaneous injection [product monograph] [Internet]. St-Laurent (QC): AbbVie Corporation; 2014 Jan 17. [cited 2015 Oct 28]. Available from: http://www.abbvie.ca/content/dam/abbviecorp/ca/english/docs/HUMIRA_PM_EN.pdf

14. Inflectra (infliximab): powder for solution, sterile, lyophilized, 100 mg/vial [product monograph]. Saint-Laurent (QC): Hospira Healthcare Corporation; 2014 Jun 4.

15. Pr Stelara® (ustekinumab): 45 mg/0.5 mL, 90 mg/1.0 mL [product monograph]. Toronto: Janssen Inc.; 2014 Sep 16.

16. 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 [Internet]. 2014 Jun [cited 2015 Jul 24];73(6):1020-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4033106

17. Clinical study report: CC-10004-PSA-002. A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (cc-10004) in subjects with active psoriatic arthritis [**CONFIDENTIAL** internal manufacturer's report]. Summit (NJ): Celgene Corporation; 2013 Sep 26.

18. Clinical study report: CC-10004-PSA-003. A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (cc-10004) in subjects with active psoriatic arthritis [**CONFIDENTIAL** internal manufacturer's report]. Summit (NY): Celgene Corporation; 2015 Sep 30.

19. Clinical study report: CC-10004-PSA-004. A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (cc-10004) in subjects with active psoriatic arthritis and a qualifying psoriasis lesion [**CONFIDENTIAL** internal manufacturer's report]. Summit (NJ): Celgene Corporation; 2013 Sep 26.

20. Schafer PH, Chen P, Fang L, Wang A, Chopra R. The pharmacodynamic impact of apremilast, an oral phosphodiesterase 4 inhibitor, on circulating levels of inflammatory biomarkers in patients with psoriatic arthritis: substudy results from a phase III, randomized, placebo-controlled trial (PALACE 1). J Immunol Res [Internet]. 2015 [cited 2015 Jul 24];2015:906349. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4417944

21. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, 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 Mar;42(3):479-88.

22. CDR submission: Otezla® (apremilast) for treatment of active psoriatic arthritis. Company: Celgene Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Celgene Inc.; 2015 Jun 18.

23. Health Canada reviewer's report: Otezla (apremilast) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2015.

24. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) [Internet]. In: Otezla (apremilast) for psoriatic arthritis. Company: Celgene Corp. Application no.: 205437. Approval date: 03/21/2015. Silver Spring (MD): FDA; 2015 [cited 2015 Jul 2]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205437Orig1s000TOC.cfm.

25. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s) [Internet]. In: Otezla (apremilast). Company: Celgene Corp. Application no.: 205437. Approval date: 03/21/2015. Silver Spring (MD): FDA; 2015 [cited 2015 Jul 2]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205437Orig1s000TOC.cfm.

26. Committee for Medicinal Products for Human Use. Assessment report: Otezla [Internet]. London: European Medicines Agency; 2014 Nov 20. Report No.: EMA/CHMP/476353/2014. [cited 2015 Jul 22]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003746/WC500182629.pdf

27. van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum. 1998 Oct;41(10):1845-50.

28. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980 Feb;23(2):137-45.

29. Mease PJ, Ganguly R, Wanke L, Yu E, Singh A. How much improvement in functional status is considered important by patients with active psoriatic arthritis: applying the outcome measures in rheumatoid arthritis clinical trials (OMERACT) group guidelines. Ann Rheum Dis. 2004 Jun 9;63(Sup 1):391-2. Annual European Congress of Rheumatology (EULAR).

30. Mease PJ, Woolley JM, Bitman B, Wang BC, Globe DR, Singh A. Minimally important difference of Health Assessment Questionnaire in psoriatic arthritis: relating thresholds of improvement in functional ability to patient-rated importance and satisfaction. J Rheumatol. 2011 Nov;38(11):2461-5.

31. Clegg DO, Reda DJ, Mejias E, Cannon GW, Weisman MH, Taylor T, et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs cooperative study. Arthritis Rheum. 1996 Dec;39(12):2013-20.

32. Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, et al. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomized, controlled trials of two TNF inhibitors. Ann Rheum Dis [Internet]. 2006 Apr 27 [cited 2015 Oct 28];65(10):1373-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1798317/pdf/1373.pdf

33. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis [Internet]. London: EMA; 2006 Dec 14. [cited 2015 Sep 3]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003413.pdf

34. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol. 2005 Sep;23(5 Suppl 39):S100-S108.

35. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995 Jan;38(1):44-8.

36. van Gestel AM, Prevoo ML, van't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum. 1996 Jan;39(1):34-40.

37. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Clin Exp Rheumatol. 2005 Sep;23(5 Suppl 39):S93-S99.

38. Husted JA, Gladman DD, Long JA, Farewell VT. A modified version of the Health Assessment Questionnaire (HAQ) for psoriatic arthritis. Clin Exp Rheumatol. 1995 Jul;13(4):439-43.

39. Carlin CS, Feldman SR, Krueger JG, Menter A, Krueger GG. A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. J Am Acad Dermatol. 2004 Jun;50(6):859-66.

40. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. Med Care. 1992 Jun;30(6):473-83.

41. Mease PJ, Menter MA. Quality-of-life issues in psoriasis and psoriatic arthritis: outcome measures and therapies from a dermatological perspective. J Am Acad Dermatol. 2006 Apr;54(4):685-704.

42. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med. 2001 Jul;33(5):350-7.

43. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. PharmacoEconomics. 1999 Feb;15(2):141-55.

44. Strand V, Singh JA. Improved health-related quality of life with effective disease-modifying antirheumatic drugs: evidence from randomized controlled trials. Am J Manag Care. 2008 Apr;14(4):239-53.

45. Leung YY, Ho KW, Zhu TY, Tam LS, Kun EW, Li EK. Testing scaling assumptions, reliability and validity of medical outcomes study short-form 36 health survey in psoriatic arthritis. Rheumatology (Oxford) [Internet]. 2010 Aug [cited 2015 Oct 28];49(8):1495-501. Available from: http://rheumatology.oxfordjournals.org/content/49/8/1495.full.pdf+html

46. Cheung K, Oemar M, Oppe M, Rabin R. EQ-5D user guide: basic information on how to use EQ-5D [Internet]. Version 2.0. [Rotterdam (The Netherlands)]: EuroQol Group; 2009 Mar. [cited 2015 Sep 3]. Available from: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/User_Guide_v2_March_2009.pdf

47. Wong PC, Leung YY, Li EK, Tam LS. Measuring disease activity in psoriatic arthritis. Int J Rheumatol [Internet]. 2012 [cited 2015 Sep 3];2012:839425. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3540792

48. Arumugam V, MacDermid JC. The Work Limitations Questionnaire (WLQ-25). J Physiother [Internet]. 2013 Dec [cited 2015 Sep 3];59(4):276. Available from: http://ac.els-cdn.com/S1836955313702108/1-s2.0-S1836955313702108-main.pdf?_tid=54d80610-524c-11e5-98ef-00000aacb35e&acdnat=1441292530_74b00dfad7ac943abeb01d16f16b1bce

49. Lerner D, Amick BC III, Rogers WH, Malspeis S, Bungay K, Cynn D. The Work Limitations Questionnaire. Med Care. 2001 Jan;39(1):72-85.

50. Chandran V, Bhella S, Schentag C, Gladman DD. Functional assessment of chronic illness therapy-fatigue scale is valid in patients with psoriatic arthritis. Ann Rheum Dis [Internet]. 2007 Jul [cited 2015 Sep 3];66(7):936-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1955111

51. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005 May;32(5):811-9.

52. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008 Feb;9(2):105-21.

53. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum. 1993 Jun;36(6):729-40.

54. Kwok T, Pope JE. Minimally important difference for patient-reported outcomes in psoriatic arthritis: Health Assessment Questionnaire and pain, fatigue, and global visual analog scales. J Rheumatol. 2010 May;37(5):1024-8.

55. Gladman DD, Mease PJ, Healy P, Helliwell PS, FitzGerald O, Cauli A, et al. Outcome measures in psoriatic arthritis. J Rheumatol. 2007 May;34(5):1159-66.

56. Gladman DD, Farewell V, Buskila D, Goodman R, Hamilton L, Langevitz P, et al. Reliability of measurements of active and damaged joints in psoriatic arthritis. J Rheumatol. 1990 Jan;17(1):62-4.

57. Gladman DD, Cook RJ, Schentag C, Feletar M, Inman RI, Hitchon C, et al. The clinical assessment of patients with psoriatic arthritis: results of a reliability study of the spondyloarthritis research consortium of Canada. J Rheumatol. 2004 Jun;31(6):1126-31.

58. Blackmore MG, Gladman DD, Husted J, Long JA, Farewell VT. Measuring health status in psoriatic arthritis: the Health Assessment Questionnaire and its modification. J Rheumatol. 1995 May;22(5):886-93.

59. Mease PJ, Antoni CE, Gladman DD, Taylor WJ. Psoriatic arthritis assessment tools in clinical trials. Ann Rheum Dis. 2005 Mar;64 Suppl 2:ii49-ii54.

60. van der Heijde DM, van't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis. 1990 Nov;49(11):916-20.

61. van der Heijde DM, van't Hof MA, van Riel PL, van Leeuwen MA, van Rijswijk MH, van de Putte LB. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis. 1992 Feb;51(2):177-81.

62. van Gestel AM, Anderson JJ, van Riel PL, Boers M, Haagsma CJ, Rich B, et al. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. J Rheumatol. 1999 Mar;26(3):705-11.

63. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum. 2005 Apr;52(4):1227-36.

64. Vander CB, Van Looy S, Wyns B, Westhovens R, Durez P, Van den Bosch F, et al. DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment. Arthritis Res Ther. 2005;7(5):R1063-R1071.

65. Inoue E, Yamanaka H, Hara M, Tomatsu T, Kamatani N. Comparison of Disease Activity Score (DAS)28- erythrocyte sedimentation rate and DAS28- C-reactive protein threshold values. Ann Rheum Dis [Internet]. 2007 Mar [cited 2015 Oct 28];66(3):407-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1856019/pdf/407.pdf

66. Matsui T, Kuga Y, Kaneko A, Nishino J, Eto Y, Chiba N, et al. Disease Activity Score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients in Japan. Ann Rheum Dis [Internet]. 2007 Sep [cited 2015 Oct 28];66(9):1221-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1955164/pdf/1221.pdf

67. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009 Jun;68(6):954-60.

68. Kushner I. C-reactive protein in rheumatology. Arthritis Rheum. 1991 Aug;34(8):1065-8.

69. Husted JA, Gladman DD, Farewell VT, Long JA, Cook RJ. Validating the SF-36 health survey questionnaire in patients with psoriatic arthritis. J Rheumatol. 1997 Mar;24(3):511-7.

70. Husted JA, Gladman DD, Cook RJ, Farewell VT. Responsiveness of health status instruments to changes in articular status and perceived health in patients with psoriatic arthritis. J Rheumatol. 1998 Nov;25(11):2146-55.

71. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewe R, van ver Tempel H, Mielants H, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis [Internet]. 2003 Feb [cited 2015 Sep 3];62(2):127-32. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1754445

72. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis [Internet]. 2005 [cited 2015 Oct 28];64(Suppl 2):ii65-ii68. Available from: http://ard.bmj.com/content/64/suppl_2/ii65.full.pdf

73. Choi J, Koo JY. Quality of life issues in psoriasis. J Am Acad Dermatol. 2003 Aug;49(2 Suppl):S57-S61.

74. Ashcroft DM, Wan Po AL, Williams HC, Griffiths CE. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. Br J Dermatol. 1999 Aug;141(2):185-91.

75. Feldman SR, Menter A, Koo JY. Improved health-related quality of life following a randomized controlled trial of alefacept treatment in patients with chronic plaque psoriasis. Br J Dermatol. 2004 Feb;150(2):317-26.

76. Jacobson CC, Kimball AB. Rethinking the Psoriasis Area and Severity Index: the impact of area should be increased. Br J Dermatol. 2004 Aug;151(2):381-7.

77. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis [Internet]. 2014 Jan [cited 2015 Oct 28];73(1):48-55. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3888622

78. Regnier S, Malcolm W, Allen F, Wright J, Bezlyak V. Efficacy of anti-VEGF and laser photocoagulation in the treatment of visual impairment due to diabetic macular edema: a systematic review and network meta-analysis. PLoS ONE [Internet]. 2014 [cited 2015 Aug 17];9(7):e102309. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4100770