Common Drug Review

Clinical Review Report (Resubmission)

September 2017

Drug	Apremilast (Otezla)
Indication	For treatment of adults patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Reimbursement request	[redacted]
Dosage form(s)	10 mg, 20 mg, and 30 mg oral tablets
NOC date	November 12, 2014
Manufacturer	Celgene Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in the treatment of psoriasis who provided input on the conduct of the review and the interpretation of findings.

Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
BMI	body mass index
BSA	body surface area
CDEC	Canadian Drug Expert Committee
CI	confidence interval
DLQI	Dermatology Life Quality Index
EQ-5D	EuroQol 5-Dimensions Questionnaire
IL	interleukin
LOCF	last observation carried forward
LSM	least squares mean
MCID	minimal clinically important difference
MCS	mental component summary
mITT	modified intention-to-treat
NMA	network meta-analysis
PASI	Psoriasis Area and Severity Index
PCS	physical component summary
PGA	Physician Global Assessment
PDE4	phosphodiesterase 4
RCT	randomized controlled trial
SF-36	Short Form (36) Health Survey
sPGA	static Physician Global Assessment
TNF	tumour necrosis factor

EXECUTIVE SUMMARY

Introduction

Psoriasis is a serious, chronic inflammatory skin disorder that, in its worst manifestations, may have systemic effects and possibly even be fatal, but more commonly leads to significant symptoms, including pruritus. It also affects appearance and reduces quality of life. Plaque psoriasis is characterized by well-demarcated papules that are covered by silvery scales. Moderate-to-severe psoriasis is defined by the extent of skin coverage (involvement of more than 5% to 10% of body surface area), or location (involvement of the face, palm, or sole), or severity (disease that is disabling). The manufacturer estimated there are approximately 212,500 Canadians with moderate-to-severe chronic plaque psoriasis.

Psoriasis is treated topically, including with phototherapy, and with systemic therapies, often administered concomitantly. Once patients have exceeded this 5% to 10% of their skin involvement, topical therapy becomes more problematic for the patient, as there is such a large surface area to cover. At this point, these patients tend to move to systemic therapy.[1,2] Psoriasis is essentially an immune disorder and therefore, the systemic therapies all work by suppressing components of the immune system. The first systemic therapies, often referred to as "conventional" therapies, were all small-molecule, the two most important currently being methotrexate and cyclosporine. The biologics, monoclonal antibodies, and fusion proteins were the next systemic therapies to be developed, and all of these original biologics targeted tumour necrosis factor (TNF), a key mediator of inflammation. The newest biologics, both monoclonal antibodies, target interleukins (IL). Ustekinumab blocks IL-12 and IL-23, and secukinumab, currently under review by Health Canada, blocks IL-17.

Apremilast is an orally administered phosphodiesterase type 4 (PDE4) inhibitor, given at a dose of 30 mg twice daily. Apremilast is under review for the treatment of adult patients with moderate-to-severe plaque psoriasis who have had an inadequate response to or are intolerant of conventional systemic therapy, or for whom such therapy is contraindicated. Apremilast is also approved for adult patients with active psoriatic arthritis who have had an inadequate response, intolerance, or contraindication to a prior disease-modifying antirheumatic drug.

In July 2015, the Canadian Drug Expert Committee (CDEC) issued a recommendation that apremilast not be listed for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Key reasons for the recommendation included the lack of comparative evidence (i.e., direct head-to-head studies and/or well-conducted indirect treatment comparisons) with other available therapies, and insufficient evidence to evaluate the use of apremilast in the patient population for which the manufacturer was requesting a listing: [redacted] The post-hoc analysis of patients from the ESTEEM trials that met the requested listing criteria was considered by CDEC to be merely hypothesis-generating. CDEC further indicated, in a related "Of Note," that there was a lack of data to suggest [redacted]

The resubmission is based on new clinical information. Study PSOR-010 (LIBERATE) is a double-blind randomized controlled trial that compared apremilast to placebo and etanercept to placebo, specifically in patients with moderate-to-severe psoriasis having had an inadequate response, intolerance, or

contraindication to prior conventional systemic therapies. LIBERATE was not included in the initial submission.

Indication under review
Treatment of adults patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Reimbursement criteria requested by sponsor
[redacted]

The objective of this report was to perform a systematic review of the beneficial and harmful effects of apremilast for the treatment of moderate-to-severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy. This is a resubmission based on new data submitted by the manufacturer and, therefore, can be considered an update of the original apremilast clinical review for this indication. Compared with the original protocol, the subgroup "psoriatic arthritis" was removed, as this was considered to be a separate indication rather than a subgroup, and two new comparators were added (secukinumab, ixekizumab) that had not been approved by Health Canada at the time of the original CADTH Common Drug Review (CDR) review.

Results and Interpretation

The original CDR systematic review included two pivotal, phase 3, double-blind, placebo-controlled randomized controlled trials (RCTs). Both ESTEEM-1 (N = 844) and ESTEEM-2 (N = 413) enrolled patients with moderate-to-severe plaque psoriasis for at least 12 months prior to randomization. Participants were randomized (2:1) to either apremilast or placebo. Both studies included an initial 16-week double-blind phase, which was the focus of the review, followed by a 16-week maintenance phase and a 20-week randomized treatment withdrawal phase that tested the durability of response to apremilast. A manufacturer-submitted network meta-analysis (NMA) suggested the biologics provided superior efficacy to the small-molecule drugs for psoriasis, including apremilast, based on rank ordering alone. Moreover, there was no evidence from the NMA that apremilast has superior efficacy compared with methotrexate or cyclosporine. There is uncertainty with respect to the conclusions from the NMA, because no statistical indirect treatment comparison estimates were provided by the manufacturer. The NMA did not include safety outcomes.

Key data from these ESTEEM trials, as well as the LIBERATE trial, which forms the basis of the resubmission, are summarized in Table 1 below.

TABLE 1: SUMMARY OF DATA FROM STUDIES INCLUDED IN ORIGINAL SUBMISSION (ESTEEM) AND RESUBMISSION (LIBERATE)

	ESTEEM-1	ESTEEM-2	LIBERATE
PASI 75 at week 16, patients n (%)			
Apremilast	186 (33)	79 (29)	33 (40)
Placebo	15 (5)	8 (6)	10 (12)
Etanercept	-	-	40 (48)
Difference in proportions (95% CI):	27.8 (23.1, 32.5)	23.0 (16.3, 29.6)	27.5 (14.9, 40.1)

	ESTEEM-1	ESTEEM-2	LIBERATE
apremilast versus placebo	$P < 0.0001$[a]	$P < 0.0001$[a]	$P < 0.0001$[b]
Difference in proportions (95% CI): etanercept versus placebo	-	-	[redacted]
DLQI total score mean (SD) change at week 16			
Apremilast	–6.6 (–6.7)	–6.7 (7.0)	–8.3 (7.7)
Placebo	–2.1 (5.7)	–2.8 (7.2)	–3.8 (5.6)
Etanercept	-	-	–7.8 (6.5)
Difference in proportions (95% CI): apremilast versus placebo	–4.5 (–5.4 to –3.6) $P < 0.0001$[c]	–4.0 (–5.3 to –2.8) $P < 0.0001$[d]	[redacted]
Difference in proportions (95% CI): etanercept versus placebo	-	-	[redacted]
Adverse events, patients n (%), week 16			
Apremilast	388 (69)	185 (68)	58 (70)
Placebo	157 (56)	82 (60)	50 (60)
Etanercept	-	-	44 (53)
Serious adverse events, patients n (%), week 16			
Apremilast	12 (2)	5 (2)	3 (4)
Placebo	8 (3)	3 (2)	0
Etanercept	-	-	1 (1)

ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; DLQI = Dermatology Life Quality Index; LS = least squares; PASI = Psoriasis Area and Severity Index; SD = standard deviation.
[a] Two-sided 95% CI is based on the normal approximation. Two-sided *P* value is based on the two-sided chi-square test.
[b] The two-sided *P* value is from a CMH test stratified by body mass index at screening. The CI is weighted using CMH weights according to the number of participants in the two strata.
[c] Based on an ANOVA model for the change from baseline at week 16, with treatment group as a factor. Unadjusted means and *P* values are provided. The two-sided *P* value for slope homogeneity is < 0.05.
[d] Based on an ANCOVA model for the percentage change from baseline at week 16, with treatment group as a factor and the baseline value as a covariate. Means (LS means) and *P* values were adjusted by covariate. The two-sided *P* value for slope homogeneity is > 0.05.
[e] Based on an ANCOVA model for the change from baseline at week 16. The LS means and *P* values are presented from the ANCOVA adjusted for covariates.
Source: Clinical Study Reports for ESTEEM-1, ESTEEM-2,[3,4] and LIBERATE.[5]

Included Studies

One double-blind RCT, LIBERATE, was submitted by the manufacturer as the basis for its resubmission to CDR, and no other new double-blind RCTs that met our inclusion criteria were identified after a systematic review of the literature. LIBERATE was a 16-week double-blind RCT with an 88-week open-label extension that compared apremilast and etanercept with placebo. No comparisons of apremilast with etanercept were planned for this study. The primary outcome compared the proportion of apremilast- versus placebo-treated patients with a Psoriasis Area and Severity Index 75 (PASI 75) response at week 16. The first secondary outcome was the proportion of etanercept versus placebo patients achieving PASI 75 at week 16. Other secondary outcomes, tested in a hierarchical fashion, included several comparisons of apremilast versus placebo:

- proportion of Physician Global Assessment (PGA) responders
- change from baseline in affected body surface area (BSA)
- proportion of PASI 50 responders
- change from baseline in total Dermatology Life Quality Index (DLQI)

- and differences in the Short Form (36) Health Survey (SF-36) mental component summary scores.

This was followed by testing of the same outcomes for etanercept versus placebo.

Efficacy

The resubmission was intended to address gaps in evidence identified from the previous CDEC Recommendation, such as a lack of a direct comparison with other available therapies and the population relevant to the proposed reimbursement criteria (patients with moderate-to-severe psoriasis and failure, intolerance, or contraindication to prior conventional systemic therapy). While the latter gap was addressed, LIBERATE was not designed to compare apremilast with etanercept; therefore, this gap remains.

The proportion of patients achieving a PASI 75 by week 16, between apremilast and placebo, was the primary outcome. A higher proportion of patients treated with apremilast achieved PASI 75 versus placebo (40% versus 12% of patients, respectively), and this difference was statistically significant (difference in proportions between groups of 27.5%; 95% confidence interval [CI], 14.9 to 40.1; $P < 0.0001$). There was also a higher proportion of patients treated with etanercept who achieved PASI 75 compared with placebo (48% versus 12%), and this difference was statistically significant (difference in proportions between groups [95% CI] of [redacted]. The proportion of patients achieving PASI 50 responses, apremilast versus placebo, was reported as a secondary outcome, and there were more apremilast-treated patients who achieved PASI 50 after 16 weeks when compared with placebo ([redacted]) and this difference between groups was statistically significant (difference in proportions between groups [95% CI] of [redacted]. A higher proportion of etanercept-treated patients achieved PASI 50 after 16 weeks versus placebo ([redacted]), but due to an earlier failure in the statistical hierarchy, this comparison of this outcome should not have been tested. There were more apremilast-treated versus placebo-treated patients who achieved PASI 90 after 16 weeks ([redacted]), and this difference was statistically significant (difference in proportions between groups [95% CI] of [redacted]), although this was an exploratory outcome and not adjusted for multiple comparisons. A higher proportion of etanercept-treated than placebo-treated patients achieved PASI 90 ([redacted]), and this difference was also statistically significant (difference in proportions between groups [95% CI] of [redacted]) although, again, not adjusted for multiple comparisons. The clinical expert on this review believes that PASI 75 remains a reasonable choice for primary outcome; however, because expectations of treatment success have increased over time, the PASI 90 has become a more relevant outcome than the PASI 50.

Quality of life was assessed as a secondary outcome, both using the DLQI and the mental component summary of the SF-36. In the hierarchy, testing was performed comparing apremilast with placebo first, then etanercept versus placebo. Although there was a statistically and clinically significant improvement from baseline in DLQI total scores for apremilast versus placebo, this was not the case when apremilast was compared with placebo using the [redacted]. Due to this failure to achieve statistical significance, all testing should have ceased and, therefore, no comparisons of etanercept with placebo should have been performed. Therefore, the efficacy of etanercept versus placebo cannot be ascertained with respect to quality of life, while the efficacy of apremilast was mixed, with a statistically and clinically significant response versus placebo in a disease-specific instrument, but failure to achieve statistical significance on the [redacted]. The clinical expert believed the DLQI to be a more relevant outcome in this indication than the [redacted].

Additional secondary outcomes were also assessed in the hierarchy and, due to the failure of apremilast to achieve statistical significance for the [redacted], statistical testing was performed for apremilast versus placebo for several of these outcomes, but should not have been performed for etanercept versus placebo. Therefore, although apremilast demonstrated statistically significant improvements versus placebo for outcomes such as proportion of patients achieving Static Physician Global Assessment (sPGA) responses and percentage change in affected BSA, the efficacy of etanercept versus placebo for these outcomes cannot be assessed.

Harms

There were numerically more adverse events (70% versus 53%), serious adverse events (4% versus 1%), and withdrawal due to adverse events (4% versus 2%) for apremilast versus etanercept. The most notable harm for apremilast continues to be weight loss, and the manufacturer reported changes in weight under safety in LIBERATE. A weight loss of more than 5% to 10% of body weight occurred in numerically more apremilast patients than placebo ([redacted] of patients, respectively), while weight decrease reported as an adverse event occurred in 1% of patients in each of the apremilast and placebo groups. The extension study to LIBERATE did not identify any unexpected safety signals; however, few conclusions can be drawn from the extension study data because it followed patients only for 52 weeks, there was no comparator group, the population was likely highly selected, and the results appeared to be sensitive to missing data.

Place in Therapy

According to the clinical expert consulted by CDR, conventional systemic therapies (such as methotrexate and cyclosporine) and the biologics serve the patient's needs very well and there are very few patients whose psoriasis would be refractory to these treatments.

Apremilast is an oral drug alternative to the traditional systemic treatments. Patients may be concerned about the potential adverse effects of the traditional drugs. The clinical expert consulted indicated that apremilast may be considered for patients who have failed or are intolerant of the traditional systemics, and who do not want to take biologics (because of needle phobia, for example). This, however, is likely a minority of patients (probably less than 5%). In general, the biologics provide better efficacy than apremilast (based on evidence from the manufacturer-provided indirect treatment comparisons), and most patients would opt for the higher efficacy treatment, according to the clinical expert consulted.

As apremilast is not immunosuppressive, it may be preferred for immunocompromised patients. However, biologics are not absolutely contraindicated and may be used in these patients with proper monitoring.

Conclusions

One manufacturer-sponsored multi-centre double-blind RCT, the LIBERATE study, was submitted by the manufacturer and met the inclusion criteria for this resubmission review. In addition to an apremilast and a placebo group, LIBERATE also contained an etanercept group; however, the study was designed to compare apremilast with placebo and etanercept with placebo, but not to compare apremilast with etanercept. Patients with moderate-to-severe plaque psoriasis who had failed or had an intolerance or contraindication to prior conventional systemic therapy were randomized 1:1:1 to one of these three interventions over a 16-week initial treatment phase. Apremilast and etanercept were both statistically superior to placebo for the primary outcome of proportion of patients achieving PASI 75, while apremilast also significantly improved the results of the PGA and affected BSA, and the quality of life scores on the DLQI versus placebo. However, apremilast did not improve the [redacted]

versus placebo and, due to the hierarchical testing procedure, this meant that the only outcome to be tested for etanercept was PASI 75. The harms data suggest there may be a numerically higher risk of adverse events with apremilast versus etanercept. However, the study was not designed to make such comparisons; therefore, this must be considered hypothesis-generating. Overall, while this resubmission does provide evidence of efficacy for apremilast versus placebo in a population that more closely resembles the manufacturer-requested reimbursement criteria, there is still no direct comparison of apremilast with any systemic therapy or biologic. In a manufacturer-submitted NMA, [redacted], and no comparisons were made to other conventional systemic therapies, which are likely the more relevant comparators for apremilast.

TABLE 2: SUMMARY OF RESULTS

	LIBERATE		
	Apremilast N = 83	Placebo N = 84	Etanercept N = 83
PASI 75			
Patients at week 16, N (%)	33 (39.8)	10 (11.9)	40 (48.2)
Difference in proportions versus placebo (95% CI)	27.5 (14.9 to 40.1)		[redacted]
CMH *P* value[a]	*P* < 0.0001		[redacted]
sPGA			
sPGA response, week 16, N (%)	18 (21.7)	3 (3.6)	[redacted]
Difference in proportions versus placebo (95% CI)[a]	18.0 (8.4 to 27.7)		[redacted]
CMH *P* value[a]	*P* = 0.0005		[redacted]
Psoriasis-affected BSA			
Mean (SD) at baseline	27.1 ([redacted])	27.3 ([redacted])	28.4 ([redacted])
Mean (SD) % change at week 16	–48.25 (35.10)	–16.54 (36.90)	–56.52 (31.56)
LS mean (95% CI)	–47.7 (–55.20 to –40.12)	–16.3 (–23.71 to –8.81)	–56.1 (–63.63 to –48.59)
Difference in LS means versus placebo (2-sided 95% CI)[b]	–31.40 (–43.33 to –19.46)		–39.85 (–51.78 to –27.92)
CMH *P* value[a]	*P* < 0.0001		Failed hierarchy[c]
DLQI total score			
Mean (SD) at baseline	13.8 (6.6)	11.4 (6.3)	12.5 (7.0)
Mean (SD) change at week 16	–8.3 (7.7)	–3.8 (5.6)	–7.8 (6.5)
LS mean change (95% CI)	–8.4 (–9.84 to –6.88)	–3.9 (–5.34 to –2.42)	–7.8 (–9.28 to –6.34)
Difference in LS means versus placebo (2-sided 95% CI)[b]	–4.48 (–6.82 to –2.14)		–3.94 (–6.27 to –1.60)
P value	*P* < 0.0001		Failed hierarchy[c]
SF-36 MCS			
Mean (SD) at baseline	42.78 (12.70)	44.33 (11.01)	45.63 (10.78)
Mean (SD) change at week 16	4.26 (10.36)	2.64 (9.16)	4.35 (9.63)
LS mean change from baseline (95% CI)	3.5 (1.62 to 5.38)	2.6 (0.72 to 4.43)	4.8 (2.92 to 6.67)
Difference in LS means versus placebo (2-sided 95% CI)[b]	0.93 (–2.05 to 3.90)		2.22 (–0.75 to 5.19)

	LIBERATE		
	Apremilast N = 83	Placebo N = 84	Etanercept N = 83
2-sided *P* value	0.7112		Failed hierarchy [c]
Harms			
Patients with > 0 SAEs, N (%)	3 (4)	0	1 (1)
Notable harms			
Weight loss > 5% to 10% (not reported as an AE), N (%)	8 (10)	3 (4)	5 (6)
Weight decrease (reported as AE), N (%)	1 (1)	1 (1)	0

ANCOVA = analysis of covariance; BSA = body surface area; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; DLQI = Dermatology Life Quality Index; LOCF = last observation carried forward; LS = least squares; PASI = Psoriasis Area and Severity Index; SD = standard deviation; SF-36 MCS = mental component summary of the Short Form (36) Health Survey; sPGA = Static Physician Global Assessment.

[a] The two-sided *P* value is from a CMH test stratified by the body mass index at screening. The CI is weighted using CMH weights according to the number of participants in the two strata.

[b] Based on an ANCOVA model for the change from baseline at week 16. The LS means and *P* values are presented from the ANCOVA adjusted for covariates.

[c] Outcome in statistical hierarchy that was tested after a previous outcome had failed to achieve statistical significance and, therefore, should not have been tested.

Source: Clinical Study Report for LIBERATE.[5]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Psoriasis is a serious, chronic inflammatory skin disorder that, in its worst manifestations, may have systemic effects and can even be fatal, but more commonly leads to significant symptoms, including pruritus. It also affects appearance and reduces quality of life. The appearance is most often characterized by scaly erythematous papules and plaques, and plaque psoriasis is the most common form of psoriasis. Plaque psoriasis is characterized by well-demarcated papules that are covered by silvery scales. Moderate-to-severe psoriasis is defined by the extent of skin coverage (involvement of more than 5% to 10% of body surface area), or location (involvement of the face, palm, or sole), or severity (disease that is disabling). Once patients have exceeded 5% to 10% skin involvement, topical therapy becomes more problematic for the patient, as there is such a large surface area to cover. At this point, these patients tend to move to systemic therapy (see next section).[1,2]

There are approximately one million people who suffer from psoriasis in Canada, and 125 million worldwide. Of these, approximately 90% have plaque psoriasis.[6] Based on a paper by Levy et al., the manufacturer estimated there were approximately 212,500 Canadians with moderate-to-severe chronic plaque psoriasis.[7]

1.2 Standards of Therapy

Psoriasis is treated topically, including with phototherapy, and with systemic therapies, often administered concomitantly. Topical therapies are often corticosteroids of varying potencies; however, emollients, coal tar, vitamin D analogues, and topical retinoids may also be used. Phototherapies may be either strictly topical (ultraviolet B light on involved skin) or combine a systemic agent like psoralen with phototherapy. The fact that topical therapies are applied locally is an advantage with respect to reduced risk of harms, but also a disadvantage in that widely disseminated lesions will require large amounts of topical therapy, creating an added burden for the patient. Psoriasis is essentially an immune disorder and, therefore, the systemic therapies all work by suppressing components of the immune system. The first systemic therapies, often referred to as “conventional” therapies, were all small-molecule, the two most important currently being methotrexate, an antimetabolite also used to treat some cancers and rheumatoid arthritis, and cyclosporine, a potent immunosuppressant also used to prevent organ transplant rejection. Both of these drugs have significant toxicities associated with them. The biologics, monoclonal antibodies, and fusion proteins were the next systemic therapies to be developed, and all of these original biologics targeted tumour necrosis factor (TNF), a key mediator of inflammation. The newest biologics, both monoclonal antibodies, target interleukins (IL). Ustekinumab blocks IL-12 and IL-23, and secukinumab, currently under review by Health Canada, blocks IL-17. High cost is a common drawback of the biologics for psoriasis, as well as the fact that they must all be administered by injection. The TNF inhibitors have all been associated with elevated risk of certain cancers with long-term use, and increased risk of infection, including tuberculosis. The association between TNF inhibitor use and increased risk of cancer is less well defined and more controversial in psoriasis, according to the clinical expert consulted by the CADTH Common Drug Review (CDR) for this review. Ustekinumab has also been associated with increased infection risk and malignancy and, more recently, serious skin reactions.[2]

1.3 Drug

Apremilast is an orally administered phosphodiesterase type 4 (PDE4) inhibitor, given at a dose of 30 mg twice daily. Apremilast is under review for the treatment of [redacted]. Apremilast is also approved for patients with active psoriatic arthritis in adults who have had an inadequate response, intolerance, or contraindication to a prior disease-modifying antirheumatic drug.

Indication under review
Treatment of adults patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Reimbursement criteria requested by sponsor
[redacted]

TABLE 3: KEY CHARACTERISTICS OF SMALL-MOLECULE INHIBITORS AND BIOLOGICS

Small Molecules			
	Apremilast	**Cyclosporine**	**Methotrexate**
Mechanism of Action	PDE4 inhibitor	Calcineurin inhibitor inhibits IL-2, preventing T-cell activation	Antimetabolite; folate antagonist
Indication[a]	Patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy	Psoriasis	Psoriasis
Route of Administration	Oral	Oral	Oral
Recommended Dose	30 mg twice daily	– 2.5 mg/kg/day given in two divided oral doses, 12 hours apart – Dose may be titrated to achieve effect – Total daily dose should not exceed 5 mg/kg/day	– Weekly single oral, IM, or IV dose schedule: 10 mg to 25 mg per week until adequate response is achieved – Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded
Serious Side Effects/Safety Issues	No serious harms detected in RCTs with a 16-week follow-up	– Infections – Nephrotoxicity – Hypertension	– Bone marrow suppression – Hepatotoxicity – Nephrotoxicity – Alopecia – Stomatitis

Biologics: TNF Inhibitors			
	Infliximab	**Adalimumab**	**Etanercept**
Mechanism of Action	– TNF inhibitor – Chimeric monoclonal antibody	– TNF inhibitor – Recombinant human monoclonal antibody	– TNF inhibitor – Fusion protein
Indication[a]	Indicated for patients with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, infliximab should be used after phototherapy has been shown to be ineffective or inappropriate.	Indicated for patients with chronic moderate-to-severe psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, adalimumab should be used after phototherapy has been shown to be ineffective or inappropriate.	For patients with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Route of Administration	IV	Subcutaneous	Subcutaneous
Recommended Dose	– 5 mg/kg given as an IV infusion followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter – If a patient does not show an adequate response at week 14, after infusions at weeks 0, 2, and 6, no additional treatment with infliximab should be given	– 80 mg administered subcutaneously, followed by 40 mg subcutaneously every other week starting one week after the initial dose – Continuing therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period	A 50 mg dose is given twice weekly (administered 3 or 4 days apart) for 3 months followed by a reduction to a maintenance dose of 50 mg per week. A maintenance dose of 50 mg given twice weekly has also been shown to be efficacious.
Serious Side Effects/Safety Issues	– Infection – Cancer	– Infection – Cancer	– Infection – Cancer

Biologics: Other			
	Ustekinumab	**Secukinumab**	**Ixekizumab**
Mechanism of Action	– IL-12 and IL-23 inhibitor – Fully human monoclonal antibody	– IL-17A inhibitor – Human monoclonal antibody	– IL-17A inhibitor – Humanized monoclonal antibody
Indication[a]	Patients with chronic moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy	Moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy	Moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Route of Administration	Subcutaneous	Subcutaneous	Subcutaneous
Recommended Dose	– 45 mg at weeks 0 and 4, then every 12 weeks thereafter; alternatively, 90 mg may be used in patients with a body weight greater than 100 kg – For patients who respond inadequately to dosing every 12 weeks, consideration may be given to treating as often as every 8 weeks – Consideration should be given to discontinuing treatment in patients who have shown no response after 12 weeks of treatment	– 300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, and 3, followed by monthly maintenance dosing starting at week 4.	– 160 mg by subcutaneous injection at week 0, then 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks.
Serious Side Effects/Safety Issues	– Infection – Cancer – **Serious skin reactions (exfoliative dermatitis and erythrodermic psoriasis)**	– Infection – Exacerbations of Crohn's disease	– Infection – Exacerbations of Crohn's disease and ulcerative colitis

PDE4 = phosphodiesterase type 4; IL = interleukin; IM = intramuscular; IV = intravenous; RCT = randomized controlled trial; TNF = tumour necrosis factor.

[a] Health Canada indication.

Source: Product monographs (from the Compendium of Pharmaceuticals and Specialties database[8]) for apremilast,[9] cyclosporine, methotrexate, infliximab, adalimumab, etanercept, ustekinumab, and secukinumab; and for ixekizumab, available at the manufacturer's website.[10]

2. SUBMISSION HISTORY

In July 2015, the CADTH Canadian Drug Expert Committee (CDEC) issued a recommendation that apremilast not be listed for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Key reasons for the recommendation included the lack of comparative evidence (i.e., direct head-to-head studies or well conducted indirect treatment comparisons) with other available therapies and insufficient evidence to evaluate the use of apremilast in the patient population for which the manufacturer was requesting a listing: [redacted]. The ESTEEM studies both included patients with moderate-to-severe plaque psoriasis, but did not require patients to have tried or to have had a contraindication to prior systemic therapy. In its proposed reimbursement criteria, the manufacturer had suggested apremilast be funded for patients [redacted]. However, only about one-third of patients had received prior conventional systemic therapy, thus limiting any conclusions that could be drawn regarding this key component of their listing criteria. In addition, there was uncertainty regarding the assessment of "treatment failure" and whether patients had truly failed previous treatment in the ESTEEM studies. The post-hoc analysis of patients from the ESTEEM trials that met the requested listing criteria was considered by CDEC to be hypothesis-generating. Therefore, two key limitations from the original submission were the lack of a head-to-head comparison, and a lack of data in the population in which apremilast is intended to be used. CDEC further indicated, in a related "Of Note," that there was a lack of data to suggest [redacted].

The CDR systematic review included two pivotal, phase 3, double-blind, placebo-controlled randomized controlled trials (RCTs). Both ESTEEM-1 (N = 844) and ESTEEM-2 (N = 413) enrolled patients with moderate-to-severe plaque psoriasis for at least 12 months prior to randomization. Participants were randomized (2:1) to either apremilast or placebo. Both studies included an initial 16-week double-blind phase, which was followed by a 16-week maintenance phase where patients originally assigned to apremilast remained on the drug, while patients originally assigned to placebo were switched to apremilast. Finally, weeks 32 to 52, referred to as the randomized treatment withdrawal phase, tested the durability of response to apremilast. At week 32, responders (those achieving a Psoriasis Area and Severity Index score of at least 75 (PASI 75) in ESTEEM-1 and 50 in ESTEEM-2) were re-randomized to either continue on apremilast or switch to placebo.

The proportion of patients achieving PASI 75 at 16 weeks was the primary outcome of both ESTEEM-1 and ESTEEM-2. Statistically significantly higher proportions of patients who received apremilast (33% and 29%) compared with patients who received placebo (5% and 6%) achieved PASI 75 at 16 weeks in both ESTEEM-1 (difference in proportions of 27.8% [95% confidence interval (CI), 23.1 to 32.5; $P < 0.0001$]) and in ESTEEM-2 (difference in proportions of 23.0% [95% CI, 16.3% to 29.6%; $P < 0.0001$). At 16 weeks, apremilast improved quality of life on the Dermatology Quality of Life Index (DLQI) compared with placebo in both ESTEEM-1 (difference in least squares [LS] means of –4.5 [95% CI, –5.4 to –3.6; $P < 0.0001$]) and ESTEEM-2 (difference in LS means of –4.0 [95% CI, –5.3 to –2.8; $P < 0.0001$]). These improvements were both statistically and clinically significant, based on the minimal clinically important difference (MCID) for the DLQI of 3.2.

In ESTEEM-1, 69% of apremilast and 56% of placebo patients reported an adverse event after 16 weeks of therapy, while in ESTEEM-2, 68% of apremilast and 60% of placebo patients experienced an adverse event. The most common adverse events were diarrhea (18% of apremilast patients versus 7% of placebo across studies) and nausea (17% of apremilast patients versus 7% of placebo). Serious adverse events were reported in 2% of apremilast and 3% of placebo patients after 16 weeks in ESTEEM-1, and in 2% of each of the apremilast and placebo groups in ESTEEM-2. No single serious adverse event occurred in more than a single patient. Withdrawals due to adverse event occurred in 5% of apremilast patients and 3% of placebo after 16 weeks in ESTEEM-1, and in 6% and 5% of patients in ESTEEM-2, respectively. The most common reason for withdrawal across groups was nausea. Aside from gastrointestinal adverse effects, weight loss was a notable harm associated with apremilast, and the proportion of patients who lost more than 5% to 10% of body weight was 12% for apremilast versus 6% for placebo in ESTEEM-1, and 14% versus 3%, respectively, in ESTEEM-2. Weight decrease as an adverse event was reported in 1% and 2.4% of patients in ESTEEM-1 and ESTEEM2, respectively.

A manufacturer-submitted network meta-analysis (NMA) suggested the biologics provided superior efficacy to the small-molecule drugs for psoriasis, including apremilast, based on rank ordering alone. Moreover, there was no evidence from the Δ that apremilast has superior efficacy compared with methotrexate or cyclosporine. The mean ± standard deviation probability of achieving PASI 75 with apremilast was [redacted], while it was [redacted] with methotrexate, [redacted] with cyclosporine, and [redacted] with infliximab. There is uncertainty with respect to the conclusions from the NMA, because no statistical indirect treatment comparison estimates were provided by the manufacturer. The NMA did not include safety outcomes.

The initial recommendation came at the April CDEC meeting, and there was a request for reconsideration that was considered at the July 2015 CDEC meeting.[11]

2.1 Basis of Resubmission

The resubmission is based on new clinical information. Study PSOR-010 (LIBERATE) is a double-blind RCT that included both a placebo and an active comparator, specifically in patients with moderate-to-severe psoriasis having had an inadequate response, intolerance, or contraindication to prior conventional systemic therapies. LIBERATE was ongoing at the time of the initial apremilast submission and, therefore, was not included in the initial CDR review. The reimbursement request in the resubmission is for the [redacted]. The only modification from the original criteria is that the original criteria specified "**adult** patients," while this new reimbursement criteria do not; however, apremilast is indicated only for adults, so this minor change in wording is unlikely to have any relevance.

LIBERATE was submitted to address the issue of lack of direct comparison with an active drug, and to target a population more directly related to the reimbursement request, as patients in LIBERATE were to have had an inadequate response, intolerance or contraindication to conventional systemic therapy. Additionally, LIBERATE was submitted because it included a group with an active drug (etanercept); however, the study was not designed to compare apremilast with placebo; therefore, there remains no direct comparison of apremilast to an active comparator.

3. OBJECTIVES AND METHODS

3.1 Objectives

To perform a systematic review of the beneficial and harmful effects of apremilast for the treatment of moderate-to-severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy.

3.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies provided in the manufacturer's submission to CDR, as well as those meeting the selection criteria presented in Table 4.

Compared with the original protocol, the subgroup "psoriatic arthritis" was removed, as this was considered to be a separate indication rather than a subgroup, and two new comparators were added (secukinumab, ixekizumab), which had not been approved at the time of the original CDR review.

Any studies included in the previous CDR review were excluded from the current review.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	– Adult patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy – Subgroups: patients who have an inadequate response to, are intolerant of, or have contraindications to, systemic therapy
Intervention	Apremilast 30 mg twice daily alone, or in combination with other drug or non-drug therapies for moderate-to-severe plaque psoriasis
Comparators	As monotherapy or in combination: **systemic:** – methotrexate – cyclosporine – acitretin – etanercept – infliximab – adalimumab – ustekinumab – secukinumab – ixekizumab **topical*:*** – tazarotene – vitamin D analogues (e.g., calcitriol, calcipotriol) – topical corticosteroids
Outcomes	**Key efficacy outcomes:** – health-related quality of life (DLQI, EQ-5D)[a] – Psoriasis Area Severity Index[a] – physician global assessments (e.g., scalp, palmoplantar)[a] – proportion of body surface area involved[a] **Other efficacy outcomes:** – other symptoms (e.g., pruritus, nail) [a] **Harms outcomes:** – AEs

	– SAEs – WDAEs – notable harms (neuropsychiatric effects, weight loss, gastrointestinal)
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Outcome was identified as important to patients (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–) through 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).

No filters were applied to limit the 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. This report makes use of a literature search conducted in December 2014 for the original apremilast CDR review. For the current report, database searches were rerun on March 24, 2016 to capture any articles published since the initial search date. See **Error! eference source not found.** for the detailed search strategies.

Regular alerts were established to update the search until the CDEC meeting on July 20, 2016. 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 (www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases (free), and 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. The grey literature search was also updated to include documents made available since December 2014.

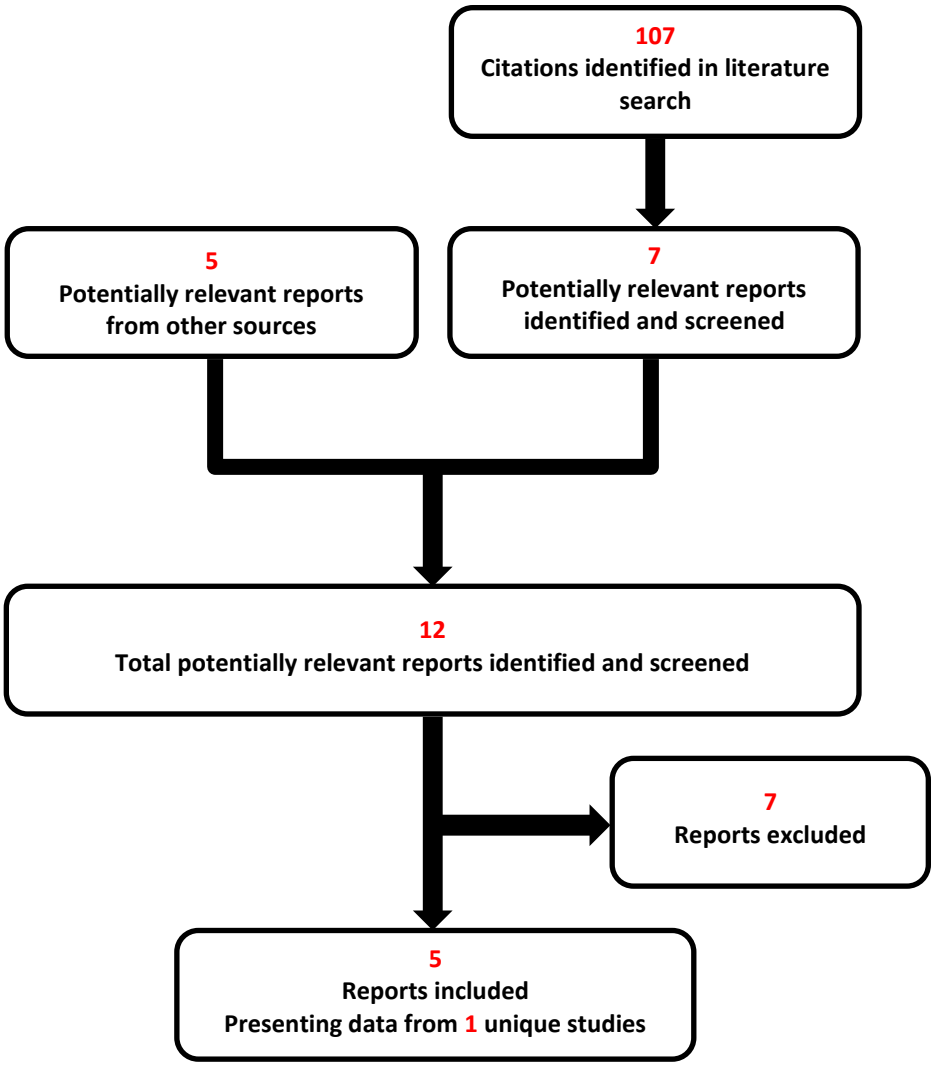
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final 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 **Error! Reference source not found.**.

4. RESULTS

4.1 Findings from the Literature

One study was 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 **Error! Reference source not found.**.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



QUOROM = Quality of Reporting of Meta-analyses.

TABLE 5: STUDY DESIGN

		LIBERATE
DESIGNS & POPULATIONS	**Study Design**	Double-blind randomized controlled trial
	Locations	65 sites
	Randomized (N)	N = 250

	Inclusion Criteria	– Males or females ≥ 18 years of age
		– Diagnosis of chronic plaque psoriasis for at least 12 months prior to screening
		– Moderate-to-severe plaque psoriasis at screening and baseline as defined by:
		  – PASI score ≥ 12 and
		  – BSA ≥ 10% and
		  – sPGA ≥ 3 (moderate)
		– Candidates for phototherapy and/or systemic (including etanercept) therapy
		– In good health (except for psoriasis) as judged by the investigator, based on medical history, physical examination, 12-lead electrocardiogram, clinical laboratories, and urinalysis
		– Had an inadequate response, intolerance, or contraindication to at least one conventional systemic agent for the treatment of psoriasis
		– Had no prior exposure to biologics for treatment of psoriatic arthritis or psoriasis
		– Had none of the following:
		  – No history of latent or active TB prior to screening visit
		  – No signs or symptoms suggestive of active TB in medical history or upon physical examination
		  – No recent close contact with anyone who had active TB

	Exclusion Criteria	– Had failed more than three systemic drugs for the treatment of psoriasis – Psoriasis flare or rebound within four weeks prior to screening
DRUGS	**Intervention**	– Apremilast 30 mg orally twice daily – Etanercept 50 mg subcutaneous once weekly
	Comparator(s)	Placebo
DURATION	**Phase**	
	Screening	Up to 35 days
	Double-blind	16 weeks
	Extension	Weeks 16 to 104
	Follow-up	4 weeks
OUTCOMES	**Primary End Point**	Proportion of participants with either apremilast or placebo who achieved at least PASI 75 at week 16 from baseline
	Other End Points	The first secondary efficacy end point was the proportion of participants treated with either etanercept or placebo who achieved PASI 75 at week 16. Other secondary efficacy end points in this study were all for comparison of apremilast versus placebo, and etanercept versus placebo, and were as follows: – proportion of participants with an sPGA score of clear (0) or almost clear (1), with at least a 2-point reduction at week 16 – percentage change from baseline in the affected body surface area (BSA, %) at week 16 – proportion of participants who achieved PASI 50 at week 16 – change from baseline in DLQI total score at week 16 – change from baseline in mental component summary score of SF-36 v2 at week 16 – proportion of participants with an LS-PGA score of clear (0) or almost clear (1) at week 16

		LIBERATE
NOTES	**Publications**	None

BSA = body surface area; DLQI = Dermatology Life Quality Index; LS-PGA = Lattice System Physician Global Assessment; MCS = mental component summary; PASI = Psoriasis Area and Severity Index; sPGA = Static Physician Global Assessment; TB = tuberculosis.
Note: 5 additional reports were included: Clinical Study Report for LIBERATE;[5] CADTH Common Drug Review request for additional information,[12] manufacturer's submission,[13] and US Food and Drug Administration clinical and statistical reviews.[14,15]
Source: Clinical Study Report for LIBERATE.[5]

4.2 Included Studies

4.2.1 Description of Studies

One study was included in this resubmission. LIBERATE was a multi-centre, multinational, manufacturer-sponsored double-blind RCT that compared apremilast to placebo and etanercept to placebo, over a 16-week double-blind treatment phase. Randomization of 250 patients was carried out in a 1:1:1 ratio, and was stratified by body mass index (BMI) (≥ 30 kg or < 30 kg/m^2). The primary objective of the study was to compare apremilast to placebo while the secondary objective was to compare etanercept to placebo. No comparisons were planned that directly compared apremilast with etanercept. LIBERATE had additional extension phases, described subsequently.

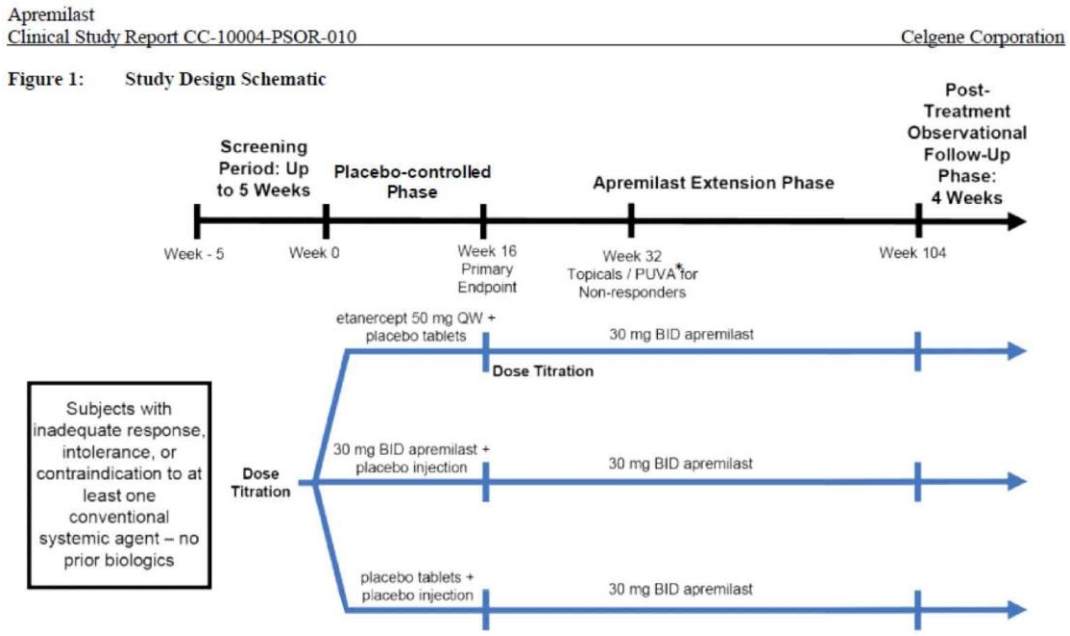
a) Apremilast Extension Phase (Weeks 16 to 104)

All participants were to be switched to, or were to continue with, apremilast at week 16. Participants originally randomized to placebo or etanercept at week 0 were to be switched to apremilast at week 16. Dose titration blister cards were to be used for participants switching from etanercept to apremilast; dummy titration blister cards were to be used for participants in the other two dosing groups. Dose titration blister cards were to be given at week 16. Beginning with the week 17 visit, all participants were to receive bottles of study drug tablets. All participants were to maintain this dosing through week 104.

Blinding of dose titration or no dose titration was to be maintained as both etanercept or apremilast have PASI 75 responses of approximately 40%, and PASI 50 responses of approximately [redacted]. Therefore, nearly half the participants would have had an inadequate response. Hence, non-response would not enable one to identify the treatment assignment (etanercept, apremilast, or placebo) made at week 0.

At week 32, for participants deemed non-responders — i.e., PASI improvement of less than 50% compared with the baseline visit (< PASI 50) — the investigator had the option of adding topical therapy and/or ultraviolet B therapy to their treatment regimens.

FIGURE 2: DESIGN OF LIBERATE



BID = twice daily; QW = once weekly.

Source: Clinical Study Report for LIBERATE.[5]

4.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients had moderate-to-severe plaque psoriasis at screening based on PASI, body surface area (BSA), and Static Physician Global Assessment (sPGA). Patients were candidates for systemic or phototherapy; however, they were to have had an inadequate response, intolerance, or contraindication to at least one conventional systemic drug for the treatment of psoriasis. They also were to have had no prior exposure to biologics for treatment of psoriatic arthritis or psoriasis (Table 5).

b) Baseline Characteristics

The average age of patients in LIBERATE was around 45 years, and the majority of patients (approximately 63%) were male, and the vast majority ([redacted]) were Caucasian. The average PASI score was nearly 20, and the majority of patients (approximately [redacted]) had a PASI score of 20 or less. Most patients ([redacted]) had never used phototherapy, but only a small number ([redacted]) had never used conventional systemic therapies (Table 6).

There were some numerical differences between groups with respect to baseline characteristics. There was a larger proportion of males in the placebo group (70%) compared with the other two groups (59% in each). The proportion of patients with PASI scores of 20 or less was numerically higher with apremilast ([redacted]) than with etanercept ([redacted]). A numerically larger proportion of etanercept patients had never used phototherapy ([redacted]) compared with apremilast ([redacted]), and a numerically larger proportion of etanercept patients had never used conventional systemic therapies ([redacted]) compared with apremilast ([redacted]) or placebo ([redacted]).

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS

	LIBERATE		
	Apremilast N = 83	Placebo N = 84	Etanercept N = 83
Mean (SD) age, years	46.0 (13.6)	43.4 (14.9)	47.0 ((14.1)
Male gender, n (%)	49 (59)	59 (70)	49 (59)
Race			
Caucasian	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Black/African American	[redacted]	[redacted]	[redacted]
Native American/Pacific Islander	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Weight, mean (SD) kg	88.5 (19.6)	89.5 (22.8)	88.1 (20.4)
Mean (SD) BMI, kg/m^2	29.2 (5.8)	29.5 (6.6)	29.9 (6.4)
BMI < 30	[redacted]	[redacted]	[redacted]
Duration of plaque psoriasis, mean (SD) years	19.7 (12.7)	16.6 (12.1)	18.1 (11.7)
History of guttate-erythrodermic psoriasis or sudden intensification in psoriasis, n (%)	12 (14.5)	8 (9.5)	10 (12.0)
Psoriatic arthritis history			
Asymmetric oligoarthritis	[redacted]	[redacted]	[redacted]
Symmetric polyarthritis	[redacted]	[redacted]	[redacted]
Predominant DIP joint involvement	[redacted]	[redacted]	[redacted]
Predominant spondylitis	[redacted]	[redacted]	[redacted]
Arthritis mutilans	[redacted]	[redacted]	[redacted]
Total PASI score			
Mean ([redacted])	19.3 ([redacted])	19.4 ([redacted])	20.3 ([redacted])
Patients ≤ 20%, n (%)	[redacted]	[redacted]	[redacted]
Patients > 20%, n (%)	28 (34)	32 (38)	34 (41)
BSA involvement			
Mean ([redacted]) %	27.1 ([redacted])	27.3 ([redacted])	28.4 ([redacted])
Patients ≤ 20%, n (%)	[redacted]	[redacted]	[redacted]
Patients > 20%, n (%)	45 (54)	42 (50)	47 (57)
Prior phototherapies, n (%)			
Used	[redacted]	[redacted]	[redacted]
Never used	[redacted]	[redacted]	[redacted]
Number of prior conventional systemic therapies, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
≥ 3	[redacted]	[redacted]	[redacted]
Reasons patient was not treated with conventional therapies, n (%)			
Clinical contraindication	[redacted]	[redacted]	[redacted]
Patient drinks alcohol	[redacted]	[redacted]	[redacted]
Compliance concerns	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

BMI = body mass index; BSA = body surface area; DIP = distal inter-phalangeal; PASI = Psoriasis Area and Severity Index; SD = standard deviation.
Source: Clinical Study Report for LIBERATE.[5]

4.2.3 Interventions

LIBERATE employed a double-dummy design to maintain blinding. During the 16-week double-blind phase, patients in the apremilast group received oral apremilast 30 mg twice daily, as well as a once-weekly placebo subcutaneous injection of saline, while patients in the etanercept group received oral placebo twice daily, as well as a once-weekly subcutaneous injection of etanercept 50 mg. Patients in the placebo group received oral placebo twice daily and subcutaneous saline once weekly.

The manufacturer selected a once-weekly dosing regimen for etanercept (50 mg once weekly) rather than the twice-weekly regimen recommended in the product monograph[8] for initiation (first three months of therapy) in patients with chronic plaque psoriasis (the maintenance dose may either be once or twice weekly). The reason given for using a once-weekly regimen was to improve adherence to therapy, and the manufacturer cited a number of papers that demonstrate the efficacy of a once-weekly regimen in patients with moderate-to-severe plaque psoriasis.

All participants were to be switched to, or were to continue with, apremilast at week 16. Participants originally randomized to placebo or etanercept at week 0 were to be switched to apremilast at week 16. At week 32, for participants deemed non-responders, i.e., PASI improvement of less than 50% compared with the baseline visit (< PASI 50), the investigator had the option of adding topical therapy and/or ultraviolet B therapy to their treatment regimens.

4.2.4 Outcomes

The PASI was determined for all patients throughout the study.

The PASI is a measure of psoriatic disease severity, taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface–area involvement on defined anatomical regions. The PASI scores range from 0 to 72, with higher scores indicating greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on four anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the four anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score. The MCID for the PASI is unknown (0). A PASI 75 represents a 75% reduction in PASI scores; a PASI 50 is a 50% reduction, and so on.

The sPGA is an assessment by the investigator of the overall disease severity at the time of evaluation. The sPGA is a 5-point scale ranging from 0 (clear) to 4 (severe); the total score represents a summary assessment of the severity of the three primary signs of the disease: erythema, scaling, and plaque elevation. When making the assessment of overall severity, the investigator was instructed to factor in areas that had already been cleared (i.e., had scores of 0) and to not just to evaluate remaining lesions for severity (i.e., the severity of each sign was to be averaged across all areas of involvement, including cleared lesions). In the event of different severities across disease signs, the sign that is the predominant feature of the disease was to be used to help determine the sPGA score. In addition to the aforementioned description provided in the protocol, investigators were provided with guidance on the sPGA evaluation, which stipulated that, if the outline of the original lesions could not be discerned, it was appropriate to conduct the evaluation in the context of the patient population, i.e., moderate-to-severe psoriasis with at least 10% BSA affected. The MCID for the Physician Global Assessment (PGA) is unknown (0).

Affected BSA is a measurement of involved skin. The overall BSA affected by psoriasis is estimated based on the palm area of the participant's hand (entire palmar surface or "handprint"), which equates to approximately 1% of total BSA. The MCID for affected BSA is unknown (0).

The nail assessment/Nail Psoriasis Severity Index assessed one target thumbnail or fingernail representing the worst nail psoriasis involvement at baseline for nail matrix psoriasis and nail bed psoriasis. For nail matrix, each quadrant of the nail is evaluated for any of the features of interest (pitting, leukonychia, red spots in the lunula, and crumbling), and scores are recorded based on the number of quadrants with any of these features (i.e., if all four quadrants have these features, the score would be 4). A similar protocol is followed for nail bed features (onycholysis, splinter hemorrhages, subungual hyperkeratosis, salmon patch dyschromia)—again, with scores from 0 to 4.[16] The sum of these two scores, nail matrix and nail bed, is the total score for that nail (therefore, a range from 0 to 8). Thus, higher scores indicate greater nail psoriasis severity. The number of fingers with psoriasis nail involvement was also counted. No MCID was found for this instrument.

A Scalp Physician Global Assessment (ScPGA) was used to assess scalp involvement if present at baseline. The 6-point ScPGA scale ranges from 0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe), to 5 (very severe). No MCID was found for this instrument.

The Palmoplantar Physician Global Assessment (PPPGA) was used to assess palms of hands and soles of feet for psoriasis involvement if present at baseline. The 5-point PPPGA scale ranges from 0 (clear), 1 (minimal), 2 (mild), 3 (moderate), to 4 (severe). No MCID was found for this instrument.

The DLQI was to be assessed by the participant upon arrival at the site, before any other procedures or assessments were performed. The DLQI contains 10 items. The DLQI total score has a possible range of 0 to 30, with 30 corresponding to the worst quality of life, and 0 corresponding to the best score. The DLQI can be grouped into six subscales: symptoms and feelings, daily activities, leisure, work/school, personal relationships, and treatment. Scores for four of the subscales (symptoms and feelings, daily activities, leisure, and personal relationships) range from 0 to 6; scores for two of the subscales (work/school and treatment) range from 0 to 3. Higher scores indicate poorer quality of life. The MCID is considered to be 3.2 for the DLQI total score (0).

The Short Form (36) Health Survey (SF-36) is a general health status instrument that has been used extensively in clinical trials in many disease areas.[17] The SF-36 consists of eight health domains: physical functioning), role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[18] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries: the physical component summary (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 MCID for either the PCS or MCS of the SF-36 is typically between 2.5 and 5 points,[19-21] with the developer of the SF-36 suggesting a threshold of 3 points for the MCID, with a corresponding standard deviation of 0.3.[22]

For pruritus, the participant was asked to assess itch in the previous week by placing a vertical stroke on a 100-mm visual analogue scale on which the left-hand boundary represented no itch at all, and the right-hand boundary represented itch as worst itch imaginable. The distance from the mark to the left-hand boundary was to be recorded. No MCID was found for this instrument.

4.2.5 Statistical Analysis

Approximately 240 participants were to be randomized in a 1:1:1 ratio to the three treatment groups up to week 16. Sample size estimation for the primary end point was based on the results of the phase 2b study, CC-10004-PSOR-005. A chi-square test with a 0.05 two-sided significance level provided 90% power to detect a 20 percentage point difference (30% versus 10%) between apremilast and placebo for the proportion of participants achieving at least a PASI 75 at week 16 when the sample size is approximately 82 participants per treatment group (i.e., with a total sample size of about 240 participants).

The primary efficacy end point was analyzed using the Cochran–Mantel–Haenszel test controlling for the BMI categories at baseline (BMI ≥ 30 or BMI < 30) at the two-sided 0.05 significance level. The two-sided 95% CI for the treatment difference of the PASI 75 response rates (apremilast – placebo) based on the normal approximation was also provided.

For the analyses of the week 16 end points, missing values were imputed using the last observation carried forward (LOCF) method. These included the primary efficacy end point, the first secondary efficacy end point, other secondary efficacy end points, and exploratory efficacy end points. In addition, for the primary and secondary end points, PASI 75 response and PASI 50 response, supportive analyses were performed: treating missing values as non-responders (non-responder imputation), and treating dropouts due to adverse event or lack of efficacy as non-responders and other dropouts using LOCF.

Statistical comparisons were to be conducted in a hierarchal order to maintain the overall two-sided 0.05 significance level. Statistical significance for the secondary end points was to be claimed conditional on the statistically significant results observed for the primary end point, and all the other secondary efficacy end points preceding it in the hierarchal order. Specifically, the proportion of participants treated with either etanercept 50 mg weekly or placebo who achieved at least a PASI 75 at week 16 from baseline was to be analyzed similar to the primary end point using the Cochran–Mantel–Haenszel test at the two-sided 0.05 significance level; statistical significance was to be claimed conditional on the statistically significant result achieved for the primary end point. The remaining secondary end points were to be tested sequentially in the order specified in the secondary end point section; that is, an sPGA score of clear (0) or almost clear (1) and at least a two-point reduction from baseline, BSA (%) per cent change from baseline, PASI 50 proportion, DLQI total score change from baseline, SF-36v2 MCS score change from baseline, and a LS-PGA score of clear (0) or almost clear (1), for the week 16 assessments. The comparison between apremilast versus placebo for all these endpoints was to be evaluated first. Subsequently, the comparison between etanercept 50 mg weekly versus placebo was to be tested in the same hierarchal order as above. No statistical comparisons were planned between the two active treatment groups.

Subgroup analyses for comparisons of the proportion of participants between active treatments and placebo who achieved PASI 75 at week 16 based upon baseline demographics (age, sex, race), baseline disease characteristics, and region were to be provided to determine the robustness of the treatment effect. Subgroup analyses were also to be carried out for PASI 50 response at week 16, sPGA response at week 16, and LS-PGA response (defined as clear or almost clear) at week 16 during the placebo-controlled phase.

a) Analysis Populations

Modified Intention-To-Treat Population

The modified intention-to-treat (mITT) population was the primary population for efficacy analyses. The mITT population was to consist of all participants who were randomized and received at least one dose of the study drug and had both baseline PASI and at least one post-treatment PASI evaluation. Participants were to be included in the treatment group to which they were randomized.

Per-Protocol Population

The per-protocol population was to consist of all participants included in the mITT population and who had had no protocol violations that may have substantially affected the results of the PASI evaluation during the placebo-controlled phase (weeks 0 to 16).

Safety Population

Placebo-Controlled Phase

The safety analyses for the placebo-controlled phase were based on the safety population, which included all participants who were randomized and received at least one dose of the study drug. Participants were to be included in the treatment group corresponding to the study drug they actually received.

4.3 Patient Disposition

There were numerical differences in the proportion of patients who discontinued the core study: [redacted]on etanercept, [redacted]on apremilast, and 11% on placebo discontinued (Table 7). The most common reason for withdrawal from placebo was lack of efficacy ([redacted]), and the most common reason for withdrawal from apremilast was withdrawal by the patient ([redacted]). With etanercept, there was no reason for withdrawal that occurred in more than 1% of patients.

TABLE 7: PATIENT DISPOSITION

	LIBERATE		
	Apremilast	Placebo	Etanercept
Screened, N	350		
Randomized, N (%)	83 (100)	84 (100)	83 (100)
Randomized and treated, N (%)	83 (100)	84 (100)	83 (100)
Discontinued, N (%)	6 (7)	9 (11)	2 (2)
Adverse event	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]
Non-compliance with study drug	[redacted]	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Completed and entered extension phase	[redacted]	[redacted]	[redacted]
Completed but did not enter extension phase	[redacted]	[redacted]	[redacted]
Primary reason for not entering extension phase			
Adverse event	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]
Non-compliance with study drug	[redacted]	[redacted]	[redacted]

	LIBERATE		
	Apremilast	Placebo	Etanercept
Withdrawal by patient	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Study terminated by sponsor	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
mITT, N	[redacted]	[redacted]	[redacted]
Per-protocol, N	[redacted]	[redacted]	[redacted]
Safety, N	[redacted]	[redacted]	[redacted]

mITT = modified intention-to-treat.
Source: Clinical Study Report for LIBERATE.[5]

4.4 Exposure to Study Treatments

Exposure to study drug varied from a low of [redacted] to a high of [redacted]. Apremilast patients were exposed to treatment for [redacted].

4.5 Critical Appraisal

4.5.1 Internal Validity

The manufacturer accounted for multiplicity in the 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 only continued on subsequent outcomes for as long as testing reveals statistical significance on the previous outcome. However, in LIBERATE the manufacturer continued to conduct and report the results of statistical testing after failure to achieve statistical significance on the [redacted], describing those subsequent outcomes as achieving "nominal" statistical significance. The results of these statistical tests, which are in violation of their own statistical protocol, are not reported in this CDR review. Additionally the hierarchy was designed in such a way that, aside from PASI 75 responders, all other key secondary outcomes had to be tested first with apremilast versus placebo before testing comparisons for etanercept versus placebo. Due to the failure of apremilast to achieve statistical significance versus placebo on the second-to-last secondary outcome ([redacted]), this resulted in no formal comparisons being done between etanercept and placebo after PASI 75 responses, and this represents a significant gap in evidence that limits the conclusions that can be drawn from this study.

Although the withdrawal rates were not high in any of the groups, there were numerical differences in withdrawals between groups, with the lowest rate being [redacted] and the highest [redacted]. In the primary analysis, missing values were imputed using LOCF, and were supported by sensitivity analyses for outcomes like PASI 75 and PASI 50 that treated missing values as non-responders, or treated missing patients who withdrew due to adverse event or lack of efficacy as non-responders. This latter method is likely more appropriate, as at least in the case of "lack of efficacy," it reflects the actual reason a given patient withdrew from the study. Results for either sensitivity analysis did not differ markedly from the primary analysis for the primary end point of PASI 75 responders.

There were some numerical differences between groups with respect to baseline characteristics, including PASI scores (the proportion of patients with PASI scores of 20 or less was numerically higher

with apremilast than with etanercept). Randomization was stratified by BMI alone, and it is not clear why this was chosen as a stratification factor instead of PASI scores, for example. These differences in PASI scores might have biased results either in favour of apremilast (if apremilast patients had more extensive disease, they may have been more responsive to therapy) or against apremilast (if having more extensive disease meant apremilast patients were harder to treat).

Findings from the subgroup analyses had limited power to detect differences between groups, as the overall sample in LIBERATE was relatively small.

4.5.2 External Validity

The placebo-controlled phase of the included study was only 16 weeks in duration. Given that apremilast employs a novel mechanism of action, this might not be sufficient follow-up to assess efficacy and, more notably, safety. For example, the TNF inhibitors have, throughout their history, been associated with elevated risk of certain cancers. Because risk of cancer can only be determined over the course of several years of follow-up, the association between TNF inhibitors and cancer took many years to be elucidated and, to this day, remains unclear for certain cancers. Therefore, while a 16-week follow-up may be sufficient to determine certain safety issues, it is not likely long enough for others. Psoriasis is a chronic condition, and patients may be treated with a single therapy for many years.

The primary outcome of both included studies was the proportion of patients achieving a PASI 75. This appears consistent with the other studies in chronic plaque psoriasis and is considered a clinically meaningful trial outcome, according to the clinical expert consulted by CDR. Some of the limitations of PASI as an assessment include the fact that it often does not correlate well with quality of life. In the included studies for this and the original review, this does not appear to have been an issue, at least for the DLQI, as statistically significant improvements were seen across PASI and DLQI.

There is a lack of direct, head-to-head comparisons of apremilast versus another active control, such as methotrexate or one of the biologics. Although LIBERATE included both an apremilast and an etanercept treatment group, the study was not designed to directly compare the two groups; rather, each was compared with placebo. Therefore, only indirect treatment comparisons can be made between apremilast and etanercept in this study, and these comparisons have significant limitations that introduce bias into the analysis and reduce confidence in any conclusions that are drawn. In addition, due to a relatively early failure in the statistical hierarchy when comparisons of secondary outcomes were being performed for apremilast versus placebo, most of the comparisons of etanercept with placebo should not have even been tested, as described under internal validity; therefore, this further limits any conclusions that can be drawn regarding even the efficacy of etanercept versus placebo.

In LIBERATE, patients received a once-weekly regimen of etanercept rather than the twice weekly one recommended in the product monograph[8] for this indication. Although the manufacturer cites adherence as the reason, and cites a number of papers that suggest a once-weekly regimen is efficacious for this population, this is a generalizability issue. The manufacturer did not indicate whether a once-weekly regimen has been demonstrated to be as efficacious as a twice-weekly regimen and, given that twice weekly is the recommended regimen, the manufacturer would be expected to provide clear evidence that this is the case.

4.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 3). See **Error! Reference source not found.** for detailed efficacy data.

4.6.1 Psoriasis Area and Severity Index

The proportion of patients achieving PASI 75 by week 16, between apremilast and placebo, was the primary outcome. A higher proportion of patients treated with apremilast achieved PASI 75 versus placebo (40% versus 12% of patients, respectively) and this difference was statistically significant (difference in proportions between groups [95% CI] of 27.5 [14.9 to 40.1]; $P < 0.0001$) (Table 8). There was also a higher proportion of patients treated with etanercept who achieved PASI 75 compared with placebo (48% versus 12%), and this difference was statistically significant (difference in proportions between groups [95% CI] of [redacted].

The proportion of patients achieving PASI 50 was reported as a secondary outcome and the proportion of patients achieving PASI 90 was reported as an exploratory outcome. There were more apremilast-treated patients who achieved PASI 50 after 16 weeks when compared with placebo ([redacted] versus [redacted]), and this difference between groups was statistically significant (difference in proportions between groups [95% CI] of [redacted]. A higher proportion of etanercept-treated patients achieved PASI 50 after 16 weeks versus placebo ([redacted] versus [redacted]); however, due to an earlier failure in the statistical hierarchy, this comparison of this outcome should not have been tested. There were more apremilast-treated versus placebo-treated patients who achieved PASI 90 (Table 10) after 16 weeks ([redacted] versus [redacted]), and this difference was statistically significant (difference in proportions between groups [95% CI] of [redacted], although this was an exploratory outcome and not adjusted for multiple comparisons. A higher proportion of etanercept-treated than placebo-treated patients achieved PASI 90 ([redacted] versus [redacted]), and this difference was also statistically significant (difference in proportions between groups [95% CI] of [redacted] although, again, not adjusted for multiple comparisons.

a) Subgroups

No interaction *P* values were reported in the subgroup analyses, and no *P* values were provided for comparisons within subgroups. Responses in both apremilast and etanercept groups were numerically lower in patients without prior phototherapy, or those who had failed one conventional systemic therapy (Table 11).

4.6.2 Quality of Life

The reduction (improvement) from baseline in DLQI total score after 16 weeks was reported as a secondary outcome, and there was an improvement in DLQI total score for apremilast versus placebo (least squares mean [LSM] [95% CI] change of [redacted] versus [redacted], respectively) and this difference between groups was statistically significant (difference in LSM [95% CI] between groups of [redacted] (Table 8). Given the MCID for the DLQI of 3.2, these differences versus placebo would also be considered clinically significant. There was also an improvement from baseline for etanercept versus placebo (LSM [95% CI] change of [redacted] versus [redacted], respectively); however, due to an earlier failure in the statistical hierarchy, this comparison of this outcome should not have been tested. This difference versus placebo would be considered clinically significant, based on the MCID.

The change from baseline in SF-36 (MCS) was reported as a secondary outcome, and the change from baseline in SF-36 (MCS) for apremilast versus placebo (LSM change from baseline [95% CI] of [redacted]) was not statistically significant between the two groups (difference in LSM [95% CI] between groups of [redacted] (Table 8). This failure to achieve statistical significance at this point in the hierarchy is where subsequent statistical testing should have ceased.

4.6.3 Physician Global Assessment

There was a higher proportion of apremilast versus placebo patients achieving an sPGA response at week 16 (22% versus 4%, respectively), and this difference was statistically significant (difference in proportions between groups [95% CI] of [redacted] (Table 8). There was a higher proportion of patients treated with etanercept that achieved an sPGA response at week 16 (29% versus 4%); however, due to an earlier failure in the statistical hierarchy, this comparison of this outcome should not have been tested.

4.6.4 Affected Body Surface Area

The proportion of affected BSA was reduced with apremilast versus placebo, and this difference (LSM reduction of [redacted] versus [redacted]) was statistically significant (difference in LSM [95% CI] between groups of [redacted]) (Table 8). The proportion of affected BSA was also reduced with etanercept versus placebo (LSM reduction from baseline of [redacted] versus [redacted]); however, due to an earlier failure in the statistical hierarchy, this comparison of this outcome should not have been tested.

4.6.5 Other Efficacy Outcomes

Other efficacy outcomes of interest included additional measures of symptoms, including the Pruritus Visual Analogue Scale, Nail Psoriasis Severity Index score, scalp PGA, and palmoplantar PGA, all of which were exploratory outcomes in LIBERATE and, therefore, statistical analysis was not adjusted for multiple comparisons (Table 10). The improvement from baseline to 16 weeks in [redacted] was statistically significant for apremilast compared with placebo, and for etanercept compared with placebo. [redacted], both the proportion of patients achieving response and the change from baseline after 16 weeks were statistically significantly improved with etanercept versus placebo, but not with apremilast versus placebo. There were statistically significant improvements in [redacted] for both apremilast and etanercept versus placebo, but for [redacted], there were no statistically significant improvements for either apremilast or etanercept versus placebo.

TABLE 8: KEY EFFICACY OUTCOMES

	LIBERATE		
	Apremilast N = 83	Placebo N = 84	Etanercept N = 83
PASI 75			
Patients at week 16, N (%)-LOCF	33 (39.8)	10 (11.9)	40 (48.2)
Difference in proportions versus placebo (95% CI)	27.5 (14.9 to 40.1)		[redacted]
CMH *P* value[a]	*P* < 0.0001		[redacted]
Patients at week 16, N (%) NRI	[redacted]	[redacted]	[redacted]
Patients at week 16, N (%) NRI/LOCF	[redacted]	[redacted]	[redacted]
sPGA			
sPGA response, week 16, N (%)	[redacted]	[redacted]	[redacted]
Difference in proportions versus placebo (95% CI)[a]	[redacted]		[redacted]
CMH *P* value[a]	[redacted]		[redacted]
Affected BSA			
Mean (SD) at baseline	[redacted]	[redacted]	[redacted]
Mean (SD) % change at week 16	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Difference in LS means versus placebo (2-sided	[redacted]		[redacted]

	LIBERATE		
	Apremilast N = 83	Placebo N = 84	Etanercept N = 83
95% CI)[c]			
CMH *P* value[a]	[redacted]		[redacted]
DLQI total score			
Mean (SD) at baseline	[redacted]	[redacted]	[redacted]
Mean (SD) change at week 16	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
Difference in LS means versus placebo (2-sided 95% CI)	[redacted]		[redacted]
P value	[redacted]		[redacted]
SF-36 MCS			
Mean (SD) at baseline	[redacted]	[redacted]	[redacted]
Mean (SD) change at week 16	[redacted]	[redacted]	[redacted]
LS mean change from baseline (95% CI)	[redacted]	[redacted]	[redacted]
Difference in LS means versus placebo (2-sided 95% CI)	[redacted]		[redacted]
2-sided *P* value	[redacted]		[redacted]

ANCOVA = analysis of covariance; BSA = psoriasis-affected body surface area; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; DLQI = Dermatology Life Quality Index; LOCF = last observation carried forward; LS = least squares; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index; SD = standard deviation; SF-36 MCS = Short Form (36) Health Survey mental component summary; sPGA = Static Physician Global Assessment; SD = standard deviation.

[a] The two-sided *P* value is from a CMH test stratified by the BMI at screening. The CI is weighted using CMH weights according to the number of participants in the two strata.

[b] Based on an ANCOVA model for the change from baseline at week 16. The LS means and *P* values are presented from the ANCOVA adjusted for covariates.

[c] Outcome in statistical hierarchy that was tested after a previous outcome had failed to achieve statistical significance and, therefore, should not have been tested.

Source: Clinical Study Report for LIBERATE.[5]

4.7 Harms

Only those harms identified in the review protocol are reported subsequently (see section 3.2).

4.7.1 Adverse Events

The proportion of patients experiencing an adverse event was numerically higher with apremilast (70%) compared with either placebo (60%) or etanercept (53%) (Table 9). The most common adverse events with apremilast were headache (13% with apremilast versus 6% in each of the placebo and etanercept groups), nausea (11% with apremilast, 2% with placebo, 5% with etanercept) and diarrhea (11% with apremilast, 8% with placebo, 1% with etanercept).

4.7.2 Serious Adverse Events

Serious adverse events after 16 weeks were reported in 4% of patients treated with apremilast, 1% of etanercept patients, and none of the patients treated with placebo (Table 9). Regarding specific serious adverse events, there were no specific serious adverse events that occurred in more than one patient.

4.7.3 Withdrawal Due to Adverse Events

The proportion of patients who withdrew due to an adverse event by 16 weeks was 4% with apremilast, and 2% in each of the placebo and etanercept groups (Table 9). Regarding specific adverse events that lead to withdrawal, there were no adverse events that occurred in more than one patient.

4.7.4 Mortality

There were no deaths in the study.

4.7.5 Notable Harms

Weight loss was identified as a notable harm for this review, and the manufacturer reported changes in body weight as part of its safety analysis. The proportion of patients with a loss of more than 5% to 10% of body weight after 16 weeks was numerically higher with apremilast ([redacted]) than with placebo ([redacted]) or etanercept ([redacted]) (Table 9). Far fewer patients were reported as having "weight decreased" as an adverse event, [redacted] of patients in the apremilast and placebo groups, and [redacted] in the etanercept group.

TABLE 9: HARMS

	LIBERATE		
	Apremilast N = 83	Placebo N = 84	Etanercept N = 83
AEs			
Patients with > 0 AEs, N (%)	58 (70)	50 (60)	44 (53)
Most common (≥ 5% in any group), n (%)			
Headache	11 (13)	5 (6)	5 (6)
Nausea	9 (11)	2 (2)	4 (5)
Diarrhea	9 (11)	7 (8)	1 (1)
URTI	6 (7)	2 (2)	2 (2)
Tension headache	5 (6)	4 (5)	3 (4)
Nasopharyngitis	4 (5)	8 (10)	8 (10)
SAEs			
Patients with > 0 SAEs, N (%)	3 (4)	0	1 (1)
Most common SAEs			
Most common reasons	None in more than 1 patient		
WDAEs			
WDAEs, N (%)	3 (4)	2 (2)	2 (2)
Most common reasons	None in more than 1 patient		
Deaths			
Number of deaths, N (%)	0	0	0
Notable harms			
Weight loss > 5% to 10% (not reported as AE)	[redacted]	[redacted]	[redacted]
Weight decreased (reported under AEs)	[redacted]	[redacted]	[redacted]
Treatment duration (weeks) mean (SD)	[redacted]	[redacted]	[redacted]

AE = adverse event; SAE = serious adverse event; SD = standard deviation; URTI - upper respiratory tract infection; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for LIBERATE.[5]

5. DISCUSSION

5.1 Summary of Available Evidence

The original CDR review of apremilast included two pivotal phase 3 double-blind RCTs, ESTEEM-1 (N = 844) and ESTEEM-2 (N = 413), both of which compared apremilast to placebo, randomized in a 2:1 fashion. Both studies had three phases: an initial 16-week double-blind phase where patients were randomized 2:1 to either apremilast or placebo, followed by a 16-week phase where patients on placebo were switched to apremilast (therefore, all patients in the study were on apremilast at this point). Then, at week 32, responders were re-randomized to either continue on apremilast or switch to placebo in order to test durability of response. The ESTEEM studies both included patients with moderate-to-severe plaque psoriasis, but did not require patients to have tried or to have a contraindication to prior systemic therapy. In their proposed reimbursement criteria, the manufacturer had suggested apremilast be funded for patients [redacted]. However, only about one-third of patients had tried prior conventional systemic therapy, thus limiting any conclusions that could be drawn regarding this key component of their reimbursement criteria. Therefore, two key limitations from the original submission were the lack of a head-to-head comparison, and a lack of data in the population in which apremilast is intended to be used.

One double-blind RCT, LIBERATE, was submitted by the manufacturer as the basis for its resubmission to CDR, and no other new double-blind RCTs that met our inclusion criteria were identified after a systematic review of the literature. LIBERATE was a 16-week double-blind RCT with an 88-week open-label extension that compared apremilast and etanercept to placebo. No comparisons of apremilast to etanercept were planned for this study. The study included patients with moderate-to-severe plaque psoriasis who had an inadequate response, intolerance, or contraindication to at least one conventional systemic drug for the treatment of psoriasis. All patients appear to have met the criteria of having either tried or having had a contraindication to prior conventional systemic therapy. The primary outcome compared the proportion of apremilast- versus placebo-treated patients with a PASI 75 response at week 16. The first secondary outcome was the proportion of etanercept versus placebo patients achieving PASI 75 at week 16. Other secondary outcomes, tested in a hierarchical fashion, included several comparisons of apremilast versus placebo (proportion of PGA responders, change from baseline in affected BSA, proportion of PASI 50 responders, change from baseline in total DLQI, and SF-36 MCS).

5.2 Interpretation of Results

5.2.1 Efficacy

The resubmission was intended to address evidence gaps identified from the previous CDEC Recommendation, such as a lack of comparative evidence (i.e., direct head-to-head studies and/or well conducted indirect treatment comparisons) versus other available therapies and in the population relevant to the proposed reimbursement criteria (patients with moderate-to-severe psoriasis with an inadequate response or intolerance/contraindication to prior conventional therapies). LIBERATE, however, was not designed to compare apremilast to etanercept and, therefore, this gap remains. Both drugs were statistically significantly superior to placebo for the primary and first secondary outcome of proportion of patients achieving PASI 75. There were numerical differences in the proportion of patients with PASI 75 with etanercept (48% of patients) and apremilast (40%). Due to a failure in the statistical hierarchy, all other efficacy comparisons of etanercept versus placebo should not have been tested, so this provides an additional challenge when trying to indirectly compare efficacy results with apremilast to that of etanercept in LIBERATE. In summary, the LIBERATE study, which is the study that formed the

basis of the manufacturer's resubmission, does not provide direct comparative evidence of apremilast to a biologic, and even the data that could inform an indirect treatment comparison are limited. Additionally, the manufacturer has also not provided a study that directly compares apremilast to a conventional systemic drug. This type of direct comparison might actually be more relevant, considering where the manufacturer appears to be positioning apremilast.

In its executive summary to the submission, the manufacturer notes that it is targeting a population for [redacted]. These would be patients, according to the manufacturer, who [redacted], although it is not clear how exactly the latter group would be defined. Therefore, a comparison to other systemic therapies may be more informative than a comparison to a biologic, as the manufacturer is essentially stating that systemic therapies are the only option in the population for which apremilast is being targeted. Presumably, these patients would normally receive another systemic therapy after an inadequate response to a prior systemic therapy, for example. The clinical expert on this review agrees that in the clinical community, apremilast is viewed as another option among systemic therapies. In the manufacturer-submitted NMA, the focus was on comparisons to biologics, and [redacted] Additionally, etanercept, ustekinumab 45 mg, ustekinumab 90 mg, and ustekinumab 45 mg/90 mg [redacted]. However, it should be noted that there are more gastrointestinal adverse events that occur initially in patients on apremilast and these tend to subside later in treatment. That being said, these gastrointestinal events were not separated out in a separate analysis; therefore, no definitive conclusions can be made.

Patients in LIBERATE were to have moderate-to-severe psoriasis, and to have had an inadequate response or intolerance or contraindication to prior conventional therapies. Apremilast was statistically superior to placebo for the primary outcome of proportion of patients achieving PASI 75, as well as a number of secondary outcomes such as PGA, change from baseline in BSA involvement, and quality of life measured by the DLQI. Apremilast was not statistically superior to placebo when [redacted]; however, according to the clinical expert, the DLQI is of more clinical relevance, as it is a disease-specific instrument. In their input to CDR, patients clearly identified quality of life as an important consideration in their disease. In LIBERATE, most of the patients (between [redacted], depending on group) had failed on at least one conventional or systemic therapy. Although no interaction *P* values were reported in the subgroup analysis, results suggest that responses were numerically lower in both apremilast and etanercept groups in patients who were treatment-experienced versus those who were treatment-naive. The small sample sizes in LIBERATE (less than 100 patients per group) also reduce confidence in any subgroup analyses performed, due to the sample size in each subgroup. There were too few patients who had previously failed two or more therapies to draw any conclusions regarding the efficacy of apremilast in patients who had failed multiple systemic therapies.

5.2.2 Harms

The data from LIBERATE revealed numerically higher proportions of patients treated with apremilast had adverse events compared with etanercept (70% versus 53%). Although LIBERATE was not powered to assess harms and no statistical comparisons were planned, this generates the hypothesis that apremilast may have a higher risk of adverse effects compared with a biologic. The nature of the adverse events has not changed since the original CDR review of apremilast, as the most common issues seem to be gastrointestinal (nausea) and headache. Weight loss was once again a notable harm of this review and

again there was a numerically higher proportion of patients who lose from 5% to 10% of body weight with apremilast versus its comparators, although the differences between groups were small and were not evident when weight decrease was reported as an adverse event rather than pre-defined criteria. Weight loss appears as a safety issue under Warnings and Precautions in the apremilast product monograph. The extension study to LIBERATE (summarized in 0) did not identify any unexpected safety signals; however, few conclusions can be drawn from the extension study because it followed patients only for 52 weeks. There was no comparator group, the population was likely highly selected, and the results appeared to be sensitive to missing data.

5.3 Potential Place in Therapy

The information in this section is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Currently available treatments for moderate-to-severe psoriasis include the traditional systemics (methotrexate, cyclosporine, acitretin) and the biologics (anti-TNF, anti–IL-12/23 and anti–IL-17). According to the clinical expert consulted by CDR, these drugs serve the patient's needs very well and there are very few patients whose psoriasis would be refractory to these treatments.

Apremilast is an oral drug alternative to the traditional systemic treatments. Patients may be concerned about the potential adverse effects of the traditional drugs. The clinical expert consulted indicated that apremilast may be considered for patients who have failed or are intolerant of the traditional systemics and who do not want to take biologics (because of needle phobia, for example). This, however, is likely a minority of patients (probably less than 5%). In general, the biologics provide better efficacy than apremilast (based on evidence from the manufacturer-provided indirect treatment comparisons), and most patients would opt for the higher efficacy treatment, according to the clinical expert consulted.

As apremilast is not immunosuppressive, it may be preferred for immunocompromised patients. However, biologics are not absolutely contraindicated and may be used in these patients with proper monitoring.

6. CONCLUSIONS

One manufacturer-sponsored multi-centre double-blind RCT, the LIBERATE study, was submitted by the manufacturer and met the inclusion criteria for this resubmission review. In addition to an apremilast and a placebo group, LIBERATE also contained an etanercept group; however, the study was designed to compare apremilast with placebo and etanercept with placebo, but not to compare apremilast with etanercept. Patients with moderate-to-severe plaque psoriasis and who had failed or had an intolerance or a contraindication to prior conventional systemic therapy were randomized 1:1:1 to one of these three interventions over a 16-week initial treatment phase. Apremilast and etanercept were both statistically superior to placebo for the primary outcome of proportion of patients achieving PASI 75, while apremilast also significantly improved measures of the PGA, and affected BSA and the quality of life scores on the DLQI versus placebo. However, apremilast did not improve the [redacted] versus placebo and, due to the hierarchical testing procedure, this meant that the only outcome to be tested for etanercept was PASI 75. The harms data suggest that there may be a numerically higher risk of adverse events with apremilast versus etanercept. However, the study was not designed to make such comparisons; therefore, this must be considered hypothesis-generating. Overall, while this resubmission does provide evidence of efficacy for apremilast versus placebo in a population that more closely resembles the manufacturer-requested reimbursement criteria, there is still no direct comparison of apremilast with any systemic therapy or a biologic. In a manufacturer-submitted NMA, [redacted], and no comparisons were made to other conventional systemic therapies, which are likely the more relevant comparators for apremilast.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CDR staff based on the input provided by patient groups.

1. Brief Description of Patient Group Supplying Input
The Canadian Skin Patient Alliance (CSPA) submitted input for this review. The CSPA is a non-profit organization serving patients with dermatological conditions. It focuses on advocacy, education, and support for more than 20 allied or affiliated disease-specific organizations.

In the past 12 months, the CSPA has received project-based and/or unrestricted funding from AbbVie, Amgen, Galderma, GlaxoSmithKline, Janssen, Merck, and Novartis. No conflicts of interest were declared for this submission.

2. Condition-Related Information
Information for this submission was obtained from two patient questionnaires (2014, 2016) that were administered online via social media channels, through social media and online discussion boards, and through email to clinical dermatologists involved in the clinical trial in order to facilitate patient connections.

Patients with psoriasis experience scales and plaques that can occur anywhere on their bodies. Physical symptoms of psoriasis include painful bleeding, cracking, crusting, and flaking lesions; scales; and plaques; many also experience severe itch. In addition, many patients experience joint pain and hair loss. Psoriasis also affects patients psychologically, with most experiencing embarrassment, self-confidence issues, and depression. In addition, patients also reported problems with concentration and a negative impact on their ability to sleep. Many patients are asked about their condition (particularly the scales and flakiness). They often have to explain that they are not contagious; this further increases embarrassment and affects self-esteem. Most patients try to hide their lesions, with some wearing particular clothing (e.g., pants rather than skirts, no bathing suits) or wearing their hair in a certain manner (for coverage).

Since lesions often affect the scalp and other more prominent or intimate areas of the body, patients also experience isolation and intimacy issues due to the embarrassment of the unsightly lesions. This was evident in the statement of one patient, *"Because I am single, since I was born I don't expose myself to others. How do you have intimacy with someone when you are covered with red patches, flaking like crazy the whole life? It's not easy."* The joint pain, lesion pain, and pain from itching lesions can also limit activities such as employment, socialization, everyday household chores, and sports. Patients have stated that employment or trips to the gym have ceased due to the unsightliness of the lesions. One patient provided perspective into their pain by stating, *"I have had problems with day-to-day rituals, as the pain and scale was so bad I could not use common soaps, etc., to cleanse."* In addition, many patients have to increase their amount of household care and cleaning due to the accumulation of flakes, along with changing clothing, *"I have had to leave to go home to change my clothes due to flaking."* This also affects travel for many patients, as evidenced by the statement, *"When we travel, we bring our own linens."*

Caregivers of patients with psoriasis often experience increases in the amount of house cleaning, such as vacuuming, bedding changes, and laundry, along with helping patients who are in pain with simple household chores (e.g., cooking, bathing, and mobility in, out, and around the house). In addition, time

is also taken away to care for the patient, as some patients require help in applying creams, going to phototherapy appointments, or travelling to infusion clinics (should the patient be on infusion biologics). Caregivers often find themselves negatively affected psychologically and dysfunctional, as the whole family tends to absorb the shame, depression, and isolation associated with the disease. Evidence of this was provided by a patient who stated, *"[it] has impacted my husband tremendously in our family business as well as our home life."*

3. Current Therapy-Related Information

Current therapy for patients with psoriasis includes topical ointments, creams, gels, or foams, phototherapy, methotrexate, adalimumab, infliximab, etanercept, ustekinumab, and cyclosporine. These therapies were observed to be slightly, moderately, or very effective for psoriasis skin plaques and spots, overall pain, scale, redness, and shedding; however, they were not effective for stiffness or pain. Issues, adverse events, and the inefficacy of current therapy that caused some patients to cease their treatment included treatment cost, time associated with treatment (e.g., phototherapy or infusion treatment), heart disease, and stomach issues. Around one-third of survey respondents indicated they had issues accessing approved treatments, found infusions and phototherapy inconvenient, or found that cost was a barrier to treatment.

4. Expectations About the Drug Being Reviewed

Patients with psoriasis responded that they believed that any treatment that would allow them to live a normal life (to stop worrying about the unsightly plaques and scales and to allow them the freedom to go out in public without being judged) without having their life interrupted by frequent visits for phototherapy or long travel times or distances to access infusion clinics, would be welcome. Even some relief from the itch, scales, flaking, and associated joint pain would be of benefit to these patients. For those already on biologics, another option was always welcome due to the chance that their current biologic would stop working. In addition, patients with needle phobias would welcome apremilast as an oral biologic option.

In patients with apremilast experience, many observed that it cleared up their lesions and reduced their swelling, and they were faced with mild (as opposed to severe) outbreaks that usually cleared up quickly. However, one patient did note that there was a marked decline in efficacy with long-term (more than one year) apremilast treatment, with joint pain and skin flares increasing. Adverse events experienced in patients on apremilast treatment included stomach aches/cramps, stomach tightness, dizziness, headaches, increased bowel movements, body aches, slight tremor, nausea, and insomnia; many of these were mild and ceased after being on treatment for a while. Patients on apremilast did find the oral dosing convenient and found it increased adherence.

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:	March 24, 2016
Alerts:	Weekly search updates until July 20, 2016
Study Types:	No search filters were applied
Limits:	Update of the original December 2014 search Human filter was applied 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
exp	Explode a 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
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
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 or UP7QBP99PN).rn,nm.
2	(Otezla* or apremilast* or otezia* or cc 10004 or cc10004 or HSDB 8221).ti,ab,ot,kf,hw,rn,nm.
3	or/1-2
4	3 use pmez
5	*Apremilast/

MULTI-DATABASE STRATEGY	
#	**Searches**
6	(Otezla* or apremilast* or otezia* or cc 10004 or cc10004 or HSDB 8221).ti,ab,kw.
7	or/5-6
8	7 use oemezd
9	conference abstract.pt.
10	8 not 9
11	4 or 10
12	exp animals/
13	exp animal experimentation/ or exp animal experiment/
14	exp models animal/
15	nonhuman/
16	exp vertebrate/ or exp vertebrates/
17	or/12-16
18	exp humans/
19	exp human experimentation/ or exp human experiment/
20	or/18-19
21	17 not 20
22	11 not 21
23	remove duplicates from 22

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. 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:	March 2016
Keywords:	Otezla (apremilast)
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 searching health-related grey literature" (https://www.cadth.ca/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

Reference	Reason for Exclusion
Sobell JM, Foley P, Toth D, Mrowietz U, Girolomoni G, Goncalves J, et al. Effects of Apremilast on Pruritus and Skin Discomfort/Pain Correlate With Improvements in Quality of Life in Patients With Moderate to Severe Plaque Psoriasis. Acta Derm Venereol. 2016 Feb 2;96(4):514-20. Rich P, Gooderham M, Bachelez H, Goncalves J, Day RM, Chen R, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: Results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). J Am Acad Dermatol. 2016. Jan;74(1):134-42. Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). Br J Dermatol [Internet]. 2015 Dec [cited 2016 Apr 14];173(6):1387-99. Available from: http://onlinelibrary.wiley.com/doi/10.1111/bjd.14164/epdf Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Acad Dermatol. 2015 Jul;73(1):37-49.	**Study included in previous review**
Nguyen CM, Leon A, Danesh M, Beroukhim K, Wu JJ, Koo J. Improvement of Nail and Scalp Psoriasis Using Apremilast in Patients With Chronic Psoriasis: Phase 2b and 3, 52-week Randomized, Placebo-Controlled Trial Results. J Drugs Dermatol. 2016 Mar 1;15(3):272-6	**Includes phase 2b**
Edwards CJ, Blanco FJ, Crowley J, Birbara CA, Jaworski J, Aelion J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). Ann Rheum Dis [Internet]. 2016 Jan 20 [cited 2016 Apr 14]. Available from: http://ard.bmj.com/content/early/2016/02/01/annrheumdis-2015-207963.full.pdf+html 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 [Internet]. 2015 Mar [cited 2016 Apr 14];42(3):479-88. Available from: http://www.jrheum.org/content/42/3/479.full.pdf+html	**Psoriatic arthritis**

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 10: OTHER EFFICACY OUTCOMES

	LIBERATE		
	Apremilast N = 83	Placebo N = 84	Etanercept N = 83
PASI 50			
Patients at week 16, n (%) LOCF	[redacted]	[redacted]	[redacted]
Difference in proportions (2-sided 95% CI) [a]	[redacted]		[redacted]
CMH *P* value	[redacted]		[redacted]
PASI 90			
Patients at week 16, n (%) [95% CI][a]	[redacted]	[redacted]	[redacted]
Difference in proportions (2-sided 95% CI)	[redacted]		[redacted]
CMH *P* value	[redacted]		[redacted]
Pruritus VAS			
Mean (SD) at baseline	[redacted]	[redacted]	[redacted]
Mean (SD) change at week 16	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Difference in LS means (2-sided 95% CI)[b]	[redacted]		[redacted]
2-sided *P* value	[redacted]		[redacted]
NAPSI score			
Baseline, mean (SD), N	[redacted]	[redacted]	[redacted]
Mean % (SD) change from baseline	[redacted]	[redacted]	[redacted]
LS mean % change from baseline (95% CI)			[redacted]
Difference in LS means (2-sided 95% CI) [b]	[redacted]		[redacted]
2-sided *P* value	[redacted]		[redacted]
Patients with a NAPSI-50 at week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference in proportions (2-sided 95% CI)[a]	[redacted]		[redacted]
CMH *P* value	[redacted]		[redacted]
Scalp Physician Global Assessment			
Score 0 or 1 at week 16, n/N (%)	[redacted]	[redacted]	[redacted]
Difference in proportions (2-sided 95% CI)[a]	[redacted]		[redacted]
CMH *P* value	[redacted]		[redacted]
Score 0, 1, or 2 at week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference in proportions (2-sided 95%CI)	[redacted]		[redacted]
CMH *P* value	[redacted]		[redacted]
Palmoplantar (PPPGA)			
Score 0 or 1 at week 16, n/N (%)	[redacted]	[redacted]	[redacted]
Difference in proportions (2-sided 95%CI)[a]	[redacted]		[redacted]
2-sided *P* value[j]	[redacted]		[redacted]
Score of 0, 1 or 2, n/N (%)	[redacted]	[redacted]	[redacted]

	LIBERATE		
	Apremilast N = 83	Placebo N = 84	Etanercept N = 83
Difference in proportions (2-sided 95%CI)[a]	[redacted]		[redacted]
2-sided *P* value	[redacted]		[redacted]

CI = confidence interval; CMH = Cochran–Mantel–Haenszel; LOCF = last observation carried forward; LS = least squares; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PPPGA = Palmoplantar Psoriasis Physician Global Assessment; ScPGA = Scalp Physician Global Assessment; SD = standard deviation; VAS = visual analogue scale.
[a] Two separate tests were completed: one for apremilast versus placebo and one for etanercept versus placebo. The *P* value is from a CMH test stratified by the body mass index at screening. The CI is weighted using CMH weights according to the number of participants in the two strata.
[b] Based on an ANCOVA model for the percentage change from baseline at week 16. If the slopes in [b] are homogeneous, the LS means and *P* values are presented from the ANCOVA adjusted for covariates. If the slopes in [b] are non-homogeneous, then the model includes only treatment and screening body mass index category, and the adjusted means for treatment and *P* value for treatment are provided.
[c] Outcome in statistical hierarchy that was tested after a previous outcome had failed to achieve statistical significance and therefore should not have been tested.
[d] Exploratory outcome not within the hierarchy; therefore, not adjusted for multiplicity.
Source: Clinical Study Report for LIBERATE.[5]

TABLE 11: SUBGROUP DATA

PASI 75: Patients With Response, n (%)	LIBERATE		
	Apremilast N = 83	Placebo N = 84	Etanercept N = 83
Prior phototherapy			
Yes	[redacted]	[redacted]	[redacted]
Difference versus placebo [2-sided 95% CI]	[redacted]		[redacted]
No	[redacted]	[redacted]	[redacted]
Difference versus placebo [2-sided 95% CI]	[redacted]		[redacted]
Failed conventional systemic therapy			
0	[redacted]	[redacted]	[redacted]
Difference versus placebo [2-sided 95% CI]	[redacted]		[redacted]
1	[redacted]	[redacted]	[redacted]
Difference versus placebo [2-sided 95% CI]	[redacted]		[redacted]
2 or higher	[redacted]	[redacted]	[redacted]
Difference versus placebo [2-sided 95% CI]	[redacted]		[redacted]
Failed biologic therapy	[redacted]		
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Failed TNF blocker	[redacted]		
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]

CI = confidence interval; PASI = Psoriasis Area and Severity Index; TNF = tumour necrosis factor.
Source: Clinical Study Report for LIBERATE.[5]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- Dermatology Life Quality Index (DLQI)
- Short Form (36) Health Survey (SF-36)
- Physician Global Assessment (PGA)
- Psoriasis Area Severity Index (PASI)
- Psoriasis Symptom Diary.

Findings

TABLE 12: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	MCID	References
DLQI	A 10-item, dermatology-specific quality-of-life questionnaire	Yes	3.2	Mattei et al. 2014,[23] Ruderman et al. 2003,[24] Shikiar et al. 2006[25]
PGA	Single estimate of a patient's disease severity at a given time based on induration, erythema, and scaling	Yes	Unknown	Feldman et al. 2004,[26] Weisman et al. 2003[27]
PASI	Numeric score ranging from 0 to 72, based on assessments of four body areas and severity of induration, erythema, and scaling	Yes	Unknown	Ashcroft et al. 1999,[28] Carlin et al. 2004,[29] Feldman et al. 2004,[26] Gourraud et al. 2012[30]
Psoriasis Symptom Diary	A 20-item, psoriasis-specific patient-reported outcome questionnaire	Yes	2.0 to 3.0	Lebwohl et al. 2014,[31] Strober et al. 2013[32]
SF-36	This consists of eight health domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health), of which a subscale score can be calculated. It also provides 2 component summary scores: PCS and MCS. Scores range from 0 to 100, with higher scores indicating better health.	Only responsiveness for psoriasis	2.5 to 5	Mease et al. 2006,[33] Fendl and Ware 2014[34]

DLQI = Dermatology Quality of Life Index; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; MCS = mental component summary; PCS = physical component summary; PGA = Physician Global Assessment modified 2011; MCID = minimal clinically important difference; PASI = Psoriasis Area Severity Index; SF-36 = Short Form (36) Health Survey.

Dermatology Life Quality Index

The DLQI is a widely used dermatology-specific quality-of-life instrument. It is a 10-item questionnaire that assesses six different aspects that may affect quality of life.[24,35] These aspects are symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[24,35] The maximum score per aspect is either 3 or 6, and the scores for each can be expressed as a percentage of either 3 or 6. Each of the 10 questions is scored from 0 (not at all) to 3 (very much), and the overall DLQI is calculated by summing the score of each question resulting in a numeric score between 0 and

30 (or a percentage of 30).[24,35] The higher the score, the more quality of life is impaired. In terms of the effect on a patient's life, the meaning of the DLQI scores is as follows:[36]

- 0 to 1 = no effect
- 2 to 5 = small effect
- 6 to 10 = moderate effect
- 11 to 20 = very large effect
- 21 to 30 = extremely large effect.

The DLQI has shown good reliability and construct validity.[24] The estimated minimal clinically important difference (MCID) for the DLQI in patients with psoriasis is 3.2.[23] Estimates of the minimal important difference (the smallest difference a patient would regard as beneficial) have ranged from 2.3 to 5.7.[25]

The limitations associated with the DLQI are as follows:

- Concerns have been identified regarding unidimensionality and the behaviour of items of the DLQI in different psoriatic patient populations with respect to their age, gender, culture, etc.[36]
- The patient's emotional aspects may be under-represented and this may be one reason for unexpectedly low DLQI scores in patients with more emotionally disabling diseases such as vitiligo. To overcome this, it is suggested that the DLQI be combined with more emotionally oriented measures such as the mental component of the SF-36 scales, or the Hospital Anxiety and Depression Scale.[36]
- The non-availability of benchmarks for the MCID of DLQI scores in general dermatological conditions is also a limitation, although there have been some attempts to determine these differences for specific conditions such as psoriasis.[36]
- The DLQI may lack sensitivity in detecting change from mild to severe psoriasis.[37]

Medical Outcomes Study (Short Form [36] Health Survey)

The SF-36 is a general health status instrument that has been used extensively in clinical trials in many disease areas.[17] The SF-36 consists of eight health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[18] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries: the physical component summary (PCS) and the mental component summary (MCS), which are 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 of 10 in the general US population,[18] enabling scores to be meaningfully compared across different studies.[22] Therefore, all scores above or below 50 are considered above or below average for the general US population.[18,22]

Validity and reliability of the SF-36 in patients with psoriasis is lacking; however, in one systematic review by Frendl and Ware[34] that observed SF-36 concordance and its MCID across many different indications in studies that looked at drug therapy effectiveness, the SF-36 was observed to be responsive (when compared with primary clinical measures) in patients with psoriasis. In addition, of the 10 psoriasis studies identified, net PCS or MCS improvement of at least 3 points was observed in 70% of these studies.

The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 and 5 points,[19-21] with the developer of the SF-36 suggesting a threshold of 3 points for the MCID with a corresponding standard deviation of 0.3.[22]

Physician Global Assessment

The PGA is used to determine a single estimate of the patient's overall severity of disease at a given point in time. Various PGAs have been used in psoriasis with different descriptions and scores.[38] Psoriatic lesions are graded for induration, erythema, and scaling based on scales of 0 to 4, which are then averaged over all lesions.[39] The Table 13 highlights the scoring for induration, erythema, and scaling:

TABLE 13: SCORING SYSTEM FOR PHYSICIAN GLOBAL ASSESSMENT

Score	Induration	Erythema	Scaling
0	No evidence	No evidence of erythema although hyperpigmentation may be present	No evidence of scaling
1	Minimal	Faint erythema	Minimal; occasional fine scale
2	Mild or slight	Light red colouration	Fine scale dominates
3	Elevated	Red colouration	Moderate; coarse scale predominates
4	Marked	Dark- to deep-red colouration	Marked; thick, non-tenacious scale dominates

Source: Cappelleri et al.[39]

The sum of the three scales are added and then divided by three (I + E + S ÷ 3) to obtain a final PGA score, as follows:

- 0 = cleared, except for residual discolouration
- 1 = minimal — majority of lesions have individual scores for I + E + S ÷ 3 that average 1
- 2 = mild — majority of lesions had have individual scores that average 2
- 3 = moderate — majority of lesions have individual scores that average 3
- 4 = severe — majority of lesions have individual scores that average 4.

The PGA is more subjective than the PASI in that there is no attempt to quantify the individual elements of plaque morphology or body surface area (BSA) involvement.[26,27] There have also been fewer studies using PGA than PASI. This outcome is considered reliable using test–retest data and internal consistency.[27] However, inter-rater reliability due to variability, especially in untrained observers, is poor.[27] Many studies now employ only the final value of clear or almost clear as treatment success. Although it would seem the PGA may be less likely to be open to interpretation, different studies have used different definitions of clear or almost clear, making comparisons between treatments difficult.[27] Construct and content validity are considered strong within a study, but comparison with other studies, as well as relationship to other methods, are problematic due to the variability in data collection, analysis, and reporting method.[27]

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.[29]

In calculating the PASI, severity is determined by dividing the body into four regions: head, upper extremities, trunk and lower extremities that account for 10%, 20%, 30%, and 40% of the total BSA, respectively.[40] 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). 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%
- 6 = 90% to 100%.

The following formula is used to calculate the PASI score:
$\text{PASI} = 0.1\ (E_h + I_h + S_h)\ A_h + 0.2\ (E_u + I_u + S_u)\ A_u + 0.3\ (E_t + I_t + S_t)\ A_t + 0.4\ (E_l + I_l + S_l)\ A_l$
where E = erythema, I = induration, S = scaling, A = area, h = head score, t = trunk score, u = upper extremities, and l = lower extremities score.[40] PASI 75 is a dichotomous scale (Yes/No); PASI 75 means the patient achieved ≥ 75% improvement from baseline PASI score.

A number of limitations of the PASI have been identified and include the following:

- 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's-rated clinical severity.[41]
- There are significant inter-rater reliability issues regarding the measurement of BSA.[26,28] There has been some work regarding the development of imaging and analysis systems to objectively measure BSA.[42]
- PASI scores can vary substantially between experienced and inexperienced physicians, raising concerns for inter-rater reliability.[38]
- Improvements in PASI score are not linearly related to severity or improvements in psoriasis.[26,29] The extent of psoriatic involvement is measured using a scale of one to six and the areas corresponding to each score are non-linear.
- Some severe disease (clinically) may be scored low. For example, scores as low as 3 (on palms and soles) may represent psoriasis that disables a patient from work and 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 above 40 are rare).[28] The validity of this scale may be overrated, in part because of the skew toward lower scores.[30]
- There is little research on the reliability of the assessments for erythema, , and induration, together with overall PASI scores.[28]
- Criterion validity is restricted by the lack of a "gold standard" measure of psoriatic severity.[43]
- The PASI lacks sensitivity as erythema, scaling, 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 percentage improvement in PASI (e.g., reduction of T cells, loss of K16 expression and reduction in epidermal thickness).[29]

- Little work has been done to determine the clinical relevance of derived PASI scores.[28]

Psoriasis Symptom Diary

The Psoriasis Symptom Diary is a 20-item, psoriasis-specific, electronic diary to assess symptom severity, symptom bother, and disease impact.[31,32] Patients are asked to recall their disease experience over the preceding 24 hours.[31,32] The severity and bother of the following symptoms are assessed: itching, stinging, burning, pain, scaling, and skin colour.[31,32,44] Impact items ask about patient embarrassment, restricted movement due to psoriasis, and avoidance of activities requiring interaction with other people.[31,32] A 0 to 10 numeric scale is used to assess impact, symptom severity, and symptom bother; higher scores indicate more severe impact, bother, or severity (0 = symptom not experienced, 10 = symptom "as bad as you can imagine").[31,32] Patients are prompted to respond to questions about bother only when they have indicated a score greater than 0 for the severity questions.[32] For example, if a patient indicates a score greater than 0 for skin cracking, they are then asked how bothered they are by their skin cracking. Responses for skin colour are categorical and include: pink; light red or brown; bright red or purple; deep, dark red, purple or brown; grey, white, or silver.[31,32] The Psoriasis Symptom Diary was developed in accordance with the US Food and Drug Administration's guidelines for development of new patient-reported outcome instruments, which require patient input in the instrument development.[31,44]

The MCIDs for Psoriasis Symptom Diary severity items (itching, burning, stinging, cracking, pain, and scaling) and change in skin colour are estimated to be 2.0 to 3.0.[32] An anchor-based approach was used to determine the MCID; means and standard deviations for Psoriasis Symptom Diary item scores were calculated and compared with levels of change on the Patient Global Impression of Change.[32] The Psoriasis Symptom Diary has shown good construct validity; symptom severity items were associated with the Investigator's Global Assessment (IGA) and PASI, while other items are associated with the DLQI.[32,44] Items on itching for the Psoriasis Symptom Diary are associated with the Pruritus Visual Analogue Scale, DLQI, IGA, and PASI.[32,44] The Psoriasis Symptom Diary has also shown good discriminant validity, sensitivity to patient change,[32] and treatment benefit.[44]

The Psoriasis Symptom Diary has several limitations. The tool was developed using a small sample of patients.[31] Additionally, its validity was assessed using a predominantly Caucasian patient population (96% Caucasian), and it may not be generalizable to other populations; this is especially a consideration for items such as skin colour.[32] As a daily diary, compliance with the tool outside of the clinical trial environment is yet to be examined.[32]

Conclusion

Several instruments are used when assessing psoriasis disease severity. The PASI is one of the most widely used tools. While it has some noted limitations, the PASI is considered the gold standard for measuring severity of psoriasis.[42] The Psoriasis Symptom Diary is used to assess a patient's symptom experience.[31]

Quality of life measures are also important in the assessment of psoriasis severity. The DLQI is a dermatology-specific quality of life measure. DLQI has been validated for use in the psoriasis patient population, with an estimated MCID of 3.2.[23] The EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D) is a general health–specific quality-of-life measure. There is evidence for the concurrent validity of the EQ-5D in the psoriasis patient population, as it correlates well with DLQI and PASI.[45] Quality of life remains an important consideration for assessing severity of disease for patients with psoriasis.

APPENDIX 6: SUMMARY OF OTHER STUDIES

1. Objective

To summarize the results from the 52-week extension study of the LIBERATE trial.[12] The LIBERATE study was a multinational, multi-site, phase 3b, randomized, and placebo-controlled trial that assessed the efficacy and safety of apremilast 30 mg twice daily in patients with moderate-to-severe plaque psoriasis. Patients on placebo or etanercept (encompassing the third group of the 1:1:1 randomization scheme) were switched to apremilast 30 mg twice a day at week 16 of the original study, and efficacy and safety were assessed through 104 weeks. The following summary is based on unpublished data from a manuscript provided by the manufacturer.[12]

2. Findings

Study Design

At week 16 of the LIBERATE study, patients on placebo or etanercept were switched to apremilast 30 mg twice daily, while patients on apremilast continued their original regimen. Patients in the placebo/apremilast group did not receive any apremilast dose titration, while patients in the etanercept/apremilast group did receive apremilast dose titration. The original blinding that occurred for the 16-week LIBERATE study was maintained through the week 104 visit. At the discretion of the investigator, topical therapy (e.g., corticosteroids or retinoids), vitamin D analogue preparations, and/or phototherapy were available to patients who did not achieve a PASI 50 score at week 32. The primary end point of interest in the extension study was a Psoriasis Area and Severity Index score of 75 (PASI 75). The secondary end points included mean change from baseline in the Dermatology Quality of Life Index (DLQI), DLQI minimal clinically important difference, achievement of DLQI scores of 0 or 1, achievement of a Static Physician Global Assessment (sPGA) of 0 or 1, mean change in body surface area affected from baseline of the LIBERATE study, visual analogue scale scores for pruritus, skin/discomfort/pain, and mean percentage change in Nail Psoriasis Severity Index score. Only those end points specifically relating to the main study reported in this submission were examined; hence, only the PASI 50, PASI 75 scores, the ScPGA scores, and the mean change in DLQI from baseline are reported.

Results

Out of the full analysis set (n = 250) of patients who were randomized to receive placebo (n = 84), apremilast (n = 83), or etanercept (n = 83), [redacted] completed the placebo-controlled phase of LIBERATE (weeks zero to 16). As patient disposition was not provided in detail in the manuscript, all that can be determined was that there were [redacted] patients in the placebo/apremilast group, [redacted] patients were in the apremilast/apremilast group, and [redacted] patients were in the etanercept/apremilast group at the start of the extension phase. The percentage of patients who withdrew was not provided in any specific detail. Results were obtained from any patient who entered the apremilast extension study (during week 16 to week 52) and received at least one dose of apremilast. Missing data for the main analyses were handled using last observation carried forward (LOCF) methodology, while missing values for any sensitivity analyses (of which a description was not provided) were handled by using non-responder imputation.

Patient Characteristics

No baseline patient characteristics were provided at the commencement of the extension study; they were provided only from the commencement of the LIBERATE study.

Clinical Efficacy Outcomes

At week 52, PASI 75 response was maintained in more than half of patients (52.7%) in the apremilast/apremilast group, while 53.4% and 57.0% of patients achieved PASI 75 response in the placebo/apremilast and etanercept/apremilast groups, respectively. Similar PASI 50 responses were evident in the placebo/apremilast and apremilast/apremilast treatment groups at week 52 ([redacted], respectively); however, the percentage of PASI 50 responses in the etanercept/apremilast group was higher ([redacted]%). Mean changes in the total DLQI scores from baseline were similar between the placebo/apremilast and etanercept/apremilast treatment groups ([redacted], respectively), but were larger in the apremilast/apremilast treatment group ([redacted]). Similar improvements were observed in the Scalp Physician Global Assessment (ScPGA) scores in the apremilast/apremilast and etanercept/apremilast groups ([redacted], respectively), while that in the placebo/apremilast group was higher ([redacted]).With regard to mean changes in psoriasis-affected body surface area from baseline, the [redacted] had the least amount of change ([redacted]), followed by the [redacted] ([redacted]) and the [redacted] ([redacted]). Detailed efficacy results (including the non-responder imputation results) are provided in Table 14.

TABLE 14: PRIMARY AND SECONDARY EFFICACY OUTCOME MEASURES AT WEEK 52

	PL/APR[a] n = 73				APR/APR[a]				ETA/APR[a]			
	PL Week 16 N = 84		Week 52 N = 74		ETA Week 16 N = 83		Week 52 N = 74		ETA Week 16 N = 83		Week 52 N = 79	
	LOCF	NRI	LOCF	NRI	LOCF	NRI	LOCF	NRI	LOCF	NRI	LOCF	NRI
Primary end point, n (%)												
PASI 75	10 (11.9)		39 (53.4)		33 (39.8)		39 (52.7)		40 (48.2)		45 (57.0)	
P value	-		-		< 0.0001		-		< 0.0001		-	
Secondary end points												
PASI 50, n (%)												
P value												
ScPGA, n (%)												
P value												
Change in total DLQI score from baseline, mean (SD)												
P value												
% change in psoriasis-affected BSA, mean (SD)												
P value												

APR = apremilast; BSA = body surface area; DLQI = Dermatology Life Quality Index; ETA = etanercept; LOCF = last observation carried forward; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index; PL = placebo; SD = standard deviation; scPGA= Scalp Physician Global Assessment.

[a] Included were any patient who entered and received at least one dose of apremilast during week 16 to week 52 extension phase; although missing data were handled with LOCF methodology and sensitivity analyses used non-responder imputation for missing values.

[b] An "ScPGA score of 0 (clear) or 1 (almost clear) with a ≥ 2-point reduction from baseline."[12]

Source: CADTH Common Drug Review request for additional information.[12]

Safety

One or more adverse events occurred in similar proportions in all groups through the 52 weeks, ranging from 56.2% to 62.0%. The most common adverse events that occurred in ≥ 5% of patients included diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, headache, and sinusitis. The proportion of patients experiencing diarrhea was similar in the apremilast/apremilast and etanercept/apremilast groups (5.4% and 7.6%, respectively); however, it was higher in the placebo/apremilast group (17.8%). The authors theorized that this may have been due to the lack of apremilast titration in patients switching from placebo to apremilast at week 16. One or more serious adverse events occurred in a slightly higher proportion of patients in the placebo/apremilast group (5.5%) when compared with the apremilast/apremilast and etanercept/apremilast groups (2.7% and 2.5%, respectively). One serious infection of mastoiditis occurred in a patient in the apremilast/apremilast group, and one psychiatric event of suicidal ideation occurred in a patient in the placebo/apremilast group. No serious cardiac events, malignancies, of tuberculosis were reported in the 52-week extension phase. The mean weight changes from baseline were [redacted] in the placebo/apremilast, apremilast/apremilast, and etanercept/apremilast groups, respectively. Details harms results are provided in Table 15.

TABLE 15: HARMS

	PL/APR[a] n = 73	APR/APR n = 74	ETA/APR[b] n = 79
AEs, n (%)			
≥ 1 AE	41 (56.2)	44 (59.5)	49 (62.0)
AEs occurring in ≥ 5% of patients, n (%)			
Diarrhea	13 (17.8)	4 (5.4)	6 (7.6)
Nausea	4 (5.5)	3 (4.1)	5 (6.3)
URTI	3 (4.1)	4 (5.4)	1 (1.3)
Nasopharyngitis	3 (4.1)	2 (2.7)	4 (5.1)
Headache	4 (5.5)	2 (2.7)	2 (2.5)
Sinusitis	0	1 (1.4)	4 (5.1)
AEs leading to drug withdrawal, n (%)			
≥ 1 AE	3 (4.1)	3 (4.1)	2 (2.5)
SAEs, n (%)			
≥ 1 SAE	4 (5.5)	2 (2.7)	2 (2.5)

AE = adverse event; APR = apremilast; ETA = etanercept; PL = placebo; SAE = serious adverse event; URTI = upper respiratory tract infection.

[a] No dose titration for apremilast.

[b] Apremilast dose titration.

Source: CADTH Common Drug Review request for additional information.[12]

Limitations

The main limitations of the extension phase are the lack of a detailed description of the patient disposition through the 52 weeks and the fact that patients who entered the extension phase were likely a select population. In addition, without the disposition details, it is impossible to ascertain what the characteristics were of the patients who dropped out of the study and the accompanying reasons for their discontinuation. While it has been observed that etanercept tends to lose its effectiveness at a median time of 33 days in patients with psoriasis,[46] there is still some uncertainty regarding any

potential effects of etanercept at 52 weeks, considering there are numerical differences between the apremilast/apremilast and etanercept/apremilast groups (i.e., especially in the PASI 50, PASI 75, and sPGA results). While sensitivity analyses were performed in the first 16 weeks of the LIBERATE study, there was no mention of what specific sensitivity analyses were performed in the extension study; however, non-responder imputation results for these sensitivity analyses were provided alongside the LOCF results accompanying the main analyses. In addition, the results appeared to be sensitive to discontinuations based on the differences in treatment effects between the two methods for imputing missing data; results using LOCF analyses generally indicated better responses than when non-responder imputation was used at the week 52 end point.

3. Summary

Data from the extension study to LIBERATE suggest that more than 50% of patients originally randomized to apremilast were able to maintain a PASI 75 through the 52 weeks of treatment. In addition, sustained improvements were observed in their mean changes in total DLQI from baseline. However, the lack of a comparator, the select population, the potential for some sort of a carry-over effect in the etanercept/apremilast group, and the lack of detailed patient disposition all limit the ability to ascertain the true efficacy of apremilast in this patient population. It appears that continuation of apremilast or switching to apremilast from placebo or etanercept was associated with an acceptable safety profile. Adverse events occurred in 56.2% to 62.0% of patients in the extension phase, with the most common adverse events being diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, headache, and sinusitis.

APPENDIX 7: SUMMARY OF COMPARATORS

Introduction

Background

To summarize and critically appraise the manufacturer-supplied network meta-analysis (NMA)[47] that was provided to supplement the apremilast resubmission. No direct comparisons have been performed between apremilast and the biologics used in the treatment of patients with moderate-to-severe plaque psoriasis who were previously treated with conventional systemic therapy; therefore, an NMA was performed to ascertain the comparative efficacy and safety of the aforementioned treatments.

Methods

One indirect treatment comparison (ITC), supplied as an NMA, was provided by the manufacturer regarding the treatment of patients with moderate-to-severe plaque psoriasis. No other ITCs were identified through a supplemental literature search conducted by the CADTH Common Drug Review (CDR).

Description of Manufacturer-Provided Indirect Treatment Comparison

Methods for the Manufacturer-Supplied Indirect Treatment Comparison

Study Eligibility and Selection Process

The eligibility criteria for the NMA included randomized controlled trials (RCTs) of patients aged 18 years or older with plaque psoriasis (studies that may have also included pediatric patients were included if there was a subgroup analysis of adults with the appropriate outcomes) who were previously treated with, or were contraindicated or intolerant to, conventional systemic therapies. The RCTs must have included one of the following treatments: apremilast, adalimumab, etanercept, infliximab, secukinumab, or ustekinumab. In addition, the RCTs must have included one of the aforementioned treatments as monotherapy, and reported on one or more efficacy (e.g., Psoriasis Area and Severity Index [PASI], Dermatology Quality of Life Index [DLQI]), or on safety outcomes (e.g., adverse events [AEs], serious adverse events [SAEs]). Open-label studies were permitted for inclusion if they were randomized and had a control group. Exclusion criteria included non-randomized studies, dosing studies with an absence of a comparator group, single-group studies, studies with no accompanying full-text publication, and studies that focused on nail psoriasis.

A systematic search of PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and clinicaltrials.gov databases was performed to identify all relevant publications up to September 3, 2013, with an updated search run as of April 13, 2015. In addition, a grey literature search was performed to identify potentially relevant systematic reviews, meta-analyses, and health technology assessments that may have been missed in the electronic database searches. Two independent reviewers selected and provided at least one reason for their inclusion of potentially relevant articles based on abstracts, with any discrepancies resolved by consensus or a third independent reviewer. Two reviewers independently selected relevant full-text articles based on the inclusion and exclusion criteria. Only treatment groups in the included studies where patients received regulator-approved dosing regimens were analyzed.

The initial database search included 878 articles, of which 163 were chosen for full-text review, along with four records identified from clinicaltrials.gov, and one from the grey literature search of systematic reviews, meta-analyses, and health technology assessments. ESTEEM 1 and 2 and PSOR-10 were provided in full clinical study report form. In total, 30 studies were identified, the majority of which

(93%) were placebo-controlled. A list of included and excluded studies was provided with reasons accompanying the list of excluded studies.

Data Extraction

Two independent reviewers extracted the data based on a data extraction form that was developed in Microsoft Access. Data were reconciled and verified for any discrepancies.

Outcome-of-interest data were extracted and reported only from the randomized, placebo-controlled periods of the studies, with only the first randomized and controlled phase being used if studies allowed for early escape or were of a crossover design. In cases where there were multiple sources of data, all sources were reviewed and reconciled, with the reviewers extracting data from the primary trial publication in the situation where there were discrepancies between sources. Intention-to-treat data were extracted in studies that presented several methods of evaluating treatment response. Only data from the recommended or usual doses in Canada were extracted. The included dosing regimens included:

- apremilast: 30 mg twice every day
- adalimumab: loading dose of 80 mg, then 40 mg every other week
- etanercept: 50 mg twice every week for three months, followed by 50 mg once every week
- infliximab: 5 mg/kg at zero, two, and six weeks, then every eight weeks
- secukinumab: 300 mg (initial dosing at zero, one, two, and three weeks, followed by monthly dosing)
- ustekinumab: 45 mg initially (90 mg for patients weighing more than 100 kg) and four weeks later, then every 12 weeks thereafter.

Trial and Patient Characteristics of Studies Included in the Indirect Treatment Comparison

Specific trial and patient characteristics are provided in Table 16.

The majority of included studies enrolled adult patients with moderate-to-severe chronic plaque psoriasis, with baseline body surface area and PASI scores of ≥ 10. In addition, the majority of studies enrolled more males. The mean ages ranged from 39 to 51 years, and mean psoriasis durations generally ranged from 15 to 20 years. Study sample size was variable and ranged from 32 to 814 patients per treatment group. Inclusion criteria were similar regarding prior and concomitant medication use, with most studies not allowing concomitant therapies such as systemic agents and phototherapy during the study. (It should be noted that some studies made no mention of concomitant medication use.) The majority of studies included patients who were reported as having failed, or having had an insufficient response to, previous conventional systemic (e.g., methotrexate, cyclosporine) or topical therapy. In addition, some studies included patients naive to biological drugs, while others allowed prior use of biologics.

Overall, studies were included in the NMA that closely resembled the characteristics of the pivotal apremilast trials, and the analysis used the post–conventional systemic therapy group from the ESTEEM 1 and 2 trials and the entire PSOR-10 population (which was composed of patients with an inadequate response to, or who were contraindicated or intolerant of, at least one conventional systemic drug).

Comparators

The comparators of interest included biologics that have been approved for the treatment of patients with plaque psoriasis who had previously received conventional systemic therapies. These included

adalimumab, etanercept, infliximab, secukinumab, and ustekinumab. At the time of this NMA, ixekizumab had not been approved for this indication.

Outcomes

The primary outcomes of interest included PASI scores and safety outcomes such as AEs and SAEs. In addition, other efficacy outcomes (such as health-related quality of life measured by the DLQI), discontinuations, and other safety outcomes (such as discontinuations due to AEs, and specific harms such as gastrointestinal AEs, infections, serious infections, and malignancies) were also of interest as long as they were reported in enough studies to include in a separate NMA.

TABLE 16: TRIAL AND PATIENT CHARACTERISTICS OF INCLUDED STUDIES IN THE NETWORK META-ANALYSIS

Treatment	N[a]	% BSA Affected, Mean (SD)[a]	PASI Score, Mean (SD)[a]	Prior Therapies[a]					Inclusion Criteria (Disease Type, Severity, Medication History)[a]
				Topical Agent (%)	Photo-therapy (%)	Conventional Systemic Agents (%)	Biologic Agents (%)	Systemic Agents (%)	
Placebo-Controlled Trials									
Apremilast versus placebo trials (4 trials)									
APR 30 mg BID	83, 562	24.4 (14.7), 27.1 (15.6)	18.7 (7.2), 19.3 (7.0)	6.0[b]	28.9, 31.3[b]	37.7, 79.5[b]	0, 33.6[b]	53.4, 57.3[b]	• Moderate-to-severe plaque psoriasis • ≥ 18 years of age[b] • ≥ 10% BSA[b] • PASI ≥ 12[b] • PGA ≥ 3[b] • Biologic-, APR-, and ETA-naive[c]
Placebo	84, 282	21.0 (11.2), 27.6 (15.8)	18.1 (5.7), 20.0 (8.0)	1.2[b]	22.6, 31.3[b]	36.2, 83.3[b]	0, 32.1[b]	44.3, 53.3[b]	
Adalimumab versus placebo trials (4 trials)									
ADA 40 mg EOW + 80 mg loading	43, 814	25.8 (15.5), 33.6 (19.9)	16.7 (NR), 30.2 (10.9)	75.9, 95.3[b]	17.0, 23.3[b]	23.1, 41.9[b]	11.9[b]	82.4[b]	• Plaque psoriasis (moderate-to-severe)[d] • ≥ 5%–10% BSA • PASI ≥ 10–12 • Anti-TNF (and MTX)[e]-naive
PL	46, 398	25.6 (14.8), 46.7 (20.0)	16.0 (NR), 29.1 (11.8)	72.9, 95.7[b]	14.8, 71.3[b]	22.1, 37.0[b]	13.3[b]	90.6[b]	
MTX	110	NR	NR	NR	NR	NR	NR	87.3[b]	
Etanercept versus placebo trials (7 trials)									
ETA 50 mg BIW[j]	62, 335	24.1 (15.0), 29.9 (1.6)[f]	18.3 (7.6), 19.5 (8.8)	92.2, 95.0[b]	19.4, 72.0[b]	17.5, 38.1[b]	3.2, 14.2[b]	94.0[g]	• Plaque psoriasis • Excluding active guttate, erythrodermic, or pustular[b] • ≥ 10% BSA • PASI ≥ 10–12 • PGA ≥ 3[b] • ≥ 30% scalp surface area affected, with a PSSI of ≥ 15[g]
Placebo	62, 307	22.1 (13.4), 28.8 (1.4)[f]	18.1 (7.4), 18.6 (8.6)	91.2, 97.2[b]	16.7, 71.0[b]	16.1, 39.4[b]	4.2, 14.7[b]	93.0[g]	

Treatment	N[a]	% BSA Affected, Mean (SD)[a]	PASI Score, Mean (SD)[a]	Prior Therapies[a]					Inclusion Criteria (Disease Type, Severity, Medication History)[a]
				Topical Agent (%)	Photo-therapy (%)	Conventional Systemic Agents (%)	Biologic Agents (%)	Systemic Agents (%)	
									• Anti–IL-12/23p40- and ETA-naive[b] • Anti-TNF-naive[b]
Infliximab versus placebo trials (6 trials)									
IFX 5 mg/kg at week 0, 2, 6	11, 314	28.7 (16.4), 45.6 (21.4)[b]	20.4 (7.5), 31.9 (12.8)	90.4, 100.0[b]	27.4, 68.7[b]	11.1, 57.1[b]	14.3, 33.3[b]	88.9, 94.3[b]	• Moderate-to-severe plaque psoriasis[h] • ≥ 5%[h]–10% BSA • PASI ≥ 12[h] • Failed on conventional systemic treatment[b] or treated with psoralen-UVA[g] • Anti-TNF (or infliximab)-naive[b] • Failed topical treatment[g]
Placebo	11, 208	28.4 (17.6), 50.2 (27.3)[b]	19.8 (7.7), 33.1 (15.6)	92.8, 100.0[b]	29.8, 73.7[b]	13.5, 68.4[b]	13.3, 31.4[b]	82.4, 94.7[b]	
Ustekinumab (45 mg) only versus placebo trials (2 trials)									
UST 45 mg at week 0 ,4, (16)[i]	61, 160	35.1 (18.5), 41.8 (24.4)	23.2 (9.5), 25.2 (11.9)	95.0, 96.7	37.5, 80.3	70.5[b]	11.9, 21.3	39.4[b]	• Moderate-to-severe[b] plaque psoriasis • ≥ 10% BSA • PASI ≥ 12
Placebo	60, 162	35.1 (19.6), 35.8 (21.4)	22.7 (9.5), 22.9 (8.6)	96.9, 98.3	37.0, 86.7	71.7[b]	6.8, 15.0	42.6[b]	
Ustekinumab (2 dosing groups) versus placebo trials (3 trials)									
UST 45 mg at week 0, 4 and then every 12 weeks	64, 409	25.9 (15.5), 47.0 (23.7)	19.4 (6.8), 30.1 (12.9)	96.0, 100.0	56.3, 69.9	54.5, 55.3[b]	1.6, 52.5	73.4[b]	• Moderate-to-severe[g] plaque psoriasis • ≥ 10% BSA • PASI ≥ 12 • Anti–IL-12/23-naive[h]
UST 90 mg at week 0, 4, and then every 12 weeks	62, 411	25.2 (15.0), 46.6 (19.7)	19.7 (7.6), 28.7 (11.2)	93.4, 100.0	65.0, 82.3	54.5, 55.1[b]	0.0, 50.8	83.9[b]	

Treatment	N[a]	% BSA Affected, Mean (SD)[a]	PASI Score, Mean (SD)[a]	Prior Therapies[a]					Inclusion Criteria (Disease Type, Severity, Medication History)[a]
				Topical Agent (%)	Photo-therapy (%)	Conventional Systemic Agents (%)	Biologic Agents (%)	Systemic Agents (%)	
Placebo	32, 410	26.1 (17.4), 49.8 (22.5)	19.4 (7.5), 30.3 (11.8)	94.9, 100.0	58.8, 67.3	55.7, 58.8[b]	0.0, 50.2	65.6[b]	
Secukinumab versus placebo trial (1 trial)									
SEC 300 mg[j]	245	32.8 (19.3)	22.5 (9.2)	NR	NR	52.2	28.6	66.5	• Plaque psoriasis • ≥ 18 years of age • ≥ 10% BSA • PASI ≥ 12
Placebo	248	29.7 (15.9)	21.4 (9.1)	NR	NR	43.5	29.4	58.9	
Etanercept versus ustekinumab (2 dosing groups) trial (1 trial)									
ETA 50 mg BIW	347	23.8 (13.9)	18.6 (6.2)	96.8	64.6	57.3	11.8	NR	• Plaque psoriasis • ≥ 10% BSA • PASI ≥ 12 • PGA ≥ 3 • Inadequate response or contraindication to ≥ 1 conventional systemic treatments • UST- and ETA-naive
UST 45 mg at week 0 and 4	209	26.7 (17.8)	20.5 (9.2)	96.7	66.0	61.7	12.4	NR	
UST 90 mg at week 0 and 4	347	26.1 (17.6)	19.9 (8.4)	96.8	66.3	52.4	10.4	NR	
Etanercept versus secukinumab versus placebo trial (1 trial)									
ETA 50 mg BIW	326	33.6 (18.0)	23.2 (9.8)	NR	NR	62.6	13.8	65.6	• Plaque psoriasis • ≥ 18 years of age • ≥ 10% BSA • PASI ≥ 12
SEC 300 mg	327	34.3 (19.2)	23.9 (9.9)	NR	NR	59.6	11.6	63.0	
Placebo	326	35.2 (19.1)	24.1 (10.5)	NR	NR	61.0	10.7	62.6	

Treatment	N[a]	% BSA Affected, Mean (SD)[a]	PASI Score, Mean (SD)[a]	Prior Therapies[a]					Inclusion Criteria (Disease Type, Severity, Medication History)[a]
				Topical Agent (%)	Photo-therapy (%)	Conventional Systemic Agents (%)	Biologic Agents (%)	Systemic Agents (%)	
Secukinumab versus ustekinumab trial (1 trial)									
SEC 300 mg	337	32.6 (17.8)	21.7 (8.5)	NR	NR	64.7	14.2	66.8	• Plaque psoriasis • ≥ 18 years of age • ≥ 10% BSA • PASI ≥ 12 • Inadequately controlled on topical, prior systemic, or phototherapy
UST 45/90 mg/kg	339	32.0 (16.8)	21.5 (8.1)	NR	NR	65.8	13.0	68.1	

ADA = adalimumab; APR = apremilast; BID = twice daily; BIW = twice every week; BSA = body surface area; EOW = every other week; ETA = etanercept; IFX = infliximab; IL = interleukin; MTX = methotrexate; NR = not reported; PASI = Psoriasis Area and Severity Index; PL = placebo; PGA = Physician Global Assessment; PSSI = Psoriasis Scalp Severity Index; SD = standard deviation; SEC = secukinumab; TNF = tumour necrosis factor; UST = ustekinumab; UVA = ultraviolet A.

[a] Range (minimum, maximum) is provided from all trials that included one of the specific treatments of interest.

[b] One or more of the trials did not report on this characteristic.

[c] Only specified in the PSOR-010 trial.

[d] Only 2 trials specifically mentioned that patients had moderate-to-severe plaque psoriasis.

[e] Only 1 trial had patients who were also MTX-naive.

[f] The bracketed number represents the standard error.

[g] Mentioned in only 1 trial.

[h] Omitted in 1 trial only.

[I] One trial included this time point.

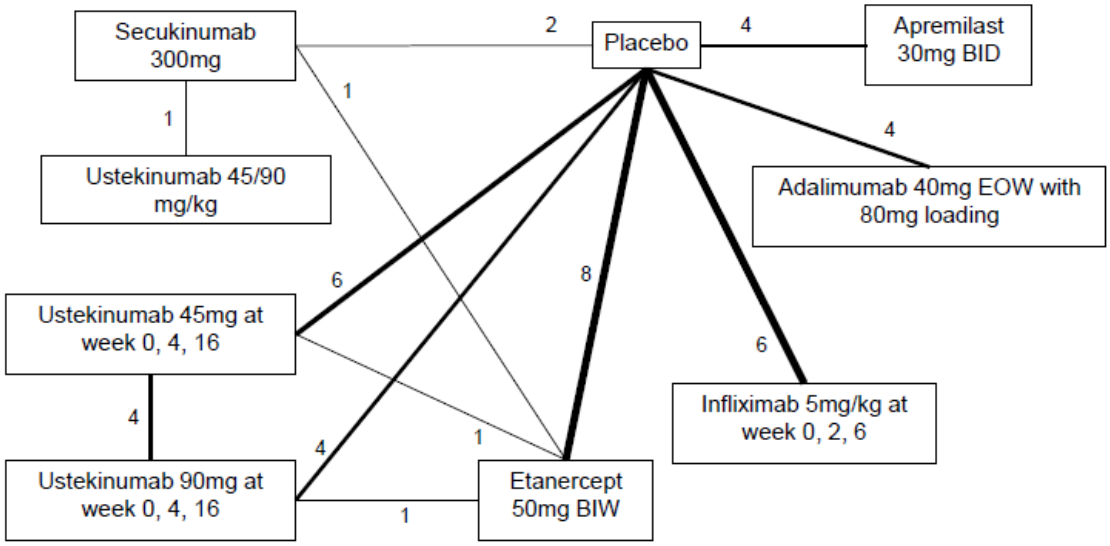
[j] The dosing regimen is potentially unclear, as the description was not provided in the network meta-analysis.

Source: Manufacturer-provided indirect treatment comparison.[47]

Quality Assessment of Included Studies
The critical appraisal of the included studies was performed using a tool developed by the National Institute for Health and Clinical Excellence.

Evidence Network
The only evidence network provided in the ITC was that for the PASI outcomes, due to its complexity and size (it includes all of the trials). It is provided in Figure 3.

FIGURE 3: NETWORK OF TREATMENTS FOR PASI OUTCOMES



BID = twice daily; BIW = twice every week; EOW = every other week; PASI = Psoriasis Area and Severity Index

Source: Manufacturer-provided indirect treatment comparison.[47]

Indirect Treatment Comparison Methods
Bayesian NMA analyses were conducted using WinBUGS software. Both fixed- and random-effects models were evaluated for each outcome, with the model selection determined by model fit statistics, specifically, the deviance information criterion. All outcomes were reported as odds ratios (ORs) with corresponding 95% credible intervals (CrI) except for DLQI results, which were reported as the mean difference from baseline with 95% CrIs. Non-informative priors were used, and all results were based on 50,000 iterations following a burn-in of 10,000. Sample values during the burn-in period were excluded.

With regard to the efficacy analysis (PASI and DLQI) population, the manufacturer used the post–conventional systemic patient subpopulations from the pivotal ESTEEM 1 and 2 and PSOR-10 trials as the comparator for the other (total trial) populations. PASI 75 data for patients (in the ESTEEM trials) with no systemic therapies versus patients with one or more systemic therapies were examined in order to test for comparability. No significant differences in the ORs were observed between the two groups, indicating that the subset of the ESTEEM 1 and 2 trials and the PSOR-10 trial was considered comparable to the population in the other trials. For the safety analysis, all patients in all trials were included.

The authors assessed the comparability of the data by looking at the most appropriate time point to use in their analysis. Scatter plots were created to identify possible associations between treatment outcomes and time to follow-up and baseline PASI scores (with visualization of outlier data and

similarities). Trials with data in the 12 to 16 week time range were assumed acceptable for comparison, as no trends of either increases or decreases in PASI 75 effects were observed during these times.

Heterogeneity was assessed using the Q-statistic for PASI 50, 75, and 90, as there were three or more studies that compared the same set of treatments for these outcomes. Comparisons with *P* values of less than 0.1 were considered heterogeneous. The PASI 50 results with etanercept 50 mg twice a week versus placebo were considered heterogeneous. When the one trial was removed in a sensitivity analysis (Bagel 2012; due to the low placebo probability of achieving the PASI 50 outcome), the *P* value increased, thereby confirming the hypothesis that this trial had a significant impact on the heterogeneity observed in the primary analysis. The PASI 75 results with apremilast 30 mg twice daily indicated that a high placebo response rate of the ESTEEM 2 trial (compared with ESTEEM 1 and Papp 2012) was the major source of heterogeneity. With regard to PASI 90 results, heterogeneity was observed with adalimumab 40 mg every other week (with 80 mg loading) and was perhaps due to the higher placebo response rate in the CHAMPION trial. In a sensitivity analysis where this trial was removed, the *P* value for the Q-statistic increased, suggesting the CHAMPION trial was a major source of heterogeneity. In addition, heterogeneity was observed with ustekinumab 90 mg; the PHOENIX 2 trial had the smallest placebo response and largest ustekinumab response (it was also the largest trial, with 400 patients per group). The manufacturer reported that, ". . . no statistical adjustment for heterogeneity (such as a meta-regression) was possible."[47]

Consistency of the network of data was examined using the consistency "of the ratio between treatment effects estimated directly from the data or indirectly from the mixed treatment comparison."[47] The authors indicated that inconsistency was possible when the following were compared with etanercept: ustekinumab 45 mg, ustekinumab 90 mg, and secukinumab. However, no inconsistency was observed between the results of the NMA and the observed head-to-head data.

Results

Clinical Efficacy

With regard to the PASI 50, 75, and 90 outcomes, [redacted]. Results were similar between both the fixed- and random-effects models. Statistically significantly larger mean improvement differences from baseline in DLQI change when compared with [redacted] that included this outcome in their corresponding trials. Of these, [redacted] had the largest mean difference from baseline followed by [redacted]. Detailed results are provided in Table 17.

TABLE 17: CLINICAL OUTCOME RESULTS (AS ODDS RATIO) COMPARING BIOLOGICS WITH APREMILAST 30 MG

	ADA 40 mg EOW With 80 mg Loading		ETA 50 mg BIW		IFX 5 mg/kg at Week 0, 2, 6		SEC 300 mg		UST 45 mg at Week 0, 4 and Q12W		UST 90 mg at Week 0, 4 and Q12W		UST 45 mg/90 mg	
	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE
PASI 50, OR														
Median	[redacted]													
95% CrI	[redacted]													
PASI 75, OR														
Median	[redacted]													
95% CrI	[redacted]													
PASI 90, OR														
Median	[redacted]													
95% CrI	[redacted]													
DLQI difference from baseline,[a] OR														
Mean difference	[redacted]													
95% CrI	[redacted]													

ADA = adalimumab; BIW = twice a week; CrI = credible interval; DLQI = Dermatology Quality of Life Index; EOW = every other week; ETA = etanercept; FE = fixed-effects; NA = not available; NR = not reported; OR = odds ratio; PASI = Psoriasis Area and Severity Index; Q12W = every 12 weeks; RE = random-effects; SEC = secukinumab; UST = ustekinumab.
Note: The apremilast population used for the comparisons was patients on apremilast 30 mg post–conventional systemics.
[a] The model results of the DLQI analysis in the post–conventional systemic therapy population had a deviance information criterion of 93.06 for the fixed-effects model, and 86.574 for the random-effects model.
[b] Not included in this network.
Source: Manufacturer-provided indirect treatment comparison.[47]

Safety

When compared with apremilast 30 mg, [redacted] had statistically significantly lower odds of inducing overall AEs using both the fixed- and random-effects models. In addition, [redacted] had statistically significantly lower odds of discontinuations due to AEs when compared with apremilast (evidenced using both the fixed- and random-effects models). While no statistically significant differences in ORs were observed for most biologics when compared with apremilast for discontinuations, the fixed-effect model for both [redacted] did show statistically significantly lower odds when compared with apremilast; however, the random-effects model (the more conservative model) did not show this significance.

No statistically significant differences in ORs were evident between [redacted] for infections, SAEs, serious infections, or malignancies. In addition, no information was provided regarding gastrointestinal AEs. Detailed data regarding the harms analysis is provided in Table 18.

TABLE 18: HARMS RESULTS (AS ODDS RATIO) COMPARING BIOLOGICS TO APREMILAST 30 MG

	ADA 40 mg EOW With 80 mg Loading		ETA 50 mg BIW		IFX 5 mg/kg at Week 0, 2, 6		SEC 300 mg		UST 45 mg at Week 0, 4 and Q12W		UST 90 mg at Week 0, 4 and Q12W		UST 45 mg/90 mg	
	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE
Overall AEs,[a] OR														
Median	[redacted]													
95% CrI	[redacted]													
Infections,[b] OR														
Median	[redacted]													
95% CrI	[redacted]													
SAEs,[c] OR														
Median	[redacted]													
95% CrI	[redacted]													
Serious Infections,[d] OR														
Median	[redacted]													
95% CrI	[redacted]													
Malignancies,[f] OR														
Median	[redacted]													
95% CrI	[redacted]													
Discontinuations,[g] OR														
Median	[redacted]													
95% CrI	[redacted]													
Discontinuations due to AEs,[h] OR														
Median	[redacted]													

	ADA 40 mg EOW With 80 mg Loading		ETA 50 mg BIW		IFX 5 mg/kg at Week 0, 2, 6		SEC 300 mg		UST 45 mg at Week 0, 4 and Q12W		UST 90 mg at Week 0, 4 and Q12W		UST 45 mg/90 mg	
	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE
95% CrI	[redacted]													

ADA = adalimumab; AE = adverse event; BIW = every week; CrI = credible interval; DIC = deviance information criterion; ETA = etanercept; EOW = every other week; FE = fixed-effects; IFX = infliximab; OR = odds ratio; Q12W = every 12 weeks; RE = random-effects; SAE = serious adverse event; SEC = secukinumab; UST = ustekinumab.

[a] The model results of the overall AEs analysis had a DIC of 85.983 for the fixed-effects model and 88.14 for the random-effects model.

[b] The model results of the infections analysis had a DIC of 80.09 for the fixed-effects model and 81.74 for the random-effects model.

[c] The model results of the SAEs analysis had a DIC of 79.56 for the fixed-effects model and 81.13 for the random-effects model.

[d] The model results of the serious infections analysis had a DIC of 47.15 for the fixed-effects model and 48.99 for the random-effects model.

[e] Not included in this network.

[f] The model results of the malignancies analysis had a DIC of 42.61 for the fixed-effects model and 44.25 for the random-effects model.

[g] The model results of the discontinuation analysis had a DIC of 104.25for the fixed-effects model and 104.31 for the random-effects model.

[h] The model results of the discontinuations due to AEs analysis had a DIC of 93.91 for the fixed-effects model and 95.51 for the random-effects model.

Source: Manufacturer-provided indirect treatment comparison.[47]

Critical Appraisal

Based on the information reported in the manufacturer's submitted NMA documents, a comprehensive systematic review was performed with a two-stage selection process, whereby articles were first selected based on titles and abstracts, and then full-text articles were retrieved and examined for their inclusion criteria. In addition, data extraction was performed with reasonable verification steps to ensure the data extracted were correct. Many aspects of the conduct of the NMA were well reported and appeared appropriate, such as discussion and reasoning provided for the type of models used (random- or fixed-effects, model choice guided by the deviance information criterion), using appropriate measures for continuous and dichotomous outcomes, the assessment of heterogeneity, and the inclusion of a network diagram (although only one was provided). In-depth discussions supporting the manufacturer's use of the aforementioned were provided to explain the relevance and appropriateness of each.

There appeared to be some differences observed among the trials, most notably with regard to some patient baseline characteristics and trial methods. Regarding patient characteristics, differences were most evident regarding previous treatment history (including not only previous therapies, but also including patients who were treatment-naive and those who were treatment-experienced). In addition, a sensitivity analysis was not conducted on this particular patient characteristic; therefore, the consistency and generalizability of the results to all patient populations contains some degree of uncertainty. With regard to the trial methodology, differences were observed between trials with regard to sample sizes (as there was substantial variation in treatment groups between trials, with a per–treatment group range of 32 to 814), and time points related to outcome assessments. The manufacturer provided assessments indicating there was no apparent trend that treatment effect (versus placebo) increased or decreased over the range of time points available from trials. The potential impact of the large variation in sample size for certain network links on the power and precision of the NMA is uncertain. While most trials reported prior systemic therapy use (of at least 50%), some studies did not report this; therefore, the authors assumed the trials contained post–conventional therapy patients, which may not be a valid assumption. In addition, while almost all studies did not allow concomitant therapies, some studies made no specific mention of this and, therefore, it is unknown whether some patients were actually treated differently from the majority of patients, thus furthering the uncertainty surrounding the estimates of effect.

While the manufacturer sought to examine the efficacy and safety of the approved biologics relative to apremilast, more robust and conclusive results would have been achieved had the manufacturer included all appropriate comparators, including all conventional systemic therapies (e.g., cyclosporine and methotrexate) and phototherapy. Without all of the comparators, one cannot make a comprehensive decision regarding the efficacy and safety surrounding the use of apremilast for patients with chronic plaque psoriasis.

The trials included in the NMA were generally short-term (mostly < 16 weeks); hence, there remains uncertainty as to the longer-term comparative efficacy and safety of apremilast. In addition, there remains uncertainty surrounding one of the prior treatment therapy groups (observed in the patient characteristics) and in one of the treatment groups that was often used in the analysis (specifically the ustekinumab 45 mg/90 mg group). With regard to the grouping of prior therapies (Table 16), no description was provided for the "Systemic Agents" group and how it was different (if at all) from the "Conventional Systemic Agents" group. For the treatment groups, there was also no formal explanation regarding whether the ustekinumab 45 mg/90 mg group included patients who had been treated with both, or whether this was a combined group.

The PASI efficacy outcome was assessed in all trials (included as either PASI 50, 75, or 90) and the DLQI was also assessed in a significant number of trials. This was important, according to the clinical expert assigned to this formulary submission, as these are two of the most prominent efficacy outcome measures examined in psoriasis trials and clinically relevant for patients. In addition, safety outcomes were assessed in the NMA, which is also relevant for clinical practice and for patients; however, the manufacturer did not provide a separate NMA analysis for gastrointestinal AEs, presumably due to the lack of reporting of these symptoms in the trials. Doses and dosing regimens are all applicable to the Canadian population, as only those that have been approved for use in Canada were included in this NMA. In addition, the manufacturer identified four studies that were rated "poor" quality; however, no sensitivity analysis was provided to ensure that the removal of these studies affected the effect estimates produced through the NMA.

The manufacturer provided additional sensitivity analyses using the total population of the ESTEEM 1 and 2 studies. The results indicated that the OR of PASI 75 for all treatments versus apremilast was similar to the original analysis; therefore, one can assume that no bias or uncertainty was introduced into the results.

Conclusion

The manufacturer-provided ITC[47] included a comprehensive systematic review and, for the most part, a comprehensive Bayesian NMA. While the methodology appeared mostly sound for the NMA, there were some limitations associated with the trial methods and baseline characteristics of the included studies, along with the apremilast comparator group being the systemic-experienced subpopulation for the efficacy analysis, instead of the entire population.

Statistically significant results favouring all of the biologic treatments over apremilast were evident [redacted] With regard to harms, [redacted] all provided statistically significantly lower odds of overall occurrence of adverse events relative to apremilast (with both the fixed- and random-effects models). In addition, [redacted] also provided statistically significantly lower odds of discontinuations due to AEs relative to [redacted]. There were no statistically significance differences between treatments with regard to the other safety outcomes (SAEs, discontinuations, infections, serious infections, and malignancies).

Based on the available indirect evidence, the most conservative conclusion is that the biologic agents approved for the treatment of patients with chronic moderate-to-severe plaque psoriasis provide [redacted] relative to apremilast 30 mg. In addition, [redacted]. There were no other significant differences with regard to the harms data.

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