Common Drug Review
Clinical Review Report

November 2016

Drug	ustekinumab (Stelara) Injection
Indication	The treatment of adult patients with active psoriatic arthritis alone or in combination with methotrexate.
Listing request	For use alone, or in combination with methotrexate, for the treatment of moderate to severe psoriatic arthritis following failure or intolerance to methotrexate or other DMARDs, or anti-TNF alpha therapies.
Manufacturer	Janssen Inc.

This 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 rheumatology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH 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.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

ACR	American College of Rheumatology
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
CDR	CADTH Common Drug Review
CRP	C-reactive protein
DLQI	Dermatology Life Quality Index
DAS	Disease Activity Score
DMARD	disease-modifying antirheumatic drug
ESR	erythrocyte sedimentation rate
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire–Disability Index
ICUR	incremental cost-utility ratio
IL	interleukin
MASES	Maastricht Ankylosing Spondylitis Disease Activity Score
MCS	mental component summary (of the SF-36)
MCID	minimal clinically important difference
MTC	mixed treatment comparison
NSAID	nonsteroidal anti-inflammatory drug
PCS	physical component summary (of the SF-36)
PASI	Psoriasis Area Severity Index
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
QALY	quality-adjusted life-year
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
TNF	tumour necrosis factor
VAS	visual analogue scale
vdHS	van der Heijde-Sharp scale

EXECUTIVE SUMMARY

Introduction

The objective of this report is to perform a systematic review of the beneficial and harmful effects of ustekinumab 45 mg or 90 mg for the treatment of active psoriatic arthritis in adults, alone or in combination with methotrexate. Ustekinumab is a fully human IgG1 kappa monoclonal antibody that binds to the shared p40 subunit of interleukin (IL)-12 and IL-23[1] and is administered by subcutaneous injection of 45 mg or 90 mg at weeks 0 and 4 and every 12 weeks thereafter.[2]

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that can be associated with psoriasis, a skin disease.[2] This seronegative form of arthritis can cause inflammation of the peripheral and axial joints, enthesitis, dactylitis, psoriatic skin lesions, and symptoms such as fatigue that are linked to systemic inflammation. Several classes of drugs are employed in the treatment of PsA, including nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs; i.e., methotrexate, sulfasalazine, and leflunomide), immunosuppressives (cyclosporine), and tumour necrosis factor (TNF) alpha inhibitors (i.e., etanercept, infliximab, golimumab, adalimumab, and certolizumab). Methotrexate remains the most frequently used DMARD despite limited evidence (two small controlled trials of inadequate power) that evaluated methotrexate for PsA.[3,4]

Indication under review
The treatment of adult patients with active psoriatic arthritis alone or in combination with methotrexate.
Listing criteria requested by sponsor
For use alone, or in combination with methotrexate, for the treatment of moderate to severe psoriatic arthritis following failure or intolerance to methotrexate or other DMARDs, or anti-TNF alpha therapies.

Results and Interpretation

Included Studies

Two manufacturer-sponsored, published, double-blind randomized controlled trials, PSUMMIT1 and PSUMMIT2 (N = 927 total), evaluating the efficacy and harms of ustekinumab 45 mg and 90 mg compared with placebo in patients with active psoriatic arthritis were included in the systematic review. The patients were blinded for 108 weeks (PSUMMIT1) and 60 weeks (PSUMMIT2), but only the first 24 weeks of both studies were placebo-controlled. The primary outcome in both studies was the proportion of patients achieving American College of Rheumatology (ACR) score 20 response at week 24. Patients are considered ACR 20 responders if they achieve a 20% improvement from baseline in swollen and tender joint counts as well as for any three of the five ACR criteria. Patients included in both trials had active disease either despite having been treated with DMARDs or NSAIDs or both, or as a result of intolerance to DMARDs or NSAIDs or both. No concomitant DMARDs, with the exception of methotrexate, were allowed during the study. Patients who previously used anti-TNF alpha therapy were not eligible for PSUMMIT1, but 60% of patients in PSUMMIT2 had previously used anti-TNF alpha therapy.

The studies allowed early escape at week 16, and all patients taking placebo were reassigned to ustekinumab at week 24. This design has numerous limitations, including the fact that patients who meet early escape criteria are not randomized to dose escalation or another type of strategy. Early

escape, while common in psoriatic arthritis trials based on ethical considerations, limits the interpretation and clinical relevance of the trial data.

Efficacy

In both trials there was a statistically significantly greater proportion of ACR 20 responders at week 24 in both ustekinumab 45 mg and 90 mg groups compared with placebo ($P < 0.001$ for all comparisons versus placebo). In PSUMMIT1, the mean percentage difference (95% confidence interval [CI]) for ustekinumab 45 mg versus placebo was 20% (11% to 28%), and, for ustekinumab 90 mg versus placebo, it was 27% (18% to 36%). In PSUMMIT2, the absolute risk reduction (95% CI) for ustekinumab 45 mg versus placebo was 24% (11% to 36%), and, for ustekinumab 90 mg versus placebo, it was 24% (11% to 36%).

In general, there were more secondary outcomes with statistically significant results in PSUMMIT1 than in PSUMMIT2. This may have been related to the smaller sample size in PSUMMIT2, or the different population (anti-TNF alpha experienced patients). Statistically significant improvements in ACR 50 response (i.e., a 50% improvement from baseline in swollen and tender joint counts) were observed in both trials favouring ustekinumab 45 mg and 90 mg versus placebo, but, for ACR 70 response rates (i.e., a 70% improvement from baseline in swollen and tender joint counts), the differences were statistically significant only in PSUMMIT1. The van der Heijde-Sharp (vdHS) scale, also known as the modified Sharp scale, measures radiographic changes. Scores range from 0 to 528, with higher scores indicating greater disease severity. The vdHS scores showed statistically significantly less worsening in the ustekinumab groups relative to placebo in the manufacturer's pooled analysis of both trials (placebo 1.0 versus ustekinumab 45 mg 0.4 versus ustekinumab 90 mg 0.4). The differences were statistically significant, but the clinical relevance of a difference of 0.6 on a scale that ranges from 0 to 528 is uncertain. Other secondary outcomes that measured impact on psoriatic arthritis symptoms showed statistically significant differences favouring ustekinumab 45 mg and 90 mg versus placebo in PSUMMIT1, including the Health Assessment Questionnaire–Disability Index (HAQ-DI) score change, Psoriatic Arthritis Response Criteria (PsARC) response, Disease Activity Score (DAS 28) response, DAS 28 remission, incidence of dactylitis and enthesitis, and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI 20/50/70). However, in PSUMMIT2, there were no statistically significant improvements for ustekinumab 45 mg versus placebo for DAS 28 remission, enthesitis, dactylitis or BASDAI 20/50/70.

Skin response was measured in patients with 3% or more of body surface area affected at baseline (approximately three-quarters of the study populations). Treatment with ustekinumab 45 mg and 90 mg resulted in statistically significant improvements in Psoriasis Area Severity Index (PASI) 75 response rate and Dermatology Life Quality Index (DLQI) score change at week 24 in both trials ($P < 0.001$ for all comparisons versus placebo).

Patient-reported outcomes showed statistically significant improvements in quality of life (Short Form [36] Health Survey [SF-36] physical component), work productivity, and time lost from work. There were no clear improvements seen in measures of employability. The SF-36 mental component results were not statistically significantly different for the ustekinumab 45 mg dose in PSUMMIT1 or for either ustekinumab dose in PSUMMIT2. This could indicate that ustekinumab has a positive impact on physical functioning, although the clinical significance of the differences between ustekinumab and placebo were uncertain at week 24.

In PSUMMIT2, the ACR 20 and PAS I75 response rates were lower in patients who had previously used an anti-TNF alpha drug compared with those who had not previously used an anti-TNF alpha drug. Similar observations have been made in observational studies of psoriatic arthritis that examined the response to subsequent anti-TNF drugs following failure of a trial with a first anti-TNF drug.[5,6] PSUMMIT1 and PSUMMIT2 do little to address the question of selecting optimal treatment strategies for patients who are non-responders to a TNF alpha inhibitor. One could simply observe that, similar to switching to a second anti-TNF alpha drug, the likelihood of response is lower after switching to ustekinumab from an anti-TNF drug.

Harms

The only placebo-controlled data likely unbiased by patient early escape are from week 16 for both studies; all data after this time point are of limited value for harms assessment. At week 16, the rates of serious adverse events (SAEs) in the treatment groups of both studies ranged from 2% to 5%. There were no obvious trends or differences observed between treatment and placebo for any specific SAE. Approximately half of all patients experienced an adverse event through week 16. The rates of total adverse events were similar across treatment groups. The most common group of adverse events was infections, and the most common specific adverse event was nasopharyngitis. Through week 16, withdrawals due to adverse events were lower in the ustekinumab groups compared with placebo. While there were no statistical analyses performed on the harms data at week 16, there did not appear to be any new issues related to harm for ustekinumab relative to the information already presented in the product monograph for psoriasis.

While the manufacturer reported incidence of adverse events up to week 108 (PSUMMIT1) and week 60 (PSUMMIT2), these data have limited valued in understanding the risks associated with ustekinumab because there was no control group (see APPENDIX 4: DETAILED OUTCOME DATA) [redacted] There were several malignancies reported, including B-cell lymphoma, renal cell carcinoma, and squamous cell carcinoma in PSUMMIT1. In PSUMMIT2, there was a single case of breast cancer.

The harms profile of ustekinumab in patients with psoriatic arthritis deserves further study in long-term controlled and observational studies. The PSUMMIT1 and PSUMMIT2 trials excluded patients who were at increased risk of developing specific adverse events associated with the use of ustekinumab (e.g., serious infections) and thus may not reflect the incidence in clinical practice.

Other Considerations

ACR 20 and PAS I75 are commonly used end points in psoriatic arthritis trials. The ACR 20 and PAS I75 response rates in the PSUMMIT1 and PSUMMIT2 trials appear lower than the rates observed for the same outcomes at the same time point in trials using anti-TNF alpha drugs in psoriatic arthritis (see APPENDIX 6: SUMMARY AND APPRAISAL OF MANUFACTURER-SUBMITTED MIXED TREATMENT COMPARISON). It is difficult to draw conclusions without head-to-head trials, since the difference may be related to trial population differences. However, the manufacturer's mixed treatment comparison (MTC) suggested ustekinumab had consistently lower response rates for outcomes related to psoriatic arthritis and psoriasis compared with other anti-TNF alpha drugs.

Pharmacoeconomic Summary

Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis in which ustekinumab, golimumab, infliximab, adalimumab, and etanercept were compared with placebo. The analysis was based mainly on patients' response to treatment, which was estimated using PsARC. Patients who achieve a PsARC response continue treatment, while those who do not discontinue treatment. Within the model, patients could stay in their current health state or transition to conventional management (equivalent to placebo) based on their PASI75 response and Health Assessment Questionnaire–Disability Index (HAQ-DI) scores from the clinical trials. The manufacturer included analyses for both anti-TNF alpha naive and anti-TNF alpha experienced patients. In the anti-TNF alpha naive comparison, the comparators are other similarly indicated DMARDs (golimumab, infliximab, adalimumab, and etanercept) and placebo, while in the anti-TNF alpha experienced population, the comparator was placebo. The base case assesses response at 24 weeks for ustekinumab, while all other treatments are assessed at 12 weeks. For the anti-TNF alpha naive population, where possible and appropriate, the relative treatment effects for each comparator for PsARC and PASI response rates were estimated using MTC techniques. In the anti-TNF alpha experienced population, efficacy values were taken directly from the PSUMMIT2 study for the subgroup of patients who had received prior anti-TNF alpha therapy.

Results of Manufacturer's Analysis

In the anti-TNF alpha naive population, ustekinumab is associated with an incremental cost per quality-adjusted life-year (QALY) gained of $40,958 compared with placebo. When compared with other biologic treatment, ustekinumab was less effective (fewer QALYs) but slightly less expensive than adalimumab, etanercept, and infliximab. Ustekinumab was dominated (more expensive and less effective) by golimumab.

In the anti-TNF alpha experienced population, the incremental cost-utility ratio (ICUR) for ustekinumab compared with placebo was $46,962 per QALY gained.

Interpretations and Key Limitations

The manufacturer's MTC reported that other biologic treatments are associated with greater clinical benefits in terms of PsARC, ACR 20, and PAS I75 response. Drug treatment costs for the majority of the biologics are less than that of ustekinumab. Consequently, based on the manufacturer's analysis, there are biologic treatments that are more cost-effective than ustekinumab. CADTH Common Drug Review (CDR) noted limitations with the manufacturer's analysis that impacted disease progression assumptions.

Results of CADTH Common Drug Review Analysis

CDR reanalyses tested several identified limitations, resulting in an ICUR of $73,082 for ustekinumab compared with placebo for the most likely scenario in patients with no prior exposure to anti-TNF alpha treatment and $82,611 for patients with prior anti-TNF alpha experience.

Pharmacoeconomic Conclusions

Based on the manufacturer's MTC, other biologics appear to have greater clinical efficacy compared with ustekinumab, but ustekinumab treatment costs are greater than other biologics (with the exception of infliximab) for patients with no prior exposure to anti-TNF alpha treatment. For patients with prior exposure to anti-TNF alpha treatment, CDR estimated that the ICUR for ustekinumab could be $82,611 compared with placebo, under more conservative scenarios.

Conclusions

In two double-blind randomized controlled trials in patients with active psoriatic arthritis, ustekinumab 45 mg or 90 mg was associated with improved rates of ACR 20 response at week 24 compared with placebo. Other outcomes such as the HAQ-DI, PAS I75, PsARC, DAS 28 response, DLQI, and SF-36 also showed statistically significant improvements favouring ustekinumab versus placebo at week 24. Some outcomes did not reach statistical significance in PSUMMIT2 at week 24, such as proportion of patients with enthesitis, dactylitis, DAS 28 remission, and disease activity. The focus of the analyses of both trials was the week 24 time point, and an early escape rule was applied to all statistical analyses at this time point, potentially weakening the internal validity of the results.

There is a risk of serious harm such as malignancies and infections for ustekinumab, which is similar to other anti-TNF alpha drugs used to treat psoriatic arthritis. Without direct comparisons, it is not possible to ascertain the risks relative to these other commonly used drugs. Given that psoriatic arthritis is a chronic condition that will be treated over a lifetime, a 24-week controlled trial is a short duration to evaluate harms.

TABLE 1: SUMMARY OF RESULTS FOR PSUMMIT1 AT WEEK 24

Outcome	PL N = 206	UST 45 mg N = 205	MDC (95% CI), *P* value UST 45 mg Versus PL	UST 90 mg N = 204	MDC (95% CI), *P* value UST 90 mg Versus PL
Outcomes Related to Psoriatic Arthritis					
ACR 20	47/206 (23%)	87/205 (42%)	20 (11 to 28), *P* < 0.001	101/204 (50%)	27 (18 to 36) *P* < 0.001
ACR 50	18/206 (9%)	51/204 (25%)	16 (9 to 23) *P* < 0.001	57/204 (28%)	19 (12 to 26) *P* < 0.001
ACR 70	5/206 (2%)	25/204 (12%)	10 (5 to 15) *P* < 0.001	29/204 (14%)	12 (7 to 17) *P* < 0.001
HAQ-DI **Mean baseline score (SD)** **Change at week 24 (SD)** **Improvement ≥ 0.3 units, n (%)**	 1.24 (0.65) –0.10 (0.39) 58/206 (28%)	 1.22 (0.61) –0.31 (0.52) 98/205 (48%)	 *P* < 0.001 *P* < 0.001	 1.22 (0.63) –0.40 (0.51) 97/204 (48%)	 *P* < 0.001 *P* < 0.001
PsARC response, n (%)	77/206 (37%)	115/205 (56%)	19 (9 to 28)[a] *P* < 0.001	132/204 (65%)	27 (18 to 37)[a] *P* < 0.001
DAS 28 response, n (%)	71/206 (35%)	135/205 (66%)	*P* < 0.001	138/204 (68%)	*P* < 0.001
DAS 28 remission, n (%)	17/206 (8%)	42/205 (20%)	*P* < 0.001	40/204 (20%)	*P* < 0.001
Patients with dactylitis,[b] n (%)	70/92 (76%)	56/99 (57%)	*P* = 0.005	53/95 (56%)	*P* = 0.004
Patients with enthesitis,[c] n (%)	111/137 (81%)	96/140 (69%)	*P* = 0.018	90/148 (61%)	*P* < 0.001
BASDAI 20,[d] n (%) **BASDAI 50, n (%)** **BASDAI 70, n (%)**	16/61 (26%) 8/61 (13%) 0	25/51 (49%) 12/51 (24%) 7/51 (14%)	*P* = 0.013 *P* = 0.13 *P* = 0.003	35/60 (58%) 19/60 (32%) 9/60 (15%)	*P* < 0.001 *P* = 0.01 *P* = 0.002
Outcomes Related to Psoriasis					
PASI 75[f]	16/146 (11%)	83/145 (57%)	46 (37 to 56)[a] *P* < 0.001	93/149 (62%)	52 (42 to 61)[a] *P* < 0.001
DLQI **Mean change from baseline (SD)[f]** **Score of 0 or 1, n (%)[g]**	[redacted] 11/132 (8%)	[redacted] 48/129 (37%)	*P* < 0.001 *P* < 0.001	[redacted] 71/134 (53%)	*P* < 0.001 *P* < 0.001

Outcome	PL N = 206	UST 45 mg N = 205	MDC (95% CI), *P* value UST 45 mg Versus PL	UST 90 mg N = 204	MDC (95% CI), *P* value UST 90 mg Versus PL
Quality of Life Outcomes					
SF-36 Physical Component Baseline score Change at week 24	[redacted] 1.40 (7.09)	[redacted] 4.89 (9.33)	*P* < 0.001	[redacted] 6.22 (8.75)	*P* < 0.001
SF-36 Mental Component Baseline score Change at week 24	[redacted] 1.53 (9.58)	[redacted] 3.35 (10.02)	*P* = 0.065	[redacted] 4.79 (10.05)	*P* < 0.001

ACR = American College of Rheumatology score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; DAS = Disease Activity Score; DLQI = Dermatology Life Quality Index; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire–Disability Index; NSAID = nonsteroidal anti-inflammatory drugs; MDC = mean difference of change; RF = rheumatoid factor; PL = placebo; PASI = Psoriasis Area Severity Index; PsARC = Psoriatic Arthritis Response Criteria; SF-36 = Short Form (36) Health Survey; TNF = tumour necrosis factor; UST = ustekinumab.

[a] CDR calculated.

[b] Analysis only included patients with at least one digit with dactylitis at baseline.

[c] Analysis only included patients with Maastricht ankylosing spondylitis enthesitis score ≥ 1 at baseline.

[d] BASDAI was measured only in patients with spondylitis and peripheral joint involvement at baseline.

[e] Analysis only included patients with ≥ 3% body surface area affected by psoriasis at baseline.

[f] Analysis only included patients with ≥ 3% body surface area with psoriasis skin involvement at baseline.

[g] Analysis only in patients with DLQI score > 1 at baseline.

Note: Data are n (%), n/N (%) or mean (SD).

Source: Manufacturer's Clinical Study Report for PSUMMIT1.[7]

TABLE 2: SUMMARY OF RESULTS FOR PSUMMIT2 AT WEEK 24

Outcome	PL N = 104	UST 45 mg N = 103	MDC (95% CI), *P* value UST 45 mg versus PL	UST 90 mg N = 105	MDC (95% CI), *P* value UST 90 mg versus PL
Outcomes Related to Psoriatic Arthritis					
ACR 20	21 (20%)	45 (44%)	24 (11 to 36) *P* < 0.001	46 (44%)	24 (11 to 36) *P* < 0.001
ACR 50	7 (7%)	18 (18%)	11 (2 to 20)[a] *P* = 0.018	24 (23%)	16 (7 to 25)[a] *P* < 0.001
ACR 70	3 (3%)	7 (7%)	4 (–2 to 10)[a] *P* = 0.17	9 (9%)	6 (–1 to 12)[a] *P* = 0.06
HAQ-DI **Mean baseline score (SD)** **Change at week 24 (SD)** **Improvement ≥ 0.3 units, n (%)**	 1.25 (0.72) –0.03 (0.38) 17/104 (16%)	 1.34 (0.70) –0.21 (0.46) 35/103 (34%)	 *P* = 0.002 *P* = 0.003	 1.29 (0.67) –0.22 (0.44) 40/105 (38%)	 *P* < 0.001 *P* < 0.001
PsARC response, n (%)	[redacted]	[redacted]	[redacted][a]	[redacted]	[redacted][a]
DAS 28 response at week 24, n (%)	31/104 (30%)	56/103 (54%)	*P* < 0.001	56/105 (53%)	*P* < 0.001
DAS 28 remission at week 24, n (%)	4/104 (4)	11/103 (11)	*P* = 0.06	16/105 (15%)	*P* = 0.005
Patients with dactylitis[b] at week 24, n (%)	25/33 (76%)	30/46 (65%)	*P* = 0.31	22/38 (58%)	*P* = 0.12
Patients with enthesitis[c] at week 24, n (%)	60/68 (88%)	53/70 (76%)	*P* = 0.045	49/70 (70%)	*P* = 0.005
BASDAI 20,[d] n (%) **BASDAI 50, n (%)** **BASDAI 70, n (%)**	10/18 (56%) 1/18 (6%) [redacted]	15/25 (60%) 7/25 (28%) [redacted]	*P* = 0.68 *P* = 0.07 [redacted]	11/21 (52%) 8/21 (38%) [redacted]	*P* = 0.94 *P* = 0.019 [redacted]
Outcomes Related to Psoriasis					
PASI 75 at week 24[e]	4/80 (5)	41/80 (51)	46 (34 to 58)[a] *P* < 0.001	45/81 (56)	51 (39 to 63)[a] *P* < 0.001
DLQI **Mean change from baseline (SD)[f]** **Score of 0 or 1, n (%)[g]**	 8/72 (11%)	 26/73 (36%)	 *P* < 0.001	 29/68 (43%)	 *P* < 0.001

Outcome	PL N = 104	UST 45 mg N = 103	MDC (95% CI), *P* value UST 45 mg versus PL	UST 90 mg N = 105	MDC (95% CI), *P* value UST 90 mg versus PL
Quality of Life Outcomes					
SF-36 Physical Component **Baseline score** **Mean change at week 24 (SD)**	29.4 [redacted]	28.0 [redacted]	[redacted]	28.2 [redacted]	[redacted]
SF-36 Mental Component **Baseline score** **Mean change at week 24 (SD)**	41.8 [redacted]	43.7 [redacted]	[redacted]	41.4 [redacted]	[redacted]

ACR = American College of Rheumatology score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; DAS = Disease Activity Score; DLQI = Dermatology Life Quality Index; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire–Disability Index; NSAID = nonsteroidal anti-inflammatory drugs; MDC = mean difference of change; RF = rheumatoid factor; PL = placebo; PASI = Psoriasis Area Severity Index; PsARC = Psoriatic Arthritis Response Criteria; SF-36 = Short Form (36) Health Survey; TNF = tumour necrosis factor; UST = ustekinumab.

[a] CDR calculated.

[b] Analysis only included patients with at least one digit with dactylitis at baseline.

[c] Analysis only included patients with Maastricht ankylosing spondylitis enthesitis score ≥ 1 at baseline.

[d] BASDAI was only measured in patients with spondylitis and peripheral joint involvement at baseline.

[e] Analysis only included patients with ≥ 3% body surface area affected by psoriasis at baseline.

[f] Analysis only included patients with ≥ 3% body surface area with psoriasis skin involvement at baseline.

[g] Analysis only in patients with DLQI score > 1 at baseline.

Note: Data are n (%), n/N (%) or mean (SD).

Source: Manufacturer's Clinical Study Report PSUMMIT2.[8]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that can be associated with psoriasis, a skin disease.[2] This seronegative form of arthritis can cause inflammation of the peripheral and axial joints, enthesitis, dactylitis, psoriatic skin lesions and symptoms, such as fatigue, that are linked to systemic inflammation. It results in significant disease burden, functional impairment, increased comorbidity and mortality, and reduced health-related quality of life.[2,9,10] Approximately 2% of the population have psoriasis, and between 20%[10,11] and 40%[12] of patients with skin and nail psoriasis are reported to have PsA, suggesting its prevalence is similar to that of rheumatoid arthritis.[10] If left untreated or if treatment is suboptimal, destructive changes to joints and bone proliferation are common and quality of life can further decrease.[2,3] With effective treatment, functional disabilities and quality of life can effectively be improved;[11] however, there is no one treatment regimen that works on every person and, hence, different treatment options are required.

1.2 Standards of Therapy

Clinical practice guidelines provide definitions of mild, moderate, and severe psoriatic arthritis, but these definitions vary with the symptoms being considered.[13] For example, with respect to peripheral arthritis, mild disease is considered involvement of fewer than five joints with no damage on radiography; moderate disease is considered five or more joints with damage on radiography and moderate impact on function and quality of life; and severe disease is considered involvement of five or more joints with severe damage on radiography and a severe impact on function and quality of life. With respect to psoriasis, body surface area (BSA) involvement of less than 5% and a Psoriasis Area Severity Index (PASI) score greater than 5 is considered mild disease; non-response to topical therapies and a PASI score less than 10 is considered moderate disease; BSA involvement of more than 10% and a PASI score more than 10 is considered severe disease. With respect to enthesitis, mild disease is considered involvement of one or two sites with no loss of function; moderate disease is considered involvement of more than two sites or loss of function; and severe disease is considered loss of function or involvement of more than two sites and failure of response. Other symptoms that should be assessed for severity include spinal disease and dactylitis. Therefore, severity of disease in psoriatic arthritis is difficult to classify and can depend on how the disease manifests itself in each person and how severe the various symptoms are.

Several drug classes are employed in the treatment of PsA, including nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs; i.e., methotrexate, sulfasalazine, and leflunomide), immunosuppressives (cyclosporine), and tumour necrosis factor (TNF) alpha inhibitors (i.e., etanercept, infliximab, golimumab, adalimumab, and certolizumab). Methotrexate remains the most frequently used DMARD despite limited evidence (two small controlled trials of inadequate power) that evaluated methotrexate for PsA.[3,4] Should the DMARDs fail or if there are contraindications, the next line of treatment is the biologic TNF alpha inhibitors. If the first TNF alpha inhibitor fails, then another TNF alpha inhibitor can be offered.

1.3 Drug

Ustekinumab is a fully human IgG1 kappa monoclonal antibody that binds to the shared p40 subunit of interleukin (IL)-12 and IL-23.[1] It has an alternative mechanism of action, in which interaction of the IL-12/IL-23 p40 subunit with IL-12R beta 1 is prevented and blocks further signalling.[3] Ustekinumab is administered by subcutaneous injection of 45 mg or 90 mg at weeks 0 and 4 and every 12 weeks thereafter.[2] Ustekinumab is also indicated for the treatment of adults with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[1]

Indication under review
The treatment of adult patients with active psoriatic arthritis alone or in combination with methotrexate.
Listing criteria requested by sponsor
For use alone, or in combination with methotrexate, for the treatment of moderate to severe psoriatic arthritis following failure or intolerance to methotrexate or other DMARDs, or anti-TNF alpha therapies.

TABLE 3: KEY CHARACTERISTICS OF USTEKINUMAB AND OTHER ANTI-TNF DRUGS

	Ustekinumab	Other Anti-TNF Drugs[a]
Mechanism of Action	Binds to the shared p40 subunit of human cytokines IL-12 and IL-23, preventing their binding to the IL-12R beta 1 receptor protein on surface immune cells.	Inhibits binding of TNF to TNF receptors.
Indication[b]	Alone or in combination with MTX, ustekinumab is indicated for the treatment of adult patients with active PsA. Ustekinumab is indicated in adult patients for the treatment of chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy.	**ADA, ETA, GOL (PsA-specific indications only)** Alone or in combination with MTX, in adult patients with PsA the drug is indicated for: • reducing signs or symptoms • inhibiting progression of structural damage • improving physical function. **CERT** In adult patients with moderately to severely active PsA who have failed one or more DMARD(s), is indicated for: • reducing signs or symptoms • inhibiting progression of structural damage assessed by X-ray • improving physical function. **INF** In patients with PsA, in indicated for: • reducing signs or symptoms • inducting major clinical response • inhibiting progression of structural damage • improving physical function.
Route of Administration	SC	**ADA, ETA, GOL, CERT:** SC **INF:** IV
Recommended Dose	• 45 mg administered at weeks 0 and 4, then every 12 weeks thereafter • Alternately, 90 mg may be used in patients with a body weight > 100 kg	**ADA:** 40 mg administered every other week **ETA:** 50 mg per week **GOL:** 50 mg once a month, on same date each month **CERT:** loading dose of 400 mg (given as 200 mg separate SC injections) at weeks 0, 2, and 4, followed by 200 mg every 2 weeks or 400 mg every 4 weeks (may be considered) **INF:** 5 mg/kg as IV infusion followed with additional similar doses at 2 and 6 weeks after initial infusion, then every 8 weeks thereafter.
Serious Side Effects/ Safety Issues	• infections and reactivation of latent infections • injection site reactions • malignancies • RPLS	• infections, **particularly opportunistic ones such as TB** • malignancies • allergic reactions • injection or infusion site reactions

ADA = adalimumab; CERT = certolizumab pegol; DMARD = disease-modifying antirheumatic drugs; ETA = etanercept; GOL = golimumab; IL = interleukin; INF = infliximab; IV = intravenous injection; MTX = methotrexate; PsA = psoriatic arthritis; PsO = plaque psoriasis; RPLS = reversible posterior leukoencephalopathy syndrome; SC = subcutaneous injection; TB = tuberculosis; TNF = tumour necrosis factor.

[a] Includes those indicated for psoriatic arthritis in Canada: adalimumab, etanercept, golimumab, certolizumab pegol, and infliximab.

[b] Health Canada indication.

Source: Stelara product monograph,[1] adalimumab product monograph,[14] etanercept product monograph,[15] golimumab product monograph,[16] certolizumab pegol product monograph,[17] and infliximab product monograph.[18]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of ustekinumab 45 mg or 90 mg for the treatment of active psoriatic arthritis in adults, alone or in combination with methotrexate.

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies provided in the manufacturer's submission to CADTH Common Drug Review (CDR) supporting the Health Canada indication as well as those meeting the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with active psoriatic arthritis Subgroups: • Patients with inadequate response to standard therapy • Patients with inadequate response to other biological response modifiers
Intervention	Ustekinumab alone or in combination with methotrexate
Comparators	Individual or combination therapy with: • biological response modifiers (e.g., infliximab, etanercept, adalimumab, golimumab and certolizumab) or • other DMARDs including methotrexate • NSAIDs • placebo
Outcomes	**Key efficacy outcomes:** • Radiographic changes • Outcome measures of psoriatic arthritis symptoms (e.g., DAS 28, EULAR response, ACR 20/50/70, PsARC) • Psoriatic outcome measures (e.g., PASI) • Quality of life **Harms outcomes:** • Mortality, SAEs, AEs (infections, allergic reactions and malignancies), WDAEs
Study Design	Published and unpublished DB RCTs

ACR = American College of Rheumatology; AE = adverse event; DAS = Disease Activity Score; DB = double-blind; DMARD = disease-modifying antirheumatic drug; EULAR = European League Against Rheumatism; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; PASI = Psoriasis Area Severity Index; PsARC = Psoriatic Arthritis Response Criteria; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

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 through 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 concept was Stelara (Ustekinumab).

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

The initial search was completed on April 10, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on September 17, 2014. 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 CADTH Grey Matters checklist (http://www.cadth.ca/en/resources/ finding-evidence-is/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug regulatory approvals, advisories and warnings, drug class reviews, databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two 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 5. Excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

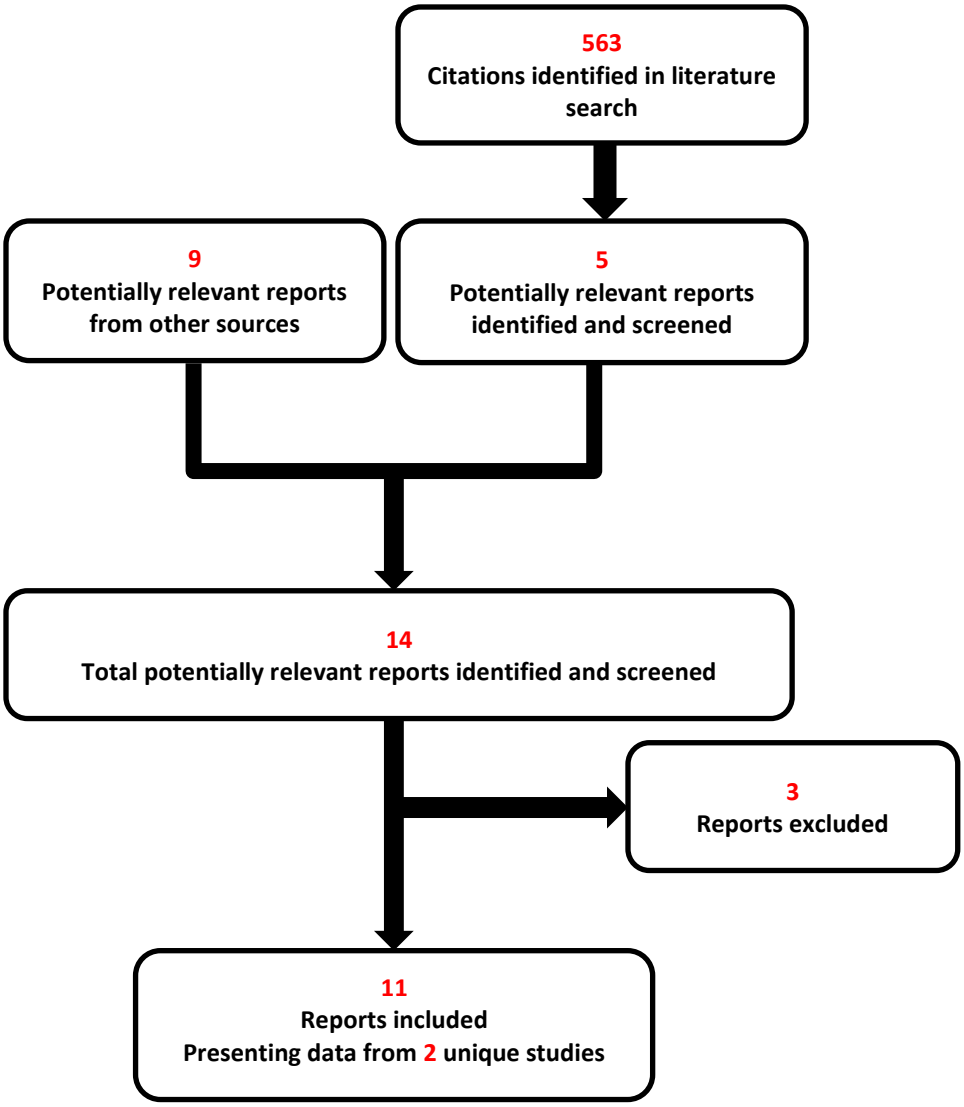
Statistical calculations performed by CDR reviewers were done using Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com, updated 2013/04/06, accessed May 2014.

3. RESULTS

3.1 Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

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



QUOROM = Quality of Reporting of Meta-analyses.

TABLE 5: DETAILS OF INCLUDED STUDIES

		PSUMMIT1	PSUMMIT2
DESIGNS & POPULATIONS	**Study Design**	DB RCT	
	Locations	104 sites – Europe, Russia, Asia-Pacific, North America	71 sites – Europe, North America, Russia
	Screened (N) **Randomized (N)**	1,174 615	597 312 (including 180 with prior anti-TNF alpha usage)
	Inclusion Criteria	Active PsA for > 6 months despite DMARD or NSAID therapy;[a] ≥ 5 swollen and ≥ 5 tender joints; CRP ≥ 0.3 mg/dL; ≥ 1 of the PsA subsets;[b] and active plaque psoriasis or a documented history of plaque psoriasis	Same as PSUMMIT1 and between 150 and 180 patients could have been previously treated with anti-TNF alpha drug(s), i.e., ≥ 8 weeks of therapy with etanercept, adalimumab, golimumab, or certolizumab or at least 14 weeks of therapy with infliximab; or documented intolerance of anti-TNF alpha therapy
	Exclusion Criteria	Any prior use of any anti-TNF alpha drugs; use of B or T cell depleters within 12 months of study drug	Infliximab, golimumab, or certolizumab within 12 weeks prior to study; adalimumab or etanercept within 8 weeks prior study drug; natalizumab, efalizumab, rituximab, alemtuzumab, or visilizumab within 12 months of screening; alefacept within 3 months prior to study; abatacept at any time prior to study
DRUGS	**Intervention**	Ustekinumab 45 mg weeks 0 and 4, then every 12 weeks; Ustekinumab 90 mg weeks 0 and 4, then every 12 weeks	
	Comparator(s)	Placebo	
DURATION	**Study time points**		
	Early escape permitted	16 weeks	
	Placebo crossover, sponsor unblinded, primary end point	24 weeks	
	Last dose	88 weeks	40 weeks
	Follow-up ends, sites and patients unblinded	108 weeks	60 weeks
OUTCOMES	**Primary End Point**	% with ACR 20 at week 24[c]	

		PSUMMIT1	PSUMMIT2
	Other End Points	HAQ-DI at week 24, ACR 50/ACR 70 at week 24, change in total radiographic scores of hands and feet at week 24,[c] DAS 28, SF-36, Pt/PGA, dactylitis, enthesitis, VAS pain score, PsARC, BASDAI, PASI, DLQI, work-related outcomes, biomarkers, pharmacokinetics, pharmacogenomics, antibodies to ustekinumab	Same as for PSUMMIT1 and also including modified van der Heijde-Sharp radiographic scores for hands and feet, Functional Assessment of Chronic Illness Therapy–Fatigue questionnaire
NOTES	**Publications**	Primary report: McInnes et al. 2013[9] Pooled radiography: Kavanaugh et al. 2014[19]	Primary report: Richlin et al. 2014[20] Pooled radiography: Kavanaugh et al. 2014[19]

ACR = American College of Rheumatology; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein; DAS = Disease Activity Score; DB = double-blind; DLQI = Dermatology Life Quality Index; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire–Disability Index; NSAID = nonsteroidal anti-inflammatory drug; PASI = Psoriasis Area Severity Index; Pt/PGA = patient/physician global assessment; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; RCT = randomized controlled trial; SF-36 = Short Form (36) Health Survey; TNF = tumour necrosis factor; VAS = visual analogue scale.

[a] Active PsA despite current or previous DMARD and/or NSAID therapy. DMARD therapy is defined as taking a DMARD for at least three months, or evidence of DMARD intolerance. NSAID therapy is defined as taking an NSAID for at least four weeks or evidence of NSAID intolerance.

[b] PsA subsets: distal interphalangeal (DIP) joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis or spondylitis with peripheral arthritis.

[c] The primary objective to evaluate the inhibition of structural damage was moved to a secondary objective during the course of both trials and the corresponding co-primary end point for the inhibition of structural damage was moved to a secondary end point.

Source: Manufacturer's Clinical Study Reports and publications for PSUMMIT1[7,9,21,22] and PSUMMIT2,[8,20,23] radiographic reports,[19,24] and Health Canada Reviewer's Report.[25] Note: 1 additional report was included.[2]

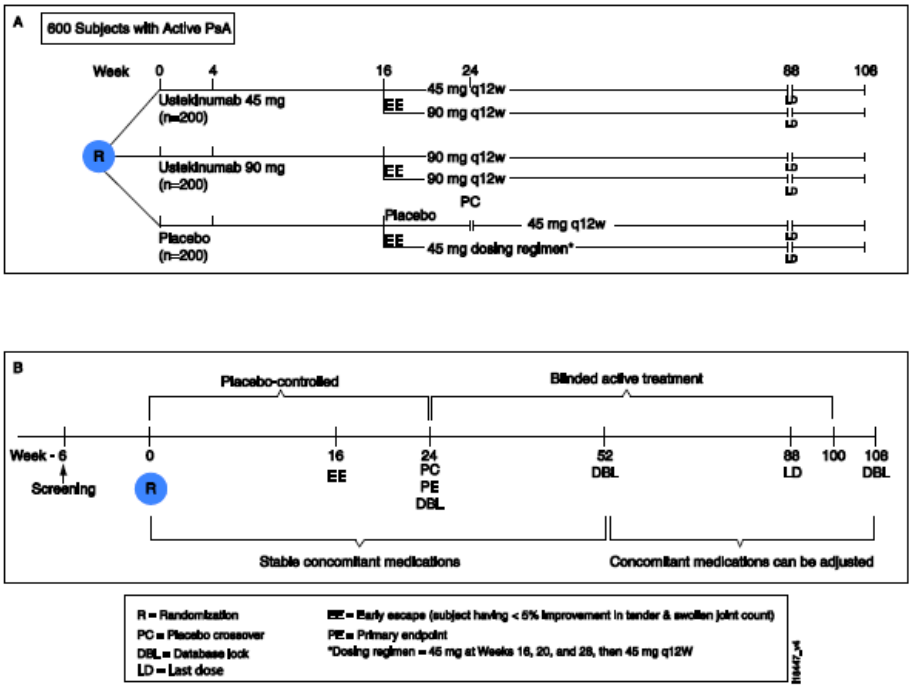
3.2 Included Studies

3.2.1 Description of studies

Both studies were randomized, double-blind, placebo-controlled, parallel, multi-centre, three-group studies (with early escape at week 16) of ustekinumab in patients with PsA. Patients received treatment with ustekinumab 45 mg, 90 mg, or placebo injected subcutaneously at weeks 0 and 4 followed by every 12 weeks dosing thereafter, with the last dose at week 88 (PSUMMIT1, Figure 2) or week 40 (PSUMMIT2, Figure 3). All patients randomized to placebo crossed over to receive ustekinumab at weeks 24 and 28 followed by every 12 weeks dosing thereafter. Patients were followed for efficacy through week 100 (PSUMMIT1) and week 52 (PSUMMIT2) and for safety through week 108 (PSUMMIT1) or week 60 (PSUMMIT2). Treatment randomization in both studies was 1:1:1, and minimization methods were used. The randomization was stratified by investigational site, baseline weight (≤ 100 kg or > 100 kg) and baseline methotrexate usage (yes/no).

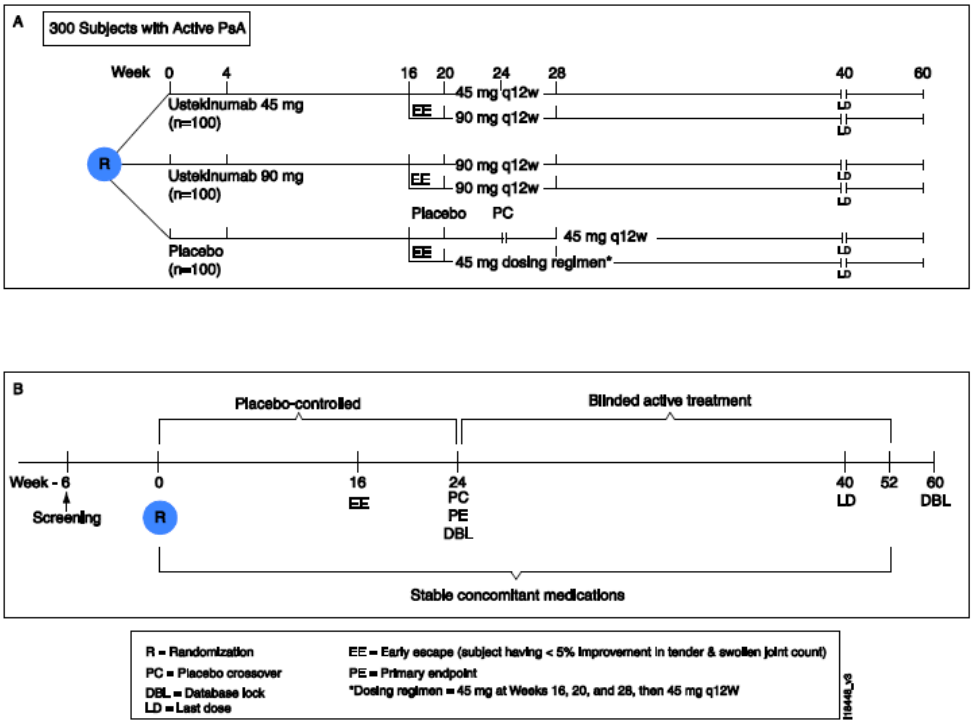
At week 16 of both studies, patients with less than 5% improvement from baseline in both tender and swollen joint counts in the 45 mg and placebo groups were eligible for early escape, following which they received ustekinumab 90 mg (for those previously in the 45 mg group) or 45 mg (for those previously in the placebo group). Patients randomized to placebo who did not qualify for early escape could cross over to receive ustekinumab 45 mg at weeks 24 and 28, followed by every 12 weeks dosing thereafter.

FIGURE 2: PSUMMIT1 SCHEMATIC OF STUDY THROUGH WEEK 108



Source: Manufacturer's Clinical Study Report for PSUMMIT1.[7]

FIGURE 3: PSUMMIT2 SCHEMATIC OF STUDY THROUGH WEEK 60



Source: Manufacturer's Clinical Study Report for PSUMMIT2.[8]

3.2.2 Populations

a) Inclusion and exclusion criteria

Patients included in PSUMMIT1 had active psoriatic arthritis despite having been treated with DMARDs or NSAIDs or both, or as a result of intolerance to DMARDs or NSAIDs or both. No concomitant DMARDs, with the exception of methotrexate, were allowed in the study at entry. Patients who were on a stable dose of methotrexate, NSAIDs, or oral corticosteroids were eligible for enrolment, but patients who previously used anti-TNF alpha therapy were not eligible. Patients were ineligible if there was any prior use of abatacept; usage of alefacept within the previous 3 months; or usage of natalizumab, efalizumab or drugs that deplete B or T cells within the previous 12 months.

Inclusion and exclusion criteria were similar for PSUMMIT2; however, there was an additional requirement that between 50% and 60% of enrolled patients must have been previously treated with anti-TNF alpha drugs. This change in the PSUMMIT2 procedures occurred after the trial began.

b) Baseline characteristics

Baseline demographic characteristics were generally well balanced across treatment groups. A slight majority of patients were male in PSUMMIT1 and a slight majority was female in PSUMMIT2. Mean age was 47 or 48 years across treatment groups in both trials, with a mean weight of approximately [redacted] kg. In the overall trial populations, the mean duration of psoriatic arthritis was seven to eight years. These and other baseline characteristics appear representative of patients with active PsA and were balanced among treatment groups (Table 6).

[redacted]

Cardiovascular risk factors in the trial population were reflective of patients typically diagnosed with PsA: [redacted]

In PSUMMIT2, when comparing patients with and without prior anti-TNF alpha exposure, patients with prior anti-TNF alpha exposure had longer median durations of disease (psoriasis, 13.55 years; PsA, 6.7 years) compared with patients who were anti-TNF alpha naive (psoriasis, [redacted] years; PsA, [redacted] years). Additionally, a higher proportion of patients who had prior anti-TNF alpha exposure were not taking methotrexate at baseline ([redacted]%) compared with patients who were anti-TNF alpha naive ([redacted]%). When comparing patients with and without prior anti-TNF alpha exposure, patients with prior anti-TNF alpha exposure tended to have higher values on the ACR core set of measurements for baseline PsA disease characteristics compared with patients who were anti-TNF alpha naive.

TABLE 6: DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

	PSUMMIT1			PSUMMIT2		
Patient Characteristic	**PL N = 206**	**UST 45 mg N = 205**	**UST 90 mg N = 204**	**PL N = 104**	**UST 45 mg N = 103**	**UST 90 mg N = 105**
Mean age (SD)	47 (12)	47 (13)	47 (12)	48 (11)	48 (11)	48 (12)
Male, n (%)	108 (52)	106 (52)	116 (57)	51 (49)	48 (47)	49 (47)
White race, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean weight, kg (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% weighing > 100 kg, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PsA subtypes, n (%)						
DIP joint arthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthritis mutilans	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asymmetric peripheral arthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Polyarticular arthritis with no RA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spondylitis with peripheral arthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean PsA duration (SD), years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean psoriasis duration (SD), years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 3% BSA affected with psoriasis, n (%)	146 (71)	145 (71)	149 (73)	80 (77)	80 (78)	81 (78)
Current MTX usage, n (%)	96 (47)	99 (48)	101 (50)	49 (48)	54 (52)	52 (50)
Previous anti-TNF alpha usage, n (%)	NA	NA	NA	62 (60)	60 (58)	58 (55)
Mean number of swollen joints (SD), 0 to 66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean number of tender joints (SD), 0 to 68	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean CRP, mg/L (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSA = body surface area; CRP = C-reactive protein; DIP = distal interphalangeal; MTX = methotrexate; NA = not assessed; PL = placebo; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SD = standard deviation; TNF alpha = tumour necrosis factor alpha; UST = ustekinumab.
Source: Manufacturer's Clinical Study Reports PSUMMIT1[7] and PSUMMIT2.[8]

3.2.3 Interventions

TABLE 7: DOSING REGIMEN IN PSUMMIT1 AND PSUMMIT2

	Initial Randomly Assigned Treatment Schedule	Early Escape at Week 16 for Patients With < 5% Improvement From Baseline in Both Tender and Swollen Joint Counts
Ustekinumab 45 mg (n = 205)	Ustekinumab 45 mg at weeks 0 and 4, followed by q12w dosing with the last dose at week 88 (PSUMMIT1) or week 40 (PSUMMIT2). At weeks 20 and 24, patients received placebo to maintain the blind.	Ustekinumab 90 mg at week 16, followed by 90 mg q12w dosing with the last dose at week 88 (PSUMMIT1) or week 40 (PSUMMIT2). At weeks 20 and 24, patients received placebo to maintain the blind.
Ustekinumab 90 mg (n = 204)	Ustekinumab 90 mg at weeks 0 and 4, followed by q12w dosing with the last dose at week 88 (PSUMMIT1) or week 40 (PSUMMIT2). At weeks 20 and 24, patients received placebo to maintain the blind.	The same dosage schedule was to be continued.
Placebo (n = 206)	Placebo at weeks 0, 4, 16, and 20. At weeks 24 and 28, patients received ustekinumab 45 mg followed by q12w dosing with the last dose at week 88 (PSUMMIT1) or week 40 (PSUMMIT2).	Ustekinumab 45 mg at weeks 16, 20, and 28, followed by 45 mg q12w dosing with the last dose at week 88 (PSUMMIT1) or week 40 (PSUMMIT2). At week 24, patients received placebo to maintain the blind.

q12w = every 12 weeks.
Source: Manufacturer's Clinical Study Reports PSUMMIT1[7] and PSUMMIT2.[8]

To maintain the blind, all randomized patients received each administration of study drug as two subcutaneous injections in two different locations (e.g., ustekinumab plus placebo; placebo plus placebo). Dosing regimens are reported in Table 7.

a) Concomitant medications

Patients were allowed to use stable methotrexate (≤ 25 mg per week) and stable prednisone (≤ 10 mg per day equivalent) throughout both trials only if they were receiving stable doses of these treatments in the time period preceding the trial (four weeks before the trial for methotrexate and two weeks before the trial for prednisone). NSAID use and dose adjustments were permitted during the trial. Topical corticosteroids were not permitted during the trial, except the equivalent of hydrocortisone cream with a concentration of 2.5% or less. Approximately half of the study patients were taking methotrexate at baseline in both studies.

b) Prior medications

The proportion of patients who had taken prior medications for psoriatic arthritis or psoriasis was similar across treatment groups in both studies. In the overall study populations, approximately 73% had taken one or two DMARDs, and the most common DMARD taken was methotrexate (PSUMMIT1: [redacted]%, PSUMMIT2: [redacted]%), followed by sulfasalazine ([redacted]%) and leflunomide ([redacted]%). Approximately [redacted]% of patients had taken corticosteroids, [redacted]% had taken NSAIDs, and [redacted]% had taken cyclosporine.

[redacted].

In PSUMMIT2, the total number of patients with prior anti-TNF alpha exposure was 180. Of these, 60%, 58%, and 55% of patients were in the placebo, 45 mg, and 90 mg groups, respectively. In patients with prior anti-TNF alpha exposure, the most commonly used anti-TNF alpha drugs across all treatment groups were adalimumab (101 out of 180 patients) and etanercept (115 out of 180 patients). Approximately half of these patients used the anti-TNF alpha drug for more than one year. In PSUMMIT2, 81 out of 180 patients used one anti-TNF alpha drug, 54 out of 180 patients used two, and 45 out of 180 patients used three or more.

3.2.4 Outcomes

See APPENDIX 5: VALIDITY OF OUTCOME MEASURES for a detailed description of the outcome measures used in the included studies.

a) American College of Rheumatology 20/50/70

The American College of Rheumatology (ACR) criteria[26] for assessing joint status (originally developed for rheumatoid arthritis [RA] patients) provide a composite measure of 20% or greater, 50% or greater, or 70% or greater improvement in both swollen and tender joint counts and at least three of five additional disease criteria, including patient/physician global assessment of disease activity (10 cm visual analogue scale [VAS]), Health Assessment Questionnaire (HAQ), patient assessment of pain intensity and levels of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). The ACR 20 is generally accepted as the minimally clinically important difference (MCID) indicating a response to treatment.

The primary outcome in both included studies was the proportion of patients achieving ACR 20 response at week 24.

b) Psoriatic Arthritis Response Criteria: Psoriatic Arthritis Response Criteria (PsARC)[27] measures signs and symptoms of PsA assessed by tender and/or swollen joint count, physician global assessment (5-point Likert scale), and patient global assessment (5-point Likert scale). To be a PsARC responder, a patient must have at least a 30% reduction in tender or swollen joint count, as well as a 1-point reduction on the 5-point patient or physician global assessment scales and no worsening on any score.

c) Disease Activity Score 28 and C-reactive protein: DAS 28 criteria consist of four components: swollen joints (28 count), tender joints (28 count), patient global assessment of disease activity, and CRP. Overall scores range from 0 to 9.4, with higher scores indicating greater disease activity. DAS score of less than 2.6 is considered remission. Patients were considered DAS responders if they had a good or moderate response defined according to baseline DAS values, as follows:

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

d) Psoriasis Area 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 greater 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 US Food and Drug Administration.[28]

e) Health Assessment Questionnaire: The HAQ was developed to assess physical disability and pain in RA[29] and has been used extensively in arthritis randomized controlled trials, including for PsA. Through a self-assessed questionnaire of eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities), patients' difficulty in performing these activities is scored from 0 (without any difficulty) to 3 (unable to do). The MCID for the HAQ ranges from 0.3 to 0.35.[30-32]

f) Short-Form (36) Health Survey: The SF-36 is a 36-item general health status instrument that has been used extensively in clinical trials in many disease areas.[33] The SF-36 consists of eight health domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems.[34] The physical component summary (PCS) and the mental component summary (MCS) 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.[35-37] Leung et al.[38] reported MCIDs of 3.74 and 1.77 in PsA patients treated with anti-TNF alpha drugs for the PCS and MCS, respectively.

g) Bath Ankylosing Spondylitis Disease Activity Index: The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was originally designed to assess the severity of ankylosing spondylitis but has recently been used to assess spondyloarthropathies, including PsA.[39] The BASDAI is comprised of six items: fatigue, total back pain, pain and swelling of joints, pain at enthesis locations, severity of morning stiffness, and duration of morning stiffness. The listed symptoms are rated by patients using VAS indices, with higher results indicating increased disease activity and functional disability.[39] The MCID in psoriatic arthritis is unknown.

h) van der Heijde-Sharp Scores

The van der Heijde-Sharp (vdHS) scale, also known as the modified Sharp scale, measures radiographic changes. Scores range from 0 to 528, with higher scores indicating greater disease severity. The total score is a sum of the erosion score (0 to 320) and joint space narrowing score (0 to 208). A clinically relevant difference in psoriatic arthritis has not been established. Radiographic change was originally part of the co-primary outcome of both studies, but was removed to become a secondary outcome after the trials started.

i) Dermatology Life Quality Index

The DLQI is a 10-item instrument used to assess a patient's perspective on the impact of skin disorders on daily living. The DLQI has four item-response options, with a total score ranging from 0 to 30 and higher scores indicate greater impact of skin disorders on the patient's daily living. The manufacturer stated that a score of 0 to 1 is considered as no effect at all on patient's life, and a score of > 10 in DLQI is considered a very large effect on patient's life.[7] No evidence was identified to confirm or refute the manufacturer's claim regarding the DLQI score.

3.2.5 Statistical analysis

The sample size for both trials was estimated based on detecting a difference in ACR 20 response between ustekinumab and placebo at week 24. A last observation carried forward procedure was used to impute the missing ACR components if the patients had data for at least one ACR component at week 24. If the patients did not have data for all the ACR components at week 24 or agreed to early escape, the patients were considered not to have achieved the ACR 20 response.

Binary data (e.g., the proportion of patients with an ACR 20 response) were analyzed using the chi-square test or the Cochran-Mantel-Haenszel test adjusted for baseline methotrexate usage (yes/no). Continuous data were analyzed using an analysis of covariance test on van der Waerden normal scores adjusted for baseline methotrexate usage (yes/no). Re-randomization tests were used as the primary statistical testing method to determine *P* values for the analyses of the primary and the major secondary end points. All efficacy analyses were based on the intent-to-treat principle; thus, patients were included in the efficacy analyses according to their assigned treatment group regardless of whether they received the assigned treatment. Multiplicity adjustments were made for the analyses of the primary and the major secondary end points (see description in this section). All statistical testing was performed using a two-sided alpha level of 0.05.

An "early escape rule" was used for both trials. This impacted the statistical analysis for the primary outcome. The rule stated:

> "For subjects who qualified for early escape, including those who were randomized to the 90 mg group without dose increase, their data at or prior to week 16 were carried forward to week 20 and week 24."

It is important to note that this rule was not applied to any analysis after week 24.

In addition a "treatment failure rule" was applied to the statistical analysis. This rule stated:

> "A subject who met any one of the following treatment failure criteria was considered a treatment failure from that point onward: (1) Discontinued study drug injections due to lack of efficacy or an adverse event of worsening of PsA or psoriasis. (2) Initiated protocol-prohibited change in medication or therapy for PsA or psoriasis. If a subject was designated as a treatment failure, the baseline value was assigned to the visits after treatment failure for continuous end points, and subjects were considered non-responders at the visits after treatment failure for response end points regardless of the actual measurements."

In addition to these rules, patients with all data missing to determine the response status at week 24 were considered to not have achieved a response at week 24 for the following binary variables: ACR 20, ACR 50, ACR 70, HAQ responder, DAS 28 responder, DAS remission, PsARC responder, PASI 50, PASI 75, PASI 90, and PASI 100. Missing continuous variables at week 24 (i.e., HAQ–Disability Index [HAQ-DI], individual ACR components, and per cent improvement in PASI) were replaced by the last non-missing observation including baseline values.

A sequential procedure was used to control multiplicity for the primary and major secondary end points in both trials. The primary analysis was evaluated by comparing the proportion of patients with ACR 20 response at week 24 between the combined ustekinumab group (45 mg and 90 mg groups combined) and the placebo group and between each dose group and the placebo group. To maintain a Type I error rate of 0.05, the pairwise comparisons between each dose group and the placebo group were performed after the combined group showed a significant treatment effect compared with the placebo group at an alpha level of 0.05.

To control for multiplicity for the primary end point analysis and the major secondary end point analyses, the five major secondary analyses listed following this paragraph were performed sequentially contingent upon the success of the primary statistical analysis. That is, for each end point, the test between the combined ustekinumab group and the placebo group was performed first. If that test was significant at the $P < 0.05$ level, then the pairwise comparison between each dose group and the placebo group was performed. If at least one dose group comparison with placebo was significant at the $P < 0.05$ level, then the test for the next end point could be performed. Otherwise, the *P* values for the subsequent end points would be considered nominal. The following pre-specified order was used to analyze the major secondary end points:

1. Change from baseline in HAQ-DI score at week 24.
2. Proportion of patients (with baseline ≥ 3% BSA psoriatic involvement) who achieve a PASI 75 response at week 24.
3. Proportion of patients with ACR 50 response at week 24.
4. Proportion of patients with ACR 70 response at week 24.
5. Change from baseline in total radiographic scores of the hands and feet at week 24 based on the pooled data from PSUMMIT1 and PSUMMIT2.

Nominal *P* values were reported for all other end points.

3.3 Patient Disposition

TABLE 8: PATIENT DISPOSITION (BY RANDOMIZED TREATMENT GROUP)

	PSUMMIT1			PSUMMIT2		
	PL	**UST**	**UST 90 mg**	**PL**	**UST 45 mg**	**UST 90 mg**
Randomized, N	206	205	204	104	103	105
Discontinued study drug through week 16, n (%)	7 (3)	3 (2)	6 (3)	18 (17)	3 (3)	8 (8)
Early escape at week 16, n (%)	58 (28)	36 (18)	26 (13)	29 (28)	19 (18)	19 (18)
Discontinued study drug through week 24, n (%)	15 (7)	8 (4)	7 (3)	24 (23)	6 (6)	11 (10)
Adverse event	8 (4)	4 (2)	3 (2)	9 (9)	3 (3)	2 (2)
Lack of efficacy	3 (2)	2 (1)	1 (1)	10 (10)	1 (1)	4 (4)
Lost to follow-up	1 (1)	0	1 (1)	1 (1)	0	0
Withdrew consent	3 (2)	2 (1)	2 (1)	4 (4)	1 (1)	4 (4)
Death	0	0	0	0	0	0
Other	0	0	0	0	1 (1)	1 (1)
Discontinued study drug through week 108 (PSUMMIT1) or week 60 (PSUMMIT2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous anti-TNF alpha and discontinued study drug week 60	NA	NA	NA	[redacted]	[redacted]	[redacted]
Reason for discontinuation through week 108 (PSUMMIT1) or week 60 (PSUMMIT2), n (%)						
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PsA only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriasis only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PsA and psoriasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NA = not applicable; PsA = psoriatic arthritis; PL = placebo; TNF = tumour necrosis factor; UST = ustekinumab.
Source: Manufacturer's Clinical Study Reports PSUMMIT1[7,22] and PSUMMIT2.[8,23]

In PSUMMIT1, all patients who were randomized received at least one dose of assigned treatment, except for one patient in the placebo group. In PSUMMIT2, all randomized patients received at least one dose of assigned treatment. For detailed depiction of patient disposition, see Appendix 4. Patient disposition for both PSUMMIT1 and PSUMMIT2 are summarized in Table 8.

A sizable proportion of patients met the early escape criteria at week 16. In the ustekinumab treatment groups, 13% to 18% of patients met early escape criteria, and, in the placebo groups, 28% of patients met the early escape criteria.

At 24 weeks, regardless of treatment received, 95% (585 out of 615) of patients remained in the PSUMMIT1 and 77% (271 out of 312) of patients remained in PSUMMIT2. At end of study, 80% (490 out of 615) of patients remained in PSUMMIT1 at week 108 and 76% (238 out of 312) of patients remained in PSUMMIT2 at week 60. The most common reason for study discontinuation was lack of efficacy, and discontinuation occurred at a slightly higher frequency in the placebo group compared with the ustekinumab groups.

3.4 Exposure to Study Treatments

In PSUMMIT1, the average number of drug administrations in the ustekinumab groups was [redacted], and the average follow-up time was 92 weeks in those patients. The average number of drug administrations in the patients originally assigned to placebo was [redacted], and the average follow-up time was [redacted] weeks.

In PSUMMIT2, the average number of drug administrations in the ustekinumab groups was [redacted], and the average follow-up time was 49 weeks in those patients. The average number of drug administrations in the patients originally assigned to placebo was [redacted], and the average follow-up time was 37 weeks.

3.5 Critical Appraisal

3.5.1 Internal validity

- Both trials appeared to have applied appropriate allocation concealment, randomization, and blinding methods, including double injections to prevent early escape patients from knowing their treatment. However, the effectiveness of the blinding methods used is unknown. Some injection site reactions were reported, and, if there was any irritation caused by the drug, it may have compromised the blind.
- The baseline characteristics appeared to be well balanced within the trials, across the treatment groups. An exception to this was the CRP levels at baseline in PSUMMIT2, which were lower in the placebo group.
- A substantial number of patients changed their assigned treatment at week 16 after meeting criteria for early escape. This limits the ability to make assertions about the results beyond the week 16 time point. The proportion of early escape patients across the treatment groups differed. Data for these patients were carried forward from week 16 to the point at which the primary outcome was measured (week 24). The direction of bias associated with this analytical approach is unknown.
- The co-primary end point for the inhibition of structural damage was changed to a secondary end point in both studies, after the studies started. [redacted][40]
- Missing data for the vdHS score were handled using methods of linear extrapolation and imputation with median change. Although these methods are widely used, the validity of this method for handling radiographic data in patients with psoriatic arthritis is unknown.
- Psoriatic arthritis is a condition with a variable and heterogeneous course. It is possible that the patients in the placebo group meeting early escape criteria were experiencing a flare at 16 weeks. The impact of disease flare on early escape, especially in the placebo group, is not clear.
- There is lack of consensus regarding definitions of disease severity in psoriatic arthritis. Inclusion criteria for the trials specified active PsA despite current or previous DMARD and/or NSAID therapy. DMARD therapy was defined as taking a DMARD for at least three months or evidence of DMARD intolerance. NSAID therapy was defined as taking an NSAID for at least four weeks or evidence of NSAID intolerance. Intolerance was not defined.
- In PSUMMIT2, a higher proportion of patients withdrew from the trial in the placebo group than in the ustekinumab groups.

- One weakness of the analyses after week 24 is that, as patients withdrew, the denominator was reduced by the manufacturer to reflect this. This is illustrated along the x-axis in Figure 4 and Table 11. This may have resulted in overestimating the response rates at study end.

3.5.2 External validity

- There is variability in diagnostic criteria for psoriatic arthritis. This may have led to a heterogeneous study population, which may not reflect the demographics and disease history of some Canadian patients. This is seen, for example, in the standard deviation for the mean swollen joint count or tender joint count and also in the distribution of the subtypes of psoriatic arthritis.
- Between the trials, the baseline characteristics were similar. The exception to this was the distribution of the psoriatic arthritis subtypes, which differed between the two trials.
- Several outcomes measured in the trials have limitations, including lack of clearly defined MCID in score change in psoriatic arthritis patients (see APPENDIX 5: VALIDITY OF OUTCOME MEASURES).
- Psoriatic arthritis is a chronic disease, and patients are expected to be on treatment for many years. Although long-term harms data were reported for up to 108 weeks in PSUMMIT1, the only placebo-controlled data that exist for ustekinumab (prior to early escape) are from week 16.
- There are no head-to-head trials with other biological response modifiers in patients with psoriatic arthritis. This makes it challenging to evaluate the relative effectiveness of ustekinumab.
- Patients at high risk for specific harms (e.g., history of serious infections) were excluded. While this is a prudent approach, it limits generalizability of harms results to clinical practice, where patients who are at higher risk may be prescribed the drug.
- It is unclear if adequate dose-finding studies in psoriatic arthritis were performed prior to the PSUMMIT1 and PSUMMIT2 studies. This leaves some uncertainty about the optimal dosing and optimal dosing interval of ustekinumab in this indication, since only two doses (45 mg and 90 mg) and one interval (12 weeks) were studied.
- High-quality evidence for the use of methotrexate in psoriatic arthritis is lacking, although it is generally accepted in clinical practice as a therapeutic option. With the lack of evidence, appropriate dosing of methotrexate is unclear. In PSUMMIT1, the median dose at baseline was 15 mg per week, which is lower than recommended methotrexate doses used in RA (approximately 25 mg to 30 mg per week).
- While there is no universal definition for adequate response or intolerance to anti-TNF alpha therapy, the PSUMMIT2 trial utilized reasonable inclusion criteria for these patients. However, inclusion in PSUMMIT2 simply required a certain number of tender and swollen joints. The change in joint counts while the patient was on an anti-TNF alpha drug was not reported. Therefore, the number of swollen joints in a particular patient may have decreased from 15 to seven on an anti-TNF alpha drug, yet the patient would still be classified as a TNF failure in PSUMMIT2.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (Section 2.2, Table 4) are reported. Refer to Table 1 and Table 2 for outcome data. See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Outcomes related to psoriatic arthritis

a) American College of Rheumatology Response

The proportion of patients achieving ACR 20 at week 24 was larger in the ustekinumab 45 mg (range 42% to 44%) and 90 mg (range 44% to 50%) groups relative to placebo (range 20% to 23%), in both studies ($P < 0.001$ for all comparisons versus placebo). The early escape rule was applied to the primary outcome analysis. Therefore, response data from patients who escaped early were not included in the

numerator for the ACR calculations at week 24. For example, 58 patients in the placebo group of PSUMMIT1 met early escape criteria during PSUMMIT1. Of these, 17 (29%) patients had an ACR 20 response at week 24, but they were not included in the numerator for the purposes of analyzing the primary end point. See data presentation by early escape status in Table 9 and Table 10. Of the patients who met the criteria for early escape, the proportion of ACR 20 responders was lower in the ustekinumab 45 mg → 90 mg and 90 mg → 90 mg groups than in patients taking only placebo, in both PSUMMIT1 and PSUMMIT2.

TABLE 9: PSUMMIT1 AMERICAN COLLEGE OF RHEUMATOLOGY RESPONSE DATA BY EARLY ESCAPE STATUS

	PL Only[a]	Early Escape PL→45 mg[b]	UST 45 mg Only[a]	Early Escape 45 mg→90 mg[b]	UST 90 mg Only[a]	Early Escape 90 mg→90 mg[b]
	N randomized = 206		N randomized = 205		N randomized = 204	
Week 16						
N	143		168		173	
ACR 20	44 (31%)		70 (42%)		88 (51%)	
ACR 50	14 (10%)		31 (18%)		38 (22%)	
ACR 70	1 (1%)		11 (6%)		10 (6%)	
Week 24						
N	140		166		171	
ACR 20	48 (34%)		87 (52%)		100 (58%)	
ACR 50	18 (13%)		51 (31%)		57 (33%)	
ACR 70	5 (4%)		25 (15%)		29 (17%)	

ACR = American College of Rheumatology; PL = placebo; UST = ustekinumab.
[a] Patients who did not meet the early escape criteria.
[b] Patients who met the early escape criteria.
Source: Manufacturer's Clinical Study Reports PSUMMIT1[7] and PSUMMIT2.[8]

TABLE 10: PSUMMIT2 AMERICAN COLLEGE OF RHEUMATOLOGY RESPONSE DATA BY EARLY ESCAPE STATUS

	PL Only[a]	Early Escape PL→45 mg[b]	UST 45 mg Only[a]	Early Escape 45 mg→90 mg[b]	UST 90 mg Only[a]	Early Escape 90 mg→90 mg[b]
	N randomized = 104		N randomized = 103		N randomized = 105	
Week 16						
N	66		82		78	
ACR 20	13 (20%)		31 (38)		30 (39)	
ACR 50	3 (4%)		17 (21)		12 (15)	
ACR 70	1 (2)		4 (5)		4 (5)	
Week 24						
N	66		80		76	
ACR 20	21 (32)		45 (56)		46 (60)	
ACR 50	7 (11)		18 (22)		24 (32)	
ACR 70	3 (4)		7 (9)		9 (12)	

ACR = American College of Rheumatology; PL = placebo; UST = ustekinumab.
[a] Patients who did not meet the early escape criteria.
[b] Patients who met the early escape criteria.
Source: Manufacturer's Clinical Study Reports PSUMMIT1[7] and PSUMMIT2.[8]

The placebo-adjusted ACR 20/50/70 response rates in the ustekinumab 45 mg dose group were lower than in the ustekinumab 90 mg dose group at week 24 in both trials. However, the difference was very small, and no statistical comparisons were made between the ustekinumab 45 mg and 90 mg dose groups.

At week 24, statistically significant results were observed for all ustekinumab doses versus placebo for the proportion of patients achieving ACR 50 response. However, the proportion of ustekinumab patients achieving ACR 70 response versus placebo achieved statistical significance only in the PSUMMIT1 trial.

For each of the individual components of the ACR response criteria, ustekinumab 45 mg and 90 mg were both statistically significantly better, compared with placebo.

b) American College of Rheumatology Long-Term Response Rates

The data at week 100 and week 52 are presented in Table 11. After week 24, all patients were taking ustekinumab both trials. At week 108 in PSUMMIT1, response rates ranged from 44% to 69% (ACR 20), 22% to 50% (ACR 50), and 4% to 27% (ACR 70). The ACR response rates for PSUMMIT2 at week 52 were similar. At study end, the ACR response rate in the group that originally received placebo was similar to the rate in those patients who were originally assigned ustekinumab.

TABLE 11: SELECTED OUTCOMES AT WEEK 100

	PL→45 mg		UST 45 mg		UST 90 mg	
	Early Escape[a]	Crossover[b]	45 mg Only[c]	Early Escape 45 mg→90 mg[a]	UST 90 mg Only[c]	Early Escape 90 mg→90 mg[a]
PSUMMIT1 Week 108						
Patients randomized	[redacted]	131	169	[redacted]	178	[redacted]
ACR 20	[redacted]	84/122 (69%)	89/151 (59%)	[redacted]	103/153 (67%)	[redacted]
ACR 50	[redacted]	49/122 (40%)	63/151 (42%)	[redacted]	76/153 (50%)	[redacted]
ACR 70	[redacted]	24/122 (20%)	41/151 (27%)	[redacted]	38/153 (25%)	[redacted]
DAS 28 response	[redacted]	91/122 (75%)	113/151 (75%)	[redacted]	118/153 (77%)	[redacted]
PASI 75	[redacted]	56/83 (68%)	74/101 (74%)	[redacted]	85/116 (73%)	[redacted]
ACR 20 and PASI 75	56/121 (46%)		61/119 (51%)		74/126 (59%)	
PSUMMIT1 Week 52						
Patients randomized	[redacted]	48	75	[redacted]	76	[redacted]
ACR 20	[redacted]	25 (52%)	39 (52%)	[redacted]	43 (57%)	[redacted]
ACR 50	[redacted]	14 (29%)	23 (31%)	[redacted]	24 (32%)	[redacted]
ACR 70	[redacted]	5 (10%)	11 (15%)	[redacted]	16 (21%)	[redacted]
DAS 28 response	[redacted]	35 (73%)	50 (67%)	[redacted]	53 (70%)	[redacted]
PASI 75	[redacted]	21/35 (60%)	34/56 (61%)	[redacted]	39/60 (65%)	[redacted]

ACR = American College of Rheumatology; DAS = Disease Activity Score; PASI = Psoriasis Area Severity Index; PL = placebo; UST = ustekinumab.

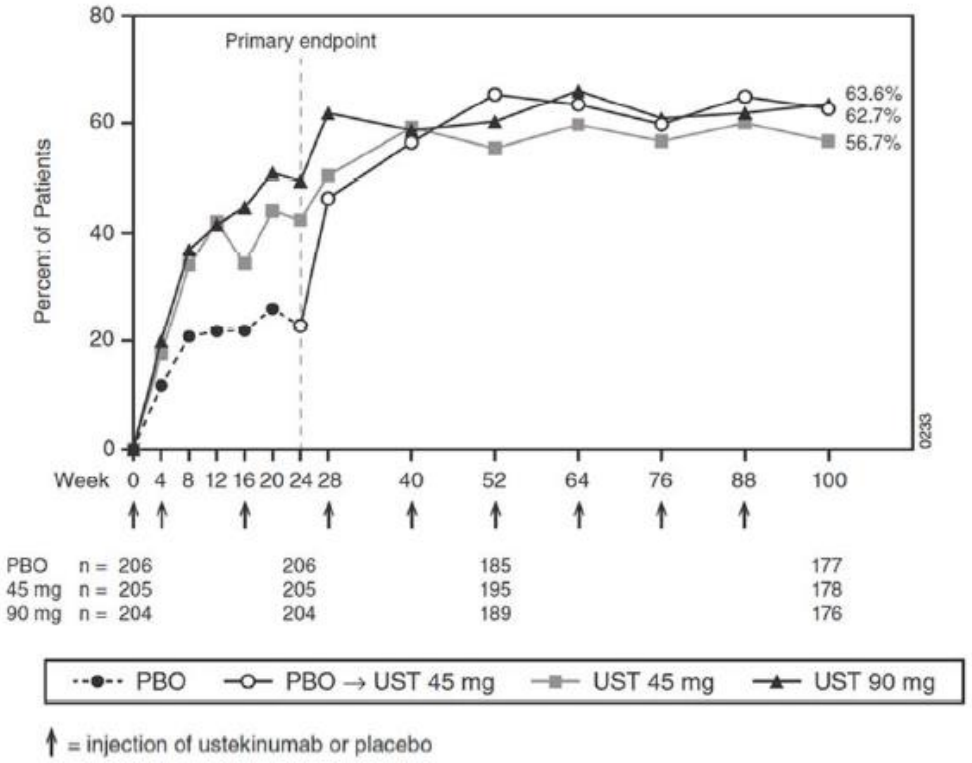
[a] Patients who met the early escape criteria at week 16.

[b] Patients who crossed over at week 24.

[c] Patients who did not meet the early escape criteria at week 16.

Source: Manufacturer's Clinical Study Reports for PSUMMIT1.[21,22]

FIGURE 4: AMERICAN COLLEGE OF RHEUMATOLOGY 20 RESPONSE RATES TO WEEK 108, PSUMMIT1



PBO = placebo; UST = ustekinumab.
Source: Manufacturer's Clinical Study Report for PSUMMIT1.[22]

c) Health Assessment Questionnaire

Baseline mean HAQ scores ranged from [redacted] across treatment groups. At week 24, the mean change in scores decreased (improved) from baseline for all treatment groups, including placebo. The mean score change in ustekinumab 45 mg and 90 mg groups was statistically significantly improved relative to that in the placebo group in both trials. The proportion of patients with an improvement of 0.3 or more was greater in the ustekinumab 45 mg and 90 mg groups relative to placebo (statistically significant for all comparisons).

d) Psoriatic Arthritis Response Criteria

In both trials, there were statistically significant greater proportions of PsARC responders in the ustekinumab 45 mg and 90 mg groups compared with placebo at week 24 ($P < 0.001$). There did not appear to be a trend indicating any additional benefit of the 90 mg dose compared with the 45 mg dose.

e) Disability Activity Score 28

The proportion of patients achieving DAS 28 remission was not statistically significantly different between ustekinumab and placebo in PSUMMIT2, but there was a statistically significant difference observed in PSUMMIT1. At week 24, the proportion of patients in the ustekinumab 45 mg and 90 mg groups achieving a DAS response was higher than placebo ($P < 0.001$) in both trials. There did not appear to be a benefit for 90 mg compared with the 45 mg dose of ustekinumab.

f) Dactylitis

Dactylitis refers to entire inflammation of a digit. The presence and severity of dactylitis was assessed in both hands and feet using a scoring system from 0 to 3 (0 – no dactylitis, 1 – mild dactylitis, 2 – moderate dactylitis, and 3 – severe dactylitis). The analysis was performed only in the patients who had dactylitis in one digit or more at baseline. At week 24, the proportion of patients with dactylitis was lower in the patients who took ustekinumab 45 mg or 90 mg, relative to placebo, in the PSUMMIT1 trial. There were no statistically significant differences seen in the PSUMMIT2 trial at week 24.

g) Enthesitis

The Maastricht Ankylosing Spondylitis Disease Activity Score (MASES) measures enthesitis, which refers to inflammation of the location where tendons and ligaments insert into the bone. The original MASES scale was modified for PsA to include plantar fascia. Thirteen sites were assessed, and total scores ranged from 0 to 13. The analysis was performed by the manufacturer only in patients with psoriatic arthritis MASES greater than 1 at baseline. Of these patients, at week 24, statistically significant reductions in the proportion of patients with enthesitis were seen for all ustekinumab versus placebo comparisons in both studies. [redacted]

h) Bath Ankylosing Spondylitis Disease Activity Index

The BASDAI is a patient self-assessment and consists of six questions relating to the five major symptoms of ankylosing spondylitis. It has not been validated for patients with psoriatic arthritis. Only patients with spondylitis with peripheral joint involvement as their primary arthritic presentation of PsA completed the BASDAI using a VAS (0 to 10 cm) to indicate the degree of their symptoms over the past week for each scale criterion. Higher scores indicate greater disease. The manufacturer indicated that a score decrease of 50% was considered clinically meaningful. In PSUMMIT1 and PSUMMIT2, there was a statistically significant difference between ustekinumab 90 mg and placebo for the BASDAI 50 response, but not between ustekinumab 45 mg and placebo at week 24.

i) van der Heijde-Sharp Scores

The primary analysis performed by the manufacturer was a pooled analysis of radiographic results from both trials (Table 12). In the pooled analysis, across all treatment groups the median change in total modified vdHS score from baseline was 0. The mean change in total modified vdHS score from baseline at week 24 was significantly less for patients in the ustekinumab 45 mg and 90 mg groups compared with patients in the placebo group. There was no statistically significant difference between ustekinumab 45 mg or 90 mg and placebo for the proportion of patients with no change (i.e., ≤ 0 points).

In the analysis of the data for each trial separately, it was clear that the mean score changes reached statistical significance because of the PSUMMIT1 data. [redacted] Nine per cent of all patients had missing radiographic data at week 24. Interpolation and imputation data methods were used to generate radiographic scores for these patients.

TABLE 12: PSUMMIT1 AND PSUMMIT2 POOLED ANALYSIS OF RADIOGRAPHIC DATA AT WEEK 24

	PL N = 310	UST 45 mg N = 308	MDC (95% CI), *P* value UST 45 mg versus PL	UST 90 mg N = 309	MDC (95% CI), *P* value UST 90 mg versus PL
Baseline vdHS total score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total vdHS, MCFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erosion score, MCFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
JSN score, MCFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total vdHS, median change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with change ≤ 2.01, n (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with change ≤ 0.0, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; JSN = joint space narrowing; MCFB = mean change from baseline; MDC = mean difference of change; PL = placebo; SD = standard deviation; UST = ustekinumab; vdHS = van der Heijde-Sharp scale.
[a] 2.01 was defined as the "smallest detectable change" by the manufacturer.
Source: Manufacturer's Clinical Study Report.[19,24]

3.6.2 Outcomes related to psoriasis

a) Psoriasis Area Severity Index

PASI is a measure of the extent and severity of psoriasis lesions; absolute scores range from 0 to 72, with higher scores representing more severe psoriasis. PASI 75 responders are those with a 75% improvement from baseline scores. Only patients with a BSA involvement of 3% or more at baseline had a PASI assessment (approximately three-quarters of all randomized patients). The proportion of patients achieving PASI 75 response in ustekinumab compared with placebo was higher for both doses in both trials at week 24. The absolute risk reduction for ustekinumab versus placebo ranged from 46% to 52% over both trials. This means that, for approximately every two patients treated with ustekinumab over a 24-week period, one would achieve a PASI 75 response.

b) Dermatology Life Quality Index

The DLQI scores decreased (improved) in all placebo and ustekinumab group versus baseline by week 24 of both studies. There were statistically significant improvements in score for ustekinumab 45 mg and 90 mg versus placebo in both trials at week 24. The mean improvement relative to placebo was approximately 5 to 6 points.

3.6.3 Health-related quality of life and work-related outcomes

a) Short Form (36) Health Survey

The SF-36 measures quality of life based on both a physical component and a mental component. Scores range from 0 to 100, with higher scores indicating better health status. Statistically significant improvements in the physical component were observed for ustekinumab 45 mg and 90 mg versus placebo at week 24, and the score difference was approximately 3 to 5 points versus placebo across study groups. At week 24, the only statistically significant improvements observed for the mental component was for the ustekinumab 90 mg dose versus placebo in PSUMMIT1.

b) Time lost from work

[redacted]

c) Employability

[redacted]

d) Work productivity

[redacted]

[redacted]

3.6.4 Other outcomes

a) Antibodies to ustekinumab

[redacted] In PSUMMIT2, 26 out of 279 (9.3%) of patients who were exposed to ustekinumab had at least one positive test for ustekinumab antibodies by week 60.

ACR and PASI response subgroup analyses: The manufacturer performed numerous subgroup analyses of the ACR response data. Selected analyses are presented in Table 15 and Table 16 in APPENDIX 4: DETAILED OUTCOME DATA. No statistical comparisons were performed for these analyses by the manufacturer. The difference in proportion of ACR 20 responders between ustekinumab and placebo was slightly larger in patients who did not take methotrexate, compared with those who took methotrexate in both studies. The impact of ustekinumab on PASI 75 response rates in patients not taking methotrexate also appeared slightly higher compared with those taking methotrexate.

In PSUMMIT2, the ACR 20 and PASI 75 response rates were higher in patients who were anti-TNF alpha naive, compared with patients who had previously taken anti-TNF alpha drugs. However, the differences in response rates of ustekinumab relative to placebo in the anti-TNF alpha experienced patients compared with the anti-TNF alpha naive patients were similar.

In spite of the observation that ustekinumab had slightly higher response rates for some outcomes in patients not taking methotrexate compared with patients taking methotrexate, the Stelara product monograph concluded that concomitant methotrexate has no impact on the efficacy of ustekinumab in psoriatic arthritis.

3.7 Harms

Only those harms identified in the review protocol are reported (see 2.2.1 Protocol).

Selected harms data with a focus on the week 16 time point are presented in this section (Table 13 and Table 14). Week 16 data allow a comparison of patients before early escape was permitted. See APPENDIX 4: DETAILED OUTCOME DATA for harms data reported to week 108 (Table 17, PSUMMIT1) and week 60 (Table 18, PSUMMIT2) and for long-term registry data (Table 19).

3.7.1 Mortality

There were no deaths in either trial through week 16.

3.7.2 Serious adverse events

The rates of serious adverse events in the treatment groups of both studies ranged from 1% to 5%. In patients taking ustekinumab, SAEs included syncope, renal injury, duodenitis, gastroduodenitis, chronic pancreatitis, cholecystitis, spinal compression fracture, anxiety, depression, acute renal failure, and cervical polyp. In patients taking placebo, SAEs included pyrexia, chronic cholecystitis, hyperglycemia, depression, interstitial lung disease, hypertension, joint dislocation, radius fracture, angina pectoris, and foot deformity. There were no obvious trends or differences observed between treatment and placebo for any specific SAE.

There were no patients who reported serious infections up to week 24 in PSUMMIT1. Through week 16 of PSUMMIT2, one patient taking placebo had a serious infection (interstitial lung disease). No patients reported tuberculosis or other opportunistic infections through week 16. No malignancies were reported through week 24 in PSUMMIT1. In PSUMMIT2, one malignancy was reported through week 24 in the ustekinumab 90 mg group. A patient had a non-serious event of squamous cell carcinoma in an area of cleared plaque psoriasis (onset study day 22). [redacted] There was one SAE of angina pectoris reported in PSUMMIT1 in a patient taking placebo. There was one cardiovascular SAE (cerebrovascular accident) in PSUMMIT1 in a patient taking ustekinumab 45 mg between weeks 16 and 24.

3.7.3 Adverse events and withdrawals due to adverse events

Approximately half of all patients experienced an adverse event through week 16. The rates of total adverse events were similar across treatment groups. The most common group of adverse events was infections, and the most common specific adverse event was nasopharyngitis. Approximately 2% of all study patients had injection site reactions through week 24. All of these reactions were classified as mild. [redacted]

Through week 16, withdrawals due to adverse events were lower in the ustekinumab groups compared with placebo. [redacted]

TABLE 13: PSUMMIT1 HARMS RESULTS WEEK 16

	PL N = 205	UST 45 mg N = 205	UST 90 mg N = 204
Any adverse event	91 (44%)	84 (41%)	89 (44%)
Common AE (> 2%)			
Nasopharyngitis	8 (4%)	8 (4%)	11 (5%)
Headache	2 (1%)	10 (5%)	4 (2%)
URTI	10 (5%)	5 (2%)	9 (4%)
Arthralgia	3 (2%)	4 (2%)	6 (3%)
Nausea	0	4 (2%)	6 (3%)
Diarrhea	0	5 (2%)	4 (2%)
Hypertension	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
WDAE	3 (2%)	1 (0.5%)	2 (1%)
SAE	4 (2%)	4 (2%)	3 (2%)
Infections	43 (21%)	34 (17%)	40 (20%)
Injection site reactions,[a] number of reactions/ number of injections	[redacted]	[redacted]	[redacted]

AE = adverse event; PL = placebo; SAE = serious adverse event; URTI = upper respiratory tract infection; UST = ustekinumab; WDAE = withdrawal due to adverse event.

[a] Through week 24. Even patients in the ustekinumab treatment groups received placebo as a second injection to maintain blindedness.

Note: data are number of patients with event (%).

Source: Manufacturer's Clinical Study Report for PSUMMIT1.[7]

TABLE 14: PSUMMIT2 HARMS RESULTS WEEK 16

	PL N = 104	UST 45 mg N = 103	UST 90 mg N = 104
Any adverse event	57 (55%)	65 (63%)	63 (61%)
Common AE (>2%)			
Nasopharyngitis	5 (5%)	8 (8%)	10 (10%)
Headache	4 (4%)	5 (5%)	5 (5%)
Arthralgia	1 (1%)	5 (5%)	4 (4%)
URTI	4 (4%)	5 (5%)	3 (3%)
Fatigue	0	5 (5%)	2 (2%)
Nausea	2 (2%)	4 (4%)	3 (3%)
Back pain	0	1 (1%)	4 (4%)
Diarrhea	3 (3%)	4 (4%)	1 (1%)
Oropharyngeal pain	0	4 (4%)	1 (1%)
WDAE	8 (8%)	2 (2%)	2 (2%)
SAE	5 (5%)	0	1 (1%)
Infections	25 (24%)	30 (29%)	26 (25%)
Injection site reactions,[a] number of reactions/ number of injections	[redacted]	[redacted]	[redacted]

AE = adverse event; PL = placebo; SAE = serious adverse event; URTI = upper respiratory tract infection; UST = ustekinumab; WDAE = withdrawal due to adverse event.

[a] Through week 24. Even patients in the ustekinumab treatment groups received placebo as a second injection to maintain blindedness.

Note: Data are number of patients with event (%).

Source: Manufacturer's Clinical Study Report for PSUMMIT2.[8]

4. DISCUSSION

4.1 Summary of Available Evidence

Two manufacturer-sponsored, published, double-blind, randomized controlled trials, PSUMMIT1 and PSUMMIT2 (N = 927 total), evaluating the efficacy and harms of ustekinumab 45 mg and 90 mg compared with placebo in patients with psoriatic arthritis were included in the systematic review. The primary outcome was the proportion of patients achieving ACR 20 response at week 24. The primary outcome was met in both studies. The studies allowed early escape at week 16, and all patients taking placebo were reassigned to ustekinumab at week 24. This design has numerous limitations, including the fact that patients who meet early escape criteria are not randomized to dose escalation or another type of strategy. Early escape, while common in psoriatic arthritis trials based on ethical considerations, limits the interpretation and clinical relevance of the trial data.

4.2 Interpretation of Results

4.2.1 Efficacy

The inclusion criteria for PSUMMIT1 appear to be reflective of patients with psoriatic arthritis treated in Canadian clinical practice. The baseline characteristics of patients in PSUMMIT2 were very similar to those of PSUMMIT1, in spite of the fact that 60% of patients in PSUMMIT2 had previously used anti-TNF alpha therapy. For inclusion in PSUMMIT1, patients were required to have active psoriatic arthritis for at least six months, despite treatment with a DMARD for three months or an NSAID for four weeks, or intolerance to DMARDs or NSAIDs. These criteria are less stringent than the criteria applied to using anti-TNF alpha drugs for psoriatic arthritis by some of the public drug plans in Canada. The Ontario Exceptional Access Program, for example, requires "severe active disease (five or more swollen joints and radiographic evidence of psoriatic arthritis) despite treatment with methotrexate (20 mg per week) for at least three months and one of leflunomide (20 mg per day) or sulfasalazine (1 g twice daily) for at least three months."[41] Some international guidelines also suggest at least two adequate trials before assessing failure of DMARD therapy.[12]

In general, there were more secondary outcomes with statistically significant results in PSUMMIT1 than in PSUMMIT2. This may be related to the smaller sample size in PSUMMIT2 or the different population (anti-TNF alpha experienced patients).

ACR 20 and PASI 75 are commonly used end points in psoriatic arthritis trials. The ACR 20 and PASI 75 response rates in the PSUMMIT1 and PSUMMIT2 trials appear lower than the rates observed for the same outcomes at the same time point in trials using anti-TNF alpha drugs in psoriatic arthritis (see APPENDIX 6: SUMMARY AND APPRAISAL OF MANUFACTURER-SUBMITTED MIXED TREATMENT COMPARISON). It is difficult to draw conclusions without head-to-head trials since the difference may be related to trial population differences; however, the manufacturer's mixed treatment comparison suggested ustekinumab had consistently lower response rates for outcomes related to psoriatic arthritis and psoriasis, compared with anti-TNF alpha drugs.

Ustekinumab is indicated for use with or without methotrexate. Half of the patients in the PSUMMIT1 and PSUMMIT2 trials used concomitant methotrexate, and a larger percentage had used it prior to the trials. This does not mean methotrexate should always be given before ustekinumab, although this may be the common approach in clinical practice. The comments about methotrexate in the indication reflect the results of the manufacturer's subgroup analyses, which showed that ustekinumab had higher

response rates than placebo for several outcomes, including ACR 20 and PASI 75 in patients with or without concurrent methotrexate.

An important treatment objective in psoriatic arthritis is inhibition of progression of structural damage.

In PSUMMIT2, the ACR 20 and PASI 75 response rates were lower in patients who had previously used an anti-TNF alpha drug. Similar observations have been made in observational studies in psoriatic arthritis that examined the response to subsequent anti-TNF drugs after a trial with a first.[5,6] PSUMMIT1 and PSUMMIT2 do little to address the question of selecting optimal treatment strategies for patients who are non-responders to a TNF inhibitor. One could simply observe that, similar to switching to a second anti-TNF alpha drug, the likelihood of response is lower after switching to ustekinumab from an anti-TNF drug.

Patients who were eligible for early escape in the ustekinumab 45 mg and 90 mg groups tended to have lower rates of response than those not eligible for early escape (Table 8). The ustekinumab product monograph suggests that "90 mg was efficacious in a higher percentage of…. patients than the 45 mg dose" for patients with plaque psoriasis, but does not make the same conclusion about patients with psoriatic arthritis. The ustekinumab product monograph gives some guidance on adjusting dosing interval and discontinuing therapy in non-responders for the psoriasis indication; however, no such guidance is provided for the psoriatic arthritis indication. This is a product that will likely be used long-term and could increase risk of serious harm in some patients. Therefore, the lack of guidance on optimal dose, dose frequency, and duration of therapy in psoriatic arthritis is an important omission.

4.2.2 Harms

The only placebo-controlled data uncontaminated by patient early escape are from week 16 for both studies. The limitations of this analysis were stated earlier. While there were no statistical analyses performed on the harms data at week 16, there did not appear to be any new issues related to harms of ustekinumab relative to the information already presented in the product monograph for psoriasis.

The harms highlighted in the ustekinumab product monograph include infections (e.g., tuberculosis activation; serious bacterial, fungal, and viral infections; diverticulitis; cellulitis; pneumonia; appendicitis; cholecystitis and sepsis), malignancies and reversible posterior leukoencephalopathy syndrome. The ustekinumab needle cover on the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

While the manufacturer reported incidence of adverse events up to week 108 (PSUMMIT1) and week 60 (PSUMMIT2), these data have limited valued in understanding the risks associated with ustekinumab because there was no control group (see APPENDIX 4: DETAILED OUTCOME DATA). There were no deaths in either trial, and rates of SAEs ranged from 0 to [redacted]% across the various treatment groups.

[redacted]

The harms profile of ustekinumab in patients with psoriatic arthritis deserves further study in long-term controlled and observational studies. The PSUMMIT1 and PSUMMIT2 trials excluded patients who were at increased risk of developing specific adverse events associated with the use of ustekinumab (e.g., serious infections) and thus may not reflect the incidence in clinical practice.

5. CONCLUSIONS

In two double-blind, randomized controlled trials in patients with active psoriatic arthritis, ustekinumab 45 mg or 90 mg was associated with improved rates of ACR 20 response at week 24 compared with placebo. Other outcomes such as the HAQ-DI, PASI 75, PsARC, DAS 28 response, DLQI, and SF-36 also showed statistically significant improvements favouring ustekinumab versus placebo at week 24. Some outcomes did not reach statistical significance in PSUMMIT2 at week 24, such as proportion of patients with enthesitis, dactylitis, DAS 28 remission, and disease activity. The focus of the analyses of both trials was the week 24 time point, and an early escape rule was applied to all statistical analyses at this time point, potentially weakening the internal validity of the results.

Risk of serious harm, such as malignancies and infections, exist for ustekinumab, similar to other anti-TNF alpha drugs used to treat psoriatic arthritis. Without direct comparisons, it is not possible to ascertain the risks relative to these other commonly used drugs. Given that psoriatic arthritis is a chronic condition that will be treated over a lifetime, a 24-week controlled trial is a short duration to evaluate harms.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Group(s) Supplying Input
Four patient groups submitted input.

The Canadian Skin Patient Alliance is a non-profit patient organization that aims to advocate for, educate, and support its affiliated disease-specific organizations and patients suffering from dermatological conditions. Conflicts of interest include corporate membership, joint workings, sponsorship, or funding arrangements with AbbVie, Amgen, GlaxoSmithKline, LEO Pharma, Merck, Novartis, Roche, and Valeant. The Alliance has not received funding from Janssen in over a year; however, it is in discussions with Janssen for project-specific funding for 2014. It is supported in this submission by the Canadian Association of Psoriasis Patients, an affiliated non-profit organization that serves psoriasis and psoriatic arthritis patients in Canada. Both organizations declared no conflict of interest in the preparation of the submission.

The Canadian Psoriasis Network, through research, outreach, and education, seeks to both educate and empower individuals living with psoriasis and those caring for them. It receives some of its operating budget from industry, including AbbVie and Janssen. The Canadian Psoriasis Network declared no conflict of interest in the preparation of this submission.

The Arthritis Society is a national charity that provides information and programs for people with arthritis, funding for research projects investigating the causes of and potential treatments for arthritis, and funding to train rheumatologists. The Arthritis Society receives the vast majority of funding from individual donors. Over the past 12 months it has received funding from pharmaceutical manufacturers including: AbbVie, Amgen, Bayer, Bristol-Myers Squibb, Celgene, Eli Lilly, GlaxoSmithKline, Janssen, Novartis, Pfizer, Roche and UCB. The Arthritis Society and Janssen Inc. are members of the Arthritis Alliance of Canada, and the President and CEO of The Arthritis Society is also the Chair of the Arthritis Alliance of Canada. No declaration regarding conflict of interest in the preparation of the submission was made.

Arthritis Consumer Experts (ACE) is a national arthritis patient organization led by people living with the disease that provides free education and information programs to people with arthritis. ACE also provides support for research projects and organizations through its JointHealth family of evidence-based education and information programs. ACE's membership and program subscribers include people with arthritis, their families, their caregivers, rheumatologists, and other health professionals. ACE operates as a non-profit group on unrestricted grants from public and private sector organizations, including AbbVie, Amgen Canada, Arthritis Research Centre of Canada, BIOTECanada, Bristol-Myers Squibb Canada, Canadian Institutes of Health Research, Canadian Rheumatology Research Consortium, Celgene Inc., GlaxoSmithKline, Hoffmann-La Roche Canada, Janssen, Pfizer Canada, Purdue Pharma, Takeda Canada, and the University of British Columbia, as well as individual donations from the public. ACE declared no conflict of interest in the preparation of the submission.

2. Condition and Current Therapy-Related Information

Methods used for ascertaining patient information included one-on-one interviews and interactions, questionnaires, social media, literature reviews, and online surveys. Experiences from patients, caregivers, and physicians were sought using many of the aforementioned methods. In addition, The Canadian Skin Patient Alliance also accessed information from the recently completed Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey.

Psoriatic arthritis is an autoimmune disease that usually begins slowly and spreads to joints over weeks or months; however, it can develop quickly and be severe. Patients diagnosed with psoriatic arthritis suffer from a multitude of symptoms that impact daily activities and living. Joint pain, swelling, and stiffness due to inflammation can be crippling, leaving patients unable to perform simple tasks such as bending down, dressing, sitting for prolonged periods of time, walking on both flat surfaces and stairs, getting in and out of bed and the bath, turning on faucets, opening jars, using a computer, and washing and drying themselves. Flare-ups can also cause the jaw to lock up, making it difficult to eat. Psoriatic arthritis can also cause inflammation in tendons around the joints and sausage-like swelling of fingers or toes. Pain associated with the arthritis can lead to sleepless nights. Emotionally, patients experience helplessness, frustration, fear, anxiety, and depression as they are often unable to work, can lose their independence, and require constant assistance to perform daily tasks. If they are able to work, they are often fearful of losing their jobs as a result of missing days to visit the doctor or get surgical treatment related to their psoriatic arthritis. Additionally, patients have to deal with increased weight gain due to their limited ability to move, which further adds to their frustration.

Many patients diagnosed with psoriatic arthritis also have the disfiguring psoriatic plaques that are often associated with this disease. They deal with cracking, bleeding, crusty, and itchy lesions, which can additionally be very painful. The psoriatic plaques often increase the sense of frustration, fear, depression, suicidality, and isolation, as many are embarrassed about these lesions. Patients have admitted to halting intimacy due to the unsightly lesions and have often been made to feel like modern-day lepers.

Caregivers are often referred to as the unsung heroes in the patients' battle with the disease. Patients reported that, "Caregivers may have to help with needles which can be tricky and often scary." They are responsible for helping those afflicted with simple tasks and for carrying out daily activities, including increased household work due to the increased vacuuming and laundering associated with the flaking from the psoriatic plaques. They often suffer emotionally, as they constantly observe the pain of those they love and must take charge of most household situations.

There is no cure for psoriatic arthritis — a treatment plan includes medication, education, physiotherapy, occupational therapy, and a healthy diet. Patients who are diagnosed early and start treatment immediately are often able to control their disease, thus avoiding severe joint damage, and are able to lead active and productive lives. Current medications used to treat psoriatic arthritis include nonsteroidal anti-inflammatory drugs, steroids, prednisone, disease-modifying antirheumatic drugs (hydroxychloroquine, leflunomide, sulfasalazine, and cyclosporine), methotrexate, and biologics. For some patients, these treatments effectively control their symptoms. However, patients on existing treatments can experience several adverse events, including stomach trouble, tiredness, high blood pressure, fever, physical and mental fatigue, dactylitis, night sweats, weight loss, increased bruising and bleeding, jaundice, dark urine, loss of appetite, rapid heart rate, light-headedness, nausea, and itching. In addition, fears of liver toxicity associated with long-term use of methotrexate, of kidney dysfunction with cyclosporine, and of lymphoma with infliximab are a reason for apprehension or discontinuation. There is

also the fear, based on patient experience, that these existing medications (particularly methotrexate and the currently available biologics) eventually become ineffective as the body adapts. Without a larger array of alternatives, patients may be left without effective treatment alternatives.
While most patients tolerate the side effects associated with treatment, there remain other barriers. The high price of biologics, the restricted and complex procedures for access, the lack of affordable treatment options, the loss of efficacy in current treatment, the inconvenience of infusion therapies, and the requirement for refrigeration represent significant barriers to treatment.

3. Related Information About the Drug Being Reviewed
Stelara is a biologic. Patients with psoriatic arthritis and psoriasis would like other options because everyone responds differently and because drugs that have been effective in managing symptoms can suddenly stop working. Stelara raises the hope that their symptoms may be controlled. Patients are excited about the prospect of a new biologic that has fewer side effects and a less frequent dosing schedule. Patients who travel frequently with work and struggle to carry medications requiring refrigeration, or those who are phobic about needles, see a clear benefit. Also, as the only IL 12/23 biologic, this treatment provides an option currently not available to psoriatic arthritis patients for whom other treatment options may either not work as well or have ceased to provide relief. Patients comment that making the medication available in pill form would be preferable. They also expect any success story for Stelara to parallel the results from the data and studies of previous treatment methods for other similar medication.

Those patients with direct experience with Stelara reported that it was either good or excellent with regard to its effectiveness at reducing joint pain, swelling, and stiffness. They also reported that Stelara was effective in addressing the skin lesions. Some patients claimed that this medication provided life-changing and liberating results. In addition to the clinical effectiveness and reductions in adverse events (although lower back pain and perhaps a bout with pneumonia were two mentioned), the quarterly dosing schedule (every three months) increased both adherence and convenience. One concern that was noted was that some patients on Stelara appeared to experience an increase in stress. This was thought to be brought on by the worry associated with the high cost of treatment and group health insurance premiums.

Patients feel Stelara for psoriatic arthritis meets an unmet need. It is the only IL12/23 alternative with infrequent dosing and easier use, and is thus beneficial for 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:	April 10, 2014
Alerts:	Weekly search updates until Sept 17, 2014
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
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
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
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	
Search Strategy	
#	**Searches**
1	(Stelara* or ustekinumab* or CNTO 1275 or CNTO1275).ti,ab,rn,nm,sh,hw,ot.
2	815610-63-0.rn,nm.
3	1 or 2
4	3 use pmez
5	(Stelara* or Ustekinumab* or CNTO 1275 or CNTO1275).ti,ab.
6	*ustekinumab/
7	5 or 6
8	7 use oemezd
9	conference abstract.pt.
10	8 not 9
11	4 or 10
12	remove duplicates from 11

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

Grey Literature

Dates for Search:	April 2014
Keywords:	Drug name, Indication
Limits:	No date or language limits used

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

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

APPENDIX 3: EXCLUDED STUDIES

Reason for Exclusion: Use of non-approved dosage

1. Clinical study report final: A phase 2, multicenter, randomized, double-blind, placebo-controlled trial of CNTO 1275, a fully human anti-IL-12 monoclonal antibody, administered subcutaneously, in subjects with active psoriatic arthritis [**CONFIDENTIAL** internal manufacturer's report]. Malvern (PA): Centocor, Inc; 2008 May 22.
2. Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, et al. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet. 2009 Feb 21;373(9664):633-40. Erratum in: Lancet. 2009 Apr 18;373(9672):1340 and Lancet. 2010 Nov 6;376(9752):1542.
3. Kavanaugh A, Menter A, Mendelsohn A, Shen YK, Lee S, Gottlieb AB. Effect of ustekinumab on physical function and health-related quality of life in patients with psoriatic arthritis: a randomized, placebo-controlled, phase II trial. Curr Med Res Opin. 2010 Oct;26(10):2385-92.

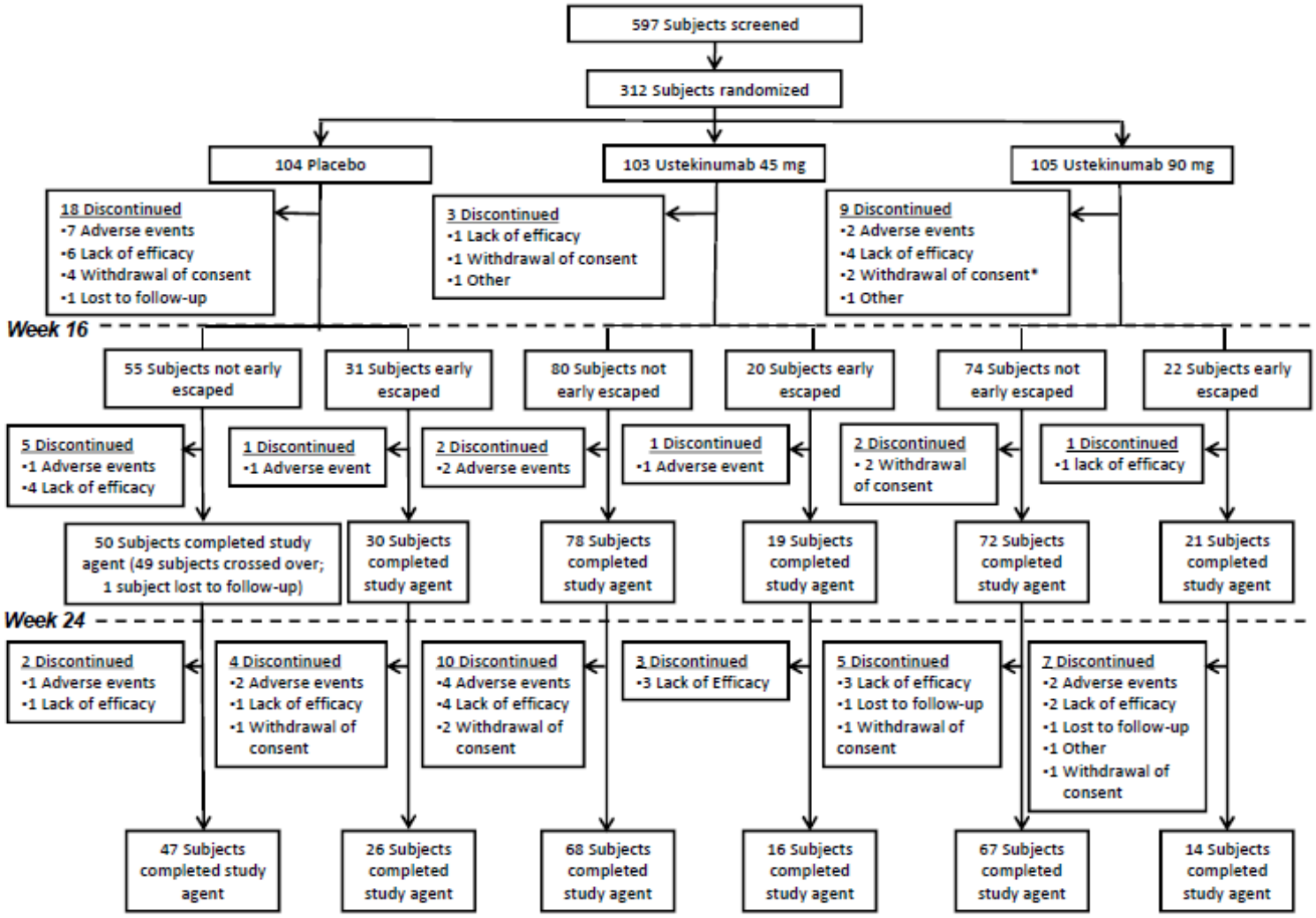
APPENDIX 4: DETAILED OUTCOME DATA

FIGURE 5: PSUMMIT1 PATIENT DISPOSITION (BY EARLY ESCAPE STATUS)

Figure 5 contained confidential information and was redacted upon request from the manufacturer.

Source: Manufacturer's Clinical Study Report for PSUMMIT1.[22]

FIGURE 6: PSUMMIT2 PATIENT DISPOSITION (BY EARLY ESCAPE STATUS)



Source: Manufacturer's Clinical Study Report for PSUMMIT2.[23]

Manufacturer–Performed Subgroup Analyses

TABLE 15: PSUMMIT1 SELECTED OUTCOMES BY SUBGROUP ANALYSES AT WEEK 24

Outcome	PL N = 206	UST 45 mg N = 205	UST 90 mg N = 204
ACR 20 at week 24			
MTX at baseline, n (%)	25/96 (26%)	43/99 (43%)	46/101 (46%)
No MTX at baseline, n (%)	22/110 (20%)	44/106 (42%)	55/103 (53%)
ACR 20 at week 24			
≤ 100 kg, n (%)	[redacted]	[redacted]	[redacted]
> 100 kg, n (%)			
PASI 75 at week 24			
MTX at baseline, n (%)	10/66 (15%)	32/66 (48%)	38/69 (55%)
No MTX at baseline, n (%)	6/80 (7%)	51/79 (65%)	55/80 (69%)

ACR = American College of Rheumatology; MTX = methotrexate; PASI = Psoriasis Area Severity Index; PL = placebo; UST = ustekinumab.
Source: Manufacturer's Clinical Study Report for PSUMMIT1.[7]

TABLE 16: PSUMMIT2 SELECTED OUTCOMES BY SUBGROUP ANALYSES AT WEEK 24

Outcome	PL N = 104	UST 45 mg N = 103	UST 90 mg N = 105
ACR 20 at week 24			
Anti-TNF alpha naive, n (%)	12/42 (29%)	23/43 (54%)	26/47 (55%)
Anti-TNF alpha experienced, n (%)	9/62 (14%)	22/60 (37%)	20/58 (34%)
ACR 20 at week 24			
MTX at baseline, n (%)	14/49 (29%)	27/54 (50%)	21/52 (40%)
No MTX at baseline, n (%)	7/55 (13%)	18/49 (37%)	25/53 (47%)
ACR 20 at week 24			
≤ 100 kg, n (%)	17/74 (22%)	32/74 (43%)	34/73 (47%)
> 100 kg, n (%)	4/30 (13%)	13/29 (44%)	12/31 (39%)
PASI 75 at week 24			
MTX at baseline, n (%)	3/29 (10%)	19/39 (49%)	22/39 (56%)
No MTX at baseline, n (%)	1/51 (2%)	22/41 (54%)	23/42 (55%)
PASI 75 at week 24			
Anti-TNF alpha naive, n (%)	3/30 (10%)	21/36 (58%)	25/40 (62%)
Anti-TNF alpha experienced, n (%)	1/50 (2%)	20/44 (46%)	20/41 (49%)

ACR = American College of Rheumatology; MTX = methotrexate; PASI = Psoriasis Area Severity Index; PL = placebo; TNF = tumour necrosis factor; UST = ustekinumab.
Source: Manufacturer's Clinical Study Report for PSUMMIT2.[8]

TABLE 17: HARMS — PSUMMIT1 THROUGH WEEK 108 IN PATIENTS RECEIVING USTEKINUMAB

	Placebo -> Ustekinumab 45 mg		Ustekinumab 45 mg		Ustekinumab 90 mg[d] N = 204
AEs	**Early Escape[a] N = 58**	**Crossover[b] N = 131**	**45 mg Only[c] N = 166**	**45 mg -> 90 mg[a] N = 36**	
Patients with > 0 AEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common AEs[e]					
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriatic arthropathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory tract infection (viral)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liver function test Abnormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs[f]					
Patients with > 0 SAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common SAEs[d]					
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B-cell lymphoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Squamous cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AEs	Placebo -> Ustekinumab 45 mg		Ustekinumab 45 mg		Ustekinumab 90 mg[d] N = 204
	Early Escape[a] N = 58	Crossover[b] N = 131	45 mg Only[c] N = 166	45 mg -> 90 mg[a] N = 36	
WDAEs[f]					
WDAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common reasons					
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriatic arthropathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B-cell lymphoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis allergic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DEATHS[f]					
Number of deaths, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Patients who early escaped at week 16.
[b] Patients who crossed over at week 24.
[c] Patients who did not early escape at week 16.
[d] Includes all patients irrespective of early escape.
[e] Frequency > 5% in at least one of the groups.
[f] Harms of interest noted in protocol; not necessarily with a frequency of ≥ 5%.
Note: The duration of follow-up and adverse events were counted from the first ustekinumab administration onward.
Source: Clinical Study Report 108-week PSUMMIT1.[22]

PSUMMIT1 Long-Term Harms

Summary of Adverse Events

Through week 60, the proportion of patients experiencing one or more adverse events was comparable between 45 mg and 90 mg groups at 77.1% and 72.5%, respectively.[22] In addition, of all the patients who were on ustekinumab (hereafter referred to as the all-ustekinumab group), 70.7% of patients experienced one or more adverse events through week 60 compared with 58.0% of patients through week 52. Infections and infestations, particularly nasopharyngitis and upper respiratory tract infection, were the most frequently reported adverse events both through week 60 and week 52.

Adverse Events by Baseline Concomitant Methotrexate Use

[redacted]

Serious Adverse Events

[redacted]

Serious Adverse Events by Baseline Concomitant Methotrexate Use

[redacted]

Serious Infections

[redacted]

Injection Site Reactions

[redacted]

Malignancies

[redacted]

Neurologic Disorders

[redacted]

TABLE 18: HARMS — PSUMMIT2 THROUGH WEEK 60 IN PATIENTS RECEIVING USTEKINUMAB

	Placebo -> Ustekinumab 45 mg		Ustekinumab 45 mg		Ustekinumab 90 mg[d] N = 105
AEs	**Early Escape[a] N = 31**	**Crossover[b] N = 49**	**45 mg Only[c] N = 80**	**45 mg -> 90 mg[a] N = 20**	
Patients with > 0 AEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common AEs[e]					
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory tract infection (viral)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriatic arthropathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs[f]					
Patients with > 0 SAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common SAEs[d]					
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bacteremia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal candidiasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Placebo -> Ustekinumab 45 mg		Ustekinumab 45 mg		Ustekinumab 90 mg[d] N = 105
AEs	**Early Escape[a] N = 31**	**Crossover[b] N = 49**	**45 mg Only[c] N = 80**	**45 mg -> 90 mg[a] N = 20**	
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Breast cancer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs[f]					
WDAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common reasons					
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriatic arthropathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Breast cancer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Squamous cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DEATHS[f]					
Number of deaths, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Patients who early escaped at week 16.
[b] Patients who crossed over at week 24.
[c] Patients who did not undergo early escape at week 16.
[d] Includes all patients irrespective of early escape.
[e] Frequency > 5% in at least one of the groups.
[f] Harms of interest noted in protocol; not necessarily with a frequency of ≥ 5%.
Note: The duration of follow-up and adverse events were counted from the first ustekinumab administration onward.
Source: Clinical Study Report PSUMMIT2.[23]

PSUMMIT2 Long-Term Harms

Summary of Adverse Events

Through week 60,[23] the proportion of patients experiencing one or more adverse events was comparable between 45 mg and 90 mg groups at 78.6% and 77.9%, respectively. In addition, of all the patients who were on ustekinumab (hereafter referred to as the all-ustekinumab group), 78.1% of patients experienced one or more adverse events through week 60 compared with 66.4% of patients through week 24. Infections and infestations, particularly nasopharyngitis and upper respiratory tract infection, were the most frequently reported adverse events both through week 60 and week 24. One possible dose-effect event rate was the frequency of bronchitis through week 60, which was observed more in the 90 mg group than the 45 mg group (8.7% and 4.9%, respectively).

Adverse Events by Baseline Concomitant Methotrexate Use

Through week 60 of the PSUMMIT2 trial, there were similar proportions of patients experiencing at least one adverse event regardless of whether or not they were treated with concomitant methotrexate (MTX). In the combined 45 mg group, 75.9% and 81.6% experienced adverse events in those receiving concomitant MTX and not receiving concomitant MTX, respectively. Likewise, in the 90 mg group, 80.4% and 75.5% experienced adverse events in those receiving concomitant MTX and not receiving concomitant MTX, respectively. Infections and infestations were the most prominent adverse events in both MTX and ustekinumab dosing strata, with nasopharyngitis being the most frequently adverse event reported. These results were consistent with results observed through week 24.

Adverse Events Patients With Prior Anti-Tumour Necrosis Factor Alpha Exposure

Through week 60, the proportions of patients experiencing at least one adverse event were comparable between the combiend 45 mg (81.7%) and 90 mg (79.3%) groups in patients with prior anti-TNF alpha exposure. Infections and infestations remained the most frequently reported adverse events, with nasopharyngitis and upper respiratory tract infection being the most frequent. These results are consistent with those observed through week 24 in the all-ustekinumab group.

Serious Adverse Events

Through week 60, eight of the reported serious adverse events were from one person. Seven additional patients reported more than one serious adverse event, with two of these patients experiencing more than one serious adverse event prior to week 24.

Serious Adverse Events by Baseline Concomitant Methotrexate Use

Through week 60, the proportions of patients reporting was low in both treatment strata, at 5.6% and 2.0% in the combined 45 mg and 90 mg groups, respectively, in those receiving MTX and 6.1% and 9.4 % in the combined 45 mg and 90 mg groups, respectively, in those not receiving MTX.

Serious Adverse Events Among Patients With Prior Anti-Tumour Necrosis Factor Alpha Exposure

Through week 60, 5.0% and 8.6% of patients experienced at least one treatment-emergent serious adverse event in the combined 45 mg and 90 mg group, respectively. In the all-ustekinumab group, 6.2% through week 60 compared with 1.5% of patients through week 24 experienced at least one serious adverse event.

Serious Infections
While no serious infections were observed through week 24, 1.9% in the 90 mg group experienced at least one infection through week 60: one patient with methicillin-sensitive *Staphylococcus aureus* bacteremia and another with gastrointestinal candidiasis and septic shock. Both patients were anti-TNF alpha experienced.

Injection Site Reactions
Through week 60, the proportion of injection site reactions was low but was highest in the 90 mg group; 0.2%, 0.3%, and 1.0% in the placebo, 45 mg, and 90 mg groups, respectively. All reactions were all determined to be mild, and no patients withdrew for this reason.

Malignancies
One malignancy (breast cancer) was reported between week 24 and week 60 in a patient in the placebo -> 45 mg group.

Neurologic Disorders
Through week 60, there were no events of either reversible posterior leukoencephalopathy syndrome or demyelination.

Psoriasis Longitudinal Assessment and Registry History and Harms
The Psoriasis Longitudinal Assessment and Registry (PSOLAR) study is a prospective, disease-based longitudinal, Janssen-sponsored registry that launched in 2007.[42] It started as a registry specifically for North America and expanded to an international study in 2009. It currently exceeds inclusion of 10,000 patients. It was designed to observe approximately 12,000 patients. These patients all have psoriasis and are either receiving, or are eligible to receive, systemic psoriasis therapies. Subsets of patients with plaque psoriasis also included in this registry include those patients with pustular psoriasis, guttate psoriasis, and psoriatic arthritis.[42] PSOLAR includes patients receiving both biologic and non-biologic therapies, while being able to accommodate approximately 4,000 patients receiving ustekinumab and infliximab (both Janssen products). Outcome and safety data are being collected for eight years post-initiation, with data collected at the commencement of the study and every six months thereafter.[42] Some baseline demographics and adverse events (including malignancies) from the PSOLAR interim analysis are reported in Table 19.

TABLE 19: RELEVANT HISTORY AND HARMS — PSORIASIS LONGITUDINAL ASSESSMENT REGISTRY FOR PATIENTS RECEIVING USTEKINUMAB

	Number of Patients (%)			
Patient Demographics				
Relevant medical history				
Patients enrolled	9,495			
Number of patients with data	9,482			
Psoriatic arthritis	3,511/9,470 (37.1)			
Previously biologic use (total n = 9,495)				
No biologics	2,729 (28.7)			
1 or 2 biologics	5,582 (58.8)			
3 or 4 biologics	1,111 (11.7)			
5 or more biologics	73 (0.8)			
Previous use of methotrexate (total n = 9,457)	3,769 (39.9)			
	Events/100 Patient-Years (Events)			
AEs in Patients with Psoriasis[a]				
Specific AEs				
Serious infections	1.40 (192)			
Malignancies[b]	0.61 (84)			
All-cause mortality	0.37 (51)			
	UST 45 mg	**UST 90 mg**	**Combined UST**	
Malignancies 5-Year Follow-Up, Rates[c] = Events/100 Patient-Years (95% CI)				
NMSC[d]	0.64 (0.41 to 0.95)	0.44 (0.28 to 0.66)	0.52 (0.39 to 0.70)	
NMSC, year 1	NR	NR	0.94 (0.61 to 1.41)	
NMSC, year 2	NR	NR	0.49 (0.21 to 0.96)	
NMSC, year 3	NR	NR	0.40 (0.15 to 0.87)	
NMSC, year 4	NR	NR	0.42 (0.15 to 0.91)	
NMSC, year 4	NR	NR	0.16 (0.03 to 0.47)	
Other malignancies[d,e]	0.59 (0.37 to 0.89)	0.61 (0.42 to 0.87)	0.60 (0.45 to 0.78)	
Other malignancies, year 1	NR	NR	0.39 (0.19 to 0.72)	
Other malignancies, year 2	NR	NR	0.97 (0.56 to 1.58)	
Other malignancies, year 3	NR	NR	0.40 (0.15 to 0.87)	
Other malignancies, year 4	NR	NR	0.77 (0.38 to 1.37)	
Other malignancies, year 5	NR	NR	0.59 (0.29 to 1.05)	
	UST	**IFL/GOL[f]**	**ETA/ADA[g]**	**Non-Biologics**
Malignancies, Unadjusted Rates (Events/100 Patient-Years)				
Malignancies (excluding NMSC)	0.60	0.65	0.60	0.61

ADA = adalimumab; AE = adverse event; CI = confidence interval; ETA = etanercept; GOL = golimumab; IFL = infliximab; NMSC = non-melanoma skin cancers; NR = not reported; PSOLAR = Psoriasis Longitudinal Assessment Registry; UST = ustekinumab.

[a] Data are presented as rates per 100 patient-years of follow-up (number of events).

[b] Excluding non-melanoma skin cancer.

[c] Rates per 100 patient-years (95% CI) by year of follow-up, cumulative rates through year 5.

[d] Cumulative rates.

[e] Malignancies included were not specified.

[f] Anti-TNF sponsor biologics.

[g] Nonsponsor biologics (almost exclusively etanercept/adalimumab).

Source: PSOLAR study,[42] PSOLAR abstract,[43] PSOLAR abstract.[44]

Malignancies — Five-Year Follow-Up

Through five years, 47 patients reported non-melanoma skin cancers, of which 40 were basal cell carcinomas and 10 were squamous cell carcinomas (4:1 ratio). Fifty-four patients reported other malignancies, the most common being prostate, melanoma, colorectal, and breast. The standardized incidence ratio was 0.98 (95% confidence interval, 0.74 to 1.29), indicating that the rates of malignancies in the PSOLAR trial after five years' follow-up was comparable to that expected from the general US (Surveillance, Epidemiology and End Results program) population.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

1. Objective

To provide information on the characteristics, validity, and clinically important differences of the scales and surrogate outcomes measured in trials included in the CADTH Common Drug Review (CDR) systematic review. These include the American College of Rheumatology (ACR) 20/50/70, Psoriatic Arthritis Response Criteria (PsARC), Disease Activity Score in 28 joints (DAS 28) based on C-reactive protein (CRP), Psoriasis Area Severity Index (PASI), Dactylitis Score, Health Assessment Questionnaire (HAQ), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and the Short Form-36 Health Survey (SF-36).

2. Findings

Currently available outcome measures in psoriatic arthritis (PsA) have largely been adopted from other conditions, such as rheumatoid arthritis (RA) and psoriasis. Hence, validity and reliability data specific to PsA are sparse. To complicate matters further, there are many different parameters of disease activity in PsA, and no single evaluation tool assesses all components of PsA, necessitating the use of multiple outcome measures in clinical trials. The various outcome measures are summarized in this appendix.

American College of Rheumatology 20/50/70

The ACR criteria[26] for assessing joint status (originally developed for RA patients) provide a composite measure of ≥ 20%, ≥ 50%, or ≥ 70% improvement in both swollen and tender joint counts and at least three of five additional disease criteria, including patient/physician global assessment of disease activity (10 cm visual analogue scale [VAS]), HAQ, patient assessment of pain intensity, and levels of CRP or ESR. The ACR joint count assesses 68 joints for tenderness and 66 joints for swelling. Assessment of the proximal (PIP) and distal interphalangeal (DIP) joints of the hands and feet (i.e., 78 joints for tenderness and 76 for swelling) is not typically included for PsA because of difficulty distinguishing between PIP and DIP joint inflammation in the toes.[45] The ACR has been shown to have good inter- and intra-observer reliability in PsA[46,47] and was shown to be a valid outcome measure in randomized controlled trials (RCTs).[48] The ACR 20 is generally accepted as the minimally clinically important difference (MCID) indicating a response to treatment, while the ACR 50 and ACR 70 more likely reflect truly important change for the long-term management of arthropathy. Of note, the ACR is a general measure of clinical response of peripheral joint disease and does not include assessment of enthesitis, dactylitis, the spine, or the skin. Consequently, it represents only part of the clinical features of PsA, necessitating the use of additional assessment instruments.

Psoriatic Arthritis Response Criteria

PsARC[27] measures signs and symptoms of PsA assessed by tender or swollen joint count, physician global assessment (5-point Likert scale), and patient global assessment (5-point Likert scale). To be a PsARC responder, a patient must have at least a 30% reduction in tender or swollen joint count, as well as a 1-point reduction on the 5-point patient or physician global assessment scales, and no worsening on any score. PsARC has been shown to be a responsive and discriminate outcome instrument in PsA RCTs.[48] However, the PsARC tends to have a higher percentage response than the ACR 20, which may be explained by the requirement that tender *or* swollen joint change is required, not both, and possibly due to the absence of the HAQ score and measurement of ESR or CRP.[49] As with the ACR, the PsARC does not account for psoriasis severity and is only a general assessment of clinical status.

Disease Activity Score 28 and C-reactive Protein

The DAS includes an assessment of 28 tender and swollen joints along with a patient global assessment of well-being to evaluate a patient's response to treatment.[50,51] The score ranges from 0 to 9.4 and is calculated using either clinical values of ESR or CRP; the reviewed trial used CRP, as follows:

DAS 28 = 0.56(√TJC28) + 0.28(√SJC28) + 0.36Ln(CRP + 1) + 0.014(PtGA)[50]

where TJC28 and SJC28 are the tender and swollen joint counts and PtGA is the patient global assessment.

The threshold values are 2.6, 3.2, and 5.1 for remission, low disease activity, and high disease activity, respectively.[52] DAS 28 and change from baseline DAS 28 values are used to derive the European League Against Rheumatism (EULAR)[51] response criteria. Responders include patients with moderate or good response, as shown:

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

The DAS components correlate well with each other and with the ACR,[50,53-55] and have been shown to be discriminant and responsive in trials.[56] However, the DAS 28 does not include assessment of DIP or lower extremity disease and, thus, may not describe the full extent of a patient's disease status. The DAS 28 using ESR is better established than using CRP, and DAS 28-ESR has been validated for use as an outcome measure in several RA trials.[48,50,52,57] DAS 28-ESR has shown the ability to discriminate between placebo and treatment in PsA trials,[56] although no formal validation has been conducted in PsA thus far. The DAS 28-CRP shows general agreement with the ESR equation in RA trials, although the DAS28-CRP tends to yield better response criteria results than the DAS 28-ESR when disagreements occur between the two.[58-60] CRP may be a more desirable clinical measurement than ESR because CRP levels are sensitive to short-term changes in disease activity, whereas ESR can be influenced by such factors as age, gender, or plasma proteins.[61] As with the ACR and PsARC, the DAS 28 is only a general assessment of clinical response.

Psoriasis Area 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 greater 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 US Food and Drug Administration.[28]

In calculating the PASI, severity is determined by dividing the body into four regions: head (h), upper extremities (u), trunk (t), and lower extremities (l), which account for 10%, 20%, 30%, and 40% of the total body surface area, respectively.[62] Each of these areas is assessed separately for erythema, induration, and scaling, which are 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%; and 6 = 90% to 100%. The following formula is used to calculate the PASI score:

PASI = 0.1 (Eh + lh + Sh) Ah + 0.2 (Eu + lu + Su) Au + 0.3 (Et +lt + St) At + 0.4 (El +ll +Sl) Al[62]

Where E = erythema, I = induration, S = scaling, A = area, h = head score, t = trunk score, u = upper extremities, and l = lower extremities score. PASI 75 is a dichotomous scale (Yes/No, patient achieved ≥ 75% improvement from baseline PASI score).

A number of limitations of the PASI have been identified:

- The PASI has been criticized as not correlating the clinical extent of the disease with quality of life and the psychological stress caused by psoriasis. The patient's measure of quality of life is often worse than the physician-rated clinical severity.[63]
- There are significant inter-rater reliability issues regarding the measurement of body surface area.[64,65]
- PASI often fails to predict severity as seen from the patient's perspective.[64,65]
- Improvements in PASI score are not linearly related to severity or improvements in psoriasis.[28,65] The extent of psoriatic involvement is measured using a scale of 1 to 6, and the areas corresponding to each score are nonlinear.
- Some severe disease (clinically) may be scored low. For example, scores as low as 3 (on palms and soles) may represent psoriasis that disables a patient from work and other life activities.
- Most patients fall into a narrow band of scores, therefore decreasing the usefulness of the full range of scores (i.e., scores higher than 40 are rare).[64]
- There is little research on the reliability of the assessments for erythema, desquamation, and induration, together with overall PASI scores.[64]
- Criterion validity is restricted by the lack of a "gold standard" measure of psoriatic severity.[66]
- The PASI lacks sensitivity, as erythema, desquamation, and induration are scored with equal weight within each of the four body regions. Thus, a reduction in scaling with a concomitant increase in skin erythema could be recorded with the same PASI score.
- Improvement of the histological phenotype of psoriasis can be underestimated by the per cent improvement in PASI (e.g., reduction of T cells, loss of K16 expression, and reduction in epidermal thickness).[28]
- Little work has been done to determine the clinical relevance of derived PASI scores.[64]

Dactylitis Score

Dactylitis is a hallmark clinical feature of PsA and occurs in roughly half of all patients with PsA.[67] In the reviewed RCT, presence and severity of dactylitis per digit of the hands and feet were physician-rated on a scale from 0 to 3, where 0 = absent and 3 = severe dactylitis, and summed to a maximum of 60;[68] the same scale has been used elsewhere.[56] Healy et al. compared the responsiveness of various dactylitis measures used in RCTs with each other and with clinical measures of PsA, and they found that this dactylitis score can detect changes in dactylitis severity with large effect sizes and that it correlated most strongly with clinical measures compared with the other dactylitis measures.[69]

Health Assessment Questionnaire

The HAQ was developed to assess physical disability and pain in RA[29] and has been used extensively in arthritis RCTs, including for PsA. Through a self-assessed questionnaire of eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities), patients' difficulty in performing this activities is scored from 0 (without any difficulty) to 3 (unable to do). The scores are adjusted for use

of aids, devices, or persons who help with the activity and are then summed and divided by the number scores answered. Scores are evaluated based on change from baseline. The MCID for the HAQ has been estimated from a phase 3 trial of etanercept in PsA[30] to be 0.3 (whereas, the MCID is 0.22 for RA). Further expanding upon this analysis, Mease et al.[31] determined that the MCID for the HAQ–Disability Index was 0.35, up 0.05 from their preliminary estimate. The MCID estimated by Kwok and Pope was 0.13 (equal bidirectional magnitudes for improvement and worsening).[32] Blackmore et al. have shown that the HAQ adequately captures clinically important changes in functional status and pain.[70] Because the HAQ focuses on physical disability, however, it may not adequately capture disability in patients with predominantly skin disease. Also, it may not adequately measure the activities affected in patients with different patterns of PsA.[71] This observation has not been evaluated in other studies to date. Modified versions of the HAQ (HAQ-S includes spinal domains and the HAQ-SK includes assessment of skin disease) have not proven to be significantly better in assessment of health status in PsA than the original HAQ.[70,72] Of note, the HAQ-SK correlated poorly with the PASI, although it does correlate with patient- and physician-assessed psoriasis severity.[72]

Short Form (36) Health Survey

The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[33] The SF-36 consists of eight health domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems.[34] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries, the physical component summaries (PCS) and the mental component summary (MCS). 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. Therefore, all scores greater than/less than 50 are considered above/below average for the general US population. Husted and colleagues[73] and Leung and colleagues[38] reported that the SF-36 is reliable and valid for assessment of patients with PsA and could be used to distinguish PsA patients from patients without PsA. In addition, the PCS and MCS summary scores support the SF-36 validity.[38] The SF-36 is equally or more responsive than the HAQ to short-term changes in perceived health status and inflammatory disease activity in patients with PsA.[74]

The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 and 5 points.[35-37] Leung et al.[38] reported MCIDs of 3.74 and 1.77 in PsA patients treated with anti-TNF alpha drugs for the PCS and MCS subsections, respectively. The MCS has also been observed to be weaker in differentiating drug and placebo effects, as shown in a phase 3 trial.[38] Limitations to consider with regard to this study include small sample size (n = 17) and the fact that MCIDs may change with either clinic settings or with baseline disease severity.[38]

Bath Ankylosing Spondylitis Disease Activity Index

The BASDAI was originally designed to assess the severity of ankylosing spondylitis but has recently been used to assess spondyloarthropathies, including PsA. This has been mainly due to the lack of other validated instruments to assess PsA.[39] The BASDAI is comprised of six items: fatigue, total back pain, pain and swelling of joints, pain at enthesis locations, severity of morning stiffness, and duration of morning stiffness. The listed symptoms are rated by patients using VAS indices, with higher results indicating increased disease activity and functional disability.[39] The total BASDAI score is calculated with the following formula:

$$\text{BASDAI} = \frac{1 + 2 + 3 + 4 + ([5 + 6] / 2)}{5}$$

While the BASDAI was observed to similarly evaluate disease activity in both peripheral and axial PsA, and to correlate highly with the patient's perceptions of arthritis activity, overall it was determined to be an ambiguous measure of assessing PsA disease activity.[75,76] In addition, the BASDAI scores were significantly lower overall in PsA when compared with scores in ankylosing spondylitis.[76]

A number of limitations of the BASDAI have been identified:

- This assessment tool is totally patient-derived.[77]
- There is limited face and construct validity.[77]
- Inflammatory markers are not included (to increase face validity); these included the exclusion of CRP and ESR.[77]
- The tool does not capture entire spectrum of disease, i.e., joint counts and physician ratings.[75,76]

APPENDIX 6: SUMMARY AND APPRAISAL OF MANUFACTURER-SUBMITTED MIXED TREATMENT COMPARISON

Objective

The objective of this review is to summarize the methods and results and to conduct a critical appraisal of a mixed treatment comparison between ustekinumab and other biologic response modifiers for the treatment of active psoriatic arthritis in patients who have not received previous anti-tumour necrosis factor (TNF) alpha therapy. This indirect comparison was provided as part of the economic submission to the CADTH Common Drug Review (CDR) for this Formulary Review.[78]

Summary of Mixed Treatment Comparison

Rationale

The manufacturer indicated that a systematic review and mixed treatment comparison were undertaken because no head-to-head trial evidence exists assessing the efficacy of ustekinumab compared with alternative therapies in adult patients with active psoriatic arthritis. Comparative data were needed in order to inform the manufacturer's economic analyses.

Methods

Eligibility criteria

In order to be eligible for inclusion, trials had to include adults with psoriatic arthritis, have a randomized design, use blinded or open-label methodology, and compare ustekinumab with placebo or one of the active comparators listed in the next paragraph.

Intervention and comparators

The primary objective was to make comparisons between ustekinumab and infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira), and golimumab (Simponi). The secondary objective was to make comparisons between ustekinumab and certolizumab pegol (Cimzia), apremilast, abatacept (Orencia), brodalumab, and secukinumab.

Outcomes

The primary outcomes of interest included in the mixed treatment comparison analysis were American College of Rheumatology (ACR) 20, Psoriatic Arthritis Response Criteria (PsARC), Psoriasis Area Severity Index (PASI) 75, and Health Assessment Questionnaire–Disability Index (HAQ-DI). Time points of interest were weeks 12 to 16 and 24.

Analysis

A Bayesian approach was used when analyzing the data, and a random effects model was fitted to the data for all outcomes. All data were measured as response to treatment, except for the HAQ-DI data, which were measured as change from baseline. Forest plots were generated, displaying odds ratios for response data or mean change in HAQ score relative to placebo. A network diagram was also presented. Data summarizing relative and absolute differences between treatments were also presented.

Authors stated that a methodology checklist was used to evaluate quality of the randomized controlled trials (RCTs), but details were not provided. Risk of bias was assessed as low for each included study, but the authors did not specify which instrument was used.

Results

Study and patient characteristics

Fifteen double-blind RCTs published between 2000 and 2014 were included in their analysis, and data were obtained from these studies from full publications, complete study reports, or supplementary material such as conference abstracts. Three trials included ustekinumab (PSUMMIT1, PSUMMIT2, and a phase 2 ustekinumab study that used an unapproved dosage of ustekinumab). Less than half of the PSUMMIT2 data were used for the main analyses because they excluded patients who previously used anti-TNF alpha therapy. All trials except one used placebo as a comparator.

Patient characteristics, demographics, and baseline characteristics were summarized for the 15 RCTs (Table 20). The duration of psoriasis ranged from a mean of 13.8 to 19.7 years and of psoriatic arthritis from 6.1 to 10.6 years. Patients had received treatment with disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids prior to most of the trials. In the majority of trials, concomitant methotrexate was permitted.

TABLE 20: BASELINE PATIENT CHARACTERISTICS OF INCLUDED STUDIES

Trial Characteristics		Patient Characteristics		
Study	**Treatment Groups, n**	**Duration of PsA, Mean (SD)**	**Duration of PsO, Mean (SD)**	**Treatment History, % Use**
ADEPT, 2005	Adalimumab	9.8 (8.3)	17.2 (12.0)	Mean number (SD)[a] DMARD: 1.5 (1.2)
	Placebo	9.2 (8.7)	17.1 (12.6)	Mean number (SD)[a] DMARD: 1.5 (1.2)
Genovese et al., 2007	Adalimumab	7.5 (7.0)	18.0 (13.2)	DMARD: 100 MTX: 80.4 NSAID: 90.2 corticosteroid: 19.6
	Placebo	7.2 (7.0)	13.8 (10.7)	DMARD: 100 MTX: 79.6 NSAID: 98 corticosteroid: 30.6
Gottlieb et al., 2009	Ustekinumab	6.15[b]	NR	DMARD: 63 immunosuppressive: 18 anti-TNF: 24
	Placebo	4.90[b]	NR	DMARD: 59 immunosuppressive: 14 anti-TNF: 31
GO-REVEAL, 2009	Golimumab 50 mg	7.2 (6.8)	NR	DMARD / NSAID: 100
	Golimumab 100 mg	7.7 (7.8)	NR	DMARD / NSAID: 100
	Placebo	7.6 (7.9)	NR	DMARD / NSAID: 100
IMPACT, 2005	Infliximab	11.7 (9.8)	16.9 (10.9)	DMARD: 100
	Placebo	11.0 (6.6)	19.4 (11.6)	DMARD: 100
IMPACT 2, 2005	Infliximab	8.4 (7.2)	16.2 (11.0)[c]	DMARD / NSAID: 100
	Placebo	7.5 (7.8)	16.8 (12.0)[c]	DMARD / NSAID: 100
McInnes et al., 2011	Secukinumab	NR	NR	NR
	Placebo	NR	NR	NR

Trial Characteristics		Patient Characteristics		
Study	**Treatment Groups, n**	**Duration of PsA, Mean (SD)**	**Duration of PsO, Mean (SD)**	**Treatment History, % Use**
Mease et al., 2000	Etanercept	9.0[b] (1.0-31.0)[c]	19.0[b] (4.0-53.0)[c]	NSAID: 100
	Placebo	9.5[b] (1.0-30.0)[c]	17.5[b] (2.0-43.0)[c]	NSAID: 100
Mease et al., 2004	Etanercept	9.0	18.3	NSAID: 100
	Placebo	9.2	19.7	NSAID: 100
Mease et al., 2011	Abatacept 3 mg	7.2 (7.4)	NR	MTX: 82 NSAID: 73 corticosteroid: 31 anti-TNF: 36
	Abatacept 10 mg	10.6 (9.4)	NR	MTX: 85 NSAID: 68 corticosteroid: 33 anti-TNF: 33
	Abatacept 30/10 mg	7.8 (7.7)	NR	MTX: 85 NSAID: 68 corticosteroid: 33 anti-TNF: 33
	Placebo	7.4 (8.0)	NR	MTX: 69 NSAID: 55 corticosteroid: 21 anti-TNF: 29
PSUMMIT1, 2012	Ustekinumab 45 mg	6.1 (6.8)	14.9 (13.0)	DMARD: 79.5 NSAID: 89.3
	Ustekinumab 90 mg	7.0 (7.6)	15.5 (12.1)	DMARD: 78.4 NSAID: 90.6
	Placebo	6.7 (7.5)	15.9 (12.8)	DMARD: 80.6 NSAID: 87.8
PSUMMIT2, 2012	Ustekinumab 45 mg	8.2 (8.6)	15.4 (11.2)	DMARD: 86.4 MTX: 83.5 NSAID: 84.3 corticosteroid: 40.2; immunosuppressive: 15.5 anti-TNF: 60
	Ustekinumab 90 mg	7.2 (7.5)	14.8 (12.7)	DMARD: 83.8 MTX: 80.0 NSAID: 81.7 corticosteroid: 29.1; immunosuppressive: 16.2 anti-TNF: 58
	Placebo	8.5 (8.5)	15.2 (11.8)	DMARD: 88.5 MTX: 86.5 NSAID: 88.5 corticosteroid: 41.3 immunosuppressive: 16.3 anti-TNF: 62

Trial Characteristics		Patient Characteristics		
Study	**Treatment Groups, n**	**Duration of PsA, Mean (SD)**	**Duration of PsO, Mean (SD)**	**Treatment History, % Use**
RAPID PsA, 2012	Certolizumab 200 mg	NR	NR	Certolizumab combined Anti-TNF: 19.8
	Certolizumab 400 mg	NR	NR	
	Placebo	NR	NR	Anti-TNF: 19.1
RESPOND, 2012	Infliximab + MTX	2.8 (2.6)	NR	DMARD:22.8 NSAID: 68.4 corticosteroid: 15.8
	MTX	3.7 (2.7)	NR	DMARD: 15.5 NSAID: 58.8 corticosteroid: 15.5
Schett et al., 2012	Apremilast b.i.d.	8.4 (NR)	15.5 (NR)	NR
	Apremilast q.d.	7.6 (NR)	18.3 (NR)	NR
	Placebo	7.3 (NR)	15.8 (NR)	NR

b.i.d. = twice daily; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; PsA = psoriatic arthritis; PsO = psoriasis; q.d. = every day; SD = standard deviation; TNF = tumour necrosis factor.

[a] Measurement different than per cent use.

[b] Presented as the median.

[c] Results obtained from Lemos et al.[79]

Source: MTC,[78] provided by manufacturer.

TABLE 21: MIXED TREATMENT COMPARISON — OUTCOMES OF INDIVIDUAL TRIALS

Trial Characteristics			Outcomes				
Study	**Treatment Group (N)**	**End Point, Weeks**	**ACR 20, %**	**PASI 75, % (N)**	**PsARC, %**	**DAS 28, %**	**HAQ-DI CFB, Mean (SD)**
ADEPT, 2005	Adalimumab	24	57.0	59.0 (69)	60.0	NR	–0.4 (0.5)
	Placebo		15.0	1.0 (69)	23.0	NR	–0.1 (0.4)
Genovese et al., 2007	Adalimumab	12	39.0	NR	51.0	NR	–0.3 (0.5)
	Placebo		16.0	NR	24.0	NR	–0.1 (0.3)
Gottlieb et al., 2009	Ustekinumab	12	42.0	52.0 (63)	NR	NR	–0.3[a]
	Placebo		14.0	5.0 (55)	NR	NR	0.0[a]
GO-REVEAL, 2009	Golimumab 50 mg	24	52.0	56.0 (102)	70.0	64.0	–0.3 (0.6)
	Golimumab 100 mg		61.0	66.0 (106)	85.0	78.0	–0.4 (0.5)
	Placebo		12.0	1.0 (73)	29.0	24.0	0.0
IMPACT, 2005	Infliximab	16	65.4	68.0 (22)	75.0	45.5[b]	–0.6
	Placebo		9.6	0.0 (17)	21.0	2.8[b]	0.0
IMPACT 2, 2005	Infliximab	24	54.0	60.0 (83)	70.0	NR	46.0[c]
	Placebo		16.0	1.0 (87)	32.0	NR	–19.4[c]
McInnes et al., 2011	Secukinumab	6	39.0	NR	NR	NR	NR
	Placebo		23.0	NR	NR	NR	NR
Mease et al., 2000	Etanercept	12	73.0	26.0 (19)	87.0	NR	83.0[c]
	Placebo		13.0	0.0 (19)	23.0	NR	3.0[c]
Mease et al., 2004	Etanercept	24	59.0[d]	23.0 (66)[d]	70.0[d]	NR	54.0[c]
	Placebo		15.0[d]	3.0 (62)[d]	23.0[d]	NR	6.0[c]
Mease et al., 2011	Abatacept 3 mg/kg	24	33.0	38.0 (21)	NR	NR	NR
	Abatacept 10 mg/kg		48.0	14.0 (21)	NR	NR	NR
	Abatacept 30/10 mg/kg		42.0	10.0 (20)	NR	NR	NR
	Placebo		19.0	5.0 (21)	NR	NR	NR
PSUMMIT1, 2012	Ustekinumab 45 mg	24	42.4	57.2 (145)	56.1	65.9	22.4[c]
	Ustekinumab 90 mg		49.5	62.4 (149)	64.7	67.6	29.4[c]

Trial Characteristics			Outcomes				
Study	**Treatment Group (N)**	**End Point, Weeks**	**ACR 20, %**	**PASI 75, % (N)**	**PsARC, %**	**DAS 28, %**	**HAQ-DI CFB, Mean (SD)**
	Placebo		22.8	11.0 (146)	37.4	34.5	2.1[c]
PSUMMIT2, 2012	Ustekinumab 45 mg	24	43.7	51.3 (80)	55.3	54.4	16.3[c]
	Ustekinumab 90 mg		43.8	55.6 (81)	51.4	53.3	15.8[c]
	Placebo		20.2	5.0 (80)	30.8	29.8	–8.9[c]
RAPID PsA, 2012	Certolizumab 200 mg	24	58.0[d]	62.2[d]	NR	NR	NR
	Certolizumab 400 mg		51.9[d]	60.5[d]	NR	NR	NR
	Placebo		24.3[d]	15.1[d]	NR	NR	NR
RESPOND, 2012	Infliximab + MTX	16	86.3	97.1 (34)	NR	56.5[b]	–1.0 (0.7)
	MTX		66.7	54.3 (35)	NR	29.7[b]	–0.6 (0.7)
Schett et al., 2012	Apremilast 20 mg	12	43.5	NR	52.5	NR	–21.5[e]
	Apremilast 40 mg		35.8	NR	50.7	NR	–10.6[e]
	Placebo		11.8	NR	22.1	NR	0.0[e]

ACR = American College of Rheumatology; CFB = change from baseline; DAS = Disease Activity Score; HAQ-DI = Health Assessment Questionnaire–Disability Index; MTX = methotrexate; NR = not reported; PASI = Psoriasis Area Severity Index; PsARC = Psoriatic Arthritis Response Criteria; SD = standard deviation.

[a] Presented as the median.

[b] Per cent improvement.

[c] Mean per cent improvement.

[d] At 12 weeks.

[e] Median per cent.

Source: MTC,[78] provided by manufacturer

Mixed Treatment Comparison

Although the objective of this analysis was to perform a mixed treatment comparison, there were no statistical indirect comparison estimates provided in the report. Selected trial characteristics and outcomes are presented in Table 21. Data were presented in tabular or graphic (forest plots) format for each drug. An example of the data presentation can be seen in the graphics following this section. The manufacturer presented a forest plot and probabilities of response for the following outcomes at two time points (week 12 to 16 and week 24): PASI 75, PsARC, and ACR 20. For the HAQ-DI results, mean change in score was presented in a forest plot.

For almost all outcomes presented, ustekinumab 45 mg and 90 mg versus placebo had lower odds ratios than all other comparators. Probabilities of response for ustekinumab 45 mg and 90 mg were also lower for almost every outcome. The authors speculate that the reason for the lower response rates in ustekinumab, relative to other drugs, is related to the high placebo response rate in the ustekinumab trials relative to the placebo response rate in the other trials. Their discussion focuses on possible explanations for this. They suggest that it is related to differences in patient populations and trial design effects such as the time of year when the majority of patients began treatment. As well, some trials had smaller placebo groups than the ustekinumab trials, which therefore had a higher probability of getting a placebo response rate of 0, inflating the subsequent odds ratio estimates.

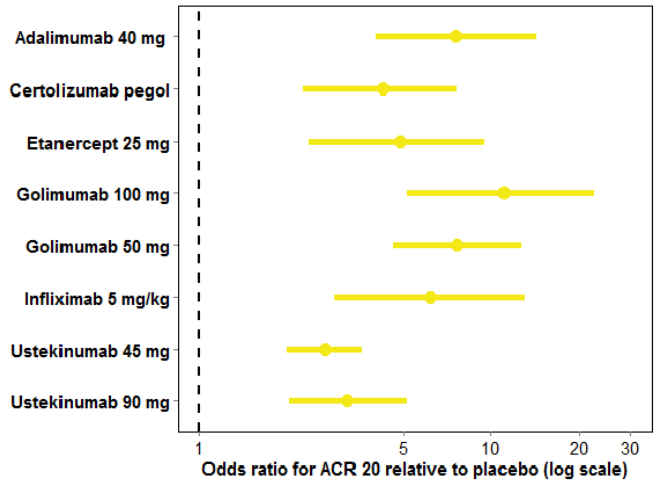
“Differences in patient populations” is a plausible hypothesis for the observed differences in the performance of ustekinumab relative to the other drugs; however, the manufacturer does not explain which population characteristics differed in such a way to affect the results. The manufacturer did not perform any meta-regression analyses to test this hypothesis.

“Trial design effects” is another plausible hypothesis, but this was not explored by the authors. For example, the authors did not explain the differences in how the trials analyzed data for patients who escaped early from placebo treatment assignment.

None of the author’s explanations appear to completely explain the reason for the lower response rates in the ustekinumab trials. For example, the placebo rates for the mean difference of change in the HAQ-DI outcome were approximately at the median level of placebo response rate across all the trials, yet ustekinumab still had low HAQ-DI results relative to the other drugs.

Other plausible hypotheses include that ustekinumab is not as effective as the other drugs, or that the onset of action is slower than other drugs. The authors did not analyze response data beyond 24 weeks.

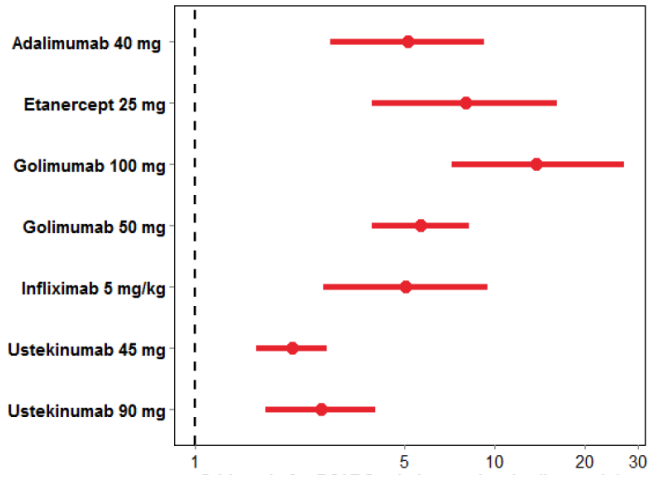
ACR 20 Response at Week 24, Odds Ratios



Predicted Probability of Achieving ACR 20 Response at Week 24

Treatment	Probability of response	
	Mean	SD
Adalimumab 40mg	0.6475842	0.0799207
Certolizumab pegol	0.5086854	0.0789423
Etanercept 25mg	0.5375655	0.0907646
Golimumab 100mg	0.7295637	0.0761233
Golimumab 50mg	0.6501119	0.0644049
Infliximab 5mg/kg	0.5983175	0.0936259
Placebo	0.195424	0.0232548
Ustekinumab 45mg	0.395288	0.0484489
Ustekinumab 90mg	0.4396863	0.0649018

PASI 75 Response at Week 24, Odds Ratios



Predicted Probability of Achieving PASI 75 Response at Week 24

Treatment	Probability of response	
	Mean	SD
Adalimumab 40mg	0.7838941	0.1824578
Etanercept 25mg	0.2594725	0.1592521
Golimumab 100mg	0.8456727	0.1127818
Golimumab 50mg	0.7826831	0.1250595
Infliximab 5mg	0.8367175	0.1625043
Placebo	0.0394758	0.0180522
Ustekinumab 45mg	0.3184193	0.1048693
Ustekinumab 90mg	0.3583425	0.1131562

Source for figures/tables: MTC[78] provided by the manufacturer.

Critical Appraisal of Network Meta-analysis

Limitations

The main limitations of this analysis are related to the incomplete reporting. No statistical indirect comparisons were provided for ustekinumab versus other comparators. In addition, odds ratios were graphically represented in forest plots, but no numeric values were provided for the odds ratios or 95% credible intervals. This allows the reader to make only visual comparisons between ustekinumab and other drugs.

There could have been more analysis of the trial designs and description of how they differed. This would have been particularly relevant if there were differences in how early escape and crossover of patients to active drug were handled.

The Discussion section was very brief and did not include any in-depth exploration of the reasons for the differences seen in efficacy for ustekinumab compared with other drugs.

Strengths

The study had a clear objective, and the methods for study selection and data extraction were transparently presented. Baseline data were presented for each study. Description of statistical methods was provided. Network diagrams were presented for each outcome. Critical appraisal details and comments are presented in Table 22.

TABLE 22: CRITICAL APPRAISAL BASED ON ISPOR NETWORK META-ANALYSIS CHECKLIST

Checklist Item	Details and Comments
Are the rationale for the study and the study objectives stated clearly?	• Rationale clearly stated – no head-to-head trials, need to determine the comparative effectiveness for performing economic evaluations
Does the methods section include the following? • Description of eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction (validity/quality assessment of individual studies)	• Search strategy and databases presented • Inclusion criteria clearly presented • Number of trials meeting eligibility criteria were clearly presented • Data extraction methods explained • PRISMA flow diagram provided describing article selection • Assessment of bias was performed, but the method was not stated
Are the outcome measures described?	• Efficacy outcomes of interest for the MTC were clearly described and rationale for their selection was explained • No explanation for why harms outcomes were not included in the MTC
Is there a description of methods for analysis/synthesis of evidence? Do the methods described include the following? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• Brief descriptions of Bayesian methods, random effects modelling, and reference to published statistical procedures were provided • Brief descriptions provided for dealing with visual data presentation (network plot, forest plot) and absolute versus relative pairwise comparisons • No clear description of how bias was handled
Are sensitivity analyses presented?	• The authors stated that a sensitivity analysis was not considered for the mixed treatment comparison due to the low number of RCTs for each drug
Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• Individual study data are summarized • Network diagrams are provided for each primary outcome • Forest plots are provided for each primary outcome of interest (but did not include numbers for results)

Checklist Item	Details and Comments
Does the study describe an assessment of model fit? Are competing models being compared?	• There is no discussion about the relative merits of these two methods in the context of this study.
Are the results of the evidence synthesis (ITC/MTC) presented clearly?	• Numeric values and credible intervals were not provided for the odds ratios (only graphic representation was provided). This is a significant reporting deficiency. • Only odds ratios and probability of response were presented for ACR 20, PsARC and PASI response data. No absolute values (e.g., absolute risk reduction, numbers needed to treat) were presented relative to placebo. Since absolute risk reduction can differ substantially from relative risk reduction, this is a significant omission.
Does the discussion include the following? • Description/summary of main findings • Internal validity of analysis • External validity • Implications of results for target audience	• The Discussion section was brief and did not include adequate discussion of the potential reasons for the observed results.

ACR = American College of Rheumatology; ISPOR = International Society of Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparison; MTC = mixed treatment comparison; PASI = Psoriasis Area Severity Index; PRISMA = Transparent Reporting of Systematic Reviews and Meta-analyses; PsARC = Psoriatic Arthritis Response Criteria; RCT = randomized controlled trial.
Source: MTC[78] provided by the manufacturer.

Summary

Due to the absence of head-to-head trials between ustekinumab and other biologic response modifiers for the treatment of psoriatic arthritis, the manufacturer undertook a systematic review of RCTs and performed a mixed treatment comparison. The efficacy estimates for ustekinumab appeared lower than estimates for adalimumab, etanercept, infliximab, and golimumab. No statistical indirect comparison estimates were provided by the manufacturer.

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