CADTH

CADTH Common Drug Review

Clinical Review Report

TILDRAKIZUMAB (ILUMYA)

(Sun Pharma Global FZE)

Indication: For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

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Abbreviations

CAPP	Canadian Association of Psoriasis Patients
CDR	CADTH Common Drug Review
CI	confidence interval
CORD	Canadian Organization for Rare Disorders
CPN	Canadian Psoriasis Network
CrI	credible interval
CSPA	Canadian Skin Patient Alliance
DLQI	Dermatology Life Quality Index
EQ-5D	EuroQol 5-Dimensions questionnaire
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels questionnaire
FAS	full analysis set
IL	interleukin
ITC	indirect treatment comparison
LS	least squares
MCID	minimal clinically important difference
NMA	network meta-analysis
PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
PY	person-year
RCT	randomized controlled trial
SD	standard deviation
SF-36	Short Form (36) Health Survey
TNF	tumour necrosis factor
WPLQ	Work Productivity and Loss Questionnaire

Drug	Tildrakizumab (Ilumya)
Indication	For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Reimbursement request	As per indication
Dosage form(s) and route of administration)/strength(s)	100 mg/mL pre-filled syringe for subcutaneous injection
NOC date	May 19, 2021
Sponsor	Sun Pharma Global FZE

Executive Summary

Introduction

Plaque psoriasis is a chronic, autoimmune skin disease characterized by the presence of erythematous inflammatory plaques that may be itchy or painful and are usually covered by silver, flaking scales.[1,2] In addition to the overt dermatological symptoms, plaque psoriasis is often associated with psychosocial symptoms and may negatively impact interpersonal relationships and performance at school or work.[1] Treatments include topical therapies, traditional systemic drugs (e.g., cyclosporine and methotrexate) and biologic therapies (e.g., interleukin [IL]-17, IL-23, and IL-12/23 inhibitors and tumour necrosis factor [TNF] alpha inhibitors). There are an estimated 500,000 to 1 million Canadians living with psoriasis.[3,4]

Tildrakizumab (Ilumya) is a humanized monoclonal antibody that belongs to the IL-23 inhibitors drug class.[5] It is approved by Health Canada for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[5] It is available as a 100 mg/mL pre-filled syringe and the recommended dose is 100 mg by subcutaneous injection at week 0, week 4, and every 12 weeks thereafter.[5] The sponsor has made a reimbursement request as per the indication.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of tildrakizumab 100 mg/mL for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Stakeholder Engagement

Patient Input

Two responses to CADTH's call for patient input for the Ilumya submission were received: a cooperative submission from the Canadian Skin Patient Alliance (CSPA), the Canadian Association of Psoriasis Patients (CAPP), and the Canadian Psoriasis Network (CPN), and a second submission from the Canadian Organization for Rare Disorders (CORD). The information used to inform the submission was based on data collected from recent submissions for risankizumab (Skyrizi) and certolizumab pegol (Cimzia) and from online disease discussion boards. In addition, CORD conducted interviews with 3 Canadian patients with moderate or severe psoriasis who had received tildrakizumab. CORD also collected survey data from 12 patients diagnosed with plaque psoriasis.

The patient groups describe psoriasis as a chronic inflammatory skin condition that may vary in severity from a minor nuisance to a painful and disabling condition. One-third of patients reported frequently feeling embarrassed, losing sleep, having problems with intimacy, and lacking self-confidence. About half of patients indicated their work is affected frequently, and they frequently experience feelings of depression. Most of the respondents reported feeling that their condition is not adequately controlled with existing therapies. The patient groups indicated that resolution of the plaques was an important treatment outcome, as was decreasing symptoms, such as itching and pain, and reducing social stigma. Moreover, the treatment should be easy to access and use, have minimal side effects, have little potential impact on organs, and/or have few other long-term negative outcomes.

Clinician Input

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

Although several biologic and non-biologic therapies are available in Canada to treat moderate-to-severe plaque psoriasis, none fulfill the criteria of an ideal treatment, which would produce a sustained clearance of plaques and an improvement in quality of life with minimal risk of adverse effects. Tildrakizumab is an additional drug in the treatment armamentarium and may increase the likelihood that a patient with moderate-to-severe plaque psoriasis will find a drug that works well and is well tolerated. It is unlikely that tildrakizumab will cause a shift in the treatment paradigm for moderate-to-severe plaque psoriasis, as prior use of methotrexate, apremilast, or cyclosporine are requirements for reimbursement of other biologics. Tildrakizumab is the third drug in the IL-23 inhibitor class in Canada and offers some dosing advantage over guselkumab (Tremfya) (maintenance dosing with tildrakizumab is every 12 weeks versus 8 weeks for guselkumab) but not over risankizumab (Skyrizi). It may be suitable for some patients who have contraindications to other biologics, such as Crohn disease for the IL-17A inhibitors, severe depression with suicidal ideation for brodalumab, and cardiac failure and multiple sclerosis for the TNF alpha inhibitors. Limited data are available for tildrakizumab in patients with psoriatic arthritis; thus, other treatment options would be preferred for this patient population.

A 75% reduction in the area affected and in the severity of plaques, measured using the Psoriasis Area and Severity Index (PASI 75 response) at 16 weeks, would be considered a clinically meaningful response to treatment; however, with tildrakizumab, clinicians would expect patients to achieve a 90% reduction (PASI 90). Discontinuation may be considered in patients who do not achieve a PASI 75 response by 16 weeks or do not maintain a PASI 75 response during maintenance therapy. In addition, discontinuation may be warranted for those whose psoriatic arthritis is not controlled, who develop a high-risk malignancy, who are undergoing surgery, or who develop a significant infection.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two multi-centre, double-blind, randomized controlled trials (RCTs) met the inclusion criteria for the systematic review (Study P010 or reSURFACE 1, and P011 or reSURFACE 2). These trials examined the efficacy and safety of tildrakizumab compared with placebo or

etanercept in adults with moderate-to-severe plaque psoriasis who were candidates for phototherapy or systemic therapy. Both trials consisted of 3 parts, as follows:

- Part 1: Week 0 to week 12. Patients were randomized 2:2:1 to tildrakizumab 100 mg or 200 mg or placebo in Study P010, and randomized 2:2:1:2 to tildrakizumab 100 mg or 200 mg, placebo, or etanercept 50 mg in Study P011.
- Part 2: Week 12 to week 28. Patients in active treatment groups continued on therapy, and those initially randomized to placebo were re-randomized to tildrakizumab 100 mg or 200 mg.
- Part 3: Week 28 to week 52 (P011) or week 64 (P010). Based on their treatment response at week 28, patients were discontinued, re-randomized, or reassigned to tildrakizumab 100 mg or 200 mg in Study P011, or to tildrakizumab 100 mg or 200 mg or placebo in Study P010.

Tildrakizumab was administered by subcutaneous injection at week 0, week 4, and every 12 weeks thereafter. Etanercept 50 mg was administered subcutaneously twice weekly during part 1 and once weekly during part 2 of Study P011.

The co-primary outcomes in both trials were the proportion of patients who achieved at least a 75% improvement in PASI score from baseline to week 12, and the proportion of patients with a Physician's Global Assessment (PGA) score of "clear" or "minimal," with at least a 2-grade reduction from baseline for tildrakizumab 200 mg and 100 mg versus placebo. Key secondary outcomes included PASI 90 or PASI 100 response at week 12. Health-related quality of life (HRQoL) was measured using the Dermatology Life Quality Index (DLQI), which is scored between 0 to 30, with lower scores indicating better quality of life; a score of 0 or 1 indicates the disease has no effect on the patient's quality of life. The DLQI is a dermatology-specific questionnaire that covers 6 domains: symptoms and feeling, daily activities, leisure, work and school, personal relationships, and bother with psoriasis treatment. Data were also provided for the PASI and PGA response, as well as the DLQI, at week 28 and at the end of the studies (week 52 or 64).

The patients enrolled in studies P010 and P011 were adults with moderate-to-severe plaque psoriasis affecting at least 10% of their body surface area (BSA) and who had a PGA score of 3 or more and a PASI score of 12 or greater. The patients enrolled in studies P010 (N = 772) and P011 (N = 1,090) were predominantly male (65% to 73% per treatment group) and White (65% to 92%), with a mean age per treatment group that ranged from 44.6 to 47.9 years. At baseline, the mean PASI score ranged from 19.3 to 20.7, and 12% to 20% of patients per group had psoriatic arthritis. Both trials were multinational and included patients from Canada.

Efficacy Results

Part 1 (Up to Week 12)

The proportion of patients who achieved a DLQI score of 0 or 1 at 12 weeks was higher among those who received tildrakizumab (40% to 47%) and etanercept (36%) than those who received placebo (5% to 8%) (Table 1). The difference in percentage of DLQI responders for the tildrakizumab 100 mg group versus placebo was 36% in P010 (95% confidence interval [CI], 29% to 43%; P < 0.001), and 32% in P011 (95% CI, 25% to 39%; P < 0.001). In Study P011, the absolute difference for tildrakizumab 100 mg versus etanercept was 5% (95% CI, −3% to 13%; P = 0.221). The between-group differences in the change from baseline in DLQI scores also favoured tildrakizumab 100 mg versus placebo, with a least squares (LS) mean difference of −7.4 points (95% CI, −8.3 to −6.5;

P < 0.001) in Study P010, and −8.2 points (95% CI, −9.3 to −7.2; P < 0.001) in Study P011. The LS mean difference between tildrakizumab 100 mg and etanercept was −1.3 (95% CI, −2.1 to −0.5; P = 0.002). The between-group differences observed exceeded the minimal important differences reported in the literature (2.2 to 6.9) for the comparison between tildrakizumab and placebo, but not compared with etanercept. Data for DLQI, however, were outside the statistical testing procedure and these results should be interpreted as supportive evidence for the effect of tildrakizumab, considering the potential for inflated type I error.

In both trials, a higher proportion of patients achieved a PGA score of "clear" or "minimal" with at least a 2-grade reduction from baseline at week 12 in the tildrakizumab 100 mg groups compared with placebo (Table 1). The difference in the proportions reported was 51% (95% CI, 44% to 57%; P < 0.001), in Study P010, and 50% (95% CI, 43% to 57%; P < 0.001), in Study P011. No statistically significant difference was detected between tildrakizumab 100 mg and etanercept (7% absolute difference; 95% CI, −0.5% to 15%; P = 0.066), which, according to the statistical testing procedure, meant that statistical testing of subsequent outcomes was stopped.

In studies P010 and P011, 6% of patients in the placebo group, 61% to 66% in the tildrakizumab groups, and 48% in the etanercept group achieved a PASI 75 response at week 12. The difference in the percentage of responders for tildrakizumab 100 mg versus placebo was 58% (95% CI, 51% to 64%) and 56% (95% CI, 48% to 62%) in studies P010 and P011, respectively (both P < 0.001). The difference between tildrakizumab 100 mg and etanercept at week 12 was not statistically significant due to the failure of a prior outcome in the statistical testing procedure (absolute difference = 13%; 95% CI, 5% to 21%) (Table 1).

Tildrakizumab 100 mg was associated with statistically significant differences versus placebo in the proportion of patients who achieved a PASI 90 response in Study P010 (absolute difference = 32%; 95% CI, 26% to 38%; P < 0.001) and Study P011 (absolute difference = 38%; 95% CI, 31% to 43%; P < 0.001). More patients in the tildrakizumab 100 mg group achieved a PASI 100 response at week 12 than in the placebo group, with an absolute difference of 13% (95% CI, 8% to 17%; P < 0.001) in Study P010, and 12% (95% CI, 9% to 17%) in P011; however, the differences between tildrakizumab 100 mg versus placebo in P011 were not statistically significant, as the testing procedures was stopped due to the failure of a prior outcome. The differences between tildrakizumab 100 mg and etanercept for PASI 90 and PASI 100 response were not statistically significant due to the failure of a prior outcome in the statistical testing procedure.

In studies P010 and P011, the results of the key efficacy outcomes (DLQI, PGA, and PASI response) were similar for the tildrakizumab 100 mg and tildrakizumab 200 mg dosage groups. Sensitivity analyses using different imputation methods for missing data were similar to the primary analysis that used nonresponder imputation methods. The treatment effects for the tildrakizumab groups versus placebo or etanercept were generally similar among subgroups for patients who had or had not received prior biologic therapy for psoriasis or failed to respond to at least 1 traditional systemic therapy.

Data from other HRQoL and work productivity outcomes were reported descriptively, with no between-group comparisons; thus, no conclusions can be drawn from these data. Neither of the studies collected patient-reported data on symptoms related to psoriasis.

Part 2 (Week 12 to Week 28) and Part 3 (Week 28 to Week 52 or 64)

In part 2, the patients who received tildrakizumab continued to show lower mean DLQI scores up to week 28, relative to baseline, suggesting improvement in HRQoL. However, no clinically important differences were detected between tildrakizumab 100 mg and etanercept (LS mean difference = −1.7; 95% CI, −2.4 to −1.0), as the mean difference did not exceed the lowest estimate of the minimal important difference reported in the literature. More patients in the tildrakizumab 100 mg group achieved a DLQI score of 1 or less than in the etanercept 50 mg weekly group (difference in percentage = 15%; 95% CI, 7% to 23%).

Among patients who continued to receive tildrakizumab 100 mg or 200 mg in studies P010 and P011, the percentage of patients who reported a PGA response at week 28 ranged from 65% to 69%, a PASI 75 response from 73% to 82%, a PASI 90 response from 52% to 59%, and a PASI 100 response from 23% to 32%. The proportion of patients with a PGA, PASI 75, PASI 90, and PASI 100 response in the etanercept 50 mg weekly group was 45%, 54%, 31%, and 11%, respectively. More patients in the tildrakizumab 100 mg group achieved a PGA or PASI 75 response than in the etanercept group; however, the differences were not statistically significant due to the failure of a prior outcome in the statistical testing procedure. Comparisons between the tildrakizumab 100 mg dosage group and etanercept for PASI 90 and PASI 100 response also favoured tildrakizumab, but these outcomes were outside the statistical testing procedure.

In part 3, patients who achieved a greater than 75% improvement in PASI score (PASI 75) at week 28 were considered responders, and those who achieved a 50% or greater improvement but less than PASI 75 were defined as partial responders. By the end of week 52 in Study P011 and week 64 in Study P010, 88% to 97% of responders who remained on tildrakizumab maintained a PASI 75 response. The percentage of partial responders who achieved a PASI 75 response at the end of the trials ranged from 40% to 79%. For the patients who were switched from placebo to tildrakizumab at week 12, 85% to 95% had a PASI 75 response at the end of the trials. In Study P011, 81% of the nonresponders and partial responders to etanercept who were switched to tildrakizumab 200 mg reported a PASI 75 response at week 52. Similar patterns were observed for PGA response.

During part 3 in Study P010, relapse (defined as a 50% reduction in maximum PASI response) was reported by 54% of the patients who were switched from tildrakizumab 100 mg to placebo, and by 44% of the patients who were switched from tildrakizumab 200 mg to placebo. Relapse was reported by 7% to 8% of responders who continued on tildrakizumab 100 mg or 200 mg during part 3.

Harms Results

The percentage of patients who reported 1 or more adverse events in part 1 of studies P010 and P011 ranged from 48% to 55% for placebo, 42% to 49% for tildrakizumab, and 54% for etanercept groups. Infections and infestations were reported by 20% to 24% of patients in the first 12 weeks of the trials, with a similar frequency across treatment groups (Table 1).

When reported for the overall study period, the exposure-adjusted incidence of infections or infestations was higher in the placebo groups (74 to 95 events per 100 person-years [PYs]) and etanercept group (86 events per 100 PYs) than in the tildrakizumab groups (45 to 57 events per 100 PYs). Serious infections, defined as those that met the criteria for a serious adverse event or that required intravenous antibiotics, were infrequent (week 12: range 0%

to 0.6%; week 52 or 64: 0.6 to 2.9 events per 100 PYs) in the pivotal trials. More patients in the etanercept group reported injection-site adverse events (2% to 9%) than in the tildrakizumab or placebo groups (0% to 3%) during the first 12 weeks of Study P011.

Serious adverse events and discontinuations due to adverse events were infrequent during the first 12 weeks of the trials. Serious adverse events were reported by 1% to 3% of patients per treatment group and discontinuations due to adverse events were reported by 0% to 2% of patients. The incidence of serious adverse events ranged from 5.1 to 13.0 events per 100 PYs, and discontinuations due to adverse events ranged from 0.8 to 5.9 events per 100 PYs during base study periods. A total of 6 deaths were reported over the total study periods. In Study P010, 1 person who received tildrakizumab 200 mg died due to aneurysm. In Study P011, 4 patients who received tildrakizumab 100 mg died (causes of death: alcoholic cardiomyopathy and steatohepatitis, acute myeloid leukemia, respiratory arrest, myocardial infarction), and 1 patient who received tildrakizumab 200 mg died due to sepsis.

Other notable harms specified in the review protocol (malignancies, cardiovascular adverse events, or drug-related hypersensitivity events) were infrequent in the first 12 weeks of the studies (0% to 0.6% of patients per treatment group) and over the entire base study (0 to 2.9 events per 100 PYs). No cases of treatment-emergent inflammatory bowel disease were reported. In Study P010, 1 patient in the tildrakizumab 200 mg group had a serious adverse event of bone tuberculosis, which led to the discontinuation of the study medication during part 2. There were no tuberculosis-related adverse events reported in Study P011. Treatment-emergent anti-drug antibodies among those who received tildrakizumab were reported in 3% to 5% of patients in part 1 and 6% to 9% of patients over the entire study period of the trials.

Table 1: Summary of Key Results From Pivotal and Protocol Selected Studies

Outcome	P010 (reSURFACE 1)			P011 (reSURFACE 2)			
	PBO N = 54	TILD 100 mg N = 309	TILD 200 mg N = 308	PBO N = 156	TILD 100 mg N = 307	TILD 200 mg N = 314	ETAN 50 mg N = 313
DLQI ≤ 1 at 12 weeks							
n (%)	8 (5.3)	126 (41.5)	132 (44.2)	12 (8.0)	119 (40.2)	145 (47.4)	108 (35.5)
Difference in % versus PBO (95% CI)[a]	Reference	36.1 (29.3 to 42.5)	38.9 (31.9 to 45.4)	NR	32.1 (24.5 to 39.1)	39.3 (31.8 to 46.1)	
P value versus PBO[a]		< 0.001[b]	< 0.001[b]		< 0.001[b]	< 0.001[b]	
Difference in % versus ETAN (95% CI)[a]		NA	NA		4.8 (−2.9 to 12.5)	11.9 (4.1 to 19.5)	Reference
P value versus ETAN[a]					0.221[b]	0.003[b]	
PGA response at week 12							
n (%)	11 (7.1)	179 (57.9)	182 (59.1)	7 (4.5)	168 (54.7)	186 (59.2)	149 (47.6)
Difference in % versus PBO (95% CI)[a]	Reference	50.9 (43.6 to 57.4)	52.1 (44.8 to 58.5)	NR	50.2 (43.2 to 56.5)	54.7 (47.9 to 60.8)	
P value versus PBO[a]		< 0.001	< 0.001		< 0.001	< 0.001	

Outcome	P010 (reSURFACE 1)			P011 (reSURFACE 2)			
	PBO N = 54	TILD 100 mg N = 309	TILD 200 mg N = 308	PBO N = 156	TILD 100 mg N = 307	TILD 200 mg N = 314	ETAN 50 mg N = 313
Difference in % versus ETAN (95% CI)[a]		NA	NA		7.3 (−0.5 to 15.0)	11.7 (4.0 to 19.3)	Reference
P value versus ETAN[a]					0.066[c]	0.003	
PASI 75 response at week 12							
n (%)	9 (5.8)	197 (63.8)	192 (62.3)	9 (5.8)	188 (61.2)	206 (65.6)	151 (48.2)
Difference in % versus PBO (95% CI)[a]	Reference	58.0 (51.0 to 64.1)	56.6 (49.6 to 62.8)	NR	55.5 (48.3 to 61.8)	59.8 (52.9 to 65.9)	
P value versus PBO[a]		< 0.001	< 0.001		< 0.001	< 0.001	
Difference in % versus ETAN (95% CI)[a]		NA	NA		13.1 (5.3 to 20.7)	17.4 (9.7 to 24.9)	Reference
P value versus ETAN[a]					NS[d]	< 0.001	
Harms up to week 12, n (%)							
SAE	1 (1)	5 (2)	8 (3)	4 (3)	4 (1)	6 (2)	7 (2)
Discontinuation due to adverse events	1 (1)	0	5 (2)	2 (1)	3 (1)	3 (1)	6 (2)
Infections and infestations (SOC), n (%)	32 (21)	64 (21)	61 (20)	33 (21)	65 (21)	68 (22)	74 (24)
Severe infections, n (%)[e]	0	1 (0.3)	1 (0.3)	1 (0.6)	0	1 (0.3)	0
Harms up to week 64 (P010) or week 52 (P011); events per 100 PYs							
SAE	5.3	5.1	8.4	11.5	6.6	6.2	13.0
Discontinuation due to adverse events	1.2	0.8	2.4	5.8	2.6	1.4	5.9
Infections and infestations (SOC)	73.8	44.8	47.4	95.2	46.8	56.5	86
Severe infections[e]	0.6	1.0	1.4	2.9	1.1	1.9	2.0

CI = confidence interval; DLQI = Dermatology Life Quality Index; ETAN = etanercept; FAS = full analysis set; NA = not applicable; NR = not reported; NS = not statistically significant; PASI 75 = at least a 75% improvement in the Psoriasis Area and Severity Index score; PBO = placebo; PGA = Physician's Global Assessment; PY = person-year; SAE = serious adverse event; SOC = system organ class; TILD = tildrakizumab.

[a] P value based on Cochran-Mantel-Haenszel test stratified by body weight (≤ 90 kg, > 90 kg) and prior exposure to biologic therapy (yes or no). Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight and prior biologic exposure with sample size weights. Patients with missing data were classified as nonresponders (FAS population).

[b] Outside the statistical testing hierarchy.

[c] The difference between groups was not statistically significant; thus, according to the statistical testing procedure, all subsequent outcomes within the hierarchy were considered non-significant.

[d] Not statistically significant according to the statistical testing procedure because the difference between tildrakizumab 100 mg and etanercept for PGA response at week 12 did not achieve statistical significance.

[e] Severe infections were defined as any infection that met the regulatory definition of an SAE or infection requiring intravenous antibiotics, whether or not reported as an SAE.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Critical Appraisal

Overall, it appears the risk of bias was low for the primary outcomes at the end of the induction period (week 12) in studies P010 and P011. Both trials used accepted methods to randomize patients, conceal treatment allocation, and maintain blinding. The frequency of withdrawals was generally low. One trial provided a head-to-head comparison with etanercept; however, this drug is no longer a preferred biologic to treat psoriasis.

After week 12, the efficacy data were based on the subpopulation of patients who entered part 2 or part 3 of the trials (i.e., not the intention-to-treat population). Most efficacy outcomes were reported descriptively based on observed case data (i.e., included only the patients with data at baseline and the end point), which could potentially overestimate the effects of tildrakizumab. Patients were switched between treatments at weeks 12 and 28 using different methods, depending on prior treatment allocation or response to therapy. In part 2 of P010 and part 3 of P011, all patients were receiving tildrakizumab, with no active or placebo control group. Although part 2 of Study P011 included an etanercept control group, according to the clinical expert consulted for this review, the dose of etanercept administered was lower than would be used in clinical practice. Therefore, the data for parts 2 and 3 of studies P010 and P011 should be interpreted with caution, given the loss of randomization, lack of control group or suboptimal active comparator, and potential attrition bias.

The trials were not designed or powered to detect rare adverse events or those with a longer lag time.

The clinical expert consulted for the review indicated that the patients enrolled were reflective of patients with moderate-to-severe psoriasis in Canada, although generalizability may be limited for patients with prior exposure to IL-23 or IL-17 inhibitors or etanercept, or those with severe psoriatic arthritis, as these patients were excluded from the studies.

Indirect Comparisons

Description of Studies

One indirect treatment comparison (ITC) submitted by the sponsor[8] and 5 other published ITCs that examined the comparative efficacy or safety of immunomodulators used to treat patients with moderate-to-severe plaque psoriasis were included in this report.[8,9,10-13] The authors of all 6 reports conducted a systematic review of RCTs in adults with moderate-to-severe psoriasis who received TNF alpha inhibitors, IL-17 inhibitors, IL-23 inhibitors, IL-12/23 inhibitors, and other systemic therapies. In 2 reports,[8,9] the network meta-analysis (NMA) was conducted using a placebo-adjusted Bayesian random-effects multinomial model, 2 reports used an unadjusted Bayesian random-effects model,[10,13] and 2 used frequentist NMA models.[11,12]

Efficacy Results

The NMA submitted by the sponsor (Institute for Clinical and Economic Review, 2018[8]) included data from 47 phase III RCTs. All immunomodulators were statistically significantly more likely to achieve a PASI 50, 75, or 90 response than placebo at the end of the induction period (10 to 16 weeks) in the base-case analysis. For tildrakizumab 100 mg versus placebo, the relative risk of achieving a PASI 75 response was 11.60 (95% credible interval [CrI], 8.84 to 15.5), and the relative risk of a PASI 90 response was 29.32 (95% CrI, 21.01 to 41.40). The indirect evidence suggests that patients who received tildrakizumab

were less likely to achieve a PASI 50, 75, and 90 response than those treated with IL-17 inhibitors (ixekizumab, brodalumab, secukinumab), other IL-23 inhibitors (guselkumab, risankizumab), and infliximab. The results also suggest that tildrakizumab was more effective in terms of PASI 50, 75, or 90 response than etanercept or apremilast. The comparisons between tildrakizumab and adalimumab, certolizumab, or ustekinumab did not statistically differ, as the 95% CrI included the null.

For the induction period, the PASI response results from the other NMAs[9-13] were generally consistent with those in the Institute for Clinical and Economic Review report.[8] No statistically significant differences were detected between tildrakizumab and other biologics in the change in DLQI in the analysis by Mahil et al.[11] Sbidian et al. (2020)[12] reported that HRQoL was poorly reported in the RCTs and was absent for several interventions. Few differences between treatments were found in HRQoL measures, and any differences noted were of unclear clinical importance.[12]

Harms Results

Four NMAs examined short-term safety outcomes.[10-13] No statistically significant differences were detected between tildrakizumab and placebo or other active treatments on the likelihood of discontinuation[10] or serious adverse events during the induction period.[12] The indirect evidence suggested that withdrawals due to adverse effects may be less likely for tildrakizumab than infliximab or ixekizumab.[11] Two ITCs suggested that the frequency of adverse events may be lower for tildrakizumab than other biologic treatments.[12,13] However, these results should be viewed with caution due to the short duration of the trials, the low power of the trials to detect infrequent adverse events, and the limitations of the ITCs.

Critical Appraisal

All 6 NMAs were based on systematic reviews and extensive evidence networks; however, recently published head-to-head studies may be missing from some of the earlier ITCs. In the ITC by Xu et al. (2019),[10] the reporting of the study selection and analysis methods was poor and the NMA excluded 3 drugs that were of interest to this review. Four ITCs did not provide a justification for the NMA model used[10-13] and, in 3 reports, no other models were tested.[10-12] Two ITCs pooled data for all doses and did not restrict analyses to licensed doses.[12,13] Two ITCs examined efficacy outcomes only, and the analysis was limited to PASI response for the induction period.[8,9] Data for HRQoL was limited due to poor reporting or the absence of this outcome in the clinical trials. All analyses were limited to the induction period due to the design of the RCTs; thus, it was not possible to examine longer-term safety or efficacy.

Although the tildrakizumab and other trials included in the NMAs used similar inclusion criteria, there was variation across trials in the proportion of patients with psoriatic arthritis, prior exposure to biologics, the timing of the outcome assessment, and region. Placebo-adjusted models were selected in 2 ITCs[8,9] in an attempt to account for potential variability; however, it is unclear to what extent placebo response is an adequate proxy for specific characteristics or effect modifiers.

Other Relevant Evidence

Description of Studies

Pooled data from the extension studies of the 2 pivotal trials provided up to 148 weeks of efficacy and safety data for tildrakizumab at 2 doses (100 mg and 200 mg).[14] Patients who

completed part 3 of Study P010 or Study P011 were eligible to enter into the open-label extension studies. These trials were ongoing at the time of this review, and interim data were extracted from a published article by Reich et al.[14]

Efficacy Results

Overall, the data suggest that clinical efficacy was maintained for the majority of patients who initially responded to tildrakizumab at week 28 and continued on treatment.[14] PASI 75 responses were maintained in approximately 75% of patients who were responders in both the tildrakizumab 100 mg and tildrakizumab 200 mg groups through 148 weeks of treatment (based on nonresponder imputation methods for missing data). The data also suggest that PASI 90 and 100 responses were stable through to 148 weeks. Furthermore, the data show that PASI 75 response was achieved and maintained for up to 148 weeks in approximately 65% of patients who showed a partial response or who did not respond to etanercept 50 mg once weekly and were switched to tildrakizumab 200 mg.

Harms Results

No major safety signals in the tildrakizumab-treated groups were identified, based on the reported exposure-adjusted incidence rates of adverse events.[14]

Critical Appraisal

The main limitations of the pooled results of the extension studies include the lack of randomization, the absence of an active comparator or placebo group, and the absence of HRQoL outcomes. The open-label study design is a further limitation. Unblinding of the study drugs can bias the reporting of end points, particularly any subjective measures included in the PASI score. The reported efficacy data were limited to a subset of patients who had shown a positive response to tildrakizumab and who were able to tolerate therapy. Initial nonresponders to tildrakizumab and responders to etanercept were excluded from part 3 of the base study and the extension studies. Furthermore, the baseline characteristics of the patients included in the efficacy analysis were not reported and, therefore, it was not possible to assess how these patients compare with the randomized study population or those in clinical practice, limiting the generalizability of the results. As only descriptive statistics were published, and without comparator groups, the interpretation of the results is limited, and the magnitude of long-term clinical benefit of tildrakizumab may be overestimated.

Conclusions

Tildrakizumab showed statistically and clinically important differences versus placebo in psoriasis disease severity, measured as a PASI 75, PASI 90, PASI 100, and PGA response at week 12 among patients with moderate-to-severe plaque psoriasis who were candidates for phototherapy or systemic therapy. However, the differences between tildrakizumab 100 mg and etanercept for these disease severity outcome measures at week 12 were not statistically significant.

Tildrakizumab also showed improvement in HRQoL (measured using the DLQI) compared with placebo but not compared with etanercept at week 12; however, HRQoL outcomes were outside the statistical testing procedure and should be interpreted as supportive evidence in view of the inflated risk of type I error.

Even though the trials reported efficacy outcomes up to 64 weeks, due to the design of the studies, conclusions on the comparative efficacy of tildrakizumab could only be drawn from the induction period (12 weeks). The longer-term data suggest that PASI response may be maintained in the majority of patients who continue tildrakizumab therapy.

Indirect evidence suggests that tildrakizumab may be less effective in inducing PASI 75, PASI 90, or PASI 100 response than IL-17 inhibitors (ixekizumab, brodalumab, secukinumab), other IL-23 inhibitors (guselkumab, risankizumab), and infliximab, but may be more effective than etanercept or apremilast.

The incidence of serious adverse events or withdrawals due to adverse events was low among patients who received tildrakizumab, and no new safety signals were identified in the longer-term extension studies. The RCTs were not designed or powered to detect rare adverse events or those with a longer lag time, and longer-term comparative safety data are lacking.

Introduction

Disease Background

Plaque psoriasis is a chronic, inflammatory skin disease caused in part by dysregulation of the immune system. It is a T cell–mediated disease primarily driven by pathogenic T cells that produce high levels of IL-17 and TNF alpha in response to IL-23.[2]

Psoriasis is characterized by the presence of erythematous inflammatory plaques that may be itchy or painful and are usually covered by silver, flaking scales.[1,2] In addition to the overt dermatological symptoms, plaque psoriasis is often associated with psychosocial symptoms, including poor self-esteem, and may affect various aspects of social functioning, including interpersonal relationships and performance at school or work.[1] According to the patient input received for this CDR review, one-third of participants indicated loss of sleep, negative effects on self-confidence, and problems with intimacy, and about half indicated their work was frequently affected. Psoriasis is associated with several comorbid conditions, including depressive symptoms, conditions associated with an increased risk of cardiovascular disease (such as type 2 diabetes, metabolic syndrome, and obesity), psoriatic arthritis, inflammatory bowel disease, and kidney disease.[3,15-21]

The severity of psoriasis may be classified as mild, moderate, or severe using criteria such as BSA involvement or scores on the PASI and DLQI. Although moderate psoriasis has been defined as a PASI of 8 or higher, and severe psoriasis defined as a PASI of 10 or greater, a DLQI of 10 or greater, or BSA involvement of 10% or greater, no consensus exists for these thresholds and variability exists in clinical practice.[3] As per the *Canadian Guidelines for the Management of Plaque Psoriasis*, the definition of moderate or severe psoriasis for clinical practice includes disease that cannot be controlled by routine skin care measures or topical therapy, or that significantly affects patient HRQoL due to the extent, the degree of physical discomfort, or the location of the plaques.[3]

Estimates of the number of Canadians living with psoriasis vary from 500,000 to 1 million.[3,4] A recent study estimated the age- and sex-standardized cumulative prevalence of psoriasis was 2.32% for Ontario in 2015.[22] Plaque psoriasis is the most common form and represents approximately 90% of cases.[3] Approximately 35% of patients with psoriasis have moderate-to-severe disease.[23]

Standards of Therapy

Plaque psoriasis requires lifelong treatment. Measures of treatment success include clearance (absence of signs of disease), control (satisfactory response to therapy as defined by the patient and/or physician), and remission (suppression of signs and symptoms over time).[3] Clearance and symptom control have been identified as treatment outcomes that are important to patients and treatment decisions depend largely on the patient's perception of their disease.

In patients with mild psoriasis, topical treatments (such as corticosteroids, vitamin D3 analogues, retinoids, anthralin, and tars) may be sufficient to control the disease; however, for those with moderate-to-severe psoriasis, systemic therapies are often required.[3,24] Traditional systemic drugs include cyclosporine and methotrexate, but long-term use may be limited by toxicity.[3] In Canada, there are several biologic drugs approved for the treatment of psoriasis (Table 2). The first biologic drugs licensed to treat plaque psoriasis

were TNF alpha inhibitors (i.e., etanercept, infliximab, and adalimumab). While effective and associated with rapid disease control, these TNF alpha inhibitors are associated with a number of safety concerns, including serious infections (e.g., sepsis, reactivated tuberculosis, viral infections), autoimmune conditions (e.g., lupus and demyelinating disorders), and malignancies such as lymphoma.[3,24] Newer biologic drugs include the IL-23 inhibitors risankizumab and guselkumab, the IL-12/23 inhibitor ustekinumab, and IL-17 inhibitors secukinumab, ixekizumab, and brodalumab. These drugs have been associated with serious infections, potential activation of inflammatory bowel disease in the case of IL-17 inhibitors, and suicidal ideation in the case of brodalumab. According to the clinical expert consulted for this review, IL-17 and IL-23 inhibitors are now chosen more frequently by Canadian dermatologists over TNF alpha inhibitors as the first biologic for the treatment of plaque psoriasis.

Drug

Tildrakizumab is a humanized monoclonal antibody that binds to the IL-23 cytokine and inhibits its interaction with the IL-23 receptor.[5] It is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[5] It is available as a 100 mg/mL pre-filled syringe and the recommended dose is 100 mg by subcutaneous injection at week 0, week 4, and every 12 weeks thereafter.[5] The sponsor has submitted a reimbursement request as per the indication.

Table 2: Key Characteristics of Biologic Drugs for the Treatment of Psoriasis

Biologic	Indication[a]	Route of administration	Recommended dose	Serious adverse effects or safety issues
IL-23 inhibitors				
Tildrakizumab (Ilumya)	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.	Subcutaneous	100 mg administered by subcutaneous injection at week 0, week 4, and every 12 weeks thereafter.	Infection
Risankizumab (Skyrizi)	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.	Subcutaneous	150 mg (two 75 mg injections) administered by subcutaneous injection at week 0, week 4, and every 12 weeks thereafter.	Infection, hypersensitivity reactions
Guselkumab (Tremfya)	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.	Subcutaneous	100 mg administered at week 0 and week 4 followed by maintenance dosing every 8 weeks thereafter.	Infection
IL-12/23 inhibitors				
Ustekinumab (Stelara)	In adult patients for the treatment of chronic moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Treatment of chronic moderate-to-severe plaque psoriasis in adolescent patients from 12 to 17 years of age who are inadequately controlled by or are intolerant to other systemic therapies or phototherapies.	Subcutaneous	45 mg at weeks 0 and 4, then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg. For patients who respond inadequately to dosing every 12 weeks, consideration may be given to treating as often as every 8 weeks. Dose of 0.75 mg/kg is recommended in pediatric patients weighing < 60 kg.	Infection, malignancy, serious hypersensitivity reactions

Biologic	Indication[a]	Route of administration	Recommended dose	Serious adverse effects or safety issues
IL-17 inhibitors				
Brodalumab (Siliq)	Treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.	Subcutaneous	210 mg at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.	Suicidal ideation and behaviour, Crohn disease, Infection
Secukinumab (Cosentyx)	Treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.	Subcutaneous	300 mg with initial dosing at weeks 0, 1, 2, 3, and 4 followed by monthly maintenance dosing.	Infection, inflammatory bowel disease, serious hypersensitivity reactions
Ixekizumab (Taltz)	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.	Subcutaneous	160 mg at week 0; followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks.	Infection, serious hypersensitivity reactions, inflammatory bowel disease
TNF inhibitors				
Infliximab (Remicade, Inflectra, Renflexis)	Treatment of adult patients with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, infliximab should be used after phototherapy has been shown to be ineffective or inappropriate.	IV	5 mg/kg followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. If a patient does not show an adequate response at week 14 after infusions at weeks 0, 2, and 6, no additional treatment with infliximab should be given.	Infection, malignancies, cardiovascular events, hematologic abnormalities, hepatic abnormalities, hypersensitivity reactions, autoimmunity and immunogenicity, neurologic events
Adalimumab (Humira, Hadlima)	Treatment of adult patients with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, adalimumab should be used after phototherapy has been shown to be ineffective or inappropriate.	Subcutaneous	Initial dose of 80 mg followed by 40 mg every other week starting 1 week after the initial dose. Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.	Malignancies, infection, congestive heart failure, hematologic events, hypersensitivity reactions, autoimmunity and immunosuppression, neurologic events

Biologic	Indication[a]	Route of administration	Recommended dose	Serious adverse effects or safety issues
Etanercept (Enbrel[b])	Treatment of adult patients with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Treatment of pediatric patients ages 4 to 17 years with chronic severe psoriasis who are candidates for systemic therapy or phototherapy.	Subcutaneous	Adults: Starting dose of 50 mg dose given twice weekly (administered 3 or 4 days apart) for 3 months followed by a reduction to a maintenance dose of 50 mg per week. A maintenance dose of 50 mg given twice weekly has also been shown to be efficacious.	Infections, malignancies, neurologic events, hematologic events, congestive heart failure, autoimmunity
			Pediatric patients: 0.8 mg/kg per week (up to a maximum of 50 mg per week).	

IL = interleukin.

[a] Health Canada indication.

[b] Biosimilar etanercept products are not approved by Health Canada for the treatment of plaque psoriasis.

Source: Product monograph.[5,25-36]

Stakeholder Engagement

Patient Group Input

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

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

Two responses to CADTH's call for patient input for the Ilumya submission were received: a cooperative submission from the CSPA, the CAPP and the CPN, and a second submission from CORD.

CAPP is a national, non-profit organization formed to better serve the needs of patients with psoriasis across the country. CAPP is a partner organization of the CSPA, which is an organization that strives to improve the quality of life for all Canadians with psoriasis. Together, CAPP's and CSPA's mission is to be a resource and advocate for patients with psoriasis and their families to improve patient care and quality of life. The CPN is a national, non-profit organization dedicated to enhancing the quality of life of individuals living with psoriasis and psoriatic arthritis by providing current information on research and treatment options, and by working with others to build awareness and advocacy about the complexities of these conditions. CSPA, CAPP, and CPN stated they did not receive any help from outside their groups to complete this submission or to collect or analyze the data used in the submission. Over the past 2 years, the CSPA received up to $5,000 in funding from Janssen, and between $10,000 and $50,000 from AbbVie, Pfizer, and Merck. CAPP reporting receiving $5,000 to $10,000 from AbbVie, Amgen, Novartis, UCB, Leo Pharma, and between $10,000 and $50,000 from Janssen, Eli Lilly, and Bausch Health. In the past 2 years, CPN received between $10,000 and $50,000 from Amgen, Novartis, Eli Lilly, Leo, Pfizer, and Celgene, and in excess of $50,000 from AbbVie and Janssen.

CORD is a Canadian national network of organizations for those with rare disorders. CORD advocates on behalf of those with rare disorders by working with governments, researchers, clinicians, and industry to promote research, diagnosis, treatment, health policy, and health care systems and services for all rare disorders in Canada. CORD indicated that it collaborated with CBCN to administer a survey to gather information for this submission but received no other help to analyze data or complete the submission. CORD reported having received $10,000 to $50,000 in funding over the last 2 years from Innomar Strategies.

2. Condition-Related Information

The information used to inform the submission was based on data collected from other recent submissions for risankizumab (Skyrizi) and certolizumab pegol (Cimzia) and from online disease discussion boards. In addition, CORD conducted interviews with 3 Canadian patients with moderate or severe psoriasis who received Ilumya (2 males and 1 female patient who were between 42 and 63 years of age and had been diagnosed with plaque psoriasis more than 10 years ago). CORD also collected survey data from 12 patients diagnosed with plaque psoriasis when they were between 19 and 35 years of age (9 patients), or older than 35 years (3 patients). Of these patients, 67% had been diagnosed more than 10 years ago.

The patient groups describe psoriasis as a chronic inflammatory skin condition that affects the regeneration of skin cells. While normal skin cells grow and shed in 28- to 30-day cycles, the skin cells of someone affected with psoriasis grow more rapidly. As a result, the

skin cells also shed very quickly and pile up on the skin's surface, creating sores or lesions called plaques. The patient groups describe thick, silvery scales that can form on top of the plaques, which can be itchy and painful. Psoriasis usually affects the elbows, knees, and scalp, but it can also arise on the palms of the hands, soles of the feet, nails, genitals, and torso. According to the patient groups, psoriasis is a persistent, chronic condition that may come and go — flare-up, then go into remission. During flare-ups, psoriasis causes itchiness and pain in the inflamed skin. The skin may also crack and bleed. Psoriasis can range from a few dandruff-like scales to widespread patches that cover large areas of skin. For many people, psoriasis is nothing more than a nuisance. For others, it is an embarrassment. And for a few, it is a painful and disabling condition.

In the patient input received for Cimzia (n = 16), 74% of respondents reported feeling that their condition is not adequately controlled. When asked how patients feel when their condition is not being effectively treated, one-third of patients reported frequently feeling embarrassed, losing sleep, having problems with intimacy, and lacking self-confidence. About half of patients indicated their work is affected frequently, and they frequently experience feelings of depression. One patient reported, "I just feel awful. Flakes everywhere. It's depressing for me and I don't feel like going to the gym or eating well when I don't like myself." Another patient stated, "It affected my job which involved representing the company. I was embarrassed and unable to concentrate. And sometimes the pain would be really bad; you can't prepare for it."

When asked how their condition affects their day-to-day life, 81% indicated it affects what they decide to wear, 50% indicated they have trouble sleeping, and 31% indicated they had to miss social events. Additionally, 62.5% reported feeling depressed, 37.5% reported joint pain, and 56% reporting weight gain. One-quarter of respondents stated that psoriasis did not affect their day-to-day lives.

According to the patient groups, psoriasis also impacts the family members and caregivers of patients with psoriasis. Survey respondents reported having emotional (66%), financial (55%), and social (33%) challenges. Respondents also reported missing school or work (33%), difficulties with intimacy (33%), and a lack of support or information about psoriasis (44%).

3. Current Therapy Related Information

The majority of respondents had experience with multiple types of therapies, including skin creams or ointments (topical corticosteroids, vitamin D analogues), phototherapy, oral systemic drugs, and biologics.

According to the patient input submission from the CSPA, 58% of the respondents to the Cimzia submission indicated their current medications were "very convenient" to use. When asked about side effects, half reported "none," while others reported fatigue, dryness, thinning skin, hair loss, and weight gain. When asked about unmet needs in their current treatment, respondents reported they "still have new outbreaks" and that their treatments are "only temporary fixes." Six written comments were received describing the lack of efficacy of their treatments, which led to the discontinuation of the treatment. Lastly, 3 comments received described challenges accessing treatment.

According to the patient input submission from CORD, approximately one-third of patients have used methotrexate (Rheumatrex) and/or cyclosporine in the past. None of the patients reported still taking these drugs. Approximately 41% of the respondents reported

experience with at least 1 TNF inhibitor (i.e., etanercept [Embrel], infliximab [Remicade], adalimumab [Humira], and certolizumab pegol [Cimzia]). All patients reported taking an anti-IL therapy (i.e., ustekinumab [Stelara], secukinumab [Cosentyx], and ixekizumab [Taltz], brodalumab [Siliq], and guselkumab [Tremfya]), with one-quarter of respondents currently taking these medications. Three-fourths of patients reported taking the drug under review, tildrakizumab (Ilumya). When asked an open-ended question with respect to the effectiveness of the available therapies, mixed responses were received, including, "I think this is a tricky question because all the previous methods provided some relief for varying periods of time" and, "I would say that the treatment has been about 60% effective, meaning that for a period of time, I was able to walk more because my feet were better and I was able to sleep better because I had less pain at night. But that only lasted about 6 months." Some patients mentioned adverse effects associated with treatments, such as kidney damage with cyclosporin, and the gastrointestinal effects of methotrexate. Phototherapy required frequent visits to the clinic, which was inconvenient for patients.

Overall, all respondents had experience with 1 or more types of therapy. However, based on the survey and interview responses, many patients reported the treatments as ineffective in addressing their key concerns: the appearance of plaques, pain, daily functioning, social life, quality of life, and psychological distress.

4. Expectations About the Drug Being Reviewed

The 3 patients interviewed by CORD had experience with tildrakizumab in a clinical trial. The patients were unanimous in their opinion that the drug was "highly effective" in the most important outcome measure, which was identified as clearing their skin. According to the patient group submission, all 3 patients were astonished at how quickly and effectively the drug worked. One patient reported: "Frankly, after all the hype and disappointments with other treatments, you really don't expect any treatment to work 100%, but this is pretty close. I can't even complain about the small remaining patches." Another patient indicated, "I can't imagine not having this drug. I hope somebody is listening and appreciates what this means to patients like me." Additionally, patients reported that tildrakizumab changed their life; they were able to return to work and participate in physical activities, and it improved their outlook on life. Patients commented that the 12-week dosing of tildrakizumab was convenient. Although patients acknowledged that the long-term impact is still unknown, in the shorter term, tolerability was good. When asked about the importance of having tildrakizumab available to all patients with moderate-to-severe plaque psoriasis, all respondents agreed that it was "very important."

Generally, the patient groups noted the single most important outcome was the resolution of the plaques. Moreover, the treatment should be easy to access and use, have minimal side effects, have little potential impact on organs, and/or have few other long-term negative outcomes. According to the patient input received from the CSPA, 73% of respondents indicated itching and 53% indicated pain, as well as bleeding, diabetes, heart disease, depression, and social stigma, were important aspects to be able to control.

5. Additional Information

The CSPA added that choice is a fundamental value for patients with psoriasis. It is more than "just a skin disease" and, additionally, it is estimated that up to 30% of patients develop psoriatic arthritis as well as other diseases such as depression, cardiovascular disease, and cancer. The patient group made reference to a recent CAPP report called *Pso Serious 2018: A Report on Access to Care and Treatment for Psoriasis Patients in Canada*

(http://www.canadianpsoriasis.ca/images/CAPPreportOctober27finalclean.pdf). Lastly, the CSPA added that all patients are looking for a treatment that will control all of their symptoms but, ultimately, they would like a cure for psoriasis.

CORD indicated that patients are highly positive about the benefits of Ilumya; however, it is not apparent when Ilumya would be introduced in the line of therapies. The patient group suggests that given its ease of use, lack of side effects, and strong benefits, it should not be offered as a "last resort" treatment but, rather, should be considered as an earlier option.

Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of plaque psoriasis.

Description of the Current Treatment Paradigm for the Disease

When a new patient with moderate-to-severe plaque psoriasis presents to a dermatologist, a careful history is taken to determine all prior therapies, and patients are screened for comorbidities and potential contraindications to systemic therapies. If the patient has not received an appropriate topical therapy, nor an adequate trial of phototherapy, a trial of topical therapy alone or topical therapy combined with phototherapy may be offered. Frequently, a combination of topical drugs is prescribed from the labelled drug categories, including corticosteroids, calcipotriol, and retinoids. Off-label calcineurin inhibitors are also used to treat facial and intertriginous involvement. The most common phototherapy modality for plaque psoriasis in Canada is narrow-band ultraviolet B phototherapy, but broad-band phototherapy is still used in some clinics. Phototherapy is offered only to those patients for whom travel to a dermatologist's office 2 to 3 times weekly is practical. As such, phototherapy is not available to a significant proportion of patients living in rural Canada.

If adequate improvement cannot be achieved with topical therapy and/or phototherapy, the discussion turns toward systemic therapies. The most commonly offered first systemic drug for generalized plaque psoriasis is oral methotrexate, with a minimum trial duration of 3 months to assess efficacy. An alternative is apremilast (assuming third-party coverage is in place), which may be offered to patients who express concerns over methotrexate toxicity and the requirement for continuous laboratory monitoring. If the patient's condition does not respond to methotrexate and, assuming there are no contraindications, the patient may be offered a trial of cyclosporine for a minimum of 12 weeks to assess efficacy. This treatment is notable for its rapid action and high efficacy and, thus, can be useful to stabilize the patient after a severe flare-up. However, its toxicities in terms of renal dysfunction and hypertension are problematic. In addition, most guidelines stipulate a maximum treatment duration of 2 years. If the patient's main problem is palmoplantar plaque psoriasis, then a trial of therapy with acitretin is offered, assuming the patient is not a female of child-bearing potential.

Provided reimbursement is not an issue, most dermatologists today would choose an IL-17A or IL-23 inhibitor as the first biologic drug due to their high efficacy. IL-17 drugs would be chosen ahead of IL-23 drugs in patients with psoriatic arthritis. In some regions,

ustekinumab may still be used as a first biologic drug but new starts with the TNF alpha inhibitors are dropping off, particularly for etanercept and infliximab. Assuming an effective biologic drug is chosen, treatment must be continued indefinitely for efficacy to continue.

Treatment Goals

An ideal treatment in plaque psoriasis would produce a sustained PASI 100 response in all patients with little or no risk of adverse effects. This treatment would be easily accessed by the patient and convenient to administer. The PASI 100 response would translate to improved quality of life (i.e., a DLQI score of near zero). An ideal treatment would also benefit 1 or more of the comorbidities, particularly psoriatic arthritis. An ideal medication would produce remission without the need for continuous long-term administration or could be administered intermittently as required when the patient reaches a predetermined PASI score after interruption of therapy.

Unmet Needs

Although several biologic and non-biologic therapies are available in Canada to treat moderate-to-severe plaque psoriasis, none fulfill the criteria of an ideal treatment.

At present, it is not possible to predict with certainty whether a patient will respond adequately to any of the 10 available biologics. In addition, not all drugs are suitable for all patients (Crohn disease is a contraindication to the IL-17A inhibitors, severe depression with suicidal ideation a contraindication to brodalumab, and cardiac failure and multiple sclerosis a contraindication to the TNF alpha inhibitors). Thus, tildrakizumab, if approved, will be an additional drug in the treatment armamentarium and will increase the likelihood that the patient and the physician will find a drug that works well and is well tolerated. Within the IL-23 inhibitor drug class, tildrakizumab offers some dosing advantage over guselkumab (every 12 weeks maintenance dosing versus 8 weeks), but not over risankizumab. The potential for intermittent therapy with tildrakizumab, and for efficacy in patients with psoriatic arthritis or those whose condition has not responded to another IL-23 inhibitor, are currently unknown.

Place in Therapy

Due to their high efficacy, dermatologists may favour the IL-23 inhibitors, including tildrakizumab, as the first biologic drug of choice along with the IL-17A inhibitors. Because there are limited data regarding the efficacy of the IL-23 inhibitors in psoriatic arthritis, it is anticipated the IL-17 drugs will, for now, be favoured over the IL-23 drugs in patients with psoriatic arthritis. It is unlikely that dermatologists will combine tildrakizumab with methotrexate or apremilast, as commonly occurred with the TNF alpha inhibitors.

It is unlikely that tildrakizumab will cause a shift in the treatment paradigm for moderate-to-severe plaque psoriasis, as prior use of methotrexate, apremilast, or cyclosporine is generally required for reimbursement. Many patients respond well to these treatments without significant toxicity, and methotrexate and cyclosporine are more cost-effective options.

Patient Population

Tildrakizumab is appropriate for adult patients with moderate-to-severe plaque psoriasis who are suitable candidates for systemic therapy. Most health care payers would limit use to patients with a minimum PASI score of 12 and BSA involvement of at least 10%. The diagnosis of psoriasis in all cases is made clinically and is not a challenging diagnosis for

dermatologists, so misdiagnosis is very unlikely. Basic lab testing prior to starting tildrakizumab, as with all other biologic drugs, would be HIV serology, viral hepatitis screening, and screening for latent tuberculosis. Tildrakizumab, unlike the IL-17A inhibitors, could be prescribed for a patient with concomitant Crohn disease.

Limited data are available for tildrakizumab in patients with psoriatic arthritis; thus, other treatment options would be preferred for this patient population. At present, it is not possible to predict which patients would be more likely to respond to tildrakizumab.

Assessing Response to Treatment

The PASI score and, in some practices, the DLQI at 16 weeks, could be used to assess whether a patient is responding to therapy. PASI score is used in clinical practice to assess the efficacy of other biologics, as it is a requirement for reimbursement. A formal PGA, as was used in the clinical trials for tildrakizumab, is not used in clinical practice; however, informal evaluations of the patient's overall progress, including the patient's input, are frequently conducted in practice.

A PASI 75 response at 16 weeks would be considered a clinically meaningful response to treatment. With tildrakizumab, clinicians would expect patients to achieve a PASI 90 response. If, at the initial 16-week visit, the patient has achieved a PASI 90 or PASI 100 response, the patient would likely be offered follow-up in 1 year, but patients may be seen earlier if response wanes or the patient is concerned about a possible adverse event. Follow-up in 12 to 24 weeks after the initial 16-week visit may be appropriate for patients showing a lesser treatment response (e.g., those only just achieving a PASI 75 response) to determine if there has been additional improvement or a further drop in efficacy.

Discontinuing Treatment

The following would be reasons to discontinue treatment:

- Failure to reach a PASI 75 improvement at 16 weeks.
- Failure to maintain a PASI 75 response during the maintenance phase. In Canada, typically, the dosage would be increased and a topical therapy added to determine if response can be recaptured.
- Failure of the drug to control psoriatic arthritis in patients with concomitant arthritis.
- Development of a high-risk malignancy, particularly if the patient's oncologist is advising immunotherapy.
- Elective surgery (e.g., orthopedic, gastrointestinal, genitourinary) and development of significant infections. In most cases, these result in temporary discontinuation followed by resumption of the drug.

Prescribing Conditions

Tildrakizumab will most likely be administered by the patient at home after appropriate training, but could also be administered at a community infusion clinic or at the prescribing dermatologist's office.

A dermatologist will be required to diagnose, treat, and monitor patients on tildrakizumab. The patient may be co-managed by dermatology and rheumatology specialists if psoriatic arthritis is present.

Clinical Evidence

The clinical evidence included in the review of tildrakizumab is presented in 3 sections. Section 1, the systematic review, includes pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those studies that were selected according to an a priori protocol. Section 2 includes indirect evidence from the sponsor and indirect evidence selected from the literature that met the selection criteria specified in the review. Section 3 includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of tildrakizumab 100 mg/mL syringe for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient population	Adults ≥ 18 years with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Subgroups: • disease severity • biologic-naive versus biologic-experienced • systemic therapy-naive versus systemic therapy-exposed • prior treatment failure or intolerance
Intervention	Tildrakizumab 100 mg administered by subcutaneous injection at week 0, 4, and every 12 weeks thereafter
Comparators	When used as monotherapy or as combination therapy: • Biologic drugs targeting interleukins: Brodalumab, guselkumab, ixekizumab, risankizumab, secukinumab, ustekinumab • Biologic drugs targeting TNF alpha: Adalimumab, certolizumab pegol, etanercept, infliximab • Non-biologic systemic drugs: Acitretin, apremilast, cyclosporine, methotrexate
Outcomes	**Efficacy outcomes:** • HRQoL (e.g., DLQI, SF-36, EQ-5D)[a] • skin clearance or psoriasis score (e.g., PASI response, Physician's Global Assessment)[a] • psoriasis-related symptoms (e.g., PSI)[a] • productivity[a] • relapse **Harms outcomes:** AEs, SAEs, WDAEs, mortality, notable harms (including infections, reactivation of tuberculosis, injection-site reactions, hypersensitivity events, immunogenicity, cardiovascular adverse events, malignancy, inflammatory bowel disease)

Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions questionnaire; HRQoL = health-related quality of life; PASI = Psoriasis Area and Severity Index; PSI = Psoriasis Symptom Inventory; RCT = randomized controlled trial; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; TNF = tumour necrosis factor; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[37]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was psoriasis. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on September 10, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on March 17, 2021.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[38] Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Two CADTH 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 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings from the Literature

A total of 2 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

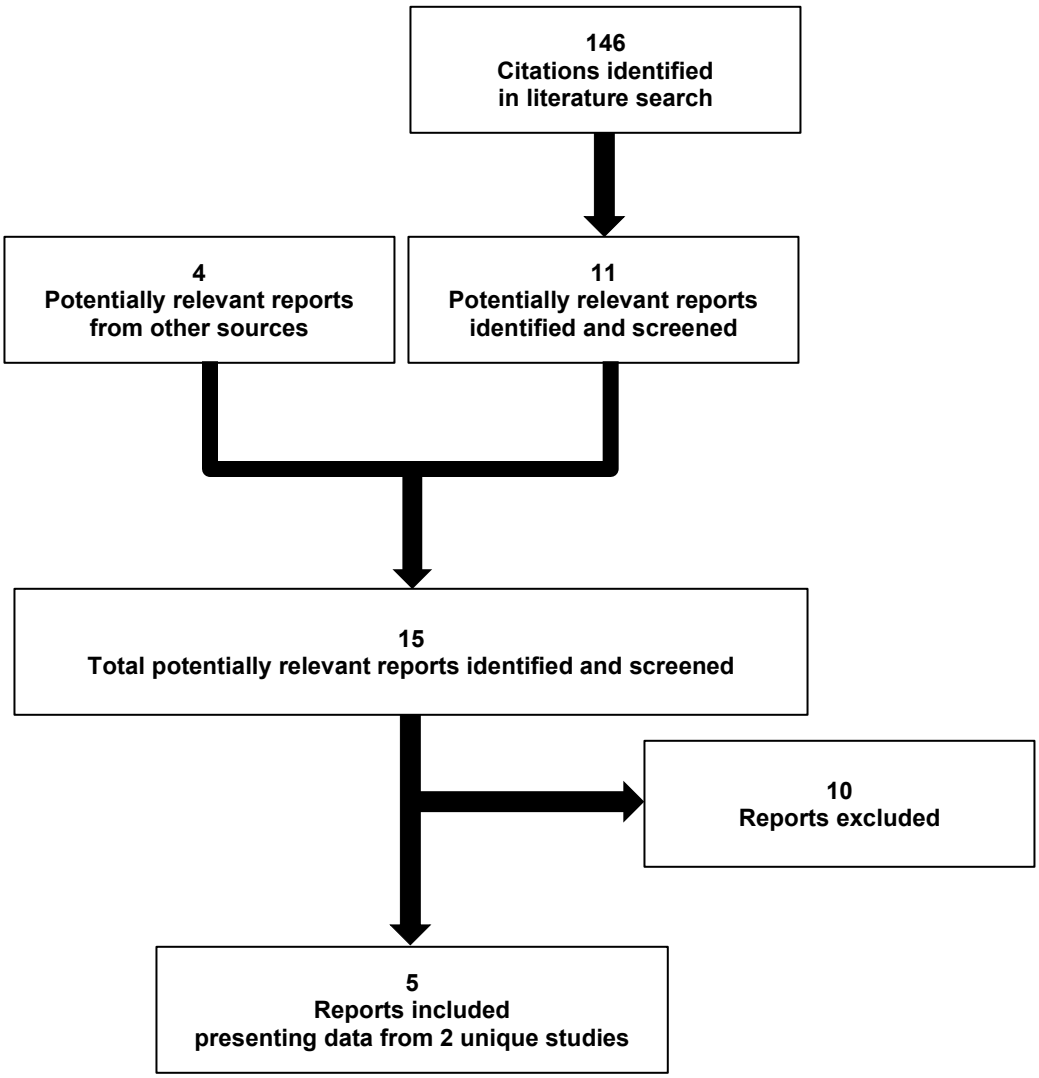


Table 4: Details of Included Studies

	Characteristic	P010 (reSURFACE 1)	P011 (reSURFACE 2)
Designs & Populations	**Study design**	DB RCT	DB RCT
	Locations	Australia, Canada, Japan, UK, US	Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Italy, Israel, Netherlands, Poland, US
	Randomized (N)	772	1,090
	Inclusion criteria	• ≥ 18 years of age with moderate-to-severe plaque psoriasis (affecting ≥ 10% BSA, PGA score ≥ 3, PASI score ≥ 12) • Candidate for phototherapy or systemic therapy • Enrolled a maximum of 30% of patients with psoriatic arthritis and 40% with prior exposure to biologic therapy for psoriasis	
	Exclusion criteria	• Predominantly a non-plaque form of psoriasis • Prior use of tildrakizumab or other interleukin 23 or 17 antagonists (both trials), or etanercept (P011 only) • Active or latent tuberculosis, infection with HIV or hepatitis B or C • Infection requiring antibiotic therapy within last 2 weeks of screening or severe infection requiring hospitalization or intravenous antibiotics within 8 weeks • Administered live vaccine within last 4 weeks • Prior malignancy • Hospitalization for acute cardiovascular event, illness, or surgery within past 6 months • Uncontrolled hypertension or diabetes, or clinically significant organ dysfunction or laboratory abnormalities • Severe psoriatic arthritis controlled with medication • Expected to require topical therapy, phototherapy, or systemic therapy for psoriasis during the trial • Had received topical treatments for psoriasis within 2 weeks of randomization; conventional systemic therapies, systemic corticosteroids, or phototherapy within 4 weeks; or biologic therapies within 12 weeks	
Drugs	**Intervention**	• Tildrakizumab 100 mg • Tildrakizumab 200 mg • Administered SC at week 0, 4, and every 12 weeks thereafter (see Interventions section for details)	• Tildrakizumab 100 mg • Tildrakizumab 200 mg • Administered SC at week 0, 4, and every 12 weeks thereafter (see Interventions section for details)
	Comparator(s)	Placebo	• Etanercept 50 mg twice weekly (part 1) and once weekly (part 2) • Placebo
Duration	**Phase**		
	Part 1	12 weeks	12 weeks
	Part 2	16 weeks	16 weeks
	Part 3	36 weeks	24 weeks
	Follow-up	20 weeks	20 weeks

	Characteristic	P010 (reSURFACE 1)	P011 (reSURFACE 2)
Outcomes	**Primary end point**	Co-primary: • proportion who achieved a PASI 75 response at week 12 • proportion who achieved PGA response at week 12	Co-primary: • proportion who achieved a PASI 75 response at week 12 • proportion who achieved PGA response at week 12
	Secondary and exploratory end points	Secondary: • PASI 90 • PASI 100 • PASI 75 and PGA response at other time points • DLQI ≤ 1 • change from baseline in DLQI Other: • EQ-5D • SF-36 • Work Productivity and Loss Questionnaire • harms	Secondary: • PASI 90 • PASI 100 • PASI 75 and PGA response at other time points • DLQI ≤ 1 • change from baseline in DLQI Other: • harms
Notes	**Publications**	Reich (2017)[39]	Reich (2017)[39]

BSA = body surface area; DB = double blind; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions questionnaire; PASI 75, 90, 100 = at least a 75%, 90%, or 100% reduction in the Psoriasis Area and Severity Index score; PGA = Physician's Global Assessment; RCT = randomized controlled trial; SF-36 = Short Form (36) Health Survey; SC = subcutaneous.

Note: Two additional reports were included (FDA medical and statistical report[40] and CADTH Common Drug Review submission[41]).

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Description of Studies

Two multi-centre double-blind RCTs met the inclusion criteria for the systematic review (Study P010 and P011). These trials examined the efficacy and safety of tildrakizumab compared with placebo or etanercept in adults with moderate-to-severe plaque psoriasis. Both trials consisted of 3 parts, which are outlined subsequently and shown in Figure 2 and Figure 3:

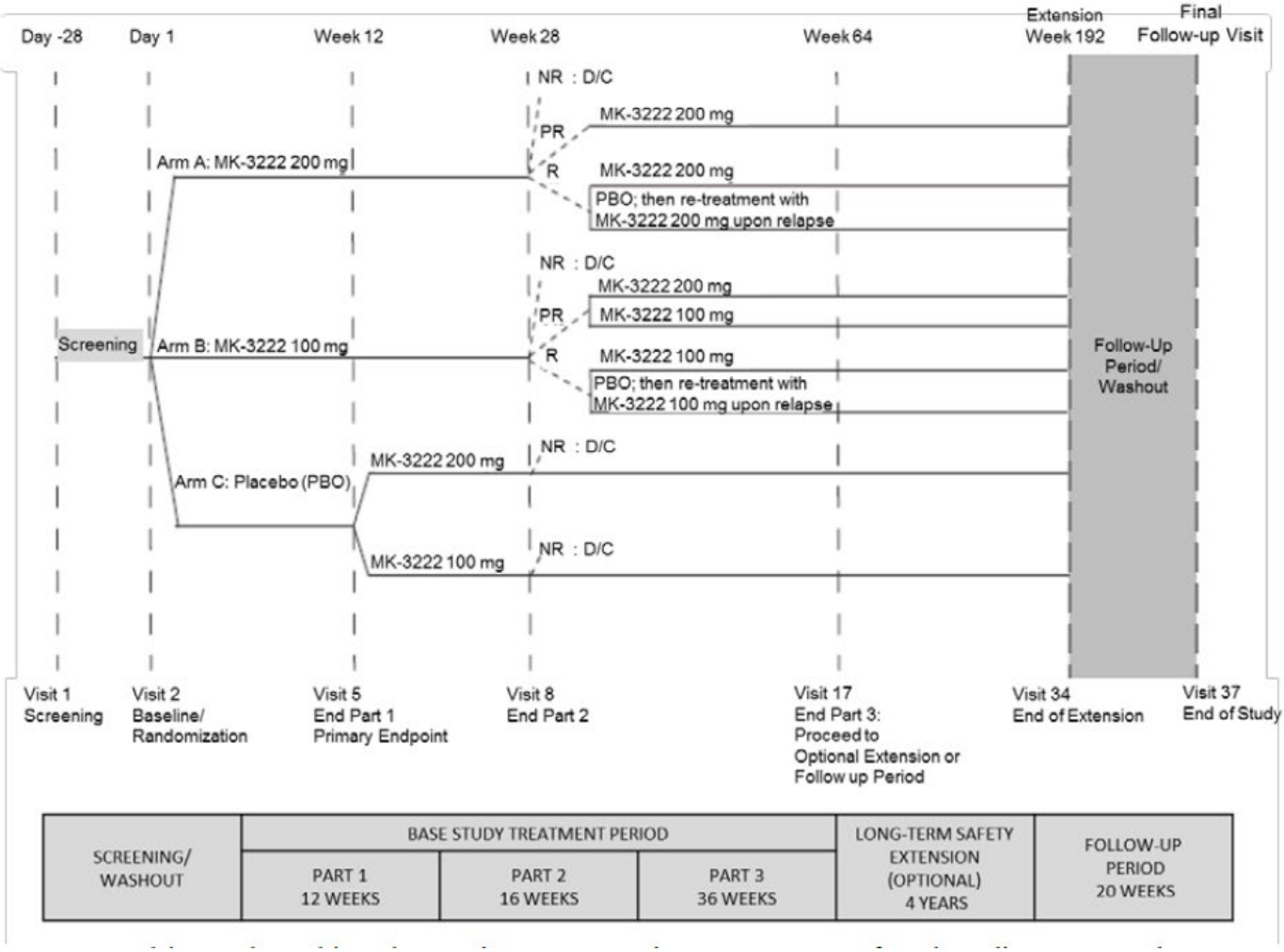
- Part 1: Week 0 to week 12. Patients were randomized 2:2:1 to tildrakizumab 100 mg or 200 mg or placebo in Study P010, and randomized 2:2:1:2 to tildrakizumab 100 mg or 200 mg, placebo, or etanercept 50 mg in Study P011.
- Part 2: Week 12 to week 28. Patients in active treatment groups continued on therapy, and those initially randomized to placebo were re-randomized to tildrakizumab 100 mg or 200 mg.
- Part 3: Week 28 to week 64 (P010) or week 52 (P011). Patients were discontinued, re-randomized, or reassigned to tildrakizumab or placebo based on their treatment response at week 28 (see Interventions section for details).

Patients were randomized using an interactive voice or web response system by region. Randomization was stratified by body weight (≤ 90 kg or > 90 kg) and prior biologic therapy (yes or no). In Study P010, randomization for patients from Japan was also stratified by psoriatic arthritis at baseline (yes or no). At week 12 and 28, re-randomization of patients was stratified by region (i.e., North America, Europe, Japan) and body weight (≤ 90 kg or > 90 kg).

Study P010 randomized 772 patients from Australia, Canada, Japan, the UK, and the US (including 16 Canadian study sites). Study P011 randomized 1,090 patients from Europe, Canada, Israel, and the US (12 Canadian study sites).

For both trials, those patients who completed the base study (parts 1, 2, and 3) were eligible to enter a long-term extension study. The extension studies were ongoing at the time of this review.

Figure 2: Study Design for P010 (reSURFACE 1)

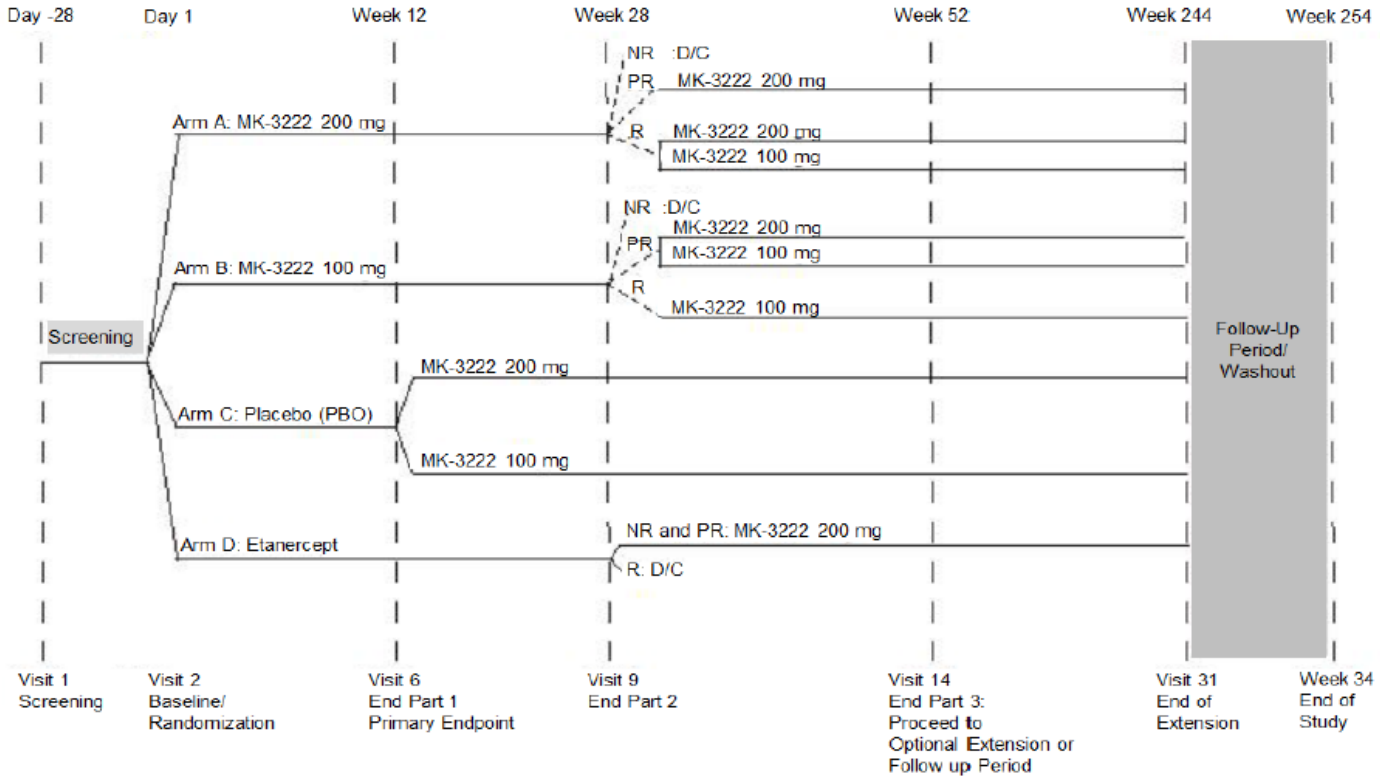


D/C = discontinuation; MK-3222 = tildrakizumab; NR = nonresponders; PASI = Psoriasis Area and Severity Index; PBO = placebo; PR = partial responders; R = responders.

Note: Nonresponders were patients who achieved a < 50% improvement in PASI response from baseline. At week 28, nonresponders were discontinued. Partial responders were patients who achieved ≥ 50% but < 75% improvement in PASI response from baseline. Responders were patients who achieved ≥ 75% PASI response from baseline.

Source: Clinical Study Report for Study P010.[6]

Figure 3: Study Design for P011 (reSURFACE 2)



SCREENING/ WASHOUT	BASE STUDY TREATMENT PERIOD			LONG-TERM SAFETY EXTENSION (OPTIONAL) 4 YEARS	FOLLOW-UP PERIOD 20 WEEKS
	PART 1 12 WEEKS	PART 2 16 WEEKS	PART 3 24 WEEKS		

D/C = discontinuation; MK-3222 = tildrakizumab; NR = nonresponders; PASI = Psoriasis Area and Severity Index; PBO = placebo; PR = partial responders; R = responders.

Note: Nonresponders were patients who achieved a < 50% improvement in PASI response from baseline. At week 28, the nonresponders in arms A and B were discontinued. Partial responders were patients who achieved ≥ 50% but < 75% improvement in PASI response from baseline. Responders were patients who achieved ≥ 75% PASI response from baseline.

Source: Clinical Study Report for Study P011.[7]

Populations

Inclusion and Exclusion Criteria

The patients enrolled in studies P010 and P011 were adults with moderate-to-severe plaque psoriasis affecting at least 10% of their BSA and who had a PGA score of 3 or more and a PASI score of 12 or greater. In the studies, a maximum of 40% of patients enrolled could have prior exposure to biologics (defined as efalizumab, alefacept, infliximab, adalimumab, etanercept, or ustekinumab). A maximum of 30% of patients enrolled could have psoriatic arthritis (Table 4).

Patients were excluded if they had previously used tildrakizumab or other IL-23 or IL-17 antagonists, or etanercept (P011 only), or were likely to require topical, phototherapy, or systemic therapies for psoriasis during the trial. Patients who were receiving topical or

systemic therapies for psoriasis had to undergo a washout period of 2 to 12 weeks prior to enrolment. Also excluded were patients with tuberculosis, HIV, or hepatitis B or C; those who had a recent infection, cardiovascular event, or surgery; or those who had severe psoriatic arthritis controlled with medication.

Baseline Characteristics

The patients enrolled in P010 and P011 were predominantly male (65% to 73% per treatment group) and White (65% to 92%), with a mean age per treatment group that ranged from 44.6 to 47.9 years. At baseline, the mean PASI score ranged from 19.3 to 20.7, and 12% to 20% of patients per group had psoriatic arthritis (Table 5).

The baseline characteristics were generally similar between groups within trials, with a few differences noted between studies. The proportion of patients who were Asian was higher in P010 than in P011 because Study P010 included sites in Japan. Also, the percentage of patients who had prior exposure to biologics for psoriasis was higher in Study P010 (23%) than in Study P011 (12% to 13%), and the percentage who had received phototherapy was lower (P010, 28% to 29%; P011, 40% to 44%). The percentage of patients who had received prior cyclosporine therapy ranged from 8% to 16% and from 17% to 26% for methotrexate.

Table 5: Summary of Baseline Characteristics (ITT)

Characteristic	P010 (reSURFACE 1)			P011 (reSURFACE 2)			
	Placebo N = 155	TILD 100 mg N = 309	TILD 200 mg N = 308	Placebo N = 156	TILD 100 mg N = 307	TILD 200 mg N = 314	ETAN 50 mg N = 313
Male, n (%)	100 (65)	207 (67)	226 (73)	112 (72)	220 (72)	225 (72)	222 (71)
Age, years, mean (SD)	47.9 (13.6)	46.4 (13.1)	46.9 (13.2)	46.4 (12.2)	44.6 (13.6)	44.6 (13.6)	45.8 (14.0)
Weight, kg, mean (SD)	87.5 (26.0)	88.5 (23.9)	88.9 (24.1)	88.7 (22.7)	89.4 (22.1)	88.4 (21.2)	88.0 (21.5)
Race, n (%)							
White	101 (65)	217 (70)	209 (68)	144 (92)	279 (91)	284 (90)	289 (92)
Black	6 (4)	12 (4)	8 (3)	1 (1)	7 (2)	8 (3)	8 (3)
Asian	42 (27)	70 (23)	83 (27)	3 (2)	9 (3)	14 (5)	10 (3)
Other/ missing	6 (4)	10 (3)	8 (3)	8 (5)	12 (4)	8 (3)	6 (2)
Percentage BSA affected, mean (SD)	29.6 (17.3)	29.7 (17.4)	30.9 (17.8)	31.3 (14.8)	34.2 (18.4)	31.8 (17.2)	31.6 (16.6)
Psoriatic arthritis, n (%)	19 (12)	54 (18)	60 (20)	23 (15)	48 (16)	42 (13)	41 (13)
PASI score, mean (SD)	19.3 (7.1)	20.0 (7.9)	20.7 (8.5)	20.0 (7.6)	20.5 (7.6)	19.8 (7.5)	20.2 (7.4)
PGA score, n (%)							
< 3	0	1 (< 1)	0	7 (5)	11 (4)	14 (5)	7 (2)
3	111 (72)	206 (67)	202 (66)	91 (58)	196 (64)	193 (62)	193 (62)
4	41 (27)	95 (31)	95 (31)	52 (33)	95 (31)	97 (31)	103 (33)
5	2 (1)	7 (2)	11 (4)	5 (3)	5 (2)	7 (2)	7 (2)
Prior treatments							
Biologics, n (%)[a]	35 (23)	71 (23)	71 (23)	20 (13)	39 (13)	38 (12)	37 (12)
Adalimumab	12 (8)	20 (7)	33 (11)	8 (5)	13 (4)	12 (4)	16 (5)
Etanercept	19 (12)	43 (14)	39 (13)	0	0	1 (< 1)	1 (< 1)

Characteristic	P010 (reSURFACE 1)			P011 (reSURFACE 2)			
	Placebo N = 155	TILD 100 mg N = 309	TILD 200 mg N = 308	Placebo N = 156	TILD 100 mg N = 307	TILD 200 mg N = 314	ETAN 50 mg N = 313
Infliximab	2 (1)	4 (1)	4 (1)	1 (1)	6 (2)	5 (2)	2 (1)
Ixekizumab	0	1 (< 1)	0	NR	NR	NR	NR
Ustekinumab	1 (1)	3 (1)	0	NR	NR	NR	NR
Non-biologic, n (%)							
Acitretin	7 (5)	11 (4)	12 (4)	11 (7)	30 (10)	28 (9)	22 (7)
Apremilast	3 (2)	17 (6)	12 (4)	2 (1)	4 (1)	2 (1)	1 (< 1)
Cyclosporine	20 (13)	37 (12)	40 (13)	13 (8)	49 (16)	37 (12)	36 (12)
Methotrexate	28 (18)	53 (17)	63 (21)	41 (26)	80 (26)	81 (26)	80 (26)
Phototherapy	43 (28)	88 (29)	85 (28)	62 (40)	124 (40)	125 (40)	137 (44)
Topical corticosteroids	85 (55)	173 (56)	166 (54)	65 (42)	121 (39)	141 (45)	126 (40)
Topical antipsoriatics	37 (24)	87 (28)	87 (28)	59 (38)	133 (43)	133 (42)	127 (41)

BSA = body surface area; ETAN = etanercept; ITT = intention to treat; NR = not reported; PASI = Psoriasis Area Severity Index; PGA = Physician's Global Assessment; SD = standard deviation; TILD = tildrakizumab.

[a] Randomization stratification variable that included prior use of efalizumab, alefacept, infliximab, adalimumab, ustekinumab, etanercept.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Interventions

Patients were randomized to receive placebo or tildrakizumab 100 mg or 200 mg in studies P010 and P011. Doses were administered subcutaneously via pre-filled syringes at week 0, week 4, and every 12 weeks thereafter. Study P011 also included an etanercept group where patients received a dose of etanercept 50 mg subcutaneously twice weekly during part 1 (up to 12 weeks), and then 50 mg once weekly until week 28. To maintain blinding, the placebo injections used in the trials were identical in appearance and packaging to tildrakizumab or etanercept. All patients allocated to active treatments received additional placebo doses to maintain blinding.

Table 6 describes the treatment allocation for parts 1, 2, and 3 for each study, including crossover from placebo to tildrakizumab, crossover between tildrakizumab doses, or crossover from tildrakizumab to placebo.

- Part 1: Week 0 to week 12. Tildrakizumab 100 mg or 200 mg or placebo in Study P010, or tildrakizumab 100 mg or 200 mg or placebo or etanercept in Study P011.
- Part 2: Week 12 to week 28. Patients in active treatment groups continued on therapy, and those initially randomized to placebo were re-randomized to tildrakizumab 100 mg or 200 mg.
- Part 3: Week 28 to week 64 (P010) or week 52 (P011). Patients were discontinued, re-randomized, or reassigned to tildrakizumab or placebo, based on their treatment response at week 28 (Table 6). Responders (PASI ≥ 75) in P010 were re-randomized to continue on the same dose of tildrakizumab or to placebo. In P011, responders to tildrakizumab 200 mg were re-randomized to tildrakizumab 100 mg or 200 mg, while responders to tildrakizumab 100 mg remained on the same dose. In both studies, partial responders (≥ PASI 50 and < PASI 75) to tildrakizumab 200 mg continued on the same dose and those in the tildrakizumab 100 mg group were re-randomized to 100 mg or 200 mg doses. Partial responders and nonresponders (PASI < 50) to etanercept

50 mg once weekly were crossed over to tildrakizumab 200 mg (week 32, week 36, and every 12 weeks thereafter).

In Study P011, patients were allowed to self-administer the study drug injections once they had demonstrated their ability, whereas, in Study P010, all doses of the study drug were administered at the study site.

Prohibited medications included topical psoriasis therapies, conventional systemic psoriasis drugs (e.g., cyclosporine, methotrexate, acitretin, fumaric acid esters), phototherapy, injectable or oral corticosteroids, and other biologic drugs, including alefacept.

Table 6: Treatment Allocation for Part 1, 2, and 3 of P010 and P011

Detail		Tildrakizumab 200 mg	Tildrakizumab 100 mg	Placebo	Etanercept
Study P010					
Part 1: Week 0 to 12	Patients randomized 2:2:1 at week 0	Tildrakizumab 200 mg at week 0 and 4	Tildrakizumab 100 mg at week 0 and 4	Placebo at week 0 and 4	NA
Part 2: week 12 to 28	Active treatment groups continued therapy; placebo group was re-randomized at week 12	Continue tildrakizumab 200 mg[a]	Continue tildrakizumab 100 mg[a]	Re-randomized 1:1 to tildrakizumab 200 mg or 100 mg administered at week 12 and week 16	NA
Part 3: week 28 to 64[b]	Patients who were nonresponders at week 28 were discontinued from the study[c]	• Partial responders[c] continued on tildrakizumab 200 mg every 12 weeks • Responders[c] were re-randomized 1:1 to tildrakizumab 200 mg every 12 weeks or placebo every 4 weeks until relapse[d]	• Partial responders[c] re-randomized to tildrakizumab 100 mg or 200 mg every 12 weeks. • Responders[c] were re-randomized 1:1 to tildrakizumab 100 mg every 12 weeks or placebo every 4 weeks until relapse[d].	Partial responders and responders[c] continued on active treatment as assigned at week 12	NA
P011					
Part 1: week 0 to 12	Patients randomized 2:2:1:2 at week 0	Tildrakizumab 200 mg at week 0 and 4, plus placebo for etanercept	Tildrakizumab 100 mg at week 0 and 4, plus placebo for etanercept	Placebo at week 0 and 4, plus placebo for etanercept	Etanercept 50 mg twice weekly, plus placebo for tildrakizumab
Part 2: week 12 to 28	Active treatment groups continued therapy; placebo group was re-randomized at week 12	Continue tildrakizumab 200 mg[a,e]	Continue tildrakizumab 100 mg[a,e]	Re-randomized 1:1 to tildrakizumab 200 mg or 100 mg administered at week 12 and week 16[e]	Etanercept 50 mg once weekly[a]

Detail		Tildrakizumab 200 mg	Tildrakizumab 100 mg	Placebo	Etanercept
Part 3: week 28 to 52	• Patients reassigned to treatments based on response • Matching placebo administered to maintain blinding	• Nonresponders discontinued at week 28[c] • Partial responders[c] continued on tildrakizumab 200 mg every 12 weeks • Responders[c] were re-randomized 1:1 to tildrakizumab 200 mg or 100 mg every 12 weeks	• Nonresponders discontinued at week 28[c] • Partial responders[c] re-randomized 1:1 to tildrakizumab 200 mg or 100 mg every 12 weeks • Responders[c] continued on tildrakizumab 100 mg every 12 weeks	Partial responders and responders[c] continued on active treatment as assigned at week 12	• Responders were discontinued at week 28 • Nonresponders and partial responders were switched to tildrakizumab 200 mg (administered at week 32, 36, and 48)

NA = not applicable; PASI = Psoriasis Area and Severity Index.

[a] To maintain blinding, patients received a placebo injection at week 12 and a tildrakizumab dose at week 16.

[b] To maintain blinding, patients received a placebo or tildrakizumab injection every 4 weeks.

[c] Nonresponders had < 50% change in PASI score from baseline, partial responders had 50% ≤ PASI < 75%, and responders had PASI ≥ 75% at week 28.

[d] Relapse was defined as a 50% reduction in maximum PASI response. Once relapse occurred, patients resumed their prior tildrakizumab dose administered at the relapse visit, 4 weeks later, and then every 12 weeks until week 64.

[e] Patients received placebo for etanercept every week.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Outcomes

In studies P010 and P011, the co-primary outcomes were the proportion of patients who achieved at least a 75% improvement in the PASI score from baseline to week 12, and the proportion of patients with a PGA score of “clear” or “minimal” with at least a 2-grade reduction from baseline for tildrakizumab 200 mg and 100 mg doses versus placebo. Secondary and exploratory outcomes of interest to this review are listed in Table 7. Patients in Study P010 were evaluated for efficacy and safety outcomes at week 0, 4, 8, 12, 16, 22, 28, 32, 36, 40, 44, 48, 52, 56, 60, and 64. Those enrolled in P011 were evaluated using the same schedule up to week 52.

Table 7: Outcomes Reported in Studies P010 and P011

Outcome and time point	Comparator	P010	P011
Part 1			
PASI 75 response and PGA response at week 12	Placebo	Primary	Primary
PASI 90 response at week 12	Placebo	Key secondary	Key secondary
PASI 100 response at week 12	Placebo	Key secondary	Key secondary
PASI 75 response and PGA response at week 12	Etanercept	NA	Key secondary
PASI 90 response at week 12	Etanercept	NA	Key secondary
PASI 100 response at week 12	Etanercept	NA	Key secondary
DLQI ≤ 1 at week 12	Placebo	Other secondary	Other secondary
Change from baseline to week 12 in DLQI score	Placebo	Other secondary	Other secondary
Change from baseline to week 12 in EQ-5D, SF-36	Placebo	Exploratory	NR
Change from baseline to week 12 in PASI score	Placebo	Other secondary	Other secondary

Outcome and time point	Comparator	P010	P011
Change from baseline to week 12 in WPLQ	—	Other	NR
Part 2 or 3			
PASI 75 and PGA response at week 28	Etanercept	NA	Key secondary
PASI 75 response at week 28	—	Other secondary	—
PASI 75 and PGA response at week 52 or 64	—	Other secondary	Other secondary
PASI 90, PASI 100 response at week 28, 52, or 64	—	Other secondary	Other secondary
DLQI score ≤ 1 at week 28, 52, or 64	—	Other secondary	Other secondary
Change from baseline to week 28 in DLQI score and PASI score	—	Other secondary	Other secondary
Change from baseline to week 52 or 64 in DLQI score and PASI score	—	Other secondary	Other secondary
Proportion of patients who relapsed following withdrawal of tildrakizumab (week 28 to 64)	—	Other secondary	NA
Change from baseline to week 28, 64 in EQ-5D, SF-36	—	Exploratory	NR
Change from baseline to week 28 in WPLQ	—	Other	NR

DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions questionnaire; NA = not applicable; NR = not reported; PASI 75, 90, 100 = at least a 75%, 90%, or 100% reduction in the Psoriasis Area and Severity Index score; PGA = Physician's Global Assessment; SF-36 = Short Form (36) Health Survey; WPLQ = Work Productivity and Loss Questionnaire.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

A detailed discussion of the validity of outcomes measures described in this section is provided in Appendix 4.

Health-Related Quality of Life

The DLQI is a dermatology-specific questionnaire that has been used to assess the impact of skin disease on a patient's HRQoL. It is a 10-item questionnaire that covers 6 domains: symptoms and feeling, daily activities, leisure, work and school, personal relationships, and bother with psoriasis treatment. Each item is scored on a 4-point Likert scale: 0 (not at all affected or not relevant), 1 (a little affected), 2 (a lot affected), and 3 (very much affected). The overall DLQI score is a numeric score from 0 to 30, with lower scores indicating better quality of life.[42,43] The final numeric score translates to the effect of the patient's disease on their quality of life, where 0 to 1 = no effect, 2 to 5 = small effect, 6 to 10 = moderate effect, 11 to 20 = very large effect, and 21 to 30 = extremely large effect. The DLQI has shown a strong correlation with the EuroQol 5-Dimensions questionnaire (EQ-5D) index score and the bodily pain and social functioning domains of the Short Form (36) Health Survey (SF-36). It may, however, lack conceptual validity for the psychological impact of psoriasis. There is evidence of responsiveness and test–retest reliability. Estimates of the minimal important difference range from 2.2 to 6.9.

In Study P010, HRQoL was also measured using the SF-36 and EQ-5D 3-Levels (EQ-5D-3L) instruments.

The EQ-5D-3L questionnaire is a generic, preference-based, HRQoL measure.[44] It includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is divided into 3 levels (1, 2, 3) representing "no problems," "some problems," and "extreme problems," respectively. The 5 questions are scored and together contribute to an EQ-5D index (utility) score between 0 and 1, where 0 represents death and

1 represents perfect health. Different utility functions are available that reflect the preferences of specific populations (e.g., US, UK). In the P010 and P011 studies, the EQ-5D index score was calculated using the US scoring algorithm for US patients and, for all other patients, the EU algorithm was used.[6] The evidence for the validity of the EQ-5D in the psoriasis population is limited. Good correlation between the EQ-5D and DLQI and PASI score has been reported; however, the EQ-5D may not be as responsive to change as the DLQI.[45,46] The estimated minimal clinically important difference (MCID) for the EQ-5D has been shown to range from 0.09 to 0.20 (mean 0.22 ± 0.14) in the population of patients with psoriasis.[46] This range, compared with the MCID range of 0.033 to 0.074 for the general population, suggests that a larger difference in EQ-5D score is necessary for patients with psoriasis to regard the change as clinically beneficial.[47]

The SF-36 is a 36-item, general health–status instrument that consists of 8 health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[48,49] The SF-36 also provides 2 component summaries, the Physical Component Summary (PCS) and Mental Component Summary (MCS), derived from aggregating the 8 domains according to a scoring algorithm. All domains scores are based on a scale of 0 to 100, with higher scores indicating higher quality of life. The estimated MCID for the PCS and MCS scores ranged from 2.57 to 3.91 and 3.89 to 6.05, respectively, in patients with moderate-to-severe plaque psoriasis.[46]

Psoriasis Area and Severity Index

The PASI is a widely used instrument in psoriasis trials that grades the extent and severity of psoriatic lesions. It combines an assessment of the BSA affected in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration or infiltration (thickness) in each region. Scores range from 0 to 72 points. In general, a PASI score over 10 represents more severe disease.[50] A 75% reduction in the PASI score (i.e., PASI 75), is used as a benchmark in clinical trials for psoriasis.[51] While the PASI 75 is still used as a primary efficacy end point in clinical trials, the treatment goal in clinical practice has shifted to achievement of PASI 90 or PASI 100, according to the clinical expert consulted for this review. PASI scores have shown a weak-to-moderate correlation with DLQI scores, good inter-rater reliability, and moderate intra-rater reliability. Responsiveness may be weak, especially when the BSA affected is less than 10%.

In Study P010, relapse was defined as a reduction in maximum PASI response by 50% for patients whose condition had responded to tildrakizumab at week 28 and were switched to placebo.

Physician's Global Assessment

The PGA is a composite score of physician assessment of erythema, average thickness, and scaling of the patient's psoriatic lesions.[52] The static version of the PGA was used in studies P010 and P011, which is a measurement of the disease severity at a given time point. To generate the PGA score, psoriatic lesions are graded for erythema, thickness, and scaling based on a scale of 0 to 5 (e.g., 0 = no erythema; 5 = deep red coloration). These scores are then averaged across all lesions to obtain a single estimate of the patient's overall severity of disease at that time. Higher scores indicate a more severe condition. The composite score falls on a scale of 0 to 5, interpreted as follows:

0 = cleared, except for residual discoloration

1 = minimal

2 = mild

3 = moderate

4 = marked

5 = severe

In studies P010 and P011, PGA response was defined as a PGA score of "clear" or "minimal" with at least a 2-grade reduction from baseline, which is generally accepted as a clinically meaningful score. PGA has shown reliable test–retest reliability, but inter-rater reliability may be low. It has shown a weak-to-moderate correlation with DLQI, and a strong correlation with PASI scores. No information on responsiveness was found.

Work Productivity and Loss Questionnaire

The Work Productivity and Loss Questionnaire (WPLQ) is a disease-specific patient-reported productivity questionnaire for the evaluation of the impact of the patient's psoriasis on their work.[6] The questionnaire addresses patient absenteeism and presenteeism due to psoriasis and/or psoriatic arthritis, including productivity loss, over a recall period of 4 weeks. It consists of 10 items: patient's occupation, occupational impact on psoriasis, patient's employment status over time, reasons for missing work, reasons for impaired productivity, patient's usual working days per week, missed days due to psoriasis, partially missed days due to psoriasis, days worked with psoriasis, and hours worked with psoriasis.[6] The questionnaire also addresses reasons for impaired productivity, missing work, or unemployment, with possible responses: health care visits, unable or uncomfortable to travel, too much pain to work, too uncomfortable to work, and unable to concentrate and work. No information was found on the construct and content validity of the questionnaire, or evidence on its reliability and responsiveness. The sponsor indicated that the WPLQ is being used in Study P010 to inform the economic model.[6]

Harms

In the pivotal trials, an adverse event was defined as any untoward medical occurrence in a patient administered a drug, but the event did not have to have a causal relationship with the drug. A serious adverse event was any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolongation of hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, was associated with overdose, or was another important medical event.

Infections that required intravenous antibiotics were identified as events of clinical interest in both studies. A blinded clinical adjudication committee reviewed all serious cardiovascular events and deaths to determine if they met pre-specified criteria for major adverse cardiovascular events (non-fatal stroke or myocardial infarction, unstable angina, coronary revascularization, and sudden death or confirmed cardiovascular death).

Statistical Analysis

In both trials, the co-primary outcomes (PASI 75 response and PGA response at 12 weeks) were analyzed using a Cochran-Mantel-Haenszel test stratified by body weight (≤ 90 kg or > 90 kg) and prior biologic therapy (yes or no), for each tildrakizumab dose compared with placebo. Patients with missing data were analyzed as nonresponders in the base-case analysis. Sensitivity analyses were conducted using last observation carried forward and multiple imputation methods to address missing PASI or PGA score data. The primary analysis was based on the full analysis set (FAS), with supporting analyses based on the

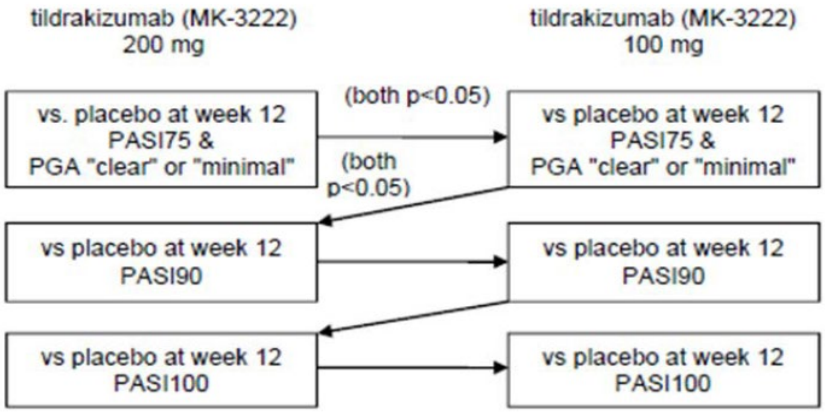
intention-to-treat population or per-protocol population. In part 1, key secondary dichotomous outcomes were analyzed using the same Cochran-Mantel-Haenszel model and nonresponder imputation methods, whereas other secondary or exploratory outcomes were analyzed based on observed case data with no imputation for missing data. The changes from baseline to week 12 in the DLQI score were analyzed using a constrained longitudinal data analysis method adjusted for body weight (≤ 90 kg, > 90 kg), prior biologic exposure (yes or no) and the interaction of treatment by time. Other secondary or exploratory outcomes from parts 2 and 3 of the trials were reported descriptively for the FAS with no imputation for missing data (i.e., observed case).

Study P010 was estimated to have 99% power to detect a 57% difference between tildrakizumab and placebo for the PASI 75 response and a 55% difference in the PGA response based on a planned sample size of 750 patients randomized 2:2:1. Study P011 had 99% power to detect a 57% difference between tildrakizumab and placebo in PASI 75 response and a 55% difference in PGA response based on a planned sample size of 1,050 patients. These calculations assumed that 10% of placebo patients would achieve a PASI 75 response and a PGA response in both trials. In addition, the study had 98% power to detect a 17% difference between tildrakizumab and etanercept for the PASI 75 response, assuming a response rate of 56% in patients on etanercept, and a 20% difference in the PGA response rate, assuming 49% of patients on etanercept would meet the criteria for PGA response. Tests were 2-sided with a significance level of alpha 0.05. No references were provided to support the assumed tildrakizumab and placebo response values used in the power calculations.

Several subgroup analyses were planned a priori in both studies, including those subgroups based on body weight and prior exposure to biologic therapy for psoriasis (which were stratification factors at randomization), subgroups based on the failure of at least 1 traditional systemic therapy, and subgroups based on age, gender, race, region, TNF antagonist response, and psoriatic arthritis. There was no control for multiplicity among the subgroups reported, and it is unclear if the balance in baseline characteristics between groups was evaluated for the subgroups reported.

Familywise type I error was controlled for in both trials using a gate-keeping sequential procedure, as shown in Figure 4 and Figure 5. Both the PASI 75 and PGA response analyses had to be statistically significant ($P < 0.05$) in order for the testing to continue, as shown in the figures.

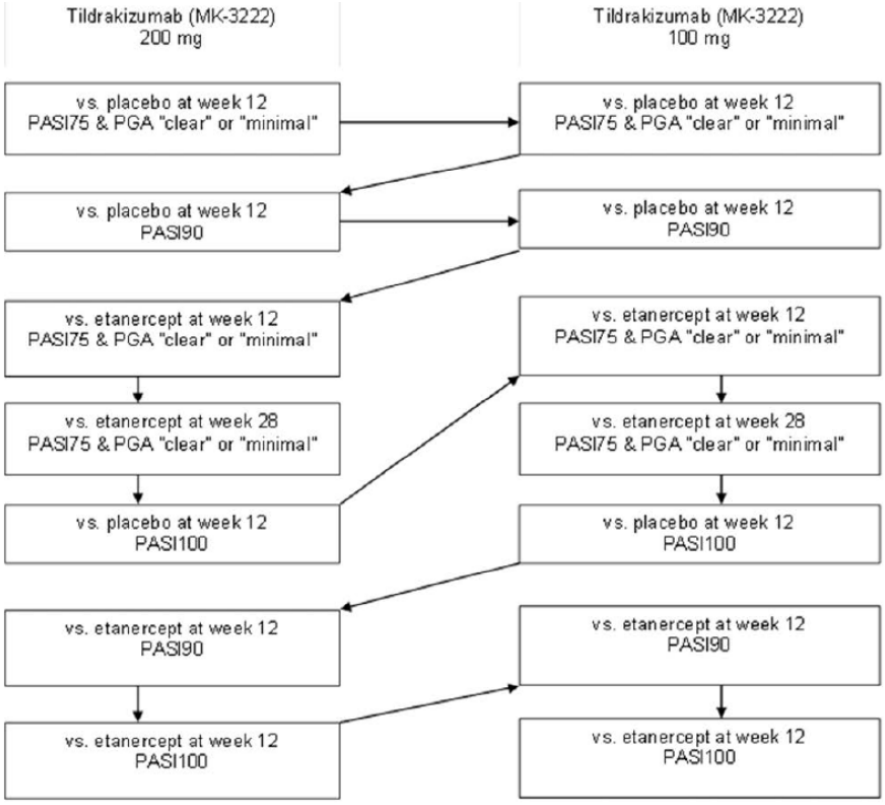
Figure 4: Multiplicity Strategy for Study P010 (reSURFACE 1)



MK-3222 = tildrakizumab; PASI 75, 90, 100 = at least a 75%, 90%, or 100% reduction in the Psoriasis Area and Severity Index score; PGA = Physician's Global Assessment; vs = versus.

Source: Clinical Study Report for Study P010.[6]

Figure 5: Multiplicity Strategy for Study P011 (reSURFACE 2)



MK-3222 = tildrakizumab; PASI 75, 90, 100 = at least a 75%, 90%, or 100% reduction in the Psoriasis Area and Severity Index score; PGA = Physician's Global Assessment; vs = versus.

Source: Clinical Study Report for Study P011.[7]

Analysis Populations

In both studies, efficacy analyses were conducted based on the FAS in studies P010 and P011, which were defined separately for parts 1, 2, and 3. The FAS for each study part was defined as all randomized patients who received at least 1 dose of the study medication in part 1, 2, or 3, based on the assigned treatment for that part of the study.

The intention-to-treat population included all randomized patients according to the assigned treatment. The per-protocol population included all patients in the FAS who met key eligibility and evaluability criteria. The safety population included all randomized patients who received at least 1 dose of the study drug, based on the treatment received, and was defined separately for part 1, part 2, and part 3.

Results

Patient Disposition

Overall, 772 (79%) of 977 patients and 1,090 (79%) of 1,372 patients who were screened for entry into studies P010 and P011 were randomized. The main reason for screening failure was the patient did not meet the study's inclusion criteria, or they met the exclusion criteria.

In Study P010, of the 772 patients who were randomized in part 1, 743 (96%) entered part 2, and 676 (88%) entered part 3. At 12 weeks (end of part 1), 6%, 3%, and 3% discontinued in the placebo, tildrakizumab 100 mg, and tildrakizumab 200 mg groups, respectively (Table 8) and, over the base study (up to 64 weeks), 20%, 19%, and 14% of patients, respectively, were discontinued (Table 9). The most frequently reported reasons for withdrawal in the placebo and tildrakizumab 100 mg groups were withdrawal by patient and lack of efficacy and, in the tildrakizumab 200 mg group, the most common reasons were withdrawal by patient and adverse events.

Of the 1,090 patients randomized in Study P011, 1,025 (94%) entered part 2, and 794 (73%) entered part 3. At 12 weeks, the frequency of discontinuation was 9% for placebo, 4% and 5% for the tildrakizumab groups, and 8% for etanercept (Table 8). According to the protocol, at week 28, responders in the etanercept group, as well as nonresponders in the tildrakizumab groups, were discontinued from the trial. As a result, the overall frequency of withdrawals was higher for the etanercept group than for other groups. Over the base study (up to 52 weeks), 16%, 22%, 14%, and 64% of patients discontinued in the placebo, tildrakizumab 100 mg, tildrakizumab 200 mg, and etanercept groups, respectively (Table 9). The reasons for discontinuation were generally similar between groups except for "other protocol-specified criteria," which was reported more frequently in the tildrakizumab and etanercept groups than in the placebo group.

Table 8: Patient Disposition for Part 1

Patient disposition	P010 (reSURFACE 1)			P011 (reSURFACE 2)			
	PBO	TILD 100 mg	TILD 200 mg	PBO	TILD 100 mg	TILD 200 mg	ETAN 50 mg
Screened, N	977			1,372			
Randomized, N (%)	772 (79)[a]			1,090 (79)[b]			
	155[a]	309	308	156	307	314	313
Part 1							
Discontinued, N (%)	9 (6)	9 (3)	10 (3)	14 (9)	12 (4)	14 (5)	24 (8)
Reason for study drug discontinuation, N (%)							
Adverse events	0	0	5 (2)	2 (1)	1 (< 1)	2 (1)	5 (2)
Lack of efficacy	2 (1)	1 (< 1)	0	2 (1)	0	1 (< 1)	0
Lost to follow-up	1 (1)	2 (1)	1 (< 1)	3 (2)	2 (1)	1 (< 1)	3 (1)
Non-compliance with study drug	0	0	0	0	0	1 (< 1)	0
Physician decision	1 (1)	3 (1)	0	0	0	0	4 (1)
Pregnancy	0	0	1 (< 1)	0	1 (< 1)	0	1 (< 1)
Progressive disease	1 (1)	0	0	0	0	0	1 (< 1)
Protocol violation	1 (1)	0	1 (< 1)	1 (1)	1 (< 1)	2 (1)	0
Withdrawal by patient	3 (2)	3 (1)	2 (1)	5 (3)	7 (2)	5 (2)	6 (2)
Other protocol-specified criteria	0	0	0	1 (1)	0	2 (1)	4 (1)
FAS, N	154	309	308	156	307	314	313
Safety, N	154	309	308	156	307	314	313

ETAN = etanercept; FAS = full analysis set; TILD = tildrakizumab.

[a] Total randomized excludes 1 patient who was assigned to the placebo group but withdrew before receiving treatment. The most common reasons for screen failure were did not meet inclusion criteria or had exclusion criteria (n = 189), withdrawal by patient (n = 8), and lost to follow-up (n = 7).

[b] The most common reasons for screen failure were did not meet inclusion criteria or met exclusion criteria (n = 234), withdrawal by patient (n = 33), and lost to follow-up (n = 14).

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Table 9: Patient Disposition for Part 1, 2, and 3

Patient disposition	P010 (reSURFACE 1)			P011 (reSURFACE 2)			
	PBO	TILD 100 mg	TILD 200 mg	PBO	TILD 100 mg	TILD 200 mg	ETAN 50 mg
Part 1, 2, and 3							
Discontinued, N (%)	31 (20)	59 (19)	44 (14)	25 (16)	66 (22)	44 (14)	199 (64)
Reason for study drug discontinuation, N (%)							
Adverse events	1 (1)	3 (1)	10 (3)	3 (2)	6 (2)	5 (2)	10 (3)
Death	0	0	1 (< 1)	0	3 (1)	0	0
Lack of efficacy	8 (5)	12 (4)	4 (1)	4 (3)	2 (1)	1 (< 1)	6 (2)
Lost to follow-up	4 (3)	9 (3)	4 (1)	5 (3)	7 (2)	4 (1)	5 (2)
Non-compliance with study drug	0	2 (1)	1 (< 1)	0	0	1 (< 1)	1 (< 1)
Physician decision	2 (1)	6 (2)	1 (< 1)	0	0	1 (< 1)	4 (1)
Pregnancy	1 (1)	0	1 (< 1)	0	2 (1)	0	2 (1)

Patient disposition	P010 (reSURFACE 1)			P011 (reSURFACE 2)			
	PBO	TILD 100 mg	TILD 200 mg	PBO	TILD 100 mg	TILD 200 mg	ETAN 50 mg
Progressive disease	1 (1)	1 (< 1)	0	0	0	0	1 (< 1)
Protocol violation	1 (1)	1 (< 1)	4 (1)	1 (1)	1 (< 1)	2 (1)	0
Withdrawal by patient	10 (7)	14 (5)	11 (4)	9 (6)	12 (4)	13 (4)	10 (3)
Other protocol-specified criteria	3 (2)	11 (4)	7 (2)	3 (2)	33 (11)	17 (5)	160 (51)

ETAN = etanercept; FAS = full analysis set; PBO = placebo; TILD = tildrakizumab.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Exposure to Study Treatments

In Study P010, the mean duration of exposure to placebo, tildrakizumab 100 mg, and tildrakizumab 200 mg was 23.0 weeks, 52.9 weeks, and 54.4 weeks, respectively. In Study P011, the mean duration of exposure to tildrakizumab 100 mg and tildrakizumab 200 mg was 48.6 weeks and 41.3 weeks, respectively. The mean duration of exposure was 11.6 weeks for placebo, 11.4 weeks for etanercept 50 mg twice daily (part 1), and 15.4 weeks for etanercept 100 mg (part 2). The mean durations reported include exposure to treatments in all 3 parts of the studies and reflect transient crossover to different therapies (see Table 6 for details of treatment switches).

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported subsequently. See Appendix 3 for detailed efficacy data. Although data from both tildrakizumab dosage groups have been included in this report, the text of the report focuses on the results for the 100 mg dose, as this is the recommended dose according to the draft product monograph that was available at the time.

Dermatology Life Quality Index

Part 1 (Week 0 to Week 12)

The HRQoL measures in studies P010 and P011 were designated as secondary or exploratory outcomes that were outside the statistical testing procedures and therefore were not controlled for multiplicity. DLQI data were missing for 3% to 4% of patients in the placebo group, 2% to 5% in the tildrakizumab group, and 3% in the etanercept group.

The proportion of patients who achieved a DLQI score of 0 or 1 at 12 weeks was higher among those who received tildrakizumab (40% to 47%) and etanercept (36%) than those who received placebo (5% to 8%) (Appendix 3, Table 33). The absolute difference in percentage for the tildrakizumab 100 mg group versus placebo was 36.1% in P010 (95% CI, 29.3% to 42.5%; P < 0.001) and 32.1% in P011 (95% CI, 24.5% to 39.1%; P < 0.001). Similar differences were observed between tildrakizumab 200 mg and placebo. In Study P011, the absolute difference for tildrakizumab 100 mg versus etanercept was 4.8% (95% CI, −2.9% to 12.5%; P = 0.221).

The difference in LS means for the change from baseline in DLQI scores favoured the tildrakizumab 100 mg and tildrakizumab 200 mg dosage groups versus placebo (Table 10). The LS mean difference reported for tildrakizumab 100 mg versus placebo was −7.4 in P010 (95% CI, −8.3 to −6.5; P < 0.001) and −8.2 in P011 (95% CI, −9.3 to −7.2; P < 0.001). The LS mean difference between tildrakizumab 100 mg and etanercept was −1.3 (95% CI,

−2.1 to −0.5; P = 0.002). The 12-week findings for the 200 mg tildrakizumab dosage group were similar. The between-group differences observed exceeded the minimal important differences reported in the literature (2.2 to 6.9) for the comparison between tildrakizumab and placebo, but not compared with etanercept.

Table 10: Change From Baseline in DLQI Score (Part 1 FAS)

Treatment group	Total N	Baseline	Week 12		Treatment group difference		
		Mean (SD)	Mean (SD)	Mean change from baseline (SD)	N	Difference in LS means (95% CI) versus placebo, P value[a]	Difference in LS means (95% CI) versus ETAN, P value[a]
P010 (reSURFACE 1)							
Placebo	155	13.2 (7.25)	11.1 (7.89)	−2.1 (6.52)	154	Reference	
Tildrakizumab 100 mg	309	13.9 (6.68)	3.9 (4.55)	−10.0 (6.66)	309	−7.4 (−8.3 to −6.5), P < 0.001[b]	NA
Tildrakizumab 200 mg	308	13.2 (6.87)	3.4 (3.94)	−9.8 (6.63)	308	−7.7 (−8.6 to −6.8), P < 0.001[b]	NA
P011 (reSURFACE 2)							
Placebo	156	13.7 (6.98)	12.0 (7.41)	−1.6 (5.97)	NR	Reference	NR
Tildrakizumab 100 mg	307	14.8 (7.24)	4.2 (5.00)	−10.6 (7.00)	NR	−8.2 (−9.3 to −7.2), P < 0.001[b]	−1.3 (−2.1 to −0.5), P = 0.002[b]
Tildrakizumab 200 mg	312	13.2 (7.03)	3.5 (4.98)	−9.7 (6.81)	NR	−8.3 (−9.3 to −7.3), P < 0.001[b]	−1.4 (−2.2 to −0.6), P = 0.001[b]
Etanercept 50 mg	312	14.5 (7.20)	5.4 (6.32)	−9.1 (7.38)	NR	NR	Reference

CI = confidence interval; DLQI = Dermatology Life Quality Index; ETAN = etanercept; FAS = full analysis set; LS = least squares; NA = not applicable; NR = not reported; SD = standard deviation.

[a] Based on a constrained longitudinal data analysis model that included terms for time, time by treatment interaction, body weight (≤ 90 kg, > 90 kg) and prior exposure to biologic therapy for psoriasis (yes or no).

[b] Outside the statistical testing hierarchy.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Part 2 (Week 12 to Week 28)

At week 12, 74 and 72 patients in Study P010 and 70 and 72 patients in Study P011 who were initially randomized to placebo were re-randomized and assigned to tildrakizumab 100 mg and tildrakizumab 200 mg, respectively. Patients initially randomized to tildrakizumab continued on the same dosage during part 2, and those in the etanercept group had their dose decreased to 50 mg once weekly. The proportion of patients with missing DLQI data at week 28 ranged from 0% to 7% per treatment group.

The proportion of patients with a DLQI score of 1 or less at week 28 ranged from 38% to 54% for patients who received tildrakizumab 100 mg, from 56% to 65% for those who received tildrakizumab 200 mg, and was 39% among those who received etanercept. The absolute difference between tildrakizumab 100 mg and etanercept was 15% (95% CI, 7% to

23%) and 26% between tildrakizumab 200 mg and etanercept (95% CI, 18% to 33%) (Table 34).

All tildrakizumab groups reported a reduction in DLQI scores at week 28, with mean changes from baseline ranging from −8.5 points (standard deviation [SD] = 6.5) to −11.7 points (SD = 7.2). The mean change from baseline in the etanercept group was −9.8 points (SD = 7.3). The LS mean difference reported was −1.7 points (95% CI, −2.4 to −1.0) for tildrakizumab 100 mg versus etanercept and −2.2 points (95% CI, −2.9 to −1.5) for tildrakizumab 200 mg versus etanercept, which did not exceed the minimal important differences reported in the literature (Table 11).

Part 3 (Week 28 to Week 52 or 64)

Among patients who achieved a PASI 75 response and who continued on tildrakizumab 100 mg in part 3 of Study P010, 59 of the 113 patients (52%) had a DLQI score of 1 or less at week 64. Ten of the 52 patients (19%) who were switched from tildrakizumab 100 mg to placebo (and did not relapse) also had a DLQI score of 1 or less at week 64. Among partial responders (i.e., a response from PASI 50 to < PASI 75 at week 28), 4 of the 16 (25%) patients who remained on tildrakizumab 100 mg and 6 of the 18 (33%) patients who were switched to the 200 mg dose had a DLQI score of 1 or less at week 64. Of the patients initially randomized to placebo who were switched to tildrakizumab 100 mg at week 12, 45 of the 65 (69%) patients reported a DLQI score of 1 or less at week 64.

At week 52 in Study P011, 69% (141 out of 205) of responders and 42% (8 out of 19) of partial responders who continued on tildrakizumab 100 mg reported a DLQI score of 1 or less. Two of the 19 partial responders (11%) who were switched from tildrakizumab 100 mg to 200 mg at week 28 reported a DLQI score of 1 or less at week 52. Among the patients initially randomized to placebo who were switched to tildrakizumab 100 mg at week 12, 58% (37 out of 64) achieved a DLQI score of 1 or less at week 52. Of the nonresponders and partial responders switched from etanercept to tildrakizumab 200 mg, 56 of the 116 (48%) patients reported a DLQI score of 1 or less at week 52.

Other HRQoL Measures

Data for the EQ-5D-3L index score and SF-36 mental and physical health component scores were reported as exploratory outcomes in Study P010 and have been summarized in Table 35 and Table 36. No between-group comparisons were reported, and data were missing for 3% to 7% of patients per group.

At baseline, the mean EQ-5D-3L index score was 0.7 points (SD = 0.23) for placebo and 0.7 points (SD = 0.25) in the tildrakizumab 100 mg group. At week 12, the placebo group reported a mean change from baseline of 0 points (SD = 0.26) and the tildrakizumab 100 mg group reported a mean change of 0.2 points (SD = 0.27). The mean change from baseline was the same at 28 weeks (0.2 points; SD, 0.22 to 0.30) for all patients who received tildrakizumab.

At baseline, the SF-36 mental health component scores were similar across groups and ranged from 45.3 (SD = 11.4) to 46.8 (SD = 11.2). The placebo group reported a mean change from baseline to week 12 of −0.7 points (SD = 7.5) compared with a 3.9-point change (SD = 9.4) for the tildrakizumab 100 mg group. At week 28, all patients were receiving either tildrakizumab 100 mg or 200 mg, and the mean change from baseline ranged from 3.7 points (SD = 9.0) to 6.7 (SD = 10.0) points. Mean baseline physical health component scores ranged from 46.8 (SD = 9.5) to 47.7 (SD = 9.3), with a 12-week mean

change from baseline of 1.0 points (SD = 6.7) for placebo and 3.7 points (SD = 7.7) for tildrakizumab 100 mg. The week 28 change from baseline data ranged from 2.3 points (SD = 8.5) to 4.2 (SD = 7.9).

Disease Severity Score

Part 1 (Week 0 to Week 12)

PGA and PASI 75 data at week 12 were missing for 3% to 6% of patients in the tildrakizumab groups and 6% to 10% of patients in the placebo groups of studies P010 and P011.[40] The extent of missing data in the etanercept group was not reported.

Physician's Global Assessment

In both studies, PGA response was defined as a PGA score of "clear" or "minimal," with at least a 2-grade reduction from baseline, which is generally accepted as a clinically meaningful score. In both trials, a higher proportion of patients achieved a PGA response at week 12 in the tildrakizumab 100 mg groups compared with the placebo groups. The difference in the proportions reported was 51% in Study P010 (95% CI, 44% to 57%; P < 0.001) , and 50% in Study P011 (95% CI, 43% to 57%; P < 0.001). Similar results were reported for the tildrakizumab 200 mg groups (Table 11). Although the differences between tildrakizumab 200 mg and etanercept achieved statistical significance (absolute difference = 12%; 95% CI, 4% to 19%; P = 0.003), no statistically significant difference was detected between tildrakizumab 100 mg and etanercept (absolute difference = 7%; 95% CI, −0.5% to 15%; P = 0.066), which, according to the statistical testing procedure, meant that statistical testing of subsequent outcomes was stopped.

Table 11: PGA Response at Week 12 (FAS)

Treatment group	Total N	PGA response at week 12				
		n (%)	Difference in % versus placebo (95% CI)[a]	P value versus placebo[a]	Difference in % versus etanercept (95% CI)[a]	P value versus etanercept[a]
P010 (reSURFACE 1)						
Placebo	154	11 (7.1)	Reference		NA	
Tildrakizumab 100 mg	309	179 (57.9)	50.9 (43.6 to 57.4)	< 0.001		
Tildrakizumab 200 mg	308	182 (59.1)	52.1 (44.8 to 58.5)	< 0.001		
P011 (reSURFACE 2)						
Placebo	156	7 (4.5)	Reference		NR	
Tildrakizumab 100 mg	307	168 (54.7)	50.2 (43.2 to 56.5)	< 0.001	7.3 (−0.5 to 15.0)	0.066[b]
Tildrakizumab 200 mg	314	186 (59.2)	54.7 (47.9 to 60.8)	< 0.001	11.7 (4.0 to 19.3)	0.003
Etanercept	313	149 (47.6)	NR		Reference	

CI = confidence interval; FAS = full analysis set; NA = not applicable; NR = not reported; PGA = Physician's Global Assessment.

[a] P value based on Cochran-Mantel-Haenszel test stratified by body weight (≤ 90 kg, > 90 kg) and prior exposure to biologic therapy (yes or no). Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight and prior biologic exposure with sample size weights. Patients with missing data were classified as nonresponders.

[b] The difference between groups was not statistically significant; thus, according to the statistical testing procedure, all subsequent outcomes within the hierarchy were considered non-significant.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Psoriasis Area and Severity Index

In studies P010 and P011, 6% of patients in the placebo group, 61% to 66% in the tildrakizumab groups, and 48% in the etanercept group achieved a PASI 75 response at week 12. The difference in the percentage of responders for tildrakizumab 100 mg versus placebo were 58% (95% CI, 51% to 64%) and 56% (95% CI, 48% to 62%) in studies P010 and P011, respectively (both P < 0.001). The results observed were similar for the comparison between tildrakizumab 200 mg and placebo (Table 12). The difference between tildrakizumab 100 mg and etanercept for PASI 75 at week 12 (absolute difference = 13%; 95% CI, 5% to 21%) was not statistically significant due to the failure of a prior outcome in the statistical hierarchical testing procedure.

Tildrakizumab 100 mg was associated with statistically significant differences versus placebo in the proportion of patients who achieved a PASI 90 response in Study P010 (absolute difference = 32%; 95% CI, 26% to 38%; P < 0.001) and Study P011 (absolute difference = 38%; 95% CI, 31% to 43%; P < 0.001) (Table 13). More patients in the tildrakizumab 100 mg group achieved a PASI 100 response at week 12 than in the placebo group, with an absolute difference of 13% (95% CI, 8% to 17%; P < 0.001) in Study P010 and 12% (95% CI, 9% to 17%) in P011; however, the differences between tildrakizumab 100 mg versus placebo in P011 were not statistically significant, as the testing procedures were stopped due to the failure of a prior outcome (Table 14). The differences between tildrakizumab 100 mg and etanercept for a PASI 90 and PASI 100 response were deemed not statistically significant due to the failure of a prior outcome in the statistical hierarchical testing procedure. The PASI 90 and PASI 100 results for tildrakizumab 200 mg versus placebo or etanercept were similar to the 100 mg tildrakizumab dosage group and are shown in Table 13 and Table 14.

Subgroup and Sensitivity Analyses for Co-Primary Outcomes

Study P010 and P011 results for PASI 75, PASI 90, PASI 100, and PGA response were similar in the primary analyses and in sensitivity analyses (based on the intention-to-treat or per-protocol populations, and for the FAS population with last observation carried forward or multiple imputation methods for missing data).

Subgroup data for PGA and PASI 75 responses are shown in Appendix 3 (Table 37, Table 38, and Table 39). The treatment effects for the tildrakizumab groups versus placebo or etanercept were generally similar among the subgroups of patients who had or had not received prior biologic therapy for psoriasis or did not respond to at least 1 traditional systemic therapy. Treatment-by-subgroup interaction P values were not reported in either study.

Table 12: PASI 75 Response at Week 12 (FAS)

Treatment group	Total N	PASI 75 response at week 12				
		n (%)	Difference in % versus placebo (95% CI)[a]	P value versus placebo[a]	Difference in % versus etanercept (95% CI)[a]	P value versus etanercept[a]
P010 (reSURFACE 1)						
Placebo	154	9 (5.8)	Reference		NA	
Tildrakizumab 100 mg	309	197 (63.8)	58.0 (51.0 to 64.1)	< 0.001		
Tildrakizumab 200 mg	308	192 (62.3)	56.6 (49.6 to 62.8)	< 0.001		
P011 (reSURFACE 2)						
Placebo	156	9 (5.8)	Reference		NR	
Tildrakizumab 100 mg	307	188 (61.2)	55.5 (48.3 to 61.8)	< 0.001	13.1 (5.3 to 20.7)	NS[b]
Tildrakizumab 200 mg	314	206 (65.6)	59.8 (52.9 to 65.9)	< 0.001	17.4 (9.7 to 24.9)	< 0.001
Etanercept	313	151 (48.2)	NR		Reference	

CI = confidence interval; FAS = full analysis set; NA = not applicable; NR = not reported; NS = not statistically significant; PASI 75 = at least a 75% improvement in Psoriasis Area and Severity Index score; PGA = Physician's Global Assessment.

[a] P value based on Cochran-Mantel-Haenszel test stratified by body weight (≤ 90 kg, > 90 kg) and prior exposure to biologic therapy (yes or no). Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight and prior biologic exposure with sample size weights. Patients with missing data were classified as nonresponders.

[b] Not statistically significant according to the statistical testing procedure because the difference between tildrakizumab 100 mg and etanercept for PGA response at week 12 did not achieve statistical significance.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Table 13: PASI 90 Response at Week 12 (FAS)

Treatment group	Total N	PASI 90 response at week 12				
		n (%)	Difference in % versus placebo (95% CI)[a]	P value versus placebo[a]	Difference in % versus etanercept (95% CI)[a]	P value versus etanercept[a]
P010 (reSURFACE 1)						
Placebo	154	4 (2.6)	Reference		NA	NA
Tildrakizumab 100 mg	309	107 (34.6)	32.1 (25.9 to 38.0)	< 0.001		
Tildrakizumab 200 mg	308	109 (35.4)	32.9 (26.8 to 38.8)	< 0.001		
P011 (reSURFACE 2)						
Placebo	156	2 (1.3)	Reference		NR	
Tildrakizumab 100 mg	307	119 (38.8)	37.5 (31.1 to 43.4)	< 0.001	17.4 (10.3 to 24.4)	NS[b]
Tildrakizumab 200 mg	314	115 (36.6)	35.3 (29.2 to 41.1)	< 0.001	15.2 (8.3 to 22.1)	NS[b]
Etanercept	313	67 (21.4)	NR	NR	Reference	

CI = confidence interval; FAS = full analysis set; NA = not applicable; NR = not reported; NS = not statistically significant; PASI 90 = at least a 90% improvement in Psoriasis Area and Severity Index score.

[a] P value based on Cochran-Mantel-Haenszel test stratified by body weight (≤ 90 kg, > 90 kg) and prior exposure to biologic therapy (yes or no). Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight and prior biologic exposure with sample size weights. Patients with missing data were classified as nonresponders.

[b] Not statistically significant. Statistical testing was stopped due to failure in a previous outcome in the statistical hierarchy.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Table 14: PASI 100 Response at Week 12 (FAS)

Treatment group	Total N	PASI 100 response at week 12				
		n (%)	Difference in % versus placebo (95% CI)[a]	P value versus placebo[a]	Difference in % versus etanercept (95% CI)[a]	P value versus etanercept[a]
P010 (reSURFACE 1)						
Placebo	154	2 (1.3)	Reference		NA	NA
Tildrakizumab 100 mg	309	43 (13.9)	12.7 (8.0 to 17.3)	< 0.001		
Tildrakizumab 200 mg	308	43 (14.0)	12.7 (8.3 to 17.2)	< 0.001		
P011 (reSURFACE 2)						
Placebo	156	0	Reference		NR	
Tildrakizumab 100 mg	307	38 (12.4)	12.4 (8.5 to 16.6)	NS[b]	7.6 (3.3 to 12.3)	NS[b]
Tildrakizumab 200 mg	314	37 (11.8)	11.7 (7.8 to 16.0)	< 0.001	7.0 (2.8 to 11.6)	NS[b]
Etanercept	313	15 (4.8)	NR	NR	Reference	

CI = confidence interval; FAS = full analysis set; NA = not applicable; NR = not reported; NS = not statistically significant; PASI 100 = 100% improvement in Psoriasis Area and Severity Index score.

[a] P value based on Cochran-Mantel-Haenszel test stratified by body weight (≤ 90 kg, > 90 kg) and prior exposure to biologic therapy (yes or no). Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight and prior biologic exposure with sample size weights. Patients with missing data were classified as nonresponders.

[b] Not statistically significant. Statistical testing was stopped due to failure in a previous outcome in the statistical hierarchy.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Part 2 (Week 12 to 28)

Overall, 96% of patients in P010 and 94% of patients initially randomized in Study P011 entered part 2. PGA or PASI response data were missing for 1% to 10% of patients at week 28.

The proportion of patients with a PASI 75 response over time is shown in Figure 6 and Figure 7. Graphs for PGA response and PASI 90 and PASI 100 response in the pivotal trials are shown in Appendix 3 (figures 12 to 17) (observed case data). These graphs show that the proportion of patients receiving tildrakizumab who achieved a PASI 75 or PGA response were relatively stable from week 12 to 28, whereas the proportion of patients with a PASI 90 or PASI 100 response may increase over time.

Patients Initially Randomized to Placebo: In both trials, the results for part 2 were reported descriptively based on observed case data (no imputation for missing data).

In Study P010, 74 and 72 patients initially randomized to placebo were re-randomized at week 12 and assigned to tildrakizumab 100 mg and 200 mg, respectively. At week 28, 77% (54 out of 70) of patients in the tildrakizumab 100 mg group and 86% of patients (56 out of 65) in the tildrakizumab 200 mg group had achieved a PASI 75 response. A PASI 90 response was reported in 41 and 34 patients (59% and 52%), and a PASI 100 response was reported in 22 and 17 patients (31% and 26%) in the tildrakizumab 100 mg and tildrakizumab 200 mg groups, respectively. At week 28, 53 out of 70 patients (76%) and 46 out of 65 patients (71%) achieved a PGA response in the tildrakizumab 100 mg and tildrakizumab 200 mg groups, respectively.

In Study P011, 142 patients in the placebo group were re-randomized at week 12 to tildrakizumab 100 mg (N = 70) and 200 mg (N = 72). At week 28, 58% (38 out of 66) of

patients who received tildrakizumab 100 mg and 74% (50 out of 68) who received tildrakizumab 200 mg were reported to have achieved a PASI 75 response. The number of patients with a PASI 90 response was 26 (39%) and 33 (49%), and a PASI 100 response was 9 (14%) and 13 (19%) at week 28 for the tildrakizumab 100 mg and tildrakizumab 200 mg groups, respectively. At week 28, 50% (33 out of 66) of patients in the placebo to tildrakizumab 100 mg group, and 68% (46 out of 68) of patients in the placebo to tildrakizumab 200 mg group achieved a PGA response.

Patients Initially Randomized to Active Treatment: In Study P011, the proportion of patients who achieved a PGA or PASI 75 response at week 28 were key secondary outcomes and were analyzed with missing data imputed as nonresponders. The absolute difference between tildrakizumab 100 mg and etanercept for a PGA response was 20% (95% CI, 12% to 27%) at week 28 and 20% (95% CI, 12% to 28%) for PASI 75 response. These differences were not statistically significant due to the failure of a prior outcome in the gate-keeping sequential testing procedure. At week 28, the proportion of patients responding was statistically significantly higher for tildrakizumab 200 mg versus etanercept for both PGA response (absolute difference = 24%; 95% CI, 16% to 32%) and PASI 75 response (absolute difference = 19%; 95% CI, 12% to 27%) (Table 15).

The proportions of patients with a PASI 90 or PASI 100 response at week 28 were reported based on the patients in the FAS for part 2 that had available data (i.e., no imputation for missing data). These outcomes were outside the statistical testing procedure. In the tildrakizumab 100 mg and tildrakizumab 200 mg groups, 56% and 58% achieved a PASI 90 response, and 23% and 27% achieved a PASI 100 response at week 28 compared with 31% (PASI 90) and 11% (PASI 100) in the etanercept group (Table 15). For tildrakizumab 100 mg versus etanercept at week 28, the difference in percentage for a PASI 90 response was 25% (95% CI, 17% to 33%), and 12% (95% CI, 6% to 18%) for a PASI 100 response (results were similar for tildrakizumab 200 mg versus etanercept).

Among patients who received tildrakizumab in Study P010, the percentage of patients who reported a response at week 28 ranged from 66% to 69% for a PGA response, 80% to 82% for a PASI 75 response, 52% to 59% for a PASI 90 response, and 24% to 32% for a PASI 100 response. These values were generally similar to the percentages reported in Study P011 (Table 15). Results were reported descriptively, with no imputation for missing data; no statistical testing was performed.

Table 15: PGA and PASI Response at Week 28 (Part 2) in Patients Randomized to Active Treatment Groups in Part 1 (FAS)

Outcome	P010 (reSURFACE 1)		P011 (reSURFACE 2)[a]		
	TILD 100 mg N = 299	TILD 200 mg N = 298	TILD 100 mg N = 294	TILD 200 mg N = 299	ETAN 50 mg N = 289
PGA response at week 28					
n (%)	188/285 (66.0)	199/288 (69.1)	190 (64.6)	207 (69.2)	131 (45.3)
Difference in % (95% CI) versus etanercept[b,c]	NA	NA	19.6 (11.7 to 27.3)	24.1 (16.2 to 31.7)	Reference
P value[b]			NS[d]	< 0.001	
PASI 75 response at week 28					
n (%)	229/285 (80.4)	236/288 (81.9)	216 (73.5)	217 (72.6)	155 (53.6)
Difference in % (95% CI) versus etanercept[b,c]	NA	NA	20.1 (12.4 to 27.6)	19.2 (11.5 to 26.7)	Reference
P value[b]			NS[d]	< 0.001	
PASI 90 response at week 28					
n (%)	147/285 (51.6)	170/288 (59.0)	161/290 (55.5)	169/293 (57.7)	85/277 (30.7)
Difference in % (95% CI) versus etanercept[b]	NA	NA	24.9 (17.0 to 32.6)	27.1 (19.1 to 34.7)	Reference
P value[b]			< 0.001[e]	< 0.001[e]	
PASI 100 response at week 28					
n (%)	67/285 (23.5)	91/288 (31.6)	66/290 (22.8)	79/293 (27.0)	31/277 (11.2)
Difference in % (95% CI) versus etanercept[b]	NA	NA	11.7 (5.6 to 17.9)	15.7 (9.4 to 22.1)	Reference
P value[b]			< 0.001[e]	< 0.001[e]	

CI = confidence interval; ETAN = etanercept; FAS = full analysis set; NA = not applicable; NS = not statistically significant; PASI 75, 90, 100 = at least a 75%, 90%, or 100% improvement in Psoriasis Area and Severity Index score; PGA = Physician's Global Assessment; TILD = tildrakizumab.

[a] Based on the FAS for part 2 that included 96%, 95%, and 92% of patients originally randomized to tildrakizumab 100 mg or 200 mg or etanercept in Study P011.

[b] P value based on Cochran-Mantel-Haenszel test stratified by body weight (≤ 90 kg, > 90 kg) and prior exposure to biologic therapy (yes or no). Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight and prior biologic exposure with sample size weights.

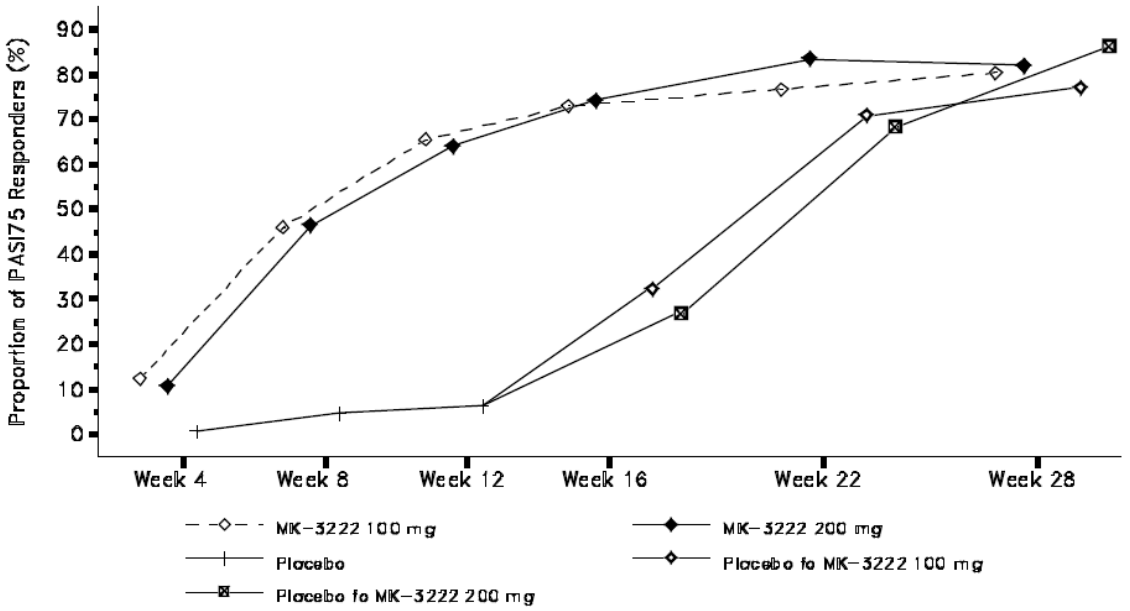
[c] Patients with missing data were classified as nonresponders.

[d] Not statistically significant. Statistical testing was stopped due to failure in a previous outcome in the statistical hierarchy.

[e] Outside the statistical testing procedure.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

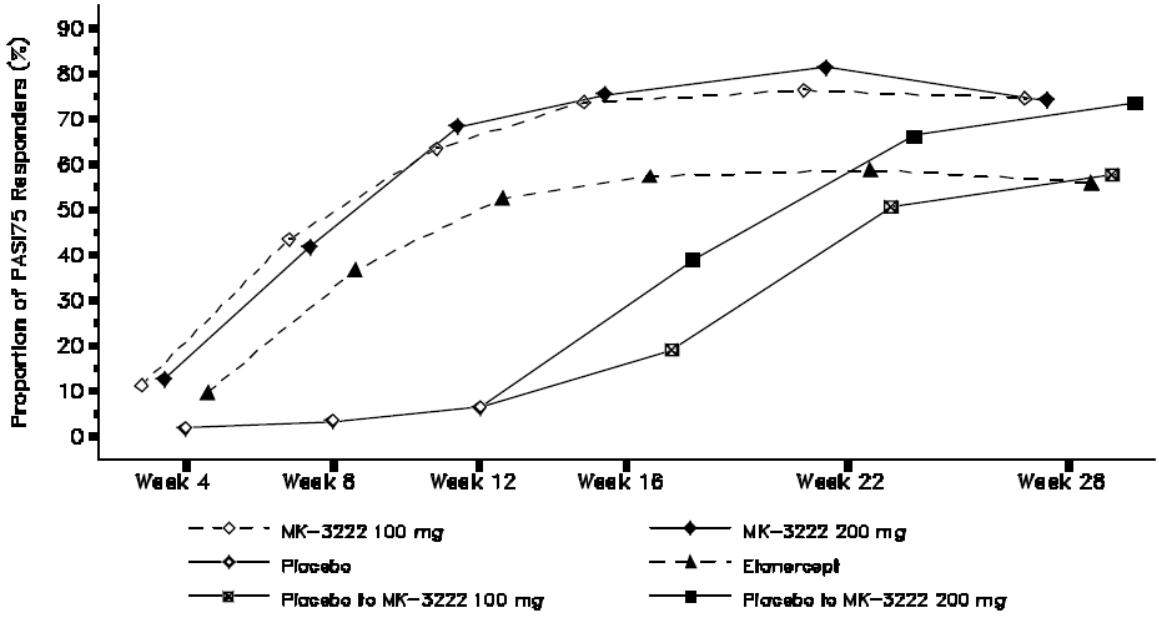
Figure 6: Proportion of Patients with PASI 75 Response up to 28 Weeks — Study P010 (OC)



MK-3222 = tildrakizumab; OC = observed case; PASI 75 = at least a 75% improvement in Psoriasis Area and Severity Index score.

Source: Clinical Study Report for Study P010.[6]

Figure 7: Proportion of Patients With PASI 75 Response Up to 28 Weeks — Study P011 (OC)



MK-3222 = tildrakizumab; OC = observed case; PASI 75 = at least a 75% improvement in the Psoriasis Area and Severity Index score.

Source: Clinical Study Report for Study P011.[7]

Part 3 (Week 28 to Week 52 or 64)

In both trials, data on the proportion of patients with a PASI response over time were reported descriptively, based on patients who received at least 1 dose of the study drug in part 3 and had outcome measurements at baseline and the end point. There was no imputation for missing data. All of the 676 patients who completed part 2 of Study P010 entered part 3, which was 88% of the 772 patients who were initially randomized. For Study P011, 995 patients completed part 2 and 794 patients entered part 3 (78% of the randomized population). End-of-study PASI 75 data were missing for 5% to 16% of patients in Study P010 and 2% to 14% of patients in Study P011.

In part 3 of Study P010, patients in the tildrakizumab groups who had a PASI 75 response at week 28 were re-randomized to either placebo or continued the same tildrakizumab dose every 12 weeks. At week 64, 88% to 94% of patients who remained on tildrakizumab had a PASI 75 response compared with 49% to 57% of the patients who were switched to placebo who did not relapse (Table 16). Among those who relapsed while on placebo, 83% to 86% of those reinitiated on tildrakizumab responded and reported a PASI 75 response at week 64.

In Study P011, patients initially randomized to tildrakizumab 200 mg who were responders at week 28 were re-randomized to tildrakizumab 100 mg or 200 mg. Patients who were initially randomized to tildrakizumab 100 mg and who were responders at week 28 continued on the same dose. At week 52, 94% to 97% of patients remained PASI 75 responders (Table 16).

In both studies, partial responders in the tildrakizumab 200 mg group continued on the same dose, whereas partial responders in the tildrakizumab 100 mg group were re-randomized to tildrakizumab 100 mg or 200 mg every 12 weeks. The proportion of patients with a PASI 75 response at the end of part 3 ranged from 40% to 75% in Study P010 and from 68% to 79% in Study P011 (Table 17). Among those initially randomized to placebo, responders and partial responders at week 28 continued the tildrakizumab dose they were assigned at week 12. Among those patients, 85% to 95% reported a PASI 75 response at the end of the study (Table 18). Of the patients initially randomized to etanercept in Study P011, nonresponders or partial responders at week 28 were switched to tildrakizumab 200 mg, and 81% achieved a PASI 75 response at week 52 (Table 18).

Data for PASI 90 and PASI 100 responders, partial responders, and those initially randomized to placebo or etanercept are reported in Table 16, Table 17, and Table 18.

Among responders in Study P010, a PGA response was reported for 62% to 76% who remained on tildrakizumab, and 32% to 42% who were switched to placebo. The percentage of partial responders who achieved a PGA response at week 64 ranged from 16% to 38%. For the patients who were switched from placebo to tildrakizumab at week 12, 75% to 81% had a PGA response at the end of the trial. In Study P011, 78% to 85% of responders and 42% to 58% of partial responders achieved a PGA response at week 52. Among those initially randomized to placebo and switched to tildrakizumab, 56% to 77% reported a PGA response, and for those who were switched from etanercept to tildrakizumab, 69% reported a PGA response at week 52.

Table 16: PASI 75, 90, and 100 Response in Part 3 Among Patients Who Were Responders at Week 28 (FAS)

Treatment	Total entered in part 3, N[a]	Total at end of study, N	PASI 75, n (%)[b]	PASI 90, n (%)	PASI 100, n (%)
P010 week 64[c]					
TILD 100 mg to placebo	112	51	25 (49)	11 (22)	2 (4)
TILD 100 mg to TILD 100 mg	114	112	98 (88)	65 (58)	36 (32)
Placebo relapse to TILD 100 mg[d]		35	30 (86)	17 (49)	8 (23)
TILD 200 mg to placebo	119	60	34 (57)	19 (32)	6 (10)
TILD 200 mg to TILD 200 mg	117	114	107 (94)	85 (75)	46 (40)
Placebo relapse to TILD 200 mg[d]		30	25 (83)	12 (40)	7 (23)
P011 week 52[e]					
TILD 100 mg to TILD 100 mg	212	204	191 (94)	160 (78)	72 (35)
TILD 200 mg to TILD 100 mg	110	104	98 (94)	71 (68)	39 (38)
TILD 200 mg to TILD 200 mg	108	105	102 (97)	86 (82)	49 (47)

FAS = full analysis set; PASI 75, 90, 100 = at least a 75%, 90%, or 100% improvement in Psoriasis Area and Severity Index score; TILD = tildrakizumab.

[a] Number of patients with data at week 32 or 36. The number of patients who entered part 3 and were assigned to each treatment group was not reported.

[b] Percentage calculated based on number of patients at end of study.

[c] Descriptive data with no imputation for missing data. Results presented for patients who received at least 1 dose of the study drug in part 3 and had baseline and week 64 PASI data. Denominator decreased over time as patients withdrew and those who relapsed crossed over to tildrakizumab.

[d] Includes patients who relapsed and then received at least 12 weeks of tildrakizumab therapy. Relapsed patients who did not received at least 12 weeks of active treatment were excluded.

[e] Descriptive data with no imputation for missing data. Results presented for patients who received at least 1 dose of the study drug in part 3 and had baseline and week 52 PASI data.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Table 17: PASI 75, 90, and 100 Response in Part 3 Among Patients Who Were Partial Responders at Week 28 (FAS)

Treatment	N[a]	PASI 75, n (%)	PASI 90, n (%)	PASI 100, n (%)
P010 week 64[b]				
TILD 100 mg to TILD 100 mg	16	12 (75)	2 (13)	1 (6)
TILD 100 mg to TILD 200 mg	18	9 (50)	2 (11)	1 (6)
TILD 200 mg to TILD 200 mg	38	15 (40)	2 (5)	0
P011 week 52[b]				
TILD 100 mg to TILD 100 mg	19	13 (68)	8 (42)	6 (32)
TILD 100 mg to TILD 200 mg	19	15 (79)	5 (26)	1 (5)
TILD 200 mg to TILD 200 mg	60	40 (67)	19 (31.7)	6 (10)

FAS = full analysis set; PASI 75, 90, 100 = at least a 75%, 90%, or 100% improvement in Psoriasis Area and Severity Index score; TILD = tildrakizumab.

[a] The number of patients who received at least 1 dose of the study drug in part 3 and who had data at baseline and at week 64 (P010) or week 52 (P011). The number of partial responders in each group who entered part 3 was 19, 19, and 44 for Study P010, and 21, 21, and 61 for Study P011.[53]

[b] Descriptive data with no imputation for missing data.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7] Additional data provided by sponsor.[53]

Table 18: PASI 75, 90, and 100 Response in Part 3 for Patients Randomized to Placebo or Etanercept in Part 1 (FAS)

Treatment	N[a]	PASI 75, n (%)	PASI 90, n (%)	PASI 100, n (%)
P010 week 64[b]				
Placebo to TILD 100 mg	65	55 (85)	42 (65)	28 (43)
Placebo to TILD 200 mg	59	56 (95)	43 (73)	20 (34)
P011 week 52[b]				
Placebo to TILD 100 mg	63	54 (86)	30 (48)	15 (24)
Placebo to TILD 200 mg	66	61 (92)	42 (64)	26 (39)
Etanercept to TILD 200 mg	113	92 (81)	47 (42)	18 (16)

FAS = full analysis set; PASI 75, 90, 100 = at least a 75%, 90%, or 100% improvement in Psoriasis Area and Severity Index score; TILD = tildrakizumab.

[a] Number of patients who received at least 1 dose of the study drug in part 3 and who had data at baseline and week 64 (P010) or week 52 (P011).

[b] Descriptive data with no imputation for missing data.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Psoriasis-Related Symptoms

Neither of the studies collected patient-reported data on symptoms related to psoriasis.

Productivity

Data from the WPLQ were collected and reported descriptively in Study P010 (Appendix 3, Table 40). The percentage of patients who were unable to work due to psoriasis or psoriatic arthritis ranged from 6% to 11% at baseline, 7% to 9% at week 12, and from 4% to 9% at week 28. On average, patients had missed 0.6 days (SD = 1.5 to 1.8) of work in the past 4 weeks due to psoriasis or psoriatic arthritis at baseline. At week 12, patients in the tildrakizumab 100 mg group had missed 0.2 days (SD = 0.8) compared with 0.7 days (SD = 3.0) in the placebo group. At week 28, the mean number of days of work missed due to psoriasis in the last 4 weeks ranged from 0.1 (SD = 0.3) to 0.2 (SD = 0.6) across the tildrakizumab groups.

Relapse

In Study P010, patients in the tildrakizumab groups who were PASI 75 responders at week 28 were re-randomized to placebo or continued with the prior tildrakizumab dose and were monitored for relapse (defined as a 50% reduction in maximum PASI response). During part 3, relapse was reported by 54% of the patients who were switched from tildrakizumab 100 mg to placebo, and by 44% of the patients who were switched from tildrakizumab 200 mg to placebo. Relapse was reported by 7% to 8% of responders who continued on tildrakizumab during part 3 (Table 19).

During part 3 of Study P010, no patients who were responders to tildrakizumab experienced a rebound of disease (defined as worsening of psoriasis over baseline [PASI > 125%], or new pustular, erythrodermic, or inflammatory psoriasis occurring within 2 months of stopping therapy) after switching from tildrakizumab to placebo at week 28.

Table 19: Relapse During Part 3 of Study P010

Detail	TILD 100 mg (part 2) to placebo (part 3)	TILD 100 mg (part 2) to TILD 100 mg (part 3)	TILD 200 mg (part 2) to placebo (part 3)	TILD 100 mg (part 2) to TILD 100 mg (part 3)
N	113	116	117	116
Number of responders who experienced relapse between week 28 and week 64, n (%)[a]	61 (54.0)	8 (6.9)	51 (43.6)	9 (7.8)

PASI = Psoriasis Area and Severity Index; TILD = tildrakizumab.

[a] Relapse was defined as a 50% reduction in maximum PASI response.

Source: Additional data provided by sponsor.[53]

Harms

Only those harms identified in the review protocol are reported subsequently. See Table 20 and Table 21 for detailed harms data.

Adverse Events

The percentage of patients who reported 1 or more adverse events in part 1 ranged from 48% to 55% for the placebo, 42% to 49% for the tildrakizumab, and 54% for the etanercept groups (Table 20). Overall, infections and infestations were the most commonly reported class of adverse events, with nasopharyngitis reported most frequently. More patients in the etanercept group reported injection-site adverse events (2% to 9%) than in the tildrakizumab or placebo groups (0% to 3%).

The incidence of adverse events reported during the base study in P010 (64 weeks) and P011 (52 weeks) ranged from 128 to 248 events per 100 PYs for placebo, 72 to 82 events per 100 PYs for tildrakizumab, and 149 events per 100 PYs for etanercept (Table 21). Nasopharyngitis, upper respiratory tract infections, and headache were the most commonly reported adverse events.

Serious Adverse Events

Serious adverse events were reported by 1% to 3% of patients during the first 12 weeks of studies P010 and P011 (Table 20). Over the base study periods, 5.3 to 11.5 serious adverse events per 100 PYs were reported among placebo-treated patients, 5.1 to 8.4 events per 100 PYs were reported for those who received tildrakizumab, and 13.0 events per 100 PYs were reported for those who received etanercept (Table 21).

Withdrawals Due to Adverse Events

During the first 12 weeks of studies P010 and P011, 0% to 2% of patients per treatment group stopped therapy due to adverse events (Table 20). Over parts 1 to 3, the incidence of stopping treatment due to adverse events ranged from 1.2 to 5.8 events per 100 PYs for placebo, 0.8 to 2.6 events per 100 PYs for tildrakizumab, and 5.9 events per 100 PYs for etanercept (Table 21). The only adverse event reported in more than 1 patient was pancreatic carcinoma, which was reported as the reason for stopping treatment in 2 patients who received tildrakizumab 200 mg in Study P010.

Mortality

In Study P010, there was 1 death due to aneurysm reported in a patient who had received tildrakizumab 200 mg. In Study P011, there were a total of 5 deaths, including 4 patients who received tildrakizumab 100 mg (causes of death: alcoholic cardiomyopathy and steatohepatitis, acute myeloid leukemia, respiratory arrest, myocardial infarction), and 1 patient who received tildrakizumab 200 mg (cause of death: sepsis).

Notable Harms

Infections and infestations were reported by 20% to 24% of patients in the first 12 weeks of the trials, with a similar frequency across treatment groups (Table 20). When reported for the overall study period, the exposure-adjusted incidence of infections or infestations was higher in the placebo groups (74 to 95 events per 100 PYs) and etanercept group (86 events per 100 PYs) than in the tildrakizumab groups (45 to 57 events per 100 PYs) (Table 21). Serious infections, defined as those that met the criteria for a serious adverse event or that required intravenous antibiotics, were infrequent (week 12, 0% to 0.6%; week 52 or 64, 0.6 to 2.9 events per 100 PYs). In Study P010, 1 patient in the tildrakizumab 200 mg group had a serious adverse event of bone tuberculosis, which led to the discontinuation of study medication during part 2. There were no tuberculosis-related adverse events reported in Study P011.

Other notable harms specified in the review protocol (malignancies, cardiovascular adverse events, or drug-related hypersensitivity events) were infrequent in the first 12 weeks of the studies (0% to 0.6% of patients per treatment group) and over the entire base study (0 to 2.9 events per 100 PYs). No cases of treatment-emergent inflammatory bowel disease were reported.

In Study P010, 28 patients (4.6%) who had received tildrakizumab tested positive for treatment-emergent anti-drug antibodies during part 1, and 67 (8.9%) tested positive over parts 1, 2, and 3. Among those with treatment-emergent anti-drug antibodies who received tildrakizumab 100 mg (N = 13), 5 patients (38%) had a PASI 75 response and 6 (46%) had a PGA response at week 12. For those who received tildrakizumab 200 mg and reported treatment-emergent anti-drug antibodies, the PASI 75 response rate (7 out of 15 patients; 47%) and PGA response rate (7 out of 15 patients; 47%) at week 12 was also lower than the overall study population.

Treatment-emergent anti-drug antibodies were reported in 20 patients (3.3%) in part 1, and 50 (5.8%) patients in parts 1, 2, and 3 of Study P011 who received tildrakizumab. The proportion of patients with treatment-emergent anti-drug antibodies who achieved a PASI 75 response at week 12 was 92% (12 of 13) and 86% (6 of 7) in the tildrakizumab 100 mg and tildrakizumab 200 mg groups, respectively. PGA response was achieved by 69% (9 of 13) and 71% (5 of 7) of those with anti-drug antibodies who received tildrakizumab 100 mg and 200 mg, respectively.

Table 20: Summary of Harms at Week 12

Harms	P010 (reSURFACE 1)[a]			P011 (reSURFACE 2)[a]			
	Placebo N = 54	TILD 100 mg N = 309	TILD 200 mg N = 308	Placebo N = 156	TILD 100 mg N = 307	TILD 200 mg N = 314	ETAN 50 mg N = 313
Patients with ≥ 1 adverse event							
n (%)	74 (48)	146 (47)	130 (42)	86 (55)	136 (44)	155 (49)	169 (54)
Most common events[b]							
Nasopharyngitis	8 (5)	24 (8)	20 (7)	12 (8)	41 (13)	35 (11)	36 (12)
Upper respiratory tract infection	9 (6)	10 (3)	15 (5)	1 (1)	0	4 (1)	5 (2)
Sinusitis	4 (3)	4 (1)	3 (1)	1 (1)	6 (2)	9 (3)	1 (< 1)
Arthralgia	4 (3)	9 (3)	5 (2)	3 (2)	6 (2)	2 (1)	6 (2)
Headache	3 (2)	5 (2)	8 (3)	6 (4)	15 (5)	15 (5)	15 (5)
Cough	3 (2)	9 (3)	9 (3)	3 (2)	2 (1)	8 (3)	5 (2)
Pruritus	6 (4)	8 (3)	1 (< 1)	3 (2)	4 (1)	8 (3)	9 (3)
Psoriasis	8 (5)	3 (1)	0	4 (3)	1 (< 1)	1 (< 1)	2 (1)
Gastroenteritis	2 (1)	4 (1)	8 (3)	1 (1)	1 (< 1)	2 (1)	6 (2)
Injection-site erythema	0	2 (1)	1 (< 1)	1 (1)	2 (1)	2 (1)	27 (9)
Injection-site pain	0	1 (< 1)	0	3 (2)	9 (3)	8 (3)	10 (3)
Injection-site reaction	0	1 (< 1)	0	1 (1)	1 (< 1)	2 (1)	14 (5)
Injection-site swelling	0	1 (< 1)	1 (< 1)	2 (1)	2 (1)	2 (1)	7 (2)
Fatigue	1 (1)	9 (3)	2 (1)	4 (3)	6 (2)	4 (1)	4 (1)
Hypertension	0	1 (< 1)	2 (1)	5 (3)	2 (1)	2 (1)	3 (1)
Patients with ≥ 1 SAE							
n (%)	1 (1)	5 (2)	8 (3)	4 (3)	4 (1)	6 (2)	7 (2)
SAE reported in 2 or more patients	—	—	—	—	—	—	—
Patients who stopped treatment due to adverse events							
n (%)	1 (1)	0	5 (2)	2 (1)	3 (1)	3 (1)	6 (2)
Events reported in 2 or more patients	—	—	—	—	—	—	—
Deaths							
n (%)	0	0	0	0	1 (0.3)	0	0
Notable harms							
Infections and infestations (SOC), n (%)	32 (21)	64 (21)	61 (20)	33 (21)	65 (21)	68 (22)	74 (24)
Severe infections, n (%)[c]	0	1 (0.3)	1 (0.3)	1 (0.6)	0	1 (0.3)	0
Malignancies, n (%)[d]	0	0	0	0	1 (0.3)	1 (0.3)	1 (0.3)

Harms	P010 (reSURFACE 1)[a]			P011 (reSURFACE 2)[a]			
	Placebo N = 54	TILD 100 mg N = 309	TILD 200 mg N = 308	Placebo N = 156	TILD 100 mg N = 307	TILD 200 mg N = 314	ETAN 50 mg N = 313
Non-melanoma skin cancer, n (%)	0	0	0	0	1 (0.3)	1 (0.3)	1 (0.3)
Melanoma skin cancer, n (%)	0	0	0	0	0	0	0
Confirmed extended MACE, n (%)[e]	0	1 (0.3)	1 (0.3)	0	0	0	1 (0.3)
Inflammatory bowel disease, n (%)	NR	NR	NR	NR	NR	NR	NR
Drug-related hypersensitivity events, n (%)[f]	0	0	1 (0.3)	1 (0.6)	1 (0.3)	0	0

ETAN = etanercept; MACE = major adverse cardiovascular event; NR = not reported; SAE = serious adverse event; SOC = system organ class; TILD = tildrakizumab.

[a] Included all randomized patients who received at least 1 dose of the study drug in part 1, according to the treatment received.

[b] Frequency > 2% in any treatment group.

[c] Severe infections defined as any infection that met the regulatory definition of an SAE or infection requiring intravenous antibiotics whether or not reported as an SAE.

[d] Excluding carcinoma in situ of the cervix.

[e] Extended major cardiovascular events included: non-fatal myocardial infarction, non-fatal stroke, unstable angina, coronary revascularization, and cardiovascular death that are confirmed as cardiovascular or sudden.

[f] Hypersensitivity reactions included anaphylaxis, urticaria angioedema, and so forth.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Table 21: Summary of Harms During Part 1, 2, and 3 of Studies P010 and P011

Harms	P010 (reSURFACE 1)[a]			P011 (reSURFACE 2)[a]			
	Placebo N = 387	TILD 100 mg N = 383	TILD 200 mg N = 399	Placebo N = 156	TILD 100 mg N = 487	TILD 200 mg N = 527	ETAN 50 mg N = 313
Person-weeks exposure	8,904	20,268	21,795	1,808	23,763	21,780	8,005
Patients with ≥ 1 adverse event							
n (events per 100 PYs)	219 (128.3)	283 (72.9)	306 (73.3)	86 (248.2)	328 (72.0)	344 (82.4)	228 (148.6)
Most common events							
Influenza	15 (8.8)	16 (4.1)	21 (5.0)	3 (8.7)	12 (2.6)	16 (3.8)	5 (3.3)
Nasopharyngitis	34 (19.9)	70 (18.0)	63 (15.1)	12 (34.6)	112 (24.6)	119 (28.5)	63 (41.1)
Upper respiratory tract infection	31 (18.2)	37 (9.5)	53 (12.7)	1 (2.9)	15 (3.3)	27 (6.5)	11 (7.2)
Arthralgia	6 (3.5)	19 (4.9)	16 (3.8)	3 (8.7)	26 (5.7)	14 (3.4)	10 (6.5)
Cough	12 (7.0)	21 (5.4)	20 (4.8)	3 (8.7)	14 (3.1)	19 ()4.6	8 (5.2)
Psoriasis	20 (11.7)	6 (1.5)	9 (2.2)	4 (11.5)	5 (1.1)	4 (1)	12 (7.8)
Injection-site erythema	1 (0.6)	3 (0.8)	3 (0.7)	1 (2.9)	5 (1.1)	5 (1.2)	28 (18.3)

Harms	P010 (reSURFACE 1)[a]			P011 (reSURFACE 2)[a]			
	Placebo N = 387	TILD 100 mg N = 383	TILD 200 mg N = 399	Placebo N = 156	TILD 100 mg N = 487	TILD 200 mg N = 527	ETAN 50 mg N = 313
Injection-site hematoma	NR	NR	NR	1 (2.9)	6 (1.3)	6 (1.4)	4 (2.6)
Injection-site pain	1 (0.6)	2 (0.5)	0	3 (8.7)	10 (2.2)	12 (2.9)	11 (7.2)
Injection-site pruritis	0	2 (0.5)	1 (0.2)	0	1 (0.2)	6 (1.4)	5 (3.3)
Injection-site reaction	1 (0.6)	1 (0.3)	1 (0.2)	1 (2.9)	2 (0.4)	4 (1)	17 (11.0)
Injection-site swelling	1 (0.6)	1 (0.3)	1 (0.2)	2 (5.8)	3 (0.7)	4 (1)	7 (4.6)
Headache	6 (3.5)	12 (3.1)	18 (4.3)	6 (17.3)	29 (6.4)	30 (7.2)	19 (12.4)
Patients with ≥ 1 SAE							
n (events per 100 PYs)	9 (5.3)	20 (5.1)	35 (8.4)	4 (11.5)	30 (6.6)	26 (6.2)	20 (13.0)
Cardiac disorders (SOC)	0	1 (0.3)	5 (1.2)	1 (2.9)	5 (1.1)	3 (0.7)	2 (1.3)
Infections and infestations SOC	1 (0.6)	4 (1.0)	6 (1.4)	1 (2.9)	4 (0.9)	8 (1.9)	2 (1.3)
Neoplasms (benign, malignant, and unspecified SOC)	3 (1.8)	5 (1.3)	6 (1.4)	0	8 (1.8)	4 (1)	5 (3.3)
Patients who stopped treatment due to adverse events							
n (events per 100 PYs)	2 (1.2)	3 (0.8)	10 (2.4)	2 (5.8)	12 (2.6)	6 (1.4)	9 (5.9)
Events reported by 2 or more patients	—	—	Pancreatic carcinoma	—	—	—	—
Deaths							
n (events 100 PYs)	0	0	1 (0.2)	0	4 (0.9)	1 (0.2)	0
Notable harms							
n (events 100 PYs)							
Infections and infestations (SOC)	126 (73.8)	174 (44.8)	198 (47.4)	33 (95.2)	213 (46.8)	236 (56.5)	132 (86)
Severe infections[b]	1 (0.6)	4 (1.0)	6 (1.4)	1 (2.9)	5 (1.1)	8 (1.9)	3 (2.0)
Malignancies[c]	2 (1.2)	5 (1.3)	6 (1.4)	0	8 (1.8)	4 (1.0)	4 (2.6)
Non-melanoma skin cancer	2 (1.2)	5 (1.3)	4 (1.0)	0	4 (0.9)	3 (0.7)	2 (1.3)
Melanoma skin cancer	0	0	0	0	1 (0.2)	0	0
Confirmed extended MACE[d]	1 (0.6)	1 (0.3)	5 (1.2)	0	2 (0.4)	1 (0.2)	1 (0.7)
Inflammatory bowel disease	NR	NR	NR	NR	NR	NR	NR

Harms	P010 (reSURFACE 1)[a]			P011 (reSURFACE 2)[a]			
	Placebo N = 387	TILD 100 mg N = 383	TILD 200 mg N = 399	Placebo N = 156	TILD 100 mg N = 487	TILD 200 mg N = 527	ETAN 50 mg N = 313
Drug-related hypersensitivity events[e]	0	1 (0.3)	1 (0.2)	1 (2.9)	4 (0.9)	1 (0.2)	0

ETAN = etanercept; MACE = major adverse cardiovascular event; NR = not reported; PY = person-year; SAE = serious adverse event; SOC = system organ class; TILD = tildrakizumab.

[a] All patients who received at least 1 dose of the study drug in parts 1, 2, or 3, based on treatment received. Events were counted in each treatment group based on the treatment the patient received at the time of the adverse event (i.e., patients could be included in more than 1 treatment group due to crossover between drugs at week 12 and week 28).

[b] Severe infections defined as any infection that met regulatory definition of an SAE or infection requiring intravenous antibiotics whether or not reported as an SAE.

[c] Excluding carcinoma in situ of the cervix.

[d] Extended major cardiovascular events included: non-fatal myocardial infarction, non-fatal stroke, unstable angina, coronary revascularization, and cardiovascular deaths that are confirmed as cardiovascular or sudden.

[e] Hypersensitivity reactions included anaphylaxis, urticaria angioedema, and so forth.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Critical Appraisal

Internal Validity

Both trials used accepted methods to randomize patients and conceal treatment allocation. The studies randomized patients using an interactive voice or web response system, by region, and stratified by body weight and prior biologic exposure. The trials used a double-dummy design to maintain blinding, with identical-looking placebos. No substantial differences in the frequency of adverse events were noted that may have led to unblinding; however, given the magnitude of differences in treatment response observed, some patients receiving active treatments may have inferred the treatment received. At baseline, the patient characteristics within trials appeared to be similar between groups, and the frequency of withdrawals during the first 12 weeks of the trials was low (3% to 9%); the reasons for withdrawal were balanced across groups. The primary analyses at week 12 were based on the randomized and treated population (FAS), which included all but 1 patient from the intention-to-treat population. Overall, it appears the risk of bias was low for the primary outcomes at the end of the induction period (part 1) in studies P010 and P011.

The trials were designed to compare the 100 mg and 200 mg doses of tildrakizumab with placebo and etanercept (P011). Tildrakizumab 100 mg, administered subcutaneously at week 0, week 4, and every 12 weeks thereafter, was consistent with the Health Canada–approved dosage. Patients were required to stop previous treatments for psoriasis for a pre-specified period, thereby minimizing potential carry-over effects.

The co-primary outcomes in both trials were PGA and PASI 75 responses, which reflect the physician's assessment of the area affected and severity of plaques. A PASI 75 response is an accepted outcome for psoriasis trials;[51] however, a PASI 90 or PASI 100 response is the goal of therapy, according to the clinical expert consulted for the review. The expert stated that PGA response is not used in clinical practice. Although PASI response has been extensively validated and is highly producible, this measure has been criticized for not correlating the clinical extent of the disease with quality of life and the psychological stress caused by psoriasis. For example, a PASI score as low as 3 on the palms and soles may represent psoriasis that disables a patient from work and other life activities. The score also

lacks sensitivity to body sites such as the nails, feet, face, genitalia, and symptoms such as pruritus, or other disease-related comorbidities.[54,55] Both trials assessed HRQoL using a validated disease-specific instrument (DLQI); however, these outcomes were outside the statistical testing procedures. EQ-5D, SF-36, and productivity data were reported descriptively, with no between-group comparison; thus, no conclusions could be drawn from this data. Neither study collected patient-reported data on symptoms related to psoriasis.

The trials were powered to test for differences between tildrakizumab and placebo as well as etanercept for the co-primary outcomes. Familywise type I error was controlled for the co-primary and key secondary outcomes in both trials using a gate-keeping sequential procedure. Numerous other secondary and exploratory outcomes were tested, and these should be interpreted considering the inflated risk of type I error. Nonresponder imputation methods were used to address missing data for key binary outcomes, which is considered a standard approach. Sensitivity analyses that used last observation carried forward and multiple imputation methods for missing data showed results similar to the primary analysis, as did the worst-case scenario analysis conducted by the FDA (tildrakizumab imputed as nonresponders; placebo imputed as responders).[40] Several subgroup analyses were planned in the protocol, and treatment effects were generally similar across subgroups; however, treatment-by-subgroup interactions were not reported.

The efficacy data reported for parts 2 and 3 of the trials had a number of important limitations. After week 12, efficacy data were based on the subpopulation of patients who entered part 2 or part 3 of the trials (i.e., not the intention-to-treat population). Most efficacy outcomes for parts 2 and 3 were reported descriptively based on observed case data, which could potentially inflate the effects of tildrakizumab, as patients who were responding poorly are more likely to have withdrawn. Patients were switched between treatments at week 12 and week 28 based on different criteria or methods, depending on prior treatment allocation or response to therapy. In part 3, patients who were intolerant or did not respond to tildrakizumab were excluded, as were responders to etanercept. In part 2 of P010 and part 3 of P011, all patients were receiving tildrakizumab, with no active or placebo control group. Although part 2 of Study P011 included an etanercept control group, according to the clinical expert consulted for this review, the dose of etanercept administered was lower than would be used in clinical practice. As a result, the relative treatment effect of tildrakizumab may be inflated by the choice of comparator. Therefore, data for parts 2 and 3 of studies P010 and P011 should be interpreted with caution given the loss of randomization, lack of a control group or suboptimal active comparator, and potential attrition bias.

Safety data were reported for each part of the trials separately and as exposure-adjusted incidence rates over the entire 52- or 64-week study period. Of note, the safety data for parts 2 and 3 share some of the limitations described for the efficacy data. The exposure-adjusted incidence rate data attempt to control for crossovers between treatments; however, since there was no washout between therapies, it is possible that adverse events with a longer lag time may be attributed to the wrong exposure. The trials did not have a sufficient sample size or duration to detect rare adverse events or those with a long lag time.

External Validity

The studies enrolled patients with moderate-to-severe plaque psoriasis who were candidates for systemic therapy or phototherapy. These patients were predominantly male (65% to 73%) and White (65% to 91%), with a mean age per treatment group that ranged

from 44.6 to 47.9 years. In the trials, 12% to 20% of patients per group had psoriatic arthritis and those with severe psoriatic arthritis that was controlled with medication were excluded. The clinical expert consulted for the review indicated that the patients enrolled were reflective of patients with moderate-to-severe psoriasis in Canada.

Generalizability may be limited for patients with prior exposure to IL-23 or IL-17 inhibitors or etanercept, as these patients were excluded from the studies. All patients were required to stop topical therapies for psoriasis; however, in clinical practice, patients usually continue topical treatments while receiving biologic therapies.

Limited direct evidence was available comparing tildrakizumab with other biologics or systemic therapies. The selection of etanercept as an active control may not reflect current practice, as this drug is not a preferred treatment for psoriasis in Canada. Although etanercept was 1 of the biologics used to treat psoriasis when these trials were designed, it is less effective than other biologics, such as adalimumab (also available at the start of these trials), and the IL-17 drugs, which are currently the preferred drugs in Canada. Therefore, the effectiveness of tildrakizumab compared with other biologics or systemic therapies remains uncertain.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

Direct evidence for tildrakizumab versus other systemic therapies for treating psoriasis was available for etanercept only, with no RCTs comparing tildrakizumab with other drugs. The aim of this section is to review the indirect evidence comparing tildrakizumab with other biologic and non-biologic systemic therapies used to treat moderate-to-severe plaque psoriasis in Canada.

CADTH conducted a literature search and reviewed the sponsor's submission for potentially relevant ITCs. The ITC search was conducted in MEDLINE on September 16, 2019; it combined the concept of "psoriasis" with CADTH's ITC filter. Conference abstracts were excluded, and no date limit was used. Titles, abstracts, and full-text articles were screened for inclusion by 1 reviewer based on the population, intervention, comparator, and outcome criteria outlined in Table 3. An update to the literature search was conducted in January 2021.

The sponsor submitted an ITC conducted by the Institute for Clinical and Economic Review, which was used to inform the sponsor's pharmacoeconomic model.[8] Eight other potentially relevant ITCs were identified in the September 2019 literature search. Four reports did not include tildrakizumab in their analysis and therefore were excluded.[56-59] One ITC was excluded because it reported only data comparing drug classes, not individual drugs to treat psoriasis.[60] One other ITC was excluded because its literature search was outdated (up to December 2016) and only phase II trial[61] data for tildrakizumab were included in the analysis.

Another 6 relevant ITCs were identified in the January 2021 literature search update.[11-13,62-64] Three ITCs were not summarized due to their limited scope,[62-64] as they were less comprehensive than the sponsor-submitted ITC. These reports assessed tildrakizumab versus 1 to 3 other drugs of interest to this review.

A total of 6 ITCs met the inclusion criteria and have been summarized in this section.[8-13]

Description of the Indirect Comparisons

Six ITCs that examined the comparative efficacy or safety of tildrakizumab in patients with moderate-to-severe plaque psoriasis were included in this clinical review. These were authored by the Institute for Clinical and Economic Review,[8] Sawyer et al. (2019),[9] Xu et al. (2019[10] and 2020[13]), Mahil et al.,[11] and Sbidian et al. (2020).[12] These ITCs included TNF alpha inhibitors, IL-17 inhibitors, IL-23 inhibitors, IL12/23 inhibitors, and other systemic therapies used in Canada to treat moderate-to-severe plaque psoriasis. All of these reports examined efficacy in terms of PASI response at the end of the induction period. Two reports also analyzed data on the PGA, 3 analyzed HRQoL,[10-12] and 4 analyzed safety outcomes.[10-13]

Methods of the Institute for Clinical and Economic Review ITC

Objectives

The objective of the systematic review and NMA by the Institute for Clinical and Economic Review was to update its previous review (published in 2016) of immunomodulator treatments for moderate-to-severe plaque psoriasis in adults.

Study Selection Methods

English-language RCTs, comparative observational studies, and high-quality systematic reviews were eligible to be included in the systematic review if they included adult patients with moderate-to-severe plaque psoriasis receiving treatment with immunomodulators (TNF alpha inhibitors; IL-17, IL-23, and IL-12/23 drugs; or apremilast) (Table 22).

The outcomes of interest were the proportion of patients achieving a PASI 50, 75, 90, or 100 response; PGA response; HRQoL; symptoms of psoriasis; treatment tolerability; and adverse events. Trials of any duration were eligible for inclusion. No criteria related to the dose of treatments were specified. Subgroups of interest included Asian patients, those with psoriatic arthritis, and those with prior biologic exposure.

Table 22: Study Selection Criteria for Sponsor-Submitted ITC

Characteristic	ICER (2018)[8]
Population	Adult patients with moderate-to-severe plaque psoriasis
Intervention	• Immunomodulating drugs used for the treatment of plaque psoriasis: ○ TNF alpha inhibitors: Adalimumab, etanercept, infliximab, certolizumab pegol ○ IL-17 drugs: Secukinumab, ixekizumab, brodalumab ○ IL-12/23 drug: Ustekinumab ○ IL-23 drugs: Guselkumab, tildrakizumab, risankizumab ○ Anti-PDE4 drug: Apremilast • Any duration of treatment
Comparator	• Placebo • Any of the interventions of interest
Outcome	• PASI 50, 75, 90, or 100 • PGA or IGA • DLQI or other HRQoL measures • Symptom control (e.g., PSI) • Treatment tolerability (i.e., discontinuation due to adverse events) • Treatment-related adverse events (e.g., infection)
Study design	• Phase III RCTs, comparative observational studies and high-quality systematic reviews

Characteristic	ICER (2018)[8]
	• Phase II RCTs that evaluated unique subpopulations or outcomes not available from phase III RCTs
Publication characteristics	Published in English
Exclusion criteria	• Phase I or single-arm trials • Trials of immunomodulators used as combination treatment

DLQI = Dermatology Life Quality Index; HRQoL = health-related quality of life; ICER = Institute for Clinical and Economic Review; IGA = Investigator's Global Assessment; IL = interleukin; ITC = indirect treatment comparison; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index score; PDE4 = phosphodiesterase type 4; PGA = Physician's Global Assessment; PSI = Psoriasis Symptom Inventory; RCT = randomized controlled trial; SR = systematic review; TNF = tumour necrosis factor.

Source: Table adapted from data in ICER - Targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: Effectiveness and value[8]

Literature searches were conducted for articles published from January 1, 1996 to January 2, 2018 from multiple databases (Embase, MEDLINE, and Cochrane Library databases) in addition to grey literature. Two reviewers independently screened titles, abstracts, and full-text articles for inclusion. For each study included in the review, study design details, patient information, intervention information and efficacy, and safety outcomes were extracted. The review authors utilized the US Preventive Services Task Force criteria to determine the quality of the included studies.

ITC Analysis Methods

The base-case NMA used a placebo-adjusted Bayesian random-effects model to calculate PASI response at the end of the induction period (10 to 16 weeks). The model used a multinomial likelihood approach with a probit link, which facilitated the inclusion of data from trials that used different thresholds for PASI response. The PASI response data from phase III RCTs were used to calculate ordered categorical data with 4 groups: less than 50%, 50% to 74%, 75% to 89%, and 90% or greater improvement in PASI score. The placebo response was assumed to be common across trials, and a covariate for the placebo response rate was included in the adjusted model to provide control from known and unknown differences between-study populations.

The analysis used non-informative priors, 50,000 burn-in cycles, and an additional 50,000 iterations for parameter estimation using 3 chains (JAGS software 4.3.0 via R using the R2jags package). Convergence was determined through trace plots. The NMA provided the efficacy output for every possible treatment comparison in terms of relative risk and 95% CrIs.

The FDA-approved or -proposed dose at the end of the induction period was included in the NMA, with 3 exceptions. The model included only the 300 mg dose of secukinumab (150 mg dose was excluded). Also, the weight-based and other dosing regimens for ustekinumab and for certolizumab pegol were pooled and analyzed as 1 dosage group for each of these drugs. Only the tildrakizumab 100 mg dose was included in the NMA, as per the recommended dose.

No method to assess potential inconsistency, statistical heterogeneity, or model fit was described in the published report. Although the systematic review gathered data on a number of outcomes, such as DLQI or harms, PASI response was the only outcome analyzed in the NMA.

Two subgroup analyses were conducted: first by excluding 7 trials with 100% Asian populations, and second by excluding 11 trials that had prior biologic exposure in less

than 5% of the enrolled population. Sensitivity analyses were conducted using a model with no placebo adjustment, and a placebo-adjusted model that used multiple covariates across PASI levels (i.e., 3 betas: PASI 50, 75, and 90).

Results of Institute for Clinical and Economic Review ITC

Summary of Included Studies

A total of 53 RCTs and 13 observational studies met the inclusion criteria for the systematic review. Five trials were phase II studies that reported on subgroups of interest, 1 study was an investigator-initiated RCT, and the other 47 were phase III RCTs. Only data from phase III RCTs were included in the NMA. Sixteen RCTs were head-to-head studies, 11 of which also included a placebo group. Forty-six of the phase III RCTs were double blind.

The trials used similar inclusion criteria with respect to age (≥ 18 years), BSA affected (≥ 10%), PASI score (≥ 12), and PGA (≥ 3), and enrolled those who had had plaque psoriasis for 6 or more months and who were candidates for phototherapy or systemic therapy. Most trials required a washout of prior therapies and prohibited the use of other psoriasis treatments during the trials.

All but 4 of the RCTs were rated to be of good or fair quality. Three risankizumab studies and 1 trial comparing secukinumab and ustekinumab were available only in the grey literature and were not rated. Following the induction period, many of the trials removed blinding, re-randomized patients to different treatment groups, or measured outcomes at different time points. Thus, the review authors stated it was difficult to assess safety and efficacy beyond the induction phase.

The mean age of patients enrolled in the trials ranged from 39 to 50 years (median of 45 years) and the mean duration of psoriasis ranged from 11 to 22 years (median of 18 years). Baseline PASI scores across trials ranged from 15 to 33 (median of 20). Across the studies, 3% to 37% of patients had psoriatic arthritis at baseline and 0% to 57% had received prior biologic therapy. Fewer patients had prior biologic exposure in the trials for older anti-TNF drugs (median of 0%) compared with the newer biologics (median of 16.5%). The authors stated that, given the between-study heterogeneity observed, placebo adjustment was necessary to control for some of the differences in patient characteristics and possible unknown confounders. A summary of the baseline characteristics of the phase III RCTs is shown in Table 23.

Table 23: Summary of Phase III RCTs Included in Sponsor-Submitted ITC

Drug	Number of trials	Total patients	Induction period (weeks)	PASI score (mean)	Age (years)	Psoriasis duration (years)	Previous biologics, %	Psoriatic arthritis, %
Placebo-controlled studies with or without an active comparator								
Adalimumab	4	2,077	16 or 12	24	44	16	2	20
Etanercept	7	3,775	12	20	44	17	6	25
Infliximab	3	1,396	10	23	43	17	8	25
Certolizumab pegol	3	1,020	16 or 12	20	46	18	30	18
Ustekinumab	5	2,566	12	23	44	17	25	21
Secukinumab	4	2,403	12	22	45	18	26	20
Ixekizumab	3	3,866	12	24	46	19	27	NR

Drug	Number of trials	Total patients	Induction period (weeks)	PASI score (mean)	Age (years)	Psoriasis duration (years)	Previous biologics, %	Psoriatic arthritis, %
Brodalumab	3	4,373	12	23	45	19	33	22
Apremilast	3	1,505	16	19	46	19	31	NR
Guselkumab	2	1,829	16	22	44	18	21	19
Tildrakizumab	2	1,862	12	20	46	NR	17	NR
Risankizumab	3	1,504	16	20	48	NR	42	NR
Active-comparator controlled trials								
Etanercept / infliximab	1	48	12	17	44	20	15	11
Etanercept / ustekinumab	1	903	12	20	45	19	11	28
Ustekinumab / secukinumab	1	679	12	22	45	18	14	19
Ustekinumab / ixekizumab	1	302	12	20	44	18	14	NR
Ustekinumab / secukinumab	1	1,102	12	21	45	17	22	NR

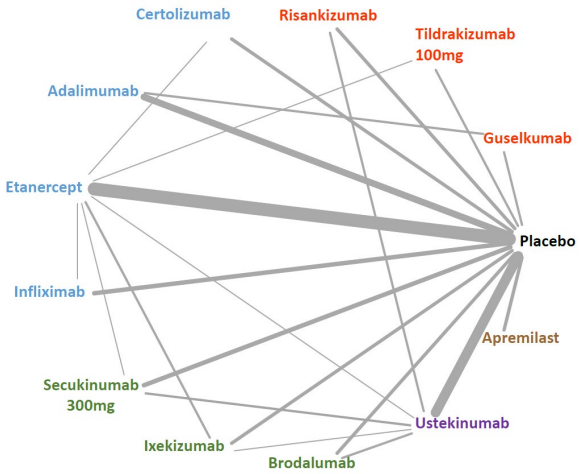
ITC = indirect treatment comparison; NR = not reported; PASI = Psoriasis Area and Severity Index; RCT = randomized controlled trial.

Source: Table adapted from ICER- Targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: Effectiveness and value[8]

Results

The evidence network for PASI response is shown in Figure 8.

Figure 8: Evidence Network for Base-Case Analysis of Psoriasis Area Severity Index Response



Note: The lines connecting therapies represent direct comparisons observed in a clinical trial; the number of lines and their thickness represent how many trials measured the contrast.

Source: Figure reproduced from ICER - Targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: Effectiveness and value[8]

All immunomodulators were statistically significantly more likely to achieve a PASI 50, 75, or 90 response than placebo at the end of the induction period (10 to 16 weeks) in the

base-case analysis. For tildrakizumab 100 mg versus placebo, the relative risk of achieving a PASI 75 response was 11.60 (95% CrI, 8.84 to 15.5), and the relative risk of a PASI 90 response was 29.32 (95% CrI, 21.01 to 41.40) (Table 24). The indirect evidence suggests that patients who received tildrakizumab were less likely to achieve a PASI 50, 75, or 90 response than those treated with IL-17 inhibitors (ixekizumab, brodalumab, secukinumab), other IL-23 inhibitors (guselkumab, risankizumab), and infliximab. The data suggest that tildrakizumab was more effective in terms of PASI 50, 75, or 90 response than etanercept or apremilast. The comparisons between tildrakizumab and adalimumab, certolizumab, or ustekinumab did not statistically differ, as the 95% CrI included the null.

The head-to-head estimates from the NMA were consistent with the direct evidence for tildrakizumab versus etanercept. The subgroup and sensitivity analyses performed (biologic-experienced studies, multinational studies, unadjusted model, and model with multiple covariates across PASI levels) showed results that were generally similar to the base-case analysis.

Table 24: Base-Case Comparisons From the Network Meta-Analysis of the Median Relative Risk (95% CrI) of PASI 50, 75, and 90 Responses

Treatment	PASI 50, RR (95% CrI)	PASI 75, RR (95% CrI)	PASI 90, RR (95% CrI)
Tildrakizumab 100 mg versus:			
Placebo	**5.27 (4.25 to 6.66)**	**11.60 (8.84 to 15.5)**	**29.32 (21.01 to 41.40)**
Apremilast	**1.37 (1.21 to 1.58)**	**1.71 (1.39 to 2.14)**	**2.28 (1.66 to 3.17)**
Adalimumab	0.94 (0.86 to 1.00)	0.88 (0.76 to 1.00)	0.81 (0.64 to 1.00)
Certolizumab	0.95 (0.88 to 1.02)	0.91 (0.79 to 1.05)	0.85 (0.68 to 1.09)
Etanercept	**1.11 (1.04 to 1.20)**	**1.22 (1.07 to 1.38)**	**1.37 (1.11 to 1.68)**
Infliximab	**0.89 (0.82 to 0.94)**	**0.79 (0.68 to 0.89)**	**0.66 (0.52 to 0.81)**
Brodalumab	**0.86 (0.79 to 0.92)**	**0.72 (0.63 to 0.81)**	**0.56 (0.44 to 0.68)**
Guselkumab	**0.85 (0.78 to 0.91)**	**0.71 (0.61 to 0.81)**	**0.54 (0.42 to 0.67)**
Ixekizumab	**0.85 (0.78 to 0.91)**	**0.70 (0.60 to 0.79)**	**0.53 (0.41 to 0.65)**
Risankizumab	**0.85 (0.78 to 0.91)**	**0.70 (0.60 to 0.79)**	**0.52 (0.41 to 0.65)**
Secukinumab	**0.88 (0.80. 0.93)**	**0.76 (0.65 to 0.85)**	**0.61 (0.48 to 0.75)**
Ustekinumab	0.94 (0.88 to 1.00)	0.88 (0.78 to 1.00)	0.82 (0.66 to 1.00)

CrI = credible interval; PASI 50, 75, 90 = at least a 50%, 75% or 90% reduction in the Psoriasis Area and Severity Index score; RR = relative risk.

Note: Estimates in bold have 95% CrIs that do not include 1 and were interpreted as statistically significant. RR and 95% CrI < 1 indicate a lower response rate for tildrakizumab versus comparator treatment.

Source: Table adapted from ICER - Targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: Effectiveness and value[8]

Critical Appraisal of the Institute for Clinical and Economic Review ITC

The authors of the Institute for Clinical and Economic Review report used accepted methods to conduct the systematic review. These methods included a search of multiple databases, as well as the grey literature, and a 2-stage duplicate selection process. The inclusion and exclusion criteria used for screening were provided and lists of the included and excluded references with accompanying reasons were reported. The comparators and their dosing regimens included in the analysis were appropriate for Canadian decision-makers. The risk of bias was assessed using the checklist from the US Preventive Services Task Force criteria, although the detailed results of these assessments were not provided

and no plan regarding the handling of a potentially high risk of bias in the studies was reported. The literature search was conducted in January 2018; thus, more recently published studies were missing from the analysis. One notable example is the ECLIPSE trial, published in 2019, that compared guselkumab with secukinumab.[65] Moreover, the authors limited the analysis to phase III RCTs, thus excluding a number of studies. It is unclear what impact the inclusion of phase II trials may have had on the results.

The review authors conducted a qualitative assessment of the patient and trial characteristics of the included studies to determine if they were sufficiently similar to conduct the NMA. They concluded that the age of patients and the duration of psoriasis were comparable across studies; however, other sources of heterogeneity were observed. There was variation across trials in the proportion of patients with psoriatic arthritis and those with prior exposure to biologics, the region where trials were conducted (i.e., Asia versus a multinational trial), and the timing of the outcome assessment (10 to 16 weeks). Given the potential for between-study heterogeneity, the authors used a placebo-adjusted random-effects model as the base case. They stated that adjustment of the placebo response rate may account, to some degree, for the differences in baseline patient characteristics. Adjusting for the variation in response rates in the placebo groups across trials has been endorsed by National Institute for Health and Care Excellence.[66] There are limitations to the adjusting for placebo approach because there is an assumption that study and patient characteristics (that are effect modifiers of the relative treatment effect) are also prognostic factors of the outcome with placebo.[67,68] And, given it is unclear to what extent placebo response is an adequate proxy for specific characteristics or effect modifiers, uncertainty remains as a result of such analysis. The use of placebo response rate is an attempt to account for potential variability in effect modifiers, but it is unclear if these effect modifiers have the same level of effect on the active arms. Sensitivity analyses were conducted using an unadjusted model and using a placebo-adjusted model that used multiple covariates across PASI levels. The results of these models were generally similar to the base-case analysis. The authors also conducted a subgroup analysis to examine the potential impact of race and treatment experience as potential effect modifiers, and these analyses showed results similar to the base case. Given the potential for between-trial heterogeneity, a random-effects, placebo-adjusted model was likely appropriate; however, the authors did not provide evidence that the base-case model provided a better model fit than the alternate models tested.

The authors provided a qualitative comparison of the direct evidence and the results of the NMA but, otherwise, the report did not include an assessment of inconsistency or statistical heterogeneity. The NMA was limited to the analysis of PASI response. Key efficacy and safety outcomes that were identified in the CDR review protocol (e.g., HRQoL, infections, or discontinuation due to adverse events), were not analyzed in the NMA. Although the authors stated that some outcomes, such as the DLQI, were inconsistently reported in the trials, there was no explanation provided for limiting the analysis to PASI response. The analysis was also limited to the evaluation of treatment effects for the induction period; however, given the issues with the design of the trials after induction, it was not possible to assess longer-term outcomes.

Summary of Other ITCs

Five additional ITCs[9-13] were found that evaluated the comparative efficacy or safety of biologics and other systemic therapies for moderate-to-severe psoriasis. These reports have been summarized in tables 25 to 29.

The aim of the systematic review and ITC by Sawyer et al. (2019)[9] was to compare the efficacy of the IL-17 drugs with IL-23 and other systemic biologic and non-biologic drugs for moderate-to-severe plaque psoriasis. This NMA analyzed data from 77 RCTs that included the patient population and immunomodulators relevant to Canada. PASI 50, 75, 90, and 100 response data at the end of the induction period (week 10 to 16) were analyzed using a random-effects Bayesian multinomial model. The findings were similar to those reported in the Institute for Clinical and Economic Review report,[8] with data suggesting tildrakizumab 100 mg was less effective in terms of PASI response than IL-17 inhibitors (brodalumab, ixekizumab, secukinumab), other IL-23 inhibitors (risankizumab and guselkumab), and infliximab, and that tildrakizumab was more effective than etanercept, apremilast, dimethyl fumarate, and placebo. No statistical differences were detected between tildrakizumab and ustekinumab, and adalimumab and certolizumab pegol. The study was funded by Leo Pharma.

Xu et al. (2019)[10] conducted a systematic review and an NMA of 13 biologics used to treat moderate-to-severe psoriasis. Induction-period data from 54 RCTs were analyzed using a Bayesian random-effects model for the following outcomes: PASI 50, 75, 90, and 100 response; PGA; DLQI; infection; headache; and discontinuation. The data suggest that tildrakizumab was inferior to IL-17 inhibitors, other IL-23 inhibitors, and infliximab, and superior to etanercept and placebo in terms of PASI response at the end of the induction period. No statistical differences were found between tildrakizumab and placebo or other active treatments in the likelihood of discontinuation. This review had several limitations, including unclear study selection methods and a limited evidence base (in part due to exclusion of interventions of interest to this review). Some outcomes analyzed were not clearly defined. Reporting of NMA methods was incomplete, with no justification of the model used and no testing of alternative models.

The objective of the report by Mahil et al.[11] was to evaluate the comparative efficacy and tolerability of 11 biologic treatments for psoriasis recommended by the National Institute for Health and Care Excellence. The review included 62 RCTs and pooled outcome data reported at the end of the induction period (10 to 16 weeks) using a frequentist random-effects NMA model. The results suggested that tildrakizumab, at licensed doses, may be more effective than etanercept and methotrexate, but less effective than secukinumab, brodalumab, ixekizumab, guselkumab, and risankizumab in terms of PASI response. No statistically significant differences were detected between tildrakizumab and other biologics in the change in DLQI. The indirect evidence suggests that withdrawals due to adverse effects during the induction period may be less likely for tildrakizumab than infliximab or ixekizumab; however, these results should be viewed with caution due to the short duration of the trials and the low frequency of events across the network. The authors of the ITC concluded that most biologics, including tildrakizumab, show similar short-term efficacy and tolerability at 10 to 16 weeks. Mahil et al.[11] did not provide a comprehensive review of study heterogeneity; there was no justification provided for the NMA model selected and no other models were tested.

Xu et al. (2020)[13] conducted an NMA to evaluate the efficacy and safety of 14 biologic drugs for the treatment of moderate-to-severe plaque psoriasis. This study combined short-term data (up to week 16) from 60 RCTs using a Bayesian random-effects model. The results of the NMA suggested tildrakizumab was more effective in terms of PASI 90 response than etanercept or placebo, but less effective than secukinumab, ixekizumab, and risankizumab. The indirect evidence suggested the risk of adverse events may be lower for tildrakizumab than brodalumab, etanercept, infliximab, ixekizumab, and secukinumab. This analysis had a number of limitations that may affect the internal validity of the results. The data extraction excluded cases where patients stopped or withdrew due to treatment failure before reaching the end point, which does not follow the intention-to-treat principle and likely biases the results. It was unclear what drug doses were included in the model and how study heterogeneity was assessed. Due to these limitations, the results of this NMA should be interpreted with caution.

The objective of the report by Sbidian et al. (2020)[12] was to compare the safety and efficacy of conventional systemic drugs, small-molecule drugs, and biologics for patients with moderate-to-severe psoriasis. This systematic review included 140 RCTs, and data from 113 RCTs were included in at least 1 pairwise meta-analysis or the frequentist NMA. The indirect evidence suggested that tildrakizumab was more effective as induction therapy (PASI 90 response) than etanercept, most small-molecule or conventional treatments, and placebo, but was less effective than secukinumab, ixekizumab, guselkumab, risankizumab, and infliximab. There were no statistically significant differences between tildrakizumab and most other treatments for the change from baseline in HRQoL. No statistically significant differences were detected between tildrakizumab and placebo or other active treatments on the likelihood of serious adverse events. The indirect evidence suggested that tildrakizumab may be associated with a lower risk of adverse events than most other comparators. Due to the broad scope of the review, the inclusion of non-licensed doses, and the pooling of data from week 8 to week 24, these analyses may have greater heterogeneity than other more focused ITCs. The results for safety should be interpreted with caution, given the short duration of the trials and lack of power to detect infrequent events.

Table 25: Summary of ITC by Sawyer et al. (2019)

Characteristic	Sawyer et al. (2019)[9]
Selection criteria	
Population	Adult patients with moderate-to-severe plaque psoriasis
Intervention	Immunomodulators at licensed doses: • TNF alpha inhibitors: Adalimumab, etanercept, infliximab, certolizumab pegol • IL-17 inhibitors: Secukinumab, ixekizumab, brodalumab • IL-12/23 inhibitors: Ustekinumab • IL-23 inhibitors: Guselkumab, tildrakizumab, risankizumab • Anti-PDE4 drug: Apremilast • Fumaric acid ester: Dimethyl fumarate
Comparator	• Placebo • Any of the interventions of interest • Unlicensed doses of biological or non-biological therapies
Outcomes	PASI: 50, 75, 90, 100 response at the end of the induction period (10 to 16 weeks)
Study design	English-language RCTs

Characteristic	Sawyer et al. (2019)[9]
Methods	
Literature search	MEDLINE, MEDLINE in process, Embase, Cochrane Library (January 1, 2000 to November 22, 2018), reference lists and conference abstracts searched
NMA methods	• Bayesian random-effects multinomial likelihood model with probit link adjusted for placebo response (WinBUGS v1.4). PASI response was modelled as a discrete dependent variable that takes ordered multinomial outcomes (PASI 50, 75, 90, 100) • PASI 50 response in placebo group was used to inform the baseline event rate • Each dose of drug modelled as separate node • Adjusted and unadjusted models were tested with model fit informed by the statistical significance of the placebo arm regression coefficient, and if there was a reduction in between-trial heterogeneity • Inconsistency assessed using a random-effects unrelated mean effects model • Model was run with 3 chains with 20,000 iteration burn-in, and 20,000 simulations for parameter estimation • Convergence confirmed through inspection of Brook-Gelman-Rubin diagnostic and history plots • Results reported as the median absolute and relative risk of each PASI response with 95% CrI • Sensitivity analyses: ○ excluded trials with < 5% biologic exposure ○ used 12-week versus 16-week data for secukinumab ○ excluded studies with < 50 patients per group
Results	
Number of included studies	• 83 RCTs included in SR • 77 RCTs included in the NMA (34,816 patients)
Summary of included trials	Study enrolment criteria were similar across trials. Baseline patient characteristics varied in terms of prior treatments for psoriasis, but were broadly similar in terms of age and PASI score. There were differences in the timing of outcome measures for the induction period (10 to 24 weeks). Most trials were rated as low risk of bias.
Key findings	Findings were similar to the 2018 ICER report, with the NMA estimates suggesting tildrakizumab 100 mg was less effective in terms of PASI response than IL-17 drugs (brodalumab, ixekizumab, secukinumab), other IL-23 drugs (risankizumab and guselkumab), and infliximab. Tildrakizumab was more effective than etanercept, apremilast, dimethyl fumarate, and placebo. No statistical differences were detected between tildrakizumab and ustekinumab, and adalimumab and certolizumab pegol. Similar results reported for the subgroup and sensitivity analysis as the base-case analysis. The 95% CrI for pairwise comparisons were generally wider, based on Sawyer model, than in the ICER report.
Critical appraisal	• Systematic review methods were generally acceptable; however, study screening was conducted by 1 reviewer, with only half of the articles verified by a second reviewer • Included a comprehensive evidence base of trials with the population and interventions that were relevant to Canada; missing some recently published trials • Limited discussion of between-study heterogeneity • Analytical methods appear to be acceptable; DIC values were not reported and model fit was based on other parameters • No evaluation of HRQoL or safety outcomes
Funding	Leo Pharma

CrI = credible interval; DIC = deviance information criterion; HRQoL = health-related quality of life; ICER = Institute for Clinical and Economic Review: IL = interleukin; ITC = indirect treatment comparison; NMA = network meta-analysis; PASI 50, 75, 90, 100 = at least a 50%, 75%, 90%, or 100% reduction in the Psoriasis Area and Severity Index score; PDE4 = phosphodiesterase type 4; RCT = randomized controlled trial; SR = systematic review; TNF = tumour necrosis factor.

Source: Sawyer et al. (2019).[9]

Table 26: Summary of ITC by Xu et al. (2019)

Characteristic	Xu et al. (2019)[10]
Selection criteria	
Population	Adult patients with moderate-to-severe plaque psoriasis (average age around 40 to 50 years)
Intervention	Immunomodulators at licensed doses: • TNF alpha inhibitors: Adalimumab, etanercept, infliximab • IL-17 drugs: secukinumab, ixekizumab, brodalumab • IL-12/23 drug: Ustekinumab, briakinumab[a] • IL-23 drugs: Guselkumab, tildrakizumab • Other: Alefacept,[a] efalizumab,[a] itolizumab[a]
Comparator	• Placebo • Any of the interventions of interest
Outcomes	• Short-term outcomes reported at 12 to 16 weeks • Efficacy: PASI 50, 75, 90, 100; PGA, DLQI • Safety: infection, headache, discontinuation
Study design	English-language RCTs or quasi-randomized trials
Methods	
Literature search	Embase and PubMed (up to August 8, 2018); reference lists searched
NMA methods	• Bayesian random-effects model with MCMC methods (WinBUGS 1.4.3, and STATA 13.0) • Results reported as OR and 95% CrI • Inconsistency assessed using node splitting methods and net heat plots • Publication bias assessed using funnel plots
Results	
Number of included studies	54 trials (13,657 patients)
Summary of included trials	53 trials were double blind and 1 was open label. The average age of patients was 45.1 years, and disease duration was 17.8 years; outcomes were reported at week 12 to 16.
Key findings	• Indirect evidence for PASI response suggests tildrakizumab was statistically inferior to secukinumab, brodalumab, ixekizumab, guselkumab, and infliximab. No statistical differences were found between tildrakizumab and adalimumab or ustekinumab. Tildrakizumab was more effective than etanercept, alefacept, and placebo. • Data for the PGA and DLQI could not be interpreted because the thresholds used to define these response variables were not reported. • Tildrakizumab was not included in the NMA for headache or infection. • No statistical differences were detected between tildrakizumab and placebo or other active treatments on the likelihood of discontinuation.
Critical appraisal	• Methods used to conduct the SR were unclear; some study selection criteria were vague. • Methods state study quality was assessed using the Cochrane risk-of-bias tool, but the Jadad score was reported instead. • The NMA did not include certolizumab pegol, risankizumab, or apremilast, which were of interest to this CADTH review, but included other drugs that are not available in Canada (alefacept, briakinumab, itolizumab, efalizumab). • Unclear what doses were included in the model. • Although safety and efficacy outcomes were analyzed, some outcomes were not clearly defined (i.e., PGA and DLQI, discontinuation). • No justification was provided for the random-effects model selected; no other models were tested. No information provided on priors, burn-in, chains, assessment of convergence, or model fit. • Appears there was no or limited assessment of study homogeneity.

Characteristic	Xu et al. (2019)[10]
Funding	None

CrI = credible interval; DLQI = Dermatology Life Quality Index; HRQoL = health-related quality of life; IL = interleukin; ITC = indirect treatment comparison; MCMC = Markov chain Monte Carlo; NMA = network meta-analysis; OR = odds ratio; PASI 50, 75, 90, 100 = at least a 50%, 75%, 90%, or 100% reduction in the Psoriasis Area and Severity Index score; PGA = Physician's Global Assessment; RCT = randomized controlled trial; SR = systematic review; TNF = tumour necrosis factor.

[a] Not approved for use in Canada.

Source: Xu et al. (2019).[10]

Table 27: Summary of Mahil et al.

Characteristic	Mahil et al. (2020)[11]
Selection criteria	
Population	All people with psoriasis with moderate-to-severe disease being treated primarily for their skin disease
Intervention	Immunomodulators all doses and durations: • TNF alpha inhibitors: Adalimumab, etanercept, infliximab, certolizumab pegol • IL-17 drugs: Secukinumab, ixekizumab, brodalumab • IL-12/23 drug: Ustekinumab (2 doses based on body weight) • IL-23 drugs: Guselkumab, tildrakizumab, risankizumab
Comparator	• Placebo • Methotrexate (within standard dose range 15 to 25 mg) • Any of the interventions of interest
Outcomes	• Clear or nearly clear (minimal residual activity [PASI > 90] or score of 0 or 1 on PGA) • Change in DLQI (mean or median change from baseline) • PASI 75 • Drug withdrawal due to adverse events • Serious infection and tuberculosis
Study design	• English-language RCTs or systematic reviews • Studies with a minimum of 50 patients (25 per group) where the proportion of patients being treated primarily for psoriatic arthritis was < 50%
Methods	
Literature search	MEDLINE, Embase, PubMed, and Cochrane (up to September 7, 2018); reference lists searched
Analysis methods	• Frequentist random-effects NMA model (STATA 13) • Also conducted hierarchical cluster analysis that simultaneously evaluated efficacy and tolerability • Primary analyses based on all doses with sensitivity analyses restricted to licensed doses • Results reported as odd ratio and absolute difference, with 95% CI for binary outcomes and mean difference with 95% CI for continuous outcomes • Inconsistency assessed using visual inspection of forest plots, chi square test of inconsistency, and loop-specific inconsistency plots and inconsistency factors • Publication bias assessed using funnel plots
Results	
Number of included studies	62 RCTs (31,899 patients)
Summary of included trials	• Risk of bias for most studies (> 80%) was rated as low (based on Cochrane tool). • The average age of patients was 44.7 years; 69% were male. Baseline PASI scores ranged from 8 to 30. Where reported, all studies included patients with prior conventional systemic treatment use, and 41 RCTs (66%) included patients with prior biologic exposure. • Outcomes reported at 10 to 16 weeks.
Key findings	• At licensed doses, indirect evidence for PASI 90 or PGA 0 or 1 suggests tildrakizumab was statistically inferior to secukinumab, brodalumab, ixekizumab, guselkumab, and risankizumab. No

Characteristic	Mahil et al. (2020)[11]
	statistical differences were found between tildrakizumab and adalimumab, ustekinumab, infliximab, or certolizumab pegol. Tildrakizumab was more effective than etanercept, methotrexate, and placebo. Results were similar for the analysis of PASI 75, except that tildrakizumab was statistically inferior to infliximab. • No statistically significant differences were detected between tildrakizumab and other biologic drugs for the change in DLQI. • The indirect evidence suggests withdrawals due to adverse events were less likely for tildrakizumab than infliximab or ixekizumab, but not compared with placebo or other biologics or methotrexate; however, the authors stated that these results should be interpreted with caution due to the low frequency of withdrawal events across the network and the short duration of the trials. No analysis of the risk of infection was possible due to insufficient data in the literature. • The hierarchical cluster analysis suggested adalimumab, certolizumab pegol, ustekinumab, secukinumab, brodalumab, guselkumab, risankizumab, and tildrakizumab formed a cluster of biologics with high efficacy and tolerability.
Critical appraisal	• The methods used to conduct the SR and NMA were clear. • NMA did not include apremilast, acitretin, or cyclosporin, but included all biologics of interest to this review. • No justification was provided for the random-effects model selected; no other models were tested. No information was provided on model fit. • Appears there was limited assessment of study homogeneity.
Funding	Independent of the pharmaceutical industry

CI = confidence interval; DLQI = Dermatology Life Quality Index; HRQoL = health-related quality of life; IL = interleukin; ITC = indirect treatment comparison; NMA = network meta-analysis; PASI 75, 90 = at least a 75% or 90% reduction in the Psoriasis Area and Severity Index score; PGA = Physician's Global Assessment; RCT = randomized controlled trial; SR = systematic review; TNF = tumour necrosis factor.

Source: Mahil et al. (2020).[11]

Table 28: Summary of ITC By Xu et al. (2020)

Characteristic	Xu et al. (2020)[13]
Selection criteria	
Population	Patients with moderate-to-severe plaque psoriasis
Intervention	Immunomodulators (no information on doses included in the review): • TNF alpha inhibitors: adalimumab, etanercept, infliximab, certolizumab pegol • IL-17 drugs: secukinumab, ixekizumab, brodalumab, bimekizumab[a] • IL-12/23 drug: ustekinumab, briakinumab[a] • IL-23 drugs: guselkumab, tildrakizumab, risankizumab, mirikizumab[a]
Comparator	• Placebo • Any of the interventions of interest
Outcomes	• Short-term outcomes reported at 16 weeks (or time point closest to 16 weeks) • Efficacy: PASI 75, 90, PGA score of 0 or 1 • Safety: infection, adverse events
Study design	Published, English-language, double-blind RCTs with a sample size ≥ 30 patients
Methods	
Literature search	PubMed, Web of Science, and Cochrane Library (up to March 13, 2020) reference lists searched
Analysis methods	• Pairwise meta-analysis (STATA 11.0) (random-effects model if I2 > 50%) • Bayesian random-effects model with MCMC methods (WinBUGS 1.4.3) • Results reported as RR and 95% CrI • Model fit for fixed- and random-effects NMA models were assessed using DIC • Inconsistency assessed using DerSimonian-Laird method • Publication bias assessed using funnel plots and Egger's test

Characteristic	Xu et al. (2020)[13]
Results	
Number of included studies	60 trials (34,020 patients)
Summary of included trials	Trials were rated as good quality with a mean modified Jadad score of 5.9 (range 4 to 7). The average disease duration was 17.9 years, and mean PASI score was 20.4 at baseline.
Key findings	• Indirect evidence for PASI 90 response suggests tildrakizumab was statistically inferior to secukinumab, ixekizumab, and risankizumab. No statistically significant differences were found between tildrakizumab and adalimumab, certolizumab pegol, brodalumab, guselkumab, infliximab, or ustekinumab. Tildrakizumab was more effective than etanercept and placebo. • No statistical differences were detected between tildrakizumab and placebo on the likelihood of adverse events. The indirect evidence suggested the risk of adverse events may be lower for tildrakizumab than brodalumab, etanercept, infliximab, ixekizumab, and secukinumab.
Critical appraisal	• Reporting of the methods used to conduct the SR lacked detail; some study selection criteria were vague. • Study quality was assessed using the modified Jadad score, which may not fully capture the risk of bias. • The NMA did not include any non-biologic systemic treatments of interest to this review and analyzed some biologics that are not available in Canada (briakinumab, bimekizumab, mirikizumab). • Unclear what doses were included in the model, or at what time points the outcomes were measured. • No justification was provided for the random-effects model selected. Although a fixed-effect model was also tested, these results were not discussed and no DIC values were reported. • Appears there was limited assessment of study homogeneity. The authors reported there was moderate statistical heterogeneity detected in the pairwise meta-analysis. • Data extraction excluded any patients who withdrew or stopped due to treatment failure prior to the end point, which likely biases the results.
Funding	National Natural Science Foundation of China

CI = confidence interval; CrI = credible interval; DIC = deviance information criterion; IL = interleukin; ITC = indirect treatment comparison; MCMC = Markov chain Monte Carlo; NMA = network meta-analysis; PASI 75, 90 = at least a reduction of 75% or 90% in the Psoriasis Area and Severity Index score; RCT = randomized controlled trial; RR = relative risk; SR = systematic review; TNF = tumour necrosis factor.

[a] Not approved in Canada.

Source: Xu et al. (2020).[13]

Table 29: Summary of ITC by Sbidian et al.

Characteristic	Sbidian et al. (2020)[12]
Selection criteria	
Population	Adult patients with moderate-to-severe plaque psoriasis, including those with psoriatic arthritis, who required systematic treatment.
Intervention	Systemic treatments at any dose or duration: • TNF alpha inhibitors: Adalimumab, etanercept, infliximab, certolizumab pegol • IL-17 drugs: Secukinumab, ixekizumab, brodalumab, bimekizumab[a] • IL-12/23 drug: Ustekinumab • IL-23 drugs: Guselkumab, tildrakizumab, risankizumab, mirikizumab[a] • Small molecules: Apremilast, tofacitinib, deucravacitinib (BMS-986165)[a] • Systemic conventional treatments: Fumaric acid esters, acitretin, cyclosporin, methotrexate
Comparator	• Placebo (or other treatment required for network synthesis). • Any of the interventions of interest.
Outcomes	Short-term outcomes reported in the induction phase (8 to 24 weeks): • Efficacy: PASI 75, 90; PGA 0 or 1; HRQoL (DLQI or other disease-specific instruments)

Characteristic	Sbidian et al. (2020)[12]
	• Safety: SAE, any adverse event • Longer-term PASI 75 or 90 at 52 weeks
Study design	Published or unpublished phase II to IV RCTs in any language.
Methods	
Literature search	Cochrane, MEDLINE, Embase, and LILACS database (up to January 31, 2019), clinical trials registries, regulatory body websites, and other grey literature sources, conference proceedings, relevant article reference lists.
NMA methods	• Pairwise meta-analysis (Review Manager 5). • Frequentist multivariate NMA model (STATA 14) based on pooled data for all dosages. • Sensitivity analyses: separate node for different doses, excluding trials with high risk of bias, or sample size < 50 patients, including the only study reporting data between 12 and 16 weeks, and excluding trials in patients who were systemic treatment-naive. • Imputed patients with missing data as not having achieved a PASI response or an adverse event, with sensitivity analyses based on complete cases (i.e., ignoring missing patients). • Results reported as RR or SMD and 95% CI. • Inconsistency assessed using a loop-splitting approach, side-splitting methods, and fitting the design by treatment interaction model. • Publication bias assessed using funnel plots.
Results	
Number of included studies	140 trials (51,749 patients), of which 113 studies (47,085 patients) were included in a meta-analysis or NMA for at least 1 outcome.
Summary of included trials	• 82 trials compared systemic treatment against placebo; 41 were head-to-head trials and 17 had both an active comparator and a placebo. The sample size of trials ranged from 10 to 1,881 patients; 117 trials were multi-centre studies. The mean age of patients was 45 years (range 27 to 56.5 years), and mean baseline PASI score was 20 (range 9.5 to 39). • 41 studies were rated as low risk of bias, and 57 at high risk of bias. • Outcomes were reported at week 8 to 24.
Key findings	• Indirect evidence for PASI 90 response suggests tildrakizumab was statistically inferior to secukinumab, ixekizumab, guselkumab, risankizumab, and infliximab as induction therapy. No statistically significant differences were found between tildrakizumab and adalimumab, brodalumab, certolizumab pegol, ustekinumab, or cyclosporin. The data suggest that tildrakizumab was more effective than etanercept, most small-molecule or conventional treatments, and placebo. Results were similar for proportion of patients with PGA 0 or 1. • The NMA for PASI 75 response suggests tildrakizumab was more effective than etanercept, small-molecule or conventional treatments, and placebo. • The change from baseline in HRQoL was not statistically significantly different for tildrakizumab versus ixekizumab, guselkumab, risankizumab, infliximab, adalimumab, certolizumab pegol, ustekinumab, etanercept, and methotrexate. The differences between groups in HRQoL favoured tildrakizumab versus apremilast and placebo, but not brodalumab. • No statistically significant differences were detected between tildrakizumab and placebo or other active treatments on the likelihood of SAE. • The indirect evidence suggested that tildrakizumab was associated with a lower risk of adverse events than most other treatments.
Critical appraisal	• Methods used to conduct the SR were clear. • NMA included drugs that were not of interest to this review. • Primary analysis pooled all doses; however, only licensed doses are of interest to the CADTH review. • No justification was provided for the model selected, it was unclear if fixed- or random-effects models were used, or if multiple models were tested. • The analysis was based on a comprehensive network of studies that included conventional treatments, small molecules and biologic drugs at any dose, and pooled results reported between 8 and 24 weeks. Due to the broad scope of the review, it may have greater heterogeneity than other NMAs included in this report. Sbidian et al. conducted a comprehensive qualitative and quantitative

Characteristic	Sbidian et al. (2020)[12]
	assessment of study heterogeneity and numerous sensitivity analyses were conducted that examined the impact of potential sources of heterogeneity. The results of the sensitivity analyses were generally similar to the results of the primary analyses and no major inconsistency was detected between direct and indirect evidence. • Information on quality of life was poorly reported and was absent for several of the interventions. It is unclear if any of the differences detected were clinically meaningful. • Results for SAEs should be interpreted cautiously, given the short duration of the trials and lack of power to detect infrequent events.
Funding	National Institute of Health Research

CI = confidence interval; DLQI = Dermatology Life Quality Index; HRQoL = health-related quality of life; IL = interleukin; ITC = indirect treatment comparison; MCMC = Markov chain Monte Carlo; NMA = network meta-analysis; PASI 75, 90 = at least a 75% or 90% reduction in the Psoriasis Area and Severity Index score; PGA = Physician's Global Assessment; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SMD = standardized mean difference; SR = systematic review; TNF = tumour necrosis factor.

[a] Not approved in Canada.

Source: Sbidian et al. (2020).[12]

Other Relevant Studies

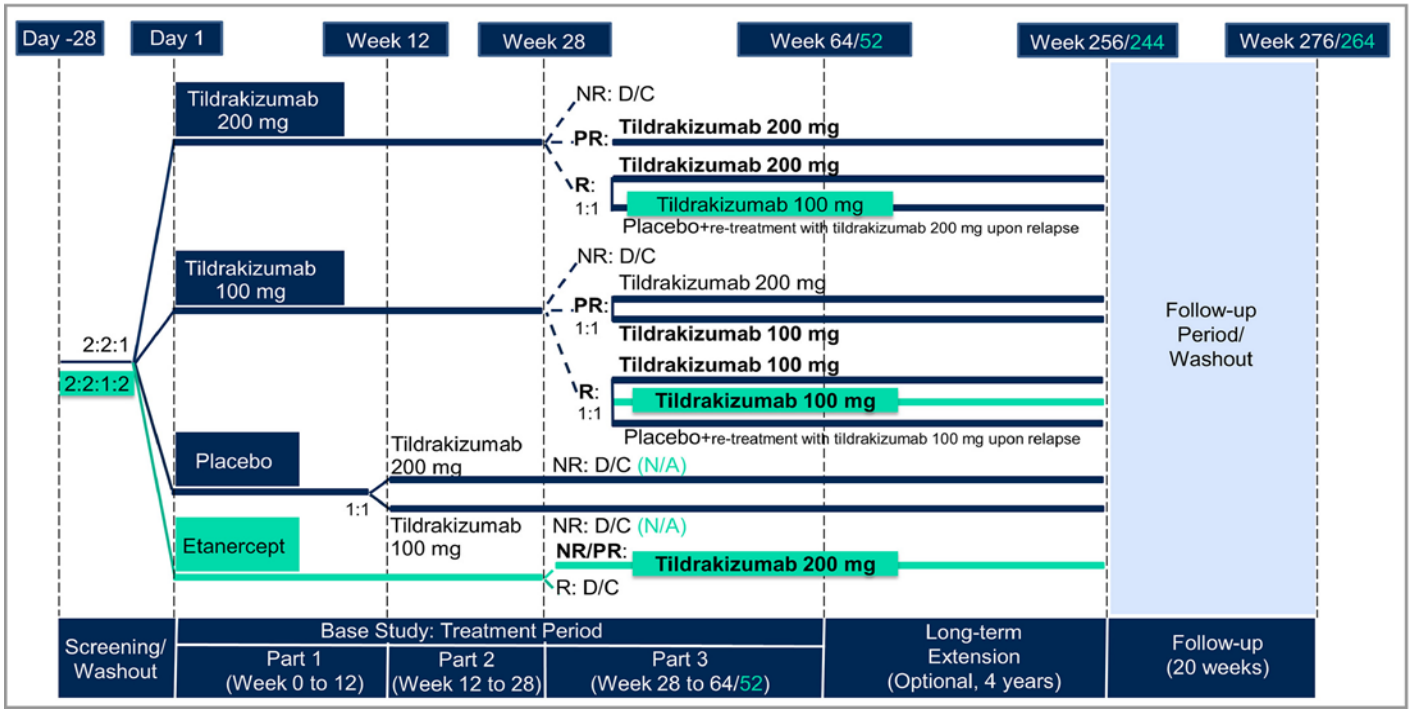
Long-Term Extension Studies

Long-term extension studies for both the P010 (reSURFACE 1) and P011 (reSURFACE 2) RCTs were ongoing at the time of the review. The relevant long-term efficacy and safety data were not available in the interim clinical study reports and, therefore, were extracted from a published journal article by Reich et al. (data cut-off of September 2019; estimated completion date was December 2020).[14] The pooled long-term efficacy and safety data for tildrakizumab from the 2 trials were available up to 148 weeks (2-year extension period), and a summary of the data is provided subsequently.

Methods

As described earlier in this report, P010 and P011 were 3-part, parallel-group, double-blinded, randomized, placebo-controlled phase III trials. Patients enrolled in both the P010 and P011 trials who completed part 3 (up to week 64 or 52, respectively) were entered into an optional, long-term open-label extension study to evaluate the efficacy and safety of tildrakizumab up to week 256 and week 244, respectively (Figure 9).[14] Clinical efficacy was assessed based on PASI 75, 90, and 100 response rates, as in the base studies, as well as absolute PASI scores (data not reported in this report). During the extension period, efficacy measurements were collected every 12 weeks. Safety assessments consisted of reporting all adverse events, including treatment-emergent adverse events and serious adverse events, as well as adverse events of special interest. Responders to tildrakizumab were defined as patients with a 75% or greater improvement in PASI (PASI 75), partial responders were defined as patients with a 50% to less than 75% improvement in PASI (PASI 50 to 75), and nonresponders were defined as patients with a less than 50% improvement in PASI (PASI < 50). Results were reported for 3 groups: patients who were responders to tildrakizumab 100 mg or 200 mg at week 28 and who continued tildrakizumab treatment in both studies, patients who were partial responders to tildrakizumab 100 mg or 200 mg at week 28 and who continued treatment tildrakizumab in both studies, and patients who were partial responders or nonresponders to etanercept 50 mg at week 28 and were switched to tildrakizumab 200 mg in Study P011.

Figure 9: Study Designs of P010 and P011 Base and Long-Term Extension Studies



D/C = discontinue; N/A = not applicable; NR = nonresponder; PR = partial responder; R = responder.

Source: Reproduced from Reich K, Warren RB, Iversen L, et al., Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: Pooled analyses of 2 randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. *British Journal of Dermatology*, June 19, 2019, through Creative Commons Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/148 weeks).[14]

Populations

As the long-term data were derived from Study P010 and P011, the study populations were the same as those reported earlier in this report. The pooled baseline characteristics from both studies at the time of randomization in the base studies were provided in the article by Reich et al.[14] The baseline characteristics of patients in the FAS for part 3 (efficacy analysis) or for those who entered into the extension study were not provided.

Interventions

The interventions in the P010 and P011 base studies are the same as previously reported in this review and are briefly summarized as follows:

- Part 1: Week 0 to week 12. Patients were randomized 2:2:1 to tildrakizumab 100 mg or 200 mg or placebo in P010, and randomized 2:2:1:2 to tildrakizumab 100 mg or 200 mg or placebo or etanercept 50 mg in P011.
- Part 2: Week 12 to week 28. Patients in active treatment groups continued on therapy, and those initially randomized to placebo were re-randomized to tildrakizumab 100 mg or 200 mg.
- Part 3: Week 28 to week 64 (P010) or week 52 (P011). Responders (PASI ≥ 75) in P010 were re-randomized to continue on the same dose of tildrakizumab or to placebo. In P011, responders to tildrakizumab 200 mg were re-randomized to tildrakizumab 100 mg or 200 mg, while responders to tildrakizumab 100 mg remained on the same

dose. Partial responders and nonresponders (PASI < 50) to etanercept 50 mg were crossed over to tildrakizumab 200 mg (week 32, week 36, and every 12 weeks thereafter).

In both trials, partial responders (PASI 50 to 75) to tildrakizumab 200 mg remained on the same dose, while partial responders to tildrakizumab 100 mg were re-randomized to tildrakizumab 100 mg or 200 mg (weeks 0, 4, and every 12 weeks thereafter). In P011, etanercept 50 mg was administered twice weekly in part 1 and once weekly in part 2. At the end of each study (week 64 or week 52), patients who completed part 3 with at least a partial response were entered into an optional long-term extension study up to week 192 (P010) or week 244 (P011). Patient disposition for all 3 parts of the 2 trials is summarized in Figure 10.[14]

Outcomes

The efficacy outcomes (PASI 75, 90, or 100) presented in this section correspond to the currently available pooled long-term data at the 148-week time point. The safety outcomes (treatment-emergent adverse events, serious adverse events, and adverse events of special interest) correspond to pooled harms data between week 0 and week 148.

Statistical Analysis

The analysis presented in Reich et al. focuses on 148-week efficacy data in patients who were responders (achieving PASI ≥ 75) or partial responders (achieving PASI 50 to 75) to tildrakizumab 100 mg or 200 mg at week 28 and who continued treatment with tildrakizumab in both Study P010 and Study P011. Long-term 148-week data are also available for patients who were partial responders or nonresponders (achieving PASI < 50) to etanercept 50 mg at week 28 and who were crossed over to tildrakizumab 200 mg in the P011 study (Figure 9).[14] Safety data for the 148-week period, pooled across both studies, were also available.

Efficacy analyses were performed on the FAS of part 3 of both studies, which includes all patients who entered part 3 (week 28) and received at least 1 dose of the assigned study treatment. An analysis was performed separately on the 3 groups: responders and partial responders to tildrakizumab 100 mg and tildrakizumab 200 mg, and partial responders or nonresponders to etanercept 50 mg. The presented data are based on nonresponder imputation, where patients with missing data were treated as nonresponders. Sensitivity analyses were conducted based on the observed case data and using multiple imputation methods for missing data. The 95% CIs are reported.[14]

Safety analyses were conducted on all of the tildrakizumab-treated patients and were based on the all-patients-as-treated population, which includes all randomized patients who received at least 1 dose of the assigned study treatment. Safety data are reported for weeks 0 to 148 as exposure-adjusted incidence rates (i.e., events per 100 PYs). Events were counted in each treatment group based on the treatment the patient received at the time of the adverse event (i.e., patients could be included in more than 1 treatment group due to crossover between drugs at weeks 12 and 28). Exposure-adjusted incidence rates were computed using the number of events, adjusted by the total PYs of follow-up for each treatment, where the total PYs of follow-up was the sum of the individual exposures in years for all patients by treatment, taking treatment crossovers into account.[14]

Patient Disposition

Patient disposition is summarized in Figure 10. At the first efficacy end point (week 28), there were 121 partial responders to etanercept 50 mg, who were then switched to tildrakizumab 200 mg, 369 responders (329 responders, 40 partial responders) to tildrakizumab 100 mg, and 329 responders (227 responders, 102 partial responders) to tildrakizumab 200 mg, who continued on the same dose of tildrakizumab. Of these patients, 107 (34%), 335 (54%), and 304 (49%) entered the extension period, respectively. Overall, 29.7% of patients initially randomized to etanercept, 46.3% of patients initially randomized to tildrakizumab 100 mg, and 42.2% of patients initially randomized to tildrakizumab completed week 148.[14]

Exposure to Study Treatments

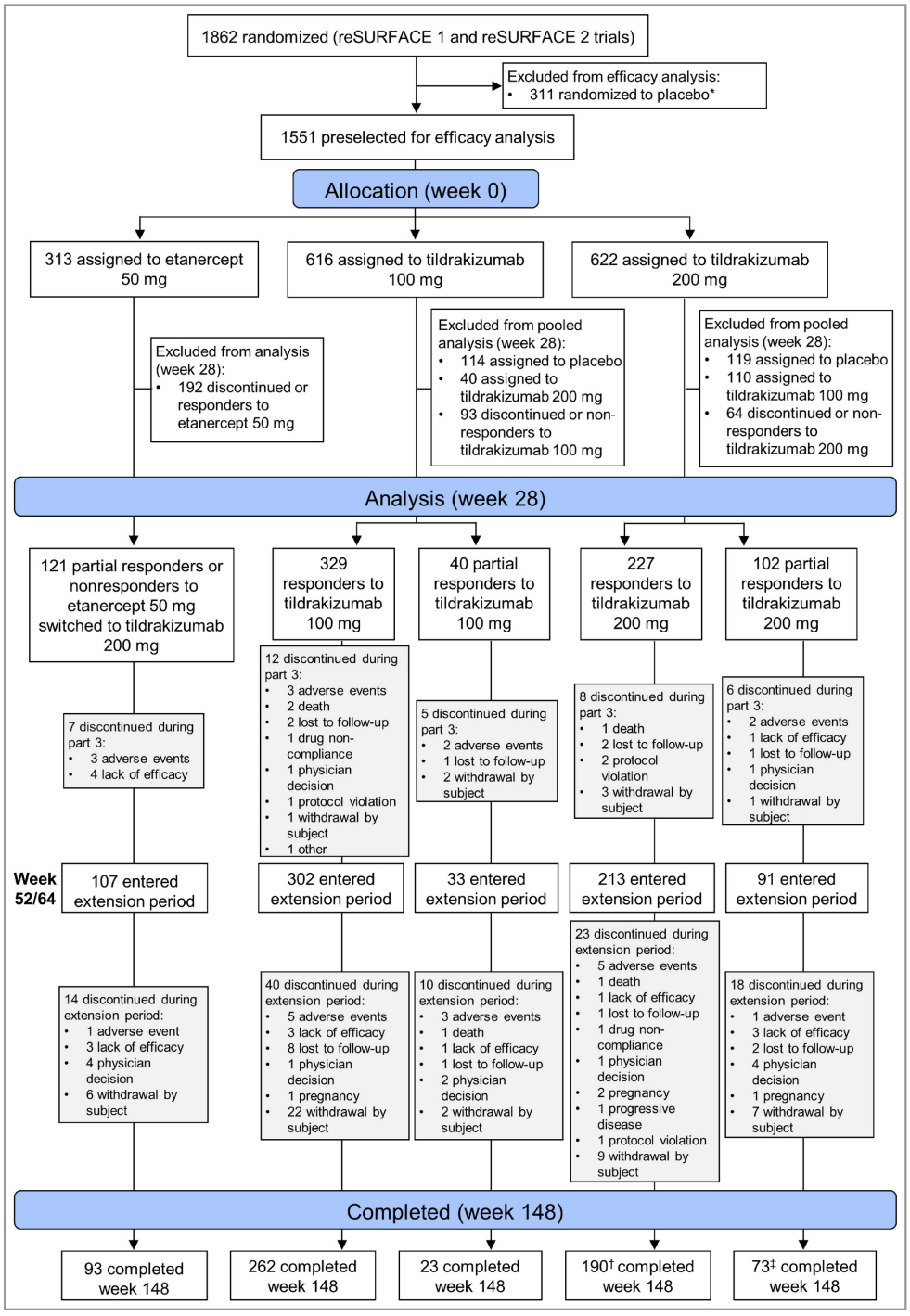
In the 148-week period (base studies plus 2-year extension period), the total exposure to tildrakizumab 100 mg and tildrakizumab 200 mg was 4,061.2 PYs.[14]

Efficacy

The proportions of responders to tildrakizumab 100 mg or 200 mg based on PASI 75, 90, and 100 responses at weeks 28, 52, and 148 are shown in Figure 11 (a) and (b), respectively. The proportion of partial responders to tildrakizumab 100 mg or 200 mg based on PASI 75, 90, and 100 responses at weeks 52 and 148 are presented in Table S3 in the article by Reich et al.[14] The nonresponder imputation method to account for missing data is reported. Responses were maintained at week 148, which represents a 2-year extension period. The proportion of partial responders or nonresponders to etanercept 50 mg who were switched to tildrakizumab 200 mg at week 29 are presented in Figure 11 (c).

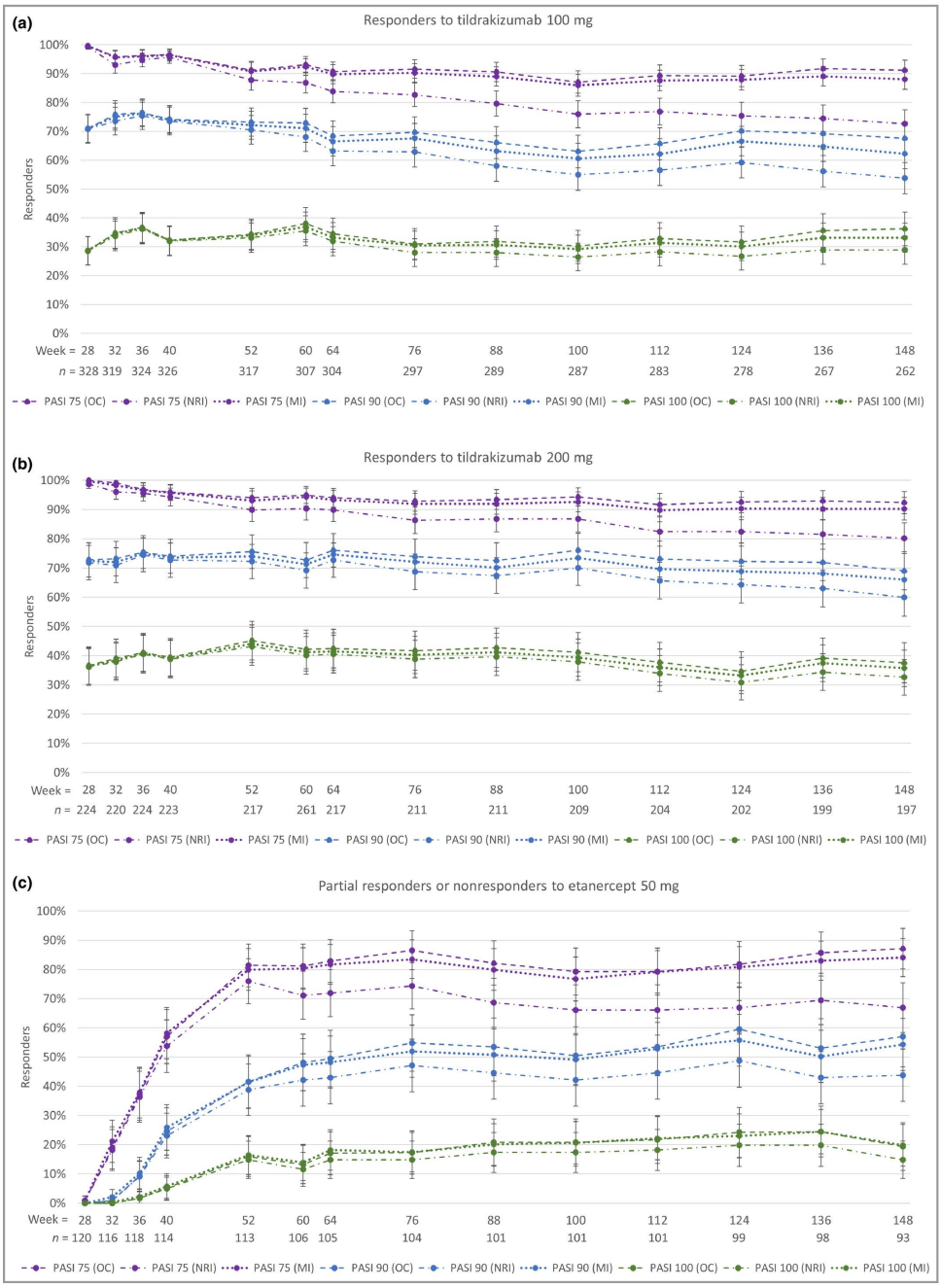
At week 148, 72.6%, 53.8%, and 28.9% of patients who were responders to tildrakizumab 100 mg, and 80.2%, 59.9%, and 32.6% of patients who were responders to tildrakizumab 200 mg, reported PASI 75, 90, and 100 responses, respectively. Furthermore, the 32.5%, 25.0%, and 10.0% of patients who were partial responders to tildrakizumab 100 mg, and the 47.1%, 27.5%, and 12.8% of patients who were partial responders to tildrakizumab 200 mg, reported PASI 75, 90, and 100 responses, respectively. For patients who were initially partially or nonresponsive to etanercept 50 mg and were switched to tildrakizumab 200 mg, 66.9%, 43.8%, and 14.9% of patients reported PASI 75, 90, and 100 responses, respectively. Overall, the treatment response observed up to week 148 was similar among patients who received tildrakizumab 100 mg and 200 mg.

Figure 10: Patient Disposition for P010 (reSURFACE 1) and P011 (reSURFACE 2) base and extension studies



Source: Reproduced from Reich K, Warren RB, Iversen L, et al., Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: Pooled analyses of 2 randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. *British Journal of Dermatology*, June 19, 2019, through Creative Commons Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/.[14]

Figure 11: PASI 75, 90, and 100 Response Up to Week 148 Among Responders to Tildrakizumab, and Partial Responders or Nonresponders to Etanercept 50 mg Who Switched to Tildrakizumab 200 mg



OC = observed case; MI = multiple imputation; NRI = nonresponder imputation; n = number of cases in the OC analyses; PASI = Psoriasis Area and Severity Index.

Note: Error bars represent 95% confidence intervals.

Source: Reproduced from Reich K, Warren RB, Iversen L, et al., Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: Pooled analyses of 2 randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. *British Journal of Dermatology*, June 19, 2019, through Creative Commons Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/.[14]

Harms

The summary of harms for week 0 to week 148 for tildrakizumab 100 mg and 200 mg, placebo, and etanercept is presented in Table 30.[14] The exposure-adjusted incidence rate for treatment-emergent adverse events was 35.2, 37.2, 148.6, and 148.6 events per 100 PYs, respectively. The most common treatment-emergent adverse event in all treatment groups was nasopharyngitis, which comprised 10.2, 9.8, 22.4, and 41.1 events per 100 PYs in the tildrakizumab 100 mg group, tildrakizumab 200 mg group, placebo group, and etanercept group, respectively. Other frequent adverse events occurring at a rate of at least 5% in 1 or more of the treatment groups were infections such as upper respiratory tract infections, influenza, bronchitis, and sinusitis. Few patients discontinued the study due to adverse events; 75, 52, 6, and 19 patients discontinued due to any type of adverse event in the tildrakizumab 100 mg, tildrakizumab 200 mg, placebo, and etanercept groups, respectively.[14] Rates of drug-related serious adverse events were low in the tildrakizumab 100 mg (0.79 events per 100 PYs) and tildrakizumab 200 mg (0.54 events per 100 PYs) groups. Nine deaths were reported up to week 148: 6 patients in the tildrakizumab 100 mg group and 3 patients in the tildrakizumab 200 mg group. Of the 9 deaths, 6 occurred during the base studies (causes of death: steatohepatitis and alcoholic cardiomyopathy, acute myeloid leukemia, respiratory arrest, myocardial infarction, aneurysm, and sepsis), and 3 occurred during the extension period of P011 (causes of deaths: intoxication by the combined effects of fluoxetine and cyclobenzaprine, an unknown reason of death, and a case of asphyxiation due to a tractor accident). Reich et al. indicated that all deaths in the extension study were assessed by the investigators and determined to be not related to the study medication.[14] One case of suicide attempt was reported in the tildrakizumab 200 mg group (0.05 events per 100 PYs).

A summary of severe infections, malignancies, confirmed extended MACEs, and hypersensitivity reactions are reported in Table 31.[14] The most common severe infection was cellulitis: 3 patients in the tildrakizumab 100 mg group (0.15 events per 100 PYs), 4 patients in the tildrakizumab 200 mg group (0.20 events per 100 PYs), 2 patients in the placebo group (0.97 events per 100 PYs), and 1 patient in the etanercept 50 mg group (0.65 events per 100 PYs), followed by herpes zoster and urosepsis. Severe infections appeared to be higher in the etanercept group (1.96 events per 100 PYs; 95% CI, 0.00 to 4.21). Injection-site reactions were higher in the etanercept group (40.41 events per 100 PYs; 95% CI, 30.15 to 50.68) compared with the tildrakizumab 200 mg group (2.30 events per 100 PYs; 95% CI, 1.63 to 2.97). The most common malignancies (excluding non-melanoma skin cancer) were breast cancer and lung adenocarcinoma, and the most common non-melanoma skin cancer was basal cell carcinoma. One patient in the tildrakizumab 100 mg group developed malignant melanoma (0.05 events per 100 PYs). The most common MACEs were coronary artery disease: 4 patients in the tildrakizumab 200 mg group (0.20 events per 100 PYs), acute myocardial infarction (3 patients in the tildrakizumab 200 mg group [0.15 events per 100 PYs] and 1 patient in the tildrakizumab 100 mg group [0.05 events per 100 PYs]), and cerebellar infarction (1 patient in the placebo group [0.49 events per 100 PYs]). One case of suspected new-onset Crohn disease occurred in the tildrakizumab 100 mg group (0.05 events per 100 PYs).[14]

Table 30: Summary of Harms for Week 0 to Week 148 (Events per 100 PYs of Exposure)

	Tildrakizumab 100 mg	Tildrakizumab 200 mg	Placebo	Etanercept 50 mg
Total patient-years of follow-up	2014·49	2046·71	205·30	153·42
TEAE	709; 35·20 (32·55–37·84)	761; 37·18 (34·49–39·88)	305; 148·6 (131·6–165·6)	228; 148·6 (128·9–168·3)
SAE	118; 5·86 (4·78–6·94)	112; 5·47 (4·44–6·51)	13; 6·33 (2·82–9·84)	20; 13·04 (7·21–18·87)
Deaths	6; 0·30 (0·05–0·54)	3; 0·15 (0·00–0·32)	0; 0·00	0; 0·00
Drug-related AE	229; 11·37 (9·87–12·87)	263; 12·85 (11·27–14·43)	73; 35·56 (27·23–43·88)	112; 73·00 (59·21–86·80)
Drug-related SAE	16; 0·79 (0·40–1·19)	11; 0·54 (0·21–0·86)	2; 0·97 (0·00–2·35)	5; 3·26 (0·34–6·17)
Discontinued due to AE	34; 1·69 (1·11–2·27)	25; 1·22 (0·73–1·71)	4; 1·95 (0·00–3·90)	9; 5·87 (1·96–9·78)
Discontinued due to SAE	19; 0·94 (0·51–1·38)	16; 0·78 (0·39–1·17)	1; 0·49 (0·00–1·46)	5; 3·26 (0·34–6·17)
Discontinued due to drug-related AE	15; 0·74 (0·36–1·13)	7; 0·34 (0·08–0·60)	1; 0·49 (0·00–1·46)	4; 2·61 (0·00–5·21)
Discontinued due to drug-related SAE	7; 0·35 (0·08–0·61)	4; 0·20 (0·00–0·39)	0; 0·00	1; 0·65 (0·00–1·96)

The data are represented as n; events per 100 patient-years of exposure (95% confidence interval). TEAE, treatment-emergent AE; SAE, serious AE.

AE = adverse event; PY = person-year; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Source: Reproduced from Reich K, Warren RB, Iversen L, et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: Pooled analyses of 2 randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. *British Journal of Dermatology*, June 19, 2019, through Creative Commons Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/.[14]

Table 31: 148-Week Cumulative Exposure-Adjusted Incidence Rates of AEs of Special Interest

	Tildrakizumab 100 mg	Tildrakizumab 200 mg	Placebo	Etanercept 50 mg
Severe infection[a]	23; 1·14 (0·67–1·62)	23; 1·12 (0·66–1·59)	2; 0·97 (0·00–2·35)	3; 1·96 (0·00–4·21)
Malignancy (excluding NMSC)	11; 0·55 (0·22–0·88)	8; 0·39 (0·11–0·67)	0; 0·00	2; 1·30 (0·00–3·15)
NMSC	10; 0·50 (0·18–0·81)	10; 0·49 (0·18–0·80)	2; 0·97 (0·00–2·35)	2; 1·30 (0·00–3·15)
Melanoma	1; 0·05 (0·00–0·15)	0; 0·00	0; 0·00	0; 0·00
Confirmed extended MACE[b]	8; 0·40 (0·12–0·68)	11; 0·54 (0·21–0·86)	1; 0·49 (0·00–1·46)	1; 0·65 (0·00–1·96)
Injection-site reaction[c]	39; 1·94 (1·32–2·56)	47; 2·30 (1·63–2·97)	11; 5·36 (2·13–8·59)	62; 40·41 (30·15–50·68)
Drug-related hypersensitivity reaction[d]	6; 0·30 (0·05–0·54)	3; 0·15 (0·00–0·32)	1; 0·49 (0·00–1·46)	0; 0·00

The data are represented as n; events per 100 patient-years of exposure (95% confidence interval). MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; SAE, serious AE. [a]Defined as any infection meeting the regulatory definition of an SAE, or any infection requiring intravenous antibiotics whether reported as an SAE or not. [b]Defined as nonfatal myocardial infarction, nonfatal stroke, unstable angina, coronary revascularization, resuscitated cardiac arrest, and cardiovascular deaths that were confirmed as 'cardiovascular' or 'sudden'. [c]The following preferred terms were included: injection-site bruising, injection-site discomfort, injection-site dryness, injection-site erythema, injection-site haematoma, injection-site haemorrhage, injection-site hypoaesthesia, injection-site induration, injection-site inflammation, injection-site oedema, injection-site pain, injection-site papule, injection-site paraesthesia, injection-site pruritus, injection-site reaction, injection-site swelling and injection-site urticaria. This information was only collected for AEs in the base study. [d]The following preferred terms were included: angio-oedema, hypersensitivity, injection-site urticaria, lip swelling, swelling face, swollen tongue and urticaria.

AE = adverse event; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; SAE serious adverse event.

Source: Reproduced from Reich K, Warren RB, Iversen L, et al., Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: Pooled analyses of 2 randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. *British Journal of Dermatology*, June 19, 2019, through Creative Commons Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/.[14]

Critical Appraisal

The main limitations of the pooled results of the 2 extension studies include the lack of randomization, the absence of an active comparator or placebo group, the reporting of descriptive summary statistics, and the absence of HRQoL outcomes. As with most extension studies, an additional limitation is the open-label study design; unblinding of the study drugs can bias the reporting of end points, particularly any subjective measures included in the PASI score. The reported efficacy data were limited to a subset of patients who had shown a positive response to tildrakizumab and who were able to tolerate therapy; initial nonresponders to tildrakizumab and responders to etanercept were excluded from part 3 of the base study and the extension studies. Furthermore, Reich et al. did not report the baseline characteristics of the patients included in the efficacy analysis; thus, it is not possible to assess how these patients compare with the randomized study population or those in clinical practice, limiting the generalizability of the results. As only descriptive statistics were published, and without comparator groups, the interpretation of the results is limited, and the magnitude of long-term clinical benefit of tildrakizumab may be overestimated.

Discussion

Summary of Available Evidence

Two multi-centre, double-blind, RCTs met the inclusion criteria for the systematic review (Study P010 and Study P011). These trials examined the efficacy and safety of tildrakizumab compared with placebo or etanercept in adults with moderate-to-severe plaque psoriasis who were candidates for phototherapy or systemic therapy.

In addition, 6 ITCs were included in this report that examined the comparative efficacy or safety of tildrakizumab versus TNF alpha inhibitors, IL-17 inhibitors, IL-23 inhibitors, IL-12/23 inhibitors, and other systemic therapies used in Canada to treat patients with moderate-to-severe plaque psoriasis.[8,9,10-13] Pooled safety and efficacy data from 2 ongoing open-label extension studies were also summarized (data up to 148 weeks).[14]

Interpretation of Results

Efficacy

Plaque psoriasis may have a substantial impact on patients' quality of life, and patients report that the disease frequently impacted their emotional well-being and social interactions. The pivotal trials captured the effects of tildrakizumab on HRQoL using a validated disease-specific instrument (DLQI); however, DLQI was a secondary outcome that was outside the statistical testing procedure. Since HRQoL was not a primary objective of the trials, it limits the conclusions that can be drawn from these data. At week 12, more patients who received tildrakizumab 100 mg reported a DLQI score of 0 or 1 (suggesting no impact of psoriasis on HRQoL) compared with placebo, with absolute differences ranging from 32% to 39%. The change from baseline to week 12 in the mean DLQI score also favoured tildrakizumab over placebo, with differences that exceeded the minimal important difference. The differences between tildrakizumab and etanercept for DLQI, however, were not statistically significant at week 12, and not clinically meaningful at week 28. These data suggest that tildrakizumab may have a positive impact on HRQoL in the short term, relative to placebo. However, this effect was similar to that of etanercept, even though the latter was deemed suboptimal in treatment dosage during part 2 of Study P011, according to the clinical expert consulted for this review.

In the 2 pivotal trials, tildrakizumab showed statistically and clinically important differences versus placebo for the co-primary outcomes (PASI 75 and PGA response) at week 12. Although PASI 75 is a validated and accepted outcome in clinical trials, the main goal of therapy is clearance of plaques and, according to the clinical expert, PASI 90 is the expected target response for IL-23 and IL-17 drugs available in Canada. For both doses of tildrakizumab, patients were more likely to achieve a PASI 90 or PASI 100 response than placebo at 12 weeks, with between-group differences in the percentage of responders ranging from 32% to 38% for PASI 90, and 12% to 13% for PASI 100. Tildrakizumab 100 mg, the Health Canada–recommended dose, failed to achieve statistical significance compared with etanercept for PGA response at week 12. Thus, all further testing of outcomes in the statistical hierarchy was stopped, and comparisons between tildrakizumab 100 mg versus etanercept were deemed not statistically significantly different for PASI 75, 90, and 100 response at week 12. The indirect evidence from 6 NMAs suggests that tildrakizumab 100 mg was more effective in inducing PASI 75, 90, or 100 response than etanercept.[8-13]

In general, the results for the 100 mg and 200 mg dosage groups of tildrakizumab were similar, as were the sensitivity analyses that used methods other than nonresponder imputation to address missing data. The PASI 75 and PGA results data were similar for subgroups of interest to this review, although no treatment-by-subgroup interaction P values were reported.

The 12-week data for studies P010 and P011 were rated as low risk of bias; however, data for part 2 and part 3 of the trials had a number of important limitations. After week 12, efficacy data were based on the subpopulation of patients who entered part 2 or part 3 of the trials (i.e., not the intention-to-treat population). Moreover, efficacy outcomes were reported descriptively based on observed case data, which could potentially inflate the effects of tildrakizumab as, in general, patients who are doing poorly are more likely to drop out. Patients were switched between treatments at weeks 12 and 28 using different methods, depending on prior treatment allocation or response to therapy and, for parts of the trials, there was no control group, as all patients were receiving tildrakizumab. Although part 2 of Study P011 included an etanercept control group, according to the clinical expert consulted for this review, the dose of etanercept administered was lower than would be used in clinical practice and may be considered suboptimal and inflate the relative treatment effects of tildrakizumab. Due to the switches in therapy, loss of randomization, lack of a control group or use of a suboptimal active control, and potential attrition bias, the data for parts 2 and 3 of the pivotal trials are difficult to interpret.

Descriptive data showed that the proportion of patients in the tildrakizumab groups who achieved a PASI 75 or PGA response were relatively stable from week 12 to 28, whereas the proportion of patients with a PASI 90 or 100 response showed increases over time. However, no statistical testing was performed to examine the time trends for these data. Although the point estimates favoured tildrakizumab 100 mg versus etanercept in the proportion of patients with a PASI 75 or PGA response at week 28, the differences were not statistically significant according to the statistical testing procedure.

In part 3 of the trials, only patients who showed a partial response or PASI 75 response to tildrakizumab were eligible to continue, whereas only those who were nonresponders or partial responders to etanercept were enrolled in part 3 of P011. The available data for part 3 suggest that the majority of patients who achieved a PASI 75 response may maintain that response. Approximately half of patients who had achieved a PASI 75 response with tildrakizumab 100 mg reported a relapse after being switched to placebo, compared with 7% of patients who remained on tildrakizumab 100 mg.

The pooled long-term data from the 2 pivotal trials provided up to 148 weeks (2-year extension data) of efficacy and safety data for tildrakizumab at 2 doses (100 mg and 200 mg). Overall, the data suggest that clinical efficacy was maintained for the majority of patients who initially responded to tildrakizumab at week 28 and continued on treatment.[14] PASI 75 responses were maintained in approximately 75% of patients who were responders in both the tildrakizumab 100 mg and tildrakizumab 200 mg groups through 148 weeks of treatment (based on nonresponder imputation methods). The data also suggest that PASI 90 and 100 responses were stable throughout the 148 weeks. Furthermore, the data show that PASI 75 was achieved and maintained for up to 148 weeks in approximately 65% of patients who initially partially responded or did not respond to etanercept 50 mg and were switched to tildrakizumab 200 mg. These data should be interpreted with caution considering the limitations, which include the lack of randomization and blinding, the

absence of an active comparator or placebo group, reporting of descriptive summary statistics, and the absence of HRQoL outcomes.

Tildrakizumab has not been compared head-to-head with any other immunomodulators besides etanercept, but indirect evidence suggests it may be less effective than IL-17 inhibitors (ixekizumab, brodalumab, secukinumab), other IL-23 inhibitors (guselkumab, risankizumab), and infliximab in terms of PASI 75 or 90 response in the induction period.[8-13] The 6 NMAs that provided supporting evidence to this review were based on systematic reviews of RCTs in adults with moderate-to-severe psoriasis who received TNF alpha inhibitors, IL-17 inhibitors, IL-23 inhibitors, IL12/23 inhibitors, and other systemic therapies. In 2 reports,[8,9] the NMA was conducted using a placebo-adjusted Bayesian random-effects multinomial model, 2 reports used an unadjusted Bayesian random-effects model,[10,13] and 2 used frequentist NMA models.[11,12] Although these analyses have some limitations, the efficacy findings of all 6 were consistent. The design of the included RCTs was such that it was not possible to analyze longer-term effects; thus, comparative data for tildrakizumab beyond the induction period are lacking. Moreover, indirect evidence on the impact of an immunomodulator on HRQoL was limited.

The clinical expert consulted for the review indicated that the patients enrolled were reflective of patients with moderate-to-severe psoriasis in Canada. Generalizability may be limited for patients with prior exposure to IL-23 or IL-17 inhibitors or etanercept, as these patients were excluded from the studies. All patients were required to stop topical therapies for psoriasis; however, in clinical practice, patients usually continue topical treatments while receiving biologic therapies. According to the clinical expert, it is unlikely that tildrakizumab will cause a shift in the treatment paradigm for moderate-to-severe plaque psoriasis, as prior use of methotrexate, apremilast, or cyclosporine is generally required for reimbursement. However, dermatologists may favour the IL-17 and IL-23 inhibitors, including tildrakizumab, as the first biologic drug of choice due to their high efficacy.

Harms

The frequency of adverse events, including infections or infestations, was similar across the tildrakizumab, placebo, and etanercept groups during the induction period of the pivotal trials. Withdrawals due to adverse events, serious adverse events, and serious infections were infrequent. Other notable harms specified in the review protocol (malignancies, cardiovascular adverse events, drug-related hypersensitivity events) were also infrequent. Among those who received tildrakizumab, treatment-emergent anti-drug antibodies were reported in 6% to 9% of patients over 52 to 64 weeks; however, the clinical relevance of the antibodies is unclear. Although no major safety signals were observed based on data up to 148 weeks from the base and extension studies, these trials were not designed or powered to detect rare adverse events or those with a longer lag time.

Although only 1 tuberculosis-related adverse event was reported, patients with active or latent tuberculosis were excluded from the trials. The trials also excluded patients with recent acute infections or who had a chronic HIV or hepatitis B or C infection. Although no increased risk of infection was observed among those who received tildrakizumab in the trials, additional data are required to evaluate the risk of infection in clinical practice.

Four NMAs examined short-term safety outcomes.[10-13] No statistically significant differences were detected between tildrakizumab and placebo or other active treatments on the likelihood of discontinuation[10] or serious adverse events during the induction period.[12] The indirect evidence suggested that withdrawals due to adverse effects may be less likely for

tildrakizumab than infliximab or ixekizumab.[11] Two ITCs suggested that the frequency of adverse events may be lower for tildrakizumab than other biologic treatments.[12,13] However, these results should be viewed with caution due to the short duration of the trials, the low power of the trials to detect infrequent adverse events, and the limitations of the ITCs.

Conclusions

Tildrakizumab showed statistically and clinically important differences versus placebo in psoriasis disease severity, measured as a PASI 75, PASI 90, PASI 100, and/or PGA response at week 12 among patients with moderate-to-severe plaque psoriasis who were candidates for phototherapy or systemic therapy. However, the differences between tildrakizumab 100 mg and etanercept for these outcome measures of disease severity at week 12 were not statistically significant.

At week 12, tildrakizumab also showed improvement in HRQoL (measured using the DLQI) compared with placebo but not compared with etanercept; however, HRQoL outcomes were outside the statistical testing procedure and should be interpreted as supportive evidence in view of the inflated risk of type I error.

Even though the trials reported efficacy outcomes up to 64 weeks, due to the design of the studies, conclusions on the comparative efficacy of tildrakizumab could only be drawn from the induction period (12 weeks). The longer-term data suggest that PASI response may be maintained in the majority of patients who continue tildrakizumab therapy.

Indirect evidence suggests that tildrakizumab may be less effective in inducing PASI 75, 90, or 100 response compared with IL-17 inhibitors (ixekizumab, brodalumab, secukinumab), other IL-23 inhibitors (guselkumab, risankizumab), and infliximab, but may be more effective than etanercept or apremilast.

The incidence of serious adverse events or withdrawals due to adverse events was low among patients who received tildrakizumab, and no new safety signals were identified in the longer-term extension studies. The RCTs were not designed or powered to detect rare adverse events or those with a longer lag time, and longer-term comparative safety data are lacking.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) Cochrane Central Register of Controlled Trials (CCTR) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 10, 2019
Alerts:	Weekly search updates until project completion
Limits:	Publication date limit: none used Language limit: None used Conference abstracts: excluded

SYNTAX GUIDE	
/	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 terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
.jw	Journal word title
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

MULTI-DATABASE STRATEGY
1. (ilumya* or tildrakizumab or ilumetri* or MK3222 or MK-3222 or SCH900222 or SCH-900222 or SUNPG1622 or SUNPG-1622 or SUNPG1623 or SUNPG-1623 or UNIIDEW6X41BEK or DEW6X41BEK).ti,ab,kf,ot,hw,rn,nm.
2. 1 use medall
3. *tildrakizumab/
4. (ilumya* or tildrakizumab or ilumetri* or MK3222 or MK-3222 or SCH900222 or SCH-900222 or SUNPG1622 or SUNPG-1622 or SUNPG1623 or SUNPG-1623).ti,ab,kw,dq.
5. 3 or 4
6. 5 use oemezd
7. 2 or 6
8. conference abstract.pt.
9. conference review.pt.
10. 8 or 9
11. 7 NOT 10
12. Remove duplicates

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. [Search – Studies for Ilumya AND psoriasis]	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search parameters: Studies for Ilumya AND psoriasis]	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Cochrane Central	*Same MeSH, keywords, and limits used as per MEDLINE search,*	

Grey Literature

Dates for Search:	September 6, 2019
Keywords:	Ilumya, psoriasis
Limits:	None used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

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

Appendix 2: Excluded Studies

Table 32: Excluded Studies

Reference	Reason for exclusion
1. Reich K, Warren RB, Iversen L, et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: pooled analyses of 2 randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. Br J Dermatol 2019. 2. Papp K, Thaci D, Reich K, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase Iib randomized placebo-controlled trial. Br J Dermatol 2015;173:930-9. 3. Papp KA, Reich K, Blauvelt A, et al. Efficacy of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of 3 randomized controlled trials at weeks 12 and 28. J Eur Acad Dermatol Venereol 2019;33:1098-106. 4. Kimball AB, Kerbusch T, van Aarle F, et al. Assessment of the effects of immunogenicity on the pharmacokinetics, efficacy and safety of tildrakizumab. Br J Dermatol 2019;27:27. 5. Kimball AB, Papp KA, Reich K, et al. Efficacy and safety of tildrakizumab for plaque psoriasis with continuous dosing, treatment interruption, dose adjustments, and switching from etanercept: results from phase 3 studies. Br J Dermatol 2019;05:05. 6. Elewski B, Menter A, Crowley J, et al. Sustained and continuously improved efficacy of tildrakizumab in patients with moderate-to-severe plaque psoriasis. J Dermatolog Treat 2019:1-6. 7. Blauvelt A, Reich K, Papp KA, et al. Safety of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of 3 randomized controlled trials. Br J Dermatol 2018;179:615-22. 8. Blauvelt A, Sofen H, Papp K, et al. Tildrakizumab efficacy and impact on quality of life up to 52 weeks in patients with moderate-to-severe psoriasis: A pooled analysis of 2 randomized controlled trials. J Eur Acad Dermatol Venereol 2019. 9. Bissonnette R, Fernandez-Penas P, Puig L, Mendelsohn AM, Rozzo SJ, Menter A. Incidence of cardiovascular events among tildrakizumab-treated patients with moderate-to-severe plaque psoriasis: pooled data from 3 large randomized clinical trials. J Eur Acad Dermatol Venereol 2019;12:12.	Study design
10. Jauslin P, Kulkarni P, Li H, et al. Population-Pharmacokinetic Modeling of Tildrakizumab (MK-3222), an Anti-Interleukin-23-p19 Monoclonal Antibody, in Healthy Volunteers and Subjects with Psoriasis. Clin Pharmacokinet 2019 ;58 :1059-68.	Population

Appendix 3: Detailed Outcome Data

Table 33: Proportion of Patients With a DLQI Score of 1 or Less (Part 1 FAS)

Treatment group	Total N[a]	DLQI score ≤ 1 at week 12			DLQI score ≤ 1 at week 12	
		n (%)	Difference in % versus placebo (95% CI)[b]	P value[b]	Difference in % versus etanercept (95% CI)	P value
P010 (reSURFACE 1)						
Placebo	150	8 (5.3)	Reference		NA	NA
Tildrakizumab 100 mg	304	126 (41.5)	36.1 (29.3 to 42.5)	< 0.001[c]		
Tildrakizumab 200 mg	299	132 (44.2)	38.9 (31.9 to 45.4)	< 0.001[c]		
P011 (reSURFACE 2)						
Placebo	150	12 (8.0)	Reference		NR	NR
Tildrakizumab 100 mg	293	119 (40.2)	32.1 (24.5 to 39.1)	< 0.001[c]	4.8 (−2.9 to 12.5)	0.221[c]
Tildrakizumab 200 mg	306	145 (47.4)	39.3 (31.8 to 46.1)	< 0.001[c]	11.9 (4.1 to 19.5)	0.003[c]
Etanercept 50 mg	304	108 (35.5)	NR	NR	Reference	

CI = confidence interval; DLQI = Dermatology Life Quality Index; FAS = full analysis set; NA = not applicable; NR = not reported.

[a] Number of patients with data at week 12.

[b] P value based on Cochran-Mantel-Haenszel test stratified by body weight (≤ 90 kg, > 90 kg) and prior exposure to biologic therapy (yes or no). Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight and prior biologic exposure with sample size weights. No imputation for missing data.

[c] Outside the statistical testing hierarchy.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Table 34: DLQI Results for Part 2

Outcome	P010 (reSURFACE 1)				P011 (reSURFACE 2)				
	PBO to TILD 100 mg N = 74	PBO to TILD 200 mg N = 72	TILD 100 mg N = 299	TILD 200 mg N = 298	PBO to TILD 100 mg N = 70	PBO to TILD 200 mg N = 72	TILD 100 mg N = 294	TILD 200 mg N = 299	Etanercept 50 mg N = 298
Proportion of patients with a DLQI score ≤ 1 at week 28									
N	71	68	290	289	68	69	290	297	282
n (%)[a]	37 (52)	38 (56)	152 (52)	164 (57)	26 (38)	39 (57)	157 (54)	193 (65)	111 (39)
Difference in % (95% CI) versus etanercept[b]	NA	NA	NA	NA	NA	NA	15.0 (6.9 to 22.9)	25.7 (17.7 to 33.4)	Reference
P value versus etanercept[b]							< 0.001[c]	< 0.001[c]	
Change from baseline in DLQI to week 28									
N	71	67	287	288	67	69	294	299	289
Baseline mean (SD)[a]	12.5 (8.0)	13.6 (6.5)	13.8 (6.8)	13.2 (6.9)	13.5 (6.9)	13.0 (6.6)	14.8 (7.2)	13.2 (7.0)	14.5 (7.2)

Outcome	P010 (reSURFACE 1)				P011 (reSURFACE 2)				
	PBO to TILD 100 mg N = 74	PBO to TILD 200 mg N = 72	TILD 100 mg N = 299	TILD 200 mg N = 298	PBO to TILD 100 mg N = 70	PBO to TILD 200 mg N = 72	TILD 100 mg N = 294	TILD 200 mg N = 299	Etanercept 50 mg N = 298
Mean change from baseline (SD)[a]	−9.4 (7.4)	−11.2 (6.5)	−10.8 (6.7)	−10.8 (7.2)	−8.5 (6.5)	−10.3 (6.6)	−11.7 (7.2)	−10.9 (6.9)	−9.8 (7.3)
Difference in LS means (95% CI) versus etanercept[d]	NA	NA	NA	NA	NA	NA	1.7 (−2.4 to −1.0)	−2.2 (−2.9 to −1.5)	Reference
P value versus etanercept[d]							< 0.001[c]	< 0.001[c]	

CI = confidence interval; DLQI = Dermatology Life Quality Index; FAS = full analysis set; LS = least squares; NA = not applicable; PBO = placebo; SD = standard deviation; TILD = tildrakizumab.

[a] Based on the number of patients who received at least 1 dose of the study drug in part 2 and had valid outcome data at baseline and week 28.

[b] P value based on Cochran-Mantel-Haenszel test stratified by body weight (≤ 90 kg, > 90 kg) and prior exposure to biologic therapy (yes or no). Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight and prior biologic exposure with sample size weights. No imputation for missing data.

[c] Outside the statistical testing procedure.

[d] Based on a constrained longitudinal data analysis model including terms for time, interaction of time by treatment, body weight, and prior exposure to biologic therapy for psoriasis. Includes patients who received at least 1 dose of the study drug in part 2 and who had baseline and 1 post-baseline outcome measure.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Table 35: Change From Baseline in EQ-5D Index Score — Study P010 (FAS)

P010 (reSURFACE 1)	Total N[a]	Baseline	End-of-treatment time point	
		Mean (SD)	Mean (SD)	Mean change from baseline (SD)
EQ-5D index score				
Part 1 — week 12				
Placebo	149	0.7 (0.23)	0.7 (0.28)	0.0 (0.26)
Tildrakizumab 100 mg	301	0.7 (0.25)	0.9 (0.18)	0.2 (0.27)
Tildrakizumab 200 mg	297	0.7 (0.26)	0.9 (0.18)	0.2 (0.25)
Part 2 — week 28				
Placebo to tildrakizumab 100 mg	71	0.7 (0.21)	0.9 (0.14)	0.2 (0.22)
Placebo to tildrakizumab 200 mg	67	0.7 (0.25)	0.9 (0.19)	0.2 (0.30)
Tildrakizumab 100 mg	287	0.7 (0.25)	0.9 (0.17)	0.2 (0.27)
Tildrakizumab 200 mg	288	0.7 (0.26)	0.9 (0.16)	0.2 (0.26)

CI = confidence interval; EQ-5D = EuroQol 5-Dimensions questionnaire; FAS = full analysis set; SD = standard deviation.

[a] Number of patients with data at end point. Results reported descriptively with no between-group comparisons.

Source: Clinical Study Report for Study P010.[6]

Table 36: Change From Baseline in SF-36 — Study P010 (FAS)

P010 (reSURFACE 1)	Total N[a]	Baseline	End-of-treatment time point	
		Mean (SD)	Mean (SD)	Mean change from baseline (SD)
SF-36 mental health component score				
Part 1, week 12				
Placebo	149	46.8 (11.23)	46.1 (11.37)	−0.7 (7.52)
Tildrakizumab 100 mg	301	46.4 (11.16)	50.3 (9.18)	3.9 (9.39)
Tildrakizumab 200 mg	297	45.3 (11.4)	50.9 (8.93)	5.6 (9.95)
Part 2, week 28				
Placebo to tildrakizumab 100 mg	71	46.0 (10.84)	49.7 (10.59)	3.7 (8.99)
Placebo to tildrakizumab 200 mg	67	47.7 (11.97)	52.3 (7.53)	4.7 (8.29)
Tildrakizumab 100 mg	287	46.4 (11.21)	51.4 (8.81)	5.0 (9.84)
Tildrakizumab 200 mg	288	45.5 (11.35)	52.2 (7.76)	6.7 (10.01)
SF-36 physical health component score				
Part 1, week 12				
Placebo	149	47.7 (9.28)	48.7 (9.04)	1.0 (6.58)
Tildrakizumab 100 mg	301	47.7 (9.03)	51.5 (7.52)	3.7 (7.72)
Tildrakizumab 200 mg	297	46.8 (9.50)	50.4 (8.62)	3.5 (7.13)
Part 2, week 28				
Placebo to tildrakizumab 100 mg	71	47.9 (8.27)	50.2 (9.32)	2.3 (8.45)
Placebo to tildrakizumab 200 mg	67	47.3 (10.06)	51.2 (8.39)	3.9 (7.34)
Tildrakizumab 100 mg	287	47.8 (9.01)	51.5 (7.49)	3.7 (8.02)
Tildrakizumab 200 mg	288	46.8 (9.52)	51.0 (8.62)	4.2 (7.88)

CI = confidence interval; ETAN = etanercept; FAS = full analysis set; SD = standard deviation; SF-36 = Short Form (36) Health Survey.

[a] Number of patients with data at end point. Results reported descriptively with no between-group comparisons.

Source: Clinical Study Report for Study P010.[6]

Table 37: Subgroup Analyses for PASI 75 and PGA Response at Week 12 — Study P010

Study P010 (reSURFACE 1)	Total N	PASI 75 response at week 12		PGA response at week 12	
		n (%)	Difference in % versus placebo (95% CI)	N (%)	Difference in % versus placebo (95% CI)
Prior biologic therapy for psoriasis: yes					
Placebo	34	0	Reference	1 (2.9)	Reference
Tildrakizumab 100 mg	71	39 (54.9)	55.1 (42.7 to 66.2)[a]	35 (49.3)	46.7 (32.2 to 58.8)
Tildrakizumab 200 mg	71	40 (56.3)	56.4 (44.0 to 67.4)[a]	36 (50.7)	48.0 (33.5 to 60.1)
Prior biologic therapy for psoriasis: No					
Placebo	120	9 (7.5)	Reference	10 (8.3)	Reference
Tildrakizumab 100 mg	238	158 (66.4)	58.9 (50.5 to 65.9)[a]	144 (60.5)	52.2 (43.5 to 59.6)
Tildrakizumab 200 mg	237	152 (64.1)	56.6 (48.2 to 63.8)[a]	146 (61.6)	53.3 (44.6 to 60.6)

Study P010 (reSURFACE 1)	Total N	PASI 75 response at week 12		PGA response at week 12	
		n (%)	Difference in % versus placebo (95% CI)	N (%)	Difference in % versus placebo (95% CI)
Failure to respond to at least 1 traditional systemic therapy: Yes[b]					
Placebo	38	1 (2.6)	Reference	0	Reference
Tildrakizumab 100 mg	71	46 (64.8)	62.2 (47.8 to 73.0)[c]	40 (56.3)	56.0 (43.3 to 67.2)
Tildrakizumab 200 mg	83	52 (62.7)	59.6 (46.0 to 70.3)[c]	51 (61.4)	61.0 (48.3 to 70.9)
Failure to respond to at least 1 traditional systemic therapy: No[b]					
Placebo	29	0	Reference	1 (3.4)	Reference
Tildrakizumab 100 mg	58	34 (58.6)	59.0 (43.7 to 71.0)[c]	35 (60.3)	57.7 (39.4 to 70.5)
Tildrakizumab 200 mg	57	30 (52.6)	53.2 (37.7 to 65.8)[c]	29 (50.9)	47.6 (29.6 to 61.4)

CI = confidence interval; FAS = full analysis set; PASI 75 = at least a 75% improvement in the Psoriasis Area and Severity Index score; PGA = Physician's Global Assessment.

[a] Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight with sample size weights. Patients with missing data were classified as nonresponders.

[b] Methotrexate, cyclosporine, or phototherapy.

[c] Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight and prior biologic therapy, with sample size weights. Patients with missing data were classified as nonresponders.

Source: Clinical Study Report for Study P010.[6]

Table 38: Subgroup Analyses for PGA Response at Week 12 — Study P011

Study P010 (reSURFACE 1)	Total N	PASI 75 response at week 12		
		n (%)	Difference in % versus placebo (95% CI)	Difference in % versus etanercept (95% CI)
Prior biologic therapy for psoriasis: Yes[a]				
Placebo	20	0	Reference	NR
Tildrakizumab 100 mg	39	20 (51.3)	50.7 (30.0 to 65.9)	14.4 (−6.7 to 34.4)
Tildrakizumab 200 mg	38	18 (47.4)	46.9 (27.7 to 62.6)	9.2 (−12.8 to 30.3)
Etanercept 50 mg	37	14 (37.8)	NR	Reference
Prior biologic therapy for psoriasis: No[a]				
Placebo	136	7 (5.1)	Reference	NR
Tildrakizumab 100 mg	268	148 (55.2)	50.1 (42.6 to 56.8)	6.3 (−2.1 to 14.5)
Tildrakizumab 200 mg	276	168 (60.9)	55.8 (48.4 to 62.3)	12.0 (3.8 to 20.1)
Etanercept 50 mg	276	135 (48.9)	NR	Reference
Failure to respond to at least 1 traditional systemic therapy: Yes[b,c]				
Placebo	97	4 (4.1)	Reference	NR
Tildrakizumab 100 mg	193	104 (53.9)	49.8 (41.2 to 57.5)	8.2 (−1.7 to 17.9)
Tildrakizumab 200 mg	194	114 (58.8)	54.7 (46.2 to 62.2)	131 (3.2 to 22.6)
Etanercept 50 mg	195	89 (45.6)	NR	Reference
Failure to respond to at least 1 traditional systemic therapy: No[b,c]				
Placebo	59	3 (5.1)	Reference	NR

Study P010 (reSURFACE 1)	Total N	PASI 75 response at week 12		
		n (%)	Difference in % versus placebo (95% CI)	Difference in % versus etanercept (95% CI)
Tildrakizumab 100 mg	114	64 (56.1)	50.6 (38.1 to 60.8)	6.2 (−6.3 to 18.6)
Tildrakizumab 200 mg	120	72 (60.0)	54.7 (42.4 to 64.4)	9.0 (−3.5 to 21.3)
Etanercept 50 mg	118	60 (50.8)	NR	Reference

CI = confidence interval; FAS = full analysis set; NR = not reported; PGA = Physician's Global Assessment.

[a] Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight with sample size weights. Patients with missing data were classified as nonresponders.

[b] Methotrexate, cyclosporine, or phototherapy.

[c] Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight and prior biologic therapy, with sample size weights. Patients with missing data were classified as nonresponders.

Source: Clinical Study Report for Study P011.[7]

Table 39: Subgroup Analyses for PASI 75 Response at Week 12 — Study P011

Study P010 (reSURFACE 1)	Total (N)	PASI 75 response at week 12		
		n (%)	Difference in % versus placebo (95% CI)	Difference in % versus etanercept (95% CI)
Prior biologic therapy for psoriasis: Yes[a]				
Placebo	20	0	Reference	NR
Tildrakizumab 100 mg	39	25 (64.1)	63.6 (42.8 to 77.0)	18.8 (−3.1 to 39.0)
Tildrakizumab 200 mg	38	22 (57.9)	57.5 (37.8 to 72.0)	11.8 (−10.8 to 33.2)
Etanercept 50 mg	37	17 (45.9)	NR	Reference
Prior biologic therapy for psoriasis: No[a]				
Placebo	136	9 (6.6)	Reference	NR
Tildrakizumab 100 mg	268	163 (60.8)	54.3 (46.5 to 61.1)	12.2 (3.9 to 20.4)
Tildrakizumab 200 mg	276	184 (66.7)	60.2 (52.6, 66.6)	18.1 (10.0 to 26.1)
Etanercept 50 mg	276	134 (48.6)	NR	Reference
Failure to respond to at least 1 traditional systemic therapy: Yes[b,c]				
Placebo	97	5 (5.2)	Reference	NR
Tildrakizumab 100 mg	193	114 (59.1)	54.0 (45.0 to 61.9)	14.5 (4.6 to 24.0)
Tildrakizumab 200 mg	194	120 (61.9)	56.8 (48.2 to 64.4)	17.2 (7.4 to 26.8)
Etanercept 50 mg	195	87 (44.6)	NR	Reference
Failure to respond to at least 1 traditional systemic therapy: No[b,c]				
Placebo	59	4 (6.8)	Reference	NR
Tildrakizumab 100 mg	114	74 (64.9)	57.9 (45.2 to 67.9)	11.4 (−1.2 to 23.6)
Tildrakizumab 200 mg	120	86 (71.7)	64.9 (52.6 to 74.0)	17.3 (5.0 to 29.2)
Etanercept 50 mg	118	64 (54.2)	NR	Reference

CI = confidence interval; FAS = full analysis set; NR = not reported; PASI 75 = at least a 75% improvement in the Psoriasis Area and Severity Index score.

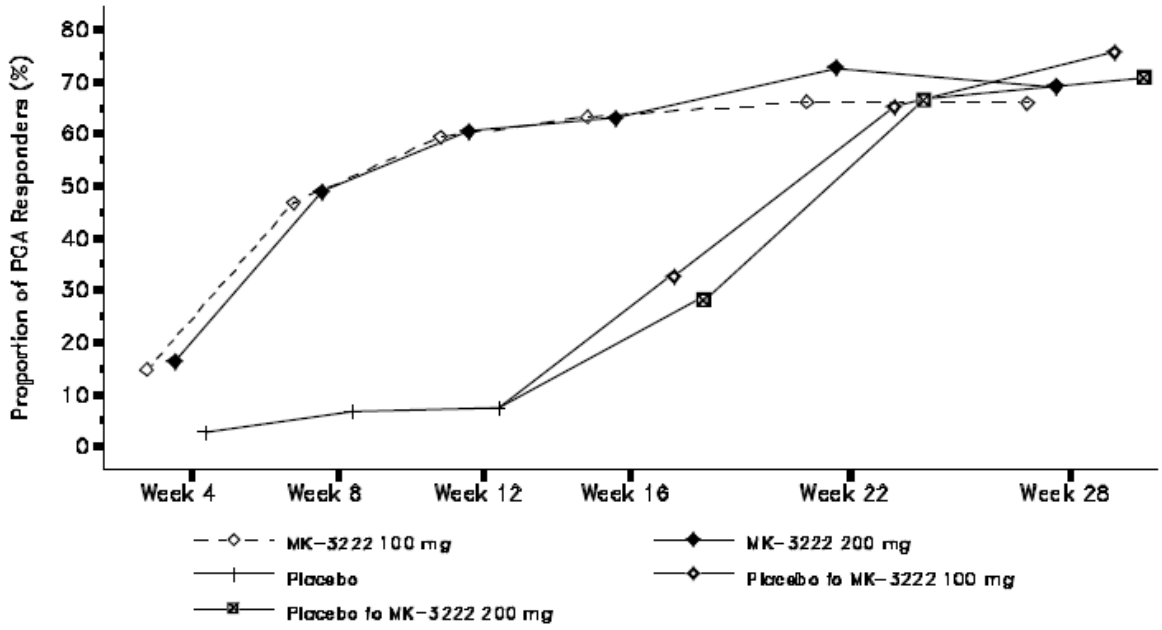
[a] Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight with sample size weights. Patients with missing data were classified as nonresponders.

[b] Methotrexate, cyclosporine, or phototherapy.

[c] Risk difference and 95% CI calculated using Miettinen-Nurminen stratified by body weight and prior biologic therapy, with sample size weights. Patients with missing data were classified as nonresponders.

Source: Clinical Study Report for Study P011.[7]

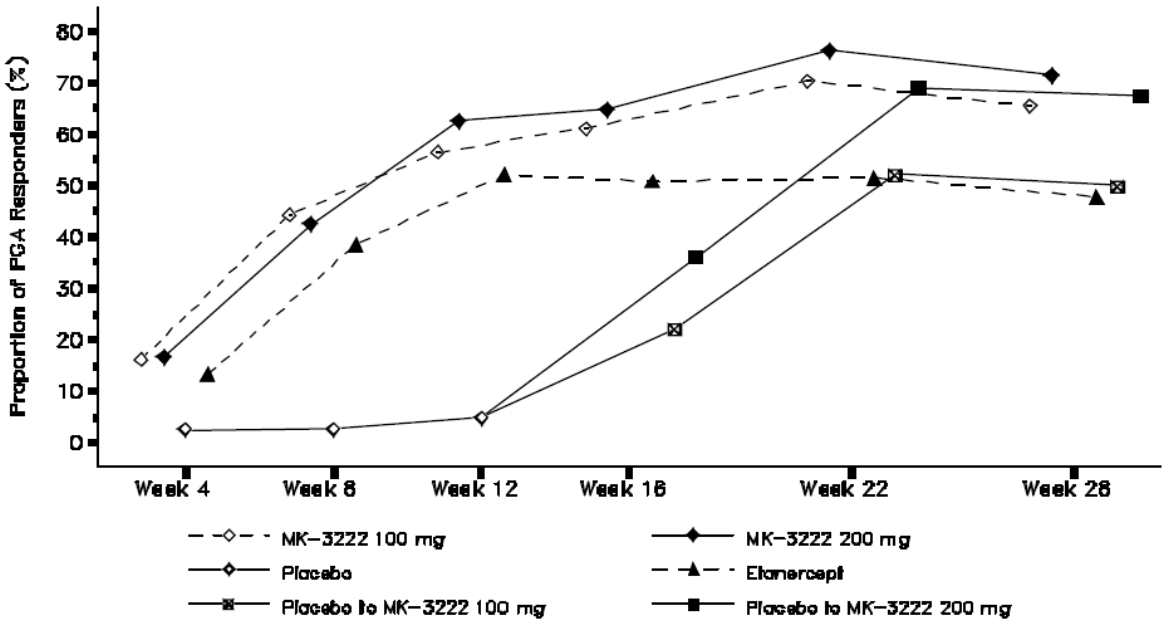
Figure 12: Proportion of Patients with PGA response up to Week 28 — Study P010 (OC)



MK-3222 = tildrakizumab; OC = observed case; PGA = Physician's Global Assessment.

Source: Clinical Study Report for Study P010.[6]

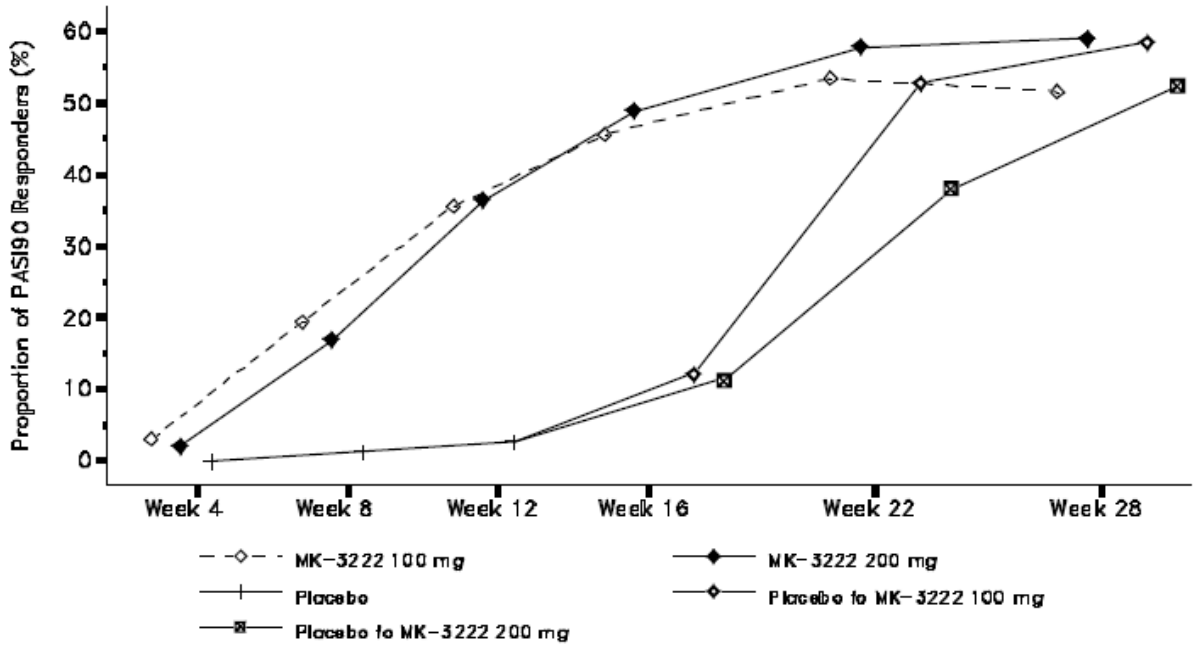
Figure 13: Proportion of Patients with PGA response up to Week 28 — Study P011 (OC)



MK-3222 = tildrakizumab; OC = observed case; PGA = Physician's Global Assessment.

Source: Clinical Study Report for Study P011.[7]

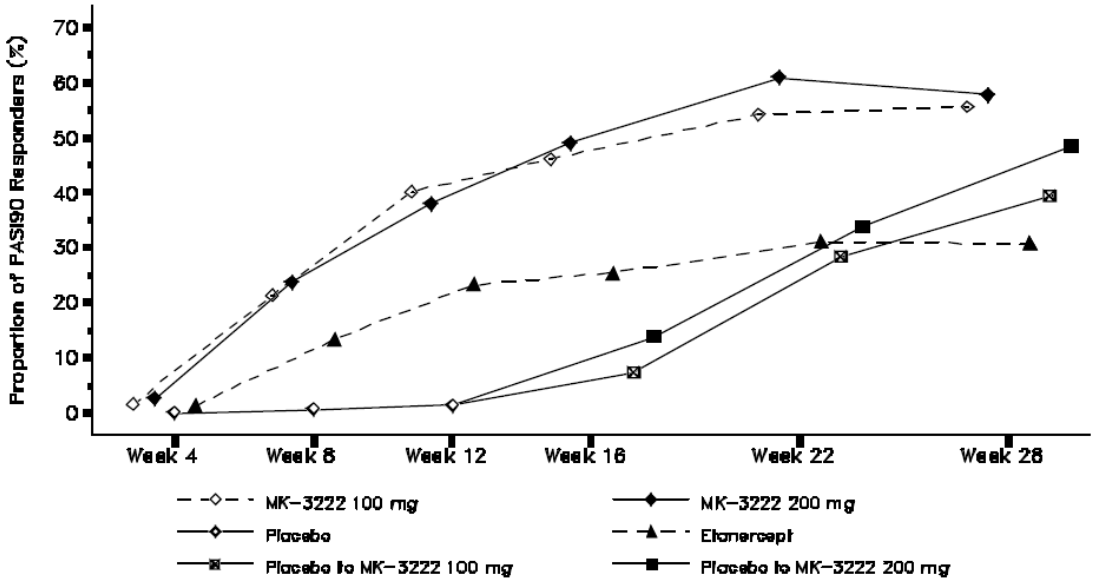
Figure 14: Proportion of Patients with PASI 90 response up to Week 28 — Study P010 (OC)



MK-3222 = tildrakizumab; OC = observed case; PASI 90 = at least a 90% improvement in Psoriasis Area and Severity Index score.

Source: Clinical Study Report for Study P010.[6]

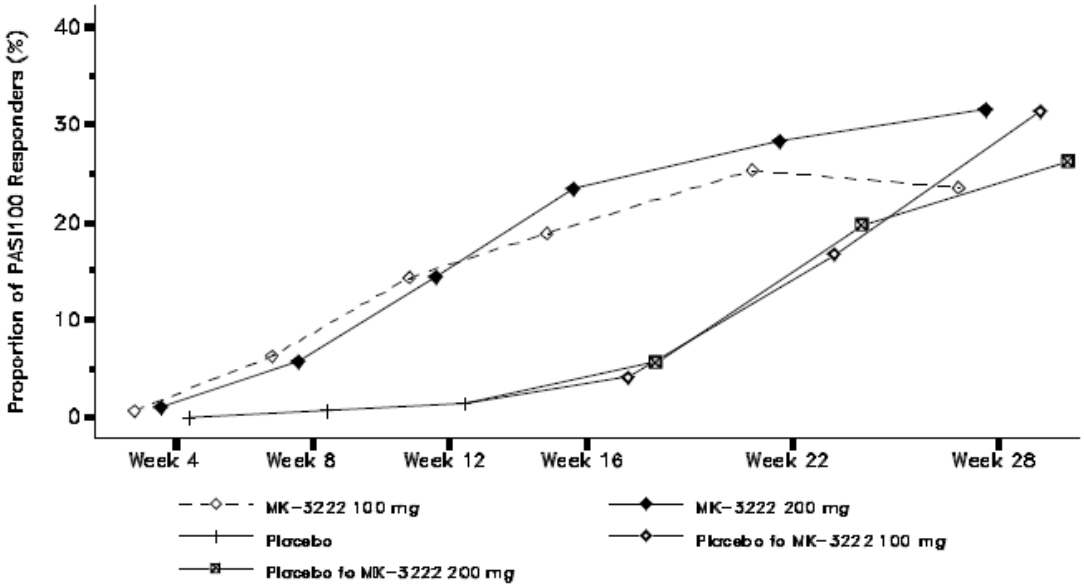
Figure 15: Proportion of Patients with PASI 90 response up to Week 28 — Study P011 (OC)



MK-3222 = tildrakizumab; OC = observed case; PASI 90 = at least a 90% improvement in Psoriasis Area and Severity Index score.

Source: Clinical Study Report for Study P011.[7]

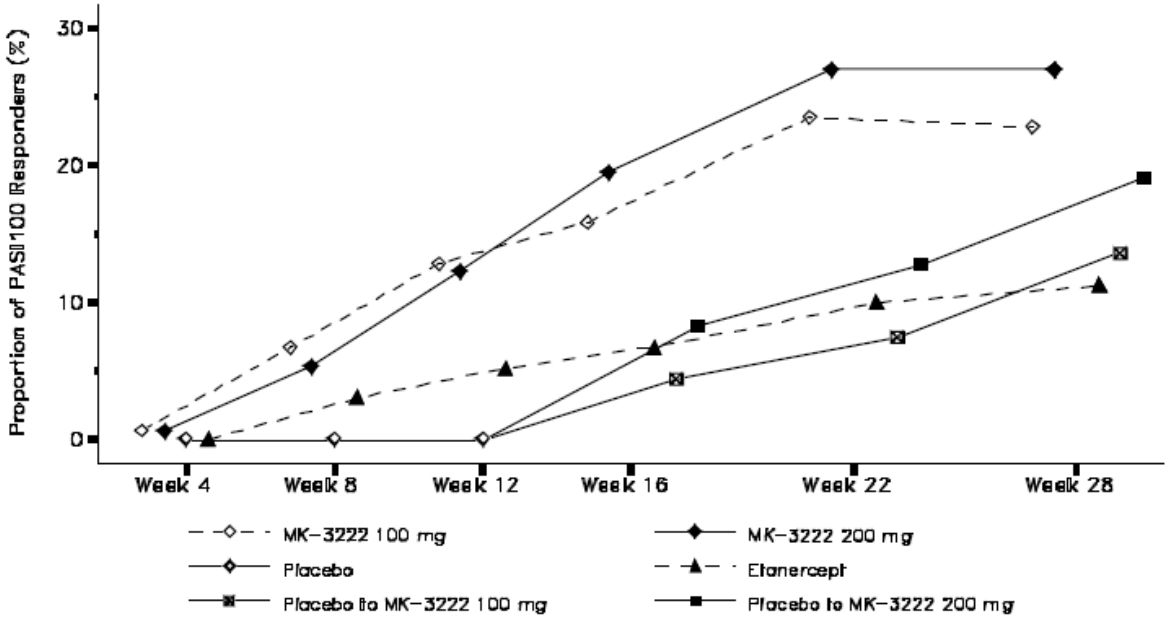
Figure 16: Proportion of Patients with PASI 100 response up to Week 28 — Study P010 (OC)



MK-3222 = tildrakizumab; OC = observed case; PASI 100 = 100% improvement in Psoriasis Area and Severity Index score.

Source: Clinical Study Report for Study P010.[6]

Figure 17: Proportion of Patients with PASI 100 response up to Week 28 — Study P011 (OC)



MK-3222 = tildrakizumab; OC = observed case; PASI 100 = 100% improvement in Psoriasis Area and Severity Index score.

Source: Clinical Study Report for Study P011.[7]

Table 40: Work and Productivity Loss Questionnaire — Study P010

P010 (reSURFACE 1)	N	Employed, n (%)	Primary reason not employed: psoriasis or psoriatic arthritis, n (%)
Patient employment over time			
Baseline			
Placebo	152	105 (69)	17 (11)
Tildrakizumab 100 mg	306	226 (74)	19 (6)
Tildrakizumab 200 mg	305	213 (70)	27 (9)
Week 12			
Placebo	147	109 (74)	13 (9)
Tildrakizumab 100 mg	303	213 (70)	21 (7)
Tildrakizumab 200 mg	297	215 (72)	21 (7)
Week 28			
Placebo to tildrakizumab 100 mg	71	50 (70)	3 (4)
Placebo to tildrakizumab 200 mg	67	46 (69)	6 (9)
Tildrakizumab 100 mg	288	209 (73)	16 (6)
Tildrakizumab 200 mg	289	209 (72)	15 (5)

P010 (reSURFACE 1)	N	Baseline mean (SD)	Time point mean (SD)	Change from baseline mean (SD)
Missed days of work in last 4 weeks due to psoriasis or psoriatic arthritis				
Baseline				
Placebo	105	0.6 (1.5)	—	—
Tildrakizumab 100 mg	226	0.6 (1.8)	—	—
Tildrakizumab 200 mg	213	0.6 (1.7)	—	—
Week 12				
Placebo	96	0.6 (1.6)	0.7 (3.0)	0.1 (1.9)
Tildrakizumab 100 mg	202	0.5 (1.4)	0.2 (0.8)	−0.3 (1.3)
Tildrakizumab 200 mg	194	0.6 (1.7)	0.2 (0.7)	−0.4 (1.5)
Week 28				
Placebo to tildrakizumab 100 mg	48	0.5 (1.0)	0.1 (0.3)	−0.4 (1.0)
Placebo to tildrakizumab 200 mg	39	0.3 (0.9)	0.1 (0.5)	−0.2 (0.9)
Tildrakizumab 100 mg	193	0.6 (1.5)	0.1 (0.6)	−0.4 (1.3)
Tildrakizumab 200 mg	190	0.6 (1.6)	0.2 (0.6)	−0.4 (1.3)

CI = confidence interval; SD = standard deviation.

Source: Clinical Study Report for Study P010.[6]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the outcome measures summarized in Table 41, and review their measurement properties including validity, reliability, responsiveness to change, and MCID.

Of the 6 outcome measures, the PASI, PGA, and DLQI are described in greater detail as these were co-primary and secondary end points, respectively, in the P010 and P011 trials under review. Validation of the generic tools EQ-5D-3L and SF-36 in patients with psoriasis was included. Of note, limited information was available on the WPLQ.

Table 41: Outcome Measures Included in Each Study

Outcome measure	P010	P011
PASI 75, 90, 100	Primary (PASI 75) Secondary (PASI 90, PASI 100)	Primary (PASI 75) Secondary (PASI 90, PASI 100)
PGA	Primary	Primary
DLQI	Secondary	Secondary
EQ-5D-3L	Exploratory	—
SF-36	Exploratory	—
WPLQ	Other	—

EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; DLQI = Dermatology Life Quality Index score; PASI 75, 90, 100 = at least a 75%, 90%, or 100% reduction in the Psoriasis Area and Severity Index score; PGA = Physician's Global Assessment; SF-36 = 36-item Short Form (36) Health Survey; WPLQ = Work Productivity and Loss Questionnaire.

Source: Clinical Study Reports for Study P010[6] and Study P011.[7]

Findings

The validity, reliability, and responsiveness of each outcome measure were summarized and evaluated. Interpretation of the reliability and validity metrics were based on the following criteria:

- Inter-rater reliability, kappa statistics (level of agreement):[69]
  - less than 0 = poor agreement
  - 0.00 to 0.21 = slight agreement
  - 0.21 to 0.40 = fair agreement
  - 0.41 to 0.60 = moderate agreement
  - 0.61 to 0.8 = substantial
  - 0.81 to 1.00 = almost perfect agreement
- Internal consistency (Cronbach's alpha) and test–retest reliability: 0.7 or greater is considered acceptable[70]
- Validity; i.e., between-scale comparison (correlation coefficient, r):[71]
  - 0.3 or less = weak
  - 0.3 to 0.5 = moderate
  - greater than 0.5 = strong

Table 42: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MCID[a]
PASI 75/90/100	Disease-specific composite severity index based on an average score of erythema, scaling and thickness of the lesions, weighted by the area of involvement. PASI scores range from 0 to 72, with higher scores indicating greater severity.	**Validity:** Construct validity was demonstrated through correlation of the PASI scores with DLQI scores ($0.36 \leq r \leq 0.54$).[72] Content validity was demonstrated by assessing the relative impact of each individual component of PASI on QoL using multiple regression analysis; BSA was most consistently associated with the DLQI score, followed by plaque induration and erythema. The scaling score was not found to be consistently associated with the DLQI score.[72] Two other studies demonstrated correlation between the PASI with the BSA and PGA scores (Pearson correlation coefficients > 0.78 and > 0.61, respectively),[73] and the LS-PGA and PGA (Spearman's rank correlation 0.92 and 0.73, respectively).[74] **Reliability:** PASI was shown to have good inter-rater reliability (ICC > 0.75), with the exception of scaling (ICC 0.72). The coefficient of variation (CV) for the PASI score was 36.9 overall, indicating moderate inter-rater reliability.[73] These results were also observed across earlier studies.[54,74,75] **Responsiveness:** The PASI score was found to have moderate sensitivity to change. Responsiveness was found to be low when the affected BSA is < 10%.[54,76]	The benchmark outcome used in clinical trials and in clinical practice is the PASI 75, i.e., 75% improvement in response. More recently, PASI 90 and PASI 100 have been used as treatment response goals.
sPGA	Six-point scale used to measure the severity of disease at a single point in time (static PGA). PGA scores range from 0 (clear) to 5 (severe).	**Validity:** Construct validity was assessed by a known-group approach; a positive relationship between the PGA and PASI scores was observed, indicating that the PGA could discriminate between different degrees of severity.[77] Content validity of the PGA was demonstrated through its association with the DLQI ($0.29 \leq r \leq 0.43$).[72] As with the PASI score, the scaling score was not found to correlate with the DLQI.[72] Conflicting reports were identified with respect to the validity of equal weighing of the 3 items (erythema, induration and scaling), and therefore a conclusion could not be drawn.[72,77] Convergent	It is generally accepted that a clinically meaningful score in the PGA is a score of "clear" or "minimal."[78] Some trials define efficacy as a 2-point reduction in the total PGA score.[55]

Outcome measure	Type	Conclusions about measurement properties	MCID[a]
		validity was also assessed between the PGA and 3 other disease severity scores. The PGA had the strongest correlation with the PASI score (Pearson = 0.79).[77] **Reliability:** The PGA was shown to have acceptable test–retest reliability (ICC 0.70).[77] Bożek et al. found good intra-rater reliability (ICC 0.87) and moderate inter-rater variability (CV 29.3).[73] Similar results were observed in previous studies.[54,74,75] **Responsiveness** of the sPGA has not been assessed to date.	
DLQI	10-item dermatology-specific quality of life questionnaire to assess limitations related to the impact of skin disease. The response options range from 0 (not affected at all) to 3 (very much affected). DLQI scores range from 0 to 30, with lower scores indicating better quality of life.	**Validity:** Construct validity of the DLQI in the psoriasis population was based on correlation of the instrument with either generic, dermatologic, or disease-specific instruments over 37 separate studies.[79] The DLQI corelated the greatest with the bodily pain (r = 0.61) and social functioning domains (r = 0.68) if the SF-36, as well as the overall EQ-5D index score (r = 0.71).[46] **Reliability:** Reliability was assessed in the original validation study of the DLQI by Finlay and Khan in a population of various skin diseases.[42] The test–retest reliability correlation coefficients were high for both the overall score (Spearman rank correlation 0.99) and for individual questions (0.95 to 0.98).[42] Slightly lower correlation coefficients (ranging from 0.56 to 0.99) were reported in a later systematic review by Basra et al.[79] **Responsiveness:** Responsiveness to change was measured by comparing DLQI data with PASI and PGA scores.[46] The DLQI demonstrated equal responsiveness to the PASI and PGA scores with correlation coefficients of r = 0.69 and r = 0.71, which was not achieved by the general tools, the EQ-5D (r = 0.44) and SF-36 (r = 0.44).[46]	The MCID of the DLQI in patients with psoriasis was estimated using 3 anchor-based methods. Estimates ranged from 2.2 to 6.9.[46] Another study in patients with psoriasis treated with adalimumab reported an MCID of 3.2.[80] In the most recent systematic review of RCTs in psoriasis, the DLQI MCID was reported to be a score change of 5.[81]
EQ-5D-3L	Generic, preference-based, health-related quality of life measure consisting of 6	The evidence for the validity of EQ-5D in the psoriasis population is limited. One study found good correlation of	Estimates of the MCID were derived using distributional and anchor-based

Outcome measure	Type	Conclusions about measurement properties	MCID[a]
	descriptive questions and a VAS. The descriptive questions comprise of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is divided into 3 levels of perceived problems ranging from "no problem" to "extreme problem" or "unable to do." The VAS records the subject's self-rated health on a 20 cm scale with end points 0 to 100 labelled "the worst health you can imagine" and the best health you can imagine," respectively.	EQ-5D with other outcome measures DQLI and PASI.[45] However, EQ-5D was not as responsive to change in patients' clinical status as the DLQI and the study authors recommend the use of EQ-5D in complement with DLQI and PASI.[45] An additional study found the EQ-5D to be highly correlated with the DLQI, though not as responsive to change in patient status.[46] EQ-5D showed similar responsiveness as the SF-36.[46]	approaches (PASI and PGA anchors).[46] Estimates ranged from 0.09 to 0.20 (mean 0.22 ± 0.14).[46]
SF-36	A 36-item general health–status instrument. It consists of 8 domains: physical function, role limitations-physical, vitality, general health perceptions, bodily pain, social function, role limitations-emotional, and mental health. A Physical Component Summary (PCS) score (PCS) and a Mental Component Summary (MCS) score can be computed. The scores range from 0 to 100, with higher scores indicating better health.	Shikiar et al. demonstrated that the bodily pain and social functioning scales of the SF-36 correlated well with the DLQI, EQ-5D, and clinical end points, and these scales were most responsive to change following psoriasis treatment.[46]	The estimated MCID for the PCS and MCS domain scores in patients with moderate-to-severe plaque psoriasis ranged from 2.57 to 3.91 and 3.89 to 6.05, respectively.[46]
WPLQ	The WPLQ is a disease-specific patient-reported productivity questionnaire for the evaluation of the impact of the subject's psoriasis on their work.[6] The questionnaire addresses subject absenteeism and presenteeism due to psoriasis and/or psoriatic arthritis, including productivity loss, over a recall period of 4 weeks. It consists of 10 items: patient occupation, occupational impact on psoriasis, patient's employment status over time, reasons for missing work, reasons for impaired productivity, patient's usual working days per week, missed days due to psoriasis, partially missed days due to psoriasis,	Currently, there is no information on the construct and content validity of the WPLQ, or its reliability and responsiveness.	NA

Outcome measure	Type	Conclusions about measurement properties	MCID[a]
	days worked with psoriasis, and hours worked with psoriasis.[6]		

EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; DLQI = Dermatology Life Quality Index; LS-PGA = Lattice System Physician's Global Assessment; MCID = minimal clinically important difference; NA = not applicable; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; QoL = quality of life; SF-36 = Short Form (36) Health Survey; sPGA = static Physician's Global Assessment; VAS = visual analogue scale.

[a] MCIDs were identified for continuous outcomes only. For outcomes measured by responder analysis (i.e., PASI and PGA), a clinically meaningful score was reported.

Psoriasis Area and Severity Index

The PASI is the most commonly used instrument for the assessment of psoriasis severity.[82,83] It is a single estimate of disease severity based on lesion characteristics weighted by area of body involvement. Psoriatic lesion characteristics are assessed separately for erythema, induration and scaling in the 4 major body areas: head, upper extremities, trunk, and lower extremities. Severity of each item is graded on a scale of 0 to 4 (0 = clear, 1 = mild, 2 = slight, 3 = moderate, 4 = severe), which is then summed by body region and weighted by the percentage of BSA involvement converted on a scale of 0 to 6 (0 = no involvement, 1 = 1% to 9%, 2 = 10% to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, 6 = 90% to 100%). The individual body region scores are then multiplied by weighting factors representing their respective proportion of the total BSA (0.1 for head, 0.2 for upper extremities, 0.3 for trunk and 0.4 for lower extremities), as in the following formula:[52]

PASI = 0.1 $(Eh$ x $Ih + Sh)\ Ah$ + 0.2 $(Eu + Iu +$ S$u)\ Au$ + 0.3 $(Et + It + St)\ At$ + 0.4 $(El + Il + Sl)\ Al$

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

The generated PASI score is a numeric score ranging from 0 to 72, with a score greater than 10 representing more severe disease.[50] In clinical trials, PASI is often reported as an overall mean percentage improvement with treatment, and is used most commonly for responder analyses.[78] A 75% reduction in the PASI score, i.e., PASI 75, is used as a benchmark in clinical trials in psoriasis.[51] While the PASI 75 is still used as a primary efficacy end point in clinical trials, the treatment goal in clinical practice has shifted to achievement of PASI 90 or PASI 100, according to the clinical expert consulted for this review. The PASI 90 or PASI 100 is scored using a dichotomous scale of yes or no; i.e., the patient achieved a 90% or greater or 100% improvement from baseline PASI score.

Validity

Simpson et al. studied data from a phase III clinical trial (N = 445) to validate 3 systems of physician-scoring psoriasis severity, which included the PASI, static PGA (sPGA), and Lattice System PGA (LS-PGA) measures.[72] Construct validity of PASI was assessed by evaluating the correlation between the PASI score and the DLQI score, a skin-related quality of life measure in grading psoriasis severity. The PASI correlated moderately with both the DLQI overall score as well as a single item of DLQI related to psoriasis symptoms ($0.36 \leq r \leq 0.54$), demonstrating that psoriasis severity is correlated with the DLQI score. The same study also investigated the content validity of the 3 measures by assessing the relative impact of the individual components of the measures on quality of life using multiple linear regression analysis; BSA was most consistently associated with DLQI scores, followed by plaque induration and erythema. The scaling score was found to be minimally and inconsistently associated with DLQI scores which may be in part due to the static measurement of scaling which does not encompass the flaking of the skin over time which can be very distressing to patients.[72] The authors therefore concluded that weighing erythema, induration and scaling equally would not accurately capture the varying degrees to which these factors affect the patient's rating of quality of life. Lastly, the construct and content validity of the PASI were found to be stronger during active treatment compared with pre-therapy.[72]

A second study of 10 trained dermatologists evaluating 9 adult patients with plaque type psoriasis assessed the correlations of PASI with other commonly used instruments in psoriasis, including BSA and the PGA.[73] The authors reported a strong correlation with both measures (Pearson correlation coefficient > 0.78 and > 0.61, respectively).[73] Similarly, Berth-Jones et al. (14 trained dermatologists, 16 patients with chronic plaque psoriasis) reported a strong correlation between PASI and the LS-PGA (Spearman's

rank correlation, r = 0.92), and a moderate correlation with the PGA (r = 0.73).[74] Berth-Jones et al. also found that the PASI and PGA were in good agreement for the clearance state (kappa = 0.64) but poor agreement for the severe state (kappa = 0.18).[74]

Reliability

The reliability of the PASI measure has been assessed in several studies.[73-75] Bożek et al. reported the interclass correlations (ICCs) for all components of the PASI to be > 0.75, indicating very good intra-rater reliability, with the exception of scaling (0.72). The highest ICC was observed for the area score (0.97). The coefficients of variation (CV) for the PASI was 36.9 overall, indicating moderate inter-rater reliability. The highest variability was observed for the head and neck (CV = 117.8) and the lowest variability was for the area score (CV = 26.8).[73] Langley et al. (17 physicians, 25 patients with psoriasis) reported similar results, with higher variability observed in the PASI scores derived by inexperienced physicians compared with experienced investigators (sigma = 3.2 versus 1.2).[75] Berth-Jones et al. found excellent intra-rater and inter-rater reliability for the PASI score (ICCs > 0.81).[74] The systematic review by Puzenat et al. (4 studies, N = 281) reported good internal consistency, limited intra-rater variation, and moderate inter-rater variation for the PASI.[54]

Responsiveness

The PASI score was found to have a moderate sensitivity to change.[54] In a review by Spuls et al., the authors commented on the responsiveness of PASI being weak when less than 10% of the BSA is affected given that the PASI score would be entirely dependent on the plaque severity scores, and therefore may underestimate the general degree of improvement.[76]

Clinical Relevance

A systematic review by Mattei et al., including 13 RCTs evaluating biologics in psoriasis, reported that a 75% or greater reduction in the PASI score translates to clinically significant quality of life improvement in patients assessed using the DLQI.[84] This is based on the several studies that have demonstrated that a reduction in PASI scores can predict a reduction in DLQI scores, particularly when the patients were achieving a PASI 75 or higher (PASI 75 versus PASI 50 to PASI 75 versus mean difference of 3.24). According to the approximate mean MCID for the DLQI of 3.2, this difference suggests a meaningful benefit in quality of life.[84,85] The clinical expert consulted for this review indicated that PASI 90 or even PASI 100 is increasingly being used in clinical settings.

Limitations

The PASI can be difficult to interpret because it is not a linear index.[55] For example, a small increase in the BSA affected from 9 to 10%, results in a doubling of the PASI score (with all other parameters constant). Moreover, the PASI lacks sensitivity at its lower end of the scale, where most patient scores fall into, leaving the higher end of the scale redundant, and decreasing the usefulness of the full range of scores (0 to 72).[54,83,86] Erythema, induration, and scaling are equally-weighted within each of the 4 body regions, therefore, a reduction in 1 item with a concomitant increase in another item could be recorded with the same PASI score. Similarly, a drastic (and maybe temporary) change in 1 subscore can change the overall score.[78]

The PASI has been criticized for not correlating the clinical extent of the disease with quality of life and the psychological stress caused by psoriasis. Improvements in the PASI score are not linearly related to severity or improvements in disease state, and therefore some severe diseases may be scored low.[74,76] For example, a PASI score as low as 3 on the palms and soles may represent psoriasis that disables a patient from work and other life activities. The score also lacks sensitivity to body sites such as the nails, feet, face, genitalia, and symptoms such as pruritus, or other disease-related comorbidities.[54,55] As a result, the sensitivity of the PASI is highly dependent on the initial baseline score, and patients with low initial scores may not achieve a PASI 75, but still have a clinically meaningful response to treatment.[75] While a highly effective treatment should overcome this lack of sensitivity, it is for these reasons why the PASI score should be accompanied by patient-reported quality of life measures.[75] PASI scores can also vary substantially between experienced and inexperienced physicians, raising concerns for inter-rater reliability. Despite these limitations, the PASI score remains the most extensively validated, and most complete score which is highly producible. It has also been shown to correlate strongly with its self-administered counterpart, the SAPASI.[54,87]

Physician's Global Assessment

The PGA is a simple measurement of the clinical signs of psoriasis, frequently used as a co-primary end point with the PASI score in psoriasis clinical trials[52]. Of note, the clinical expert consulted in this review indicated that only the PASI score is used in clinical practice. Various PGAs have been used in psoriasis with different descriptions and scores, with the most common PGA versions using 5- to 6-point scales.[52,75] There are 2 types of PGAs, a static form (sPGA) which measures the physician's measurement of the disease at a given time point, and a dynamic form in which the physician evaluates the level of improvement or deterioration from a baseline.[52,55] The static form of the PGA is preferred over the dynamic form given that it does not rely on physician's recall of the patient's disease severity observed at baseline or a previous visit. In the 2 studies under review, a 6-point, static version of the PGA was used.[6,7] To generate the sPGA score, psoriatic lesions are graded for erythema, thickness and scaling based on a scale of 0 to 5 (Table 43) that are then averaged across all lesions to obtain a single estimate of the patient's overall severity of disease at a given point in time. The 3 items are given equal weighting. The sum of the 3 scales are added and then divided by 3 [$(E + I + S)/3$] for a final sPGA score from 0 to 5, where:

0 = cleared (except for residual discoloration)

1 = minimal — majority of lesions have individual scores for erythema, induration, and scaling that average 1

2 = mild — majority of lesions have individual scores for erythema, induration, and scaling that average 2

3 = moderate — majority of lesions have individual scores for erythema, induration, and scaling that average 3

4 = marked — majority of lesions have individual scores for erythema, induration, and scaling that average 4

5 = severe — majority of lesions have individual scores for erythema, induration, and scaling that average 5

Table 43: Physician's Global Assessment Scoring

Score	Erythema	Induration	Scaling
0	No evidence of erythema; hyperpigmentation may be present	No evidence of plaque elevation	No evidence of scaling
1	Faint erythema	Minimal plaque elevation (0.25 mm)	Minimal; occasional fine scale over less than 5% of the lesion
2	Light red coloration	Mild plaque elevation (0.5 mm)	Mild; fine scale dominates
3	Moderate red coloration	Moderate plaque elevation (0.75 mm)	Moderate; coarse scale predominates
4	Bright red coloration	Marked plaque elevation (1 mm)	Marked; thick, non-tenacious scale predominates
5	Dark to deep red coloration	Severe plaque elevation (1.25 mm)	Severe; very thick, tenacious scale predominates

Source: Clinical Study Report for Study P010.[6]

Validity

The most recent study assessing the validity of the PGA evaluated data from 4 phase III clinical studies of tofacitinib in patients with psoriasis (N = 3,641).[77] Confirmatory factor analysis used to test the fit of the PGA measurement model demonstrated that equal weighting of the 3 items (erythema, induration and scaling) was appropriate, as indicated by Bentler's comparative fit index (CFI) values greater than 0.98 (acceptable fit defined as a CFI > 0.9) and standardized path coefficients all above the threshold of 0.4. Construct validity was assessed using a known-group approach, measuring the relationship between PGA and PASI through a repeated measures model. A positive relationship between the PGA and PASI scores was observed which was stable and replicable across the 4 studies, indicating that the PGA could discriminate between different degrees of disease severity.[77]

Simpson et al. evaluated the construct and content validity of the PGA by its association with the DLQI.[72] The correlation between PGA and DLQI was moderately positive ($0.29 \leq r \leq 0.43$) at post-therapy time points. As with the PASI instrument, the authors found the scaling score to be minimally and inconsistently associated with DLQI score, while erythema and induration were positively

correlated with the DLQI score. In contrast to Callis Duffin et al., Simpson and colleagues concluded that the equal weighing of the 3 items would not accurately capture the varying degrees to which these factors affect the patient's rating of quality of life.[72]

Convergent and divergent validity were assessed by determining the correlation of the PGA with 3 additional outcome measures: the PASI, patient global assessment (PtGA) and DLQI.[77] Pearson correlation coefficients between PGA and the 3 scales ranged from 0.4 to 0.79, with the strongest correlation found with PASI. These findings were consistent with a previous psychometric validation study of the PGA in a single phase III trial by Cappelleri et al.,[88] as well as several other studies.[54,73-75]

Reliability

Callis Duffin et al. evaluated consistency of PGA measurements between screening and baseline visits, when no change in terms of disease severity was expected.[77] The ICC values for the pooled data were 0.70, suggesting an acceptable test–retest reliability over a stable period. The same study assessed internal consistency reliability demonstrating that the scoring items (erythema, induration and scaling) were highly consistent with each other (Cronbach's Coefficient alpha ≥ 0.90) at the primary assessment points in all 4 trials. The internal consistency reliability was less convincing (Cronbach's Coefficient alpha 0.50 to 0.63) for the values observed at baseline, likely a result of the specific inclusion criteria of the trials.[77]

Bożek et al. also assessed the reliability of the PGA, finding very good intra-rater reliability (ICC 0.87) but moderate inter-rater variability (coefficients of variants [CVs] of 29.3 for the PGA and 36.9 for the PASI).[73] Similarly, another study reported "substantial" intra-rater reliability (ICC > 0.81), and moderate inter-rater reliability (0.61 < ICC < 0.81) for the PGA.[74] Langley et al. previously demonstrated strong and intra-rater variation with the PGA (sigma = 0.2) compared with the PASI (sigma = 2.5).[75] The systematic review by Puzenat et al. also reported low intra-observer variability but moderate inter-observer variability for the PGA.[54]

Responsiveness

No evidence regarding the responsiveness of the PGA was identified from the literature at this time.

Clinical Relevance

It is generally accepted that a clinically meaningful score in the PGA is a score of "clear" or "minimal."[78] Furthermore, some trials define efficacy as a 2-point reduction in the total PGA score.[55] To date, only 1 study has assessed the MCID for the PGA, using the PtGA score as a continuous anchor.[77] The 2 trials under review, P010 and P011, have defined a score of "clear" or "minimal" (score of 0 or 1, respectively) with a minimum of a 2-point difference as a clinically important threshold.

Limitations

The PGA is more subjective than PASI in that there is no attempt to quantify the individual elements of plaque morphology or BSA involvement.[78,82] This could lead to potentially misleading scores when there is clearance of BSA involvement, but the remaining lesions appear the same.[55] Despite this, it is possible that experienced physicians presume the extent of the psoriasis when grading each item, as demonstrated by Langley et al. where the sum of area scores from the PASI were more correlated with PGA than were the sum scores for each item.[75] The PGA has been shown to be reliable based on test–retest data and internal consistency; however, inter-rater reliability due to variability, especially in untrained observers, can be poor.[78] Furthermore, given that the PGA has many different scales and scoring variations, comparisons between studies is made very difficult.[78] Within a study, however, the PGA correlated well with the PASI and HRQoL measures.[76] Furthermore, a systematic review by Robinson et al. including 30 RCTs of biologic drugs in psoriasis from 2001 to 2010 found that the PGA (0, 1) correlated very tightly with the PASI 75 (Correlation coefficient = 0.9157), suggesting potential redundancy in measuring both scores as primary end points.[55]

Dermatology Life Quality Index

The DLQI is a widely used dermatology-specific HRQoL instrument which assesses limitations related to the impact of skin disease.[42] It is a 10-item questionnaire that covers 6 domains: symptoms and feeling, daily activities, leisure, work and school, personal relationships, and bother with psoriasis treatment. Each item is scored on a 4-point Likert scale: 0, (not at all affected/not relevant), 1 (a little affected), 2 (a lot affected), and 3 (very much affected). The overall DLQI score is a numeric score between 0 to 30, with lower scores indicating better quality of life. At least 80% of the questions must be answered for a score to be reported [42,46]

The final numeric score translates to the effect of the patient's disease on their quality of life where 0 to 1 = no effect, 2 to 5 = small effect, 6 to 10 = moderate effect, 11 to 20 = very large effect, and 21 to 30 = extremely large effect. The DLQI can be completed within a few minutes, making it a very time-efficient scoring system for use in clinical settings.[89]

Validity

The DLQI was developed in 1994, and since has been validated in many studies.[42,46,79,89-91] Construct validity of the DLQI was based on the correlation of the instrument with either generic, dermatologic, or disease-specific instruments in over 37 separate studies.[79] Shikiar et al. reported a good correlation (Correlation coefficient > 0.61) with 3 different itch measures in a study combining results from trials in moderate-to-severe plaque psoriasis (N = 1,095).[90] A later study by Shikiar et al. demonstrated excellent correlation between the DLQI and generic HRQoL instruments in a population of 147 with moderate-to-severe plaque psoriasis randomized to adalimumab versus placebo; the DLQI correlated the greatest with the bodily pain (r = 0.61) and social functioning domains (r = 0.68) of the SF-36, as well as the overall EuroQoL-5 dimensions questionnaire (EQ-5D) index score (r = 0.71).[46]

Reliability

In the original validation study by Finlay and Khan, the reliability of the DLQI was assessed with 53 patients with a variety of skin diseases by completing the questionnaire twice, 7 to 10 days apart.[42] The test–retest reliability correlation coefficients were obtained using the Spearman rank correlation test, which were high for both the overall score (0.99) and individual questions (0.95 to 0.98).[42] The good test–retest reliability of the DLQI was also confirmed in a systematic review by Basra et al., with eight of 12 international studies reporting correlation coefficients greater than 0.56, up to 0.99.[79] The same review reported good internal consistency reliability of the DLQI which is based on 22 international studies with Crohnbach's alpha coefficients ranging from 0.75 to 0.92.[79]

Responsiveness

Responsiveness to change in the clinical status of a patient was measured by comparing DLQI data with PASI and PGA scores.[46] The correlations between the DLQI and the 2 disease severity scores were r = 0.69 and r = 0.71, respectively. The DLQI demonstrated equal responsiveness to the PASI and PGA scores with correlation coefficients of r = 0.69 and r = 0.71, which was not achieved by the general tools, the EQ-5D (r = 0.44) and SF-36 (r = 0.44).[46] In a second study assessing responsiveness, Shikiar et al. contrasted change in DLQI scores in patients who were defined as clinical responders (achievement of PASI 75 response by week 12) with those characterized as nonresponders (< PASI 50); DLQI scores in responders improved by 12.17 points, compared with 1.77 points in the nonresponders subgroup (t = 9.0; effect size 0.40; P < 0.0001).[46] Additional studies demonstrating the responsiveness of the DLQI were also identified in the systematic review by Basra et al.[79,91]

MCID

Shikiar et al. estimated the MCID of the DLQI in patients with psoriasis (N = 147) using 3 anchor-based methods; MCID-1 was based on scores from near-responders (PASI improvement of 25 to 49%), MCID-2 was based on partial responders (PASI improvement 50 to 74%), and MCID-3 corresponded to the difference between nonresponders and minimal responders for the PGA score. The authors also estimated the MCID using the one-half SD of baseline scores.[46] Estimates ranged from 2.2 to 6.9.[46] It should be noted that these approaches lack patient-based anchors, and therefore do not necessarily identify the minimal difference that a patient would consider important. Another study in patients with psoriasis (N = 147) treated with adalimumab reported an MCID of 3.2.[80] In the most recent systematic review of RCTs in psoriasis, the DLQI MCID was reported to be a score change of 5.[81]

Limitations

The DLQI was the first dermatology-specific tool to evaluate skin-related quality of life, and was originally developed for use in routine practice.[42] While the tool focuses on the patient's daily functioning, it has been criticized for not fully capturing emotional and mental states.[92] Therefore, the DLQI may lack conceptual validity in the psychological consequences of living with psoriasis.

EuroQol 5-Dimensions 3-Levels Questionnaire

The EQ-5D-3L questionnaire is a generic, preference-based, HRQoL measure consisting of descriptive questions and a visual analogue scale.[44] The descriptive questions comprise of 5 dimensions, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is divided into 3 levels (1, 2, 3) representing "no problems," "some problems," "extreme problems," respectively. Respondents are asked to choose 1 level that reflects their own health state for each of the 5 dimensions. The 5 questions are scored and together contribute to the EQ-5D index (utility) score between 0 and 1, where 0 represents death, and 1 represents perfect health. Different utility functions are available that reflect the preferences of specific populations (e.g., US, UK). In the P010 and P011 studies, the EQ-5D index score was calculated using the US scoring algorithm for US patients, and for all other patients, the EU algorithm was used.[6] The second part of the tool records the subject's self-rated health on a 20 cm scale with end points 0 and 100, with respective anchors of "the worst health you can imagine" and "the best health you can imagine," respectively.[93]

The evidence for the validity of EQ-5D in the psoriasis population is limited. A Swedish observational cohort study found good correlation of EQ-5D with other outcome measures DQLI and PASI.[45] However, EQ-5D was not as responsive to change in patients' clinical status as the DLQI and the study authors recommend the use of EQ-5D in complement with DLQI and PASI.[45] An additional study found the EQ-5D to be highly correlated with the DLQI, though not as responsive to change in patient status.[46] EQ-5D showed similar responsiveness as the SF-36.[46] Estimates of the MCID for EQ-5D were derived using distributional and anchor-based approaches (PASI and PGA anchors), as described previously for the DLQI.[46] The estimated MCIDs for the EQ-5D in the psoriasis population ranged from 0.09 to 0.20 (mean 0.22 ± 0.14).[46] This estimated MCID range compared with the general MCID range of 0.033 to 0.074, suggests that a larger difference in EQ-5D score is necessary for patients with psoriasis to regard the change as clinically beneficial.[47]

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.[48,49] The SF-36 consists of 8 health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. For each of the 8 domains, a subscale score can be calculated. The SF-36 also provides 2 component summaries, the PCS and the MCS, derived from aggregating the 8 domains according to a scoring algorithm. All domains scores are based on a scale of 0 to 100, with higher scores indicating higher quality of life. The scores can also be standardized to the general US population, where an average score is 50, with an SD of 10 (t score).

A systematic review by Frendl and Ware examined SF-36 concordance and its MCID across many different indications in studies evaluating drug therapy effectiveness.[49] The SF-36 was observed to be responsive (when compared with primary clinical measures) in patients with psoriasis in these studies. In addition, of the 10 psoriasis studies identified, PCS or MCS improvement of at least 3 points versus placebo was observed in 70% of these studies.[49,94] Shikiar et al. demonstrated that the bodily pain and social functioning scales of the SF-36 correlated well with the DLQI, EQ-5D, and clinical end points, and these scales were most responsive to change following psoriasis treatment.[46]

Based on anchor data, the developer of the SF-36 proposed the following minimal mean group differences for the individual domain scores: physical functioning (3), role physical (3), bodily pain (3), general health (2), vitality (2), social functioning (3), role emotional (4), and mental health (3).[95] It should be noted that these MCID values were determined as appropriate for groups with mean t score ranges of 30 to 40. For higher t score ranges, MCID values may be higher. Furthermore, as these MCID values were based on clinical and other non–patient-reported outcomes, they do not necessarily identify the smallest difference that patients would consider important.

The MCID of the PCS and MCS was also estimated in a study involving patients with moderate-to-severe plaque psoriasis.[46] This study provided results for estimated MCID based on PASI and PGA anchor data, as described previously for the other outcome measures. The estimated MCID for the PCS and MCS domain scores ranged from 2.57 to 3.91 and 3.89 to 6.05, respectively.[46] As also noted previously, these estimates are based on non–patient-derived anchors, limiting their accuracy. Furthermore, the third estimate (using the PGA anchor) produced results that were inconsistent with the 2 other anchors, the 2 distributional based

approaches, and previous estimates of the MCID for the PCS reported in the literature. Therefore, this result is not reported in this appendix.[46]

Work Productivity and Loss Questionnaire

The WPLQ is a disease-specific patient-reported productivity questionnaire for the evaluation of the impact of the subject's psoriasis on their work.[6] The questionnaire addresses subject absenteeism and presenteeism due to psoriasis and/or psoriatic arthritis, including productivity loss over a recall period of 4 weeks. It consists of 10 items including: subject occupation, occupational impact on psoriasis, subject employment status over time, reasons for missing work, reasons for impaired productivity, subjects usual working days per week, missed days due to psoriasis, partially missed says due to psoriasis, days worked with psoriasis, and hours worked with psoriasis.[6] The questionnaire also addresses reasons for impaired productivity, missing work, or unemployment, with possible responses: health care visits, unable or uncomfortable to travel, too much pain to work, too uncomfortable to work, and unable to concentrate and work. Currently, there is no further information on the construct and content of the questionnaire, including evidence on its validity, reliability, and responsiveness. The sponsor indicated that the WPLQ is being used in the P010 to inform the economic model.[6]

Conclusions

The evaluation of severity of disease in psoriasis is largely dependent on ratings of physicals signs and symptoms. The PASI is the most commonly used summary score both in clinical trials and clinical practice of psoriasis, while the PGA is used mostly in clinical trials. Given its relative objectivity, the PASI score remains the most widely used end point, and as such all other physician-derived (PGA) and patient-reported outcome measures (DLQI, EQ-5D, SF-36) used in psoriasis have been validated against the PASI score. The PGA score is criticized for being more subjective than the PASI score, for lacking a BSA involvement component. While the DLQI is a dermatology-specific HRQoL measure, it can have limitations such as low sensitivity in darker-skinned individuals, and for measuring mental and social well-being. For the latter reason, the EQ-5D and SF-36 can be important and useful general HRQoL measures to compliment the DLQI, and to pick up additional health-related outcomes.

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