Common Drug Review
Clinical Review Report

September 2017

Drug	Ixekizumab (Taltz)
Indication	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	80 mg subcutaneous injection
NOC date	May 25, 2016
Manufacturer	Eli Lilly Canada Inc.

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

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

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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

The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this document to ensure that its contents are accurate, complete, and up-to-date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any s or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

This document is intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user's risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this document, subject to the limitations noted above. The statements and conclusions in this document are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government. Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

You are permitted to make copies of this document for non-commercial purposes, provided it is not modified when reproduced and appropriate credit is given to CADTH. You may not otherwise copy, modify, translate, post on a website, store electronically, republish, or redistribute any material from this document in any form or by any means without the prior written permission to CADTH.

Please contact CADTH's Vice-President of Corporate Services at corporateservices@cadth.ca with any inquiries about this notice or other legal matters relating to CADTH's services.

TABLE OF CONTENTS

Tables

Figure

ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
BSA	body surface area
CDR	Common Drug Review
CI	confidence interval
DB	double blind
DLQI	Dermatology Life Quality Index
EMA	European Medicines Agency
HRQoL	health-related quality of life
IL	interleukin
ITT	Intention-to-treat
LOCF	last observation carried forward
mBOCF	modified baseline observation carried forward
MCID	minimal clinically important difference
MMRM	mixed-effects model of repeated measures
NI	non-inferiority
NMA	network meta-analysis
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
PP	per-protocol
RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SF-36	Short-Form (36) Health Survey
TNF	tumour necrosis factor
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Psoriasis is a chronic, inflammatory skin disorder that commonly leads to symptoms such as pain and pruritus, as well as affecting appearance and meaningfully reducing an individual's quality of life. Plaque psoriasis is the most common form of psoriasis and is characterized by well-demarcated papules covered by silvery scales. Moderate to severe plaque psoriasis can be defined by the extent of skin coverage, with involvement of more than 5% to 10% of body surface area (BSA); location, i.e., involvement of the face, palm, or sole; or severity, if the disease's effects are disabling. The fact that plaques may be highly visible may affect self-esteem, resulting in a negative impact on social functioning. In addition, patients have an increased risk of various serious comorbidities, including inflammatory diseases at occurring sites other than the skin.[1-3]

Ixekizumab is a humanized monoclonal antibody that selectively inhibits interleukin 17A, a pro-inflammatory cytokine implicated in the pathogenesis of a variety of autoimmune diseases, including plaque psoriasis. Ixekizumab has a Health Canada indication for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[4] The manufacturer has requested that ixekizumab be evaluated for reimbursement per the Health Canada indication. The objective of this report was to perform a systematic review of the beneficial and harmful effects of ixekizumab administered by subcutaneous injection for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Results and interpretation

Included studies

Three manufacturer-sponsored, double-blind (DB) randomized controlled trials (RCTs) were included in the systematic review: UNCOVER-1 (n = 1,296),[5,6] UNCOVER-2 (n = 1,224),[5,7,8] and UNCOVER-3 (n = 1,346).[5,7,9] UNCOVER-1 was a placebo-controlled RCT evaluating the superiority of ixekizumab compared with placebo, whereas UNCOVER-2 and UNCOVER-3 were placebo-controlled and active-controlled RCTs evaluating the superiority of ixekizumab compared with placebo, as well as the non-inferiority and superiority of ixekizumab compared with etanercept. UNCOVER-1 and UNCOVER-2 also included a maintenance-dosing period, providing data up to week 60. Although this design may be relevant to regulatory agencies in order to explore the duration of remission/response, rebound and time to relapse, it is associated with several major limitations in light of the CADTH Common Drug Review (CDR) quality standard, and results are therefore presented as supportive information only. There was no study in which ixekizumab was compared directly with other interleukin inhibitors used to treat psoriasis, namely secukinumab and ustekinumab, although the manufacturer provided an indirect comparison in which a network meta-analysis (NMA) was used to compare ixekizumab with other biologic drugs used to treat psoriasis.

All three included studies had patients with moderate to severe plaque psoriasis, defined as patients with a confirmed diagnosis of chronic plaque psoriasis for at least six months who were candidates for phototherapy and/or systemic therapy and who had at least a 10% BSA involvement, a static Physician Global Assessment (PGA) score of at least 3, and a Psoriasis Area and Severity Index (PASI) score of at least 12. Various groups of patients with comorbid conditions were excluded from the included studies, including patients with current or history of lymphoproliferative disease or malignant diseases; significant uncontrolled cerebro-cardiovascular, neurological, neuropsychiatric, renal, hepatic, respiratory, gastrointestinal, endocrine, or hematologic disorders; and serious infection, active or latent

tuberculosis, HIV, hepatitis C, or some presentations of hepatitis B. Therefore, the findings are not generalizable to these patients. In terms of disease severity, the majority of patients had a baseline static PGA score of 3 or 4. The mean baseline PASI score ranged from 19 to 21, with a mean BSA involvement between 25% and 29%. Prior experience with systemic therapies was reported in 54% to 75% of patients participating in UNCOVER-1, UNCOVER-2, and UNCOVER-3; among the therapeutic options were phototherapy (31% to 48% of patients), non-biologic systemic therapy (46% to 64%), and biologic therapy (41% of patients in UNCOVER-1 and 15% to 26% of patients in UNCOVER-2 and UNCOVER-3). Efficacy assessments were based on the following co-primary outcomes after 12 weeks of treatment: the proportions of patients with at least a two-point improvement in the static PGA who achieved a PGA score of 0 or 1; and the proportions of patients achieving at least a PASI 75 score. Patients were randomized to either placebo, etanercept 50 mg subcutaneously (SC) twice weekly (UNCOVER-2 and UNCOVER-3), or to one of two ixekizumab induction regimens. However, only the dosing regimen that is consistent with the Health Canada–approved dose was included in this review, i.e., ixekizumab 160 mg SC at week 0, followed by 80 mg SC every two weeks up to week 12.

Efficacy

Results from UNCOVER-1, UNCOVER-2, and UNCOVER-3 were consistent with the conclusion that ixekizumab is superior to placebo for achieving at least a two-point improvement in the static PGA score (with achievement of a PGA score of 0 or 1) and at least a PASI 75 score after 12 weeks of treatment in patients with moderate to severe plaque psoriasis. Results from UNCOVER-2 and UNCOVER-3 also demonstrated that ixekizumab is superior to etanercept for the same co-primary outcomes, i.e., at least a two-point improvement in the static PGA (score of 0 or 1) and at least a PASI 75 score after 12 weeks of treatment in patients with moderate to severe plaque psoriasis. These two co-primary outcomes were considered to represent a clinically meaningful improvement for psoriasis patients according to the clinical expert consulted by CADTH CDR.

The proportions of patients achieving at least a two-point improvement in the static PGA (score of 0 or 1) at week 12 was 82% in the ixekizumab group compared with 3% in the placebo group in UNCOVER-1 ($P < 0.001$). Results were similar in UNCOVER-2, in which 83% of patients in the ixekizumab group compared with 2% of patients in the placebo group and 36% of patients in the etanercept group achieved the co-primary outcome ($P < 0.001$ for both comparisons). The results from UNCOVER-3 were consistent with the other included trials, with 81% of patients reaching the pre-specified PGA improvement in the ixekizumab group compared with 7% of patients with placebo and 42% of patients with etanercept ($P < 0.001$ for both comparisons). As for the second co-primary outcome, the proportions of patients achieving at least a PASI 75 score at week 12 was 89% in the ixekizumab group compared with 4% in the placebo group in UNCOVER-1 ($P < 0.001$). Results were similar in UNCOVER-2, in which 90% of patients in the ixekizumab group compared with 2% of patients in the placebo group and 42% of patients in the etanercept group achieved the primary outcome ($P < 0.001$ for both comparisons). Finally, results from UNCOVER-3 were also consistent with the other included trials, with 87% of patients reaching the pre-specified PASI 75 improvement in the ixekizumab group compared with 7% of patients with placebo and 53% of patients with etanercept ($P < 0.001$ for both comparisons).

Additional non-inferiority and superiority analyses indicated that the difference in the treatment effect of ixekizumab versus etanercept was 47% (97.5% confidence interval [CI], 40% to 54%) in UNCOVER-2 and 39% (97.5% CI, 32% to 46%) in UNCOVER-3 with regard to the proportions of patients achieving at least a two-point improvement in the static PGA (score of 0 or 1) at week 12. The treatment difference for the proportions of patients achieving at least a PASI 75 score at week 12 was 48% (97.5% CI, 41% to 55%) in UNCOVER-2 and 34% (97.5% CI, 27% to 41%) in UNCOVER-3. The results suggest that ixekizumab

is superior to etanercept for both co-primary outcomes of the included studies, because the lower bound of the two-sided 97.5% CI for the difference in proportions of responders on ixekizumab minus etanercept consistently exceeds 0%, the pre-specified superiority margin.

Health-related quality of life (HRQoL), as well as functional outcomes, were identified as important outcomes to patients living with psoriasis, according to the patient input received by CADTH. Symptoms that had the most significant impact on HRQoL, according to patients, included scales and flaking, itching, joint pain, and self-esteem. HRQoL was measured using appropriate instruments in UNCOVER-1, UNCOVER-2, and UNCOVER-3. Specifically, the disease-specific Dermatology Life Quality Index (DLQI) assessed several aspects of a patient's daily life that may be affected by psoriasis symptoms, including the aforementioned scales and flaking, itching, joint pain, and self-esteem. In addition, the more generic Short-Form (36) Health Survey (SF-36) was also used to assess HRQoL. Results from the included studies show that ixekizumab was consistently associated with a statistically significant and clinically meaningful benefit on HRQoL and function compared with placebo and etanercept, as measured by the change from baseline in DLQI total score at week 12 ($P < 0.001$ for all analyses). Overall, results from the SF-36 physical and mental component summary scores also suggested that ixekizumab was superior to placebo and etanercept, as statistical significance was reached in all analyses, with the exception of change from baseline in the SF-36 physical component summary score when ixekizumab was compared with etanercept in UNCOVER-3 ($P = 0.093$). According to the clinical expert consulted and based on estimated minimal clinically important differences (MCIDs), the SF-36 results were generally considered clinically meaningful for patients living with psoriasis. The clinical expert considered the DLQI to be the most relevant and important HRQoL instrument.

Placebo-controlled data were available to provide information on the sustainability of beneficial treatment effects observed with ixekizumab in patients with psoriasis beyond the 12-week induction-dosing period. UNCOVER-1 and UNCOVER-2 included a DB maintenance-dosing period, providing data up to week 60, during which only part of the population was randomized (0). Therefore, the strength of randomization observed for the induction period was not preserved in the overall maintenance period. The design thus likely does not ensure balance in known and unknown relevant characteristics, which limits the validity of the findings from the maintenance-dosing period. To address this issue, the manufacturer reported the results of analyses performed in a population consisting only of re-randomized responder patients, although this analysis is limited because the sample sizes were considerably diminished. Nevertheless, the results obtained at week 60 suggest that ixekizumab has sustained efficacy compared with placebo, measured by the proportions of patients achieving at least a two-point improvement in the static PGA (score of 0 or 1) and at least a PASI 75 score at week 60, in a population consisting of patients who were ixekizumab responders at week 12.

Other than the inclusion of etanercept in UNCOVER-2 and UNCOVER-3, there are no studies in which ixekizumab has been compared directly with other biologic therapies. Therefore, the manufacturer conducted an indirect comparison consisting of an NMA that compared the efficacy and safety of ixekizumab to that of the tumour necrosis factor-alpha inhibitors adalimumab, etanercept, and infliximab, and the interleukin inhibitors secukinumab and ustekinumab. [redacted]

Harms

No deaths occurred during UNCOVER-1, UNCOVER-2, or UNCOVER-3, and the overall incidence of serious adverse events (SAEs) did not differ between ixekizumab and placebo or etanercept in any of the included studies. The most commonly reported SAEs with ixekizumab across the included studies were relatively infrequent (in less than 1% of patients) and included cellulitis, appendicitis, and depression. More patients treated with ixekizumab experienced adverse events (AEs) compared with placebo; however, the incidence of AEs was similar between ixekizumab and etanercept. The most common AEs reported with ixekizumab were nasopharyngitis, injection-site reaction, upper respiratory tract infection, headache, and injection-site erythema. Withdrawal due to adverse events (WDAEs) was infrequent (in less than 1% of patients), but these were more frequently seen with ixekizumab than with placebo or etanercept. Overall, the harms results did not raise any new safety concerns, which was confirmed by the clinical expert consulted.

Some AEs of particular interest were identified by CADTH as potential harms based on the ixekizumab mechanism of action and Health Canada warnings that have been issued with regard to the risks of infections and serious hypersensitivity reaction. Other notable harms, according to clinical expert opinion, included injection-site reactions and major cardiovascular events. Infections were relatively common across the included studies. The proportions of patients experiencing infections were similar between ixekizumab and placebo in UNCOVER-1, as well as between ixekizumab and placebo or etanercept in UNCOVER-2; however, the proportions of patients reporting infections were higher with ixekizumab (21%) than with placebo or etanercept (14% and 15%, respectively) in UNCOVER-3. The proportions of patients receiving ixekizumab and experiencing injection-site reactions ranged from 15% to 20%, and were higher than those in patients receiving placebo in UNCOVER-1, UNCOVER-2, and UNCOVER-3; however, the incidence was similar between patients receiving ixekizumab and patients receiving etanercept in UNCOVER-2 and UNCOVER-3. Hypersensitivity reactions were characterized by a low incidence across the included studies, ranging from 2% to 4% of patients across treatment groups. Major cardiovascular events were infrequent and did not constitute a safety concern.

[redacted]

Key harms outcome results from the 60-week maintenance-dosing period from UNCOVER-1 and UNCOVER-2 did not raise additional concerns regarding longer-term safety of ixekizumab compared with the safety profile observed in the shorter included trials.

Conclusions

The results of three DB RCTs — UNCOVER-1, UNCOVER-2, and UNCOVER-3 — are consistent with the conclusion that ixekizumab is superior to placebo in allowing patients with moderate to severe plaque psoriasis to achieve at least a two-point improvement in the static PGA with achievement of a score of 0 or 1, and at least a PASI 75 score after 12 weeks of treatment. Ixekizumab was associated with statistically significant and clinically meaningful improvements in HRQoL and function compared with placebo and etanercept in each of the three included studies, based on the DLQI. Overall, similar findings were observed for the effects of ixekizumab on HRQoL using the SF-36. The results of UNCOVER-2 and UNCOVER-3 demonstrated that ixekizumab is superior to etanercept for the aforementioned outcomes. The safety profile of ixekizumab is similar to that of etanercept, and ixekizumab was not associated with any major harms at week 12 in the overall population or at week 60 in a small population consisting of patients who were ixekizumab responders at week 12. [redacted]

TABLE 1: SUMMARY OF RESULTS

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 351	PL n = 168	Etanercept n = 358	Ixekizumab n = 385	PL n = 193	Etanercept n = 382
CO-PRIMARY OUTCOMES IN THE INCLUDED STUDIES								
Proportions of Patients with sPGA Score of 0 or 1 at Week 12 (≥ 2-Point Improvement From Baseline)								
n (%)	354 (82)	14 (3)	292 (83)	4 (2)	129 (36)	310 (81)	13 (7)	159 (42)
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* < 0.001			*P* < 0.001		
Non-Inferiority and Superiority Analyses to Etanercept — Fixed Margin[a]								
Difference	—		47%			39%		
2-sided 97.5% CI	—		(40% to 54%)			(32% to 46%)		
Proportions of Patients Achieving ≥ PASI 75 at Week 12								
n (%)	386 (89)	17 (4)	315 (90)	4 (2)	149 (42)	336 (87)	14 (7)	204 (53)
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* < 0.001			*P* < 0.001		
Non-Inferiority and Superiority Analyses to Etanercept – Fixed Margin[a]								
Difference	—		48%			34%		
2-sided 97.5% CI	—		(41% to 55%)			(27% to 41%)		
HEALTH-RELATED QUALITY OF LIFE AND FUNCTIONAL OUTCOMES								
DLQI Total Score – Change from Baseline at Week 12								
LS mean (SE)	–11 (0.3)	–1 (0.3)	–10 (0.3)	–2 (0.4)	–8 (0.3)	–10 (0.2)	–2 (0.3)	–8 (0.2)
Difference vs. PL (95% CI); *P* value	–10 (–11 to –9); *P* < 0.001		–8 (–9 to –8); *P* < 0.001			–8 (–9 to –8); *P* < 0.001		
Difference vs. ETA (95% CI); *P* value	—		–3 (–3 to –2); *P* < 0.001			–2 (–3 to –2); *P* < 0.001		
SF-36 Physical Summary Score – Change from Baseline at Week 12								
LS mean (SE)	4.3 (0.38)	–0.2 (0.40)	3.8 (0.36)	–0.4 (0.51)	2.5 (0.36)	4.1 (0.35)	–0.3 (0.50)	3.1 (0.35)
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* = 0.013			*P* = 0.093		
SF-36 Mental Summary Score – Change from Baseline at Week 12								
LS mean (SE)	4.2 (0.44)	0.7 (0.46)	4.5 (0.40)	–0.1 (0.58)	2.5 (0.40)	4.3 (0.40)	1.1 (0.57)	2.6 (0.40)
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* < 0.001			*P* = 0.002		
KEY HARMS OUTCOMES								
Mortality, n (%)	0	0	0	0	0	0	0	0
SAEs, n (%)	6 (1.4)	5 (1.2)	5 (1.4)	2 (1.2)	8 (2.2)	9 (2.3)	5 (2.6)	5 (1.3)
AEs, n (%)	257 (59)	210 (49)	216 (62)	89 (53)	211 (59)	205 (53)	70 (36)	187 (49)
WDAEs, n (%)	10 (2.3)	6 (1.4)	6 (1.7)	1 (0.6)	5 (1.4)	9 (2.3)	2 (1.0)	4 (1.0)

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	**PL n = 431**	**Ixekizumab n = 351**	**PL n = 168**	**Etanercept n = 358**	**Ixekizumab n = 385**	**PL n = 193**	**Etanercept n = 382**
Notable Harms, n (%)								
Infections	124 (29)	106 (25)	104 (30)	46 (28)	98 (28)	82 (21)	27 (14)	59 (15)
Injection-site reactions	69 (16)	13 (3)	69 (20)	7 (4)	62 (18)	58 (15)	6 (3)	59 (15)
Hypersensitivity reactions	14 (3)	10 (2)	14 (4)	3 (2)	12 (3)	13 (3)	4 (2)	7 (2)
[redacted]								

AE = adverse event; CI = confidence interval; ETA = etanercept; LS = least squares; PASI = Psoriasis Area and Severity Index; PL = placebo; SAE = serious adverse event; SE = standard error; sPGA = static Physician Global Assessment; WDAE = withdrawal due to adverse event.

[a] Non-inferiority margin = –12%; superiority margin = 0%.

Sources: UNCOVER-1 Clinical Study Report,[6] UNCOVER-2 Clinical Study Report,[8] UNCOVER-3 Clinical Study Report.[9]

1. INTRODUCTION

1.1 Disease prevalence and incidence

Psoriasis is a serious, chronic inflammatory skin disorder that commonly leads to significant symptoms, including pain and pruritus, as well as affecting appearance and meaningfully reducing an individual's quality of life. Plaque psoriasis is the most common form of psoriasis and is characterized by well-demarcated papules covered by silvery scales. Moderate to severe plaque psoriasis can be defined by the extent of skin coverage, with involvement of more than 5% to 10% of body surface area (BSA); location, i.e., involvement of the face, palm or sole; or severity, if the disease's effects are disabling. The fact that plaques may be highly visible may affect self-esteem, resulting in a negative impact on social functioning. In addition, patients present with an increased risk of various serious comorbidities, including inflammatory diseases occurring at sites other than the skin.[1-3]

There are approximately 1 million people who suffer from psoriasis in Canada, and 125 million worldwide. Of these, approximately 90% experience plaque psoriasis.[10]

1.2 Standards of therapy

Psoriasis may be treated with topical therapies, including phototherapy, if disease is mild. Moderate to severe plaque psoriasis requires the use of systemic therapies, often administered concomitantly with topical drugs. Psoriasis is essentially an immune disorder, and therefore the systemic therapies all work by suppressing components of the immune system. For some patients with moderate to severe disease, short-term improvement and limited long-term disease control may be adequate; however, full clearance often is an achievable and appropriate treatment goal.[3]

The first systemic therapies, often referred to as "conventional therapies," were all small molecules, the two most important currently being methotrexate, an antimetabolite also used in some cancers and in rheumatoid arthritis, and cyclosporine, a potent immunosuppressant also used in prevention of organ transplant rejection. However, both of these drugs have significant toxicities associated with them. Biologic drugs were the next systemic therapies to be developed. Initially, all of these drugs targeted tumour necrosis factor (TNF), a key mediator of inflammation. TNF-alpha inhibitors include adalimumab, etanercept, and infliximab, which have all been associated with elevated risk of certain cancers with long-term use and with increased risk of infection, including tuberculosis. The newest biologic drugs target interleukins (IL) and include ustekinumab (targeting IL-12 and IL-23) and secukinumab (targeting IL-17).[2,3] Additional details regarding these treatment options are provided in Table 2.

1.3 Drug

Ixekizumab is a humanized monoclonal antibody that selectively inhibits IL-17A, a pro-inflammatory cytokine implicated in the pathogenesis of a variety of autoimmune diseases, including plaque psoriasis. Selective inhibition of IL-17A disrupts pro-inflammatory cycles without interrupting a broader set of immunological pathways that may be affected by other biologic treatments, such as TNF-alpha inhibitors.[11] Ixekizumab has a Health Canada indication for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[4] The recommended dose of ixekizumab is a 160 mg subcutaneous (SC) injection at week 0; followed by 80 mg SC at weeks 2, 4, 6, 8, 10, and 12; followed by 80 mg SC every four weeks.[4]

Indication under review
Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Listing criteria requested by sponsor
As per indication

TABLE 2: KEY CHARACTERISTICS OF BIOLOGIC DRUGS FOR THE TREATMENT OF PSORIASIS

	Infliximab	Adalimumab	Etanercept	Ustekinumab	Secukinumab	Ixekizumab
Mechanism of Action	TNF inhibitor			IL-12 and IL-23 inhibitor	IL-17A inhibitor	
Health Canada Indication	Chronic moderate to severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, should be used after phototherapy has been shown to be ineffective or inappropriate.	Chronic moderate to severe psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, adalimumab should be used after phototherapy has been shown to be ineffective or inappropriate.	Chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.	Chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Route of Administration	Intravenous	Subcutaneous				
Recommended Dose	5 mg/kg given as an intravenous infusion; followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion; then every 8 weeks thereafter. No additional treatment with infliximab should be given if a patient does not show an adequate response at week 14.	80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week, starting one week after the initial dose. Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.	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.	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 inadequately respond to dosing every 12 weeks, consideration may be given to treating as often as every 8 weeks.	300 mg with initial dosing at weeks 0, 1, 2 and 3; followed by monthly maintenance dosing starting at week 4	160 mg at week 0; followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12; followed by 80 mg every 4 weeks

Serious Side Effects / Safety Issues	Infection Cancer	Infection Cancer Serious skin reactions	Infection Serious hypersensitivity reactions	Infection Injection-site reactions Serious hypersensitivity reactions Major cardiovascular events

IL = interleukin; TNF = tumour necrosis factor.
Source: e-CPS,[12] Taltz product monograph.[4]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of ixekizumab given by SC injection for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

2.2 Methods

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

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

PATIENT POPULATION	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
INTERVENTION	Ixekizumab 160 mg subcutaneous (SC) injection at week 0; followed by 80 mg SC at weeks 2, 4, 6, 8, 10, and 12; followed by 80 mg SC every 4 weeks
COMPARATORS	***Traditional systemic drugs:*** Methotrexate, cyclosporine, acitretin, apremilast ***Biologic drugs targeting TNF-alpha:*** Adalimumab, etanercept, infliximab ***Biologic drugs targeting interleukin:*** Ustekinumab, secukinumab
OUTCOMES	***Key efficacy outcomes:*** Psoriasis Area and Severity Index (PASI) response[a] Health-related quality of life and functional outcomes (e.g., Dermatology Life Quality Index [DLQI])[a] Physician Global Assessment (PGA) ***Harms outcomes:*** Mortality, SAEs, AEs, WDAEs Notable harms, including but not limited to: • infections • injection-site reactions • serious hypersensitivity reactions • major cardiovascular events
STUDY DESIGN	Published and unpublished RCTs

AE = adverse event; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Outcomes identified as important to patients from the patient input included physical outcomes such as desquamation, itching, lesion pain, and joint pain, as well as psychological outcomes such as embarrassment and self-confidence issues. In addition, patients reported various functional outcomes of importance, such as employment, socializing, everyday household chores, and sports. Desquamation is one of the four core criteria evaluated within the PASI response. All other individual outcomes identified as important to patients are captured within the DLQI questionnaire.

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

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

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on April 21, 2016. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on September 21, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

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

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in 0.

3. RESULTS

3.1 Findings from the literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

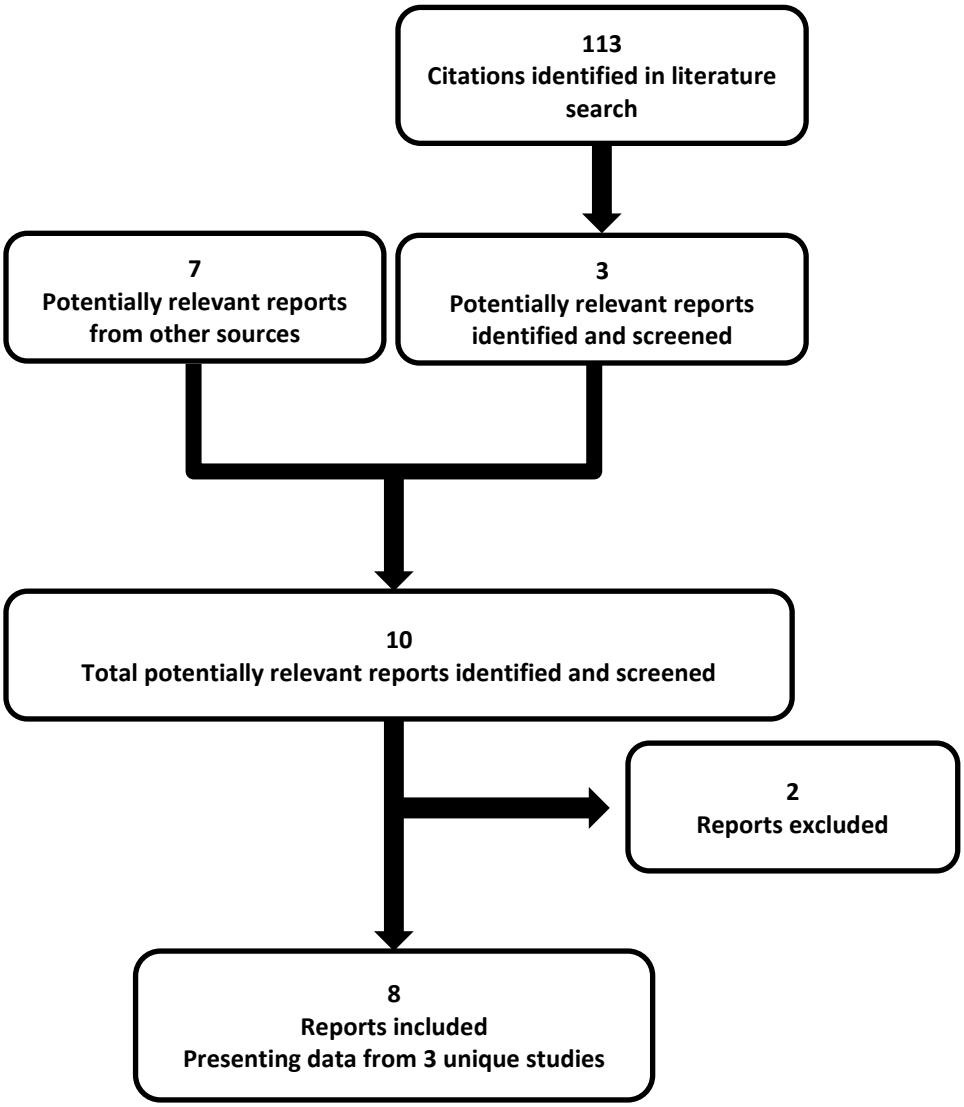


TABLE 4: DETAILS OF INCLUDED STUDIES

		UNCOVER-1	UNCOVER-2	UNCOVER-3
DESIGNS & POPULATIONS	**Study Design**	DB PL-controlled RCT	DB PL-controlled and active-controlled RCT	DB PL-controlled and active-controlled RCT
	Locations	Multi-centre (11 countries): Europe, US, Canada, Australia, Asia	Multi-centre (12 countries): Europe, US, Canada	Multi-centre (10 countries): Europe, US, Canada, Latin America
	Randomized (N)	N = 1,296	N = 1,224	N = 1,346
	Inclusion Criteria	Adult patients with a confirmed diagnosis of chronic plaque psoriasis for at least 6 months who were candidates for phototherapy and/or systemic therapy and who had ≥ 10% BSA involvement, a static PGA score ≥ 3, and a PASI score ≥ 12 at screening and at baseline		
	Exclusion Criteria	Pustular, erythrodermic, guttate, or drug-induced psoriasis; recent clinically significant flare, systemic therapy, phototherapy, potent topical steroids, or biologic therapy; prior use of any IL-17A antagonist or etanercept (UNCOVER-2 and UNCOVER-3); live vaccination; current or prior lymphoproliferative or malignant disease; significant uncontrolled cerebrovascular, cardiovascular, neurological, psychiatric, renal, hepatic, respiratory, gastrointestinal, endocrine, or hematologic disorder; serious infection, tuberculosis, HIV, hepatitis B or C		
DRUGS	**Intervention**[a]	**DB induction-dosing period:** Ixekizumab 160 mg SC (2 injections) at week 0; followed by 80 mg SC (1 injection) every 2 weeks (week 2, 4, 6, 8, and 10) **DB maintenance-dosing period:** Ixekizumab 80 mg SC (1 injection) at week 12 and every 4 weeks thereafter		
	Comparator(s)	**DB induction-dosing period:** Placebo SC (2 injections) at week 0; followed by 1 SC injection every 2 weeks **DB maintenance-dosing period:** Placebo SC injection at week 12, and every 4 weeks	**DB induction-dosing period:** Placebo SC (2 injections) at week 0; followed by 1 SC injection every 2 weeks Or Etanercept 50 mg SC twice weekly for 12 weeks **DB maintenance-dosing period:** Placebo SC injection at week 12, and every 4 weeks	**DB induction-dosing period:** Placebo SC (2 injections) at week 0; followed by 1 SC injection every 2 weeks; Or Etanercept 50 mg SC twice weekly for 12 weeks
DURATION	**Phase**			
	DB induction	12 weeks	12 weeks	12 weeks
	DB maintenance	48 weeks	48 weeks	None
	O/L extension	Ongoing		
OUTCOMES	**Co-Primary End Points**	Proportion of patients: with ≥ 2-point improvement in static PGA at week 12 (with PGA score of 0 or 1) achieving ≥ PASI 75 score at week 12		

		UNCOVER-1	UNCOVER-2	UNCOVER-3
	Other Relevant End Points	PASI 90 and PASI 100 achievement DLQI and other QoL assessments Maintenance of efficacy at week 60 Time-to-event analysis of the co-primary outcomes		
NOTES	**Publications**	Gordon et al., 2016[5]	Gordon et al., 2016[5] Griffiths et al., 2015[7]	Gordon et al., 2016[5] Griffiths et al., 2015[7]

BSA = body surface area; DB = double-blind; DLQI = Dermatology Life Quality Index; IL = interleukin; O/L = open-label; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; PL = placebo; RCT = randomized controlled trial; QoL = quality of life; SC = subcutaneous injection.
Note: 7 additional reports were included.[5,6,8,9,11,13,14]
[a] Only treatment groups that were consistent with the Health Canada–approved dosing were included in the review, i.e., ixekizumab 160 mg SC at week 0; followed by 80 mg SC at weeks 2, 4, 6, 8, 10, and 12; followed by 80 mg SC every 4 weeks.
Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8], UNCOVER-3 Clinical Study Report[9].

3.2 Included studies

3.2.1 Description of studies

Three manufacturer-sponsored double-blind (DB) randomized controlled trials (RCTs) were included in the systematic review: UNCOVER-1 (n = 1,296),[5,6] UNCOVER-2 (n = 1,224),[5,7,8] and UNCOVER-3 (n = 1,346).[5,7,9] All three trials evaluated the efficacy and safety of ixekizumab in patients with moderate to severe plaque psoriasis, based on the following co-primary outcomes, assessed at the end of the DB induction period (week 12):

- proportions of patients with at least a two-point improvement in the static Physician Global Assessment (PGA, with a score of 0 or 1)
- proportions of patients achieving at least a Psoriasis Area and Severity Index (PASI) 75 score.

UNCOVER-1 and UNCOVER-2 also included a DB maintenance period, providing data up to week 60. However, the design of the maintenance period is associated with several significant limitations; therefore, the 60-week results will be presented as supportive information only.

UNCOVER-1 (n = 1,296)[5,6] was a placebo-controlled RCT evaluating the superiority of ixekizumab compared with placebo. The study first included an induction-dosing period, which was a DB treatment period from week 0 to week 12, when the co-primary outcomes were assessed. Patients were randomized in a 1:1:1 ratio to either placebo, or to one of two ixekizumab induction regimens; however, only the dosing regimen that is consistent with the Health Canada–approved dose was included in this review, i.e., ixekizumab 160 mg SC at week 0, followed by 80 mg SC every two weeks up to week 12.

Afterwards, patients entered a maintenance-dosing period, which was a DB treatment period in a re-randomized patient population from week 12 to week 60. In terms of dosing strategies, patients who were receiving any dosage of ixekizumab during the induction period and were classified as responders (static PGA score of 0 or 1, with at least a two-point improvement from baseline) were re-randomized to receive either placebo, or one of two ixekizumab maintenance regimens. However, only the dosing regimen that is consistent with the Health Canada–approved dose was included in this review, i.e., ixekizumab 80 mg SC every four weeks. Patients achieving a response on placebo during the induction period were not part of the randomization, and they continued to receive placebo for the maintenance period. Patients classified as non-responders (static PGA score > 1) in any treatment group were also not

part of the randomization, and they were all systematically assigned to ixekizumab 80 mg SC every four weeks.

UNCOVER-2 (n = 1,224)[5,7,8] was a placebo-controlled and active-controlled RCT evaluating the superiority of ixekizumab compared with placebo, as well as the non-inferiority and superiority of ixekizumab compared with etanercept. For the 12-week DB induction-dosing period, patients were randomized in a 1:2:2:2 ratio to either placebo, etanercept 50 mg SC twice weekly, or to one of two ixekizumab induction regimens. However, only the following dosage group was included in this review per the Health Canada–approved dose: ixekizumab 160 mg SC at week 0 followed by 80 mg SC every two weeks.

For the DB maintenance period, responders from any ixekizumab treatment group were re-randomized to receive either placebo, or one of two ixekizumab maintenance regimens; however, only ixekizumab 80 mg SC every four weeks was included in this review, per the Health Canada–approved dose. Patients achieving a response on placebo or etanercept during the induction period were not part of the randomization and received placebo for the maintenance period. Patients classified as non-responders in any treatment group were automatically assigned to ixekizumab 80 mg SC every four weeks.

UNCOVER-3 (n = 1,346)[5,7,9] was a placebo-controlled and active-controlled RCT evaluating the superiority of ixekizumab compared with placebo, as well as the non-inferiority and superiority of ixekizumab compared with etanercept. For the 12-week DB induction-dosing period, patients were randomized in a 1:2:2:2 ratio to either placebo, etanercept 50 mg SC twice weekly, or to one of two ixekizumab induction regimens. However, only the following dosage group was included in this review per the Health Canada–approved dose: ixekizumab 160 mg SC at week 0 followed by 80 mg SC every two weeks. UNCOVER-3 did not include a maintenance-dosing period.

3.2.2 Populations

a) Inclusion and exclusion criteria

UNCOVER-1, UNCOVER-2, and UNCOVER-3 included adult patients with a confirmed diagnosis of chronic plaque psoriasis for at least six months who were candidates for phototherapy and/or systemic therapy and who had at least a 10% BSA involvement, a static PGA score of at least 3, and a PASI score of at least 12 at screening and at baseline.

Key exclusion criteria included pustular, erythrodermic, and/or guttate forms of psoriasis; a history of drug-induced psoriasis; or a clinically significant flare of psoriasis during the 12 weeks before baseline. Patients with prior etanercept use were excluded from UNCOVER-2 and UNCOVER-3. Other therapies precluding patients from entering UNCOVER-1, UNCOVER-2, and UNCOVER-3 included systemic non-biologic psoriasis therapy or phototherapy (within four weeks), certain classes of topical psoriasis treatment (within two weeks), previous biologic therapies (within specific washout periods), drugs that target alpha-4-integrin, or previous use of any IL-17A antagonist.

Patients were also excluded if they received or intended to receive certain vaccinations within specified time periods. The presence of the following also excluded patients from the three included trials: current or history of lymphoproliferative disease or malignant diseases; significant uncontrolled cerebro-cardiovascular, neurological, neuropsychiatric, renal, hepatic, respiratory, gastrointestinal, endocrine, or hematologic disorders; serious infection, active or latent tuberculosis, HIV, hepatitis C, or some presentations of hepatitis B; or failure to meet specific laboratory criteria.

b) Baseline characteristics

Details regarding baseline characteristics are provided in Table 5. Baseline characteristics were balanced between treatment groups within each included study. Overall, disease characteristics were consistent across UNCOVER-1, UNCOVER-2, and UNCOVER-3, with the exception of prior experience with biologic therapy, which was more common in UNCOVER-1 compared with UNCOVER-2 and UNCOVER-3.

Specifically, patients had a mean age of 45 to 46 years, with approximately one-third of patients being younger than 40 years, and less than 10% of patients being 65 years or older. The mean duration of psoriasis symptoms ranged between 18 and 20 years. In terms of disease severity, the majority of patients had a static PGA score of 3 or 4. The mean baseline PASI score ranged from 19 to 21, with a mean BSA involvement between 25% and 29%. The mean baseline Dermatology Life Quality Index (DLQI) score ranged from 12 to 13. Nail, scalp, and facial psoriasis were frequently reported among included patients; between 19% and 28% of patients also reported concomitant psoriatic arthritis. Prior experience with systemic therapies was reported in 54% to 75% of patients participating in UNCOVER-1, UNCOVER-2, and UNCOVER-3; among the therapeutic options were phototherapy (31% to 48% of patients), non-biologic systemic therapy (46% to 64%), and biologic therapy (41% of patients included in UNCOVER-1 and 15% to 26% of patients included in UNCOVER-2 and UNCOVER-3).

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Baseline Characteristics	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 351	PL n = 168	Etanercept n = 358	Ixekizumab n = 385	PL n = 193	Etanercept n = 382
Age, years								
Mean (SD)	45 (12.4)	46 (13.4)	45 (13.3)	45 (12.1)	45 (12.8)	46 (13.1)	46 (12.1)	46 (13.8)
Age Categories, n (%)								
< 40 years	153 (35)	134 (31)	131 (37)	53 (32)	119 (33)	135 (35)	50 (26)	138 (36)
≥ 40, < 65 years	254 (59)	259 (60)	195 (56)	105 (63)	217 (61)	215 (56)	130 (67)	211 (55)
≥ 65 years	26 (6)	38 (9)	24 (7)	9 (5)	21 (6)	34 (9)	13 (7)	33 (9)
Gender, n (%)								
Male	291 (67)	303 (70)	221 (63)	120 (71)	236 (66)	254 (66)	137 (71)	269 (70)
Female	142 (33)	128 (30)	130 (37)	48 (29)	122 (34)	131 (34)	56 (29)	113 (30)
BMI Categories, n (%)[a]								
Underweight	5 (1)	9 (2)	2 (1)	1 (1)	1 (< 1)	0	0	3 (1)
Normal	83 (19)	95 (22)	75 (21)	31 (19)	70 (20)	87 (23)	38 (20)	85 (22)
Overweight	135 (31)	138 (32)	128 (37)	48 (29)	109 (31)	137 (36)	73 (38)	115 (30)
Obese	160 (37)	136 (32)	116 (33)	70 (42)	130 (36)	123 (32)	65 (34)	136 (36)
Extremely obese	49 (11)	53 (12)	30 (9)	15 (9)	47 (13)	37 (10)	16 (8)	43 (11)
Duration of Psoriasis Symptoms, years								
Mean (SD)	20 (11.9)	20 (11.7)	18 (12.1)	19 (12.7)	19 (12.5)	18 (12.2)	18 (12.5)	18 (11.8)
Baseline static PGA, n (%)								
sPGA = 3	231 (53)	204 (47)	178 (51)	86 (51)	186 (52)	207 (54)	92 (48)	190 (50)
sPGA = 4	179 (41)	193 (45)	151 (43)	70 (42)	156 (44)	157 (41)	91 (47)	174 (46)
sPGA = 5	23 (5)	34 (8)	22 (6)	12 (7)	16 (5)	21 (6)	10 (5)	18 (5)
Baseline PASI Score								
Mean (SD)	20 (8.0)	20 (8.6)	19 (7.3)	21 (8.4)	19 (6.7)	21 (8.2)	21 (8.4)	21 (8.2)
Baseline Percentage of BSA								
Mean (SD)	28 (17.8)	27 (17.7)	25 (15.8)	27 (18.1)	25 (15.5)	28 (17.3)	29 (17.5)	28 (17.4)

Baseline Characteristics	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 351	PL n = 168	Etanercept n = 358	Ixekizumab n = 385	PL n = 193	Etanercept n = 382
Baseline DLQI Total Score								
Mean (SD)	13 (7.0)	13 (7.1)	12 (6.9)	13 (7.2)	13 (7.0)	12 (6.9)	13 (7.0)	12 (6.8)
Clinically Meaningful Psoriasis Locations and Associated Conditions, n (%)								
Nail psoriasis	284 (66)	283 (66)	209 (60)	113 (67)	229 (64)	229 (60)	116 (60)	236 (62)
Scalp psoriasis	393 (91)	393 (91)	320 (91)	151 (90)	322 (90)	349 (91)	176 (91)	348 (91)
Palmoplantar	140 (32)	133 (31)	104 (30)	55 (33)	95 (27)	96 (25)	54 (28)	95 (25)
Facial psoriasis	209 (48)	217 (50)	163 (46)	92 (55)	173 (48)	152 (40)	75 (39)	163 (43)
Psoriatic arthritis	119 (28)	115 (27)	87 (25)	47 (28)	79 (22)	77 (20)	42 (22)	72 (19)
Previous Use of Systemic Therapy, n (%)								
Any therapy	325 (75)	299 (69)	225 (64)	104 (62)	225 (63)	215 (56)	105 (54)	222 (58)
Phototherapy	201 (46)	185 (43)	163 (46)	74 (44)	173 (48)	151 (39)	60 (31)	157 (41)
Non-biologic	276 (64)	242 (56)	196 (56)	85 (51)	192 (54)	190 (49)	89 (46)	196 (51)
Biologic	173 (40)	181 (42)	84 (24)	43 (26)	76 (21)	58 (15)	33 (17)	60 (16)
TNF inhibitors	119 (28)	113 (26)	45 (13)	14 (8)	38 (11)	27 (7)	15 (8)	29 (8)
IL inhibitors	58 (13)	51 (12)	32 (9)	9 (5)	25 (7)	20 (5)	10 (5)	18 (5)

BMI = body mass index; BSA = body surface area; IL = interleukin; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; PL = placebo; SD = standard deviation; sPGA = static Physician Global Assessment; TNF = tumour necrosis factor.

[a] Underweight (< 18.5 kg/m^2), Normal (≥ 18.5 to < 25 kg/m^2), Overweight (≥ 25 to < 30 kg/m^2), Obese (≥ 30 to < 40 kg/m^2), Extremely obese (≥ 40 kg/m^2).

Sources: UNCOVER-1 Clinical Study Report [6], UNCOVER-2 Clinical Study Report[8], UNCOVER-3 Clinical Study Report[9].

3.2.3 Interventions

UNCOVER-1 evaluated the superiority of ixekizumab compared with placebo based on a DB trial design. During the 12-week induction-dosing phase, patients were randomized to receive one of the three following treatments:

- ixekizumab 160 mg given as two SC injections at week 0, followed by 80 mg SC every two weeks up to week 12
- ixekizumab 160 mg given as two SC injections at week 0, followed by 80 mg SC every four weeks plus placebo given as one SC injection at weeks 2, 6, and 10 up to week 12
- placebo given as two SC injections at week 0, followed by one SC injection every two weeks up to week 12.

However, only the dosing regimen that is consistent with the Health Canada–approved dose was included in this review, i.e., ixekizumab 160 mg SC at week 0, followed by 80 mg SC every two weeks. Throughout the maintenance-dosing period, patients were randomized to receive one of the three following treatments:

- ixekizumab 80 mg SC plus one placebo SC injection at week 12, and ixekizumab 80 mg SC every four weeks thereafter
- ixekizumab 80 mg SC plus one placebo SC injection at week 12, and ixekizumab 80 mg SC every 12 weeks plus placebo given as one SC injection at weeks 16, 20, 28, 32, 40, 44, 52, 56, and so on thereafter
- placebo given as two SC injections at week 12, followed by placebo given as one SC injection every four weeks thereafter.

However, only the dosing regimen that is consistent with the Health Canada–approved dose was included in this review, i.e., ixekizumab 80 mg SC at week 12 and every four weeks thereafter. The syringes and contents containing either ixekizumab or placebo for ixekizumab were visually indistinguishable from each other.

UNCOVER-2 evaluated the superiority of ixekizumab compared with placebo, as well as the non-inferiority and superiority of ixekizumab compared with etanercept, based on a DB trial design. During the 12-week induction-dosing phase, patients were randomized to receive one of the four following treatments:

- ixekizumab 160 mg given as two SC injections at week 0, followed by 80 mg SC every two weeks plus placebo for etanercept given as one SC injection twice weekly up to week 12
- ixekizumab 160 mg given as two SC injections at week 0, followed by 80 mg SC every four weeks plus placebo for ixekizumab given as one SC injection at weeks 2, 6, and 10 plus placebo for etanercept given as one SC injection twice weekly up to week 12
- etanercept 50 mg SC twice weekly plus placebo for ixekizumab given as two SC injections at week 0 followed by one SC injection every two weeks up to week 12
- placebo for ixekizumab given as two SC injections at week 0 followed by one SC injection every two weeks plus placebo for etanercept given as one SC injection twice weekly up to week 12.

However, only the dosing regimen that is consistent with the Health Canada–approved dose was included in this review. Throughout the maintenance-dosing period, patients were randomized to receive one of the three following treatments:

- ixekizumab 80 mg SC plus one placebo SC injection at week 12, and ixekizumab 80 mg SC every four weeks thereafter
- ixekizumab 80 mg SC plus one placebo SC injection at week 12, and ixekizumab 80 mg SC every 12 weeks plus placebo given as one SC injection at weeks 16, 20, 28, 32, 40, 44, 52, 56, and so on thereafter
- placebo given as two SC injections at week 12, followed by placebo given as one SC injection every four weeks thereafter.

However, only the dosing regimen that is consistent with the Health Canada–approved dose was included in this review. The syringes and contents containing either ixekizumab or placebo for ixekizumab were visually indistinguishable from each other.

UNCOVER-3 evaluated the superiority of ixekizumab compared with placebo, as well as the non-inferiority and superiority of ixekizumab compared with etanercept, based on a DB trial design. During the 12-week induction-dosing phase, patients were randomized to receive one of the four following treatments:

- ixekizumab 160 mg given as two SC injections at week 0, followed by 80 mg SC every two weeks plus placebo for etanercept given as one SC injection twice weekly up to week 12
- ixekizumab 160 mg given as two SC injections at week 0, followed by 80 mg SC every four weeks plus placebo for ixekizumab given as one SC injection at weeks 2, 6, and 10 plus placebo for etanercept given as one SC injection twice weekly up to week 12
- etanercept 50 mg SC twice weekly plus placebo for ixekizumab given as two SC injections at week 0 followed by one SC injection every two weeks up to week 12
- placebo for ixekizumab given as two SC injections at week 0 followed by one SC injection every two weeks plus placebo for etanercept given as one SC injection twice weekly up to week 12.

UNCOVER-3 did not include a maintenance-dosing period. The syringes and contents containing either ixekizumab or placebo for ixekizumab were visually indistinguishable from each other.

UNCOVER-1, UNCOVER-2, and UNCOVER-3 had similar requirements regarding concomitant medication. Limited use of topical therapies was allowed throughout the study. Patients were also able to continue their usual, stable doses of medication for concomitant diseases unless specifically excluded. Use of additional systemic drugs was discouraged.

3.2.4 Outcomes

a) Primary efficacy outcomes

The co-primary efficacy outcomes for UNCOVER-1, UNCOVER-2, and UNCOVER-3 were the following, assessed at the end of the DB induction period (week 12):

- proportions of patients with at least a two-point improvement in the static PGA (with PGA score of 0 or 1)
- proportions of patients achieving at least a PASI 75 score (i.e., a 75% reduction in the PASI score).

The PGA is used to determine a single estimate of the patient's overall severity of disease at a given point in time. Psoriatic lesions are graded for induration, erythema, and scaling based on scales of 0 to 4 that are then averaged over all lesions.[15] The patient's psoriasis is assessed based on the final PGA score as follows:

- 0 = cleared, except for residual discoloration
- 1 = minimal
- 2 = mild
- 3 = moderate
- 4 = severe.

PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It combines assessments of the extent of BSA involvement in four anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration or infiltration (thickness) in each region, producing a numeric score ranging from 0 to 72. In general, a PASI score of 5 to 10 is considered moderate disease, and a score more than 10 is considered severe. A 75% reduction in the PASI score (PASI 75) is the current benchmark for most clinical trials in psoriasis and the criterion for efficacy of new psoriasis treatments approved by the Food and Drug Administration (FDA).[16]

b) Secondary efficacy outcomes

Relevant secondary efficacy outcomes for UNCOVER-1, UNCOVER-2, and UNCOVER-3 included the following:

- proportions of patients achieving a PASI 90 (i.e., a 90% reduction in the PASI score) or a PASI 100 score (i.e., a 100% reduction in the PASI score)
- change from baseline in dermatology-specific quality of life as assessed by the DLQI score
- change from baseline in other health-related quality of life (HRQoL) outcomes, including the Short-Form (36) Health Survey (SF-36) physical component summary and mental component summary scores
- maintenance of efficacy based on the PGA and PASI 75 score at week 60 (UNCOVER-1 and UNCOVER-2).

The DLQI is a widely used dermatology-specific quality-of-life instrument. It consists of a 10-item questionnaire assessing six different aspects that may affect quality of life: symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[17,18] The higher the score, the greater the impairment in quality of life. The meaning of the DLQI scores on a patient's life is as follows, on a scale of 0 to 30:[19]

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

The estimated minimal clinically important difference (MCID) for the DLQI in patients with psoriasis is 3.2;[20] however, estimates of the smallest difference a patient would regard as beneficial have ranged from 2.3 to 5.7.[21]

The SF-36 is a generic measure of HRQoL. It comprises 36 items covering the following eight domains: physical functioning, role physical, role emotional, bodily pain, vitality, social functioning, mental health, and general health. The eight domains are aggregated to create two component summaries: the physical component summary and the mental component summary, with scores ranging from 0 to 100, with higher scores indicating better health status. The MCID is typically between 2.5 and 5.0 points.[22-24]

c) Harms outcomes

Safety outcomes included adverse events (AEs) and serious adverse events (SAEs), clinical laboratory results, and vital signs.

3.2.5 Statistical analysis

a) Statistical methods

Statistical methods were similar for UNCOVER-1, UNCOVER-2, and UNCOVER-3. Continuous data were summarized in terms of the number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical data were summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts, and percentages. All confidence intervals (CIs) and statistical tests were two-sided unless otherwise specified.

The primary analysis for all continuous efficacy and health outcome variables was performed using mixed-effects model of repeated measures (MMRM) analysis. Treatment comparisons for continuous efficacy and health outcomes variables were also made using analysis of covariance (ANCOVA). When MMRM was used, treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, baseline value, visit, and treatment-by-visit interaction terms were fitted as fixed factors. When the ANCOVA model was used, the model included treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, and baseline value.

For UNCOVER-1, treatment comparisons of dichotomous efficacy and health outcomes variables were conducted using a logistic regression analysis with treatment, geographic region, previous non-biologic systemic therapy, and baseline weight category in the model. For UNCOVER-2 and UNCOVER-3, treatment comparisons of categorical efficacy and health outcomes variables were made using a Cochran-Mantel-Haenszel test stratified by pooled centre. Secondary analysis on the dichotomous efficacy variables was conducted using a Fisher's exact test in all three included studies.

Gatekeeping strategy

A gatekeeping testing strategy for the primary analyses and major secondary analyses was implemented to control the overall type 1 error rate at a two-sided alpha level of 0.05 for the multiple comparisons. With the gatekeeper strategy, each prior comparison must have a significant difference before another comparison can be tested for significance. Outcomes included in the gatekeeper strategy were as follows:

TABLE 6: OUTCOMES INCLUDED IN THE GATEKEEPING STRATEGY (PRESENTED IN THE ORDER OF TESTING)

<table>
<tr><th></th><th>UNCOVER-1</th><th>UNCOVER-2</th><th>UNCOVER-3</th></tr>
<tr><td rowspan="2">Primary</td><td colspan="3">• sPGA (score of 0 or 1) at week 12 compared with placebo
• PASI 75 at week 12 compared with placebo</td></tr>
<tr><td></td><td colspan="2">• sPGA (score of 0 or 1) at week 12, non-inferiority to etanercept
• PASI 75 at week 12, non-inferiority to etanercept
• sPGA (score of 0 or 1) at week 12, superiority to etanercept
PASI 75 at week 12, superiority to etanercept</td></tr>
<tr><td rowspan="3">Secondary</td><td colspan="3">• sPGA (0) at week 12 compared with placebo
• PASI 90 at week 12 compared with placebo
• PASI 100 at week 12 compared with placebo</td></tr>
<tr><td rowspan="2">• Proportion of patients maintaining an sPGA (score of 0 or 1) from week 12 to week 60 compared with placebo for ixekizumab-treated patients who had an sPGA (score of 0 or 1) at week 12 and were re-randomized
• Itch NRS ≥ 4-point reduction from baseline at week 12 compared with placebo
• Change from baseline in DLQI at week 12 (mBOCF) compared with placebo
• Change from baseline in NAPSI (for fingernails) at week 12 (mBOCF) compared with placebo</td><td colspan="2">• sPGA (0) at week 12, superiority to etanercept
• PASI 90 at week 12, superiority to etanercept
• PASI 100 at week 12, superiority to etanercept</td></tr>
<tr><td>• Proportion of patients maintaining an sPGA (score of 0 or 1) from week 12 to week 60 compared with placebo for ixekizumab-treated patients who had an sPGA (score of 0 or 1) at week 12 and were re-randomized</td><td>• Proportion of patients achieving an Itch NRS ≥ 4 point reduction from baseline at week 12 compared with placebo
• Change from baseline in DLQI at week 12 compared with placebo
• Change from baseline in NAPSI (for fingernails) at week 12 compared with placebo</td></tr>
</table>

DLQI = Dermatology Life Quality Index; mBOCF = modified baseline observation carried forward; NAPSI = Nail Psoriasis Severity Index; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; sPGA = static Physician Global Assessment.

Non-inferiority and superiority margins

In UNCOVER-2 and UNCOVER-3, a non-inferiority (NI) analysis has been reported on both sPGA (score of 0 or 1) and PASI 75 at week 12 using a fixed-margin approach. The manufacturer referenced European Medicines Agency (EMA) and FDA guidelines and guidance documents to support a NI margin of –12.0% for both sPGA (score of 0 or 1) and PASI 75. This NI margin represents a ≥ 70% preservation of the etanercept treatment effect observed in historical phase 3 studies for etanercept compared with placebo. Ixekizumab would be deemed non-inferior to etanercept if the lower bound of the two-sided

97.5% CI for the difference in proportions of responders on ixekizumab minus etanercept is greater than the pre-specified margin of –12.0%. If the lower bound of the CI exceeds 0, ixekizumab would be deemed superior to etanercept. This NI analysis would be conducted only if the ixekizumab dose is significantly better than placebo, and etanercept is significantly better than placebo, in accordance with the gatekeeping strategy. Superiority analyses would be conducted in the event that NI of ixekizumab versus etanercept is demonstrated, in accordance with the gatekeeping strategy.

Sample size

The total sample size for UNCOVER-1 was planned at 1,296 patients randomized in a 1:1:1 ratio in the blinded induction-dosing period to 80 mg every two weeks, 80 mg every four weeks, or placebo. In order to account for multiple testing for the two ixekizumab groups, a two-sided Fisher's exact test at the 0.025 level was assumed. With 432 patients per treatment group, this study had greater than 99% power to test the superiority of each ixekizumab dose regimen to placebo for sPGA (score of 0 or 1) and PASI 75 at week 12.

The total planned sample size for UNCOVER-2 was 1,224 patients, while that of UNCOVER-3 was 1,225 patients, randomized in both studies at a 2:2:2:1 ratio in the blinded induction-dosing period to ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, etanercept, and placebo, respectively. In order to account for multiple testing for the two ixekizumab groups, a two-sided Fisher's exact test at the 0.025 level was assumed. Both studies had > 93% power to test the superiority of each ixekizumab dose regimen to etanercept and > 99% power to test the superiority of each ixekizumab dose regimen to placebo for sPGA (score of 0 or 1) and for PASI 75 at week 12.

The following assumptions were used in the trials for the power calculations at week 12:

- 70% for sPGA (score of 0 or 1) and PASI 75 for each ixekizumab treatment group
- 56% for sPGA (score of 0 or 1) and 53% for PASI 75 for etanercept (UNCOVER-2 and UNCOVER-3)
- 10% for sPGA (score of 0 or 1) and PASI 75 for the placebo group.

b) Imputation for missing data

Primary outcomes

Patients who discontinued study treatment at any time before week 12, or for any reason, were defined as non-responders for all categorical sPGA and PASI analyses (non-responder imputation). Randomized patients without at least one post-baseline observation were also defined as non-responders. The placebo multiple imputation method was also used for other analyses of efficacy.

Secondary outcomes

For variables that were not collected at each post-baseline visit, data may exist from visits at which the variable was not scheduled to be collected, due to early-discontinuation visits. In these situations, data from the early-discontinuation visit that does not correspond to the planned collection schedule were used in other analyses, including change from baseline to last observation carried forward (LOCF) and modified baseline observation carried forward (mBOCF) analyses. An mBOCF analysis was performed on all continuous efficacy and health outcome variables. For patients discontinuing the investigational product because of an AE, the baseline observation was carried forward to the corresponding primary end point for evaluation. For patients discontinuing the investigational product for any other reason, the last non-missing post-baseline observation before discontinuation was carried forward to the corresponding primary end point for evaluation. An LOCF analysis was also performed on all continuous efficacy and health outcomes variables. This approach is identical to the mBOCF approach, with one exception: for patients discontinuing the investigational product because of an AE, the last non-missing

post-baseline observation before discontinuation was carried forward to the corresponding end point for evaluation.

c) Analysis populations

All patients who were randomized were included in the efficacy analyses.

Intention-to-treat population

Efficacy and health outcome analyses for the induction-dosing period were conducted on the intention-to-treat (ITT) population, defined as all randomized patients, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Patients' data were analyzed according to the treatment to which the patient was assigned.

Per-protocol set

In addition, the primary analyses were repeated using the per-protocol set (PP), a subset of the ITT population defined as all randomized patients who were compliant with therapy, who did not have major protocol violations, and whose study site did not have significant issues that required a report to the regulatory agencies before week 12. Patients' data were analyzed according to the treatment to which they were assigned.

Safety population

Safety analyses were conducted on the safety population, defined as all randomized patients who received at least one dose of study treatment. Patients' data were analyzed according to the treatment to which the patient was assigned.

Maintenance-dosing-period primary population

Efficacy, health outcomes, and safety analyses for the maintenance-dosing period were conducted on the maintenance-dosing-period primary population, defined as all re-randomized patients (that is, patients randomized to ixekizumab in the induction-dosing period who achieved an sPGA of 0 or 1 and were re-randomized at week 12) who received at least one dose of study treatment during the maintenance-dosing period. Patients' data were analyzed according to the treatment to which they were re-randomized. Only information before relapse is presented.

3.3 Patient disposition

Details regarding patient disposition are provided in Table 7. These were consistent across all included trials; therefore, they will be discussed together.

The proportions of patients randomized to UNCOVER-1, UNCOVER-2, and UNCOVER-3 who discontinued the study before the end of the induction-dosing phase at week 12 ranged between 3% and 7%. Discontinuation rates throughout the studies, as well as reasons for discontinuation, were generally balanced between treatment groups within each included trial. The reasons for discontinuation (≤ 2% in each treatment group) were AEs, patient decision, protocol violation, lack of efficacy, loss to follow-up, and sponsor decision.

TABLE 7: PATIENT DISPOSITION

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab	PL	Ixekizumab	PL	Etanercept	Ixekizumab	PL	Etanercept
Enrolled, N	1,660		1,658			1,783		
Induction-Dosing Phase – Week 0 to Week 12								
Randomized – overall	1,296[a]		1,224[a]			1,346[a]		
Randomized – per group	433	431	351	168	358	385	193	382
Completed week 12, n (%)	415 (96)	407 (94)	342 (97)	158 (94)	333 (93)	363 (94)	183 (95)	369 (97)
Discontinued, n (%)	18 (4)	24 (6)	9 (3)	10 (6)	25 (7)	22 (6)	10 (5)	13 (3)
Most frequent reasons for discontinuation – induction-dosing period, n (%)								
Adverse event	10 (2)	6 (1)	4 (1)	1 (1)	5 (1)	8 (2)	2 (1)	4 (1)
Patient decision	5 (1)	6 (1)	2 (1)	2 (1)	8 (2)	4 (1)	3 (2)	2 (1)
Protocol violation	0	3 (1)	2 (1)	2 (1)	4 (1)	7 (2)	1 (1)	3 (1)
Lack of efficacy	0	7 (2)	0	3 (2)	3 (1)	1 (< 1)	0	0
Lost to follow-up	2 (1)	1 (< 1)	0	1 (1)	5 (1)	0	3 (2)	2 (1)
Sponsor decision	1 (< 1)	1 (< 1)	1 (< 1)	1 (1)	0	2 (1)	1 (1)	2 (1)
Analysis sets								
FAS, N	433	431	351	168	358	385	193	382
PP, N	406	404	291	133	295	338	165	339
Safety, N	433	431	350	167	357	384	193	382

FAS = full analysis set; PL = placebo; PP = per-protocol.
[a] Some patients were randomized to ixekizumab every four weeks up to week 12, which is not consistent with the Health Canada–approved dose and, therefore, were not included in this review (n = 432 for UNCOVER-1, n = 347 for UNCOVER-2, and n = 386 for UNCOVER-3).
Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8], UNCOVER-3 Clinical Study Report[9].

3.4 Exposure to study treatments

Details regarding exposure to study treatments are provided in
Table 8. Results were similar between treatment groups within each included study, and were also consistent across UNCOVER-1, UNCOVER-2, and UNCOVER-3.

TABLE 8: EXTENT OF EXPOSURE

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 351	PL n = 168	Etanercept n = 358	Ixekizumab n = 385	PL n = 193	Etanercept n = 382
Patient Days of Exposure								
Mean (SD)	84 (10.4)	82 (13.9)	85 (8.3)	84 (11.2)	83 (16.4)	84 (11.6)	83 (11.9)	84 (11.8)

PL = placebo; SD = standard deviation.

Unbalanced use of concomitant medication was observed in UNCOVER-1, in which more patients in the placebo group took glucocorticoids (5% with placebo versus 2% with ixekizumab) and emollients (2% with placebo versus 1% with ixekizumab), which may bias the results in favour of placebo.

3.5 Critical appraisal

3.5.1 Internal validity

a) Study design, intervention, and comparator

Three studies were included in the systematic review, with similarities in the trial designs. UNCOVER-1 was a placebo-controlled RCT, while UNCOVER-2 and UNCOVER-3 were placebo-controlled and active-controlled RCTs with etanercept as the comparator, which were generally conducted with methodological rigour with regard to the 12-week induction-dosing period. Consequently, this systematic review focuses on the primary outcome results assessed at week 12, at the end of the induction-dosing period.

UNCOVER-1 and UNCOVER-2 also included a DB maintenance-dosing period. The manufacturer indicated that the trial design was part of the regulatory agencies' guideline standard to include at least one trial in which the initial study period maybe followed by an observation period of at least two months during which responders to treatment are randomized to active drug or to placebo in order to explore the duration of remission/response, rebound, and time to relapse. However, the design of the maintenance period is associated with several significant limitations with regard to the CADTH CDR quality standard, and the 60-week results are presented as supportive information only. Indeed, the maintenance-dosing period was in a partially randomized patient population: patients classified as ixekizumab responders were re-randomized to placebo or ixekizumab, while patients achieving a response on placebo and non-responder patients in any treatment group were not part of the randomization and were systematically assigned a treatment group according to their response status and prior treatment received. In addition, the partial re-randomization process results in a mixed population of responders and non-responders in both the ixekizumab and placebo groups. Nevertheless, the manufacturer reported the results of analyses performed in a population consisting only of re-randomized responder patients; however, the sample sizes are considerably diminished. Therefore, the strength of randomization observed for the induction period was not preserved in the maintenance period. The design likely does not ensure balance in known and unknown relevant characteristics, which is a significant limitation on the validity of the findings from the maintenance-dosing period.

UNCOVER-2 and UNCOVER-3 evaluated the NI and superiority of ixekizumab compared with etanercept. Using a fixed-margin approach, ixekizumab was to be deemed non-inferior to etanercept if the lower bound of the two-sided 97.5% CI for the difference in proportions of responders on ixekizumab minus etanercept was greater than the pre-specified NI margin of –12%. The manufacturer indicated that there is no universally accepted value for what is considered to be a clinically unimportant difference between two treatments in sPGA (score of 0 or 1) or PASI 75 response. The manufacturer referenced EMA and FDA guidelines and guidance documents to support the NI margin, which the manufacturer considers a sufficiently small and clinically unimportant difference in outcomes between etanercept and ixekizumab. The fact that there is no clear justification for the choice of the NI margin is, however, mitigated by the superiority analysis results, showing that ixekizumab achieved superiority over etanercept in sPGA (score of 0 or 1) and PASI 75 response in the trials.

b) Selection, allocation, and disposition of patients

The included studies were performed using appropriate allocation strategies. Randomization was performed centrally, and patients were randomized to treatment as determined by a computer-

generated random sequence using an interactive voice response system. The trials were conducted in a DB fashion and used matching placebos whenever appropriate.

There was no obvious indication of unplanned sources of unblinding; however, there are differences in the mechanism of action of ixekizumab and etanercept. According to the clinical expert consulted, an initial response to treatment with ixekizumab is usually observed within a timeframe that is much shorter than etanercept, and non-existent with placebo. Therefore, it is possible that patients or physicians may have had indications as to which treatment group some patients were randomized.

Baseline characteristics were balanced between treatment groups within each included study. Overall, disease characteristics were also consistent across UNCOVER-1, UNCOVER-2, and UNCOVER-3, with the exception of prior experience with biologic therapy, which was more common in UNCOVER-1 compared with UNCOVER-2 and UNCOVER-3. According to the clinical expert consulted, this did not seem to be a significant issue and likely did not impact interpretation of the findings.

The proportions of patients randomized to UNCOVER-1, UNCOVER-2, and UNCOVER-3 who discontinued the study before the end of the induction-dosing phase at week 12 were generally low and ranged between 3% and 7%. Discontinuation rates throughout the studies and reasons for discontinuation were generally balanced between treatment groups within each included trial.

c) Outcome measures

The outcome measures and definitions used in UNCOVER-1, UNCOVER-2, and UNCOVER-3, including the PGA and PASI response, are considered appropriate to evaluate treatment response in psoriasis clinical trials. Patient-reported outcome measures, i.e., DLQI and SF-36, are also frequently used and are considered valid and reliable. However, the SF-36 was not part of the gatekeeping strategy, and therefore the type 1 error rate was not controlled and the statistical significance remains uncertain.

d) Statistical analysis

Each of the included studies had sufficient power to demonstrate statistical significance for testing of the primary outcomes.

Both studies were designed as NI and superiority trials. The primary statistical model for the primary efficacy outcome was tested using data from the true ITT population, which could potentially bias the results in favour of a finding of NI. Nevertheless, secondary analyses using data from the PP populations were conducted to corroborate the primary findings and were consistent with those from the ITT population that were part of the gatekeeping strategy, which provided reassurance.

The primary analysis for all continuous efficacy and health outcome variables was performed using MMRM analysis and ANCOVA. The results were consistent between the two analyses (data not shown).

An mBOCF analysis, as well as an LOCF analysis, were performed on all continuous efficacy and health outcome variables for imputation of missing data. The results were consistent between the two analyses (data not shown).

3.5.2 External validity

a) Patient selection

Inclusion and exclusion criteria in UNCOVER-1, UNCOVER-2, and UNCOVER-3 appeared relevant and reasonable. According to the clinical expert consulted, baseline characteristics were consistent with real-life patients seen in clinical practice who had prior experience with other treatment alternatives.

Various groups of patients with comorbid conditions were excluded, including current or history of lymphoproliferative disease or malignant diseases; significant uncontrolled cerebro-cardiovascular, neurological, neuropsychiatric, renal, hepatic, respiratory, gastrointestinal, endocrine, or hematologic disorders; serious infection, active or latent tuberculosis, HIV, hepatitis C, or some presentations of hepatitis B; and failure to meet specific laboratory criteria. The findings from UNCOVER-1, UNCOVER-2, and UNCOVER-3 are not generalizable to these patients.

b) Treatment regimen and length of follow-up

UNCOVER-1, UNCOVER-2, and UNCOVER-3 used various ixekizumab regimens for patients with psoriasis; however, only the dosing regimen that is consistent with the Health Canada–approved dosing was included in this review, which was deemed appropriate and realistic. The use of etanercept as a comparator, in addition to placebo, offers active treatment comparisons. Although etanercept is still used in clinical practice, newer drugs with mechanisms of action similar to ixekizumab are now available and are considered more appropriate comparators. The use of placebo and etanercept as comparators in all trials yields uncertainty regarding the effects of ixekizumab compared with other drugs targeting interleukin, i.e., ustekinumab and secukinumab. In order to inform this gap, additional evidence was gathered in the form of indirect comparisons.

Experience from clinical practice suggests that the study duration of 12 weeks was sufficient to observe the effect of ixekizumab on the various outcome measures. According to the clinical expert, initial response to ixekizumab treatment may be observed within as little as four weeks. UNCOVER-1 and UNCOVER-2 also included a DB maintenance period, providing data up to week 60 regarding the sustainability of beneficial treatment effects and long-term safety; however, this trial design is associated with several significant limitations.

c) Outcome measures

Experience from specialists' clinical practice suggests that the co-primary outcomes were both clinically meaningful measures of response to treatment. In addition, the choice of instruments selected for assessment of patient-reported outcomes was considered appropriate.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 3). See Appendix 4 for detailed efficacy data.

3.6.1 Physician global assessment

One of the co-primary efficacy outcomes for UNCOVER-1, UNCOVER-2, and UNCOVER-3 was the proportions of patients with at least a two-point improvement in the static PGA and with a PGA score of 0 or 1, which was considered a clinically meaningful improvement for patients according to the clinical expert consulted by CADTH CDR. At the end of the DB induction period (week 12), the proportions of patients achieving this primary outcome were statistically significantly higher with ixekizumab compared with placebo in all three trials ($P < 0.001$). In addition, ixekizumab was also statistically significantly

superior to etanercept on this same outcome after 12 weeks of treatment in UNCOVER-2 and UNCOVER-3 ($P < 0.001$).

Specifically, 82% of patients in the ixekizumab group compared with 3% of patients in the placebo group achieved at least a two-point improvement in the static PGA (with score of 0 or 1) at week 12 in UNCOVER-1 ($P < 0.001$). Results were similar in UNCOVER-2, in which 83% of patients in the ixekizumab group, compared with 2% of patients in the placebo group and 36% of patients in the etanercept group, achieved the primary outcome ($P < 0.001$ for both comparisons). Finally, results from UNCOVER-3 were also consistent with the other included trials, with 81% of patients reaching the pre-specified PGA improvement in the ixekizumab group, compared with 7% of patients with placebo and 42% of patients with etanercept ($P < 0.001$ for both comparisons). Results from the PP population were consistent with those from the ITT population presented (Table 11).

NI and superiority analyses were performed in order to compare the efficacy of ixekizumab versus etanercept on the PGA score in UNCOVER-2 and UNCOVER-3. Ixekizumab was to be deemed non-inferior to etanercept if the lower bound of the two-sided 97.5% CI for the difference in proportions of responders on ixekizumab minus etanercept was greater than the pre-specified NI margin of –12%, while ixekizumab was to be deemed superior to etanercept if the lower bound of the two-sided 97.5% CI for the difference in proportions of responders on ixekizumab minus etanercept exceeded 0%. With a treatment difference of 47% (97.5% CI, 40% to 54%) in UNCOVER-2 and 39% (97.5% CI, 32% to 46%) in UNCOVER-3, results from these trials show that ixekizumab is superior to etanercept on the proportions of patients with at least a two-point improvement in the static PGA (with score of 0 or 1) at week 12.

3.6.2 Psoriasis Area and Severity Index (PASI)

The other co-primary efficacy outcome for UNCOVER-1, UNCOVER-2, and UNCOVER-3 was the proportions of patients achieving at least a PASI 75 score, which was considered a clinically meaningful improvement for patients according to the clinical expert consulted by CADTH CDR. At the end of the DB induction period (week 12), the proportions of patients achieving this primary outcome were statistically significantly higher with ixekizumab compared with placebo in all three trials ($P < 0.001$). In addition, ixekizumab was also statistically significantly superior to etanercept on this same outcome after 12 weeks of treatment in UNCOVER-2 and UNCOVER-3 ($P < 0.001$).

Specifically, a total of 89% of patients in the ixekizumab group compared with 4% of patients in the placebo group achieved at least a PASI 75 score at week 12 in UNCOVER-1 ($P < 0.001$). Results were similar in UNCOVER-2, in which 90% of patients in the ixekizumab group, compared with 2% of patients in the placebo group and 42% of patients in the etanercept group, achieved the primary outcome ($P < 0.001$ for both comparisons). Finally, results from UNCOVER-3 were also consistent with the other included trials, with 87% of patients reaching the pre-specified PASI improvement in the ixekizumab group, compared with 7% of patients with placebo and 53% of patients with etanercept ($P < 0.001$ for both comparisons). Results from the PP population were consistent with those from the ITT population presented (Table 11).

NI and superiority analyses were performed in order to compare the efficacy of ixekizumab versus etanercept on the PASI score in UNCOVER-2 and UNCOVER-3. Ixekizumab was to be deemed non-inferior to etanercept if the lower bound of the two-sided 97.5% CI for the difference in proportions of responders on ixekizumab minus etanercept was greater than the pre-specified NI margin of –12%; whereas, ixekizumab was to be deemed superior to etanercept if the lower bound of the two-sided 97.5% CI for the difference in proportions of responders on ixekizumab minus etanercept exceeded 0%.

With a treatment difference of 48% (97.5% CI, 41% to 55%) in UNCOVER-2 and 34% (97.5% CI, 27% to 41%) in UNCOVER-3, results from these trials show that ixekizumab is superior to etanercept on the proportions of patients achieving at least a PASI 75 score at week 12.

Patients receiving ixekizumab were also statistically significantly more likely to achieve a PASI 90 or a PASI 100 response after 12 weeks of treatment compared with placebo and etanercept ($P < 0.001$ for all comparisons).

3.6.3 Health-Related Quality of Life and Functional Outcomes

HRQoL and functional outcomes were assessed at week 12 using the disease-specific DLQI (range from 0 = no effect to 30 = extremely large effect on a patient's life) and the generic SF-36 physical and mental component summary scores (range from 0 to 100, with higher scores indicating better levels of function and/or better health). These were both considered appropriate and relevant measures according to the clinical expert consulted by CADTH CDR. However, the SF-36 instrument was not included in the gatekeeping strategy, and it is therefore an exploratory outcome that has not been adjusted for multiplicity. Outcome measures including HRQoL instruments are reviewed in 0, and detailed outcome data are provided in Table 13 and Table 13 in Appendix 4.

Results from UNCOVER-1, UNCOVER-2, and UNCOVER-3 indicated that ixekizumab was associated with a statistically significant and clinically meaningful benefit on HRQoL and function compared with placebo, as measured by the change from baseline in DLQI total score and SF-36 physical and mental component summary scores at week 12 ($P < 0.001$ for all analyses). In addition, results from UNCOVER-2 and UNCOVER-3 indicated that ixekizumab was statistically significantly superior to etanercept, as measured by the change from baseline in DLQI total score ($P < 0.001$) and SF-36 mental summary score ($P \leq 0.002$); ixekizumab was also associated with an increased change from baseline in the SF-36 physical component summary score compared with etanercept, but statistical significance was reached only in UNCOVER-2 ($P < 0.001$).

Considering that an MCID of 2.3 to 5.7 was estimated for the DLQI,[20,21] and that an MCID of 2.5 to 5.0 was estimated for the SF-36 physical and mental component summary scores,[22-24] results were generally considered clinically significant. This was also confirmed by the clinical expert consulted by CADTH CDR.

TABLE 9: KEY EFFICACY OUTCOMES

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	**PL n = 431**	**Ixekizumab n = 351**	**PL n = 168**	**Etanercept n = 358**	**Ixekizumab n = 385**	**PL n = 193**	**Etanercept n = 382**
Co-Primary Outcomes in the Included Studies								
Proportions of Patients with sPGA Score of 0 or 1 at Week 12 (≥ 2-Point Improvement from Baseline)								
n (%)	354 (82)	14 (3)	292 (83)	4 (2)	129 (36)	310 (81)	13 (7)	159 (42)
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* < 0.001			*P* < 0.001		
Non-Inferiority and Superiority Analyses to Etanercept — Fixed Margin[a]								
Difference	—		47%			39%		
2-sided 97.5% CI	—		(40% to 54%)			(32% to 46%)		
Proportions of Patients Achieving ≥ PASI 75 at Week 12								
n (%)	386 (89)	17 (4)	315 (90)	4 (2)	149 (42)	336 (87)	14 (7)	204 (53)

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	**PL n = 431**	**Ixekizumab n = 351**	**PL n = 168**	**Etanercept n = 358**	**Ixekizumab n = 385**	**PL n = 193**	**Etanercept n = 382**
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* < 0.001			*P* < 0.001		
Non-Inferiority and Superiority Analyses to Etanercept — Fixed Margin[a]								
Difference	—		48%			34%		
2-sided 97.5% CI	—		(41% to 55%)			(27% to 41%)		
Health-Related Quality of Life and Functional Outcomes								
DLQI Total Score								
Baseline Values								
Mean (SD)	13 (7.0)	13 (7.1)	12 (6.9)	13 (7.2)	13 (7.0)	12 (6.9)	13 (7.0)	12 (6.8)
Change from Baseline at Week 12								
LS mean (SE)	–11 (0.3)	–1 (0.3)	–10 (0.3)	–2 (0.4)	–8 (0.3)	–10 (0.2)	–2 (0.3)	–8 (0.2)
Difference vs. PL (95% CI); *P* value	–10 (–11 to –9); *P* < 0.001		–8 (–9 to –8); *P* < 0.001			–8 (–9 to –8); *P* < 0.001		
Difference vs. ETA (95% CI); *P* value	—		–3 (–3 to –2); *P* < 0.001			–2 (–3 to –2); *P* < 0.001		
SF-36 Physical Summary Score								
Baseline Values								
Mean (SD)	47 (9.1)	47 (9.8)	48 (9.0)	48 (9.5)	48 (9.1)	48 (8.8)	47 (9.5)	49 (8.5)
Change from Baseline at Week 12								
LS mean (SE)	4.3 (0.38)	–0.2 (0.40)	3.8 (0.36)	–0.4 (0.51)	2.5 (0.36)	4.1 (0.35)	–0.3 (0.50)	3.1 (0.35)
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* = 0.013			*P* = 0.093		
SF-36 Mental Summary Score								
Baseline Values								
Mean (SD)	48 (11.5)	49 (11.2)	48 (11.7)	48 (10.6)	49 (10.7)	48 (11.4)	47 (11.6)	48 (11.7)
Change from Baseline at Week 12								
LS mean (SE)	4.2 (0.44)	0.7 (0.46)	4.5 (0.40)	–0.1 (0.58)	2.5 (0.40)	4.3 (0.40)	1.1 (0.57)	2.6 (0.40)
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* < 0.001			*P* = 0.002		

CI = confidence interval; ETA = etanercept; LS = least squares; PL = placebo; SE = standard error; vs. = versus.
Note: The ITT population is reported.
[a] Non-inferiority margin = –12%; superiority margin = 0%.
Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8], UNCOVER-3 Clinical Study Report[9].

3.7 Harms

Only those harms identified in the review protocol are reported below (Section 2.2.1, Protocol). See Appendix 4 for detailed harms data.

3.7.1 Adverse events

After 12 weeks of treatment, the proportions of patients receiving ixekizumab and experiencing AEs were higher than those in patients receiving placebo in UNCOVER-1, UNCOVER-2, and UNCOVER-3. However, the proportions of patients with AEs were similar between patients receiving ixekizumab and those receiving etanercept in UNCOVER-2 and UNCOVER-3. The most common AEs reported with ixekizumab across the included studies (< 12% in each treatment group) included nasopharyngitis, injection-site reaction, upper respiratory tract infection, headache, and injection-site erythema.

3.7.2 Serious adverse events

The proportions of patients experiencing SAEs were similar between patients receiving ixekizumab and placebo in UNCOVER-1, UNCOVER-2, and UNCOVER-3, as well as between patients receiving ixekizumab and etanercept in UNCOVER-2 and UNCOVER-3. Specifically, between 1.2% and 2.6% of patients in each treatment group reported at least one SAE. The most common SAEs reported with ixekizumab across the included studies (< 1% in each treatment group) included cellulitis, appendicitis, and depression.

3.7.3 Withdrawal due to adverse events

There were more WDAEs with ixekizumab than with placebo or etanercept in UNCOVER-1, UNCOVER-2, and UNCOVER-3; however, the proportions of patients discontinuing due to AEs were overall low and ranged between 0.6% and 2.3% across the included studies. The most frequent reasons for discontinuation due to AEs reported with ixekizumab (< 1% in each treatment group) were injection-site reaction, high levels of aspartate aminotransferase, and appendicitis.

3.7.4 Mortality

No deaths were reported in UNCOVER-1, UNCOVER-2, or UNCOVER-3.

3.7.5 Notable harms

Several harms outcomes of particular interest were identified by CADTH and by the manufacturer, based on the ixekizumab mechanism of action and Health Canada warnings. Infections were relatively common across the included studies. The proportions of patients experiencing infections were similar between ixekizumab and placebo in UNCOVER-1, as well as between ixekizumab and placebo or etanercept in UNCOVER-2. However, the proportions of patients reporting infections were higher with ixekizumab (21%) than with placebo or etanercept (14% and 15%, respectively) in UNCOVER-3. The proportions of patients receiving ixekizumab and experiencing injection-site reactions ranged from 15% to 20% and were higher than those in patients receiving placebo in UNCOVER-1, UNCOVER-2, and UNCOVER-3. However, the incidence was similar between patients receiving ixekizumab and those receiving etanercept in UNCOVER-2 and UNCOVER-3. Hypersensitivity reactions were characterized by a low incidence across the included studies, ranging from 2% to 4% of patients across treatment groups. Major cardiovascular events were rare.

TABLE 10: HARMS

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 350	PL n = 167	Etanercept n = 357	Ixekizumab n = 384	PL n = 193	Etanercept n = 382
Mortality, n (%)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
SAEs, n (%)	**6 (1.4)**	**5 (1.2)**	**5 (1.4)**	**2 (1.2)**	**8 (2.2)**	**9 (2.3)**	**5 (2.6)**	**5 (1.3)**
Most frequently reported SAEs, n (%)								
Cellulitis	1 (0.2)	0	0	0	1 (0.3)	0	1 (0.5)	0

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	**PL n = 431**	**Ixekizumab n = 350**	**PL n = 167**	**Etanercept n = 357**	**Ixekizumab n = 384**	**PL n = 193**	**Etanercept n = 382**
Appendicitis	1 (0.2)	0	–	–	–	1 (0.3)	0	0
Depression	–	–	1 (0.3)	0	0	1 (0.3)	0	0
AEs, n (%)	**257 (59)**	**210 (49)**	**216 (62)**	**89 (53)**	**211 (59)**	**205 (53)**	**70 (36)**	**187 (49)**
Most frequently reported AEs, n (%)								
Nasopharyngitis	50 (11.5)	41 (9.5)	35 (10.0)	17 (10.2)	36 (10.1)	26 (6.8)	11 (5.7)	19 (5.0)
Injection-site reaction	42 (9.7)	5 (1.2)	39 (11.1)	1 (0.6)	39 (10.9)	37 (9.6)	3 (1.6)	41 (10.7)
URTI	24 (5.5)	16 (3.7)	19 (5.4)	7 (4.2)	26 (7.3)	8 (2.1)	5 (2.6)	8 (2.1)
Headache	18 (4.2)	15 (3.5)	17 (4.9)	3 (1.8)	20 (5.6)	16 (4.2)	5 (2.6)	11 (2.9)
Injection-site erythema	27 (6.2)	0	12 (3.4)	2 (1.2)	18 (5.0)	12 (3.1)	0	11 (2.9)
WDAEs, n (%)	**10 (2.3)**	**6 (1.4)**	**6 (1.7)**	**1 (0.6)**	**5 (1.4)**	**9 (2.3)**	**2 (1.0)**	**4 (1.0)**
Most frequently reported WDAEs, n (%)								
Injection-site reaction	3 (0.7)	0	1 (0.3)	0	0	0	0	2 (0.5)
High levels of aspartate aminotransferase	2 (0.5)	0	–	–	–	–	–	–
Appendicitis	1 (0.2)	0	–	–	–	1 (0.3)	0	0
Notable harms, n (%)								
Infections	124 (29)	106 (25)	104 (30)	46 (28)	98 (28)	82 (21)	27 (14)	59 (15)
Injection-site reactions	69 (16)	13 (3)	69 (20)	7 (4)	62 (18)	58 (15)	6 (3)	59 (15)
Hypersensitivity reactions	14 (3)	10 (2)	14 (4)	3 (2)	12 (3)	13 (3)	4 (2)	7 (2)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; PL = placebo; SAE = serious adverse event; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8], UNCOVER-3 Clinical Study Report[9].

4. DISCUSSION

4.1 Summary of available evidence

Three manufacturer-sponsored DB RCTs were included in the systematic review: UNCOVER-1 (n = 1,296),[5,6] UNCOVER-2 (n = 1,224),[5,7,8] and UNCOVER-3 (n = 1,346).[5,7,9] UNCOVER-1 was a placebo-controlled RCT evaluating the superiority of ixekizumab compared with placebo, while UNCOVER-2 and UNCOVER-3 were placebo-controlled and active-controlled RCTs evaluating the superiority of ixekizumab compared with placebo, as well as the NI and superiority of ixekizumab compared with etanercept. UNCOVER-1 and UNCOVER-2 also included a maintenance-dosing period, providing data up to week 60. Although this design may be relevant according to regulatory agencies in order to explore the duration of remission/response, rebound, and time to relapse, it is associated with several major limitations in light of the CADTH CDR quality standard, and results are therefore presented as supportive information only. There were no studies in which ixekizumab was compared directly with other interleukin inhibitors used to treat psoriasis, namely secukinumab and ustekinumab.

All three trials included patients with moderate to severe plaque psoriasis, defined as patients with a confirmed diagnosis of chronic plaque psoriasis for at least six months who were candidates for phototherapy and/or systemic therapy and who had at least a 10% BSA involvement, a static PGA score of at least 3, and a PASI score of at least 12. Prior experience with systemic therapies was reported in 54% to 75% of patients participating in UNCOVER-1, UNCOVER-2, and UNCOVER-3; among the therapeutic options were phototherapy (31% to 48% of patients), non-biologic systemic therapy (46% to 64%), and biologic therapy (41% of patients included in UNCOVER-1 and 15% to 26% of patients included in UNCOVER-2 and UNCOVER-3). Efficacy assessments were based on the following co-primary outcomes after 12 weeks of treatment: the proportions of patients with at least a two-point improvement in the static PGA; and the proportions of patients achieving at least a PASI 75 score. Patients were randomized to either placebo, etanercept 50 mg SC twice weekly (UNCOVER-2 and UNCOVER-3), or to one of two ixekizumab induction regimens. However, only the dosing regimen that is consistent with the Health Canada–approved dose was included in this review, i.e., ixekizumab 160 mg SC at week 0, followed by 80 mg SC every two weeks up to week 12.

The included trials generally appear to have been performed with methodological rigour, with regard to the induction-dosing period up to week 12. Various groups of patients with comorbid conditions were excluded from the included studies, including patients with current or history of lymphoproliferative disease or malignant diseases; significant uncontrolled cerebro-cardiovascular, neurological, neuropsychiatric, renal, hepatic, respiratory, gastrointestinal, endocrine, or hematologic disorders; and serious infection, active or latent tuberculosis, HIV, hepatitis C, or some presentations of hepatitis B; therefore, the findings are not generalizable to these patients. The strength of evidence was reduced by the lack of trials directly comparing ixekizumab with other drugs targeting IL used in psoriasis, including secukinumab and ustekinumab.

4.2 Interpretation of results

4.2.1 Efficacy

Results from UNCOVER-1, UNCOVER-2, and UNCOVER-3 were consistent with the conclusion that ixekizumab is superior to placebo for achieving at least a two-point improvement in the static PGA score (with achievement of a PGA score of 0 or 1) and at least a PASI 75 score after 12 weeks of treatment in patients with moderate to severe plaque psoriasis. These two co-primary outcomes were considered to represent a clinically meaningful improvement for psoriasis patients according to the clinical expert

consulted by CADTH CDR. Results from UNCOVER-2 and UNCOVER-3 demonstrated that ixekizumab is superior to etanercept for the same co-primary outcomes, i.e., at least a two-point improvement in the static PGA (and with PGA score of 0 or 1) and at least a PASI 75 score after 12 weeks of treatment in patients with moderate to severe plaque psoriasis. Patients receiving ixekizumab were also statistically significantly more likely to achieve a PASI 90 or a PASI 100 response after 12 weeks of treatment compared with placebo and etanercept.

Additional NI and superiority analyses indicated that the difference in the treatment effect of ixekizumab versus etanercept was 47% (97.5% CI, 40% to 54%) in UNCOVER-2 and 39% (97.5% CI, 32% to 46%) in UNCOVER-3 with regard to the proportions of patients achieving at least a two-point improvement in the static PGA (and with PGA score of 0 or 1) at week 12. The treatment difference for the proportions of patients achieving at least a PASI 75 score at week 12 was 48% (97.5% CI, 41% to 55%) in UNCOVER-2 and 34% (97.5% CI, 27% to 41%) in UNCOVER-3. The results suggest that ixekizumab is superior to etanercept for both co-primary outcomes of the included studies, because the lower bound of the two-sided 97.5% CI for the difference in proportions of responders on ixekizumab minus etanercept consistently exceeds 0%, the pre-specified superiority margin.

HRQoL, as well as functional outcomes, were identified as important outcomes for patients living with psoriasis according to the patient input received by CADTH. Symptoms that had the most significant impact on HRQoL according to patients included scales and flaking, itching, joint pain, and self-esteem. HRQoL was measured using validated instruments in UNCOVER-1, UNCOVER-2, and UNCOVER-3. Specifically, the disease-specific DLQI instrument assessed several aspects of a patient's daily life that may be affected by psoriasis symptoms, including the aforementioned scales and flaking, itching, joint pain, and self-esteem. In addition, the more generic SF-36 instrument was also used to assess HRQoL. Results from the included studies show that ixekizumab was consistently associated with a statistically significant and clinically meaningful benefit on HRQoL and function compared with placebo and etanercept, as measured by the change from baseline in DLQI total score at week 12. Overall, results from the SF-36 physical and mental component summary scores also suggested that ixekizumab was superior to placebo and etanercept, as statistical significance was reached in all analyses, with the exception of change from baseline in the SF-36 physical summary score when ixekizumab was compared with etanercept in UNCOVER-3 (P = 0.093). However, the SF-36 instrument was not included in the gatekeeping strategy, and it is therefore an exploratory outcome that has not been adjusted for multiplicity. According to the clinical expert consulted and estimated MCIDs, the SF-36 results were generally considered clinically meaningful for patients living with psoriasis. The clinical expert considered the DLQI to be the most relevant and important HRQoL instrument.

UNCOVER-1, UNCOVER-2, and UNCOVER-3 included a proportion of patients who had previously received systemic psoriasis treatment. Prior experience with systemic therapies was reported in 54% to 75% of patients participating in UNCOVER-1, UNCOVER-2, and UNCOVER-3. This is consistent with the Health Canada indication for ixekizumab as treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Most public drug plans, however, allow patients to access biologic therapies for plaque psoriasis if they have failed one or more traditional systemic drugs (i.e., methotrexate, cyclosporine, acitretin). In the included trials, prior experience with non-biologic systemic therapy (traditional drugs) was reported in 46% to 64% of patients, while prior biologic therapy was reported in 41% of patients included in UNCOVER-1 and 15% to 26% of patients included in UNCOVER-2 and UNCOVER-3. Biologic drugs included TNF inhibitors, for which prior use was reported in 7% to 28% of patients, and interleukin inhibitors, with prior use ranging between 5% and

13%. Only limited results were available for these particular patients, in the form of treatment-by-subgroup interaction analyses.

Although TNF inhibitors such as etanercept are used as second-line drugs to treat psoriasis in clinical practice, newer drugs that target ILs, namely ustekinumab and secukinumab, are more relevant comparators for ixekizumab. However, there are no studies in which ixekizumab has been compared directly with ustekinumab or secukinumab. In order to inform this evidence gap, the review team conducted a literature search for additional evidence in the form of indirect comparisons. No published indirect comparisons were identified, but the manufacturer provided a network meta-analysis (NMA) based on a systematic review of RCTs to compare the efficacy of ixekizumab with secukinumab, ustekinumab, infliximab, adalimumab, and etanercept.

The three main efficacy outcomes of relevance to this review that were included in the NMA were the PASI response (PASI 50, 75, and 90), PGA, and DLQI. In addition, the potential harms of the various treatments were compared.

Placebo-controlled data were available to provide information on the sustainability of beneficial treatment effects observed with ixekizumab in patients with psoriasis beyond the 12-week induction-dosing period. UNCOVER-1 and UNCOVER-2 included a DB maintenance-dosing period providing data up to week 60, during which patients were only partially randomized (0). Therefore, the strength of randomization observed for the induction period was not preserved in the overall maintenance period. The design likely does not ensure balance in known and unknown relevant characteristics, which is a significant limitation to the validity of the findings from the maintenance-dosing period. However, the manufacturer reported the results of analyses performed in a population consisting only of re-randomized responder patients, with sample sizes that were considerably diminished. The results

obtained at week 60 suggest a significant sustained efficacy of ixekizumab compared with placebo regarding the proportions of patients achieving at least a two-point improvement in the static PGA (and with PGA score of 0 or 1) and at least a PASI 75 score at week 60, in a population consisting of patients who were ixekizumab responders at week 12. However, the design of the maintenance period is associated with several limitations restricting interpretation of the findings, the most notable being that a significant proportion of patients was not part of the randomization and was systematically assigned a treatment group according to response status and prior treatment received.

4.2.2 Harms

No deaths occurred during the 12-week induction period of UNCOVER-1, UNCOVER-2, or UNCOVER-3, and the overall incidence of SAEs did not differ between ixekizumab and placebo and etanercept in any of the included studies. The most commonly reported SAEs with ixekizumab across the included studies were relatively infrequent (< 1%) and included cellulitis, appendicitis, and depression. More patients treated with ixekizumab experienced AEs compared with placebo; however, the incidence of AEs was similar between ixekizumab and etanercept. The most common AEs reported with ixekizumab included nasopharyngitis, injection-site reaction, upper respiratory tract infection, headache, and injection-site erythema. WDAEs were infrequent (< 1%), but these were more frequently seen with ixekizumab than with placebo or etanercept. Overall, the harms results did not raise any new safety concerns, which was confirmed by the clinical expert consulted.

Some AEs of particular interest were identified as potential harms by CADTH based on the ixekizumab mechanism of action and Health Canada warnings, which have been issued with regard to the risks of infections and serious hypersensitivity reactions. Other notable harms, according to clinical expert opinion, included injection-site reactions and major cardiovascular events. Infections were relatively common across the included studies. The proportions of patients experiencing infections were similar between ixekizumab and placebo in UNCOVER-1, as well as between ixekizumab and placebo or etanercept in UNCOVER-2. However, the proportions of patients reporting infections were higher with ixekizumab (21%) than with placebo or etanercept (14% and 15%, respectively) in UNCOVER-3. The proportions of patients receiving ixekizumab and experiencing injection-site reactions ranged from 15% to 20% and were higher than those in patients receiving placebo in UNCOVER-1, UNCOVER-2, and UNCOVER-3. However, the incidence was similar between patients receiving ixekizumab and those receiving etanercept in UNCOVER-2 and UNCOVER-3. Hypersensitivity reactions were characterized by a low incidence across the included studies, ranging from 2% to 4% of patients across treatment groups. Major cardiovascular events were infrequent and did not constitute a safety concern. Key harms outcome results from the 60-week maintenance-dosing period from UNCOVER-1 and UNCOVER-2 did not raise additional safety signals.

[redacted]

4.3 Potential place in therapy[1]

Anecdotal evidence from clinical practice suggests that biologic therapies may become less effective over time by an estimated 20% to 30%. Therefore, a new drug such as ixekizumab may be a suitable alternative therapeutic option for patients who are no longer responsive to other currently available biologics (anti-TNF, anti-IL-12 or IL-23, and other anti-IL-17 drugs). As a result, ixekizumab will likely be viewed in clinical practice as an alternative biologic drug for patients, in addition to the currently available drugs. However, there is a perception that ixekizumab and other biologic drugs that target interleukins may provide better efficacy than TNF inhibitors and may therefore be the preferred treatment by some patients or prescribing physicians. There is no special test to identify patients who may benefit the most from biologic drugs targeting interleukins other than trial and error in clinical practice.

5. CONCLUSIONS

The results of three DB RCTs — UNCOVER-1, UNCOVER-2, and UNCOVER-3 — are consistent with the conclusion that ixekizumab is superior to placebo in allowing patients with moderate to severe plaque psoriasis to achieve at least a two-point improvement in the static PGA with achievement of a score of 0 or 1 and at least a PASI 75 score after 12 weeks of treatment. Ixekizumab was associated with statistically significant and clinically meaningful improvements in HRQoL and function compared with placebo and etanercept in each of the three included studies, based on the DLQI instrument. Overall, similar findings were observed for the effects of ixekizumab on HRQoL using the SF-36 instrument. The results of UNCOVER-2 and UNCOVER-3 demonstrated that ixekizumab is superior to etanercept for the aforementioned outcomes. The safety profile of ixekizumab is similar to that of etanercept, and ixekizumab was not associated with any major harms at week 12 in the overall population or at week 60 in a small population consisting of patients who were ixekizumab responders at week 12. [redacted]

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

APPENDIX 1: PATIENT INPUT SUMMARY

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

1. Brief Description of the Patient Group Supplying Input

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

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

2. Condition-Related Information

Information for this submission was obtained from three patient questionnaires (September 2014, and February and March 2016) that were administered online via social media channels, as well as from testimony gathered through social media and online discussion boards.

Patients with psoriasis have scales and plaques that can occur anywhere on their bodies. The most significant physical symptoms of psoriasis that patients report include scales and flaking, itching, and joint pain. Psoriasis affects patients psychologically, with most experiencing embarrassment, self-confidence issues, and depression. Many patients are asked about their condition and have to explain that it is not contagious; this further increases embarrassment and affects their self-esteem. Most patients try to hide their lesions, with some wearing particular clothing (e.g., pants rather than skirts, no bathing suits) or wearing their hair in a certain manner for coverage.

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

Caregivers of patients with psoriasis often experience a high burden of house cleaning such as vacuuming, bedding changes, and laundry, along with the added burden of helping patients who are in pain with simple household chores. In addition, some patients require help in applying creams, going to phototherapy appointments, or travelling to infusion clinics (should the patient be receiving infusion biologics). Caregivers often find themselves negatively affected psychologically, which can result in family dysfunction, as the whole family tends to absorb the shame, depression, and isolation associated with the disease.

3. Current therapy-related information

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

4. Expectations about the drug being reviewed

Patients with psoriasis would welcome any treatment allowing them to live a normal life — to stop worrying about the unsightly plaques and scales and to have the freedom to go out without being judged. They would also welcome treatments that avoid interrupting their life with frequent visits for phototherapy or long travel times and distances to access infusion clinics. Even partial relief from the itch, scales, flaking, and associated joint pain were considered of benefit by these patients. For those already taking biologic drugs, another option was always welcome given the possibility that their current biologic treatment could stop working.

In patients who had experience with ixekizumab, many had observed significant reductions in itching, clearing up of lesions or at least a reduction in their size, and clearing up of flakes and scales. While most patients claimed that ixekizumab was a successful treatment, one patient indicated that, although the treatment worked very well at the beginning, symptoms eventually returned, although they were not as bad as before starting ixekizumab. Adverse events associated with ixekizumab included injection-site reactions and pain during injection. Patients taking ixekizumab found the subcutaneous injection dosing more convenient than travelling to infusion clinics and then travelling multiple times per week for phototherapy.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	April 21, 2016
Alerts:	Weekly search updates until Sept 21, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

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

MULTI-DATABASE STRATEGY
(taltz* or ixekizumab* or LY2439821 or LY 2439821 or BTY153760O).ti,ot,ab,kf,rn,hw,nm.
(1143503-69-8 or 1329632-62-3 or "1329632623" or "1143503698").rn,nm.
1 or 2
3 use pmez
(taltz* or ixekizumab* or LY2439821 or LY 2439821 or BTY153760O).ti,ab,kw.
*ixekizumab/
5 or 6
7 use oemezd
4 or 8
remove duplicates from 9

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	April 2016
Keywords:	Ixekizumab, psoriasis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Langley et al.[25]	Inappropriate design
Gordon et al.[26]	

APPENDIX 4: DETAILED OUTCOME DATA

A1 Efficacy — Static Physician Global Assessment

TABLE 11: STATIC PHYSICIAN GLOBAL ASSESSMENT

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 351	PL n = 168	Etanercept n = 358	Ixekizumab n = 385	PL n = 193	Etanercept n = 382
Proportions of Patients with sPGA Score of 0 or 1 at Week 12 (≥ 2-Point Improvement from Baseline) Co-Primary Outcome								
ITT Population								
n (%)	354 (82)	14 (3)	292 (83)	4 (2)	129 (36)	310 (81)	13 (7)	159 (42)
OR (95% CI)	147 (81 to 265)		—			—		
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* < 0.001			*P* < 0.001		
Non-Inferiority and Superiority Analyses to Etanercept – Fixed Margin [a]								
Difference	—		47%			39%		
2-sided 97.5% CI	—		(40% to 54%)			(32% to 46%)		
PP Population								
N	N = 406	N = 404	N = 291	N = 133	N = 295	N = 338	N = 165	N = 339
n (%)	333 (82)	13 (3)	246 (85)	3 (2)	109 (37)	284 (84)	11 (7)	147 (43)
OR (95% CI)	152 (82 to 281)		—			—		
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* < 0.001			*P* < 0.001		

CI = confidence interval; ETA = etanercept; ITT = intention-to-treat; OR = odds ratio; PL = placebo; PP = per-protocol; sPGA = static Physician Global Assessment; vs. = versus.

[a] Non-inferiority margin = -12%; Superiority margin = 0%: Ixekizumab was to be deemed non-inferior to etanercept if the lower bound of the two-sided 97.5% CI for the difference in proportions of responders on ixekizumab minus etanercept was greater than the pre-specified NI margin of -12%. Ixekizumab was to be deemed superior to etanercept if the lower bound of the two-sided 97.5% CI for the difference in proportions of responders on ixekizumab minus etanercept exceeded 0%.

Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8], UNCOVER-3 Clinical Study Report[9].

A2 Efficacy — Psoriasis Area and Severity Index

TABLE 12: PSORIASIS AREA AND SEVERITY INDEX

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	**PL n = 431**	**Ixekizumab n = 351**	**PL n = 168**	**Etanercept n = 358**	**Ixekizumab n = 385**	**PL n = 193**	**Etanercept n = 382**
Proportions of Patients Achieving ≥ PASI 75 at Week 12 Co-Primary Outcome								
ITT Population								
n (%)	386 (89)	17 (4)	315 (90)	4 (2)	149 (42)	336 (87)	14 (7)	204 (53)
OR (95% CI)	224 (125 to 401)		—			—		
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* < 0.001			*P* < 0.001		
Non-Inferiority and Superiority Analyses to Etanercept – Fixed Margin[a]								
Difference	—		48%			34%		
2-sided 97.5% CI	—		(41% to 55%)			(27% to 41%)		
PP Population								
N	N = 406	N = 404	N = 291	N = 133	N = 295	N = 338	N = 165	N = 339
n (%)	363 (89)	16 (4)	267 (92)	3 (2)	127 (43)	306 (91)	10 (6)	186 (55)
OR (95% CI)	233 (127 to 427)		—			—		
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* < 0.001			*P* < 0.001		
Proportions of Patients Achieving ≥ PASI 90 at Week 12								
n (%)	307 (71)	2 (1)	248 (71)	1 (1)	67 (19)	262 (68)	6 (3)	98 (26)
OR (95% CI)	562 (138 to 2,295)		—			—		
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* < 0.001			*P* < 0.001		
Proportions of Patients Achieving PASI 100 at Week 12								
n (%)	153 (35)	0	142 (41)	1 (1)	19 (5)	145 (38)	0	28 (7)
OR (95% CI)	Non-calculable		—			—		
P value vs. PL	Non-calculable		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* < 0.001			*P* < 0.001		

CI = confidence interval; ETA = etanercept; ITT = intention-to-treat; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PL = placebo; PP = per-protocol; vs. = versus.

Note: The ITT population is reported unless otherwise specified.

[a] UNCOVER-2 and UNCOVER-3: Non-inferiority margin = –12%; superiority margin = 0%: Ixekizumab was to be deemed non-inferior to etanercept if the lower bound of the two-sided 97.5% CI for the difference in proportions of responders on ixekizumab minus etanercept was greater than the pre-specified non-interiority margin of –12%. Ixekizumab was to be deemed superior to etanercept if the lower bound of the two-sided 97.5% confidence interval (CI) for the difference in proportions of responders on ixekizumab minus etanercept exceeded 0%.

Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8], UNCOVER-3 Clinical Study Report[9].

A.3 Efficacy — Health-Related Quality of Life and Functional Outcomes

TABLE 13: DERMATOLOGY LIFE QUALITY INDEX

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 351	PL n = 168	Etanercept n = 358	Ixekizumab n = 385	PL n = 193	Etanercept n = 382
Change from Baseline in DLQI Total Score– Summary Statistics								
Baseline Values								
Mean (SD)	13 (7.0)	13 (7.1)	12 (6.9)	13 (7.2)	13 (7.0)	12 (6.9)	13 (7.0)	12 (6.8)
Change from Baseline at Week 12								
LS mean (SE)	–11 (0.3)	–1 (0.3)	–10 (0.3)	–2 (0.4)	–8 (0.3)	–10 (0.2)	–2 (0.3)	–8 (0.2)
Difference vs. PL (95% CI)	–10 (–11 to –9)		–8 (–9 to –8)			–8 (–9 to –8)		
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
Difference vs. ETA (95% CI)	—		–3 (–3 to –2)			–2 (–3 to –2)		
P value vs. ETA	—		*P* < 0.001			*P* < 0.001		

CI = confidence interval; DLQI = Dermatology Life Quality Index; ETA = etanercept; LS = least squares; PL = placebo; SD = standard deviation; SE = standard error; vs. = versus.
Note: Mixed-effects model of repeated measures (MMRM) analysis. Imputation of missing data in Table 13 was performed using a modified baseline observation carried forward (mBOCF) analysis. Analysis using a last observation carried forward (LOCF) was also performed and results were similar to those described in Table 13.
Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8], UNCOVER-3 Clinical Study Report[9].

TABLE 14: SHORT-FORM (36) HEALTH INDEX

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 351	PL n = 168	Etanercept n = 358	Ixekizumab n = 385	PL n = 193	Etanercept n = 382
Change from Baseline in SF-36 Physical Component Summary Score								
Baseline Values								
Mean (SD)	47 (9.1)	47 (9.8)	48 (9.0)	48 (9.5)	48 (9.1)	48 (8.8)	47 (9.5)	49 (8.5)
Change from Baseline at Week 12								
LS mean (SE)	4.3 (0.38)	–0.2 (0.40)	3.8 (0.36)	–0.4 (0.52)	2.5 (0.36)	4.0 (0.35)	–0.3 (0.50)	3.1 (0.35)
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs. ETA	—		*P* = 0.013			*P* = 0.093		
Change from Baseline in SF-36 Mental Component Summary Score								
Baseline Values								
Mean (SD)	48 (11.5)	49 (11.2)	48 (11.7)	48 (10.6)	49 (10.7)	48 (11.4)	47 (11.6)	48 (11.7)
Change from Baseline at Week 12								
LS mean (SE)	4.2 (0.44)	0.7 (0.46)	4.5 (0.40)	–0.1 (0.58)	2.5 (0.40)	4.3 (0.40)	1.1 (0.57)	2.6 (0.40)
P value vs. PL	*P* < 0.001		*P* < 0.001			*P* < 0.001		
P value vs.	—		*P* < 0.001			*P* = 0.002		

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 351	PL n = 168	Etanercept n = 358	Ixekizumab n = 385	PL n = 193	Etanercept n = 382
ETA								

ETA = etanercept; LS = least squares; PL = placebo; SD = standard deviation; SE = standard error; SF-36 = Short-Form (36) Health Survey; vs. = versus.
Note: MMRM analysis. Imputation of missing data in Table 13.
was performed using a modified baseline observation carried forward (mBOCF) analysis. Analysis using a last observation carried forward (LOCF) was also performed and results were similar to those described in Table 13.
Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8], UNCOVER-3 Clinical Study Report[9].

A.4 Harms Outcomes (Induction-Dosing Period — Week 12)

TABLE 15: MORTALITY AND OTHER SERIOUS ADVERSE EVENTS

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 350	PL n = 167	Etanercept n = 357	Ixekizumab n = 384	PL n = 193	Etanercept n = 382
Mortality								
n (%)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
SAEs								
n (%)	**6 (1.4)**	**5 (1.2)**	**5 (1.4)**	**2 (1.2)**	**8 (2.2)**	**9 (2.3)**	**5 (2.6)**	**5 (1.3)**
Most frequently reported SAEs (≥ 1 patient in at least one ixekizumab treatment group), n (%)								
Cellulitis	1 (0.2)	0	0	0	1 (0.3)	0	1 (0.5)	0
Appendicitis	1 (0.2)	0	–	–	–	1 (0.3)	0	0
Cholecystitis	1 (0.2)	0	–	–	–			
Drug hypersensitivity	1 (0.2)	0	–	–	–			
Lumbar radiculopathy	1 (0.2)	0	–	–	–			
Peritonitis	1 (0.2)	0	–	–	–			
Urticaria	1 (0.2)	0	–	–	–			
Suicide attempt	–	–	1 (0.3)	0	0	–	–	–
Abscess oral	–	–	1 (0.3)	0	0	–	–	–
COPD	0	1 (0.2)	1 (0.3)	0	0	–	–	–
Depression	–	–	1 (0.3)	0	0	1 (0.3)	0	0
Diabetes mellitus	–	–	1 (0.3)	0	0	–	–	–
Duodenitis	–	–	1 (0.3)	0	0	–	–	–
Gastritis	–	–	1 (0.3)	0	0	–	–	–
Esophagitis	–	–	1 (0.3)	0	0	–	–	–
Arthritis	–	–	–	–	–	1 (0.3)	0	0
Leukocyto-clastic vasculitis	–	–	–	–	–	1 (0.3)	0	0
Skin lesion	–	–	–	–	–	1 (0.3)	0	0
Biliary colic	–	–	–	–	–	1 (0.3)	0	0
Hepatic function abnormal	–	–	–	–	–	1 (0.3)	0	0
Renal impairment	–	–	–	–	–	1 (0.3)	0	0
Abdominal pain	–	–	–	–	–	1 (0.3)	0	0

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 350	PL n = 167	Etanercept n = 357	Ixekizumab n = 384	PL n = 193	Etanercept n = 382
Crohn's disease	–	–	–	–	–	1 (0.3)	0	0
Fall	–	–	–	–	–	1 (0.3)	1 (0.5)	1 (0.3)
Subdural haematoma	–	–	–	–	–	1 (0.3)	0	0
Bipolar disorder	–	–	–	–	–	1 (0.3)	1 (0.5)	0
Anxiety	–	–	–	–	–	1 (0.3)	0	0
Dehydration	–	–	–	–	–	1 (0.3)	0	0

COPD = chronic obstructive pulmonary disease; PL = placebo; SAEs = serious adverse events.
Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8], UNCOVER-3 Clinical Study Report[9].

TABLE 16: ADVERSE EVENTS

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 350	PL n = 167	Etanercept n = 357	Ixekizumab n = 384	PL n = 193	Etanercept n = 382
AEs								
n (%)	**257 (59)**	**210 (49)**	**216 (62)**	**89 (53)**	**211 (59)**	**205 (53)**	**70 (36)**	**187 (49)**
Most frequently reported AEs (≥ 1% of patients in at least one treatment group), n (%):								
Nasopharyngitis	50 (11.5)	41 (9.5)	35 (10.0)	17 (10.2)	36 (10.1)	26 (6.8)	11 (5.7)	19 (5.0)
Injection-site reaction	42 (9.7)	5 (1.2)	39 (11.1)	1 (0.6)	39 (10.9)	37 (9.6)	3 (1.6)	41 (10.7)
URTI	24 (5.5)	16 (3.7)	19 (5.4)	7 (4.2)	26 (7.3)	8 (2.1)	5 (2.6)	8 (2.1)
Headache	18 (4.2)	15 (3.5)	17 (4.9)	3 (1.8)	20 (5.6)	16 (4.2)	5 (2.6)	11 (2.9)
Injection-site erythema	27 (6.2)	0	12 (3.4)	2 (1.2)	18 (5.0)	12 (3.1)	0	11 (2.9)
Injection-site pain	7 (1.6)	9 (2.1)	13 (3.7)	2 (1.2)	4 (1.1)	8 (2.1)	3 (1.6)	5 (1.3)
Fatigue	6 (1.4)	4 (0.9)	9 (2.6)	2 (1.2)	4 (1.1)	4 (1.0)	3 (1.6)	7 (1.8)
Arthralgia	9 (2.1)	9 (2.1)	7 (2.0)	4 (2.4)	10 (2.8)	13 (3.4)	4 (2.1)	7 (1.8)
Pruritus	6 (1.4)	13 (3.0)	7 (2.0)	4 (2.4)	4 (1.1)	7 (1.8)	1 (0.5)	4 (1.0)
UTI	–	–	5 (1.4)	2 (1.2)	2 (0.6)	5 (1.3)	0	3 (0.8)
Nausea	8 (1.8)	3 (0.7)	7 (2.0)	2 (1.2)	1 (0.3)	8 (2.1)	0	2 (0.5)
Diarrhea	8 (1.8)	5 (1.2)	6 (1.7)	1 (0.6)	2 (0.6)	11 (2.9)	2 (1.0)	6 (1.6)
Oropharyngeal pain	7 (1.6)	1 (0.2)	5 (1.4)	0	5 (1.4)	4 (1.0)	3 (1.6)	2 (0.5)
Psoriasis			4 (1.1)	5 (3.0)	7 (2.0)	5 (1.3)	3 (1.6)	0
Bronchitis	6 (1.4)	4 (0.9)	5 (1.4)	3 (1.8)	5 (1.4)	–	–	–
↑ blood creatine phosphokinase	8 (1.8)	5 (1.2)	5 (1.4)	2 (1.2)	4 (1.1)	6 (1.6)	3 (1.6)	3 (0.8)
Influenza	–	–	4 (1.1)	0	5 (1.4)	–	–	–
Pharyngitis	–	–	4 (1.1)	0	5 (1.4)	–	–	–
Injection-site bruising	–	–	5 (1.4)	1 (0.6)	5 (1.4)	2 (0.5)	1 (0.5)	0
Nail psoriasis	–	–	4 (1.1)	1 (0.6)	4 (1.1)	–	–	–
Myalgia	–	–	4 (1.1)	1 (0.6)	2 (0.6)	–	–	–
Sinusitis	5 (1.2)	4 (0.9)	4 (0.9)	–	–	–	–	–

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 350	PL n = 167	Etanercept n = 357	Ixekizumab n = 384	PL n = 193	Etanercept n = 382
Back pain	4 (0.9)	4 (0.9)	–	–	–	7 (1.8)	2 (1.0)	2 (0.5)
Cough	7 (1.6)	6 (1.4)	–	–	–	6 (1.6)	0	4 (1.0)
Pain in extremity	–	–	–	–	–	4 (1.0)	0	2 (0.5)

AE = adverse event; PL = placebo; URTI = upper respiratory tract infection; UTI = urinary tract infection.
Note: Treatment emergent adverse events.
Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8], UNCOVER-3 Clinical Study Report[9].

TABLE 17: CLINICALLY SIGNIFICANT HARMS

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 350	PL n = 167	Etanercept n = 357	Ixekizumab n = 384	PL n = 193	Etanercept n = 382
Infections								
n (%)	**124 (29)**	**106 (25)**	**104 (30)**	**46 (28)**	**98 (28)**	**82 (21)**	**27 (14)**	**59 (15)**
Injection-site reactions								
n (%)	**69 (16)**	**13 (3)**	**69 (20)**	**7 (4)**	**62 (18)**	**58 (15)**	**6 (3)**	**59 (15)**
Hypersensitivity reactions								
n (%)	**14 (3)**	**10 (2)**	**14 (4)**	**3 (2)**	**12 (3)**	**13 (3)**	**4 (2)**	**7 (2)**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-anaphylaxis	12 (3)	8 (2)	13 (4)	3 (2)	11 (3)	12 (3)	4 (2)	7 (2)
Major cardiovascular events [a]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PL = placebo.
[a] Classified as cerebro-cardiovascular events.
Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8], UNCOVER-3 Clinical Study Report[9].

TABLE 18: WITHDRAWAL DUE TO ADVERSE EVENTS

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	PL n = 431	Ixekizumab n = 350	PL n = 167	Etanercept n = 357	Ixekizumab n = 384	PL n = 193	Etanercept n = 382
WDAEs								
n (%)	**10 (2.3)**	**6 (1.4)**	**6 (1.7)**	**1 (0.6)**	**5 (1.4)**	**9 (2.3)**	**2 (1.0)**	**4 (1.0)**
Most frequently reported reasons (≥ one patients in at least one ixekizumab treatment group), n (%):								
Injection-site reaction	3 (0.7)	0	1 (0.3)	0	0	0	0	2 (0.5)
Aspartate aminotransferase levels	2 (0.5)	0	–	–	–	–	–	–
Appendicitis	1 (0.2)	0	–	–	–	1 (0.3)	0	0
Ascites	–	–	1 (0.3)	0	0	–	–	–
Malaise	–	–	1 (0.3)	0	0	–	–	–
Edema peripheral	–	–	1 (0.3)	0	0	–	–	–
Steatorrhea	–	–	1 (0.3)	0	0	–	–	–
Suicide attempt	–	–	1 (0.3)	0	0	–	–	–

	UNCOVER-1		UNCOVER-2			UNCOVER-3		
	Ixekizumab n = 433	**PL n = 431**	**Ixekizumab n = 350**	**PL n = 167**	**Etanercept n = 357**	**Ixekizumab n = 384**	**PL n = 193**	**Etanercept n = 382**
Liver function test abnormal	–	–	1 (0.3)	0	0	–	–	–
Diarrhea	–	–	–	–	–	1 (0.3)	0	0
Psoriasis	0	1 (0.2)	–	–	–	1 (0.3)	1 (0.5)	0
Crohn's disease	0	0	–	–	–	1 (0.3)	0	0
Nausea	–	–	–	–	–	1 (0.3)	0	0
Osteomyelitis	–	–	–	–	–	1 (0.3)	0	0
Sarcoidosis	–	–	–	–	–	1 (0.3)	0	0
Subdural haematoma	–	–	–	–	–	1 (0.3)	0	0
Urticaria	–	–	–	–	–	1 (0.3)	0	0

PL = placebo; WDAE = withdrawal due to adverse event.
Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8], UNCOVER-3 Clinical Study Report[9].

APPENDIX 5: MAINTENANCE-DOSING PERIOD

At the end of the 12-week induction-dosing period, patients from UNCOVER-1 and UNCOVER-2 entered a double-blind maintenance period, providing data up to week 60. As the design of the maintenance period is associated with several limitations, the 60-week results are presented as supportive information only (Table 19 and Table 19). Patients who were receiving any dosage of ixekizumab during the induction period and were classified as responders were re-randomized to receive either placebo, or one of two ixekizumab maintenance regimens. However, only the dosing regimen that is consistent with the Health Canada–approved dose was included in this review, i.e., ixekizumab 80 mg by subcutaneous (SC) injection every four weeks. Patients achieving a response under placebo or etanercept (in UNCOVER-2) during the induction period were not part of the randomization and were assigned to receive placebo for the maintenance period. Patients classified as non-responders in any treatment group were also not part of the randomization, and they were all systematically assigned to ixekizumab 80 mg SC every four weeks. Efficacy and safety analyses were conducted on the maintenance-dosing-period primary population, defined as all re-randomized patients who received at least one dose of study treatment during the maintenance-dosing period. Patients' data were analyzed according to the treatment to which they were re-randomized.

TABLE 19: KEY EFFICACY OUTCOMES — WEEK 60 (PRIMARY POPULATION)

	UNCOVER-1		UNCOVER-2	
	IXE Q2W / IXE Q4W n = 119	**IXE Q2W / PL n = 117**	**IXE Q2W / IXE Q4W n = 62**	**IXE Q2W / PL n = 86**
Proportions of Patients with sPGA Score of 0 or 1 at Week 60				
n (%)	89 (75)	9 (8)	47 (76)	6 (7)
OR (95% CI)	39 (17 to 87)		—	
P value	*P* < 0.001		*P* < 0.001	
Proportions of Patients Achieving ≥ PASI 75 at Week 60				
n (%)	93 (78)	11 (9)	53 (86)	5 (6)
OR (95% CI)	38 (18 to 82)		—	
P value	*P* < 0.001		*P* < 0.001	

IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; PL = placebo; Q2W = every two weeks; Q4W = every four weeks; sPGA = static Physician Global Assessment.
Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8].

TABLE 20: KEY HARMS OUTCOMES — WEEK 60 (PRIMARY POPULATION)

	UNCOVER-1		UNCOVER-2	
	IXE Q2W / IXE Q4W n = 119	**IXE Q2W / PL n = 117**	**IXE Q2W / IXE Q4W n = 102**	**IXE Q2W / PL n = 94**
Mortality, n (%)	1 (1)	0	0	0
SAEs, n (%)	7 (5.9)	4 (3.4)	2 (2.0)	6 (6.4)
AEs, n (%)	95 (79.8)	58 (49.6)	72 (70.6)	58 (61.7)
WDAEs, n (%)	4 (3.4)	0	2 (2.1)	1 (1.0)
Notable Harms, n (%)				
Infections	33 (28.2)	66 (55.5)	37 (39.4)	58 (56.9)
Injection-site reactions	0	5 (4.2)	4 (4.3)	16 (15.7)
Hypersensitivity reactions	1 (0.9)	13 (10.9)	2 (2.1)	6 (5.9)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; IXE = ixekizumab; PL = placebo; Q2W = every two weeks; Q4W = every four weeks; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Sources: UNCOVER-1 Clinical Study Report[6], UNCOVER-2 Clinical Study Report[8].

APPENDIX 6: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

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

Findings

TABLE 21: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	MCID	References
DLQI	10-item, dermatology-specific quality-of-life questionnaire	Yes	3.2	Mattei et al. 2014[20] Ruderman et al. 2003[17] Shikiar et al. 2006[21]
PGA	Single estimate of a patient's disease severity at a given time based on induration, erythema, and scaling	Yes	Unknown	Feldman et al. 2004[27] Weisman et al. 2003[28]
PASI	Numeric score ranging from 0 to 72, based on assessments of four body areas and severity of induration, erythema, and scaling	Yes	Unknown	Ashcroft et al. 1999[29] Carlin et al. 2004[30] Feldman et al. 2004[27] Gourraud et al. 2012[31]
SF-36	Consists of eight health domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) for which a subscale score can be calculated. It also provides 2 component summary scores: physical and mental. Scores range from 0 to 100, with higher scores indicating better health.	Only responsive-ness in psoriasis	2.5 to 5.0	Mease et al. 2006[32] Fendl and Ware 2014[33]

DLQI = Dermatology Life Quality Index; MCID = minimal clinically important difference; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; SF-36 = Short-Form (36) Health Survey.

Dermatology Life Quality Index

The DLQI is a widely used dermatology-specific quality-of-life instrument. It is a 10-item questionnaire that assesses six different aspects that may affect quality of life.[17,18] These aspects are symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[17,18] The maximum score per aspect is either 3 (with a single question) or 6 (with two questions), and the scores for each can be expressed as a percentage of either 3 or 6. Each of the 10 questions is scored from 0 (not at all) to 3 (very much), and the overall DLQI is calculated by summing the score of each question resulting in a numeric score between 0 and 30 (or a percentage of 30).[17,18] The higher the score, the more quality of life is impaired. The meaning of the DLQI scores on a patient's life is as follows:[19]

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

The DLQI has shown good reliability and construct validity.[17] The estimated minimal clinically important difference (MCID) for the DLQI in patients with psoriasis is 3.2.[20] Estimates of the minimal important difference (the smallest difference a patient would regard as beneficial) have ranged from 2.3 to 5.7.[21]

Limitations associated with the DLQI are as follows:

- Concerns have been identified regarding unidimensionality and the behaviour of items of the DLQI in different psoriatic patient populations with respect to their age, gender, culture, etc.[19]
- The patient's emotional aspects may be underrepresented, and this may be one reason for unexpectedly low DLQI scores in patients with more emotionally disabling diseases, such as vitiligo. To overcome this, it is suggested that the DLQI be combined with more emotionally oriented measures such as the mental component summary of the SF-36 scales or the Hospital Anxiety and Depression Scale.[19]
- Benchmarks for the MCID of DLQI scores in general dermatological conditions are not available, although there have been some attempts to determine these differences for specific conditions such as psoriasis.[19]
- DLQI may lack sensitivity in detecting change from mild to severe psoriasis.[16]

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.[34] The SF-36 consists of eight health domains — physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[32] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries: the physical component summary (PCS) and the mental component summary (MCS), derived from aggregating the eight domains according to a scoring algorithm. The PCS and MCS scores range from 0 to 100, with higher scores indicating better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a standard deviation of 10 in the general US population,[32] enabling scores to be meaningfully compared across different studies.[33] Therefore, all scores above/below 50 are considered above/below average for the general US population.[32,33]

Evidence of the validity and reliability of the SF-36 in patients with psoriasis is lacking. However, in one systematic review by Frendl and Ware[33] that observed SF-36 concordance and its MCID across many different indications in studies that looked at drug therapy effectiveness, the SF-36 was observed to be responsive (when compared with primary clinical measures) in patients with psoriasis. In addition, of the 10 psoriasis studies identified, net PCS or MCS improvement of at least three points was observed in 70% of these studies.

The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 and 5.0 points;[22-24] however, this is not specific to psoriasis.[33]

Physician Global Assessment

The PGA is used to determine a single estimate of the patient's overall severity of disease at a given point in time. Various PGAs have been used in psoriasis with different descriptions and scores.[35] Psoriatic lesions are graded for induration (I), erythema (E), and scaling (S) based on scales of 0 to 4 that are then averaged over all lesions.[15] The following table highlights the scoring for induration, erythema, and scaling:

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

Source: Cappelleri et al.[15]

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

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

The PGA is more subjective than PASI in that there is no attempt to quantify the individual elements of plaque morphology or body surface area (BSA) involvement.[27,28] There have also been fewer studies using PGA than PASI. This outcome is considered reliable using test–retest data and internal consistency.[28] However, inter-rater reliability due to variability, especially in untrained observers, is poor.[28] Many studies now employ only the final value of "clear" or "almost clear" as treatment success. Although the PGA seems to be less likely to be open to interpretation, different studies have used different definitions of "clear" or "almost clear," making comparisons between treatments difficult.[28] Construct and content validity are considered strong within a study, but comparison with other studies as well as relationship to other methods are problematic owing to the variability in data collection, analysis, and reporting methods.[28]

Psoriasis Area and Severity Index

PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It produces a numeric score ranging from 0 to 72. In general, a PASI score of 5 to 10 is considered moderate disease, and a score more than 10 is considered severe. A 75% reduction in the PASI score (PASI 75) is the current benchmark for most clinical trials in psoriasis and the criterion for efficacy of new psoriasis treatments approved by the FDA.[16]

In calculating the PASI, severity is determined by dividing the body into four regions: head (h), upper extremities (u), trunk (t), and lower extremities (l), which account for 10%, 20%, 30%, and 40% of the total BSA, respectively.[36] Each of these areas is assessed separately for erythema, induration, and scaling, which are rated on a scale of 0 (none) to 4 (very severe). Extent of psoriatic involvement is graded as follows:

- 0 = no involvement
- 1 = 1% to 9%
- 2 = 10% to 29%
- 3 = 30% to 49%
- 4 = 50% to 69%
- 5 = 70% to 89%
- 6 = 90% to 100%.

The following formula is used to calculate the PASI score:

$$PASI = 0.1 (E_h + I_h + S_h) A_h + 0.2 (E_u + I_u + S_u) A_u + 0.3 (E_t + I_t + S_t) At + 0.4 (E_l + I_l + S_l) A_l$$ [36]

where E = erythema, I = induration, S = scaling, A = area score. PASI 75 is a dichotomous scale (Yes/No, patient achieved ≥ 75% improvement from baseline PASI score).

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

- The PASI has been criticized as not correlating the clinical extent of the disease with quality of life and the psychological stress caused by psoriasis. The patient's measure of quality of life is often worse than the physician's rated clinical severity.[37]
- There are significant inter-rater reliability issues regarding the measurement of BSA.[27,29] There has been some work regarding the development of imaging and analysis systems to objectively measure BSA.[38]
- PASI scores can vary substantially between experienced and inexperienced physicians, raising concerns for inter-rater reliability.[35]
- Improvements in PASI score are not linearly related to severity or improvements in psoriasis.[27,30] The extent of psoriatic involvement is measured using a scale of 1 to 6, and the areas corresponding to each score are non-linear.
- Some severe disease (clinically) may be scored low. For example, scores as low as 3 (on palms and soles) may represent psoriasis that disables a patient from work and other life activities.
- Most patients fall into a narrow band of scores, thereby decreasing the usefulness of the full range of scores (i.e., scores above 40 are rare).[29] Validity of this scale may be overrated, in part because of the skew toward lower scores.[31]
- There is little research on the reliability of the assessments for erythema, desquamation, and induration, together with overall PASI scores.[29]
- Criterion validity is restricted by the lack of a "gold standard" measure of psoriatic severity.[39]
- The PASI lacks sensitivity, as erythema, desquamation, and induration are scored with equal weight within each of the four body regions. Thus, a reduction in scaling with a concomitant increase in skin erythema could be recorded with the same PASI score.
- Improvement of the histological phenotype of psoriasis can be underestimated by the per cent improvement in PASI (e.g., reduction of T cells, loss of K16 expression, and reduction in epidermal thickness).[30]
- Little work has been done to determine the clinical relevance of derived PASI scores.[29]

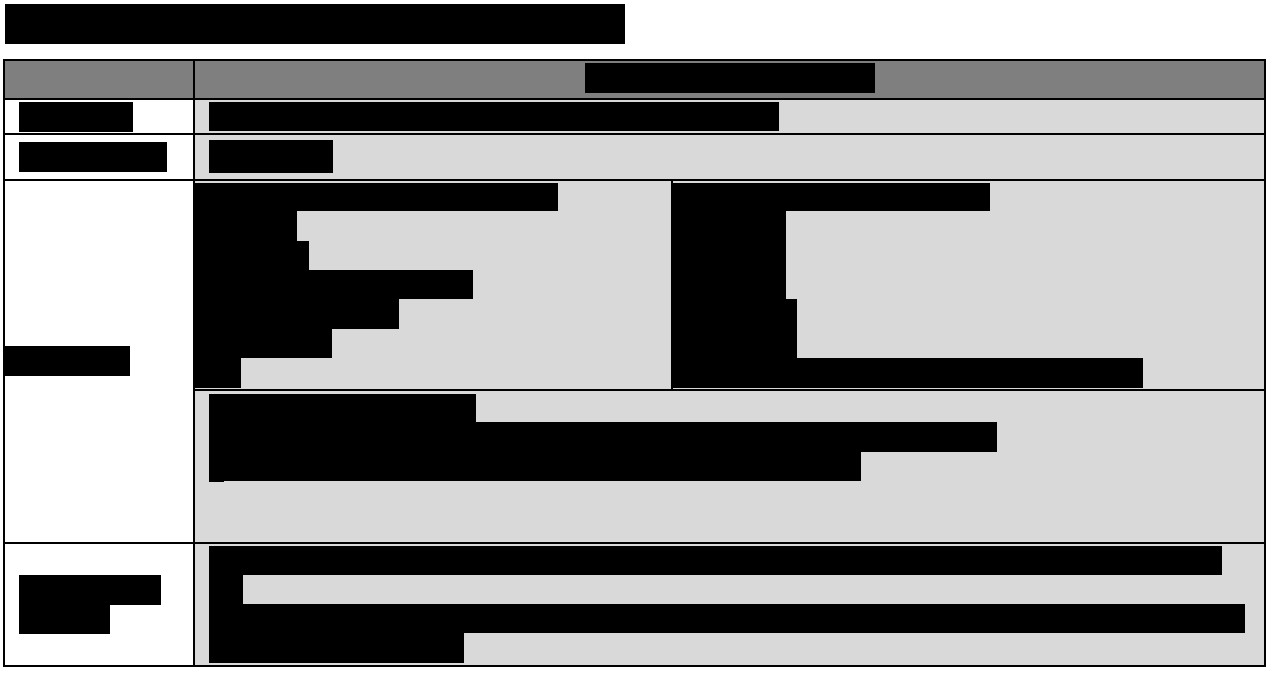
Conclusion

Several instruments are used when assessing psoriasis disease severity. The PASI is one of the most widely used tools. While there are some noted limitations of PASI, it is considered the gold standard for measuring severity of psoriasis.[38]

Quality-of-life measures are also important in the assessment of psoriasis severity. The DLQI is a dermatology-specific quality-of-life measure. DLQI has been validated for use in the psoriasis patient population, with an estimated MCID of 3.2.[20] In addition, the SF-36 is frequently used to assess quality of life; however, although it is considered responsive for patients with psoriasis, validity and reliability are lacking in this patient population. Quality of life remains an important consideration for assessing severity of disease for patients with psoriasis.

APPENDIX 7: SUMMARY OF NETWORK META-ANALYSIS[40]

[redacted]



	[redacted]
	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

[redacted]

[redacted]

[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

REFERENCES

1. Apremilast: patient drug information. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2016 [cited 2016 May 25]. Available from: www.uptodate.com Subscription required.
2. Feldman SR. Treatment of psoriasis. In: Post TW, editor. [Internet]. Waltham (MA): UpToDate; 2016 Apr 21 [cited 2016 May 25]. Available from: www.uptodate.com Subscription required.
3. Canadian Psoriasis Guidelines Committee. Canadian guidelines for the management of plaque psoriasis [Internet]. 1st ed. Ottawa: Canadian Dermatology Association; 2009. [cited 2016 Apr 19]. Available from: http://www.dermatology.ca/wp-content/uploads/2012/01/cdnpsoriasisguidelines.pdf
4. Taltz (ixekizumab): 80 mg / 1.0 mL solution for injection [product monograph]. Toronto: Eli Lilly Canada Inc.; 2016 May 25.
5. Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 Trials of Ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med. 2016 Jun 8.
6. Clinical study report synopsis: study I1F-MC-RHAZ (UNCOVER-1). A multicenter study with randomized, double-blind, placebo-controlled induction dosing period followed by a randomized maintenance dosing period and a long-term extension period to evaluate the efficacy and safety of LY2439821 in patients with moderate-to-severe plaque psoriasis [**CONFIDENTIAL** internal manufacturer's report]. Indianapolis (IN): Eli Lilly and Company; 2015 Feb 9.
7. Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet. 2015 Aug 8;386(9993):541-51.
8. Clinical study report synopsis: study I1F-MC-RHBA (UNCOVER-2). A multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of LY2439821 to etanercept and placebo in patients with moderate-to-severe plaque psoriasis [**CONFIDENTIAL** internal manufacturer's report]. Indianapolis (IN): Eli Lilly and Company; 2015 Feb 16.
9. Clinical study report synopsis: study I1F-MC-RHBC (UNCOVER-3). A 12-week multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of LY2439821 to etanercept and placebo in patients with moderate to severe plaque psoriasis with a long-term extension period [**CONFIDENTIAL** internal manufacturer's report]. Indianapolis (IN): Eli Lilly and Company; 2015.
10. Psoriasis [Internet]. Ottawa: Canadian Dermatology Association; 2016. [cited 2016 May 25]. Available from: http://www.dermatology.ca/skin-hair-nails/skin/psoriasis/#!/skin-hair-nails/skin/psoriasis/living-with-psoriasis/
11. CDR submission: Taltz (ixekizumab), 80 mg / 1.0 mL solution for injection. Company: Eli Lilly Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Toronto: Eli Lilly Canada Inc.; 2016 Mar.
12. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association; 2016 [cited 2016 May 25]. Available from: https://www.e-therapeutics.ca Subscription required.
13. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: Taltz (ixekizumab). Company: Eli Lilly and Company: Application no.: 125521. Approval date: 22/03/2016 [Internet]. Rockville (MD): FDA; 2016 Mar 22 [cited 2016 May 3]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125521Orig1s000TOC.cfm

14. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s). In: Taltz (ixekizumab). Company: Eli Lilly and Company: Application no.: 125521. Approval date: 22/03/2016 [Internet]. Rockville (MD): FDA; 2016 Mar 22 [cited 2016 May 3]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125521Orig1s000TOC.cfm
15. Cappelleri JC, Bushmakin AG, Harness J, Mamolo C. Psychometric validation of the physician global assessment scale for assessing severity of psoriasis disease activity. Qual Life Res. 2013 Nov;22(9):2489-99.
16. Fernandez-Penas P, Jones-Caballero M, Espallardo O, Garcia-Diez A. Comparison of Skindex-29, Dermatology Life Quality Index, Psoriasis Disability Index and Medical Outcome Study Short Form 36 in patients with mild to severe psoriasis. Br J Dermatol. 2012 Apr;166(4):884-7.
17. Ruderman EM, Markenson JA. Granulomatous infections and tumor necrosis factor antagonist therapies [abstract]. Poster presented at: EULAR; 2003 Jun 18; Lisbon, Portugal.
18. Simpson MJ, Chow C, Morgenstern H, Luger TA, Ellis CN. Comparison of three methods for measuring psoriasis severity in clinical studies (Part 2 of 2): use of quality of life to assess construct validity of the Lattice System Physician's Global Assessment, Psoriasis Area and Severity Index and Static Physician's Global Assessment. J Eur Acad Dermatol Venereol. 2015 Jul;29(7):1415-20.
19. Basra MKA, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol. 2008;159(5):997-1035.
20. Mattei PL, Corey KC, Kimball AB. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. J Eur Acad Dermatol Venereol. 2014 Mar;28(3):333-7.
21. Shikiar R, Willian MK, Okun MM, Thompson CS, Revicki DA. The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. Health Qual Life Outcomes [Internet]. 2006 [cited 2016 May 6];4:71. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1615869/pdf/1477-7525-4-71.pdf
22. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med. 2001 Jul;33(5):350-7.
23. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. PharmacoEconomics. 1999 Feb;15(2):141-55.
24. Strand V, Singh JA. Improved health-related quality of life with effective disease-modifying antirheumatic drugs: evidence from randomized controlled trials. Am J Manag Care. 2008 Apr;14(4):239-53.
25. Langley RG, Rich P, Menter A, Krueger G, Goldblum O, Dutronc Y, et al. Improvement of scalp and nail lesions with ixekizumab in a phase 2 trial in patients with chronic plaque psoriasis. J Eur Acad Dermatol Venereol. 2015 Sep;29(9):1763-70.
26. Gordon KB, Leonardi CL, Lebwohl M, Blauvelt A, Cameron GS, Braun D, et al. A 52-week, open-label study of the efficacy and safety of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with chronic plaque psoriasis. J Am Acad Dermatol. 2014 Dec;71(6):1176-82.
27. Feldman SR, Menter A, Koo JY. Improved health-related quality of life following a randomized controlled trial of alefacept treatment in patients with chronic plaque psoriasis. Br J Dermatol. 2004 Feb;150(2):317-26.

28. Weisman S, Pollack CR, Gottschalk RW. Psoriasis disease severity measures: comparing efficacy of treatments for severe psoriasis. J Dermatolog Treat. 2003 Sep;14(3):158-65.
29. Ashcroft DM, Wan Po AL, Williams HC, Griffiths CE. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. Br J Dermatol. 1999 Aug;141(2):185-91.
30. Carlin CS, Feldman SR, Krueger JG, Menter A, Krueger GG. A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. J Am Acad Dermatol. 2004 Jun;50(6):859-66.
31. Gourraud PA, Le Gall C, Puzenat E, Aubin F, Ortonne JP, Paul CF. Why statistics matter: limited inter-rater agreement prevents using the psoriasis area and severity index as a unique determinant of therapeutic decision in psoriasis. J Invest Dermatol. 2012 Sep;132(9):2171-5.
32. Mease PJ, Menter MA. Quality-of-life issues in psoriasis and psoriatic arthritis: outcome measures and therapies from a dermatological perspective. J Am Acad Dermatol. 2006 Apr;54(4):685-704.
33. Frendl DM, Ware JE, Jr. Patient-reported functional health and well-being outcomes with drug therapy: a systematic review of randomized trials using the SF-36 health survey. Med Care. 2014 May;52(5):439-45.
34. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. Med Care. 1992 Jun;30(6):473-83.
35. Langley RG, Ellis CN. Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System Physician's Global Assessment. J Am Acad Dermatol. 2004 Oct;51(4):563-9.
36. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis [Internet]. 2005 [cited 2016 May 6];64(Suppl 2):ii65-ii68. Available from: http://ard.bmj.com/content/64/suppl_2/ii65.full.pdf
37. Choi J, Koo JY. Quality of life issues in psoriasis. J Am Acad Dermatol. 2003 Aug;49(2 Suppl):S57-S61.
38. Hani AF, Prakasa E, Nugroho H, Affandi AM, Hussein SH. Body surface area measurement and soft clustering for PASI area assessment. Conf Proc IEEE Eng Med Biol Soc. 2012;4398-401.
39. Jacobson CC, Kimball AB. Rethinking the Psoriasis Area and Severity Index: the impact of area should be increased. Br J Dermatol. 2004 Aug;151(2):381-7.
40. MArS Market Access & Pricing Strategy GmbH. Network meta-analysis to evaluate the clinical efficacy and safety of psoriasis treatments: consolidated report of the original and NMA update [**CONFIDENTIAL** manufacturer's submission]. Boston: Adelphi Values; 2016.