Common Drug Review
Clinical Review Report

October 2015

Drug	secukinumab (Cosentyx) subcutaneous injection
Indication	For the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Listing request	To be listed in a similar manner to currently prescribed biologics administered by subcutaneous injection indicated for treatment of moderate to severe plaque psoriasis in adult patients, including the following: • Initial response should be assessed after 16 weeks, and further doses provided only for responders.
Manufacturer	Novartis Pharmaceuticals Canada Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
BSA	body surface area
CDR	CADTH Common Drug Review
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
DLQI	Dermatology Life Quality Index
EQ-5D	EuroQol Five-Dimension Health-Related Quality of Life Questionnaire
FAS	full analysis set
HRQoL	health-related quality of life
IGA	Investigator's Global Assessment
IL	interleukin
IR	incidence rate
LOCF	last observation carried forward
MCID	minimal clinically important difference
MTC	mixed treatment comparison
PGA	Physician Global Assessment
PASI	Psoriasis Area and Severity Index
PsA	psoriatic arthritis
PSD	Psoriasis Symptom Diary
PY	patient-year
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
SEC	secukinumab
SD	standard deviation
SF-36	Short-Form 36-Item Health Survey
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Psoriasis is a serious, chronic inflammatory skin disorder. Several types of psoriasis exist, including plaque, guttate, inverse, palmar-plantar, erythrodermic, and pustular psoriasis. Plaque psoriasis is the most common form of psoriasis and is characterized by well-demarcated plaques that are covered by silvery scales. Psoriasis has been associated with a loss of productivity, depression, excessive alcohol intake, Crohn disease, and an increased prevalence of malignancy. About 20% of psoriasis patients develop psoriatic arthritis, and many patients have comorbidities (for example, cardiovascular disease and metabolic syndrome). It is estimated that 200,000 Canadians have moderate to severe chronic plaque psoriasis.

Treatments for psoriasis include topical therapy, phototherapy, and systemic therapy. Systemic therapies include small-molecule inhibitors such as methotrexate, cyclosporine, and apremilast, as well as biologics such as adalimumab, infliximab, etanercept, and ustekinumab. Psoriasis is considered to have a major immune component, and the systemic therapies all target the immune response in various ways. Secukinumab is a first-in-class interleukin-17A inhibitor administered monthly as a subcutaneous injection.

The objective of this report is to perform a systematic review of the beneficial and harmful effects of secukinumab for the treatment of moderate to severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy.

Indication under review
For the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Listing criteria requested by sponsor
To be listed in a similar manner to currently prescribed biologics administered by subcutaneous injection indicated for treatment of moderate to severe plaque psoriasis in adult patients, including the following: • Initial response should be assessed after 16 weeks, and further doses provided only for responders.

Results and Interpretation

Included Studies

Four multi-centre, double-blind, parallel-group, randomized, placebo-controlled phase 3 trials were included in the systematic review: ERASURE (N = 738), FEATURE (N = 177), JUNCTURE (N = 182), and FIXTURE (N = 1,306). The randomized controlled trials enrolled adult patients with moderate to severe chronic plaque psoriasis who were inadequately controlled by topical treatments, phototherapy, or previous systemic therapy. All four trials had Canadian sites.

The co-primary efficacy outcomes were the Psoriasis Area and Severity Index (PASI) 75 response at week 12 and the Investigator's Global Assessment (IGA) modified 2011 0 or 1 (IGA 0/1) response at week 12 in all four included trials. PASI is a measure of psoriatic disease severity taking into account lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement. PASI 75 response refers to ≥ 75% improvement in PASI score compared with baseline. IGA is an investigator's impression of psoriasis severity. An IGA score of 0 indicates no signs of psoriasis; some

post-inflammatory hyperpigmentation may be present. A score of 1 indicates almost clear skin (no thickening and normal or pink [for Caucasian patients] coloration).

The trials consisted of four periods: screening (one to four weeks), induction (12 weeks), maintenance (40 weeks), and follow-up (eight weeks). At induction, patients were randomized to subcutaneous secukinumab 150 mg, secukinumab 300 mg, or placebo. Treatment was administered at weeks 0, 1, 2, 3, 4, and 8. FIXTURE included an active control group of subcutaneous etanercept 50 mg twice weekly. In the maintenance period, patients who received secukinumab 150 mg or secukinumab 300 mg in the induction period continued monthly secukinumab treatment; the last dose was given at week 48. For patients on etanercept (FIXTURE), the dose decreased to 50 mg once weekly at the start of the maintenance period. Placebo patients who were non-responders (PASI < 75) at the end of the induction period were re-randomized to secukinumab 150 mg or secukinumab 300 mg, and placebo patients who were responders (PASI ≥ 75) continued on placebo.

All four trials allowed early escape or crossover to secukinumab at week 12. The early escape design is common in modern psoriasis and rheumatological drug trials based on ethical considerations, but the study design has numerous limitations, which potentially limit the interpretation and clinical relevance of results after this time point. Generalizability of findings from all four trials may be limited, as the majority of enrolled patients were Caucasian, male, aged 65 years or younger, and had severe psoriasis.

Efficacy

The proportion of patients obtaining PASI 75 was statistically significantly higher with secukinumab 150 mg and secukinumab 300 mg compared with placebo ($P < 0.0001$ for all comparisons). Responses ranged from 67% to 72% for secukinumab 150 mg and from 76% to 87% for secukinumab 300 mg compared with 0% to 5% for placebo. Non-inferiority of secukinumab 150 mg versus etanercept and secukinumab 300 mg versus etanercept for PASI 75 at week 12 was concluded in the per-protocol analysis, as the lower limit of the 99.375% confidence interval (CI) was greater than –10%, where 10% was the pre-defined non-inferiority margin. The risk differences were [redacted]% (lower CI [redacted]%) and [redacted]% (lower CI [redacted]%) for secukinumab 150 mg and secukinumab 300 mg, respectively, compared with etanercept. Non-inferiority of secukinumab versus etanercept was also demonstrated in the full analysis set. [redacted].

More patients obtained IGA 0 or 1 response with secukinumab 150 mg or secukinumab 300 mg compared with placebo ($P < 0.0001$ for all comparisons). The proportion of patients obtaining IGA 0 or 1 ranged from 51% to 53% for secukinumab 150 mg and from 63% to 73% for secukinumab 300 mg compared with 0% to 3% for placebo. In FIXTURE, 45% of etanercept patients obtained a PASI 75 response at week 12.

A manufacturer-submitted mixed treatment comparison (MTC) compared secukinumab with adalimumab, etanercept, infliximab, methotrexate, ustekinumab, and etanercept-methotrexate combination for the outcome of PASI 75 response at week 12. Secukinumab 300 mg [redacted] adalimumab, etanercept, etanercept-methotrexate combination, methotrexate, and ustekinumab, [redacted] infliximab, in achieving PASI 75 response. Hence, secukinumab 300 mg [redacted]. However, there are uncertainties regarding these results. First, PASI results were not corroborated with other outcomes such as IGA or supported by sensitivity

analyses. As well, the study populations across trials were fairly heterogeneous for severity of psoriasis. In some trials, patients had moderate psoriasis whereas, in others, patients had more severe disease, as demonstrated by a wide range of baseline PASI. Treatment experience varied between studies, with some trials being conducted exclusively in treatment-naive patients and others in treatment-experienced patients, although the details were not provided in the MTC. The clinical expert consulted for this review indicated that treatment experience would not affect treatment response to a subsequent therapy because biologics tend to lose some effectiveness over time, but long-term PASI response was not investigated in the MTC. The review by the CADTH Common Drug Review (CDR) showed that approximately one-quarter of patients previously exposed to biologics or other systemic therapy did not respond to secukinumab 300 mg at week 12. Hence, the inclusion of treatment-naive with treatment-experienced patients in the MTC may have overestimated the results for secukinumab.

Based on input received from two patient groups, patients reported that symptoms of psoriasis interfered with their daily lives. Symptoms of itching, scaling, and pain were measured at week 12 with the use of an electronic diary in two trials in approximately 40% patients. Of these, 14% were excluded from the analysis, which only left a small subset of patients with usable data. Nonetheless, trial patients reported improvements in these three symptoms with both doses of secukinumab compared with placebo.

Health-related quality of life was quantified using two instruments, the Dermatology Life Quality Index (DLQI) and the EuroQol Five-Dimension Health-Related Quality of Life Questionnaire (EQ-5D) measured with a visual analogue scale (VAS). Compared with placebo, secukinumab patients (both doses) reported improvement in DLQI and in EQ-5D VAS. The difference in DLQI total score between secukinumab (both doses) and placebo ranged from [redacted] to [redacted] at the week 12 visit, which is greater than the minimal clinically important difference (MCID) of 3. More than half of patients treated with secukinumab 150 mg or 300 mg reported no impairment in health-related quality of life at week 12, as DLQI response of 0 or 1 was achieved in these patients. Differences between secukinumab (both doses) and placebo were also statistically significant for EQ-5D VAS; no MCID has been reported in psoriasis patients, and clinical significance of the observed difference is uncertain.

Because of the early escape study design used in the trials, only a small number of patients remained in the placebo group after the induction period. Hence, there were insufficient placebo patients for comparisons against secukinumab at week 52.

Harms

A total of two patients died (in FEATURE); one patient who had received secukinumab 150 mg died due to a cardiac arrest, and one patient who had received placebo in the induction period followed by secukinumab 300 mg at re-randomization died as a result of alcohol poisoning.

In the induction period, 58% to 64% of patients receiving secukinumab 150 mg and 51% to 70% of patients receiving secukinumab 300 mg reported experiencing at least one adverse event (AE) compared with 47% to 54% of patients on placebo. The most frequently reported AEs included nasopharyngitis, headache, diarrhea, pruritus, and hypertension. These AEs were seen more commonly with secukinumab than with placebo. With etanercept, 58% of patients reported at least one AE. For the entire treatment period (52 weeks), incidence rates (IRs) of AEs in ERASURE and FIXTURE were 236 and 270 per 100 patient-years (PYs) for secukinumab 150 mg, 246 and 252 per 100 PYs for secukinumab 300 mg, and 243 per 100 PYs for etanercept. The most common AEs were nasopharyngitis (highest IR reported with etanercept); upper respiratory tract infection and diarrhea (highest IRs with secukinumab); and hypertension and influenza (IRs similar across treatment groups).

In the induction period and for the entire treatment period, few patients experienced a serious adverse event (SAE) or withdrawal due to adverse events (WDAEs). For both treatment periods, the types of SAEs or WDAEs were varied, with only one or two patients experiencing an event for each SAE or WDAE. According to the clinical expert consulted for this review, notable potential harms of secukinumab include infection, urticaria, anaphylaxis, cardiac events, lupus-like syndrome or exacerbation of lupus, exacerbation of psoriasis, malignancy, and neurological AEs. The major concern with secukinumab, shared with other biologics, comes from the potential increase in the risk of infection and malignancy. For the entire treatment period, the IRs of infections and infestations ranged from 85 to 125 per 100 PYs with secukinumab, and the IR of malignancy was less than 3 per 100 PYs with secukinumab. There were no reports of lupus-like syndrome or exacerbation of lupus. Neurological events, termed nervous system disorders in the data collected, had IRs ranging from 41 to 81 per 100 PYs with secukinumab. There were few events of the other notable harms (urticaria, anaphylaxis, cardiac events, and exacerbation of psoriasis) reported.

The manufacturer-submitted MTC did not consider harms data in the analysis, and information comparing secukinumab with other drugs is not available. This is unfortunate, because AEs are a significant concern for patients, as stated in the patient group submissions.

Other Considerations

1. Part-way through the CDR review, secukinumab received its Notice of Compliance from Health Canada for the treatment of plaque psoriasis. The recommended dose is secukinumab 300 mg administered weekly at weeks 0, 1, 2, and 3, then monthly starting at week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg each.

2. The induction period in each trial was 12 weeks (doses given at weeks 0, 1, 2, 3, 4, and 8), and the primary and key secondary analyses were conducted based on 12-week data. Yet the listing criterion requested by the manufacturer is that an initial response be assessed after 16 weeks (i.e., two extra doses of secukinumab would be given). Data on time to PASI 75 response (an outcome not identified in the CDR protocol) were available up to 12 weeks. Other data were provided which showed that the proportion of patients with a PASI 75 response and IGA 0/1 response was highest at weeks 15 or 16 for secukinumab 300 mg (PASI 75 achieved in approximately 86% of patients at week 16 compared with 77% to 82% of patient at week 12). The clinical expert consulted for this review indicated that, while total efficacy may not be assessable at 12 weeks, a patient would be expected to have a good response to a biologic drug at this time point. Additionally, patient-driven demand for response is closer to 12 weeks. However, the clinical expert consulted for this review indicated that the decision to stop or switch treatment because of non-response would likely occur after a longer trial period; the clinical expert suggested up to six months, unless the decision were made earlier to comply with third-party funding criteria.

Conclusions

In four randomized controlled trials involving patients with moderate to severe chronic plaque psoriasis who were inadequately controlled by topical treatments, phototherapy, or previous systemic therapy, secukinumab 150 mg and secukinumab 300 mg demonstrated statistically significant benefits relative to placebo on key outcomes: PASI 75 response at week 12, IGA 0/1 response at week 12, and PASI 90 response at week 12. Secukinumab was non-inferior and superior to etanercept for PASI 75 response at week 12. Patients reported an improvement in symptoms of itching, pain, and scaling at week 12, as well as an improvement in health-related quality of life at weeks 12 and 52; however, these were considered exploratory outcomes. There were very few SAEs and very few WDAEs in the induction periods and over the course of the secukinumab trials. The most common AEs included nasopharyngitis, headache, diarrhea, pruritus, and hypertension, which occurred more frequently with secukinumab than with placebo.

The generalizability of the findings from the included studies may be limited, as the majority of enrolled patients had severe psoriasis. In addition, although early escape design is typical of these types of studies for ethical reasons, this study design potentially weakens the internal validity of efficacy and safety results after the escape time point.

A manufacturer-submitted MTC found that secukinumab 300 mg [redacted] adalimumab, etanercept, etanercept-methotrexate combination, methotrexate, and ustekinumab, [redacted] infliximab, in achieving PASI 75 response. Hence, secukinumab 300 mg [redacted]. However, there are many uncertainties regarding these results. The effect of secukinumab 300 mg may have been overestimated because treatment experience was not taken into consideration. Key limitations of the MTC included the heterogeneous populations across trials, the lack of sensitivity analyses to support the results, and the low number of trials included in each comparison.

TABLE 1: SUMMARY OF RESULTS

	ERASURE			FEATURE			JUNCTURE			FIXTURE		
SEC vs. PL (FAS) at Week 12												
	SEC 150	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**
N	245	245	247	59	59	59	61	60	61	327	327	325
Patients with PASI 75[a,b]												
n/N	174/243	200/245	11/246	41/59	44/58	0/59	43/60	52/60	2/61	219/327	249/323	16/324
%	71.6	81.6	4.5	69.5	75.9	0	71.7	86.7	3.3	67.0	77.1	4.9
RD or OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with PASI 75 who were previously exposed to and failed systemic therapy[b]												
n/N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with IGA 0/1 [a,b]												
n/N	125/244	160/245	6/246	31/59	40/58	0/59	32/60	44/60	0/61	167/327	202/323	9/324
%	51.2	65.3	2.4	52.5	69.0	0	53.3	73.3	0	51.1	62.5	2.8
RD or OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with IGA 0/1 who were previously exposed to and failed systemic therapy[b]												
n/N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI total score (LOCF)[c]												
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. PL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC vs. ETA, Non-inferiority Analysis (Per-Protocol) at Week 12												
	SEC 150	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**ETA**
N	NA	NA	NA	NA	NA	NA	NA	NA	NA	[redacted]	[redacted]	[redacted]
Patients with PASI 75 [b,d,e,f]												
n/N	NA	NA	NA	NA	NA	NA	NA	NA	NA	[redacted]	[redacted]	[redacted]
%	NA	NA	NA	NA	NA	NA	NA	NA	NA	[redacted]	[redacted]	[redacted]
RD	NA	NA	NA	NA	NA	NA	NA	NA	NA	[redacted]	[redacted]	[redacted]

	ERASURE			FEATURE			JUNCTURE			FIXTURE		
95% CI	NA	NA	NA	NA	NA	NA	NA	NA	NA	[redacted]		
Harms, Induction Period (Up to Week 12)												
	SEC 150	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**
N	245	245	247	59	59	59	61	60	61	327	326	327
Patients > 0 AEs												
n	148	135	116	34	30	28	39	42	33	191	181	163
%	60.4	55.1	47.0	57.6	50.8	47.5	63.9	70.0	54.1	58.4	55.5	49.8
Patients > 0 SAEs												
n	4	6	4	0	3	1	3	1	1	7	4	6
%	1.6	2.4	1.6	0	5.1	1.7	4.9	1.7	1.6	2.1	1.2	1.8
Patients > 0 WDAEs												
n	5	3	4	0	1	1	0	0	1	2	4	6
%	2.0	1.2	1.6	0	1.7	1.7	0	0	1.6	0.6	1.2	0.9

AEs = adverse events; CI = confidence interval; cmH = Cochran–Mantel–Haenzsel; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; ETA = etanercept; FAS = full analysis set; IGA = Investigator's Global Assessment; LOCF = last observation carried forward; NA = not applicable; PASI = Psoriasis Area and Severity Index; OR = odds ratio; PL = placebo; RD = risk difference; SAE = serious adverse event; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Cochran-Mantel-Haenszel test (ERASURE and FIXTURE) and Fisher's exact test (FEATURE and JUNCTURE).

[b] Based on non-responder imputation.

[c] Using Hodges-Lehmann estimates and van Elteren test.

[d] Mantel–Haenszel risk difference.

[e] Both doses of SEC were found to be non-inferior to ETA based on a non-inferiority margin of 10%.

[f] Results of the FAS analyses were similar to those of the per-protocol analyses.

Source: Clinical Study Reports.[1-4]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Psoriasis is a serious, chronic inflammatory skin disorder that can have a large impact on quality of life.

Several types of psoriasis exist, including plaque, guttate, inverse, palmar-plantar, erythrodermic, and pustular psoriasis.[5] Plaque psoriasis is the most common form, occurring in 90% of patients.[6,7] There are approximately 1 million people who suffer from psoriasis in Canada, and 125 million worldwide. Of these, 20% to 30% (an estimated 200,000 Canadians) have moderate to severe chronic plaque psoriasis.[8-10]

Plaque psoriasis is characterized by well-demarcated plaques that are covered by silvery scales.[5] Moderate to severe psoriasis is defined by extent of skin coverage (involvement of more than 5% to 10% of body surface area), location (involvement of the face, palm, sole, or genitals), or severity (diseas that is disabling).[5]

Psoriasis has been associated with a loss of productivity, depression, excessive alcohol intake, Crohn disease, and an increased prevalence of malignancy.[11] About 20% of psoriasis patients develop psoriatic arthritis.[7] Emerging comorbidities include cardiovascular disease and metabolic syndrome with obesity, dyslipidemia, and insulin resistance.[7,11] The relationship between psoriasis and comorbidities such as metabolic syndrome and cardiovascular disease is likely linked to the underlying chronic inflammatory nature of psoriasis and the effects of pro-inflammatory factors, such as tumour necrosis factor alpha.[11]

1.2 Standards of Therapy

Psoriasis is treated topically, with phototherapy, or with systemic therapies.[7] Topical therapies include corticosteroids of varying potencies; emollients, coal tar, vitamin D analogues, and topical retinoids may also be used. Phototherapies may either be strictly topical (ultraviolet B light on involved skin) or combine a systemic drug such as psoralen. Topical therapies have the advantage of reduced risk of harms because they are applied locally. Once patients have exceeded 5% to 10% of skin involvement, topical therapy becomes more problematic for administration, given the large surface area to cover. Systemic therapy may be required when a large area of the skin is involved or when the psoriasis is moderate or severe.[12]

Psoriasis is an immune disorder, and therefore systemic therapies work by suppressing components of the immune system. The first systemic therapies were all small molecules. The two most currently used are 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. Both of these drugs have significant toxicities associated with them.[7,10] Apremilast, an orally administered phosphodiesterase-4 inhibitor, is the newest small-molecule inhibitor indicated for moderate to severe plaque psoriasis.

The earliest biologics — etanercept, infliximab, and adalimumab — targeted tumour necrosis factor, a key mediator of inflammation. The newer generation of biologics, ustekinumab and secukinumab, block interleukin (IL). High cost is a common drawback of the biologics for psoriasis, as well as the fact that they all must be administered by injection. The tumour necrosis factor inhibitors have all been associated with elevated risk of certain cancers with long-term use as well as with increased risk of infection, including tuberculosis.[10]

TABLE 2: KEY CHARACTERISTICS OF SMALL-MOLECULE INHIBITORS AND BIOLOGICS

Drug	Mechanism of Action	Indication[a]	Route of Administration	Recommended Dose	Serious Adverse Events/Safety Issues
Small molecules					
Apremilast	PDE4 inhibitor	Patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy	Oral	30 mg twice daily	Depression and weight loss[b]
Cyclosporine	Calcineurin inhibitor; inhibits IL-2, preventing T-cell activation	Psoriasis	Oral	2.5 mg/kg/day given in two divided oral doses, 12 hours apart Dose may be titrated to achieve effect. Total daily dose should not exceed 5 mg/kg per day.	Infections Nephrotoxicity Hypertension
Methotrexate	Antimetabolite Folate antagonist	Psoriasis	Oral	Weekly single oral, IM or IV dose schedule: 10 to 25 mg per week until adequate response is achieved Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg per week should not be exceeded.	Bone marrow suppression Hepatotoxicity Nephrotoxicity Alopecia Stomatitis
Biologics					
Adalimumab	TNF inhibitor Recombinant human monoclonal antibody	Patients with chronic moderate to severe psoriasis who are candidates for systemic therapy For patients with chronic moderate plaque psoriasis, adalimumab should be used after phototherapy has been shown to be ineffective or inappropriate	Subcutaneous	80 mg administered SC, followed by 40 mg SC given every other week starting one week after the initial dose. Continued therapy beyond 16 weeks should be reconsidered in a patient not responding within this time period.	Infection Cancer
Etanercept	TNF inhibitor Fusion protein	Patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	Subcutaneous	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.	Infection Cancer

Drug	Mechanism of Action	Indication[a]	Route of Administration	Recommended Dose	Serious Adverse Events/Safety Issues
Infliximab	TNF inhibitor Chimeric monoclonal antibody	Patients with 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	Intravenous	5 mg/kg given as IV infusion followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient does not show an adequate response at week 14, after infusions at weeks 0, 2, and 6, no additional treatment with infliximab should be given.	Infection Cancer
Secukinumab	IL-17A inhibitor Fully human monoclonal antibody	Moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy	Subcutaneous	300 mg (given as 2 doses of 150 mg) SC at weeks 0, 1, 2, and 3, followed by monthly doses starting at week 4.	Too early in product life cycle
Ustekinumab	IL-12 and IL-23 inhibitor Fully human monoclonal antibody	Patients with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy	Subcutaneous	45 mg at weeks 0 and 4, then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg. For patients who respond inadequately to dosing every 12 weeks, consideration may be given to treating as often as every 8 weeks. Consideration should be given to discontinuing treatment in patients who have shown no response up to 12 weeks of treatment.	Infection Cancer Serious skin reactions (exfoliative dermatitis and erythrodermic psoriasis)

IL = interleukin; IM = intramuscular; IV = intravenous; PDE4 = phosphodiesterase-4; SC = subcutaneous; TNF = tumour necrosis factor.
[a] Health Canada indication.
[b] From US Food and Drug Administration medical review of Cosentyx.[13]
Source: Cosentyx Product Monograph[14] and e-CPS (*Compendium of Pharmaceuticals and Specialties*).[15]

1.3 Drug

Secukinumab is a first-in-class IL-17A inhibitor.[8] Increased numbers of IL-17A-producing lymphocytes and innate immune cells, and increased levels of IL-17A, have been found in the blood and skin of patients with plaque psoriasis. Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which inhibits the release of pro-inflammatory cytokines, chemokines, and mediators of tissue damage.[8]

The recommended dose of secukinumab is 300 mg by subcutaneous injection (given as two injections of 150 mg) with initial dosing at weeks 0, 1, 2, and 3, followed by monthly doses starting at week 4.[14] Notice of Compliance was received on February 27, 2015.

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Listing criteria requested by sponsor
To be listed in a similar manner to currently prescribed biologics administered by subcutaneous injection indicated for treatment of moderate to severe plaque psoriasis in adult patients, including the following: • Initial response should be assessed after 16 weeks, and further doses provided only for responders.

2. OBJECTIVES AND METHODS

2.1 Objectives

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

2.2 Methods

Studies were selected for inclusion in the systematic review 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 phototherapy or systemic therapy **Subgroups:** Body weight (< 90 kg, ≥ 90 kg) Patients with psoriatic arthritis Patients with inadequate response to or who are intolerant of, or have contraindications to, systemic therapy
Intervention	Secukinumab 150 mg to 300 mg SC injection at weeks 0, 1, 2, and 3, then monthly starting at week 4, alone or in combination with other drug or non-drug therapies for moderate to severe plaque psoriasis

Comparators	As monotherapy or in combination with:
	• **Systemic:**
	  • methotrexate
	  • cyclosporine
	  • acitretin
	  • apremilast
	  • biologic response modifiers (etanercept, infliximab, adalimumab, ustekinumab).
	• **Topical:**
	  • tazarotene
	  • vitamin D analogues (e.g., calcitriol, calcipotriol)
	  • corticosteroids.

Outcomes	**Key efficacy outcomes** • Health-related quality of life • Psoriasis Area and Severity Index (or other measures of severity) • Physician Global Assessment • Proportion of body surface area involved **Other efficacy outcomes** • Other symptoms (e.g., pruritus, nail) **Harms outcomes** • AEs • SAEs • WDAEs • Notable harms (infection, urticaria, anaphylaxis, cardiac event, lupus-like syndrome or exacerbation of lupus, exacerbation of psoriasis, malignancy, neurological AEs)
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records & daily updates via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Cosentyx (secukinumab) and chronic plaque psoriasis.

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

The initial search was completed on January 29, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on May 20, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/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 QUOROM = Quality of Reporting of Meta-analyses.

Table 4; there were no excluded studies.

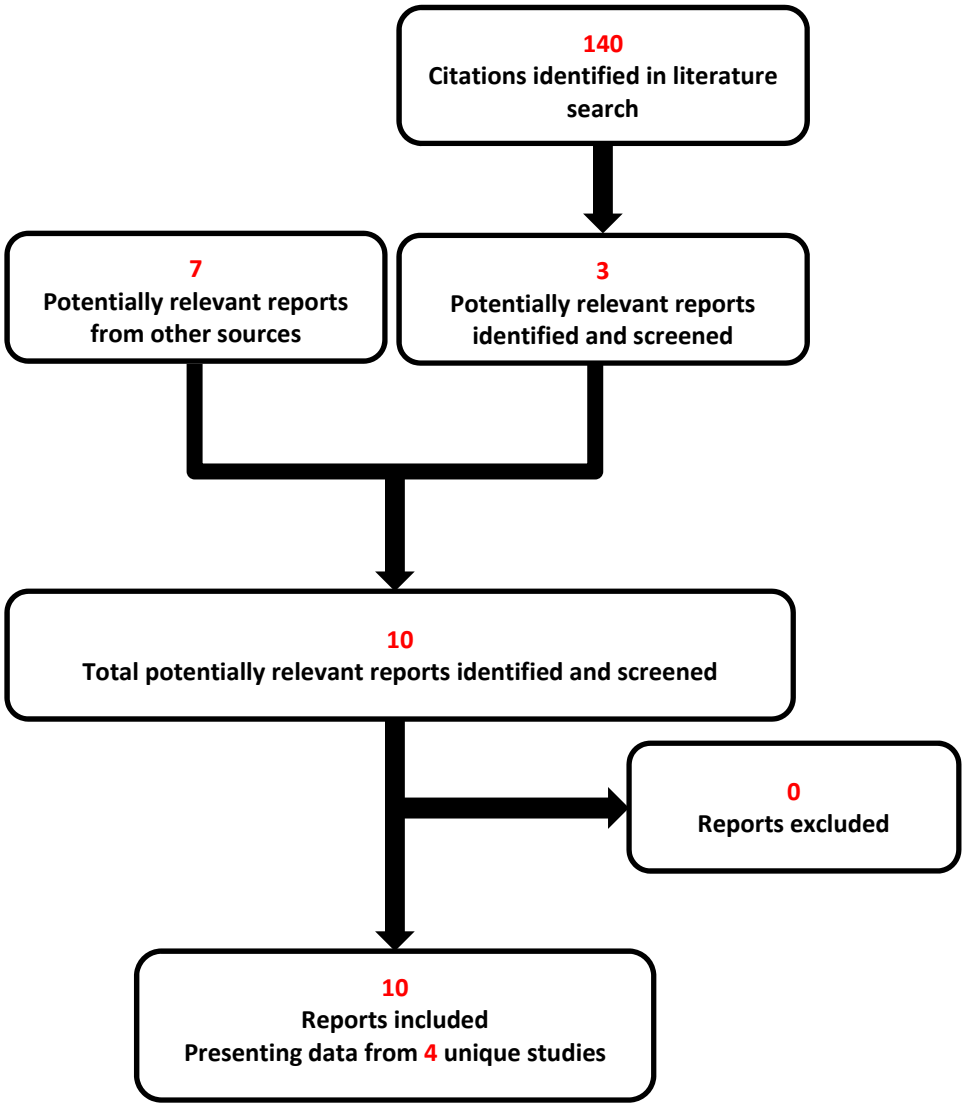
3. RESULTS

3.1 Findings From the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in QUOROM = Quality of Reporting of Meta-analyses.

Table 4 and described in Section 3.2.

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



QUOROM = Quality of Reporting of Meta-analyses.

TABLE 4: DETAILS OF INCLUDED PHASE 3 RANDOMIZED CONTROLLED TRIALS

		ERASURE (A2302)	FEATURE (A2308)	JUNCTURE (A2309)	FIXTURE (A2303)
DESIGNS & POPULATIONS	**Study Design**	MC, DB, PC, PG			MC, DB, DD, AC, PC, PG
	Locations	88 centres in 12 countries (5 Canadian centres, n = 59)	32 centres in 5 countries (4 Canadian centres, n = 19)	38 centres in 5 countries (6 Canadian centres, n = 35)	231 centres in 26 countries (15 Canadian centres, n = 53)
	Randomized (N)	738	177	182	1,306
	Inclusion Criteria	Adult outpatients with moderate to severe chronic plaque psoriasis defined as PASI ≥ 12, and IGA mod 2011 ≥ 3 and total BSA ≥ 10% who are inadequately controlled by topical treatments and/or phototherapy and/or previous systemic therapy			
	Exclusion Criteria	Psoriasis other than chronic plaque; drug-induced psoriasis; patients with active ongoing inflammatory disease, infection or significant medical problems; patients with ongoing use of prohibited treatments	Per ERASURE, and excluding patients with a history of lymphoproliferative disease or malignancy	Per ERASURE, and excluding patients with a history of lymphoproliferative disease or malignancy	Per the other 3 trials, and excluding patients with previous exposure to ETA
DRUGS	**Intervention**	SEC 150 mg or 300 mg SC weekly for 4 weeks (weeks 0, 1, 2, and 3), then monthly starting at week 4			
	Comparator(s)	Placebo			Placebo or ETA 50 mg SC twice weekly for 12 weeks then 50 mg every week
	Method of injection	Investigator-administered using LYO	Patient-administered using a PFS	Patient-administered using an AI pen	SEC and SEC-PL: investigator-administered using LYO; ETA and ETA-PL: patient-administered using PFS
DURATION	**Phase**				
	Screening	1 to 4 weeks			
	Induction	12 weeks			
	Maintenance	40 weeks			
	Follow-up	8 weeks			

		ERASURE (A2302)	FEATURE (A2308)	JUNCTURE (A2309)	FIXTURE (A2303)
OUTCOMES	**Primary End Points**	• PASI 75 response at week 12 • IGA mod 2011 0 or 1 response at week 12			
	Other End Points	• PASI 75 at week 52 • PASI 50/90/100 response at weeks 12 and 52 • PASI score over time up to weeks 12 and 52 • IGA mod 2011 at week 52 • IGA score over time up to weeks 12 and 52 • Time to PASI 75 • Relapse (maximal PASI improvement from baseline is reduced by > 50%) • Rebound (increase in PASI > 125) • DLQI at weeks 12 and 52 • EQ-5D at weeks 12 and 52 • Safety			
		• Psoriasis Symptom Diary at week 12 • PGIC • HAQ-DI	SIAQ	SIAQ	• Psoriasis Symptom Diary at week 12 • PGIC • HAQ-DI
NOTES	**Publications**	Langley et al., 2014[16]	Blauvelt et al., 2015[17]	Paul et al., 2014[18]	Langley et al., 2014[16]

AC = active control; AI = auto-injector; BSA = body surface area; DB = double-blind; DD = double-dummy; DLQI = Dermatology Life Quality Index; ETA = etanercept; EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; HAQ-DI = Health Assessment Questionnaire–Disability Index; IGA = Investigator's Global Assessment; LYO = lyophilisate in vial; MC = multi-centre; PASI = Psoriasis Area and Severity Index; PC = placebo-controlled; PFS = pre-filled syringe; PG = parallel-group; PGIC = Patient Global Impression of Change; PL = placebo; SC = subcutaneous; SEC = secukinumab; SIAQ = Self-Injection Assessment Questionnaire.
Source: Clinical Study Reports.[1-4] Three additional reports were included: CADTH Common Drug Review submission[8] and US Food and Drug Administration Medical and Statistical Reports.[13,19]

3.2 Included Studies

3.2.1 Description of Studies

Four multi-centre, double-blind, parallel-group, randomized, placebo-controlled phase 3 trials were included in the systematic review: ERASURE (N = 738),[1,16] FEATURE (N = 177),[3,17] JUNCTURE (N = 182),[4,18] and FIXTURE (N = 1,306).[2,16] One trial, FIXTURE, also included etanercept as a comparator group. The trials investigated the efficacy and safety of secukinumab in adult patients with moderate to severe chronic plaque psoriasis that was inadequately controlled by topical treatments, phototherapy, or previous systemic therapy. All four trials had Canadian sites (QUOROM = Quality of Reporting of Meta-analyses.

Table 4).

The trials consisted of four periods: screening (1 to 4 weeks), induction (12 weeks), maintenance (40 weeks), and follow-up (8 weeks). Blinding was maintained to the end of the follow-up period.

- **Screening period** (from screening to randomization): This period lasted one to four weeks and was used to assess patient eligibility for the trial and to taper off disallowed medications.
- **Induction period** (from randomization to week 12 pre-dose): The induction period started at randomization and lasted through week 12. The week 12 pre-dose visit was the end of the induction period. Any patient who discontinued during the induction period entered the treatment-free follow-up period.

- Patients assigned to the placebo group during the induction period who were Psoriasis Area and Severity Index (PASI) 75 responders entered the maintenance period and continued on placebo. PASI 75 response refers to ≥ 75% improvement in PASI score compared with baseline. PASI 75 non-responders were re-randomized to receive 150 mg or 300 mg of secukinumab during the maintenance period. All other treatment groups continued with their drug assignments regardless of response at the end of the induction period.
- **Maintenance period** (from week 12 post-dose to week 52): The maintenance period consisted of weeks 12 to 52. This period started with the dose given at week 12; the last dose was given at week 48. The week 52 visit was the end of the maintenance period. Any patient who discontinued during the maintenance period entered the treatment-free follow-up period.
- **Follow-up period:** Patients entering the treatment-free follow-up period included patients who prematurely discontinued during the induction or maintenance periods, patients who completed the induction period and did not continue into the maintenance period, and patients who completed the maintenance period but were not continuing with an extension trial.

Patients in the secukinumab treatment groups who completed the maintenance period were offered the opportunity to enter an extension study when available at their study sites (starting at week 52 with the first dose of treatment).

In the beginning of the induction period, patients were randomized to subcutaneous secukinumab 150 mg, secukinumab 300 mg, or placebo, which was administered at weeks 0, 1, 2, 3, 4, and 8. FIXTURE included an active control group of subcutaneous etanercept 50 mg twice weekly. Patients were stratified by body weight (< 90 kg and ≥ 90 kg) in all trials and by geographical region in ERASURE and FIXTURE. At the end of the induction period (start of the maintenance period), patients receiving secukinumab 150 mg or secukinumab 300 mg in the induction period continued treatment as per initial randomization until week 48. For patients on etanercept (FIXTURE), the dose decreased to 50 mg once weekly at the start of the maintenance period. Non-responders (PASI < 75) from the placebo groups were re-randomized to secukinumab 150 mg or secukinumab 300 mg for the remainder of the study. Placebo responders (PASI ≥ 75) continued on placebo (see Section 3.2.3).

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients were 18 years of age or older, with a diagnosis of moderate to severe chronic plaque psoriasis for at least six months before randomization, defined as PASI score of 12 or more and an IGA modified (mod) 2011 score of 3 or more, and a total affected body surface area (BSA) of 10% or more.

Patients were excluded from entering the trials if they had a form of psoriasis other than the chronic plaque type (for example, pustular psoriasis) or drug-induced psoriasis; required ongoing use of prohibited psoriasis treatments (detailed in next paragraph); had previous exposure to a biologic drug targeting IL-17 or its receptor; had ongoing inflammatory disease (other than psoriasis or psoriatic arthritis); were immunocompromised; had significant medical problems (for example, uncontrolled hypertension); had a history of ongoing, chronic, or recurrent infection; had a history of lymphoproliferative disease or malignancy; or had relevant clinical laboratory abnormalities (for example, low neutrophil count).

Prohibited medications and their washout periods before randomization included biologics (6- to 12-month washout), systemic immunomodulating treatments such as methotrexate and cyclosporine (four-week washout), retinoids and fumarates (four-week washout), phototherapy (two- to four-week

washout), and topical treatments such as corticosteroids and vitamin D analogues (two-week washout). Patients who were likely going to require continuing medication with prohibited medications after randomization were excluded.

b) Baseline Characteristics

Patient characteristics are detailed in Table 5 and Table 6. Overall, baseline characteristics were balanced between treatment groups in each study. The median age of patients was approximately [redacted] years; less than [redacted]% of patients were aged [redacted] years. Across trials and treatment groups, 62% to 77% of patients were male. Patients were predominately Caucasian. ERASURE and FIXTURE included a high proportion of Asian patients (approximately 20%) compared with FEATURE and JUNCTURE (< 5%).

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS: ERASURE, FEATURE, AND JUNCTURE

	ERASURE			FEATURE			JUNCTURE		
Randomized	SEC 150 (N = 245)	SEC 300 (N = 245)	PL (N = 248)	SEC 150 (N = 59)	SEC 300 (N = 59)	PL (N = 59)	SEC 150 (N = 61)	SEC 300 (N = 60)	PL (N = 61)
Age, years									
Mean	44.9	44.9	45.4	46.0	45.1	46.5	43.9	46.6	43.7
SD	13.3	13.5	12.6	15.1	12.6	14.1	14.4	14.2	12.7
Median	[redacted]								
Min, Max	[redacted]								
≥ 65 years									
n (%)	[redacted]								
Gender, n (%)									
Male	168 (69)	169 (69)	172 (69)	40 (68)	38 (64)	39 (66)	41 (67)	46 (77)	38 (62)
Race, n (%)									
Caucasian	171 (70)	171 (70)	176 (71)	51 (86)	54 (92)	57 (97)	58 (95)	56 (93)	59 (97)
Black	[redacted]								
Asian	54 (22)	52 (21)	46 (19)	2 (3)	1 (2)	1 (2)	1 (2)	3 (5)	2 (3)
Other	[redacted]								
Unknown	[redacted]								
Time since first diagnosis of psoriasis, years									
Mean	17.5	17.4	17.3	20.4	18.0	20.2	20.6	21.0	19.9
SD	12.0	11.1	12.4	13.0	11.9	14.2	14.5	13.5	12.2
Median	[redacted]								
Min, Max	[redacted]								
Baseline total BSA, %									
N	245	245	247	59	59	59	61	60	61
Mean	33.3	32.8	29.7	30.6	33.3	32.2	30.1	26.4	25.7
SD	19.2	19.3	15.9	16.6	18.0	17.4	16.7	12.8	14.7
Median	[redacted]								
Min, Max	[redacted]								
Baseline PASI score									
N	245	245	247	59	59	59	61	60	61
Mean	22.3	22.5	21.4	20.5	20.7	21.1	22.0	18.9	19.4
SD	9.8	9.2	9.1	8.3	8.0	8.5	8.9	6.4	6.7
Median	[redacted]								
Min, Max	[redacted]								
Baseline PASI, n (%)									
≤ 20	[redacted]								
> 20	[redacted]								
Severity of psoriasis, n (%)									

Randomized	ERASURE			FEATURE			JUNCTURE		
	SEC 150 (N = 245)	SEC 300 (N = 245)	PL (N = 248)	SEC 150 (N = 59)	SEC 300 (N = 59)	PL (N = 59)	SEC 150 (N = 61)	SEC 300 (N = 60)	PL (N = 61)
Moderate	[redacted]								
Severe	[redacted]								
Psoriatic arthritis present, n (%)									
Yes	46 (19)	57 (23)	68 (27)	9 (15)	9 (15)	7 (12)	16 (26)	14 (23)	12 (20)
Previous exposure to systemic therapy, n (%)									
Yes	156 (64)	163 (67)	146 (59)	45 (76)	35 (59)	39 (66)	34 (56)	34 (57)	33 (54)
Failed[a]	[redacted]								
Previous exposure to biologic therapy, n (%)									
Yes	73 (30)	70 (29)	73 (29)	28 (48)	23 (39)	26 (44)	15 (25)	15 (25)	12 (21)
Failed[a]	[redacted]								

BSA = body surface area; Max = maximum; Min = minimum; PASI = Psoriasis Area and Severity Index; PL = placebo; SD = standard deviation; SEC = secukinumab.
Source: Clinical Study Reports.[1,3,4]
[a] [redacted].[20]

Median time since first diagnosis of psoriasis was [redacted] years across treatment groups in the four trials. The majority of patients suffered from severe psoriasis with median baseline PASI score [redacted], and 11% to 20% of patients had psoriatic arthritis (PsA). Plaque psoriasis affected approximately one-third of the body (BSA 30% to 35%) in ERASURE, FEATURE, and FIXTURE, whereas it was approximately 20% in JUNCTURE. Of patients who had previously used systemic therapy (i.e., approximately 54% to 76% of patients), the majority of them had failed treatment ([redacted]% to [redacted]%). Previous exposure to biologic therapy was highest in FEATURE (39% to 48%) and lowest in FIXTURE (11% to 14%), with failures ranging from [redacted]% to [redacted]% across trials.

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS, FIXTURE

	FIXTURE			
	SEC 150 (N = 327)	SEC 300 (N = 327)	ETA (N = 326)	PL (N = 326)
Age, years				
Mean (SD)	45.4 (12.9)	44.5 (13.2)	43.8 (13.0)	44.1 (12.6)
Median (Min, Max)	[redacted]			
≥ 65 years				
n (%)	[redacted]			
Gender, n (%)				
Male	236 (72)	224 (69)	232 (71)	237 (73)
Race, n (%)				
Caucasian	219 (67)	224 (69)	219 (67)	218 (67)
Black	[redacted]			
Asian	72 (22)	73 (22)	74 (23)	72 (22)
Native American	28 (9)	22 (7)	27 (8)	25 (8)
Other	[redacted]			
Unknown	[redacted]			
Time since first diagnosis of psoriasis, years				
Mean (SD)	17.3 (12.2)	15.8 (12.3)	16.4 (12.0)	16.6 (11.6)
Median (Min, Max)	[redacted]			
Baseline total BSA, %				
Mean (SD)	34.5 (19.4)	34.3 (19.2)	33.6 (18.0)	35.2 (19.1)
Median (Min, Max)	[redacted]			

FIXTURE				
	SEC 150 (N = 327)	SEC 300 (N = 327)	ETA (N = 326)	PL (N = 326)
Baseline PASI score				
Mean (SD)	23.7 (10.5)	23.9 (9.9)	23.2 (9.8)	24.1 (10.5)
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PASI, n (%)				
≤ 20	[redacted]	[redacted]	[redacted]	[redacted]
> 20	[redacted]	[redacted]	[redacted]	[redacted]
Severity of psoriasis, n (%)				
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Psoriatic arthritis present, n (%)				
Yes	49 (15)	50 (15)	44 (14)	49 (15)
Previous exposure to systemic therapy, n (%)				
Yes	212 (65)	206 (63)	214 (66)	204 (63)
Failed[a]	[redacted]	[redacted]	[redacted]	[redacted]
Previous exposure to biologic therapy, n (%)				
Yes	45 (14)	38 (12)	45 (14)	35 (11)
Failed[a]	[redacted]	[redacted]	[redacted]	[redacted]

BSA = body surface area; ETA = etanercept; Min = minimum; Max = maximum; PASI = Psoriasis Area and Severity Index; PL = placebo; SD = standard deviation; SEC = secukinumab.
Source: Clinical Study Report.[2]
[a] [redacted].[20]

3.2.3 Interventions

Patients, investigators, persons performing the assessments, and data analysts were blinded to the identity of the treatment from the time of randomization until end of follow-up.

In ERASURE, the study drugs were administered by the investigator; treatments were reconstituted using a lyophilized formulation. In FEATURE and JUNCTURE, the study drugs were self-administered by the patient using a pre-filled syringe or an auto-injector pen, respectively. In FIXTURE, a lyophilized formulation was used: secukinumab and the secukinumab placebo (placebo-secukinumab) were administered by the investigator. Etanercept and the etanercept placebo (placebo-etanercept) were self-administered at home using a pre-filled syringe.

The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, schedule of administration, appearance, taste, and odour. An exception was the appearance of the lyophilized cake for secukinumab 150 mg powder for solution, which was slightly different from placebo-secukinumab 150 mg powder for solution. Also, the caps for the vials of secukinumab 150 mg powder and placebo-secukinumab were of different colours. Thus, to maintain blinding, an unblinded pharmacist or other unblinded personnel prepared the study treatment.

a) ERASURE, FEATURE, and JUNCTURE

At baseline, patients were assigned to one of the following three treatment groups in a ratio of 1:1:1.

- Subcutaneous secukinumab 150 mg: secukinumab 150 mg (one injection of the 150 mg dose + one injection of placebo) administered at randomization, weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and placebo (two injections per dose) administered at weeks 13, 14, and 15

- Subcutaneous secukinumab 300 mg: secukinumab 300 mg (two injections of the 150 mg dose) administered at randomization, weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and placebo (two injections per dose) administered at weeks 13, 14, and 15
- Subcutaneous placebo: placebo injections were administered to maintain double-blinding. Placebo-secukinumab (two injections per dose) was administered at randomization, weeks 1, 2, 3, 4, and 8. At week 12 (before receiving the week 12 dose), patients who had been on placebo for the initial part of the study either remained on placebo or were re-randomized to secukinumab 150 mg or secukinumab 300 mg based on their PASI 75 response to placebo at week 12:
  - Placebo PASI 75 responders continued to receive placebo-secukinumab (two injections per dose) administered at weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48
  - Placebo PASI 75 non-responders were re-randomized 1:1 to secukinumab 150 mg (one injection of the 150 mg dose + one injection of placebo) or secukinumab 300 mg (two injections of the 150 mg dose) administered at weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48

b) FIXTURE

At baseline, patients were assigned to one of the following four treatment groups in a ratio of 1:1:1:1.

- Subcutaneous etanercept: etanercept 50 mg twice per week from randomization until week 12. At week 12, patients received etanercept 50 mg every week through week 51. To maintain the blind, patients also received two placebo-secukinumab injections at randomization, weeks 1, 2, 3, 4, 8, 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48
- Subcutaneous secukinumab 150 mg: secukinumab 150 mg (one injection of the 150 mg dose + one injection of placebo-secukinumab) administered at randomization, weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and placebo-secukinumab (two injections per dose) administered at weeks 13, 14, and 15. To maintain the blind, placebo-etanercept was administered twice per week from randomization through week 12, and then once per week until week 51
- Subcutaneous secukinumab 300 mg: secukinumab 300 mg (two injections of the 150 mg dose) administered at randomization, weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and placebo-secukinumab (two injections per dose) administered at weeks 13, 14, and 15. To maintain the blind, placebo-etanercept was administered twice per week from randomization through week 12 and then once per week until week 51
- Subcutaneous placebo: placebo-etanercept twice per week until week 12 and placebo-secukinumab (two injections per dose) administered at randomization, weeks 1, 2, 3, 4, and 8. At week 12 (before receiving the week 12 dose), patients who had been on placebo for the initial part of the study either remained on placebo or were re-randomized to secukinumab 150 mg or secukinumab 300 mg based on their PASI 75 response to placebo at week 12:
  - Placebo PASI 75 responders continued to receive placebo-secukinumab at weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48, along with placebo-etanercept once a week until week 51
  - Placebo PASI 75 non-responders were re-randomized 1:1 to 150 mg or 300 mg secukinumab and received their treatment on weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48 along with weekly placebo-etanercept until week 51

Study drug dose adjustments or interruptions were not permitted during the trials. Similarly, the use of rescue medications was not permitted. Patients with intolerable scaling or itching were permitted to use bland emollients (i.e., excluding topical medications with active ingredients such as lactic acid, salicylic acid, and urea). The use of nonsteroidal anti-inflammatory drugs, analgesic treatments, or any other treatment given to treat PsA was permitted only if it was given at a stable dose for at least four weeks

before the first dose of study treatment, and if it was not on the list of prohibited medications (see Section 3.2.2a)).

c) Treatment Compliance

In ERASURE, the study drug was administered by the investigator, and the drug concentration was measured in the serum. In FEATURE and JUNCTURE, patients self-administered the study drug in the presence of the investigator. Patients were asked to return all unused medication at the end of the study. In FIXTURE, patients recorded their etanercept and placebo-etanercept doses administered at home on a paper diary. The patient returned the used syringes. Secukinumab and placebo-secukinumab were administered by the investigator.

3.2.4 Outcomes

a) Efficacy Outcomes

The co-primary efficacy outcomes were PASI 75 response at week 12 and Investigator's Global Assessment (IGA) modified 2011 0 or 1 (0/1) response at week 12 for both doses of secukinumab in all four included trials. (See Appendix 4: Testing Procedures and Power Calculations for the testing strategy.)

Various secondary outcomes related to PASI and IGA mod 2011 as well as several exploratory outcomes were recorded (Table 7). Key secondary analyses included PASI 90 response at week 12 and Psoriasis Symptom Diary (itching, pain, scaling) at week 12 in ERASURE and FIXTURE, and PASI 75 response and IGA mod 2011 0/1 response at week 12 for comparisons of secukinumab versus etanercept in FIXTURE.

Co-primary outcomes and selected secondary outcomes were evaluated by subgroups: weight at randomization (< 90 kg, ≥ 90 kg), exposure to previous therapy (systemic, biologic, or non-biologic), failure of previous therapy, and ongoing use of emollients.

TABLE 7: SECONDARY, EXPLORATORY, AND PATIENT-REPORTED OUTCOMES IN THE INCLUDED TRIALS

	ERASURE	FEATURE	JUNCTURE	FIXTURE
Secondary outcomes				
PASI 50/75/90/100 response at each visit up to week 12 and up to week 52	✓	✓	✓	✓
IGA mod 2011 0 or 1 response at each visit up to week 12 and up to week 52	✓	✓	✓	✓
PASI score over time up to week 12 and up to week 52	✓	✓	✓	✓
IGA score over time up to week 12 and up to week 52	✓	✓	✓	✓
PASI 75 response at week 52 in PASI 75 responders at week 12	✓	X	X	✓
IGA mod 2011 0 or 1 response at week 52 in IGA mod 2011 0 or 1 responders at week 12	✓	X	X	✓
Time to PASI 75 response	✓	✓	✓	✓
ACR response	E	X	X	X
Relapse	E	E	E	E
Rebound	E	E	E	E
Patient-reported outcomes				
Psoriasis Symptom Diary (items: itching, pain, scaling)	✓	X	X	✓
Psoriasis Symptom Diary (other items)	E	X	X	E
PGIC	E	X	X	✓
DLQI	✓	✓	✓	✓

	ERASURE	FEATURE	JUNCTURE	FIXTURE
EQ-5D	✓	✓	✓	✓
HAQ-DI	E	X	X	E
SIAQ	X	✓	✓	X

ACR = American College of Rheumatology; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; E = exploratory outcome; HAQ-DI = Health Assessment Questionnaire–Disability Index; IGA = Investigator's Global Assessment; mod = modified; PASI = Psoriasis Area and Severity Index; PGIC = Patient Global Impression of Change; SIAQ = Self-Injection Assessment Questionnaire.

b) Descriptions of Efficacy Outcomes

PASI: PASI is a measure of psoriatic disease severity that takes into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. PASI scores range from 0 to 72, with higher scores indicating greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on four anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the four anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score. The minimal clinically important difference (MCID) for PASI is unknown. A PASI 50/75/90 response means a ≥ 50%, ≥ 75%, or ≥ 90%, respectively, improvement in PASI score compared with baseline. A PASI 100 response means remission or complete clearing of psoriasis (PASI score = 0).

Psoriasis Symptom Diary (PSD): PSD is a 20-item, psoriasis-specific electronic diary to assess symptom severity, symptom bother, and disease impact. Patients are asked to recall their disease experience over the preceding 24 hours. The severity and bother of the following symptoms are assessed: itching, stinging, burning, pain, scaling, and skin colour. Impact items assess patient embarrassment, restricted movement due to psoriasis, and avoidance of activities requiring interaction with other people. A 0 to 10 numeric scale is used to assess impact, symptom severity, and symptom bother; higher scores indicate more severe impact, bother, or severity (0 = symptom not experienced, 10 = symptom "as bad as you can imagine"). Patients are prompted to respond to questions about bother only when they have indicated a score greater than 0 for the severity questions. For example, if a patient indicates a score greater than 0 for skin cracking, they are then asked how bothered they are by their skin cracking. Responses for skin colour are categorical and include pink; light red or brown; bright red or purple; deep, dark red, purple, or brown; grey, white, or silver. The MCID for each symptom is estimated to be 2.0 to 3.0.[21]

IGA mod 2011: IGA is an investigator's impression of psoriasis severity. The trials for secukinumab employed the IGA mod 2011, a 5-point, static scale, ranging from 0 to 4. The static IGA scale is based on a point-in-time assessment. The following outlines the possible scores on the IGA mod 2011 scale: 0 = clear (e.g., no signs of psoriasis, some post-inflammatory hyperpigmentation may be present); 1 = almost clear (e.g., no thickening, normal, or pink coloration); 2 = mild (e.g., mild thickening, pink to light red coloration); 3 = moderate (e.g., moderate thickening, dull to bright red); and 4 = severe (e.g., severe thickening, bright to deep red).The MCID for IGA mod 2011 is unknown.

Dermatology Life Quality Index (DLQI): 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.[22] These aspects are symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment. The maximum score per aspect is either 3 or 6, and the scores for each can

be expressed as a percentage of either 3 or 6. Each of the 10 questions is scored from 0 (not at all) to 3 (very much), and the overall DLQI is calculated by summing the scores of each question, resulting in a numeric score between 0 and 30 (or a percentage of 30). A higher score denotes a greater impairment in quality of life. The meaning of the DLQI scores on a patient's life is as follows: 0 or 1 = no effect, 2 to 5 = small effect, 6 to 10 = moderate effect, 11 to 20 = very large effect, and 21 to 30 = extremely large effect. The estimated MCID for DLQI in patients with psoriasis is 3.2.[23]

EuroQol Five-Dimension Health-Related Quality of Life Questionnaire (EQ-5D): EQ-5D is a generic health-related quality of life (HRQoL) questionnaire that consists of two parts. The first part is the EQ-5D descriptive system, which comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients were asked to choose the level that reflected their health state for each of the five dimensions; however, no overall index score was calculated in the included trials. The second part is a visual analogue scale that rates a patient's perceived health on a 20 cm visual analogue scale (EQ-5D VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Patients were asked to rate their health by drawing a line from an anchor box to the point on the EQ-5D VAS that best represented their health on that day. The MCID for VAS for psoriasis is unknown.

American College of Rheumatology response, Health Assessment Questionnaire–Disability Index, Patient Global Impression of Change, and Self-Injection Assessment Questionnaire were not identified in the protocol as outcomes of interest for the purpose of the CDR review. No data are presented on these outcomes.

Relapse (defined as a reduction in the achieved maximal PASI improvement from baseline of > 50%), rebound-like event (defined as an increase in PASI to > 125% of baseline PASI, or presence of new pustular psoriasis, new erythrodermic psoriasis, or more inflammatory psoriasis occurring after the last dose of study treatment received) and rebound (rebound-like event occurring within eight weeks of stopping therapy) were exploratory variables, and data are not presented for these outcomes.

c) Harms Outcomes

An adverse event (AE) was defined as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after randomization, even if the event was not considered to be related to study treatment. Medical conditions and diseases present before starting study treatment were considered AEs only if they worsened after starting study treatment. Abnormal laboratory values or test results constituted AEs only if they signalled clinical signs or symptoms, were considered clinically significant, or required therapy.

A serious AE (SAE) was defined as an event that was fatal or life-threatening; resulted in persistent or significant disability or incapacity; constituted a congenital anomaly or birth defect; required in-patient hospitalization or prolongation of existing hospitalization; or was medically significant (jeopardized the patient or could have required medical or surgical intervention to prevent one of the outcomes listed above).

3.2.5 Statistical Analysis

ERASURE, FIXTURE, and JUNCTURE were powered to show a difference between the two secukinumab doses versus placebo with respect to the co-primary end points (PASI 75 response and IGA mod 2011 0/1 response at week 12). In FIXTURE, the sample size was determined by the key secondary objective to demonstrate the non-inferiority of secukinumab versus etanercept with respect to PASI 75 response

at week 12. The IGA scale that was used in FIXTURE was different from the IGA scale used in etanercept studies (the IGA scale was modified in 2011 to a five-point scale whereas a six-point scale had been used in previous trials of biologics). Hence, comparisons of secukinumab versus etanercept were not performed for IGA. For all trials, a response rate of 5% for both PASI 75 and IGA mod 2011 score of 0/1 was assumed for placebo. The power to show a response rate of 55% for PASI 75 response and 30% for IGA mod 2011 0/1 response in the secukinumab groups based on Fisher's exact test was above 99%. Target sample sizes were 240 patients per group in ERASURE, 57 patients per treatment group in FEATURE and in JUNCTURE, and 316 patients per treatment group in FIXTURE. Power calculations for the analyses of key secondary outcomes were also carried out in ERASURE and FIXTURE. See Appendix 4: Testing Procedures and Power Calculations) for more details.

a) Analysis Populations

The randomized set included all patients who were randomized at the baseline visit. The full analysis set (FAS) included all patients to whom study treatment had been assigned and followed the intention-to-treat principle (i.e., patients were analyzed according to the treatment assigned at randomization). The safety set included all patients who took at least one dose of study drug during the treatment period; patients were analyzed according to treatment received. These definitions applied to all trials.

The per-protocol set (in FIXTURE) excluded patients in the randomized set who deviated from protocol (for example, patients who used prohibited medications or patients for whom there was accidental unblinding) and those who were non-compliant with treatment (see Section 3.2.3 for definition of compliance). This population was used in the non-inferiority testing of secukinumab versus etanercept.

b) Hypotheses and Testing Strategies

The statistical hypotheses being tested for PASI 75 response at week 12 and IGA mod 2011 0/1 response at week 12 was that there was no difference in the proportion of patients with PASI 75 response or IGA mod 2011 0/1 response at week 12 with secukinumab versus placebo. Hypotheses were also formulated for key secondary outcomes for ERASURE and FIXTURE. Closed testing procedures were used to evaluate the hypotheses. Hypotheses regarding the secukinumab doses were evaluated independently, each at the 0.025 significance level to control for type 1 error. See Appendix 4: Testing Procedures and Power Calculations) for more details.

c) Statistical Tests

The analysis of the co-primary outcomes (PASI 75 response at week 12 and IGA mod 0/1 response at week 12) was based on FAS. The primary analysis method was the stratified Cochran–Mantel–Haenszel (CMH) test. The tests were stratified by body weight (and geographical region in ERASURE and FIXTURE). In case of response rates of 0% or of 100% in one of the treatment groups, Fisher's exact test was applied instead of the cmH test.

The cmH test (or Fisher's exact test in case of a 0% or 100% response) was also used for the analyses of PASI 90 response at week 12 (secukinumab versus placebo); PASI 75 response at week 52 in secukinumab and etanercept patients with a PASI 75 response at week 12 (secukinumab versus etanercept in FIXTURE); IGA 0/1 response at week 52 in secukinumab and etanercept patients with an IGA 0/1 response at week 12 (secukinumab versus etanercept in FIXTURE); PASI 75, PASI 90, and IGA 0/1 responses at week 12 for superiority comparisons of secukinumab versus etanercept (in FIXTURE); and symptom response (for itching, scaling, and pain according to the PSD) at week 12. PASI 75 response at week 12 for non-inferiority comparisons of secukinumab versus etanercept was analyzed by Mantel–Haenszel risk difference (in FIXTURE).

The steps for the non-inferiority and superiority tests of secukinumab versus etanercept are shown in Appendix 4: Testing Procedures and Power Calculations), Figure 4. The non-inferiority comparisons of secukinumab versus etanercept were based on the CI approach. Non-inferiority was to be concluded when the lower limit of the 99.375% CI was greater than –10%, where 10% was the pre-defined non-inferiority margin (see Section d) Justification of Non-inferiority Margin).

For change from baseline in PSD at week 12, analyses of covariance with treatment, geographical region, and body weight stratum as exploratory variables, and baseline value as covariate, were performed.

The absolute value of and the percentage change from baseline in DLQI total score was analyzed with the van Elteren test (a non-parametric test similar to Wilcoxon rank sum test). Hodges-Lehmann estimates for the median, as well as confidence intervals (CIs), were derived for the absolute values and percentage change from baseline. For the number of patients achieving DLQI 0 or 1 (0/1; patients who reported no impairment in HRQoL), secukinumab groups were compared with placebo by means of Fisher's exact test.

For EQ-5D, the absolute change from baseline in the overall health state (visual analogue scale) was compared between treatments by analysis of repeated measures (no additional information provided in Clinical Study Reports on this test or its covariates).

d) Justification of Non-inferiority Margin

The non-inferiority margin for the comparison of secukinumab and etanercept was based on the results of three multi-centre, double-blind, placebo-controlled etanercept trials. The PASI 75 response rate after 12 weeks of treatment with etanercept 50 mg twice per week in the three studies was 0.46 (95% CI, 0.38 to 0.54) in Leonardi et al. 2003;[24] 0.46 (95% CI, 0.39 to 0.54) in Papp et al. 2005;[25] and 0.42 (95% CI, 0.38 to 0.48) in Tyring et al. 2006[26]. A meta-analysis of the three trials resulted in a response rate of 0.44 (95% CI, 0.40 to 0.48). A quarter of the lower limit of the CI of the pooled result of these three trials was chosen as the non-inferiority margin (25% of 40% = 10%).

e) Handling of Missing Data

- Missing baseline values were not imputed.
- If some post-baseline values were missing for PASI/ IGA outcomes, then non-responder imputation was applied. If all post-baseline values were missing, then the patient was excluded from the analysis.
- For patients who switched treatment after the induction period (i.e., placebo non-responders who escaped), PASI and IGA values from the induction period were not carried forward to the maintenance period).[20]
- For the PSD items (ERASURE and FIXTURE), four completed days were necessary to derive a weekly score (one to three missed days, consecutive or non-consecutive, were allowed). Any missing individual items were treated as missing data. Cases for which a weekly score could not be calculated (less than four completed days) were not included in the analysis.
- Other outcomes (for example EQ-5D, DLQI) were imputed with last observation carried forward (LOCF). Baseline values were not carried forward.
- Various sensitivity analyses were also performed.

3.3 Patient Disposition

Table 8 and Table 9 give the details of the patient disposition. Across the trials, most patients (≥ 92%) completed the induction period. The most common reasons for withdrawing from the trials during the induction period included patient choice and AEs. More than 80% of patients (except for JUNCTURE placebo patients) completed the maintenance period. The most common reasons for discontinuing treatment were AEs and lack of efficacy.

TABLE 8: PATIENT DISPOSITION, ERASURE, FEATURE, AND JUNCTURE

	ERASURE					FEATURE					JUNCTURE				
N (%)	SEC 150	SEC 300	PL			SEC 150	SEC 300	PL			SEC 150	SEC 300	PL		
Screened	951					209					220				
Randomized	245	245	248			59	59	59			61	60	61		
FAS	245	245	247			59	59	59			61	60	61		
Safety set	245	245	247			59	59	59			61	60	61		
Completed induction period	230 (94)	238 (97)	232 (94)			58 (98)	56 (95)	56 (95)			58 (95)	60 (100)	59 (97)		
Discontinued	15 (6)	7 (3)	16 (6)			1 (2)	3 (5)	3 (5)			3 (5)	0	2 (3)		
Reasons															
AEs	[redacted]														
Lost to follow-up	[redacted]														
Patient decision to withdraw consent	[redacted]														
Physician's decision	[redacted]														
Lack of efficacy	[redacted]														
Protocol deviation	[redacted]														
Pregnancy	[redacted]														
Entered maintenance period	230 (94)	238 (97)	232 (94)			58 (98.3)	56 (94.9)	56 (94.9)			58 (95)	60 (100)	59 (97)		
PL non-responders re-randomized	NA	NA	**SEC 150**	**SEC 300**	**PL**	NA	NA	**SEC 150**	**SEC 300**	**PL**	NA	NA	**SEC 150**	**SEC 300**	**PL**
			109	105[a]	18			29	27	0			28	28	3
Completed maintenance period	201 (82)	215 (88)	100 (92)	92 (88)	15 (83)	48 (81)	52 (88)	25 (86)	25 (93)	0	51 (84)	58 (97)	26 (93)	28 (100)	1 (33)
Discontinued	29 (13)	23 (10)	9 (8)	12 (11)	3 (17)	10 (17)	4 (7)	4 (14)	2 (7)	0	7 (12)	2 (3)	2 (7)	0	2 (67)
Reasons															
AEs	[redacted]														
Lost to follow-up	[redacted]														
Patient decision to withdraw consent	[redacted]														
Physician's decision	[redacted]														
Lack of efficacy	[redacted]														
Protocol deviation	[redacted]														
Non-compliance	[redacted]														
Pregnancy	[redacted]														
Death	[redacted]														

AE = adverse event; FAS = full analysis set; NA = not applicable; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg.

[a] One patient was missing from the analysis, and no explanation was provided in the Clinical Study Report.

Source: CADTH Common Drug Review submission[8] and Clinical Study Reports.[1,3,4]

TABLE 9: PATIENT DISPOSITION, FIXTURE

	FIXTURE					
N (%)	**SEC 150**	**SEC 300**	**ETA**	**PL**		
Screened	1,560					
Randomized	327	327	326	326		
FAS	327	327	326	325		
Safety set	327	326	323	327 [a]		
Per-protocol set	305	308	300	298		
Completed induction phase	315 (96)	312 (95)	305 (94)	301 (92)		
Discontinued	12 (4)	15 (5)	21 (6)	25 (8)		
Reasons						
AEs	[redacted]					
Lost to follow-up	[redacted]					
Patient decision to withdraw consent	[redacted]					
Physician's decision	[redacted]					
Lack of efficacy	[redacted]					
Protocol deviation	[redacted]					
Technical problem	[redacted]					
Entered maintenance phase	315	312	305	301		
				SEC 150	**SEC 300**	**PL**
PL non-responders re-randomized	NA	NA	NA	142	142	17
Completed maintenance phase	276 (84)	290 (89)	263 (81)	125 (88)	131 (92)	15 (88)
Discontinued	39 (12)	22 (7)	42 (14)	17 (12)	11 (8)	2 (12)
Reasons						
AEs	[redacted]					
Lost to follow-up	[redacted]					
Patient decision to withdraw consent	[redacted]					
Physician's decision	[redacted]					
Sponsor decision	[redacted]					
Lack of efficacy	[redacted]					
Protocol deviation	[redacted]					
Non-compliance	[redacted]					
Pregnancy	[redacted]					

AE = adverse event; ETA = etanercept; FAS = full analysis set; NA = not applicable; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; WD = withdrew consent.
[a] Two patients randomized to ETA received placebo instead.[2]
Source: CADTH Common Drug Review submission.[8]

3.4 Exposure to Study Treatments

Table 10 and Table 11 give the details of treatment exposure in the included trials. For the induction period, the median duration of exposure was [redacted] days for all treatment groups, across all trials. For the entire treatment period, median duration of exposure was approximately [redacted] days for the active groups and [redacted] days for the placebo groups.

TABLE 10: EXPOSURE TO STUDY TREATMENT, ERASURE, FEATURE, AND JUNCTURE (SAFETY SET)

	ERASURE			FEATURE			JUNCTURE		
	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL
Induction period, days									
N	245	245	247	59	59	59	61	60	61
Mean	82.4	84.1	82.0	84.1	82.4	81.3	82.1	84.4	82.0
SD	11.4	7.2	11.7	1.7	10.7	11.5	10.8	1.2	11.3
Median	[redacted]								
Min, Max	[redacted]								
Patient-years	[redacted]								
Entire treatment period, days									
N	353	349	247	[redacted]					
Mean	313.0	320.7	101.1	[redacted]					
SD	81.2	74.4	71.2	[redacted]					
Median	[redacted]								
Min, Max	[redacted]								
Patient-years	[redacted]								

Max = maximum; Min = minimum; NR = not reported; PL = placebo; SD = standard deviation; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg.
Source: Clinical Study Reports.[1,3,4]

TABLE 11: EXPOSURE TO STUDY TREATMENT, FIXTURE (SAFETY SET)

	FIXTURE			
	SEC 150	SEC 300	ETA	PL
Induction period, days				
N	327	326	323	327
Mean	83.3	82.8	82.6	81.7
SD	11.6	9.8	9.5	11.5
Median	[redacted]			
Min, Max	[redacted]			
Patient-years	[redacted]			
Entire treatment period, days				
N	469	467	323	327
Mean	317.5	320.7	331.9	95.3[a]
SD	75.4	75.3	89.7	61.0
Median	[redacted]			
Min, Max	[redacted]			
Patient-years	[redacted]			

ETA = etanercept; Max = maximum; Min = minimum; PL = placebo; SD = standard deviation; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; SD = standard deviation.
[a] Overall exposure to placebo was lower because of the early escape design.
Source: Clinical Study Report.[2]

3.5 Critical Appraisal

3.5.1 Internal Validity

Randomization was done by an electronic system (interactive response technology), which concealed treatment assignment from patients and investigators. The same electronic system was used for randomizing placebo patients who were PASI 75 non-responders at the start of the maintenance period.

The trials were blinded; the identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, schedule of administration, appearance, taste, and odour (see Section 3.2.3). FIXTURE included a double-dummy with etanercept injections and matching placebo-etanercept injections. Blinding was maintained throughout the trials, up to 52 weeks.

The trials used an early escape design. The majority of patients in the placebo groups changed their assigned treatment at week 12 after failure to obtain PASI 75. This limits the ability to make conclusions about the efficacy of secukinumab treatment beyond the week 12 time point, as randomization no longer holds. Secukinumab-treated patients who were non-responders at week 12 continued secukinumab treatment at their assigned dose to the end of the trial (i.e., they were not eligible for early escape), and hence they were given a longer period of time to respond to treatment. This study design may potentially bias the results in favour of secukinumab at week 52.

A margin of 10% was used in the non-inferiority test of secukinumab versus etanercept. The margin was obtained by pooling three trials comparing etanercept and placebo and using 25% of the lower limit of the CI. The clinical expert consulted for this review indicated that a margin of 10% or just below 10% is acceptable to suggest non-inferiority.

In FIXTURE, etanercept was chosen as the reference standard for comparison against secukinumab. Etanercept was administered at the recommended dose of 50 mg twice per week for 12 weeks, then at 50 mg weekly.[15] The manufacturer justified the choice of comparator by stating that: "Etanercept has been approved for the indication of psoriasis for over 5 years in most countries and is commonly accepted by dermatologists as an efficacious psoriasis treatment with a convenient delivery form and an acceptable safety profile. Its subcutaneous route of administration matches the route of secukinumab." (Clinical Study Report page 75).[2] The clinical expert consulted for this review indicated that etanercept is, in his opinion, the least effective of the biologics to treat psoriasis (also see Mixed Treatment Comparisons results in Appendix 7: Summary of Mixed Treatment Comparison). Thus, by using etanercept as the comparator, there was a greater likelihood that non-inferiority would be met. Similarly, the clinical expert indicated that, in his experience, infliximab is not a preferred treatment of patients because it is administered by infusion. A comparison of secukinumab versus adalimumab or versus ustekinumab would have been more appropriate.

The co-primary efficacy outcomes were PASI 75 response at week 12 and IGA mod 2011 0/1 response at week 12 in all four included trials. This is in keeping with the US Food and Drug Administration and the European Medicines Agency, which recommend that PASI and IGA be used together for evaluating the efficacy of new treatments for psoriasis.[27]

Multiplicity for secondary outcomes was accounted for in ERASURE and FIXTURE by using a sequential testing procedure (see Appendix 4: Testing Procedures and Power Calculations). Testing was done on two sets to correspond to the same secukinumab dose regimen (150 mg and 300 mg), each at the 0.025 level of significance, to control for type 1 error rate. In this procedure, statistical testing was only to be continued on subsequent outcomes when testing revealed statistical significance on the previous outcome for both sets. There were also outcomes that were tested that fell outside of the hierarchy, including results of secondary outcomes in FEATURE and JUNCTURE, most of the outcomes at week 52 for all four trials, the PSD in ERASURE, and the HRQoL outcomes (DLQI and EQ-5D) at weeks 12 and 52. Hence, there is uncertainty with respect to the comparative benefit of secukinumab for these outcomes, given the potential increased risk of type 1 error and the exploratory nature of the analyses.

The co-primary outcomes were evaluated by subgroups, which included weight at randomization (< 90 kg, ≥ 90 kg), exposure to previous systemic or biologic therapy, and failure on previous systemic or biologic therapy. Results should be interpreted with caution, as they are likely not adequately powered, given the small sample sizes, and were not adjusted for multiplicity. As patients were stratified by weight at randomization, it is expected that the known and unknown confounders would be equally distributed between treatment groups; however, for the other subgroups the randomization would not be maintained.

The symptoms of itching, pain, and scaling were included as secondary outcomes in the testing strategy for multiplicity of outcomes. However, not all centres had electronic diaries available to patients; when patients did have access to an electronic diary, they could have chosen not to use it. Thus, [redacted] ([redacted]%) patients in ERASURE and [redacted] ([redacted]%) patients in FIXTURE were diary completers. Of these, [redacted]% and [redacted]% were excluded from the analysis, respectively, which left a small subset of patients with usable data. It is unclear whether randomization would be maintained in this subset of study participants and whether potential confounders would be controlled for in the analyses of this outcome, given the potential risk of bias.

Patients who were using systemic therapies before enrolment in the trials were required to discontinue their medication. Washout periods of 6 to 12 months for biologics and 4 weeks for methotrexate and cyclosporine were to be completed before randomization. Thus, there was the potential for a worsening of the disease during the discontinuation period. This could have meant that the severity of the disease would have been augmented at baseline and not reflective of real disease activity in the patient.

Randomization was stratified by body weight. Patients who weighed less than or more than 90 kg were equally divided in FEATURE and JUNCTURE, whereas the division was approximately 60% versus 40% in ERASURE and 66% versus 34% in FIXTURE for patients < 90 kg and patients ≥ 90 kg, respectively. It was unclear why there were more patients weighing < 90 kg in these two studies, despite stratification.

3.5.2 External Validity

The trials included study sites at [redacted] Canadian centres for a total of [redacted] Canadian patients ([redacted]% of the total trial population).

The majority of patients included in the trials were men (62% to 77%), yet psoriasis affects males and females equally. Whether there are gender differences in treatment response is unknown. The clinical expert could only speculate that there would unlikely be a difference in treatment response based on gender, but only a trial could adequately address this question. Furthermore, the majority of patients (> 67%) were Caucasian, and less than [redacted]% of patients were aged 65 years or older.

In the included trials, patients were considered for inclusion if they had a PASI score of 12 or greater, IGA mod 2011 of 3 or greater, and total affected BSA 10% or more. The clinical expert consulted for this review indicated that these criteria are in line with what would be considered moderate to severe psoriasis. However, the PASI scores and total BSA at baseline were indicative of severe psoriasis (mean PASI > 20 and mean BSA > 30%). Furthermore, according to the clinical expert consulted for this review, patients with higher PASI score (more severe disease) are harder to treat. No subgroup analyses were done based on psoriasis severity. Thus, study results may not be generalizable to patients with lower disease activity, who may be candidates for treatment with a biologic.

Patients who were using systemic therapies before enrolment in the trials were required to discontinue their medication, and specific washout periods were determined. Washout periods are required in trials to ensure that the results obtained with the medication under study are not tainted by previous therapies. In clinical practice, it is unlikely there would be a washout period.

Only one-third of patients had previously received a biologic, which would indicate that patients were mostly biologic-naive. The clinical expert consulted for this review indicated that treatment history should not limit generalizability, as biologic drugs lose effect over time, and therefore both biologic-naive and biologic-experienced patients would be expected to have a similar response.

The trials included patients without regard to the location of their plaques (for example, knees or elbows, palms or soles, anal or genital psoriasis). Patient input comments from two patient group submissions revealed that many patients find lesion location to be as important as extent of coverage. Patients report that the presence of lesions in sensitive areas may affect their perceptions of their own attractiveness and sexuality. For example, patients who suffer from anal or genital psoriasis may rate their quality of life as being more impaired than patients whose psoriasis is limited to knees or elbows.

Dermatologists may or may not use the DLQI instrument in clinical practice, because this instrument is a subjective measure of HRQoL, according to the CDR clinical expert.

PSDs were not collected from all patients, as electronic diaries were not available for all trial patients or patients decided not to use one. As a result, data were collected in approximately 26% of patients. This limits the generalizability of the symptom diary results.

The trials collected harms information on secukinumab for up to 52 weeks. Chronic psoriasis requires lifelong treatment, and a 52-week trial may not be sufficiently long to determine the incidence of certain adverse events such as malignancy. Extension trials were made available to patients who wished to continue secukinumab treatment, and these trials are ongoing.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2). See Appendix 5: Detailed Outcome Data for detailed efficacy data. Results are summarized in Table 12. In the trials, secukinumab 150 mg and secukinumab 300 mg were evaluated. However, Health Canada's Notice of Compliance includes only the 300 mg dose. Since the CDR review was started before the Notice of Compliance was granted, both doses of secukinumab were included in the CDR review.

Closed testing procedures were used to evaluate the hypotheses, with each secukinumab dose evaluated independently at the 0.025 significance level. All trials achieved statistical significance for the co-primary outcomes and secondary efficacy outcomes in ERASURE and FIXTURE, and hence hierarchical testing was not stopped (see Appendix 4: Testing Procedures and Power Calculations).

Of note, there were N = 18 and N = 17 total placebo patients in ERASURE and FIXTURE, respectively, at week 52.

3.6.1 Psoriasis Area and Severity Index

a) PASI 75 Response at Week 12

PASI 75 response at week 12 was a co-primary outcome in all of the included trials, and results are detailed in Table 14, Table 15, and Table 16. The proportion of patients obtaining PASI 75 was statistically significantly higher with secukinumab 150 mg and secukinumab 300 mg compared with placebo ($P < 0.0001$ for all comparisons). Responses ranged from 67% to 72% for secukinumab 150 mg and from 76% to 87% for secukinumab 300 mg, compared with 0% to 5% for placebo. The risk differences in FEATURE and JUNCTURE were 69.5% (95 CI%, 53.9% to 81.4%) and 68.4% (95% CI, 53.1% to 79.8%) for the 150 mg dose compared with placebo, and 75.9% (95% CI, 61.5% to 86.1%) and 83.4% (95% CI, 70.7% to 91.7%) for the 300 mg dose compared with placebo, respectively. The odds ratios in ERASURE and FIXTURE were 57.6 (95% CI, 28.4 to 116.9) and 42.8 (95% CI, 23.6 to 77.6) for the 150 mg dose compared with placebo, and 82.7 (95% CI, 38.7 to 176.7) and 66.0 (95% CI, 36.1 to 120.6) for the 300 mg dose compared with placebo, respectively.

Non-inferiority of secukinumab 150 mg versus etanercept and secukinumab 300 mg versus etanercept for PASI 75 at week 12 was concluded in the per-protocol analysis, as the lower limit of the 99.375% CI was greater than –10%, where 10% was the pre-defined non-inferiority margin. The risk differences were [redacted]% (lower CI, [redacted]%) and [redacted]% (lower CI, [redacted]%) with secukinumab 150 mg and secukinumab 300 mg, respectively, compared with etanercept. Findings of the FAS analysis supported non-inferiority (lower CI 14.1% with secukinumab 150 mg and 24.1% with secukinumab 300 mg). [redacted].

Subgroups Based on Weight (< 90 kg or ≥ 90 kg)

[redacted]

Subgroups Based on Previous Treatments

[redacted] (Table 5 and Table 6). [redacted] No statistical comparisons were conducted between treatment groups within each subgroup.

Subgroups Based on Comorbid Psoriatic Arthritis

This subgroup was identified a priori in the systematic review protocol; however, analyses were not conducted for patients with PsA for PASI 75 at week 12.

b) PASI 90 Response at Week 12

PASI 90 response at week 12 was a key secondary outcome included in the closed testing for multiplicity of outcomes. Statistically significantly higher responses were obtained with secukinumab 150 mg (39% to 46% of patients with a response) and secukinumab 300 mg (54% to 60% of patients with a response) compared with placebo (less than 2% of placebo patients with a response, $P < 0.0001$ for all comparisons; Table 14 and Table 15).

c) PASI 75 Response at Week 52

Results for PASI response at week 52 are detailed in Table 17, Table 18, Table 19, and Table 20. Because of the early escape study design used in the trials, only a small number of patients remained in the placebo group after the induction period. Hence, there were insufficient placebo patients to conduct a comparison against secukinumab.

Maintenance of PASI 75 at week 52 in secukinumab patients who were responders at week 12 was achieved in 72% and 82% of secukinumab 150 mg patients and in 81% and 84% of secukinumab 300 mg patients in ERASURE and FIXTURE, respectively. Placebo responders at week 12 who maintained a PASI 75 response at week 52 included 12/18 (67%) patients in ERASURE and 10/17 (59%) patients in FIXTURE.

In FIXTURE, 73% of etanercept patients who were responders at week 12 maintained PASI 75 at week 52 (the end of the maintenance phase), and the differences between secukinumab 150 mg and etanercept and secukinumab 300 mg and etanercept were statistically significant ($P = 0.0119$ and $P = 0.0022$, respectively; Table 20).

d) Timing of PASI 75 Response

Time to PASI 75 response was not an outcome identified in the protocol. However, the highest proportion of patients achieving PASI 75 response was seen at week 16 with secukinumab 150 mg and at week 15 with secukinumab 300 mg in ERASURE, and at week 20 with secukinumab 150 mg and at week 16 with secukinumab 300 mg in FIXTURE (Figure 5 and Figure 6). Response decreased slightly over time. Additional information was provided by the manufacturer that showed 86% of patients achieved PASI 75 at week 16, compared with 77% to 82% of patients at week 12.[20]

3.6.2 Investigator's Global Assessment

a) IGA 0/1 Response at Week 12

IGA 0/1 response at week 12 was a co-primary outcome in all of the included trials and results are detailed in Table 21 and Table 22. Statistically significantly more patients obtained IGA 0 or IGA 1 response with secukinumab 150 mg or secukinumab 300 mg compared with placebo ($P < 0.0001$ for all comparisons). The proportion of patients obtaining IGA 0/1 ranged from 51% to 53% for secukinumab 150 mg and from 63% to 73% for secukinumab 300 mg compared with 0% to 3% for placebo. The risk differences in FEATURE and JUNCTURE were 52.5% (95 CI%, 35.1% to 67.2%) and 53.3% (95% CI, 36.6% to 66.7%) for the 150 mg dose compared with placebo, and 69.0% (95% CI, 53.5% to 80.5%) and 73.3% (95% CI, 58.8% to 83.9%) for the 300 mg dose compared with placebo, respectively. The odds ratios in ERASURE and FIXTURE were 44.2 (95% CI, 18.2 to 107.24) and 40.6 (95% CI, 19.8 to 83.4) for the 150 mg dose compared with placebo, and 70.5 (95% CI, 28.8 to 172.7) and 79.1 (95% CI, 36.0 to 174.1) for the 300 mg dose compared with placebo, respectively ($P < 0.0001$ for all comparisons). Statistically significant results were also obtained for secukinumab 150 mg versus etanercept and secukinumab 300 mg versus etanercept ($P < 0.0001$ for both comparisons; Table 22).

Subgroups Based on Weight

[redacted]

Subgroups Based on Previous Treatments

[redacted]

b) IGA 0/1 at Week 52

Results for IGA 0 /1 at week 52 are detailed in Table 23, Table 24, Table 25, and Table 26. Because of the early escape study design used in the trials, only a small number of patients remained in the placebo group after the induction period. Hence, there were insufficient placebo patients to conduct a comparison against secukinumab.

Maintenance of IGA 0/1 at week 52 in secukinumab patients who were responders at week 12 was achieved in 59% and 68% of secukinumab 150 mg patients and in 74% and 80% of secukinumab 300 mg patients in ERASURE and FIXTURE, respectively. Placebo responders at week 12 who maintained IGA 0/1 at week 52 included 7/18 (39%) patients in ERASURE and 5/17 (29%) patients in FIXTURE.

In FIXTURE, 57% of etanercept patients who were responders at week 12 maintained IGA 0/1 at week 52 (the end of the maintenance phase), and the difference between secukinumab 300 mg and etanercept was statistically significant (OR = 3.2; 95% CI, 1.8 to 5.5, $P < 0.0001$; Table 26).

c) Timing of IGA 0/1 Response

Time to IGA 0/1 response was not an outcome identified in the protocol. However, the highest proportion of patients achieving IGA 0/1 response was seen at week 16 with secukinumab 150 mg and at week 15 with secukinumab 300 mg in ERASURE, and at week 16 with secukinumab 150 mg and with secukinumab 300 mg in FIXTURE (Figure 7 and Figure 8). Response decreased slightly over time.

3.6.3 Symptoms of Psoriasis

Symptoms of pain, itching, or rash were measured with the PSD for a small subset of patients (approximately 26%) in ERASURE and FIXTURE (Table 27, Table 28, and Table 29). The comparisons of secukinumab versus placebo at week 12 for these three symptoms were included in the testing procedure for multiplicity of outcomes; however, the comparisons of secukinumab versus etanercept were exploratory analyses.

A higher percentage of patients receiving secukinumab and etanercept reported a decrease in itching compared with placebo: [redacted]% to [redacted]% of patients with secukinumab 150 mg, [redacted]% with secukinumab 300 mg, [redacted]% with etanercept, and [redacted]% with placebo reported a response. Results were [redacted] for both doses of secukinumab versus placebo ([redacted]).

A [redacted] of patients receiving both doses of secukinumab ([redacted]% to [redacted]% of patients reported a response) reported a decrease in pain compared with placebo ([redacted]% to [redacted]% of patients reported a response, [redacted] for all comparisons). The percentage of patients on etanercept was [redacted]% with a response.

A [redacted] of patients receiving both doses of secukinumab ([redacted]% to [redacted]% of patients reported a response) reported reduced scaling compared with placebo ([redacted]% to [redacted]% of patients reported a response, [redacted] for all comparisons). The percentage with etanercept-treated patients was [redacted]% with a response.

The least squares mean differences in absolute change from baseline to week 12 for the outcomes of itching, pain, and scaling were [redacted]

For the comparisons of secukinumab 150 mg versus etanercept and secukinumab 300 mg versus etanercept, the least squares mean differences were [redacted]

3.6.4 Body Surface Area

This was not an outcome of interest in the included trials.

3.6.5 Health-Related Quality of Life

HRQoL was measured with DLQI and EQ-5D at week 12 (all trials) and week 52 (ERASURE and FIXTURE). Statistical testing was done; however, these outcomes were not included in the testing procedure for multiplicity, and results should be considered exploratory.

a) Dermatology Life Quality Index

DLQI was reported as total score and as proportion of patients with a DLQI response of 0/1 (no impairment in HRQoL) at week 12 (Table 30 and Table 31) and week 52 (Table 32 and Table 33).

The median difference in DLQI total score at week 12 ranged from [redacted] to [redacted] when comparing secukinumab with placebo across all treatment groups and trials. The median difference in DLQI total score at week 12 was [redacted] when comparing secukinumab (both doses) with etanercept. Compared with placebo, the per cent change from baseline in DLQI total score at week 12 ranged from [redacted]% to [redacted]% for secukinumab 150 mg and from [redacted]% to [redacted]% for secukinumab 300 mg. Compared with etanercept, the difference in change from baseline in DLQI total score was [redacted]% for secukinumab 150 mg and [redacted]% for secukinumab 300 mg.

Patients with DLQI response of 0/1 at week 12 ranged from 46% to 59% with secukinumab 150 mg, 55% to 75% with secukinumab 300 mg, 35% with etanercept, and 7% to 15% with placebo.

At week 52, median DLQI total score was [redacted] to [redacted] with secukinumab 150 mg and [redacted] to [redacted] with secukinumab 300 mg compared with [redacted] and [redacted] with placebo. The per cent change from baseline ranged from [redacted]% to [redacted]% with secukinumab 150 mg, [redacted]% to [redacted]% with secukinumab 300 mg, [redacted]% with etanercept, and [redacted]% and [redacted]% with placebo.

The proportion of patients with DLQI response of 0/1 ranged from [redacted]% to [redacted]% with secukinumab 150 mg, [redacted]% to [redacted]% with secukinumab 300 mg, [redacted]% with etanercept, and [redacted]% and [redacted]% of placebo responders.

b) EuroQol Five-Dimension Health-Related Quality of Life Questionnaire

EQ-5D was measured with VAS at week 12 (Table 34 and Table 35) and at week 52 (Table 36 and Table 37).

The absolute median change from baseline in EQ-5D VAS was [redacted] with secukinumab 150 mg (change from baseline of [redacted]% to [redacted]%), [redacted] with secukinumab 300 mg (change from baseline of [redacted]% to [redacted]%), [redacted] with etanercept ([redacted]% change from baseline), and [redacted] with placebo ([redacted]% to [redacted]% change from baseline).

Comparing secukinumab with placebo, the differences in absolute change from baseline in EQ-5D VAS ranged from [redacted] across treatment groups and trials. The differences in absolute change from baseline were [redacted] for secukinumab 150 mg versus etanercept and secukinumab 300 mg versus etanercept, respectively.

At week 52, placebo responders reported absolute median change from baseline of [redacted] and median per cent change from baseline of [redacted]% and [redacted]%, whereas secukinumab groups reported absolute median change from baseline of [redacted] and median per cent change from baseline of [redacted]% to [redacted]% across treatment groups and trials.

TABLE 12: KEY EFFICACY OUTCOMES

	ERASURE			FEATURE			JUNCTURE			FIXTURE		
	SEC vs. PL (FAS)											
	SEC 150	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**
N	245	245	247	59	59	59	61	60	61	327	327	325
Patients with PASI 75 at week 12[a,b]												
n/N	174/243	200/245	11/246	41/59	44/58	0/59	43/60	52/60	2/61	219/327	249/323	16/324
%	71.6	81.6	4.5	69.5	75.9	0	71.7	86.7	3.3	67.0	77.1	4.9
RD or OR	[redacted]											
95% CI	[redacted]											
P value	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	––
Patients with PASI 75 who were previously exposed to and failed systemic therapy (week 12)[b]												
n/N	[redacted]											
%	[redacted]											
Maintenance of PASI 75 at week 52 in SEC patients who were responders at week 12												
n/N	126/174	161/200	NA	NR	NR	NR	NR	NR	NR	180/219	210/249	NA
%	72.4	80.5	NA	NR	NR	NR	NR	NR	NR	82.2	84.3	NA
Patients with IGA 0/1 at week 12[a,b]												
n/N	125/244	160/245	6/246	31/59	40/58	0/59	32/60	44/60	0/61	167/327	202/323	9/324
%	51.2	65.3	2.4	52.5	69.0	0	53.3	73.3	0	51.1	62.5	2.8
RD or OR	[redacted]											
95% CI	[redacted]											
P value	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	–
Patients with IGA 0/1 who were previously exposed to and failed systemic therapy (week 12)[b]												
n/N	[redacted]											
%	[redacted]											
Maintenance of IGA 0/1 at week 52 in SEC patients who were responders at week 12												
n/N	74/125	119/160	NA	NR	NR	NR	NR	NR	NR	113/167	161/202	NA
%	59.2	74.4	NA	NR	NR	NR	NR	NR	NR	67.7	79.7	NA
DLQI total score at week 12 (LOCF)[c]												
N	[redacted]											
Median	[redacted]											
95% CI	[redacted]											

	ERASURE			FEATURE			JUNCTURE			FIXTURE		
Difference vs. PL												
95% CI												
SEC vs. ETA, Non-inferiority Analysis (Per-Protocol)												
	SEC 150	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**ETA**
N	NA	NA	NA	NA	NA	NA	NA	NA	NA			
Patients with PASI 75 at week 12[b,d,e]												
n/N	NA	NA	NA	NA	NA	NA	NA	NA	NA			
%	NA	NA	NA	NA	NA	NA	NA	NA	NA			
RD	NA	NA	NA	NA	NA	NA	NA	NA	NA			
95% CI	NA	NA	NA	NA	NA	NA	NA	NA	NA			
1-sided CI	NA	NA	NA	NA	NA	NA	NA	NA	NA			

CI = confidence interval; DLQI = Dermatology Life Quality Index; ETA = etanercept; FAS = full analysis set; IGA = Investigator's Global Assessment; LOCF = last observation carried forward; NA = not applicable; NR = not reported; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PL = placebo; RD = risk difference; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.

[a] Cochran–Mantel–Haenszel test (ERASURE and FIXTURE) and Fisher's exact test (FEATURE and JUNCTURE).

[b] Based on non-responder imputation.

[c] Hodges-Lehmann estimates and van Elteren test.

[d] Mantel–Haenszel risk difference.

[e] Non-inferiority margin is 10%.

Source: Clinical Study Reports.[1-4]

3.7 Harms

Only those harms identified in the review protocol are reported below (Section 2.2). See Appendix 5: Detailed Outcome Data for detailed harms data. Results are summarized in Table 13. Because of the escape study design, AEs and SAEs for the entire treatment period were adjusted based on exposure and reported as incidence rate (IR) per 100 patient-years (PY) in ERASURE and FIXTURE. IRs for some of the notable harms were also available in FEATURE and JUNCTURE. Of note, after week 12, there were only 18 and 17 placebo patients left in ERASURE and FIXTURE, respectively. Hence, the harms data reported in the entire treatment period are based mainly on 12-week data and data for the 25 placebo patients after week 12.

3.7.1 Adverse Events

In the induction period, 58% to 64% (range of outcomes among studies) of patients receiving secukinumab 150 mg and 51% to 70% of patients receiving secukinumab 300 mg reported experiencing at least one AE (Table 38). With placebo and etanercept, 47% to 54% of patients, and 58% of patients, respectively, reported at least one AE. The most frequently reported AEs included nasopharyngitis, headache, diarrhea, pruritus, and hypertension. These AEs were more commonly seen with secukinumab than with placebo. These did not appear to be dose-related, although formal statistical testing was not conducted for differences.

For the entire treatment period, IRs were 236 and 270 per 100 PYs for secukinumab 150 mg, 246 and 252 per 100 PYs for secukinumab 300 mg, 323 and 330 per 100 PYS for placebo, and 243 per 100 PYs for etanercept (FIXTURE and ERASURE, respectively; Table 38). The most common AEs included nasopharyngitis (highest IR reported with etanercept); upper respiratory tract infection and diarrhea (highest IRs with secukinumab); headache, pruritus, arthralgia and nausea (highest IRs with placebo); and hypertension and influenza (IRs similar across treatment groups).

3.7.2 Serious Adverse Events

In the induction period, few patients experienced a SAE. With secukinumab, 0% to 5% (range of outcomes among studies) of patients experienced a SAE. With placebo and etanercept, there were approximately 2% and 1% of patients experiencing a SAE, respectively. For the entire treatment period, IRs were similar across trials and treatment groups, with IRs ranging from six to eight per 100 PYs. For both treatment periods, the types of SAEs were varied, with only one or two patients experiencing an event for each SAE; SAEs identified as a notable harm in the protocol are presented in Table 39.

3.7.3 Withdrawals Due to Adverse Events

In the induction period, 2% or less of patients withdrew from treatment due to an AE. For the entire treatment period, the proportions of patients withdrawing from treatment were as follows: 1% to 5% (range of outcomes among studies) with secukinumab 150 mg; 0% to 4% with secukinumab 300 mg; 4% with etanercept; and 1% to 2% with placebo. For both periods, the reasons for withdrawing from treatment were varied; WDAEs identified as a notable harm in the protocol are presented in Table 40.

3.7.4 Mortality

A total of two patients died (in FEATURE); one patient who had received secukinumab 150 mg died due to a cardiac arrest, and one patient who had received placebo in the induction period followed by secukinumab 300 mg at re-randomization died as a result of alcohol poisoning.

3.7.5 Notable Harms

Harms of interest included infection (reported as infestations and infections in the trials), urticaria, anaphylaxis, cardiac event (reported as cardiac disorders or major adverse cardiovascular events in the trials), lupus-like syndrome or exacerbation of lupus, exacerbation of psoriasis, malignancy, and neurological AEs (reported as nervous system disorders in the trials; Table 41).

No AEs of lupus-like syndrome or exacerbation of lupus were reported in the induction period or during the entire treatment period.

During the induction period, infections and infestations were frequent and occurred in 15% to 43% of secukinumab patients, in 15% to 31% of the placebo groups, and in 25% of etanercept patients. Nervous system disorders were reported in 7% to 12% of secukinumab patients, in 5% to 10% of placebo patients, and in 9% of etanercept patients. The other notable harms (cardiac disorders or major adverse cardiovascular events, malignancy, exacerbation of psoriasis, urticaria, and anaphylactic reactions) were infrequently reported.

For the entire treatment period, IRs reported for infestations and infections ranged among studies from 85 to 129 per 100 PYs for secukinumab patients, from 80 to 144 per 100 PYs for placebo groups, and 91 per 100 PYs for etanercept patients. IRs reported for nervous system disorders in secukinumab patients ranged from 14 to 28 per 100 PYs, 25 and 42 per 100 PYS for placebo patients, and 21 per 100 PYs for etanercept patients. The other notable harms were infrequently reported.

TABLE 13: SUMMARY OF HARMS (SAFETY SET)

	ERASURE			FEATURE			JUNCTURE			FIXTURE			
	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	ETA
Induction Period, n (%)													
N	245	245	247	59	59	59	61	60	61	327	326	327	323
Patients > 0 AEs													
n	148	135	116	34	30	28	39	42	33	191	181	163	186
%	60.4	55.1	47.0	57.6	50.8	47.5	63.9	70.0	54.1	58.4	55.5	49.8	57.6
Patients > 0 SAEs													
n	4	6	4	0	3	1	3	1	1	7	4	6	3
%	1.6	2.4	1.6	0	5.1	1.7	4.9	1.7	1.6	2.1	1.2	1.8	0.9
Patients > 0 WDAEs													
n	5	3	4	0	1	1	0	0	1	2	4	6	3
%	2.0	1.2	1.6	0	1.7	1.7	0	0	1.6	0.6	1.2	0.9	1.9
Deaths													
n	0	0	0	0	0	0	0	0	0	0	0	0	0
Entire Treatment Period, n (%)													
N	353	349	247	[redacted]						469	467	327	323
Patients > 0 AEs													
n	287	286	124	[redacted]						364	376	168	253
%	81.3	81.9	50.2	[redacted]						77.6	80.5	51.4	78.3
IR / 100 PY	270	246	323	[redacted]						236	252	330	243

	ERASURE			FEATURE			JUNCTURE			FIXTURE			
	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	ETA
Patients > 0 SAEs													
n	19	19	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24	27	7	20
%	5.4	5.4	2.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5.1	5.8	2.1	6.2
IR / 100 PY	6	6	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6	7	8	7
Patients > 0 WDAEs													
n	18	12	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10	14	3	12
%	5.1	3.4	2.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.1	3.0	0.9	3.7
Deaths													
n	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
%	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0

AE = adverse event; ETA = etanercept; IR = incidence rate; NR = not reported; PL = placebo; PY = patient-year; SAE = serious adverse event; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports.[1-4]

4. DISCUSSION

4.1 Summary of Available Evidence

Four multi-centre, double-blind, parallel-group, randomized, placebo-controlled phase 3 trials were included in the systematic review: ERASURE (N = 738), FEATURE (N = 177), JUNCTURE (N = 182), and FIXTURE (N = 1,306). The trials enrolled adult patients with moderate to severe chronic plaque psoriasis that was inadequately controlled by topical treatments, phototherapy, or previous systemic therapy. The co-primary efficacy outcomes were PASI 75 response at week 12 and IGA mod 2011 0/1 response at week 12 in all four included trials.

The trials consisted of four periods: screening (one to four weeks), induction (12 weeks), maintenance (40 weeks), and follow-up (eight weeks). At induction, patients were randomized to subcutaneous secukinumab 150 mg, secukinumab 300 mg, or placebo, and treatment was administered at weeks 0, 1, 2, 3, 4, and 8. FIXTURE included an active control group of subcutaneous etanercept 50 mg twice weekly. In the maintenance period, patients who received secukinumab 150 mg or secukinumab 300 mg in the induction period continued monthly secukinumab treatment; the last dose was given at week 48. For patients on etanercept (FIXTURE), the dose decreased to 50 mg once weekly at the start of the maintenance period. Non-responders (PASI < 75) from the placebo groups were re-randomized to secukinumab 150 mg or secukinumab 300 mg for the remainder of the study. Placebo responders (PASI ≥ 75) continued on placebo.

All four trials allowed early escape or crossover to secukinumab at week 12. The early escape design is common in modern psoriasis and rheumatological drug trials based on ethical considerations, but the study design has numerous limitations, which potentially limit the interpretation and clinical relevance of results after this time point. Generalizability of findings from all four trials may be limited, as the majority of enrolled patients were Caucasian, male, aged 65 years or younger, and had severe psoriasis.

4.2 Interpretation of Results

4.2.1 Efficacy

The co-primary outcomes were PASI 75 response at week 12 and IGA 0/1 response at week 12. The proportion of patients obtaining PASI 75 and IGA 0/1 responses at week 12 was statistically significantly higher with both doses of secukinumab than with placebo. The majority of patients receiving secukinumab 150 mg and secukinumab 300 mg who were responders at week 12 maintained PASI 75 or IGA 0/1 response at week 52. Similarly, a large proportion of placebo responders at week 12 maintained PASI 75 or IGA 0/1 response at week 52. The clinical expert explained that flares of psoriasis may be related to stress and may have a psychological component. The extra attention and care given to patients during a clinical trial, the greater willingness for making lifestyle changes, and the increased compliance with emollients may to some extent contribute to a reduction in plaques and symptoms of psoriasis. Hence, the magnitude of response to secukinumab could potentially be lower in a real-world setting.

PASI 75 and IGA 0/1 response rates according to body weight (< 90 kg and ≥ 90 kg) suggested a potential efficacy difference based on weight, although no formal testing was conducted. The lower efficacy in heavier patients could lead to off-label use of higher doses of secukinumab (for example, 450 mg), which would be inconsistent with the recommended dosage regimen recently approved by Health Canada. Such an increase in dose would increase the cost of therapy and potentially expose patients to a higher likelihood of AEs. However, a formal test of dose difference based on weight was not part of the statistical plan. At baseline, 54% to 76% of patients had previously been treated with systemic therapies.

This means that one-quarter to half of trial patients had never tried prior systemic therapies at baseline. No subgroup analysis was conducted for systemic treatment-naive patients. Moreover, treatment failure, according to the manufacturer, was defined as an inadequate response or intolerance to treatment, as reported by the patient. The fact that prior treatment failure could potentially be determined by the patient introduces uncertainty concerning whether all patients who were classified as having prior treatment failure did, in fact, experience treatment failure. Nonetheless, patients with failure of previous systemic therapies responded to secukinumab; however, the response was less than what was achieved in the overall trial population. This was also true for patients with or without a history of biologics use: those who failed previous biologic therapies responded to secukinumab, although IGA 0/1 response was more noticeable with secukinumab 300 mg. No subgroup analysis was done in biologic-naive patients, although the majority of patients reported never having been exposed to biologics. The clinical expert consulted for this review indicated that treatment history should not matter, as biologic drugs lose effect over time, and therefore both biologic-naive and biologic-experienced patients would be expected to have a similar response.

One trial included a head-to-head comparison of secukinumab and etanercept. Non-inferiority was concluded, as the lower limit of the 99.375% CI was greater than –10%, where 10% was the pre-defined non-inferiority margin of PASI 75 response at week 12. Furthermore, PASI 75 responses at week 12 were greatest with secukinumab, and statistically significant results were obtained in a superiority test as well. According to the clinical expert consulted for this review, etanercept is the least effective biologic to treat psoriasis when used in clinical practice, and a comparison of secukinumab with another biologic such as adalimumab or ustekinumab would have been preferable. A manufacturer-sponsored mixed treatment comparison (MTC) is summarized in Appendix 7: Summary of Mixed Treatment Comparison. The MTC compared secukinumab with adalimumab, etanercept, infliximab, methotrexate, ustekinumab, and etanercept-methotrexate combination for the outcome of PASI 75 response at week 12. As the MTC included trials which were conducted with dosage regimens not aligned with the recommended doses in product monographs, the CDR review considered regimens used at therapeutic doses. It was shown that there [redacted] secukinumab 300 mg and infliximab. Secukinumab 300 mg [redacted] adalimumab, etanercept, etanercept-methotrexate combination, methotrexate, and ustekinumab. Key limitations of the MTC included a lack of comparisons with acitretin, apremilast, or cyclosporine, a lack of analyses of harms, heterogeneous populations across trials, and a low number of trials per comparison.

PASI 90 response was a key secondary outcome; it was included in the closed testing procedure for multiplicity of outcomes in two trials. One-third to half of secukinumab patients achieved PASI 90 at week 12 compared with less than 2% of placebo patients. The clinical expert indicated that the number of responses with PASI 90 was better than what has been seen with other drugs in clinical practice.

Based on input received from two patient groups, patients reported that symptoms of psoriasis interfered with their daily lives, and they hoped that secukinumab would improve their symptoms. In the included trials, symptoms of itching, scaling, and pain were measured at week 12 with the use of an electronic diary in two trials. Patients reported statistically significant improvements in these three symptoms with secukinumab compared with placebo. The MCID for the PSD is estimated to be 2.0 to 3.0, and hence patients would have experienced a clinically relevant decrease in symptoms. For the comparisons of secukinumab 150 mg versus etanercept and secukinumab 300 mg versus etanercept, the least squares mean differences were small and unlikely to be clinically significant, as the differences did not reach MCID. However, not all study centres had electronic diaries available to patients, and hence

only 26% of patients had enough data at week 12 for inclusion in the analyses. Hence, these results would not be generalizable to the general population and should be interpreted with caution.

Patient groups commented on how their disease affected their quality of life. They stated that patients may experience depression and loss of sleep, and the presence of lesions in sensitive areas may affect their perceptions of their own attractiveness and sexuality, which may negatively affect their personal relationships. HRQoL was measured using DLQI and EQ-5D VAS. Compared with placebo, secukinumab patients reported improvement in DLQI and in EQ-5D VAS. The difference in DLQI total score between secukinumab and placebo ranged from [redacted] to [redacted] at the week 12 visit, which is greater than the MCID of 3. DLQI response of 0/1 was achieved in more than half of secukinumab patients at week 12; response was sustained to the week 52 visit. The clinical expert consulted for this review pointed out that patients who suffer from anal or genital psoriasis may rate their quality of life as more impaired than that of patients whose psoriasis is located in other areas of the body. In this respect, the change from baseline in DLQI may be greater in one set of patients than another, depending on location and perception of bothersomeness of the disease. Since location of psoriasis was not reported in the trials, the HRQoL results may not be generalizable to all patients.

4.2.2 Harms

Over the course of the four trials, two patients died. One patient in the secukinumab 150 mg group died due to a cardiac arrest, and one patient who had received placebo in the induction period followed by secukinumab 300 mg at re-randomization died as a result of alcohol poisoning.

In the patient group submissions, it was noted that adverse effects are a significant concern for patients being treated for psoriasis. Patients are concerned about the well-known adverse effects associated with systemic therapies and particularly with the various harms associated with the small-molecule inhibitors such as cyclosporine and methotrexate. There were very few SAEs, and very few withdrawals due to AEs in the induction periods and over the course of the secukinumab trials. The types of SAEs and WDAEs were varied, with only one or two patients experiencing each event. The clinical expert commented that biologics are associated with very few AEs and, in clinical practice, patients rarely discontinue treatment because of an AE. In the trials, the incidence of AEs did not appear to be related to dose, although no formal statistical testing was done to verify this. The most common AEs included nasopharyngitis, headache, diarrhea, pruritus, and hypertension, which occurred more frequently with secukinumab than with placebo. Few placebo patients did not escape to secukinumab treatment at week 12, and thus comparison with placebo is limited owing to a small sample size. The MTC did not consider harm in the analysis, and comparative information with other drugs is not available. This is unfortunate because, as mentioned previously, AEs are a significant concern for patients. Comparative safety data would assist physicians and patients in treatment choices.

The major concern with biologics comes from the potential increase in infection and malignancy. For the entire treatment period, the incidence rates of infections and infestations ranged from 85 to 125 per 100 PYs with secukinumab, and the incidence rates of malignancy was less than 3 per 100 PYs. However, chronic psoriasis requires lifelong treatment, and a 52-week trial may not be sufficiently long to determine the incidence of long-term AEs such as malignancy. Extension trials are ongoing.

Other than malignancy and infections, notable harms identified by the clinical expert included urticaria, anaphylaxis, cardiac events, lupus-like syndrome or exacerbation of lupus, exacerbation of psoriasis, and neurological events. Patients at high risk for immune-related AEs are typically excluded from trials evaluating biologics. As a result, patients with lupus and patients with neurological disorders such as

multiple sclerosis would have been excluded from enrolling in the trials. There were no reports of lupus-like syndrome or exacerbation of lupus. Neurological events, termed "nervous system disorders" in data collection, had incidence rates ranging from 41 to 81 100 PYs with secukinumab. There were few cases of other notable harms (urticaria, anaphylaxis, cardiac events, and exacerbation of psoriasis) reported.

4.3 Other Considerations

1. Part-way through the CDR review, secukinumab received its Notice of Compliance for the treatment of plaque psoriasis. The recommended dose is secukinumab 300 mg, administered weekly at weeks 0, 1, 2, and 3, then monthly starting at week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg each.

2. The induction period in each trial was 12 weeks (doses given at weeks 0, 1, 2, 3, 4, and 8), and the primary and key secondary analyses were conducted based on 12-week data. Yet the listing criterion requested by the manufacturer is that an initial response be assessed after 16 weeks (i.e., two extra doses of secukinumab would be given). Data on time to PASI 75 response (an outcome not identified in the CDR protocol) were available up to 12 weeks. Other data were provided that showed the proportion of patients with a PASI 75 response and IGA 0/1 response was highest at weeks 15 or 16 for secukinumab 300 mg (PASI 75 achieved in approximately 86% of patients at week 16 compared with 77% to 82% of patients at week 12). The clinical expert consulted for this review indicated that, while total efficacy may not be assessable at 12 weeks, a patient would be expected to have a good response to a biologic drug at this time point. Additionally, patient-driven demand for response is closer to 12 weeks. However, the clinical expert consulted for this review indicated that the decision to stop or switch treatment because of non-response would likely be made after a longer trial period; the clinical expert suggested up to six months, unless it was to comply with third-party funding criteria.

5. CONCLUSIONS

In four RCTs of patients with moderate to severe chronic plaque psoriasis that was inadequately controlled by topical treatments, phototherapy, or previous systemic therapy, secukinumab 150 mg and secukinumab 300 mg demonstrated statistically significant benefits relative to placebo on key outcomes: PASI 75 response at week 12, IGA 0/1 response at week 12, and PASI 90 response at week 12. Secukinumab was non-inferior and superior to etanercept for PASI 75 response at week 12. Patients reported an improvement in symptoms of itching, pain, and scaling at week 12 as well as an improvement in HRQoL at weeks 12 and 52; however, these were considered exploratory outcomes. There were very few serious AEs, and very few withdrawals due to AEs in the induction periods and over the course of the secukinumab trials. The most common AEs included nasopharyngitis, headache, diarrhea, pruritus, and hypertension, which occurred more frequently with secukinumab than with placebo.

The generalizability of the findings from the included studies may be limited, as the majority of enrolled patients had severe psoriasis. Additionally, although early escape design is typical of these types of studies for ethical reasons, this study design potentially weakens the internal validity of efficacy and safety results after the escape time point.

A manufacturer-submitted MTC found that secukinumab 300 mg [redacted] adalimumab, etanercept, etanercept-methotrexate combination, methotrexate, and ustekinumab, [redacted] infliximab, in achieving PASI 75 response. Hence, secukinumab 300 mg [redacted]. However, there are many uncertainties regarding these results. The effect of secukinumab 300 mg may have been overestimated because treatment experience was not taken into consideration. Key limitations of the MTC included heterogeneous populations across trials, a lack of sensitivity analyses to support the results, and a low number of trials included in each comparison.

APPENDIX 1: PATIENT INPUT SUMMARY

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

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

Arthritis Consumer Experts (ACE) and the Canadian Skin Patient Alliance (CSPA), in affiliation with the Canadian Association of Psoriasis Patients (CAPP), submitted the input for this review.

ACE is a national organization committed to educating and empowering people with arthritis to improve their quality of life. They provide evidence-based information and research decision-making training to people with arthritis to help them participate meaningfully in research organizations and government consultation. CSPA is a non-profit organization serving patients with dermatological conditions and focuses on advocacy, education, and support for more than 20 allied or affiliated disease-specific organizations. CAPP is a non-profit organization supporting patients with psoriasis and psoriatic arthritis.

ACE reported receiving support from the following sources: AbbVie Corporation, Amgen Canada, Arthritis Research Centre of Canada, BIOTECanada, Bristol-Myers Squibb Canada, Canadian Institutes of Health Research, the Canadian Rheumatology Research Consortium, Celgene Inc., GlaxoSmithKline, Hoffmann-La Roche Canada Ltd., Janssen Inc., Pfizer Canada, Purdue Pharma L.P., Sanofi Canada, St. Paul's Hospital (Vancouver), and the University of British Columbia. CSPA reported receiving support from the following sources: AbbVie, Amgen, Celgene, GSK, LEO Pharma, Merck, Novartis, Roche, and Valeant. CAPP reported receiving support from the following sources: AbbVie, Amgen, Janssen, LEO Pharma, Celgene, and Pfizer.

These organizations declared that they had no conflicts of interest in the compilation of this submission.

2. Condition and Current Therapy-Related Information

ACE obtained information for this submission from a request for patient input sent to members via email and posted on the Web; information also came from previous patient inputs or interviews, mainly from patients with psoriatic arthritis who have also experienced plaque psoriasis. CSPA and CAPP obtained information for this submission from patient questionnaires, patient feedback from information sessions, and the Multinational Assessment of Psoriasis and Psoriatic Arthritis study.

Persons with psoriasis experience lesions and plaques on their body. The physical symptoms of their disease include painful, bleeding, cracking, crusting, and flaking lesions and plaques; many experience severe itching, and some experience joint pain related to their psoriasis. Patients report losing sleep because of itching, and some have put their skin in vinegar or scratched themselves raw as "pain is preferable to itch." Patients also report limitations on activities due to their psoriasis: inability to perform day-to-day tasks, inability to participate in sports or hobbies, limited mobility, avoidance of activities that may subject them to stares and comments, and concentration issues related to sleep loss. Employment represents a challenge, as patients may be unable to consistently attend work because of pain and skin outbreaks, or when at work they may have limited productivity because they feel ill ("presenteeism"). Psoriasis patients often fear job loss when their condition is revealed, and many attempt to hide their disease. One patient reported: "I have lost jobs because people were afraid of my scales. … I have had total strangers come up to me and comment about my looks, especially as I had it on my face."

While affected body surface can indicate severity of illness, many patients find lesion location to be as important. Patients report lesions in sensitive areas that affect their perceptions of their own attractiveness and sexuality. Psychosocially, they may experience stigma, depression, suicidal ideation, shame, and feelings of helplessness and frustration. As well, they may fear shunning from others. One patient reported being asked to leave his gym because other patrons were uncomfortable with his psoriasis. Understandably, then, persons with psoriasis may isolate themselves, affecting their relationships with others. Additionally, patients may experience comorbid conditions, such as diabetes, depression, weight gain, and heart disease, while struggling to manage their psoriasis. According to one patient: *"Depression, anxiety, alcoholism and weight gain — ALL have made my life MISERABLE and I have really suffered from the pain and mental issues."*

Psoriasis also affects the lives of a patient's caregiver. The depression and impact on self-esteem of psoriasis patients negatively affect their personal relationships. Self-isolation of psoriasis patients often means that family members provide sole support for these patients. Constant cleaning associated with flaking and bleeding skin is a burden, and additional help may be required to clean and manage household tasks. Caregivers are often required to physically assist patients when their mobility is limited by joint pain (almost 70% of patients surveyed reported join pain), in addition to performing the majority of daily activities. Joint pain may limit patients' ability to dress themselves, perform personal hygiene routines, and perform tasks such as using a keyboard, opening drawers, walking, and bending to pick up items.

Current treatment includes methotrexate, cyclosporine, etanercept, adalimumab, infliximab, ustekinumab, calcipotriol and betamethasone combination, and phototherapy. Adverse effects include treatment toxicity (e.g., liver and kidney damage), fear of liver and kidney damage, nausea, headaches, malaise, and internal hemorrhage (one report after the use of methotrexate). Additional burdens include the high costs, lack of options, prohibitive time commitments, and limited ability to travel for treatments. Also noted was the struggle to access therapies, as patients and doctors must repeatedly file paperwork to qualify for treatments. Patients want options for treatment, as their current therapies may lose effectiveness in the management of their psoriasis.

3. Related Information About the Drug Being Reviewed

Patients with psoriasis are generally eager to try new medications, in the hopes of better managing their conditions. Anticipated benefits of secukinumab include the better management of psoriasis symptoms, as well as providing an additional therapy option if their current treatments are no longer effective.

The majority of those treated with secukinumab experience noted an improvement in flaking, itching, scales, and bleeding. More than half of patients who had experience with secukinumab reported an improvement in mood control, sleep, and nail psoriasis. One patient reported on secukinumab therapy: *"Symptoms are better — psoriasis almost disappeared, not as much scalp symptoms, less itching, and very good in winter — sore spots are gone."* The majority of patients found secukinumab easier to use than previous therapies, although one patient felt the cost was prohibitive and would prefer to use pills. Of patients in secukinumab trials, 30% reported side effects, although no patient found the side effects significant enough to deter secukinumab use. Three patients complained of weight gain, and one patient each complained of constipation and diarrhea.

4. Additional Information

The ACE believes that new therapies for plaque psoriasis will ultimately improve the lives of people living with psoriatic arthritis, as the prevalence of this disease in patients with psoriasis is high.

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:	January 29, 2015
Alerts:	Weekly search updates until (May 20, 2015)
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) < 1946 to Present >
Search Strategy:

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1 exp Psoriasis/
2 psoria$.ti,ab,ot,sh,hw.
3 (chronic adj3 plaque).ti,ab,ot,sh,hw.
4 (pustulosis adj palmaris).ti,ab.
5 (palmoplantar* adj pustulosis).ti,ab.
6 or/1-5
7 secukinumab.ti,ab.
8 cosentyx.ti,ab.

MULTI-DATABASE STRATEGY
9 (AIN457A or AIN457 or AIN-457 or UNII-DLG4EML025 or BLA 125-504).ti,ab,ot,sh,hw,rn,nm. (11) 10 or/7-9 11 6 and 10 Database: Embase < 1974 to 2015 January 27 > Search Strategy: --- 1 psoriasis/ or psoriasis vulgaris/ or pustular psoriasis/ 2 psoria$.ti,ab. 3 (chronic adj3 plaque).ti,ab. 4 (pustulosis adj palmaris).ti,ab. 5 (palmoplantar* adj pustulosis).ti,ab. 6 or/1-5 7 secukinumab/ 8 secukinumab.ti,ab. 9 cosentyx.ti,ab. 10 (AIN457A or AIN457 or AIN-457 or UNII-DLG4EML025 or BLA 125-504).ti,ab. 11 or/7-10 12 6 and 11 13 12 not conference abstract.pt.

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

Grey Literature

Dates for Search:	January, 2015
Keywords:	Cosentyx® (secukinumab), chronic plaque 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 evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), were searched:

- Health technology assessment agencies
- Health economics
- Clinical practice guidelines
- Drug and device regulatory approvals
- Advisories and warnings
- Drug class reviews
- Databases (free)
- Internet search.

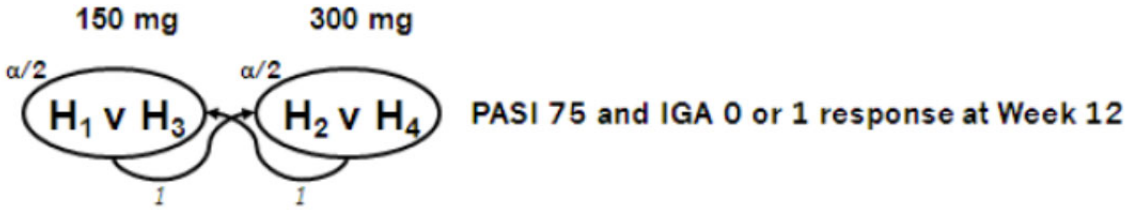
APPENDIX 3: EXCLUDED STUDIES

There were no excluded studies.

APPENDIX 4: TESTING PROCEDURES AND POWER CALCULATIONS

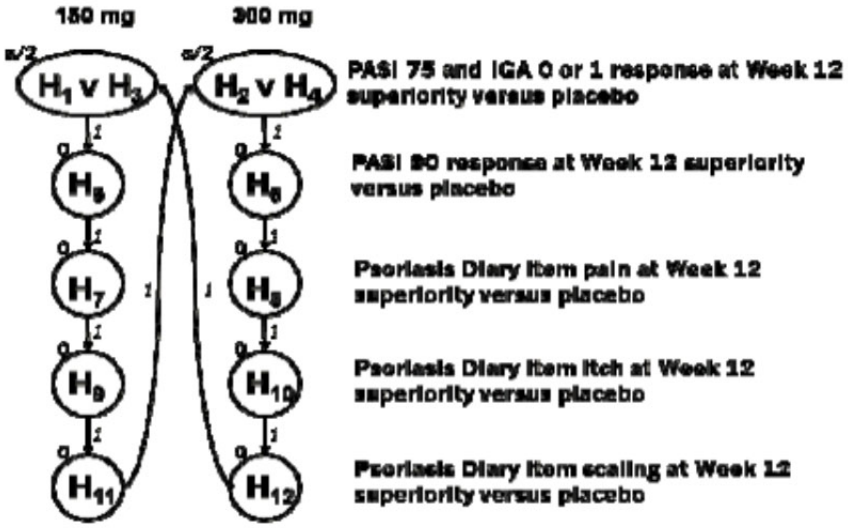
1. Testing Procedures

FIGURE 2: SEQUENTIAL TESTING PROCEDURE, FEATURE AND JUNCTURE



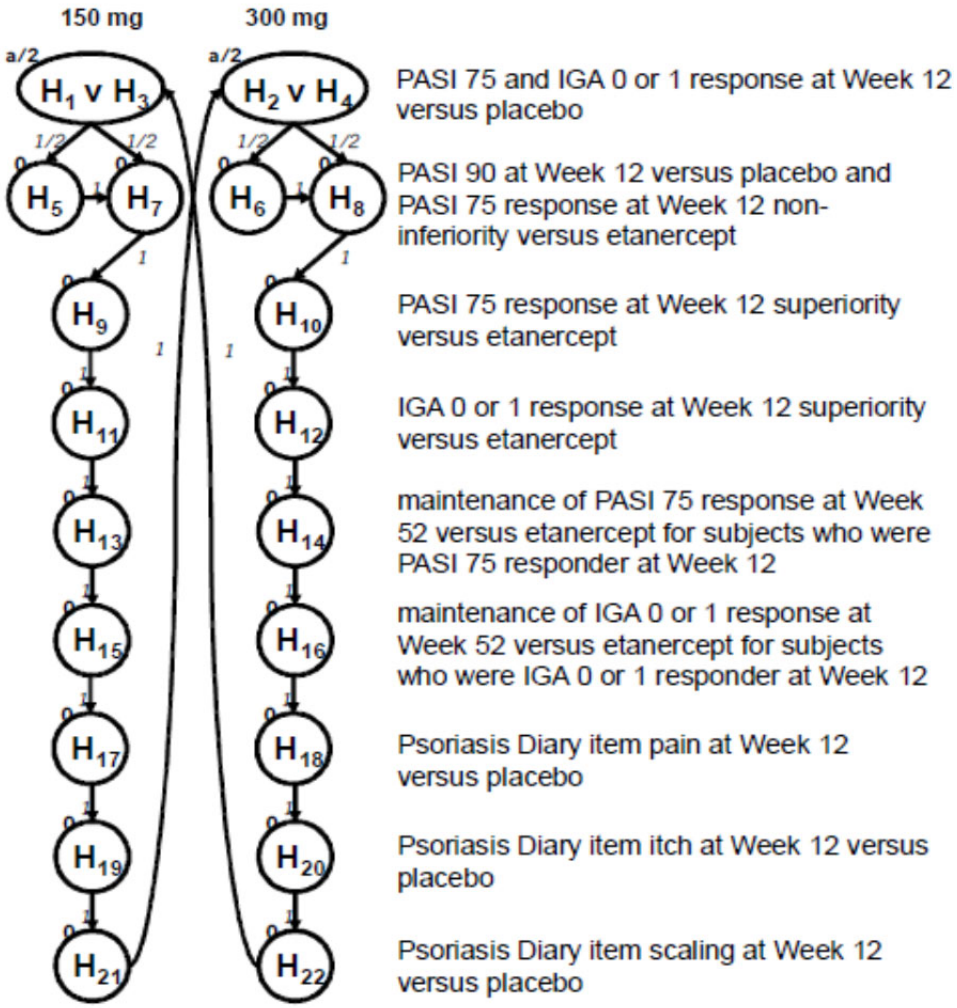
IGA = Investigator's Global Assessment; PASI = Psoriasis Area and Severity Index.
Source: Clinical Study Reports.[3,4]

FIGURE 3: SEQUENTIAL TESTING PROCEDURE, ERASURE



IGA = Investigator's Global Assessment; PASI = Psoriasis Area and Severity Index.
Source: Clinical Study Report.[1]

FIGURE 4: SEQUENTIAL TESTING PROCEDURE, FIXTURE



IGA = Investigator's Global Assessment; PASI = Psoriasis Area and Severity Index.
Source: Clinical Study Report.[2]

2. Power for Analysis of Key Secondary Outcomes

Power calculations for the analysis of key secondary outcomes were also carried out in ERASURE and FIXTURE.

ERASURE

- PASI 90 response at week 12: as per the co-primary outcomes, with secukinumab response rate of 30%.
- Psoriasis Symptom Diary (itching, pain, scaling) at week 12: as per the co-primary outcomes with Psoriasis Symptom Diary completion rate of 50%. Absolute mean change of –3.40 (standard deviation [SD] 2.82) for itching in treatment group versus –1.17 (SD 3.27) in the placebo group, of –2.51 (SD 2.40) for pain in the treatment group versus –1.07 (SD 2.19) in the placebo group, and of –3.69 (SD 3.06) for scaling in the treatment group versus –1.40 (SD 2.57) in the placebo group was assumed based on a previous study.

FIXTURE

- PASI 75 response at week 12, non-inferiority comparison of secukinumab versus etanercept: Type 1 error (one-sided) for the non-inferiority comparison of secukinumab versus etanercept was set to 0.625%. With a non-inferiority margin of 10% and assumed PASI 75 response rates of 50% for etanercept and 55% for secukinumab, 316 patients per treatment group were needed to achieve a power of 90%.
- PASI 90 response at week 12: same as ERASURE (based on Fisher's exact test with two-sided type 1 error of 1.25%).
- PASI 75 response at week 12, superiority of secukinumab versus etanercept: The trial provided 93% power to show response rates of 65% for secukinumab and 50% for etanercept, based on Fisher's exact test with two-sided type 1 error of 2.5% for each comparison. Other scenarios with lower or higher power were also given.
- PASI 75 at week 52: It was assumed that about 50% of the patients in secukinumab and etanercept treatment groups were PASI 75 responders at week 12. The power would be > 90% to show a difference in PASI 75 maintenance rates of 70% with secukinumab versus 50% with etanercept (two-sided type 1 error of 2.5%).
- Psoriasis Symptom Diary (itching, pain, scaling) at week 12: same as for ERASURE.

APPENDIX 5: DETAILED OUTCOME DATA

TABLE 14: PASI AT WEEK 12, ERASURE, FEATURE, AND JUNCTURE (FULL ANALYSIS SET)

	ERASURE			FEATURE			JUNCTURE		
SEC vs. PL	SEC 150 (N = 245)	SEC 300 (N = 245)	PL (N = 247)	SEC 150 (N = 59)	SEC 300 (N = 59)	PL (N = 59)	SEC 150 (N = 61)	SEC 300 (N = 60)	PL (N = 61)
PASI 75[a]									
n/N	174/243	200/245	11/246	41/59	44/58	0/59	43/60	52/60	2/61
%	71.6	81.6	4.5	69.5	75.9	0	71.7	86.7	3.3
% RD[b]									
95% CI									
OR[c]									
95% CI									
P value	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	–
PASI 75 in patients previously exposed and failed systemic therapy[a]									
n/N									
%									
PASI 75 in patients previously exposed and failed biologic therapy[a]									
n/N									
%									
PASI 75 in patients < 90 kg[a]									
n/N									
%									
PASI 75 in patients ≥ 90 kg[a]									
n/N									
%									
PASI 90[a]									
n/N	95/243	145/245	3/246	27/59	35/58	0/59	24/60	33/60	0/61
%	39.1	59.2	1.2	45.8	60.3	0	40.0	55.0	0
% RD[b]									
95% CI									
OR[c]									
95% CI									
P value	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	–
PASI 100[a]									
n/N	31/243	70/245	2/246	5/59	25/58	0/59	10/60	16/60	0/61
%	12.8	28.6	0.8	8.5	43.1	0	16.7	26.7	0

CI = confidence interval; NA = not applicable; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PL = placebo; RD = risk difference; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.

[a] Based on non-responder imputation.

[b] Fisher's exact test.

[c] Cochran–Mantel–Haenszel test (not performed in cases of 0 PL responders).

Source: Clinical Study Reports.[1,3,4]

TABLE 15: PASI AT WEEK 12, FIXTURE (FULL ANALYSIS SET)

	FIXTURE			
	SEC 150 (N = 327)	SEC 300 (N = 327)	ETA (N = 326)	PL (N = 325)
PASI 75				
n/N (%)	219/327 (67.0)	249/323 (77.1)	142/323 (44.0)	16/324 (4.9)
SEC vs. PL[a,b]				
OR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value	< 0.0001	< 0.0001	NA	-
Superiority test SEC vs. ETA[a,b]				
OR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value	< 0.0001	< 0.0001	–	NA
Non-inferiority test SEC vs. ETA (Mantel–Haenszel risk difference)[b]				
% RD (CI)	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75 in patients previously exposed and failed systemic therapy[b]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75 in patients previously exposed and failed biologic therapy[b]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75 in patients < 90 kg[b]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75 in patients ≥ 90kg[b]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90				
n/N (%)	137/327 (41.9)	175/323 (54.2)	67/323 (20.7)	5/324 (1.5)
SEC vs. PL[a,b]				
OR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value	< 0.0001	< 0.0001	NA	–
SEC vs. ETA[a,b]				
OR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value	< 0.0001	< 0.0001	–	NA
PASI 100[b]				
n/N (%)	47/327 (14.4)	78/323 (24.1)	14/323 (4.3)	0/324 (0)

CI = confidence interval; ETA = etanercept; NA = not applicable; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PL = placebo; RD = risk difference; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.
[a] Cochran–Mantel–Haenszel test.
[b] Based on non-responder imputation.
Source: Clinical Study Report.[2]

TABLE 16: PASI 75 AT WEEK 12, FIXTURE (PER-PROTOCOL)

	FIXTURE		
	SEC 150 (N = 305)	SEC 300 (N = 308)	ETA (N = 300)
PASI 75			
n/N (%)	212/305 (69.5)	237/306 (77.5)	135/300 (45.0)
Non-inferiority test SEC vs. ETA (Mantel–Haenszel risk difference)[a,b]			
% RD (CI)	[redacted]	[redacted]	[redacted]
1-sided CI	[redacted]	[redacted]	[redacted]

CI = confidence interval; ETA = etanercept; PASI = Psoriasis Area and Severity Index; RD = risk difference; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.
[a] Based on non-responder imputation.
[b] Non-inferiority margin is 10%.
Source: Clinical Study Report.[2]

TABLE 17: PASI AT WEEK 52, ERASURE (FULL ANALYSIS SET)

	ERASURE				
	SEC 150 (N = 245)	SEC 300 (N = 245)	Re-randomized PL Non-responders		PL Responders
			SEC 150 (N = 109)	SEC 300 (N = 105)	PL (N = 18)
PASI 75[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance of PASI 75 at week 52 in SEC patients who were responders at week 12[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NA = not applicable; PASI = Psoriasis Area and Severity Index; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg.
[a] Based on non-responder imputation.
Source: Clinical Study Report.[1]

TABLE 18: PASI AT WEEK 52, FEATURE (FULL ANALYSIS SET)

	FEATURE				
	SEC 150 (N = 59)	SEC 300 (N = 59)	Re-randomized PL Non-responders		PL Responders
			SEC 150 (N = 29)	SEC 300 (N = 27)	PL (N = 0)
PASI 75[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance of PASI 75 at week 52 in SEC patients who were responders at week 12[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NA = not applicable; NR = not reported; PASI = Psoriasis Area and Severity Index; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg.
[a] Based on non-responder imputation.
Source: Clinical Study Report.[3]

TABLE 19: PASI AT WEEK 52, JUNCTURE (FULL ANALYSIS SET)

	JUNCTURE				
	SEC 150 (N = 61)	SEC 300 (N = 60)	Re-randomized PL Non-responders		PL Responders
			SEC 150 (N = 28)	SEC 300 (N = 28)	PL (N = 3)
PASI 75[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance of PASI 75 at week 52 in SEC patients who were responders at week 12[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

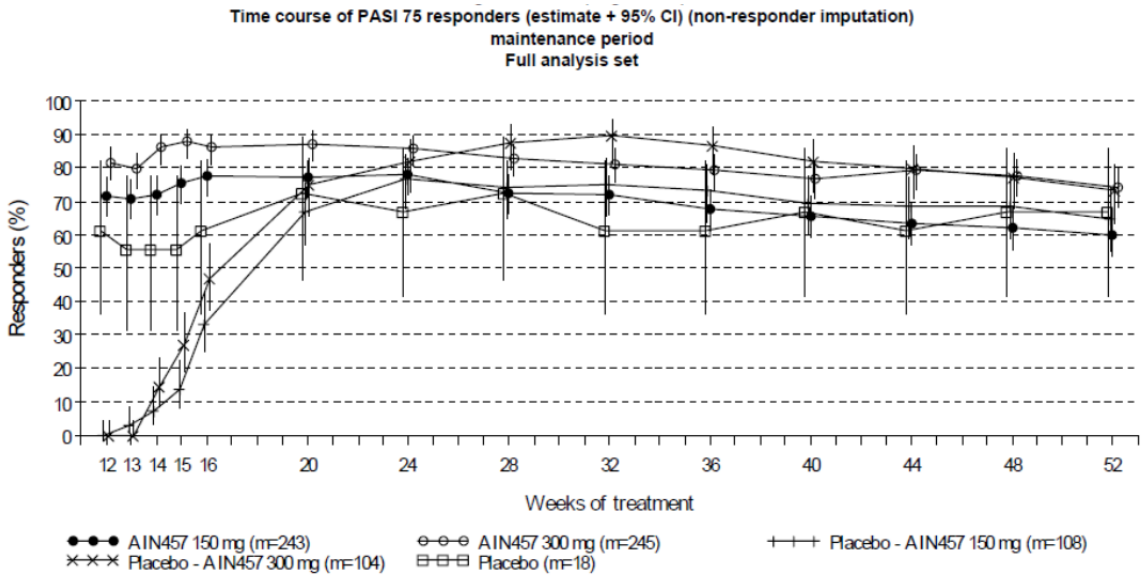
NA = not applicable; NR = not reported; PASI = Psoriasis Area and Severity Index; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg.
[a] Based on non-responder imputation.
Source: Clinical Study Report.[4]

TABLE 20: PASI AT WEEK 52, FIXTURE (FULL ANALYSIS SET)

	FIXTURE					
	SEC 150 (N = 327)	SEC 300 (N = 327)	ETA (N = 326)	Re-randomized PL Non-responders		PL Responders
				SEC 150 (N = 142)	SEC 300 (N = 142)	PL (N = 17)
PASI 75[a]						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance of PASI 75 at week 52 in patients who were responders at week 12[a, b]						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI) vs. ETA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90[a]						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100[a]						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

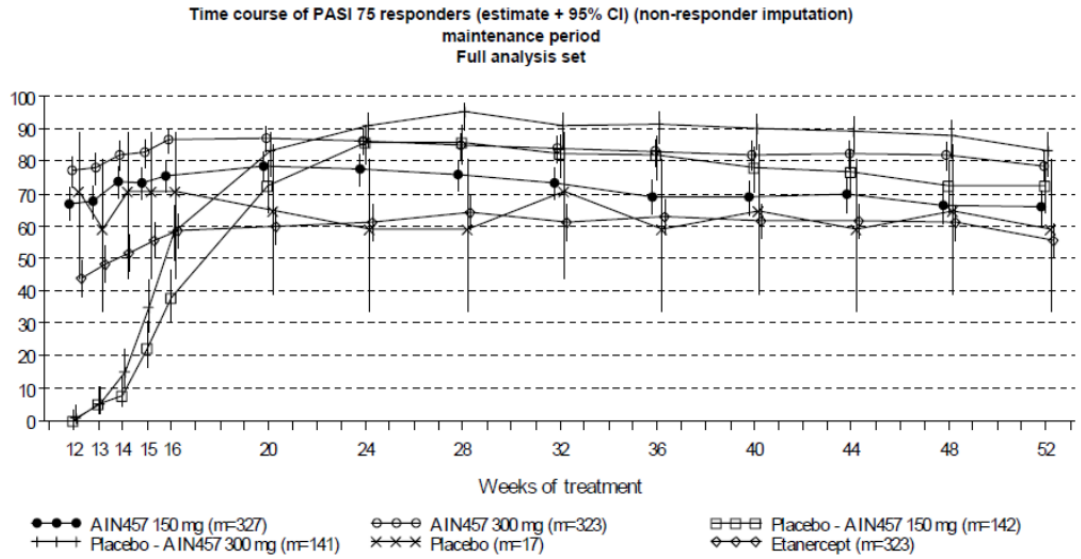
CI = confidence interval; ETA = etanercept; NA = not applicable; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.
[a] Based on non-responder imputation.
[b] Cochran–Mantel–Haenszel test.
Source: Clinical Study Report.[2]

FIGURE 5: TIME COURSE FOR PSORIASIS AREA AND SEVERITY INDEX 75 RESPONDERS, ERASURE



AIN457 = secukinumab; CI = confidence interval; PASI = Psoriasis Area and Severity Index.
Source: Clinical Study Report.[1]

FIGURE 6: TIME COURSE FOR PSORIASIS AREA AND SEVERITY INDEX 75 RESPONDERS, FIXTURE



AIN457 = secukinumab; CI = confidence interval; PASI = Psoriasis Area and Severity Index.
Source: Clinical Study Report.[2]

TABLE 21: INVESTIGATOR'S GLOBAL ASSESSMENT 0/1 AT WEEK 12, ERASURE, FEATURE, AND JUNCTURE (FULL ANALYSIS SET)

	ERASURE			FEATURE			JUNCTURE		
SEC vs. PL	SEC 150 (N = 245)	SEC 300 (N = 245)	PL (N = 247)	SEC 150 (N = 59)	SEC 300 (N = 59)	PL (N = 59)	SEC 150 (N = 61)	SEC 300 (N = 60)	PL (N = 61)
IGA 0/1[a]									
n/N	125/244	160/245	6/246	31/59	40/58	0/59	32/60	44/60	0/61
%	51.2	65.3	2.4	52.5	69.0	0	53.3	73.3	0
% RD[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	
IGA 0/1 in patients previously exposed and failed systemic therapy[a]									
n/N	53/109	65/109	2/90	14/33	13/21	0/27	10/25	15/26	0/280
%	48.6	59.6	2.2	42.4	61.9	0	40.0	57.7	0
IGA 0/1 in patients previously exposed and failed biologic therapy[a]									
n/N	12/29	11/19	1/24	7/18	6/9	0/14	2/7	3/6	0/6
%	41.1	57.9	4.2	38.9	66.7	0	28.6	50.0	0
IGA 0/1 in patients < 90 kg[a]									
n/N	75/141	103/142	3/142	22/30	25/30	0/32	17/30	28/32	0/32
%	53.2	72.5	2.1	73.3	83.3	0	56.7	87.5	0
IGA 0/1 in patients ≥ 90 kg[a]									
n/N	50/103	57/103	3/104	9/29	15/28	0/27	15/30	16/28	0/29
%	48.5	55.3	2.9	31.0	53.6	0	50.0	57.1	0

IGA = Investigator's Global Assessment; OR = odds ratio; PL = placebo; RD = risk difference; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.

[a] Based on non-responder imputation.

[b] Fisher's exact test.

[c] Cochran–Mantel–Haenszel test.

Source: Clinical Study Reports.[1,3,4]

TABLE 22: INVESTIGATOR'S GLOBAL ASSESSMENT 0/1 AT WEEK 12, FIXTURE (FULL ANALYSIS SET)

	FIXTURE			
	SEC 150 (N = 327)	SEC 300 (N = 327)	ETA (N = 326)	PL (N = 325)
IGA 0/1				
n/N (%)	167/327 (51.1)	202/323 (62.5)	88/323 (27.2)	9/324 (2.8)
SEC vs. PL[a,b]				
OR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value	< 0.0001	< 0.0001	NA	–
SEC vs. ETA[a,b]				
% OR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value	< 0.0001	< 0.0001	–	NA
IGA 0/1 in patients previously exposed and failed systemic therapy[b]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
IGA 0/1 in patients previously exposed and failed biologic therapy[b]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
IGA 0/1 in patients < 90 kg[b]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
IGA 0/1 in patients ≥ 90 kg[b]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; ETA = etanercept; IGA = Investigator's Global Assessment; NA = not applicable; OR = odds ratio; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.
[a] Cochran–Mantel–Haenszel test.
[b] Based on non-responder imputation.
Source: Clinical Study Report.[2]

TABLE 23: INVESTIGATOR'S GLOBAL ASSESSMENT 0/1 AT WEEK 52, ERASURE (FULL ANALYSIS SET)

	ERASURE				
	SEC 150 (N = 245)	SEC 300 (N = 245)	Re-randomized PL Non-responders		PL Responders
			SEC 150 (N = 109)	SEC 300 (N = 105)	PL (N = 18)
IGA 0/1[a]					
n/N (%)	101/244 (41.4)	148/245 (60.4)	53/108 (49.1)	69/104 (66.3)	7/18 (38.9)
Maintenance of IGA 0/1 at week 52 in SEC patients who were responders at week 12[a]					
n/N (%)	74/125 (59.2)	119/160 (74.4)	NA	NA	NA

IGA = Investigator's Global Assessment; NA = not applicable; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg.
[a] Based on non-responder imputation.
Source: Clinical Study Report.[1]

TABLE 24: INVESTIGATOR'S GLOBAL ASSESSMENT 0/1 AT WEEK 52, FEATURE (FULL ANALYSIS SET)

	FEATURE				
	SEC 150 (N = 59)	SEC 300 (N = 59)	Re-randomized PL Non-responders		PL Responders
			SEC 150 (N = 29)	SEC 300 (N = 27)	PL (N = 0)
IGA 0/1[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance of IGA 0/1 at week 52 in SEC patients who were responders at week 12[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IGA = Investigator's Global Assessment; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg.
[a] Based on non-responder imputation.
Source: Clinical Study Report.[3]

TABLE 25: INVESTIGATOR'S GLOBAL ASSESSMENT 0/1 AT WEEK 52, JUNCTURE (FULL ANALYSIS SET)

	JUNCTURE				
	SEC 150 (N = 61)	SEC 300 (N = 61)	Re-randomized PL Non-responders		PL Responders
			SEC 150 (N = 28)	SEC 300 (N = 28)	PL (N = 3)
IGA 0/1[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance of IGA 0/1 at week 52 in SEC patients who were responders at week 12[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

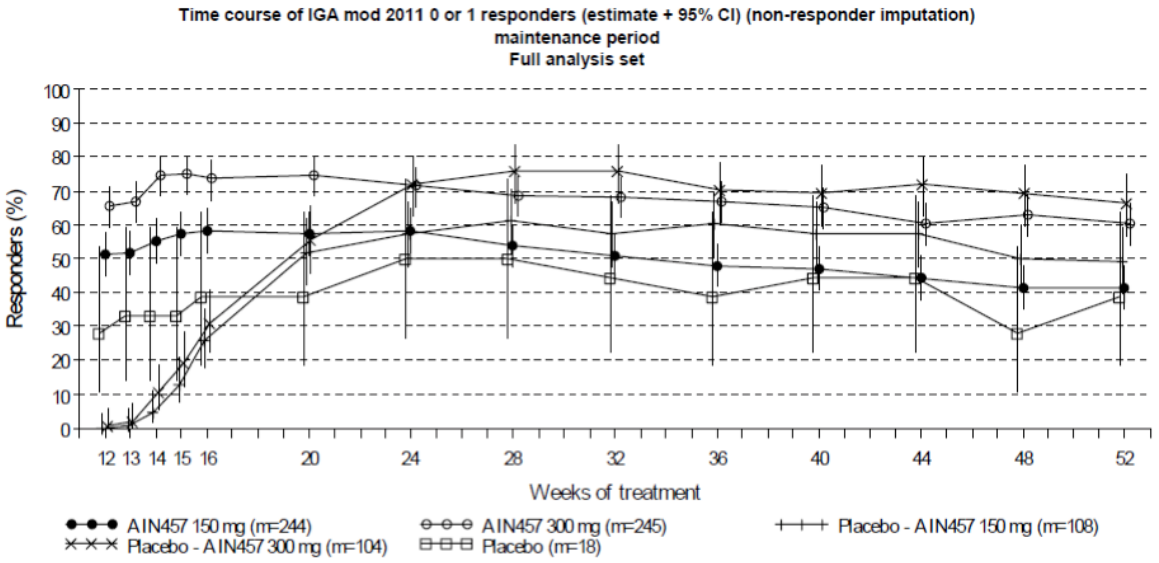
IGA = Investigator's Global Assessment; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg.
[a] Based on non-responder imputation.
Source: Clinical Study Report.[4]

TABLE 26: INVESTIGATOR'S GLOBAL ASSESSMENT 0/1 AT WEEK 52, FIXTURE (FULL ANALYSIS SET)

	FIXTURE					
	SEC 150 (N = 327)	SEC 300 (N = 327)	ETA (N = 326)	Re-randomized PL Non-responders		PL Responders
				SEC 150 (N = 142)	SEC 300 (N = 142)	PL (N = 17)
IGA 0/1						
n/N (%)	168/327 (51.4)	219/323 (67.8)	120/323 (37.2)	80/142 (56.3)	104/141 (73.8)	5/17 (29.4)
Maintenance of IGA 0/1 at week 52 in patients who were responders at week 12[a,b]						
n/N (%)	113/167 (67.7)	161/202 (79.7)	50/88 (56.8)	NA	NA	NA
OR (95% CI) vs. ETA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	0.0428	< 0.0001	–	NA	NA	NA

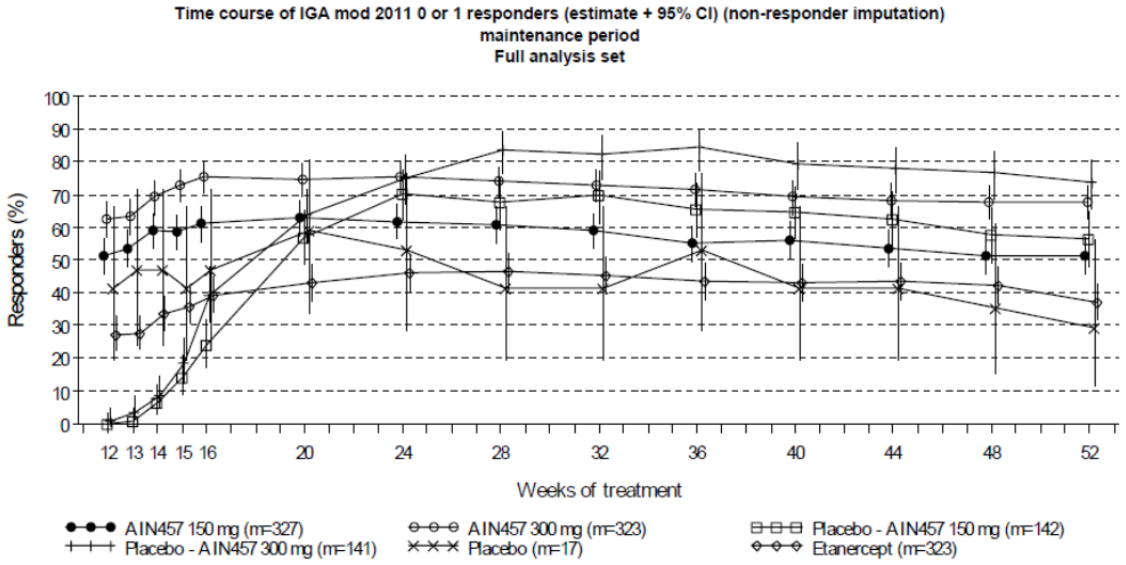
ETA = etanercept; FAS = full analysis set; IGA = Investigator's Global Assessment; NA = not applicable; OR = odds ratio; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.
[a] Based on non-responder imputation.
[b] Cochran–Mantel–Haenzsel test.
Source: Clinical Study Report.[2]

FIGURE 7: TIME COURSE FOR INVESTIGATOR'S GLOBAL ASSESSMENT 0/1 RESPONDERS, ERASURE



AIN457 = secukinumab; CI = confidence interval; IGA = Investigator's Global Assessment; mod = modified.
Source: Clinical Study Report.[1]

FIGURE 8: TIME COURSE FOR INVESTIGATOR'S GLOBAL ASSESSMENT 0/1 RESPONDERS, FIXTURE



AIN457 = secukinumab; CI = confidence interval; IGA = Investigator's Global Assessment; mod = modified.
Source: Clinical Study Report.[2]

TABLE 27: PSORIASIS DIARY SYMPTOMS AT WEEK 12, ERASURE AND FIXTURE (FULL ANALYSIS SET)

	ERASURE			FIXTURE			
	SEC 150 (N = 245)	SEC 300 (N = 245)	PL (N = 247)	SEC 150 (N = 327)	SEC 300 (N = 327)	ETA (N = 326)	PL (N = 325)
Patients with response, n/N (%)							
Itching	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC vs. PL[a]							
OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC vs. ETA[a]							
OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC vs. PL[a]							
OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC vs. ETA[a]							
OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scaling	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC vs. PL[a]							
OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ERASURE			FIXTURE			
	SEC 150 (N = 245)	SEC 300 (N = 245)	PL (N = 247)	SEC 150 (N = 327)	SEC 300 (N = 327)	ETA (N = 326)	PL (N = 325)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC vs. ETA[a]							
OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; ETA = etanercept; NA = not applicable; OR = odds ratio; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.
[a] Cochran–Mantel–Haenszel test.
Source: Clinical Study Reports.[1,2]

TABLE 28: PSORIASIS DIARY SYMPTOMS, ANCOVA FOR ABSOLUTE CHANGE FROM BASELINE TO WEEK 12, ERASURE AND FIXTURE (FULL ANALYSIS SET), SECUKINUMAB VERSUS PLACEBO

	ERASURE			FIXTURE		
SEC vs. PL[a]	SEC 150 (N = 245)	SEC 300 (N = 245)	PL (N = 247)	SEC 150 (N = 327)	SEC 300 (N = 327)	PL (N = 325)
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Itching						
Mean change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain						
Mean change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scaling						
Mean change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; PL = placebo; SE = standard error; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.
[a] Treatment, geographical region, and body weight as explanatory variables and baseline value as covariate.
Source: Clinical Study Reports.[1,2]

TABLE 29: PSORIASIS DIARY SYMPTOMS, ANCOVA FOR ABSOLUTE CHANGE FROM BASELINE TO WEEK 12, FIXTURE (FULL ANALYSIS SET), SECUKINUMAB VERSUS ETANERCEPT

	FIXTURE		
SEC vs. ETA[a]	SEC 150 (N = 327)	SEC 300 (N = 327)	ETA (N = 326)
N	[redacted]	[redacted]	[redacted]
Itching			
Mean change (SE)	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Pain			
Mean change (SE)	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Scaling			
Mean change (SE)	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

ANCOVA = analysis of covariance; CI = confidence interval; ETA = etanercept; LS = least squares; SE = standard error; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.
[a] Treatment, geographical region, and body weight as explanatory variables and baseline value as covariate.
Source: Clinical Study Report.[2]

TABLE 30: DERMATOLOGY LIFE QUALITY INDEX AT WEEK 12, ERASURE, FEATURE, AND JUNCTURE (FULL ANALYSIS SET)

	ERASURE			FEATURE			JUNCTURE		
	SEC 150 (N = 245)	SEC 300 (N = 245)	PL (N = 247)	SEC 150 (N = 59)	SEC 300 (N = 59)	PL (N = 59)	SEC 150 (N = 61)	SEC 300 (N = 60)	PL (N = 61)
DLQI total score (LOCF)[a]									
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. PL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. PL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Per cent change from baseline in DLQI total score (LOCF)[a]									
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% difference vs. PL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95 % CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ERASURE			FEATURE			JUNCTURE		
	SEC 150 (N = 245)	SEC 300 (N = 245)	PL (N = 247)	SEC 150 (N = 59)	SEC 300 (N = 59)	PL (N = 59)	SEC 150 (N = 61)	SEC 300 (N = 60)	PL (N = 61)
P value vs. PL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with DLQI response of 0/1 (LOCF)[b]									
n/N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. PL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DLQI = Dermatology Life Quality Index; LOCF = last observation carried forward; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.
[a] Using Hodges-Lehmann estimates and van Elteren test.
[b] Fisher's exact test.
Source: Clinical Study Reports.[1,3,4]

TABLE 31: DERMATOLOGY LIFE QUALITY INDEX AT WEEK 12, FIXTURE (FULL ANALYSIS SET)

	FIXTURE			
	SEC 150 (N = 327)	SEC 300 (N = 327)	ETA (N = 326)	PL (N = 325)
DLQI total score (LOCF)[a]				
N	[redacted]	[redacted]	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. PL (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. PL	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. ETA (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. ETA	[redacted]	[redacted]	[redacted]	[redacted]
Per cent change from baseline in DLQI total score (LOCF)[a]				
N	[redacted]	[redacted]	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
% difference vs. PL (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. PL	[redacted]	[redacted]	[redacted]	[redacted]
% difference vs. ETA (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. ETA	[redacted]	[redacted]	[redacted]	[redacted]
Patients with DLQI response of 0/1 (LOCF)[b]				
n/N	[redacted]	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. PL	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. ETA	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DLQI = Dermatology Life Quality Index; ETA = etanercept; LOCF = last observation carried forward; NR = not reported; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.
[a] Using Hodges-Lehmann estimates and van Elteren test.
[b] Fisher's exact test.
Source: Clinical Study Report.[2]

TABLE 32: DERMATOLOGY LIFE QUALITY INDEX AT WEEK 52, ERASURE (FULL ANALYSIS SET)

	ERASURE				
	SEC 150 (N = 245)	SEC 300 (N = 245)	Re-randomized PL Non-responders		PL Responders (N = 18)
			SEC 150 (N = 109)	SEC 300 (N = 105)	
DLQI total score (LOCF)[a]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Per cent change from baseline in DLQI total score (LOCF)[a]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with DLQI response of 0 or 1 (LOCF)					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DLQI = Dermatology Life Quality Index; LOCF = last observation carried forward; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg.
[a] Using Hodges-Lehmann estimates.
Source: Clinical Study Report.[1]

TABLE 33: DERMATOLOGY LIFE QUALITY INDEX AT WEEK 52, FIXTURE (FULL ANALYSIS SET)

		FIXTURE				
	SEC 150 (N = 327)	SEC 300 (N = 327)	ETA (N = 326)	Re-randomized PL Non-responders		PL Responders (N = 17)
				SEC 150 (N = 142)	SEC 300 (N = 142)	
DLQI total score (LOCF)[a]						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Per cent change from baseline in DLQI total score (LOCF)[a]						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with DLQI response of 0/1 (LOCF)						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DLQI = Dermatology Life Quality Index; ETA = etanercept; LOCF = last observation carried forward; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg.
[a] Using Hodges-Lehmann estimates.
Source: Clinical Study Report.[2]

TABLE 34: EQ-5D HEALTH STATE ASSESSMENT AT WEEK 12, ERASURE, FEATURE, AND JUNCTURE (FULL ANALYSIS SET)

	ERASURE			FEATURE			JUNCTURE		
	SEC 150 (N = 245)	SEC 300 (N = 245)	PL (N = 247)	SEC 150 (N = 59)	SEC 300 (N = 59)	PL (N = 59)	SEC 150 (N = 61)	SEC 300 (N = 60)	PL (N = 61)
Absolute change from baseline (LOCF)									
N	[redacted]								
Mean									
SD									
Median									
Min, Max									
Per cent change from baseline (LOCF)									
N	[redacted]								
Mean									
SD									
Median									
Min, Max									
Repeated measurement analysis of the absolute change from baseline									
N	[redacted]								
Adjusted mean									
SE									
Difference vs. PL									
95% CI									
P value vs. PL									

CI = confidence interval; EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; LOCF = last observation carried forward; Max = maximum; Min = minimum; PL = placebo; SD = standard deviation; SE = standard error; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.
Source: Clinical Study Reports.[1,3,4]

TABLE 35: EQ-5D HEALTH STATE ASSESSMENT AT WEEK 12, FIXTURE (FULL ANALYSIS SET)

	FIXTURE			
	SEC 150	SEC 300	ETA	PL
Absolute change from baseline				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]
Per cent change from baseline				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]
Repeated measurement analysis of the absolute change from baseline				
N	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. PL (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. PL	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. ETA (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. ETA	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; ETA = etanercept; Max = maximum; Min = minimum; PL = placebo; SD = standard deviation; SE = standard error; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; vs. = versus.
Source: Clinical Study Report.[2]

TABLE 36: EQ-5D HEALTH STATE ASSESSMENT AT WEEK 52, ERASURE (FULL ANALYSIS SET)

	ERASURE				
			Re-randomized From PL Group		
	SEC 150 (N = 245)	SEC 300 (N = 245)	SEC 150 (N = 109)	SEC 300 (N = 105)	PL Responders (N = 18)
Absolute change from baseline					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Per cent change from baseline					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; Max = maximum; Min = minimum; PL = placebo; SD = standard deviation; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg.
Source: Clinical Study Report.[1]

TABLE 37: EQ-5D HEALTH STATE ASSESSMENT AT WEEK 52, FIXTURE (FULL ANALYSIS SET)

		FIXTURE				
	SEC 150 (N = 327)	SEC 300 (N = 327)	ETA (N = 326)	Re-randomized PL Non-responders		PL Responders (N = 17)
				SEC 150 (N = 142)	SEC 300 (N = 142)	
Absolute change from baseline						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Per cent change from baseline						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; ETA = etanercept; Max = maximum; Min = minimum; PL = placebo; SD = standard deviation; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg.
Source: Clinical Study Report.[2]

TABLE 38: ADVERSE EVENTS (SAFETY SET)

	ERASURE			FEATURE			JUNCTURE			FIXTURE			
	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	ETA
INDUCTION PERIOD (up to week 12), n (%)													
N	245	245	247	59	59	59	61	60	61	327	326	327	323
Patients > 0 AEs	148 (60.4)	135 (55.1)	116 (47.0)	34 (57.6)	30 (50.8)	28 (47.5)	39 (63.9)	42 (70.0)	33 (54.1)	191 (58.4)	181 (55.5)	163 (49.8)	186 (57.6)
Most frequently reported AEs													
Nasopharyngitis	23 (9.4)	22 (9.0)	19 (7.7)	3 (5.1)	3 (5.1)	5 (8.5)	14 (23.0)	19 (31.7)	10 (16.4)	45 (13.8)	35 (10.7)	26 (8.0)	36 (11.1)
Headache	13 (5.3)	12 (4.9)	7 (2.8)	4 (6.8)	0	3 (5.1)	5 (8.2)	3 (5.0)	3 (4.9)	16 (4.9)	30 (9.2)	23 (7.0)	23 (7.1)
Diarrhea	4 (1.6)	5 (2.0)	3 (1.2)	2 (3.4)	5 (8.5)	1 (1.7)	0	1 (1.7)	0	12 (3.7)	17 (5.2)	6 (1.8)	11 (3.4)
Back pain	3 (1.2)	2 (0.8)	5 (1.0)	0	3 (5.1)	0	1 (1.6)	1 (1.7)	0	8 (2.4)	8 (2.5)	6 (1.8)	9 (2.8)
Pruritus	8 (3.3)	9 (3.7)	5 (2.0)	0	1 (1.7)	0	1 (1.6)	5 (8.3)	2 (3.3)	12 (3.7)	8 (2.5)	11 (3.4)	8 (2.5)
Cough	2 (0.8)	4 (1.6)	3 (1.2)	2 (3.4)	1 (1.7)	0	0	3 (5.0)	2 (3.3)	5 (1.5)	11 (3.4)	4 (1.2)	4 (1.2)
Hypertension	9 (3.7)	0	3 (1.2)	1 (1.7)	1 (1.7)	1 (1.7)	2 (3.3)	1 (1.7)	4 (6.6)	10 (3.1)	5 (1.5)	4 (1.2)	5 (1.5)
Injection-site AE[a]	0	1 (0.4)	0	0	1 (1.7)	0	0	1 (1.7)	0	0	0	0	16 (5.0)
ENTIRE TREATMENT PERIOD, n (IR per 100 PY)[b, c]													
N	353	349	247	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	469	467	327	323
Patients > 0 AEs	287 (270)	286 (246)	124 (323)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	364 (236)	376 (252)	168 (330)	253 (243)
Most frequently reported AEs													
Nasopharyngitis	69 (26)	57 (21)	20 (31)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	108 (31)	122 (35)	26 (33)	86 (36)
URTI	36 (13)	32 (11)	2 (3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26 (7)	26 (7)	3 (4)	18 (6)
Headache	24 (8)	31 (11)	10 (15)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47 (12)	58 (16)	24 (30)	40 (15)
Hypertension	21 (7)	16 (5)	3 (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22 (6)	20 (5)	4 (5)	14 (5)
ILI or influenza	17 (6)	14 (5)	3 (5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12 (3)	22 (6)	3 (4)	11 (4)
Pruritus	14 (5)	15 (5)	5 (7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21 (5)	16 (4)	11 (13)	16 (6)
Arthralgia	13 (4)	14 (5)	8 (12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33 (9)	24 (6)	10 (12)	23 (8)
Diarrhea	10 (3)	16 (5)	4 (6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36 (9)	38 (10)	7 (8)	22 (8)
Cough	5 (2)	16 (5)	3 (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15 (4)	30 (8)	4 (5)	12 (4)
Back pain	9 (3)	9 (3)	4 (6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20 (5)	31 (8)	6 (7)	26 (9)

	ERASURE			FEATURE			JUNCTURE			FIXTURE			
	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	ETA
Psoriasis	9 (3)	8 (3)	10 (15)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11 (3)	8 (2)	8 (10)	7 (2)
Nausea	8 (3)	3 (1)	8 (12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10 (3)	11 (3)	7 (8)	7 (2)

AE = adverse event; ILI = influenza-like illness; IR = incidence rate; NR = not reported; PL = placebo; PY = patient-year; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; URTI = upper respiratory tract infection.
[a] Includes rash, erythema, or swelling.
[b] IR per 100 patient-years was not reported for FEATURE or JUNCTURE.
[c] For the placebo group, data are to week 12 only in FEATURE; for JUNCTURE N = 3; for ERASURE N = 18; and for FIXTURE N = 17.
Source: Clinical Study Reports.[1-4]

TABLE 39: SERIOUS ADVERSE EVENTS (SAFETY SET)

	ERASURE			FEATURE			JUNCTURE			FIXTURE			
	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	ETA
INDUCTION PERIOD (up to week 12), n (%)													
N	245	245	247	59	59	59	61	60	61	327	326	327	323
Patients > 0 SAEs	4 (1.6)	6 (2.4)	4 (1.6)	0	3 (5.1)	1 (1.7)	3 (4.9)	1 (1.7)	1 (1.6)	7 (2.1)	4 (1.2)	6 (1.8)	3 (0.9)
Examples of SAEs[a]													
AMI	0	0	0	0	1 (1.7)	0	0	0	0	0	0	0	0
Anal abscess	0	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0
Bladder CA	1 (0.4)	0	0	0	0	0	0	0	0	0	0	0	0
BSC	1 (0.4)	0	0	0	0	0	0	0	0	0	0	0	0
Cardiac failure	1 (0.4)	0	0	0	0	0	1 (1.7)	0	0	0	0	0	0
Cellulitis	0	0	1 (0.4)	0	0	0	0	0	0	0	0	1 (0.3)	0
Crohn disease	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0
CVS accident	0	0	0	0	1 (1.7)	0	0	0	0	0	0	0	0
Dermatitis	0	0	0	0	0	1 (1.7)	1 (1.7)	0	0	0	0	0	0
Insomnia	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0
Nerve paralysis	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0
TIA	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)
Uterine leiomyoma	0	1 (0.4)	0	0	0	0	0	0	0	0	0	0	0
ENTIRE TREATMENT PERIOD, n (IR per 100 PYs) [c, d]													
N	353	349	247	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	469	467	327	323
Patients > 0 SAEs	19 (6)	19 (6)	5 (7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24 (6)	27 (7)	7 (8)	20 (7)

	ERASURE			FEATURE			JUNCTURE			FIXTURE			
	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	ETA
Examples of SAEs													
Benign skin neoplasm	0	0	1 (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
Cellulitis	0	0	1 (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1 (< 1)	1 (< 1)	1 (1)	1 (< 1)
Thyroid CA	2 (1)	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
TIA	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	1 (1)	2 (1)

AMI = acute myocardial infarction; BSC = basal cell carcinoma; CA = cancer; CVS = cardiovascular; ETA = etanercept; IR = incidence rate; NR = not reported; PL = placebo; PY = patient-year; SAE = serious adverse event; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; TIA = transient ischemic attack.
[a] Patients could report more than one SAE.
[b] Injury includes laryngeal injury, head injury, laceration, rib fracture, and tendon injury.
[c] IR per 100 patient-years was not reported for FEATURE or JUNCTURE.
[d] For placebo group, data are to week 12 only in FEATURE; for JUNCTURE N = 3; for ERASURE N = 18; for FIXTURE N = 17.
Source: Clinical Study Reports.[1-4]

TABLE 40: WITHDRAWAL DUE TO ADVERSE EVENTS (SAFETY SET)

	ERASURE			FEATURE			JUNCTURE			FIXTURE			
N (%)	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	ETA
INDUCTION PERIOD (up to week 12), n (%)													
N	245	245	247	59	59	59	61	60	61	327	326	327	323
Patients > 0 WDAEs	5 (2.0)	3 (1.2)	4 (1.6)	0	1 (1.7)	1 (1.7)	0	0	1 (1.6)	3 (0.9)	5 (1.5)	3 (0.9)	6 (1.9)
Examples of WDAEs													
Bladder CA	1 (0.4)	0	0	0	0	0	0	0	0	0	0	0	0
Cellulitis	0	0	1 (0.4)	0	0	0	0	0	0	0	0	0	0
Crohn disease	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0
CVS accident	0	0	0	0	1 (1.7)	0	0	0	0	0	0	0	0
Dermatitis, exfoliative	0	0	0	0	0	1 (1.7)	0	0	0	0	0	0	0
Eczema	0	1 (0.4)	0	0	0	0	0	0	0	0	1 (0.3)	0	0
Fall	0	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0
Herpesvirus infection	0	0	1 (0.4)	0	0	0	0	0	0	0	0	0	0
Hypertension	0	0	0	0	0	0	0	0	1 (1.7)	0	0	0	0

	ERASURE			FEATURE			JUNCTURE			FIXTURE			
N (%)	**SEC 150**	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**	**SEC 150**	**SEC 300**	**PL**	**ETA**
Injection-site AE[a]	0	0	0	0	0	0	0	0	0	0	0	0	2 (0.6)
Pharyngitis	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0
TIA	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)
Urticaria	0	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0
ENTIRE TREATMENT PERIOD, n (%) [b]													
N	353	349	247	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	469	467	327	323
Patients > 0 WDAEs	18 (5.1)	12 (3.4)	5 (2.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10 (2.1)	14 (3.0)	3 (0.9)	12 (3.7)
Examples of WDAEs													
Adenosquamous cell carcinoma	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
Aortic aneurysm	1 (0.3)	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
Aortic thrombosis	1 (0.3)	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
Arteriosclerosis	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	1 (0.3)
Atrial fibrillation	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1 (0.2)	0	0	0
Bladder CA	1 (0.3)	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
Carotid artery dissection	0	1 (0.3)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
Cellulitis	0	0	1 (0.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
Crohn disease	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1 (0.2)	0	0	0
CVA	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1 (0.2)	0	0	0
Dermatitis	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	1 (0.2)	0	0
Eczema	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	2 (0.4)	0	0
Fall	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	1 (0.2)	0	0
Hallucination	1 (0.3)	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
Herpesvirus infection	0	0	1 (0.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
Hypertension	0	1 (0.3)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2 (0.4)	0	0	0
Injection-site AE[a]	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	2 (0.6)
Ischemic stroke	1 (0.3)	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
Lung CA	1 (0.3)	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
MI	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	1 (0.3)
Nerve paralysis	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	1 (0.3)

N (%)	ERASURE			FEATURE			JUNCTURE			FIXTURE			
	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	ETA
Otitis externa	1 (0.3)	0	0	[redacted]						0	0	0	0
Pharyngitis	0	0	0							2 (0.4)		0	0
Septic vasculitis	0	0	0							0	0	0	0
Squamous cell carcinoma	0	0	0							0	0	0	0
Swelling face	1 (0.3)	0	0							0	0	0	0
TIA	0	0	0							0	0	0	1 (0.3)
Thyroid CA	1 (0.3)	0	0							0	0	0	0
Urosepsis	0	1 (0.3)	0							0	0	0	0
Urticaria	0	0	0							0	1 (0.2)	0	0

AE = adverse event; CA = cancer; CVA = cerebrovascular accident; CVS = cardiovascular; ETA = etanercept; IR = incidence rate; MI = myocardial infarction; NR = not reported; PL = placebo; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg; TIA = transient ischemic attack; WDAE = withdrawal due to adverse event.

[a] Includes edema (one patient) and rash (one patient).

[b] For placebo group, data are to week 12 only in FEATURE; for JUNCTURE N = 3; for ERASURE N = 18; for FIXTURE N = 17.

Source: Clinical Study Reports.[1-4]

TABLE 41: DEATHS AND NOTABLE HARMS (SAFETY SET)

	ERASURE			FEATURE			JUNCTURE			FIXTURE			
	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	ETA
INDUCTION PERIOD (up to week 12)													
Deaths													
n	0	0	0	0	0	0	0	0	0	0	0	0	0
Notable harms													
Infections and infestations													
n	66	72	40	12	9	9	24	26	19	101	87	63	79
%	26.9	29.4	16.2	20.3	15.3	15.3	39.3	43.3	31.1	30.9	26.7	19.3	24.5
Urticaria													
n	3	3	0	0	0	0	0	0	1	5	1	0	2
%	1.2	1.2	0	0	0	0	0	0	1.6	1.5	0.3	0	0.6
Cardiac disorders													
n	2	2	4	1	1	1	1	0	1	4	1	6	7
%	0.8	0.8	1.6	1.7	1.7	1.7	1.6	0	1.6	1.2	0.3	1.8	2.2

	ERASURE			FEATURE			JUNCTURE			FIXTURE			
	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	ETA
MACE (MI, non-fatal stroke, or CVS death)													
n	0	0	0	0	2	0	0	0	0	0	0	0	0
%	0	0	0	0	3.4	0	0	0	0	0	0	0	0
Lupus-like syndrome or exacerbation of lupus													
n	0	0	0	0	0	0	0	0	0	0	0	0	0
%	0	0	0	0	0	0	0	0	0	0	0	0	0
Exacerbation of psoriasis													
n	0	0	2	0	0	0	0	0	0	0	0	0	0
%	0	0	0.8	0	0	0	0	0	0	0	0	0	0
Neoplasm (malignant or benign)													
n	4	5	2	1	0	0	2	0	1	2	1	3	4
%	1.6	2.0	0.8	1.7	0	0	3.3	0	1.6	0.6	0.3	0.9	1.2
Malignancy													
n	2	1	1	1	0	0	1	0	0	0	0	1	0
%	0.8	0.4	0.4	1.7	0	0	1.6	0	0	0	0	0.3	0
Nervous system disorders													
n	19	20	12	4	4	3	6	5	4	30	39	31	29
%	7.8	8.2	4.9	6.8	6.8	5.1	9.8	8.3	6.6	9.2	12.0	9.5	9.0
Anaphylactic reaction													
n	0	0	0	2	3	3	0	0	0	1	0	0	0
%	0	0	0	3.4	5.1	5.1	0	0	0	0.3	0	0	0
ENTIRE TREATMENT PERIOD , n (IR per 100 PYs) [a, b]													
Deaths													
n	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
Notable harms													
Infections and infestations													
n	185	193	48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	240	269	65	170
IR	95.4	100	83.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91.9	105.4	89.5	91.4
Urticaria													
n	9	9	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9	4	0	3
IR	3.0	3.0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.2	1.0	0	1.0

	ERASURE			FEATURE			JUNCTURE			FIXTURE			
	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	SEC 150	SEC 300	PL	ETA
Cardiac disorders													
n	12	14	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16	13	6	15
IR	4.0	4.7	5.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.0	3.2	7.1	5.3
MACE (MI, non-fatal stroke, or CVS death)													
n	2	2	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2	0	0	1
IR	0.7	0.7	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.2	0	0	0.3
Lupus-like syndrome or exacerbation of lupus													
n	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
IR	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0	0	0
Exacerbation of psoriasis													
n	0	0	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	1	0	0
IR	0	0	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	NR	0	0
Neoplasm (malignant or benign)													
n	19	11	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15	20	3	10
IR	6.5	3.7	4.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3.7	5.0	3.5	3.5
Malignancy													
n	6	1	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2	3	1	2
IR	2.0	0.3	1.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Nervous system disorders													
n	41	47	16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	73	81	33	54
IR	14.8	17.2	24.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20.0	22.9	41.8	21.2
Anaphylactic reaction													
n	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1	0	0	0
IR	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	0	0	0

CVS = cardiovascular; ETA = etanercept; IR = incidence rate; MACE = major adverse cardiovascular events; MI = myocardial infarction; NR = not reported; PL = placebo; PY = patient-year; SEC 150 = secukinumab 150 mg; SEC 300 = secukinumab 300 mg.

[a] IR was not reported for some outcomes (FEATURE or JUNCTURE).

[b] For placebo group, data are to week 12 only in FEATURE; for JUNCTURE N = 3; for ERASURE N = 18; for FIXTURE N = 17.

Source: Clinical Study Reports.[1-4]

APPENDIX 6: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- Dermatology Life Quality Index (DLQI)
- EuroQol Five-Dimension Health-Related Quality of Life Questionnaire (EQ-5D)
- Investigator's Global Assessment (IGA)
- Psoriasis Area and Severity Index (PASI)
- Psoriasis Symptom Diary.

Findings

TABLE 42: 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[28] Ruderman et al. 2003[29] Shikiar et al. 2006[23]
EQ-5D	General, generic health-related quality of life questionnaire	Yes	0.09 to 0.20	Norlin et al. 2012[30] Shikiar et al. 2006[23]
IGA mod 2011	5-point (0 to 4) static scale used to assess the severity of plaque psoriasis	Yes	Unknown	Langley et al. 2013[27]
PASI	Numeric score ranging from 0 to 72, based on assessments of 4 body areas and severity of induration, erythema, and scaling	Yes	Unknown	Ashcroft et al. 1999[31] Carlin et al. 2004[32] Feldman et al. 2004,[33] Gourraud et al. 2012[34]
Psoriasis Symptom Diary	20-item, psoriasis-specific patient-reported outcome questionnaire	Yes	2.0 to 3.0	Lebwohl et al. 2014[21] Strober et al. 2013[35]

DLQI = Dermatology Quality of Life Index; EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; IGA mod 2011 = Investigator's Global Assessment modified 2011; MCID = minimal clinically important difference; PASI = Psoriasis Area and Severity Index.

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 (one or two questions per aspect).[3] These aspects are symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[3] The maximum score per aspect is either 3 or 6, and the scores for each can be expressed as a percentage of either 3 or 6. Each of the 10 questions is scored from 0 (not at all) to 3 (very much), and the overall DLQI is calculated by summing the score of each question, resulting in a numeric score between 0 and 30 (or a percentage of 30).[29] 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:[36]

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

- 21 to 30 = extremely large effect.

The DLQI has shown good reliability and construct validity.[29] The estimated MCID for the DLQI in patients with psoriasis is 3.2.[28] Estimates of the minimal clinically important difference (the smallest difference a patient would regard as beneficial) have ranged from 2.3 to 5.7.[23]

- A number of limitations of the DLQI have been identified: Concerns regarding unidimensionality and the behaviour of items of the DLQI in different psoriatic patient populations with respect to their age, gender, culture, etc.[36]
- The patient's emotional aspects may be under-represented, and this may be one reason for unexpectedly low DLQI scores in patients with more emotionally disabling diseases such as vitiligo. To overcome this, it is suggested that the DLQI be combined with more emotionally oriented measures such as the mental component of the Short-Form 36-Item Health Survey (SF-36) or HAQ scales.[36]
- Benchmarks for the minimal clinically important difference 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.[36]
- DLQI may lack sensitivity in detecting change from mild to severe psoriasis.[37]

EuroQol Five-Dimension Health-Related Quality of Life Questionnaire

The EQ-5D is a generic quality of life (QoL) instrument that may be applied to a wide range of health conditions and treatments.[38] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged 12 years or older) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[38] The second part is a 20 cm visual analogue scale (EQ-5D VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-5D VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
2. A population preference-weighted health index score based on the descriptive system
3. A self-reported assessment of health status based on the EQ-5D VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or United Kingdom [UK]). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than death, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported minimal clinically important differences (MCIDs) for this scale have ranged from 0.033 to 0.074.[39] The MCIDs were derived from patients with a variety of chronic and acute conditions, including rheumatoid arthritis, osteoarthritis, irritable bowel syndrome, and acute myocardial infarction.[40,41]

The evidence for the validity of EQ-5D in the psoriasis population is limited. A Swedish observational cohort study found good correlation of EQ-5D with outcome measures DLQI and PASI.[30] However, EQ-5D was not as responsive to change in patients' clinical status as the DLQI, and the study authors

recommend the use of EQ-5D in conjunction with DLQI and PASI.[30] An additional study found the EQ-5D to be highly correlated with the DLQI, although not as responsive to change in patient status.[23] EQ-5D showed responsiveness similar to that of another generic health-related QoL measure, the SF-36.[23] Estimates of the MCID for EQ-5D in psoriasis were derived using distributional and anchor-based approaches.[23] PASI and Physician Global Assessment (PGA) were used in the anchor-based approach for determining MCID, and are as follows: an estimate obtained using PASI scores of near-responders (PASI 25 to PASI 49), an estimate obtained using the PASI scores of partial responders (PASI 50 to PASI 74), and an estimate based on the difference between non-responders and minimal responders using the PGA.[23] The estimated MCID for EQ-5D in the psoriasis population ranges from 0.09 to 0.20.[23] This estimated MCID, compared with the general MCID range of 0.033 to 0.074, suggests that a larger difference in EQ-5D score is necessary for psoriasis patients to regard the change as clinically beneficial.

Investigator's Global Assessment

The IGA is an investigator's impression of psoriasis severity. The trials for secukinumab (ERASURE, FIXTURE, JUNCTURE, and FEATURE) employed the IGA mod 2011, a five-point static scale, ranging from 0 to 4.[1-4] The static IGA scale is based on a point-in-time assessment, as opposed to the dynamic IGA scale, which is based on a recollection of the baseline disease severity.[27] The PGA denotes scales used by clinicians, whereas the IGA is used by investigators in clinical trials.[27]

The following outlines the possible scores on the IGA mod 2011 scale:[1-4,27]

- 0 = clear (e.g., no signs of psoriasis, some post-inflammatory hyperpigmentation may be present)
- 1 = almost clear (e.g., no thickening, normal or pink coloration)
- 2 = mild (e.g., mild thickening, pink to light red coloration)
- 3 = moderate (e.g., moderate thickening, dull to bright red)
- 4 = severe (e.g., severe thickening, bright to deep red).

A recent review of the IGA reported the following advantages of this scale: it is relatively simple and easy to use; it shows good correlation with PASI; and it has high clinical construct validity, test–retest reliability, good usage of the entire range of the scale, and moderate agreement among multiple assessors.[27] Limitations of the scale include inability to measure extent of psoriasis; it may not be able to discriminate small changes in severity; it does not take into consideration non-skin symptoms; and multiple versions of the scale limit study or trial comparisons.[27] Furthermore, reliance on defining categories in part by lesion coloration reflects the a potential bias to use among Caucasian patient populations and it may not be generalizable to other populations. The MCID has not been established at this time.

Psoriasis Area and Severity Index

The PASI, a widely used instrument in psoriasis trials, assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It produces a numeric score ranging from zero to 72. In general, a PASI score of 5 to 10 is considered moderate disease, and a score of 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 US Food and Drug Administration.[32]

In calculating the PASI, severity is determined by dividing the body into four regions: head (h), upper extremities (u), trunk (t), and lower extremities (l), which account for 10%, 20%, 30%, and 40% of the total body surface area (BSA), respectively.[42] 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:

$$PASI = 0.1 (E_h + I_h + S_h) A_h + 0.2 (E_u + I_u + S_u) A_u + 0.3 (E_t + I_t + S_t) A_t + 0.4 (E_l + I_l + S_l) A_l$$ [42]

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

A number of limitations of the PASI have been identified:

- The PASI has been criticized as not correlating the clinical extent of the disease with QoL and the psychological stress caused by psoriasis. The patient's measure of QoL is often worse than the physician-rated clinical severity.[43]
- There are significant inter-rater reliability issues regarding the measurement of BSA.[31,33] There has been some work regarding the development of imaging and analysis systems to objectively measure BSA.[44]
- PASI scores can vary substantially between experienced and inexperienced physicians, raising concerns about inter-rater reliability.[45]
- Improvements in PASI score are not linearly related to severity or improvements in psoriasis.[32,33] The extent of psoriatic involvement is measured using a scale of 1 to 6, and the areas corresponding to each score are nonlinear.
- Some severe disease (clinically) may be scored low. For example, scores as low as 3 (on palms and soles) may represent psoriasis that disables a patient from work and other life activities.
- Most patients fall into a narrow band of scores, thereby decreasing the usefulness of the full range of scores (i.e., scores above 40 are rare).[31] Validity of this scale may be overrated, in part because of the skew toward lower scores.[34]
- There is little research on the reliability of the assessments for erythema, desquamation, and induration, together with overall PASI scores.[31]
- Criterion validity is restricted by the lack of a "gold standard" measure of psoriatic severity.[46]
- 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).[32]
- Little work has been done to determine the clinical relevance of derived PASI scores.[31]

Psoriasis Symptom Diary

The Psoriasis Symptom Diary is a 20-item, psoriasis-specific electronic diary to assess symptom severity, symptom bother, and disease impact.[21,35] Patients are asked to recall their disease experience over the preceding 24 hours.[21,35] The severity and bother of the following symptoms are assessed: itching, stinging, burning, pain, scaling, and skin colour.[21,35] Impact items ask about patient embarrassment, restricted movement due to psoriasis, and avoidance of activities requiring interaction with other people.[21,35] A 0 to 10 numeric scale is used to assess impact, symptom severity, symptom bother; higher scores indicate more severe impact, bother, or severity (0 = symptom not experienced, 10 = symptom "as bad as you can imagine").[21,35] Patients are prompted to respond to questions about bother only when they have indicated a score greater than 0 for the severity questions.[35] For example, if patients indicate a score greater than 0 for skin cracking, they are then asked how bothered they are by their skin cracking. Responses for skin colour are categorical and include: pink; light red or brown; bright red or purple; deep, dark red, purple, or brown; grey, white, or silver.[21,35] The Psoriasis Symptom Diary was developed in accordance with the US Food and Drug Administration's guidelines for development of new patient-reported outcome instruments, which requires patient input in the instrument development.[21]

The MCIDs for Psoriasis Symptom Diary severity items (itching, burning, stinging, cracking, pain, and scaling) and change in skin colour are estimated to be 2.0 to 3.0.[35] An anchor-based approach was used to determine the MCID; means and standard deviations for Psoriasis Symptom Diary item scores were calculated and compared with levels of change on the Patient Global Impression of Change.[35] The Psoriasis Symptom Diary has shown good construct validity; symptom severity items were associated with the IGA and PASI, while bother items are associated with the DLQI.[35] Items on itching for the Psoriasis Symptom Diary are associated with the Pruritus Visual Analog Scale, DLQI, IGA, and PASI.[35] The Psoriasis Symptom Diary has also shown good discriminant validity and sensitivity to patient change.[35]

There are several limitations of the Psoriasis Symptom Diary. The tool was developed using a small sample of patients.[21] Additionally, its validity was assessed using a predominantly Caucasian patient population (96% Caucasian), and it may not be generalizable to other populations; this is especially a consideration for items such as skin colour.[35] Adherence with the tool outside of the clinical trial environment is yet to be seen.[35]

Conclusion

Several instruments are used when assessing psoriasis disease severity. 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.[44,47,48] The Psoriasis Symptom Diary is used to assess a patient's symptom experience.[21]

QoL measures are also important in the assessment of psoriasis severity. DLQI is a dermatology-specific QoL measure. DLQI has been validated for use in the psoriasis patient population, with an estimated minimal clinically important of 3.2.[28] EQ-5D is a general health QoL measure. There is evidence for the concurrent validity of the EQ-5D in the psoriasis patient population, as it correlates well with DLQI and PASI.[30] QoL remains an important consideration for assessing severity of disease for patients with psoriasis.

APPENDIX 7: SUMMARY OF MIXED TREATMENT COMPARISON

1. Objective

This brief provides a summary and critical appraisal of the methods and main findings of a mixed treatment comparison (MTC) provided by the manufacturer of secukinumab.

2. Summary of Mixed Treatment Comparison

[redacted]

Methods

Eligibility Criteria

[redacted]

[redacted]

Mixed Treatment Comparison

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] (Table 43). [redacted]

[redacted]

TABLE 43: DEVIANCE INFORMATION CRITERIA FOR RANDOM AND FIXED EFFECTS MTC AT WEEK 12

[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]

Source: Additional manufacturer information.[20]

[redacted]

[redacted]

[redacted] in Figure 9 and Figure 10.

FIGURE 9: NETWORK DIAGRAM FOR PSORIASIS AREA AND SEVERITY INDEX 75 AT 12 WEEKS FOR BINOMIAL MTC

Figure 9 contained confidential information and was removed at the request of the manufacturer.

[redacted]

Source: CADTH Common Drug Review submission.[8]

FIGURE 10: NETWORK DIAGRAM AT 12 WEEKS FOR ORDINAL MIXED TREATMENT COMPARISON

Figure 10 contained confidential information and was removed at the request of the manufacturer.

[redacted]

Source: CADTH Common Drug Review submission.[8]

Results

Baseline Characteristics

A total of [redacted] trials were found; some trials contained multiple treatments. The MTC included [redacted]

[redacted]

[redacted]

Results of Mixed Treatment Comparison

[redacted].

[redacted] ***(Figure 11)***. [redacted]

FIGURE 11: FOREST PLOT FOR PASI 75 AT 12 WEEKS FROM BINOMIAL MTC (RANDOM EFFECTS)

Figure 11 contained confidential information and was removed at the request of the manufacturer.

[redacted]

Source: CADTH Common Drug Review submission.[8]

[redacted]
(Table 44).
[redacted]

[redacted]
(Table 44).
[redacted]

TABLE 44: PAIRWISE ODDS RATIOS FROM BAYESIAN MTC FOR PASI 75 AT 12 WEEKS (RANDOM EFFECTS)

Abbreviations	Description of Treatment Regimens[a]	SEC 150 mg OR (95% CrI)	SEC 300 mg OR (95% CrI)
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted][b]			
[redacted]			

[redacted]

[a] Recommended dosages in Canada[15] (the current recommended doses are bolded in the table):

[redacted]

[b] [redacted]

Source: CADTH Common Drug Review submission.[8]

[redacted] (Figure 12).

FIGURE 12: PREDICTED RESPONSE RATES FOR PASI 75 AT 12 WEEKS (RANDOM EFFECTS)

Figure 12 contained confidential information and was removed at the request of the manufacturer.

PASI = Psoriasis Area and Severity Index.
Source: CADTH Common Drug Review submission.[8]

Ordinal Results — PASI at 12 Weeks

[redacted] (Figure 13). [redacted]

FIGURE 13: FOREST PLOT FOR PROBIT SCORES AT 12 WEEKS FROM ORDINAL MTC MODEL (RANDOM EFFECTS)

Figure 13 contained confidential information and was removed at the request of the manufacturer.

[redacted]
Source: CADTH Common Drug Review submission.[8]

[redacted] (Table 45).

TABLE 45: PAIRWISE ODDS RATIOS FROM BAYESIAN MTC FOR PASI AT 12 WEEKS (RANDOM EFFECTS)

Abbreviations	Description of Treatment Regimens[a]	SEC 150 mg OR (95% CrI)[b]	SEC 300 mg OR (95% CrI)[b]
[redacted]			

Abbreviations	Description of Treatment Regimens[a]	SEC 150 mg OR (95% CrI)[b]	SEC 300 mg OR (95% CrI)[b]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[a] Recommended doses in Canada[15] (the current recommended doses are bolded in the table):

[redacted]

- [redacted]

b [redacted]

Source: CADTH Common Drug Review submission.

[redacted] (figure not shown).

Sensitivity Analyses

[redacted].

Heterogeneity

[redacted].

Data by Combined Treatments (Data and Figures Not Shown)

[redacted]

Data at 16 Weeks (Data and Figures Not Shown)

[redacted]

[redacted]

[redacted]

3. Critical Appraisal of Mixed Treatment Comparison

The manufacturer-submitted MTC was appraised according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[49] Details and commentary for each of the relevant items identified by ISPOR are provided in Table 46.

Strengths

Eligibility criteria for inclusion of trials into the MTC were clearly stated. The search strategy and methods for selecting studies were comprehensive. The data extraction strategy was also described. The MTC considered PASI 50/75/90, and two types of analyses, binomial and ordinal, were conducted. The addition of an ordinal analysis was to account for issues such as low response numbers. Quality was assessed for each included trial. The authors employed a Bayesian network meta-analysis and included figures that summarized the network. Pairwise comparisons and predicted response rates were presented.

Limitations

The literature search is dated, as it ended in June 2013, almost two years ago. Since then, there may have been new trials published, and these would have been excluded from the analysis, potentially affecting the conclusions of the MTC.

Baseline PASI scores [redacted] considered [redacted] for heterogeneity. [redacted].
The study populations were fairly heterogeneous for other characteristics such as age, gender, and treatment experience. Some trials included patients who were naive to biologic treatments. It is unclear whether biologic-naive patients would have a better response than biologic-experienced patients. The treatment history with other systemic therapies was not considered either. This could affect the generalizability of the findings.

The number of included trials per drug was [redacted]. A relatively low number of included trials may have introduced uncertainty into the analysis.

Study duration, an important study characteristic, was not reported for each trial. Data were analyzed at four weeks and eight weeks, and the relevance of doing so was not clear, as few patients would be expected to obtain a clinically meaningful benefit after such short periods of time. As such, it was decided not to report these results in the CDR summary. The induction period for secukinumab ended at 12 weeks in the included clinical trials. For some treatment regimens, 12 weeks would have been inadequate for patients to receive enough doses (for example, UST 45 mg or 90 mg once then repeated at 16 weeks if required); some dosage regimens were also sub-therapeutic (for example, etanercept 25 mg once weekly) or supra-therapeutic (for example, ADA 80 mg every two weeks), according to recommendations in product monographs. MTC results were also presented at 16 weeks, but because of the differences in study design, data had to be estimated for secukinumab. As these treatments are

used long-term, and as determination of response needs to be measured after at least six months of treatment, according to the clinical expert consulted for this review, 12 or 16 weeks of data may not show the real picture of how these drugs will perform against each other.

Several comparators that are used in plaque psoriasis, such as cyclosporine, acitretin, and apremilast, were not included in the analysis, perhaps because these drugs are administered orally. The reasons for excluding these comparators were not made clear in the MTC. More importantly, harms and withdrawals due to harms were not considered in the MTC, and no reasons were provided as to why they were excluded. In clinical practice, the decision to use a particular medication would be based on benefit versus risk as well as likelihood of adherence to treatment. Without information on the relative harms of these medications, half of the treatment picture is missing.

It was unclear how the analyses at 16 weeks were carried out. If placebo non-responders at 12 weeks were considered non-responders at 16 weeks, this would have biased the results in favour of secukinumab.

[redacted]

Publication bias was not assessed.

Heterogeneity between trials was assessed [redacted]. [redacted] baseline PASI [redacted]. Other potential effect modifiers were not considered; some differences between trials were present, but the cause of these differences could not be explained. Although clinical heterogeneity was assessed through sensitivity analyses (exclusion of trials with different patient characteristics from the network), the results of these analyses were not in the submission.

TABLE 46: APPRAISAL OF MANUFACTURER-SUBMITTED MTC ACCORDING TO THE ISPOR QUESTIONNAIRE

	Questions	Comments
Relevance	Is the population relevant? Disease of interest • Stage of disease and severity • Treatment history • Baseline demographics	• Relevant population • Wide range of PASI scores at baseline; some trials did not report a minimum PASI score as an inclusion criteria • Trials with patients naive or experienced to biologics were not considered separately in the MTC • Majority of trials were conducted in males
	Are any relevant interventions missing? • Have all relevant comparators been considered?	Other relevant comparators such as cyclosporine, acitretin, and apremilast were not included in the analysis.
	Are any relevant outcomes missing?	Only considered PASI; no analyses done on harms and withdrawals due to harms
	Is the context (settings and circumstances) applicable? • Is real-world compliance or adherence taken into account?	• Compliance and adherence to treatment were not taken into consideration • Treatment regimens of the comparators were, for the most part,

	Questions	Comments
		not recommended doses (some were sub-therapeutic doses).
Credibility	Did the researchers attempt to identify and include all relevant RCTs? • Search strategy targeted all RCTs for interventions of interest? • Multiple databases accessed? • Appropriate selection criteria?	The literature search was comprehensive; however, the search ended in June 2013, almost 2 years ago, which would have excluded trials meeting the inclusion criteria of the systematic review published since then. Guidelines and product monographs should have been reviewed for determining appropriate dosage regimens of the included treatments.
	Do the trials for the interventions of interest form one connected network of RCTs?	Yes
	Is it apparent that poor-quality studies were included, thereby leading to bias? Consider: • Method of randomization • Allocation concealment • Blinding • Dropout	Quality was assessed for each trial — unclear allocation concealment was common ([redacted])
	Is it likely that bias was induced by selective reporting of outcomes in the studies? • Reasons for study exclusion • Publication bias	• Study exclusions were done for 2 treatments: briakinumab, which is not marketed in Canada, and infliximab, which is administered via infusion • Publication bias not assessed
	Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that have an impact on the treatment effects) across the different treatment comparisons in the network? • A priori list of potential effect modifiers.	Baseline PASI was taken into consideration in the analysis; no other characteristics were considered.
Analysis	Were statistical methods used that preserve within-study randomization? (no naive comparisons)	Yes
	If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops), was agreement in treatment effects (i.e., consistency) evaluated or discussed?	Yes
	In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Yes
	With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	No
	Was a valid rationale provided for the use of random effects or fixed effect models?	Both were provided, but the main results focused on random effects given that it gave the most conservative results.
	If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Yes

	Questions	Comments
	If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	[redacted]
Reporting Quality and Transparency	Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes
	Are the individual study results reported?	Yes
	Are results of direct comparisons reported separately from the results of the indirect comparisons or network meta-analysis?	Yes
	Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes
	Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes
	Is the effect of important patient characteristics on treatment effects reported?	Yes

ISPOR = International Society for Pharmacoeconomics and Outcomes Research; MTC = mixed treatment comparison; PASI = Psoriasis Area and Severity Index; RCT = randomized controlled trial.

4. Summary

In the binomial MTC, there were [redacted] between secukinumab 300 mg and [redacted]

[redacted]

[redacted] (Table 47). Secukinumab 300 mg [redacted]

[redacted]

[redacted]

TABLE 47: SUMMARY OF RESULTS FOR PASI 75 AT 12 WEEKS (BINOMIAL MTC, RANDOM EFFECTS) FOR TREATMENT REGIMENS USED AT RECOMMENDED DOSES

	Treatment Regimens (At Recommended Dose in Canada for the 12-Week Duration)	Pairwise Comparison With SEC 300 OR (95% CrI)	Predicted Response Rates OR (95% CrI)
[redacted]			

[redacted]

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