Common Drug Review
Clinical Review Report

August 2016

Drug	Secukinumab (Cosentyx)
Indication	For the treatment of adult patients with active psoriatic arthritis when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. COSENTYX can be used alone or in combination with methotrexate.
Reimbursement request	[redacted]
Dosage form(s)	Pre-filled syringe or pen for subcutaneous injection, 150 mg/mL
NOC date	April 20, 2016
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

ACE	Arthritis Consumer Experts
ACR	American College of Rheumatology
AE	adverse event
CAPA	Canadian Arthritis Patient Alliance
CDR	CADTH Common Drug Review
CRP	C-reactive protein
CSA	Canadian Spondylitis Association
CSPA	Canadian Skin Patient Alliance
DAS	Disease Activity Score
DIP	distal interphalangeal
DLQI	Dermatology Life Quality Index
DMARDs	disease-modifying antirheumatic drugs
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	health assessment questionnaire-disability index
HRQoL	health-related quality of life
IDC	indirect comparison
IL	interleukin
IR	inadequate responder
IRT	interactive response technology
ITT	intention to treat
LDI	Leeds Dactylitis Index
LOCF	last observation carried forward
MAR	missing at random
MCID	minimal clinically important difference
MCS	mental component summary
MDA	minimal disease activity
MMRM	mixed-effect model repeated measures
mNAPSI	Modified Nail Psoriasis Severity Index
MTX	methotrexate
NMA	network meta-analysis
NSAID	nonsteroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PCS	physical component summary
PFS	pre-filled syringes
PIP	proximal interphalangeal
PsA	psoriatic arthritis

PsAQoL	Psoriatic Arthritis Quality of Life
RCT	randomized controlled trial
SC	subcutaneous
SAE	serious adverse event
SEC	secukinumab
SF-36	Short Form (36) Health Survey
SJC	swollen joint count
SpA	spondyloarthritis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF	tumour necrosis factor
VAS	visual analogue scale
vdH-mTSS	van der Heijde modified total Sharp score
WPAI-GH	Work Productivity and Activity Impairment – General Health

EXECUTIVE SUMMARY

Introduction

Psoriatic arthritis (PsA) is a heterogeneous disease associated with multiple and variable clinical features. Patients suffer from chronic inflammatory peripheral arthritis and may also suffer from skin and nail disease, axial disease, dactylitis, and enthesitis, highlighting how this disease affects more than just the joints of the patient.[1,2] The prevalence of PsA is suggested to be similar to that of rheumatoid arthritis[3] and is estimated to vary from 0.3% to 1% of the population.[1] Nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs; i.e., methotrexate [MTX], sulfasalazine, leflunomide), immunosuppressives (cyclosporine), tumour necrosis factor alpha (TNF alpha) inhibitors (i.e., etanercept, infliximab, golimumab, adalimumab, certolizumab), ustekinumab (a fully human IgG1 kappa monoclonal antibody that is an interleukin [IL]-12 and IL-23 inhibitor), and apremilast (a small-molecule inhibitor of phosphodiesterase 4 [PDE-4i]) are the typical drug therapies used to treat PsA.[4]

Secukinumab (SEC) is a fully human IgG1 kappa monoclonal antibody that selectively binds and neutralizes IL-17A, a naturally occurring cytokine involved in normal inflammatory and immune responses. Patients with PsA have increased levels of IL-17A in the blood. SEC targets IL-17A and inhibits its interaction with the IL-17 receptor.[5] The Health Canada Notice of Compliance is for the treatment of adult patients with active PsA when the response to previous DMARD therapy has been inadequate. SEC can be used alone or in combination with MTX.[5] The Health Canada–recommended dose for adult patients is 150 mg by subcutaneous (SC) injection, with initial dosing at weeks 0, 1, 2, and 3, followed by monthly maintenance dosing starting at week 4. For PsA patients with coexistent moderate to severe plaque psoriasis, the dosing and administration recommendations for plaque psoriasis are to be used (300 mg by SC injection, with initial dosing at weeks 0, 1, 2, and 3, followed by monthly maintenance dosing starting at week 4). If a patient is an anti-TNF alpha inadequate responder (IR) and continues to have active psoriatic arthritis, the 300 mg dose should be considered.[5]

The objective of this review is to perform a systematic review of the beneficial and harmful effects of SEC (Cosentyx) at the recommended dose for the treatment of adult patients with active PsA.

Indication under review
For the treatment of adult patients with active psoriatic arthritis when the response to previous disease-modifying antirheumatic drug (DMARD) therapy has been inadequate. COSENTYX can be used alone or in combination with methotrexate
Listing criteria requested by sponsor
[redacted]

Results and Interpretation

Included Studies

Two manufacturer-sponsored, phase 3, multi-centre, randomized, double-blind, placebo-controlled trials, FUTURE 1 (N = 606) and FUTURE 2 (N = 397), met the inclusion criteria for this systematic review. The trials included patients who had symptoms of moderate to severe PsA for at least six months. Twenty-nine per cent of patients included in FUTURE 1 were anti-TNF alpha IRs, while 37% of patients included in FUTURE 2 trial were anti-TNF alpha IRs. FUTURE 1 was a three-group superiority study that evaluated the efficacy and safety of SEC 150 mg or SEC 75 mg SC every four weeks compared with placebo, and FUTURE 2 was a four-group superiority trial that evaluated the efficacy and safety of SEC 300 mg SC, SEC 150 mg SC, or SEC 75 mg SC every four weeks compared with placebo, following the induction period in both trials. The primary efficacy end point in both included trials was the proportion of patients in each treatment group who achieved American College of Rheumatology (ACR) 20 response at week 24. Patients were considered ACR20 responders if they had at least 20% improvement from baseline in swollen and tender joint counts, as well as for any three of the five ACR criteria. At week 16 (visit 8), patients were classified as responders (improvement of 20% or more from baseline in both tender and swollen joint counts) or non-responders. In the FUTURE 1 trial, patients in the placebo group who were responders remained on placebo until week 24. At week 24, these patients were re-randomized (1:1) to receive SEC either 75 mg or 150 mg SC every four weeks. Patients in the placebo group who were non-responders were re-randomized (1:1) at week 16 to receive SEC either 75 mg or 150 mg SC every four weeks. In FUTURE 2 trial, patients in the placebo group who were non-responders were re-randomized to receive SEC 150 mg SC or 300 mg SC (1:1) every four weeks; patients in the placebo group who were responders continued to receive placebo every four weeks until week 24. At week 24, these patients were re-randomized to receive SEC 150 mg SC or 300 mg SC (1:1) every four weeks regardless of responder status. In the FUTURE 2 trial, investigators and patients remained dose-blinded until after week 52 analysis. Only SEC 150 mg and SEC 300 mg are the Health Canada–approved dose for the treatment of active PsA, and therefore only data for these doses are included in the current report.

No trials directly comparing SEC with other biologic response modifiers were found in the scientific literature. Both trials had an appropriate randomization strategy, with generally similar treatment groups at baseline. In FUTURE 1 and FUTURE 2, 69% and 66% of placebo patients, respectively, discontinued randomized treatment before week 24 (either owing to early escape or because of treatment discontinuation). This means that a substantial proportion of the outcome data at week 24 had to be imputed based on an intention-to-treat analysis. Therefore, there is a very high degree of uncertainty with respect to the findings of the studies beyond the week 16 time point. Subgroup analyses for patients with previous anti-TNF alpha use were performed. No subgroup analyses by disease severity were performed. Statistical significance of outcomes was assessed according to a hierarchical testing procedure for selected efficacy outcomes (ACR20 at week 24, Psoriasis Area and Severity Index [PASI] 75 and PASI 90 response at week 24, change from baseline in Disease Activity Score [DAS] 28-C- reactive protein [CRP] at week 24, change from baseline in the physical component summary [PCS] of the Short Form [36] Health Survey [SF-36] at week 24, change from baseline in health assessment questionnaire-disability index [HAQ-DI] at week 24, ACR50 response at week 24, and change from baseline in van der Heijde modified total Sharp score [vdH-mTSS] at weeks 24 [only in the FUTURE 1 trial]). Thus, all other outcomes, as well as subgroup analyses, were not adjusted for multiplicity and should be interpreted with caution because of the potential for inflated type I error. The reviewer focused primarily on the results from the FUTURE 2 trial, which used the SC loading and maintenance dose, matching the Health Canada–recommended dose. The FUTURE 1 trial was also reviewed, but

more as supportive data, since it uses the intravenous rather than SC route of administration for induction, which is not the dosing regimen recommended by Health Canada.

Efficacy

The primary efficacy outcome in both trials was ACR20 response at week 24. In the FUTURE 2 trial, both SEC treatment groups were statistically significantly superior to placebo for ACR20 response at week 24 (54% for SEC 300 mg versus 15% for placebo, $P < 0.0001$; 51% for SEC 150 mg versus 15% for placebo, $P < 0.0001$). In the subgroup of TNF alpha inhibitor–naive patients, a statistically significantly greater proportion of the SEC 150 mg treatment group achieved an ACR20 response at weeks 16 and 24 compared with placebo. Also, in the subgroup of TNF alpha inhibitor–IR patients, a statistically significantly greater proportion of in the SEC 150 mg and SEC 300 mg treatment groups achieved an ACR20 response at weeks 16 and 24 compared with placebo. However, these subgroup analyses (at both weeks 16 and 24) were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error. The clinical expert involved in the review noted that the difference in ACR20 response compared with placebo at 16 and 24 weeks was clinically meaningful.

Other clinical response outcomes (ACR50, ACR70, minimal disease activity [MDA], DAS 28-CRP, PASI 75, PASI 90, improvement in dactylitis and enthesitis, and Modified Nail Psoriasis Severity Index [mNAPSI]) at weeks 16 and 24 also demonstrated a statistically significant and clinically meaningful difference favouring both SEC treatment groups compared with placebo. However, all clinical response outcomes at week 16, and outcomes ACR70, MDA, and mNAPSI at week 24, were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error. Also, presence of dactylitis in the SEC 300 mg at week 16 and Leeds Dactylitis Index (LDI) in both SEC treatment groups at week 24 were not statistically significantly improved in comparison with placebo. The clinical expert involved in the review noted that the proportion of patients with complete resolution of dactylitis and enthesitis versus placebo is clinically meaningful. In addition, a claim of statistical significance could not be made for ACR50 at week 24 in the SEC 150 mg treatment group because the outcome assessed in the hierarchy (HAQ-DI) did not achieve statistical significance; hence, the hierarchical testing was stopped before testing ACR50 in the SEC 150 mg treatment group. Results of the subgroup analyses when undertaken for prior anti-TNF alpha–IR in the SEC 300 mg treatment group and anti-TNF alpha–naive in the SEC 150 mg treatment group were generally in line with results from the overall population for these outcomes, especially at week 24; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error. The effectiveness of the two dosing regimens of SEC for the treatment of PsA patients observed at week 24 appeared to be maintained up to week 52 (as was reported in the extension study in APPENDIX 6: SUMMARY OF EXTENDED DATA IN FUTURE 1 AND FUTURE 2). However, the lack of a comparator limits the conclusions that may be drawn from the dose-blind and extension phases. Overall, results seen in the SEC 150 mg treatment group in the FUTURE 1 trial appeared to be similar to those reported in the SEC 150 mg treatment group in FUTURE 2 trial.

Results of the health-related quality of life (SF-36) scores revealed an improvement from baseline in PCS scores. The difference in change from baseline between the SEC 300 mg treatment group and placebo and between the SEC 150 mg treatment group and placebo exceeded the established minimal clinically important difference (MCID), which is typically 3.74. The difference in change from baseline to week 24 in SF-36 PCS scores for both treatment groups was statistically significantly higher than in the placebo group. There were no statistically significant differences between either SEC treatment group compared

with placebo group at week 24 in the mental component summary (MCS) scores of the SF-36. The difference in change from baseline between the SEC 300 mg treatment group and the placebo group was 0.26, and the difference between the SEC 150 mg treatment group and the placebo group was 2.39. Thus, the difference between the SEC 150 mg treatment group and placebo exceeded the MCID of 1.77 for the SF-36 MCS score. Overall, similar results were seen in the SEC 150 mg treatment groups in the FUTURE 1 and FUTURE 2 trials for the SF-36. The Psoriatic Arthritis Quality of Life (PsAQoL), a quality-of-life instrument specific to psoriatic arthritis, indicated that both SEC 150 mg and SEC 300 mg groups in the FUTURE 2 trial had statistically significantly greater improvement relative to placebo for the difference in change from baseline at weeks 16 and 24; this was also true in FUTURE 1, at weeks 16 and 24. There is no MCID specified for PsAQoL; hence, it is difficult to determine whether the difference in results between SEC regimens and placebo was clinically meaningful. The Dermatology Life Quality Index (DLQI) is a widely used dermatology-specific quality-of-life instrument; it indicated that both SEC 150 mg and SEC 300 mg groups in the FUTURE 2 trial had statistically significantly greater improvement relative to placebo for mean score change at weeks 16 and 24; similarly, this was true in the FUTURE 1 trial, at weeks 16 and 24. In both trials, the difference in change from baseline between-treatment groups and placebo exceeded the established MCID (3.2) for DLQI in patients with psoriasis at weeks 16 and 24. The outcome measures MCS of the SF-36, PsAQoL, and DLQI were not part of the hierarchical analysis plan and therefore were not adjusted for multiple comparisons; hence, the level of significance is inflated and results should be interpreted taking this into consideration.

Arthritis pain in patients was assessed using patient's assessment of pain using visual analogue scale (VAS). In the FUTURE 2 trial, both SEC 150 mg and SEC 300 mg groups had statistically significantly greater improvement relative to placebo for mean score change at weeks 16 and 24; similarly, in the FUTURE 1 trial, the SEC 150 mg treatment group had statistically significantly greater improvement relative to placebo for mean score change at weeks 16 and 24. In both trials, the change between-treatment groups and placebo exceeded the established MCID of patient's assessment of pain, defined as an improvement (reduction) in pain of 10 mm on the VAS at weeks 16 and 24. Fatigue in patients was assessed using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue subscale. In both trials, the SEC treatment groups had statistically significantly greater improvement relative to placebo for mean score change at weeks 16 and 24; however, the difference in change from baseline between the treatment groups and the placebo group exceeded the established MCID (3.56) for FACIT–Fatigue in patients with rheumatoid arthritis at weeks 16 and 24 in the FUTURE 2 trial, only. The outcome measures patient's assessment of pain and FACIT–Fatigue were not part of the hierarchical analysis plan and therefore were not adjusted for multiple comparisons; hence, the level of significance is inflated and results should be interpreted taking this into consideration.

In addition to improvement in health-related quality of life in the FUTURE 2 trial, statistically significantly more patients achieved improvements in physical function (improvement of 0.30 or more in HAQ-DI score) in both SEC 150 mg treatment groups compared with placebo at weeks 16 and 24. Also, a statistically significantly greater reduction from baseline in HAQ-DI score was achieved in patients in the SEC 300 mg treatment group compared with the placebo group at week 24. However, the SEC 150 mg treatment group did not achieve a statistically significantly greater reduction from baseline in HAQ-DI score at week 24 (P = 0.0278, which was greater than the type I error [0.01666] pre-specified for this analysis). The average change from baseline in both treatment groups at weeks 16 and 24 exceeded the MCID for the HAQ-DI, which has been estimated to range from 0.3 to 0.35.

Radiographic change was assessed only in the FUTURE 1 trial, using vdH-mTSS. The mean change from baseline in vdH-mTSS was statistically significantly lower in the SEC 150 mg treatment group (0.13 points) than in the placebo group (0.57), and the between-treatment difference estimate was –0.47 for SEC 150 mg versus placebo (*P* = 0.0212). However, the results have uncertain clinical significance given that the difference between the SEC 150 mg treatment group and the placebo group was 0.47 on a scale that ranges from 0 to 528 and was assessed following 24 weeks of treatment.
In the absence of adequate head-to-head trial data for SEC with other PsA treatments, the manufacturer conducted an indirect treatment comparison (IDC) based on a systematic review of randomized controlled trials to compare the efficacy of secukinumab with that of etanercept, infliximab, adalimumab, golimumab, ustekinumab, certolizumab, and apremilast. Although the patient populations were somewhat heterogeneous and there were certain potential methodological limitations, overall, SEC demonstrated treatment effect over placebo, and no statistically significant difference was found for efficacy in terms of ACR when compared with other treatments. In addition, for PASI, SEC 150 mg and SEC 300 mg were statistically significantly better than all other therapies, with the exception of infliximab, adalimumab, golimumab 100 mg, and ustekinumab 45/90 mg.

Harms

By week 16, in FUTURE 2, adverse events (AEs) were reported in 56% of patients in the SEC 300 mg group, 57% in the SEC 150 mg group, and 58% in the placebo group. In FUTURE 1, the overall incidence of AEs was comparable between the SEC 150 mg group (64.9%) and the placebo group (58.4%) by week 16. Upper respiratory tract infection and nasopharyngitis were the most frequently reported AEs in FUTURE 2 and FUTURE 1, respectively. Risks of serious AEs were low in both studies: 5% in the SEC 300 mg treatment group, 1% to 4.5% in the SEC 150 mg groups, and 2% to 5% in the placebo groups. In FUTURE 2, higher rates of discontinuations due to AEs were reported in the placebo group (3%) compared with the SEC 300 group (2%) and the SEC 150 mg group (0%). In FUTURE 1, up to week 16, the proportion of patients discontinuing due to an AE was low and comparable between the SEC group and the placebo group (1.5% for SEC 150 mg and 2.5% for placebo). The frequency of serious infection and injection site reaction was low. There were no deaths in any of the studies after 16 weeks of therapy.

Conclusions

Based on two double-blind, randomized controlled trials (FUTURE 1 and FUTURE 2) in patients with moderate to severe PsA, treatment with SEC 150 mg (in FUTURE 1 and FUTURE 2 trials) and SEC 300 mg (FUTURE 2 trial) resulted in statistically significant and clinically meaningful improvements in clinical response (ACR20, ACR50, ACR70, MDA, DAS 28-CRP, and PASI) at weeks 16 and 24 when compared with placebo. A statistically significant and clinically significant improvement was also seen in quality of life, physical function, pain, and fatigue at 16 and 24 weeks. However, except for ACR20, ACR50, DAS 28-CRP, PCS of the SF-36, and HAQ-DI, adjustment for multiplicity was not done for all other outcomes; hence, results for these outcomes should be interpreted with caution. In both studies, a very large proportion of placebo patients discontinued randomized treatment before week 24 (either owing to early escape or because of treatment discontinuation), so claims of efficacy at week 24 are uncertain.

Overall, the incidence of treatment-emergent AEs was similar to that in the placebo groups for both SEC groups, although the study was not designed to identify between-group differences in safety. Moreover, PsA is a chronic condition that will be treated over a lifetime, and therefore a 24-week controlled trial is a short duration to evaluate harms.

A manufacturer-submitted IDC suggested no statistically significant difference for efficacy when SEC was compared with other treatments in terms of ACR; as well, the results of PASI, SEC 150 mg and SEC 300 mg were statistically significantly better than all other therapies with the exception of infliximab, adalimumab, golimumab 100 mg, and ustekinumab 45/90 mg. Harms, health-related quality of life, and patient-reported outcomes were not analyzed in the IDC, and the comparative safety between SEC and other treatments for PsA is unknown.

TABLE 1: SUMMARY OF RESULTS

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
ACR20 at week 16					
Full analysis set					
n (%)	115 (56.9)	43 (21.3)	57 (57)	60 (60)	18 (18.4)
Odds ratio (95% CI)	5.31 (3.39 to 8.31)		6.14 (3.18 to 11.86)	7.76 (3.96 to 15.22)	
P value	< 0.0001		< 0.0001	< 0.0001	
TNF alpha inhibitor–inadequate responder					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
ACR20 at week 24					
Full analysis set					
n (%)	101 (50.0)	35 (17.3)	54 (54)	51 (51)	15 (15)
Odds ratio (95% CI)	5.39 (3.37 to 8.62)		6.81 (3.42 to 13.56)	6.52 (3.25 to 13.08)	
P value	< 0.0001		< 0.0001	< 0.0001	
TNF alpha inhibitor–inadequate responder					
n/N (%)	23/59 (39.0)	10/59 (16.9)	15/33 (45)	11/37 (30)	5/35 (14)
Odds ratio (95% CI)	[redacted]		4.97 (1.53 to 16.15)	2.55 (0.78 to 8.32)	
P value	0.0062		0.0077	0.1216	
TNF alpha inhibitor–naive patients					
n/N (%)	78/143 (54.5)	25/143 (17.5)	39/67 (58)	40/63 (63)	10/63 (16)
Odds ratio (95% CI)	[redacted]		7.77 (3.36 to 17.98)	9.99 (4.22 to 23.66)	
P value	< 0.0001		< 0.0001	< 0.0001	
ACR50 at week 24					

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
n/N (%)	70/202 (34.7)	15/202 (7.4)	35/100 (35)	35/100 (35)	7/98 (7)
Odds ratio (95% CI)	[redacted]		7.15 (2.97 to 17.22)	7.54 (3.11 to 18.25)	
P value	< 0.0001		< 0.0001		
ACR70 at week 24					
n/N (%)	38/202 (18.8)	4/202 (2.0)	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	< 0.0001		[redacted]	[redacted]	
Change from baseline in DAS 28-CRP at week 24					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	4.8 (1.1)	4.9 (1.1)	4.8 (0.97)	4.9 (1.1)	4.6 (1.03)
LS mean change from baseline (SE)	–1.62 (0.084)	–0.77 (0.123)	–1.61 (0.11)	–1.58 (0.11)	–0.96 (0.15)
LS mean difference vs. PL (95% CI)	[redacted]		–0.65 (–1.02 to –0.29)	–0.62 (–0.98 to –0.26)	
P value	< 0.0001		0.0004	0.0008	
Minimal disease activity response at week 24					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Change from baseline in HAQ-DI at week 24					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	1.2 (0.67)	1.2 (0.64)	1.3 (0.6)	1.2 (0.6)	1.1 (0.7)
LS mean change (SE)	–0.40 (0.036)	–0.17 (0.047)	–0.56 (0.05)	–0.48 (0.05)	–0.31 (0·06)
LS mean difference (95% CI)	[redacted]		–0.25 (–0.40 to –0.10)	–0.17 (–0.32 to –0.02)	
P value	< 0.0001		0.0013	0.0278	
Change from baseline in SF-36 MCS at week 24					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	42.8 (11.0)	43.7 (11.4)	43.4 (12.1)	40.6 (11.5)	45.1 (10.2)
LS mean change from baseline (SE)	5.66 (0.639)	2.39 (0.911)	3.94 (0.916)	6.07 (0.917)	3.69 (1.269)
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	0.0030		[redacted]	[redacted]	
Change from baseline in SF-36 PCS at week 24					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	36.3 (8.1)	36.7 (8.1)	36.9 (7.9)	36.0 (8.1)	37.8 (8.9)
LS mean change from baseline (SE)	5.91 (0.525)	1.82 (0.715)	7.25 (0.74)	6.39 (0.73)	1.95 (0.97)

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
LS mean difference vs. PL (95% CI)	[redacted]		5.30 (2.91 to 7.69)	4.44 (2.05 to 6.83)	
P value	< 0.0001		< 0.0001	0.0003	
Change from baseline in PsAQoL at week 24					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	10.3 (5.9)	10.5 (5.9)	10.3 (5.5)	11.7 (5.4)	9.4 (5.6)
LS mean change (SE)	–3.49 (0.365)	–0.36 (0.482)	–4.23 (0.491)	–4.51 (0.491)	–1.99 (0.606)
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	< 0.0001		0.0041	0.0013	
Change from baseline in DLQI at week 24					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	12.8 (8.4)	14.4 (7.6)	11.9 (7.6)
LS mean change (SE)	[redacted]	[redacted]	–8.48 (0.890)	–8.77 (0.737)	–2.13 (1.196)
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		< 0.0001	< 0.0001	
Harms					
Deaths	0	0	0	0	0
SAEs, N (%)	9 (4.5)	10 (5.0)	5 (5)	1 (1)	2 (2)
WDAEs, N (%)	3 (1.5)	5 (2.5)	2 (2)	0	3 (3)
Patients with > 0 AEs, N (%)	131 (64.9)	118 (58.4)	56 (56)	57 (57)	57 (58)
Notable harms					
Serious infections and infestations					
Cellulitis	[redacted]	[redacted]			
Erysipelas			[redacted]	[redacted]	[redacted]
Osteomyelitis			[redacted]	[redacted]	[redacted]
Subcutaneous abscess			[redacted]	[redacted]	[redacted]
Lobar pneumonia	[redacted]	[redacted]			
Lung abscess	[redacted]	[redacted]			
Upper respiratory infection	[redacted]	[redacted]			
Viral infection	[redacted]	[redacted]			
Coronary artery disease	[redacted]	[redacted]			
Injection site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malignancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate	[redacted]	[redacted]			

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
aminotransferase increased					

ACR = American College of Rheumatology; AE = adverse event; DAS 28-CRP = Disease Activity Score 28-C-reactive protein; CI = confidence interval; DLQI = Dermatology Life Quality Index; HAQ-DI = health assessment questionnaire-disability index; LS = least squares; MCS = mental component summary; PCS = physical component summary; PL = placebo; PsAQoL = Psoriatic Arthritis Quality of Life; SAE = serious adverse event; SD = standard deviation; SE = standard error; SEC = secukinumab; SF-36 = Short Form [36] Health Survey; TNF = tumour necrosis factor; WDAE = withdrawal due to adverse event.
Source: Clinical study reports.[6,7]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Psoriatic arthritis (PsA) is a heterogeneous disease associated with multiple and variable clinical features. Patients suffer from chronic inflammatory peripheral arthritis and, in addition to this, may also suffer from skin and nail disease, axial disease, dactylitis, and enthesitis, highlighting how this disease affects more than just the joints of the patient.[1,2] It results in significant disease burden, functional impairment, increased comorbidity and mortality, and reduced health-related quality of life (HRQoL).[2,8,9] The prevalence of PsA is suggested to be similar to that of rheumatoid arthritis,[3] and it is estimated to vary from 0.3% to 1% of the population.[1] With effective treatment, functional disabilities and quality of life can be improved;[10] however, there is no one treatment regimen that works for every patient and, hence, different treatment options are required.

1.2 Standards of Therapy

Several drug classes are employed in the treatment of PsA, including nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs; i.e., methotrexate [MTX], sulfasalazine, leflunomide), immunosuppressives (cyclosporine), tumour necrosis factor alpha (TNF alpha) inhibitors (i.e., etanercept, infliximab, golimumab, adalimumab, certolizumab), ustekinumab (a fully human IgG1 kappa monoclonal antibody that is an interleukin [IL]-12 and IL-23 inhibitor), and apremilast (a small-molecule inhibitor of phosphodiesterase 4 [PDE-4i]). Although there were only two small controlled trials of inadequate power that evaluated MTX for PsA, it remains the primary treatment following use of NSAIDs.[11]

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2015 treatment recommendations for PsA indicated that, despite the lack of evidence from randomized controlled trials (RCTs), DMARDs are recommended as the primary treatment post-NSAIDs in many instances. GRAPPA's recommendation was based on data from observational studies, on the low costs and universal access of DMARDs, and on the lack of evidence that a short time delay in the introduction of more effective therapies would affect long-term function and quality of life.[4] GRAPPA also indicated that, post-NSAIDs, consideration should be given to early escalation of therapy, particularly in patients with poor prognostic factors such as increased levels of inflammatory markers or high counts of joints with active disease; TNF alpha inhibitors are strongly recommended in such patients, whereas PDE-4i drugs are conditionally recommended.[4] For patients in whom DMARD treatment has been unsuccessful, PDE-4i or biologic drugs (including TNF alpha and interleukin IL-12 and IL-23 inhibitors) are strongly recommended; in addition, a conditional recommendation was given for biologic IL-17 inhibitors. In the case of biologic-drug treatment failure, due to either inefficacy or adverse events (AEs), a conditional recommendation of switching either to an alternative biologic drug within a drug class or to a drug with a different mode of action was provided.[4]

Although there is no Canadian treatment guideline aimed specifically at management of PsA, the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada Treatment Recommendations for the Management of Spondyloarthritis[12] include the following recommendations: (1) Sulfasalazine, MTX, and leflunomide may be considered in patients with peripheral spondyloarthritis; however, these treatments have only minimal to moderate evidence of efficacy. (2) Combination therapy with a DMARD should be considered in peripheral spondyloarthritis, particularly in patients with moderate to high disease activity, poor prognostic features, or recent-onset disease, as well as in patients with inadequate response to monotherapy. (3) TNF alpha inhibitors should be offered to those

with persistent inflammation despite a trial of NSAIDs and one DMARD in patients with predominantly peripheral spondyloarthritis. (4) TNF alpha inhibitors should be offered to patients with refractory enthesitis or dactylitis accompanied by persistent inflammation. The recommendations on DMARD use in peripheral spondyloarthritis were based on PsA data, and the recommendation on TNF alpha inhibitors use was derived from PsA literature.

1.3 Drug

Secukinumab (SEC) is a fully human IgG1 kappa monoclonal antibody that selectively binds and neutralizes IL-17A, a naturally occurring cytokine involved in normal inflammatory and immune responses. Patients with PsA have increased levels of IL-17A in the blood. SEC targets IL-17A and inhibits its interaction with the IL-17 receptor. In Canada, SEC is indicated for the treatment of adult patients:

1) with active psoriatic arthritis when the response to previous DMARD therapy has been inadequate; SEC can be used alone or in combination with methotrexate
2) with active ankylosing spondylitis who have responded inadequately to conventional therapy
3) who have moderate to severe plaque psoriasis and are candidates for systemic therapy or phototherapy.[5]

Tuberculosis infection should be ruled out before initiating treatment with SEC. The Health Canada–recommended dose for adult patients is 150 mg by subcutaneous (SC) injection, with initial dosing at weeks 0, 1, 2, and 3, followed by monthly maintenance dosing starting at week 4. For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, the dosing and administration recommendations for plaque psoriasis are to be used (300 mg by SC injection, with initial dosing at weeks 0, 1, 2, and 3, followed by monthly maintenance dosing starting at week 4). If a patient is an anti-TNF alpha inadequate responder (IR) and continues to have active psoriatic arthritis, the 300 mg dose should be considered.[5]

In addition to secukinumab, five anti-TNF alpha drugs (etanercept, infliximab, golimumab, adalimumab, and certolizumab pegol), a fully human IgG1 kappa monoclonal antibody (ustekinumab), and a small-molecule inhibitor of phosphodiesterase 4 (apremilast) are currently approved in Canada for the treatment of PsA (Table 2).

Indication under review
For the treatment of adult patients with active psoriatic arthritis when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. COSENTYX can be used alone or in combination with methotrexate
Listing criteria requested by sponsor
• [redacted]

TABLE 2: KEY CHARACTERISTICS OF SECUKINUMAB, APREMILAST, ADALIMUMAB, CERTOLIZUMAB, ETANERCEPT, GOLIMUMAB, INFLIXIMAB, AND USTEKINUMAB

	Secukinumab	Apremilast	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Ustekinumab
Mechanism of action	IL-17A inhibitor Human monoclonal antibody	PDE-4i inhibitor	TNF inhibitor Recombinant human monoclonal antibody	TNF inhibitor Recombinant, humanized antibody Fab fragment	TNF inhibitor Fusion protein	TNF inhibitor Human monoclonal antibody	TNF inhibitor Chimeric monoclonal antibody	IL-12 and IL-23 inhibitor Fully human monoclonal antibody
Indication[a]	The treatment of adult patients with active psoriatic arthritis when the response to previous DMARD therapy has been inadequate. Secukinumab can be used alone or in combination with methotrexate.	The treatment of active psoriatic arthritis in adult patients who have had an inadequate response, intolerance, or contraindication to a prior DMARD.	Reducing the signs and symptoms of active arthritis and inhibiting the progression of structural damage and improving the physical function in adult PsA patients. It can be used in combination with MTX in patients who do not respond adequately to methotrexate alone.	Reducing signs and symptoms and inhibiting the progression of structural damage as assessed by radiography, in adult patients with moderately to severely active psoriatic arthritis who have failed one or more DMARDs. It can be used alone, or in combination with MTX.	Reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in adult patients with PsA. It can be used in combination with MTX in adult patients who do not respond adequately to MTX alone.	Reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active PsA. It can be used in combination with MTX in patients who do not respond adequately to MTX alone.	Reduction of signs and symptoms, induction of major clinical response, and inhibition of the progression of structural damage of active arthritis, and improvement in physical function in patients with PsA.	Treatment of adult patients with active PsA. It can be used alone or in combination with MTX.
Route of administration	SC	Oral	SC				IV	SC
Recommended dose	150 mg at weeks 0, 1, 2, and 3, followed by monthly maintenance dosing starting at week 4. For PsA patients with coexisting moderate to severe plaque psoriasis: 300 mg at weeks 0, 1, 2, and 3, followed by monthly maintenance dosing starting at week	30 mg twice daily	40 mg administered every other week as an SC injection	Loading dose of 400 mg (given as 2 SC injections of 200 mg each) initially (week 0) and at weeks 2 and 4 followed by a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks	50 mg per week in one SC injection or as two 25 mg SC injections on the same day once weekly or 3 or 4 days apart	50 mg SC once a month on same date each month	5 mg/kg given as an IV infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter	45 mg administered at weeks 0 and 4, then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg

	Secukinumab	Apremilast	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Ustekinumab
	4. Patients with PsA who are TNF alpha inhibitor–inadequate responders and continue to have active PsA: 300 mg dose should be considered							
Serious side effects / safety issues	Infections, particularly TB and serious infections Hypersensitivity reactions Exacerbations of Crohn disease	Clinically significant: weight loss Common adverse events: nausea and diarrhea	Infections, particularly opportunistic ones and TB Malignancies Allergic reactions Injection or infusion site reactions					Infections and reactivation of latent infections Injection site reactions Malignancies RPLS

DMARD = disease-modifying antirheumatic drugs; IL = interleukin; IV = intravenous injection; MTX = methotrexate; PDE-4i = phosphodiesterase 4; PsA = psoriatic arthritis; RPLS = reversible posterior leukoencephalopathy syndrome; SC = subcutaneous injection; TB = tuberculosis; TNF = tumour necrosis factor.

[a] Health Canada indication.

Source: Health Canada product monographs.[5,13-19]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of SEC (Cosentyx) at recommended doses for the treatment of adult patients with active PsA.

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies provided in the manufacturer's submission to the CADTH Common Drug Review (CDR), as well as those meeting the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with active PsA in whom the response to previous DMARD therapy has been inadequate. **Subgroups of interest:** • Body weight at baseline • Number of prior DMARDs and/or biologic response modifiers • Patients using MTX as concomitant medication vs. non-MTX • Disease severity (based on DAS 28-CRP)
Intervention	Secukinumab alone or in combination with MTX at the Health Canada–approved dosing regimen
Comparators	Individual or combination therapy with • Biological-response modifiers (e.g., infliximab, etanercept, adalimumab, golimumab, ustekinumab, certolizumab pegol) • Small-molecule inhibitor of phosphodiesterase-4 (e.g., apremilast) • DMARDs including MTX
Outcomes	**Key efficacy outcomes:** • Outcome measures of psoriatic arthritis symptoms (e.g., ACR20/50/70, DAS 28) • Measures of disability and function (e.g., HAQ-DI,[a] work productivity[a]) • Health-related quality of life (e.g., SF-36, PsAQoL)[a] **Other efficacy outcomes:** • Dactylitis index, enthesitis index, spinal disease • Symptom measures (e.g., FACIT–Fatigue[a]) • Radiographic changes • Psoriatic outcome measures (e.g., PASI, mNAPSI, BSA)[a] **Harms outcomes:** • Mortality, SAEs, AEs, WDAEs • Notable harms: serious infections (including tuberculosis), malignancies, heart failure, injection and hypersensitivity reactions, hepatotoxicity (liver function tests whether patients on MTX or not), and hematologic AEs (such as anemia or pancytopenia)
Study Design	Published and unpublished phase 3 RCTs

ACR = American College of Rheumatology; AE=adverse event; BSA = body surface area; CRP = C-reactive protein; DAS 28 = Disease Activity Score 28; DMARD = disease-modifying antirheumatic drug; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = health assessment questionnaire-disability index; MTX = methotrexate; mNAPSI = modified Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PsAQoL = Psoriatic Arthritis Quality of Life; RCT = randomized controlled trial; SAE = serious adverse events; SF-36 = Short Form (36) Health Survey; vs. = versus; WDAE = withdrawal due to adverse events.

[a] Outcomes that were considered important by the patient groups (Appendix 1: Patient Input Summary).

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with In-Process records & 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 psoriatic arthritis. No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies. The initial search was completed on March 19, 2016. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on July 20, 2016. Regular search updates were performed on databases that do not provide alert services. Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies; Health Economics; Clinical Practice Guidelines; Drug and Device Regulatory Approvals; Advisories and Warnings; Drug Class Reviews; Databases (free); Internet Search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

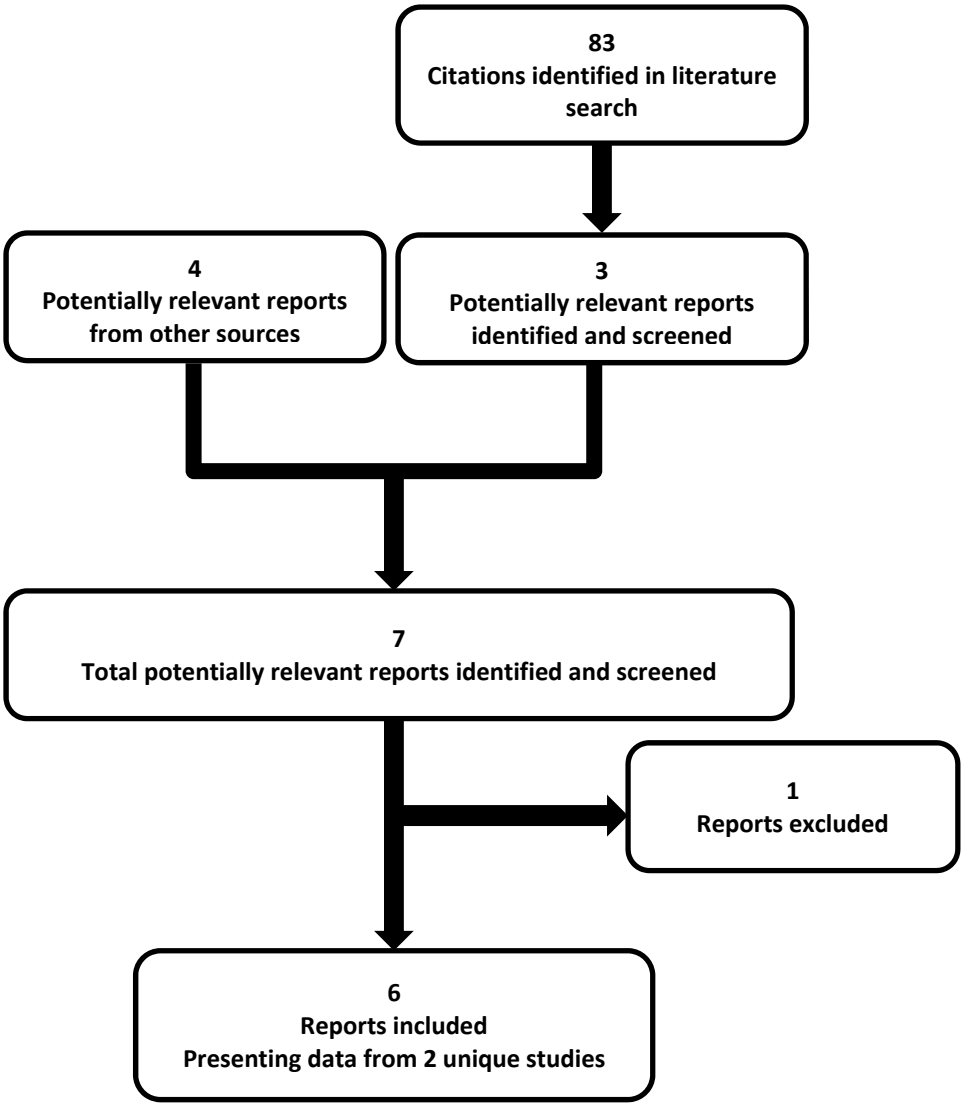


TABLE 4: DETAILS OF INCLUDED STUDIES

		FUTURE 1	FUTURE 2
DESIGNS & POPULATIONS	**Study Design**	Phase 3, placebo-controlled, DB, multi-centre RCT	
	Locations	112 centres in 19 countries (US, Canada, South America, Europe, the Middle East, Australia, and Asia)	76 centres in 10 countries (Asia, Australia, Canada, Europe, and the US)
	Randomized (N)	606	397
	Inclusion Criteria	• Patients aged ≥ 18 years • Diagnosis of moderate to severe PsA classified by CASPAR criteria, with symptoms for ≥ 6 months and with ≥ 3 tender joints and ≥ 3 swollen joints (dactylitis of a digit counts as 1 joint each) at baseline • Active plaque psoriasis with ≥ 1 psoriatic plaque of ≥ 2 cm diameter or nail changes consistent with psoriasis or a documented history of plaque psoriasis • Rheumatoid factor and anti-cyclic citrullinated peptide antibodies negative at screening • Received NSAIDs for ≥ 4 weeks before randomization with inadequate control of symptoms or intolerance to NSAIDs. Patients who were regularly taking NSAIDs as part of their PsA therapy were required to be on a stable dose for at least 2 weeks before study randomization and to remain on a stable dose up to week 24. • Concomitant oral corticosteroids (≤ 10 mg per day prednisone or equivalent) and MTX (≤ 25 mg per week) were permitted, provided the dose was stable for at least 2 and 4 weeks before randomization, respectively, and throughout the study period (or to week 24 in the case of corticosteroids). DMARDs other than MTX were not allowed during the study and required appropriate washout periods.[a] • Patients who had previously received a TNF inhibitor were eligible provided they had experienced an inadequate response after receiving an approved dose for ≥ 3 months or had stopped treatment for safety or tolerability reasons after ≥ 1 administration of TNF inhibitor. TNF inhibitors required a washout period of 4 to 10 weeks before randomization, depending on the drug.[b]	
	Exclusion Criteria	• Patients who had previously received biologic immunomodulating drugs, except for those targeting TNF, and patients who had previously been treated with more than 3 different TNF inhibitors were excluded. • Active ongoing inflammatory diseases other than PsA • History of ongoing, chronic, or recurrent infections • Evidence of active tuberculosis infection • History of malignancy within the past 5 years[c] • Known infection with HIV, hepatitis B, or hepatitis C at screening or at randomization • Pregnant or nursing (lactating) women	
DRUGS	**Intervention**	SEC IV (10 mg/kg) at weeks 0 (baseline), 2 and 4, then SEC 150 mg or SEC 75 mg SC starting at week 8 and every 4 weeks	SEC 75 mg, SEC 150 mg, or SEC 300 mg SC loading dose at weeks 0 (baseline), 1, 2, 3, and 4 and every 4 weeks thereafter
	Comparator(s)	Placebo IV at weeks 0 (baseline), 2, and 4, then placebo SC starting at week 8 and every 4 weeks	Placebo SC at weeks 0 (baseline), 1, 2, 3, and 4, and every 4 weeks thereafter

		FUTURE 1	FUTURE 2
DURATION	**Phase**		
	Screening	4 weeks	4 to 10 weeks
	Placebo early escape	16 weeks	16 weeks
	Double-blind, placebo-controlled	24 weeks (week 0 to 24)	24 weeks (week 0 to 24)
	Dose-blind, active-treatment phase	104	28 weeks (week 24 to 52)
	Open-label, active treatment	NA	204 weeks (week 52 to 256)
	Follow-up	8	12 weeks
OUTCOMES	**Primary End Point**	ACR20 response at week 24	ACR20 response at week 24
	Other End Points	• PASI 75 response at week 24[d] • PASI 90 response at week 24[d] • change from baseline in DAS 28-CRP at week 24 • change from baseline for SF-36 PCS at week 24 • change from baseline in HAQ-DI at week 24 • ACR50 response at week 24 • change from baseline in vdH-mTSS at week 24 • change from baseline in the presence of dactylitis at week 24 in the subset of patients who have dactylitis at baseline • change from baseline in the presence of enthesitis at week 24 in the subset of patients who have enthesitis at baseline • ACR70 response at week 24 • HAQ-DI response at week 24 • DAS 28 remission, low disease activity, EULAR response at week 24 • change from baseline in the Leeds Dactylitis Index (LDI) at week 24 • change from baseline for SF-36 MCS at week 24 • change from baseline for FACIT–Fatigue scores • change from baseline for PsAQoL • change from baseline for DLQI • SF-36 PCS responder (improvement of ≥ 2.5 points) • change from baseline for WPAI-GH	• PASI 75 response at week 24[d] • PASI 90 response at week 24[d] • change from baseline in DAS 28-CRP at week 24 • change from baseline for SF-36 PCS at week 24 • change from baseline in HAQ-DI at week 24 • ACR50 response at week 24 • change from baseline in the presence of dactylitis at week 24 in the subset of patients who have dactylitis at baseline • change from baseline in the presence of enthesitis at week 24 in the subset of patients who have enthesitis at baseline • ACR70 response at week 24 • HAQ-DI response at week 24 • DAS 28 remission, low disease activity, EULAR response at week 24 • change from baseline in the Leeds Dactylitis Index (LDI) at week 24 • change from Baseline for SF36-MCS at week 24 • change from baseline for FACIT–Fatigue scores • change from baseline for PsAQoL • change from baseline for DLQI • SF-36 PCS responder (improvement of ≥ 2.5 points) • change from baseline for WPAI-GH

		FUTURE 1	FUTURE 2
NOTES	**Publications**	Mease et al.[20]	McInnes et al.[21]

ACR = American College of Rheumatology; CASPAR = Classification Criteria for Psoriatic Arthritis; DAS 28-CRP = Disease Activity Score 28–C-reactive protein; DB = double-blind; DLQI = Dermatology Life Quality Index; DMARDs = disease-modifying antirheumatic drugs; EULAR = European League Against Rheumatism; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = health assessment questionnaire-disability index; IV = intravenous injection; MCS = Mental Component Summary; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PCS = physical component summaries; PsA = psoriatic arthritis; PsAQoL = Psoriatic Arthritis Quality of Life questionnaire; RCT = randomized controlled trial; SC = subcutaneous injection; SEC = secukinumab; SF-36 = Short Form (36) Health Survey; TNF = tumour necrosis factor; vdH-mTSS = van der Heijde modified total Sharp score WPAI-GH = Work Productivity and Activity Impairment–General Health questionnaire.

[a] Patients who were on a DMARD other than MTX had to discontinue the DMARD 4 weeks prior to randomization visit except for leflunomide, which had to be discontinued for 8 weeks prior to randomization unless a cholestyramine washout has been performed.

[b] ≥ 4 weeks for etanercept; ≥ 8 weeks for infliximab; ≥ 10 weeks for adalimumab, golimumab, and certolizumab.

[c] Except for basal cell carcinoma or actinic keratosis that has been treated with no evidence of recurrence in the past 3 months, in situ cervical cancer, or non-invasive malignant colon polyps that have been removed.

[d] Among patients with at least 3% of body surface area that was affected by psoriasis at baseline.

Note: 2 additional reports were included: CDR submission[22] and the European Medicines Agency report.[23]

Source: Clinical study reports.[6,7]

3.2 Included Studies

3.2.1 Description of Studies

Two trials — FUTURE 1 and FUTURE 2 — met the inclusion criteria for this review. Both trials were phase 3, multi-centre, randomized, placebo-controlled, double-blind trials. The reviewer focused primarily on the results from the FUTURE 2 trial, which used the SC loading and maintenance dose that matches the Health Canada–recommended dose. FUTURE 1 trial was also reviewed, but more as supportive data, since it uses an intravenous (IV) loading dose, which is not the dosing regimen recommended by Health Canada.

FUTURE 1 (N = 606), a three-group superiority study, evaluated the efficacy and safety of SEC 150 mg SC every four weeks or SEC 75 mg SC every four weeks compared with placebo SC injection, over a total study duration of 104 weeks. Patients were randomized in a 1:1:1 ratio to each treatment group. The placebo-controlled phase ran from randomization to week 24. At week 16 (visit 8), placebo patients were classified as responders (achieved ≥ 20% improvement from baseline in both tender joint counts [TJCs] and swollen joint counts [SJC]) or non-responders. Patients who were randomized to placebo and were classified as responders at week 16 remained on placebo until week 24, whereas those who were classified as non-responders could escape early to treatment with SEC (re-randomized [1:1] to receive either SEC 75 mg or 150 mg every four weeks, dose-blinded) for up to 104 weeks. Patients in the placebo group who continued on treatment as randomized were re-randomized (1:1) to receive either SEC 75 mg or 150 mg every four weeks from week 24 to the week 104 end point. Hence, after week 24, all patients who remained in the trial received SEC treatment, and patients and investigators were only dose-blinded after week 24. An unblinded pharmacist or unblinded qualified site personnel was appointed at each study site to prepare the study treatment. An interim analysis was performed at week 52. A selected clinical team was unblinded to the week 52 results. A final database lock occurred when all patients had completed the study. Data from the dose-blind active-treatment period are summarized in APPENDIX 6.

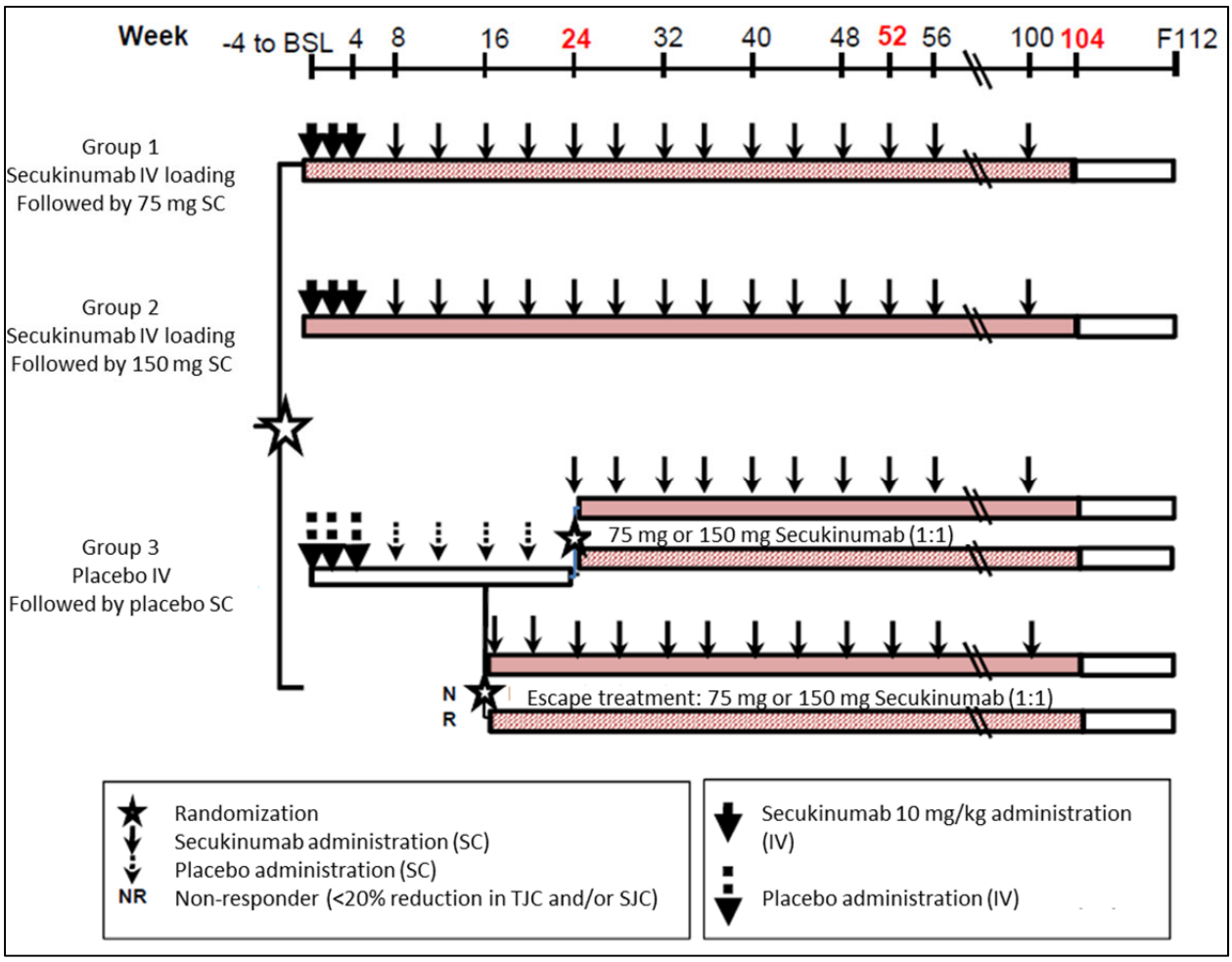
FUTURE 2 (N = 397) was a four-group superiority study evaluating the efficacy and safety of SEC 300 mg SC every four weeks, SEC 150 mg SC every four weeks, or SEC 75 mg SC every four weeks compared with placebo. Patients were randomized in a 1:1:1:1 ratio to each treatment group. The placebo-controlled phase ran from randomization to week 24. As in FUTURE 1, at week 16 patients were classified as responders (achieved ≥ 20% improvement from baseline in both TJCs and SJCs) or non-responders. Patients who were randomized to placebo and were classified as responders at week 16 remained on placebo until week 24, whereas those who were classified as non-responders could escape early to treatment with SEC (re-randomized [1:1] to receive either SEC 150 mg or 300 mg every four weeks, dose-blinded) for up to week 52. FUTURE 2 trial used a double-dummy design because the identity of the investigational treatments (pre-filled syringes [PFS]) cannot be disguised because of their different volumes (0.5 mL/1.0 mL). Patients who were randomized to SEC 300 mg received SEC 300 mg (2 × 1.0 mL) plus placebo (0.5 mL); patients who were randomized to SEC 150 mg received SEC 150 mg (1.0 mL) plus placebo (0.5 and 1.0 mL); patients who were randomized to SEC 75 mg received SEC 75 mg (0.5 mL) plus placebo (2 × 1.0 mL); and patients who were randomized to placebo received placebo (2 × 1.0 mL) and (1 × 0.5 mL). Blinding was maintained throughout the trial, up to 52 weeks. Placebo patients who were responders continued to receive placebo every four weeks until week 24. At week 24, these patients were re-randomized from placebo to SEC 150 mg or 300 mg (1:1) every four weeks regardless of responder status. During the phase after 24 weeks, all patients received SEC. Response to SEC was re-assessed at the week 52 visit, and patients who appeared to be benefiting (according to the investigator's clinical assessment) continued in the long-term treatment period after week 52 on the same treatment dose and regimen. Investigators and patients remained dose-blinded until after the week 52 assessment. Unblinding was planned after the week 52 analysis in order to eliminate the placebo injection from patients originally randomized to SEC. Patients continued to receive the same active dose of SEC as open label treatment until week 256; however, results were only available until week 52. Data from the dose-blind active-treatment period are summarized in APPENDIX 6.

In both studies, randomization at baseline and re-randomization at week 16 or week 24 were conducted by an interactive response technology (IRT) system. The patients were stratified at randomization according to whether they were TNF alpha inhibitor–naive or TNF alpha inhibitor–inadequate responders. A safety follow-up was performed for all patients, including those who terminated the study early, 12 weeks after their last dose of study treatment.

See Figure 2 and Figure 3 for study design schematics for FUTURE 1 and 2, respectively.

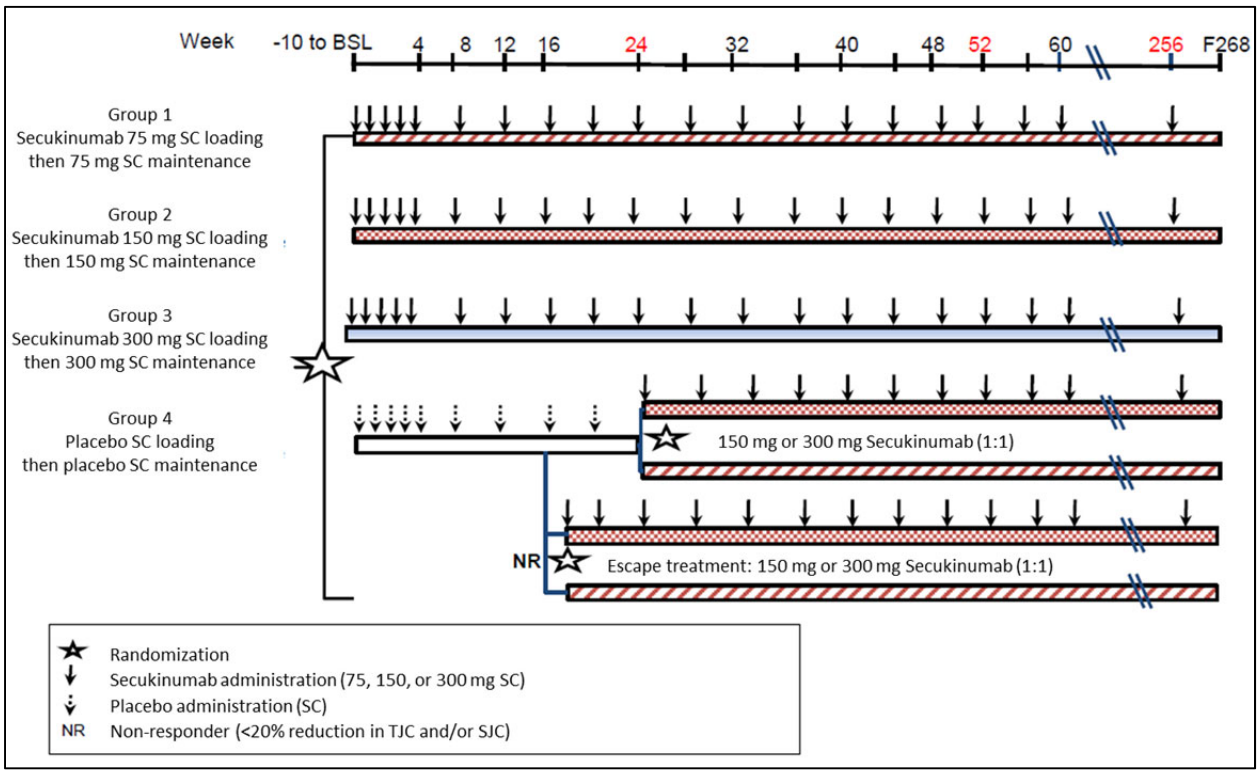
In this current CDR review, only data associated with SEC 150 mg and SEC 300 mg are reported, as these are the Health Canada–approved dosages.

FIGURE 2: FUTURE 1 SCHEMATIC DESIGN



BSL = baseline; IV = intravenous injection; SC = subcutaneous injection; SJC = swollen joint count; TJC = tender joint count.
Source: Clinical study report.[6]

FIGURE 3: FUTURE 2 SCHEMATIC DESIGN



BSL = baseline; SC = subcutaneous injection; SJC = swollen joint count; TJC = tender joint count.
Source: Clinical study report.[7]

3.2.2 Populations

a) Inclusion and Exclusion Criteria

FUTURE 1 and FUTURE 2 used the same selection criteria. To be eligible, patients had to be a male or a non-pregnant, non-lactating female of at least 18 years of age, with active PsA despite previous treatment with NSAIDs and DMARDs. Patients also had to have active plaque psoriasis or a documented history of plaque psoriasis. Patients with PsA had to have been on NSAIDs for at least four weeks before randomization, with inadequate control of symptoms or intolerance to NSAIDs. Patients taking oral corticosteroids must have been on a stable dose of 10 mg or less per day of prednisone or equivalent for at least two weeks before randomization and must have remained on a stable dose up to week 24. Patients taking MTX (≤ 25 mg per week) were allowed to continue their medication if the dose was stable for at least four weeks before randomization and if they remained on a stable dose throughout the study. Patients who were on a DMARD other than MTX discontinued the DMARD 28 days before randomization, except for leflunomide, which had to be discontinued for eight weeks before randomization unless a cholestyramine washout was performed. Patients who had been on a TNF alpha inhibitor must have experienced an IR to previous or current treatment with a TNF alpha inhibitor given at an approved dose for at least three months or must have stopped treatment due to safety/tolerability problems after at least one administration. Patients who had previously been treated with TNF alpha inhibitors were allowed entry into the study after an appropriate washout period of four to 10 weeks before randomization, depending on the drug.

Patients were excluded if they had been taking high-potency opioid analgesics (e.g., methadone, hydromorphone, or morphine). Patients who had previously received biologic immunomodulating drugs, except for those targeting TNF, and patients who had previously been treated with more than three different TNF inhibitors, were excluded. Patients with previous exposure to SEC or any other biologic drug directly targeting IL-17 or the IL-17 receptor were also excluded. Patients with active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of SEC therapy, as judged by the investigator, were excluded. Patients with underlying conditions that placed the patient at unacceptable risk for participation in an immunomodulatory therapy were excluded. Patients with a history of clinically significant liver disease or liver injury were excluded. Patients with a history of ongoing, chronic, or recurrent infectious disease or evidence of tuberculosis infection, or known infection with HIV, hepatitis B, or hepatitis C at screening or randomization, were excluded. Patients with a history of lymphoproliferative disease or any known malignancy or a history of malignancy of any organ system within the past five years were also excluded.

b) Baseline Characteristics

In FUTURE 1, baseline demographic and disease characteristics as well as previous or concomitant use of medications were similar across the study groups. In FUTURE 2, baseline demographic and disease characteristics and previous or concomitant use of medications were similar across the study groups at baseline, except for potential imbalances in baseline Psoriasis Area and Severity Index (PASI) score (mean PASI score in the SEC 150 mg was 16.2 compared with the other groups, in which it was 11.6 to 11.9), proportion of patients with psoriasis of hands and feet (39% in SEC 300 mg, 62% in SEC 150 mg, and 41% in the placebo group), proportion of patients with psoriasis of the nail (63% in SEC 300 mg, 75% in SEC 150 mg, and 66% in the placebo group), proportion of female patients (the female-to-male ratio was equal in the groups, except for the placebo group, which had 60% female and 40% male patients), proportion of patients with psoriasis affecting at least 3% of their body surface (higher in the 150 mg group [58%] compared with the other groups [41% to 44%]), and proportion of patients with dactylitis (more patients in the SEC 300 mg group had dactylitis [46%] than in the other groups (32% in the SEC 150 mg group and 28% in the placebo group) or enthesitis (fewer patients in the SEC 300 mg [56.0%] had enthesitis at baseline compared with the other groups [64% to 66%]); however, the clinical expert was did not think these imbalances would affect outcomes in a clinically meaningful way.

Across both trials, the mean age ranged from 46.5 to 49.9 years. Almost equal proportions of patients were male and female, and the majority of patients were white. Across the trials, mean PsA duration ranged from 7.5 to 8.5 years; mean SJC, from 7.8 to 13.1; mean TJC, from 13.3 to 19.4; mean PASI score, from 8.3 to 14.3; mean Health Assessment Questionnaire-Disability Index (HAQ-DI), from 1.2 to 1.3; prior anti-TNF drug use, from 29% to 37%; concomitant MTX use, from 44% to 62% (Table 5).

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Characteristics	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
Demographic characteristics					
Age, mean (SD)	49.6 (11.76)	48.5 (11.19)	46.9 (12.6)	46.5 (11.7)	49.9 (12.5)
Female, n (%)	106 (52.5)	106 (52.5)	49 (49)	45 (45)	59 (60)
Weight, kg, mean (SD)	84.2 (21.1)	80.0 (20.5)	85.4 (18.4)	91.2 (19.8)	86.2 (19.8)
Race, n (%)					
White	162 (80.2)	154 (76.2)	96 (96)	90 (90)	94 (96)
Asian	36 (17.8)	46 (22.8)	2 (2)	6 (6)	1 (1)
Disease characteristics					
PsA duration in years, mean (SD)	8.34 (8.5)	7.44 (8.1)	7.38 (7.5)	6.51 (8.2)	7.32 (7.8)
Tender joint count (0 to 78 joints), mean (SD)	23.8 (16.4)	25.1 (18.4)	20.2 (13.3)	24.1 (19.4)	23.4 (19.0)
Swollen joint count (0 to 76 joints), mean (SD)	12.5 (9.4)	14.9 (13.1)	11.2 (7.8)	11.9 (10.1)	12.1 (10.7)
DAS 28-CRP (SD)	4.8 (1.1)	4.9 (1.1)	4.8 (1.0)	4.9 (1.1)	4.7 (1.0)
Modified total Sharp score, mean (SD)	21.9 (47.5)	28.1 (62.8)	NA	NA	NA
Psoriatic arthritis pain by VAS (0 to 100), mean (SD)	55.7 (24.2)	56.7(21.1)	57.7 (19.0)	58.9 (19.8)	55.4 (22.1)
HAQ-DI (range 0 to 3), mean (SD)	1.2 (0.7)	1.2 (0.6)	1.3 (0.6)	1.2 (0.6)	1.2 (0.7)
Patient's global assessment of disease activity by VAS (0 to 100), mean (SD)	55.2 (24.0)	55.6 (21.7)	60.7 (18.9)	62.0 (19.5)	57.6 (19.8)
Physician's global assessment of disease activity by VAS (0 to 100), mean (SD)	58.3 (18.9)	56.7 (18.8)	55.0 (14.7)	56.7 (16.6)	55.0 (16.0)
Presence of enthesitis (yes), n (%)	126 (62.4)	117 (57.9)	56 (56)	64 (64)	65 (66)
Presence of dactylitis (yes), n (%)	104 (51.5)	116 (57.4)	46 (46)	32 (32)	27 (28)
Psoriasis BSA ≥ 3%, n (%)	108 (53.5)	109 (54.0)	41 (41)	58 (58)	43 (44)
PASI score ≤ 10[a]	50 (46.3)	46 (42.2)	21 (51)	25 (43)	23 (53)
PASI score > 10[a]	58 (53.7)	63 (57.8)	20 (49)	33 (57)	20 (47)
PASI, mean (SD)[a]	15.6 (13.9)	15.1 (11.6)	11.9 (8.4)	16.2 (14.3)	11.6 (8.3)
Proportion of patients with psoriasis of hands and feet, n (%)	103 (51.0)	108 (53.5)	39 (39.0)	62 (62.0)	40 (40.8)
Proportion of patients with psoriasis of the nail, n (%)	145 (71.8)	154 (76.2)	63 (63.0)	75 (75.0)	65 (66.3)
Prior and concomitant medication use					
Concomitant MTX at baseline, n (%)	121 (59.9)	125 (61.9)	44 (44)	44 (44)	50 (51)
Dose of MTX at randomization (mg/week), mean (SD)	14.56 (5.27)	14.41 (5.42)	16.11 (5.33)	17.19 (5.14)	17.60 (11.21)

Characteristics	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
Use of systemic glucocorticoid at randomization	34 (16.8)	27 (13.4)	18 (18)	23 (23)	21 (21)
Previous anti-TNF drugs, n (%)					
0	143 (70.8)	143 (70.8)	67 (67)	63 (63)	63 (64)
1	39 (19.3)	35 (17.3)	16 (16)	26 (26)	16 (16)
2 or 3	20 (9.9)	24 (11.9)	17 (17)	11 (11)	19 (19)

BSA = body surface area; DAS 28-CRP = Disease Activity Score 28–C-reactive protein; HAQ-DI = health assessment questionnaire-disability index; MTX = methotrexate; NA = not applicable; PASI = Psoriasis Area and Severity Index; PL = placebo; PsA = psoriatic arthritis; SD = standard deviation; SEC = secukinumab; TNF = tumour necrosis factor; VAS = visual analogue scale.
[a] PASI scores range from 0 to 72, with higher scores indicating more severe disease. PASI was assessed only in patients in whom psoriasis affected at least 3% of the body surface area at baseline.
Source: Clinical study reports.[6,7]

3.2.3 Interventions

In FUTURE 1, patients randomized to SEC received a loading SEC IV infusion at a dose of 10 mg/kg at weeks 0, 2, and 4, followed by either SEC 75 mg SC or SEC 150 mg SC starting at week 8 and injected every four weeks. The loading dose route of administration is not Health Canada–approved; however, this trial was included in the CDR review because it was considered pivotal by the manufacturer. At week 16 (visit 8), placebo patients were classified as responders or non-responders as described previously (section 3.2.1); if classified as responders, they remained on placebo until week 24; if classified as non-responders, they could escape early to SEC treatment. After week 24, all patients who remained in the trial received SEC treatment, and patients and investigators were only dose-blinded. Rescue medications (defined as any new therapeutic intervention or a significant change to ongoing therapy made because a patient is experiencing either no benefit from participation in the trial or worsening/exacerbation of his or her disease) were not allowed until week 24. The identity of the SEC or placebo treatments was concealed by the use of study treatments in the form of syringes or IV infusion bags filled with reconstituted SEC or placebo solutions that were identical in appearance. The investigator or assigned site staff injected or infused the treatments to patients during the study visit.

In FUTURE 2, patients randomized to the SEC groups received an SC loading injection of SEC at a dose of 300 mg, 150 mg, or 75 mg at baseline (week 0), weeks 1, 2, 3, and 4, followed by dosing every four weeks starting at week 4. A double-dummy design was used in FUTURE 2 trial, in which patients who were randomized to SEC 300 mg received SEC 300 mg (2 × 1.0 mL) plus placebo (0.5 mL); patients who were randomized to SEC 150 mg received SEC 150 mg (1.0 mL) plus placebo (0.5 and 1.0 mL); patients who were randomized to SEC 75 mg received SEC 75 mg (0.5 mL) plus placebo (2 × 1.0 mL); and patients who were randomized to placebo received placebo (2 × 1.0 mL) and (1 × 0.5 mL). Blinding was maintained throughout the trial, up to 52 weeks. At week 16, patients were classified as responders or non-responders, as described previously (section 3.2.1); if classified as non-responders, they could escape early to SEC treatment. After week 24, all patients who remained in the trial received SEC treatment, and patients and investigators were dose-blinded after week 24. Investigators and patients remained dose-blinded until week 52 analysis. Patients continued to receive the same active dose of SEC as open-label treatment from week 52 until week 256, and they no longer received the placebo injection, which had been administered to maintain the dose double-blind. Rescue medications (defined

in a similar manner as in FUTURE 1) were not allowed before week 24. The identity of the treatments was concealed by the use of study treatments in the form of PFSs for SC injection, filled with SEC or placebo that were identical in appearance. The SC injections were self-administered using the PFS under the supervision of the site staff until week 104. After week 104, the patients could elect to self-administer the PFS at home when they were not visiting the site for any other trial-related procedures. Site staff administered the injection to patients who were not able to or who felt insecure to self-administer the PFS injection.

NSAIDs, low-strength opioids, paracetamol/acetaminophen, MTX (patients on MTX received folic acid supplementation), cholestyramine to wash out leflunomide, and systemic corticosteroids were permitted during the study.

3.2.4 Outcomes

The primary efficacy end point in both included studies was the proportion of patients in each treatment group who achieved American College of Rheumatology (ACR) 20 response at week 24.

a) American College of Rheumatology 20/50/70

The ACR criteria[24] for assessing joint status (originally developed for patients with rheumatoid arthritis) provide a composite measure of 20% or more, 50% or more, or 70% or more improvement in both SJCs and TJCs and at least three of five additional disease criteria, including patient/physician global assessment of disease activity (10 cm visual analogue scale [VAS]), HAQ-DI, patient assessment of pain intensity, and levels of C-reactive protein (CRP) or erythrocyte sedimentation rate. The ACR20 is generally accepted as the minimal clinically important difference (MCID) indicating a response to treatment, whereas the ACR50 and 70 more likely reflect truly important change for the long-term management of arthropathy. The ACR is a general measure of clinical response of peripheral joint disease and does not include assessment of enthesitis, dactylitis, the spine, or the skin. ACR20 at week 24 was the primary outcome. ACR50 at week 24 was an additional secondary end point. ACR20, ACR50, and ACR70 at week 16 and ACR70 at week 24 were pre-specified exploratory end points that were not included in the hierarchical testing.

b) Minimal Disease Activity

Minimal disease activity (MDA) is a composite outcome measure, developed as a target of treatment for patients with PsA, that encompasses the different aspects of disease domains.[25] Patients were considered to have achieved MDA if they fulfilled five of seven outcome measures: TJC of one or less, SJC of one or less, PASI score of one or less or body surface area affected of 3% or less, patient pain–visual analogue scale (VAS) of 15 or less, patient global VAS of 20 or less, HAQ-DI of 0.5 or less, and one or less tender entheseal points.[26] MDA response was a pre-specified exploratory end point that was not included in the hierarchical testing.

c) Disease Activity Score 28 and C-reactive Protein

The DAS includes an assessment of 28 tender and swollen joints, along with a patient global assessment of well-being to evaluate a patient's response to treatment and a blood level to determine CRP.[27,28] The score ranges from 0 to 9.4, with higher scores indicating greater disease activity.

The threshold values are 2.6, 3.2, and 5.1 for remission, low disease activity, and high disease activity, respectively.[24] The European League Against Rheumatism (EULAR) response criteria classify patients as good or moderate responders or as non-responders to treatment, based on the individual patient's

disease severity, as measured on the current DAS 28 score, and changes in DAS 28 from baseline at the time of assessment.[29]

TABLE 6: EULAR RESPONDER CLASSIFICATION

Current DAS 28	Improvement in DAS 28 from baseline		
	> 1.2	> 0.6 to ≤ 1.2	≤ 0.6
≤ 3.2	Good	Moderate	None
> 3.2 to ≤ 5.1	Moderate	Moderate	None
> 5.1	Moderate	None	None

DAS = Disease Activity Score; EULAR = European League Against Rheumatism.
Source: Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Clin Exp Rheumatol. 2005 Sep;23 (5 Suppl 39):S93-S99.[29]

Change from baseline in the DAS 28-CRP score at week 24 was an additional secondary end point. Change from baseline in the DAS 28-CRP score at week 16, and DAS 28-CRP "good" EULAR response were pre-specified exploratory end points that were not included in the hierarchical testing.

d) Health Assessment Questionnaire

The HAQ was developed to assess physical disability and pain in rheumatoid arthritis[30] and has been used extensively in arthritis RCTs, including for PsA. Through a self-assessed questionnaire of eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities), patients' difficulty in performing these activities is scored from 0 (without any difficulty) to 3 (unable to do). The MCID for the HAQ ranges from 0.3 to 0.35.[30,31] Change from baseline in the HAQ-DI score at week 16 was a key secondary end point. Change from baseline in the HAQ-DI score at week 24 was an additional secondary end point. Change from baseline in the HAQ-DI score at week 16, and the proportion of patients with improvements in HAQ-DI of 0.30 points or more at weeks 16 and 24 were pre-specified exploratory end points that were not included in the hierarchical testing.

e) Medical Outcomes Study Short Form (36) Health Survey

The Short Form (36) Health Survey (SF-36) is a 36-item generic health-status instrument that has been used extensively in clinical trials in many disease areas.[32] The SF-36 consists of eight health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[33] The eight domains are aggregated to create two component summaries: the physical component summary (PCS) and the mental component summary (MCS). Scores range from 0 to 100, with higher scores indicating better health status. The MCID for either the PCS or MCS of the SF-36 for the change from baseline is typically between 2.5 and 5 points.[34-36] Leung and colleagues[37] reported MCIDs of change scores of 3.74 and 1.77 in PsA patients treated with anti-TNF alpha drugs for the PCS and MCS subsections, respectively. Change from baseline in the PCS score of the SF-36 at week 24 was an additional secondary end point. Change from baseline in the PCS score of the SF-36 at week 16, change from baseline in the MCS score of the SF-36 at weeks 16 and 24, and the proportion of patients with improvement of 2.5 points or more in the MCS score and the PCS score of the SF-36 at weeks 16 and 24 were pre-specified exploratory end points that were not included in the hierarchical testing.

f) Psoriatic Arthritis Quality of Life

The Psoriatic Arthritis Quality of Life (PsAQoL) is a quality-of-life instrument specific to psoriatic arthritis.[38] The PsAQoL comprises 20 items so that the score ranges from 0 to 20, with higher scores indicating worse reduced health-related quality of life (HRQoL).[38] It has been used in clinical studies and trials to assess the impact of interventions for PsA. It is well-accepted by patients and has acceptable

scaling and psychometric properties.[38] No MCID for PsAQoL was identified. Change from baseline in the PsAQoL was a pre-specified exploratory variable that was not included in the hierarchical testing.

g) Dermatology Life Quality Index

The Dermatology Life Quality Index (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.[6] 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 score 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 in terms of effect on a patient's life is as follows: 0 to 1 = no effect; 2 to 5 = small effect; 6 to 10 = moderate effect; 11 to 20 = very large effect; 21 to 30 = extremely large effect. The estimated MCID for DLQI in patients with psoriasis is 3.2.[39] Change from baseline in the DLQI was a pre-specified exploratory variable that was not included in the hierarchical testing.

h) Patient's Assessment of Pain

Patient's assessment of pain was scored on a 0 to 100 mm horizontal line on which 0 represents "no pain" and the 100 mm mark represents "pain as severe as can be imagined."[40] Patients were asked to place a vertical line on the horizontal line to indicate the level of their arthritis pain on the day of the visit.[40] The MCID of patient's assessment of pain was defined as an improvement (reduction) in pain of 10 mm or more from baseline.[40] Patients' assessment of pain is part of the ACR core set of measures in arthritis.[41] Change from baseline in the patient assessment of pain at weeks 16 and 24 were pre-specified exploratory end points that were not included in the hierarchical testing.

i) Functional Assessment of Chronic Illness Therapy–Fatigue

The Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–Fatigue) scale is a self-administered questionnaire that assesses both the physical and functional consequences of fatigue.[42] The FACIT–Fatigue was validated in a PsA cohort study conducted in Toronto and was found to be well-correlated with the modified Fatigue Severity Scale, showing high internal consistency, test–retest reliability, as well as criterion and construct validity.[43] It is a 13-item questionnaire, with each question scored from 0 to 4 for a total score range of 0 to 52. Higher scores denote lower levels of fatigue. Therefore, higher FACIT–Fatigue scores are expected with greater improvements in a patient's PsA.[42] A validated MCID for improvement in the FACIT–Fatigue is not currently available in PsA patients. The MCID for the changes from baseline in FACIT–Fatigue has been estimated to be 3.56 points in patients with rheumatoid arthritis;[44] the MCID has not been formally estimated in patients with PsA. Change from baseline in the FACIT–Fatigue score at weeks 16 and 24 were pre-specified exploratory end points that were not included in the hierarchical testing.

j) Work Productivity

Work productivity was measured by Work Productivity and Activity Impairment – General Health (WPAI-GH), which measures absenteeism, presenteeism, and impairments in unpaid activity because of health problems during the past seven days. Four main outcomes can be generated from the WPAI-GH and expressed in percentages: 1) percentage of work time missed owing to health problems for those who were currently employed; 2) percentage of impairment while working owing to health problems for those who were currently employed and actually worked in the past seven days; 3) percentage of overall work impairment owing to health problems for those who were currently employed; and 4) percentage

of activity impairment owing to health for all respondents. The recall period is two to seven days before the visit.

k) Leeds Dactylitis Index

Dactylitis, the swelling of an entire digit related to articular and periarticular inflammation, is a characteristic of inflammatory spondyloarthropathies, including PsA. Presence of dactylitis was assessed using the basic Leeds Dactylitis Index (LDI), which evaluates dactylitis using a difference of 10% or more in the circumference of the digit compared with the opposite digit.[45,46] No MCID for LDI was identified. Change from baseline in LDI at weeks 16 and 24 were pre-specified exploratory end points that were not included in the hierarchical testing.

l) Presence of Dactylitis

Presence of dactylitis at week 24 was a secondary end point for SEC pooled regimen (75 mg and 150 mg SC) and a pre-specified exploratory end point for SEC 150 mg. It was not included in the hierarchical testing.

m) Presence of Enthesitis

Presence of enthesitis at week 24 was a secondary end point for the SEC pooled regimen (75 mg and 150 mg SC) and a pre-specified exploratory end point for SEC 150 mg. It was not included in the hierarchical testing.

n) Van der Heijde Modified Total Sharp Score

The Sharp scoring system allows for the assessment of two different aspects of joint damage: articular erosions (representing direct invasion of cartilage and bone by the proliferating synovial pannus) and joint space narrowing (representing destruction of surface cartilage). The van der Heijde erosion score includes 16 joints from the hands and wrists (graded from 0 to 5) and six joints from the feet (graded from 0 to 10). The joint space narrowing score includes 15 areas from the hands and wrists (graded from 0 to 4) and six areas from the feet (also graded from 0 to 4). The van der Heijde total Sharp score was modified for psoriatic arthritis by the addition of hand distal interphalangeal joints. The maximum possible scores were 320 for erosions, 208 for joint space narrowing, and 528 for the total score. Radiographs tend to change slowly in rheumatoid arthritis, requiring at least six months to a year to detect changes in a single patient. Inter-rater and intra-rater reliability is also a concern because of the subtle nature of changes and subjective interpretation. The images themselves can also vary between samples because of positioning and quality. An MCID of 4.6 units for the van der Heijde modified total Sharp score (vdH-mTSS) was determined by a panel of experts.[47] Radiographic changes were assessed only in the FUTURE 1 trial; separate radiographs of each hand/wrist and each foot were taken at baseline and at weeks 24, 52, and 104. The readings of the radiographs and the scoring were performed centrally. A change from baseline in vdH-mTSS at week 24 (SEC pooled regimens 75 mg and 150 mg SC, and separate regimens) was an additional secondary end point.

o) Psoriasis Area and Severity Index

The PASI is an instrument widely used in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It produces a numeric score ranging from 0 to 72. In general, a PASI score of 5 to 10 is considered moderate disease, and a score 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 FDA.[48] PASI 75 and PASI 90 at week 24 were considered secondary end points, whereas PASI 75 and PASI 90 at week 24 were exploratory end points that were not included in the hierarchical testing.

p) Modified Nail Psoriasis Severity Index

The Modified Nail Psoriasis Severity Index (mNAPSI) is an instrument to assess psoriatic nail involvement in patients with PsA and nail psoriasis. For the evaluation of the mNAPSI, three features or groups of features (onycholysis and oil-drop dyschromia, pitting, and crumbling) of each fingernail are graded on a scale from 0 to 3. The mNAPSI scores range from 0 to 130 for all fingernails. The total mNAPSI score was calculated as the sum of all of the scores from available nails.[6,7] The MCID of mNAPSI is currently unknown. Change from baseline in mNAPSI at weeks 16 and 24 were pre-specified exploratory end points that were not included in the hierarchical testing.

q) Adverse Events

An adverse event (AE) was the appearance or worsening of any undesirable sign, symptom, or medical condition after the patient had signed the informed consent form, even if the event was not considered to be related to study treatment. Medical conditions/diseases present before the patient had signed the informed consent form were only considered AEs if they worsened after the patient had signed the informed consent form. Abnormal laboratory values or test results constituted AEs only if they induced clinical signs or symptoms, were considered clinically significant, or required therapy.

3.2.5 Statistical Analysis

In FUTURE 1, patients were stratified at randomization according to whether they were TNF alpha inhibitor–naive or TNF alpha inhibitor–IR. Approximately 70% of the patients were required to have received no previous anti-TNF therapy. It was anticipated that a sample size of 200 patients for each treatment group was needed to detect statistically significant differences in the proportion of patients who achieved ACR20 response between SEC treatment groups and placebo at week 24 with 90% power, assuming a response rate of 22% (indicated in previous research) in the placebo group and 49% in the SEC groups, at a two-sided significance level of 0.025, which was adjusted for the number of groups.

In FUTURE 2, patients were stratified at randomization according to whether they were TNF alpha inhibitor–naive or TNF alpha inhibitor–IR. Approximately 60% of the patients were required to have received no previous anti-TNF therapy. It was anticipated that a sample size of 100 patients for each treatment group would provide about 92% power to detect a treatment difference of 26% for the primary end point of ACR20 response at week 24 with Fisher's exact test, and about 80% power for secondary end points. The expected treatment difference of 26% for the primary end point was based on an expected overall placebo response of 21% (indicated in previous research) and an expected overall SEC response of 47%. A 5% two-sided type I error rate was used to control for type I error. Three SEC doses were tested versus placebo with respect to the primary end point (ACR20 response at week 24); thus, the type I error was split to 1.7% two-sided for each comparison. Sample sizes were based on this type I error assumption.

In both studies, the primary outcome (ACR20) and other binary outcomes were analyzed by means of logistic regression, with treatment and previous use of anti-TNF therapy as factors and body weight at baseline as a covariate. Patients who dropped out of the trial for any reason were considered non-responders from the time they dropped out through the rest of the trial. If a patient was missing all ACR components but had not dropped out of the trial, then response was imputed by using data from surrounding visits. If the visit before and after were both responses, the patient was considered a responder. Otherwise, the patient was considered a non-responder; except when the last visit was missing. In this case, data from the two previous visits were used and the aforementioned method for determining response was used. If a patient had partial missing data for a visit (i.e., only some of the ACR components), the last observation carried forward (LOCF) was used to impute the missing

components. Patients for whom responses could not be calculated at a specific time point were classified as having had no response. Patients in the placebo group who were switched to active treatment at week 16 were imputed as non-responders in the analysis at week 24. SEC-treated patients who had no response at week 16 were also imputed as non-responders at week 24.

In both studies, between-group differences in continuous outcomes (e.g., ACR components, DAS) were analyzed using a mixed-effect model repeated measures (MMRM) approach, with missing data assumed to be missing at random; with treatment regimen, analysis visit, and previous use of anti-TNF therapy as factors; and with body weight and baseline score as continuous covariates. For analyses of continuous outcomes, if all post-baseline values were missing, then missing values were not imputed and the patient was removed from the analysis of the corresponding variable; thus, the number of patients providing data to an analysis could be smaller than the number of patients in the full analysis set. The primary and key secondary efficacy analyses followed a predefined hierarchical hypothesis-testing strategy to adjust for multiplicity and to maintain a familywise type I error of 5%, in which the statistical significance of each secondary end point was investigated only if the previous end point was significant in the following sequence.

For the FUTURE 1 trial, the type I error was set to $\alpha = 5\%$ and was controlled with the proposed hierarchical testing strategy. With this hierarchical testing approach, the hypotheses were separated into two families: hypotheses H1 to H14 were the first family, and hypotheses H15 to H19 were the second family. The second-family hypotheses were tested only when all hypotheses in the first family had been rejected. Each of the hypotheses (H1 and H2) for the primary objective (based on signs and symptoms at week 24) for each SEC regimen versus placebo was tested simultaneously at $\alpha/2 = 0.025$. If at least one of H1 or H2 was rejected, then H3 or H4, respectively, was tested. If at least one of H3 or H4 was rejected, the hypothesis H5 or H6, was tested, respectively. A similar process was applied until H13 and H14. Once all hypotheses within the first family for a SEC regimen were rejected, then the respective $\alpha/2$ could be passed on to the other regimen's hypotheses within the family, if they were not already rejected at $\alpha/2$. Only when all hypotheses (H1 to H14) were rejected, the objective on joint structure end point at week 24 for testing pooled SEC doses versus placebo (H15) were tested at α. If H15 was rejected, then H16 was tested at α. Similarly, if H16 was rejected, then H17 was tested at α. If these pooled hypotheses were all rejected, then hypotheses concerning individual regimens of SEC versus placebo (H18 and H19) could be tested for a particular regimen at $\alpha/2$. Once the hypothesis of structure damage for a SEC regimen was rejected, then the respective $\alpha/2$ could be passed on to the other regimen's hypothesis, if it was not already rejected at $\alpha/2$.

Primary objectives:

- H1: SEC 75 mg is not different from placebo regimen with respect to ACR20 response at week 24
- H2: SEC 150 mg is not different from placebo regimen with respect to ACR20 response at week 24.

Secondary objectives:

- H3: SEC 75 mg is not different from placebo regimen with respect to PASI 75 response at week 24 in the subgroup of patients who have ≥ 3% skin involvement with psoriasis
- H4: SEC 150 mg is not different from placebo regimen with respect to PASI 75 response at week 24 in the subgroup of patients who have ≥ 3% skin involvement with psoriasis
- H5: SEC 75 mg is not different from placebo regimen with respect to PASI 90 response at week 24 in the subgroup of patients who have ≥ 3% skin involvement with psoriasis

- H6: SEC 150 mg is not different from placebo regimen with respect to PASI 90 response at week 24 in the subgroup of patients who have ≥ 3% skin involvement with psoriasis
- H7: SEC 75 mg is not different from placebo regimen with respect to the improvement (change) from baseline for DAS 28-CRP at week 24
- H8: SEC 150 mg is not different from placebo regimen with respect to the improvement (change) from baseline for DAS 28-CRP at week 24
- H9: SEC 75 mg SC is not different from placebo regimen with respect to the improvement (change) from baseline for SF-36 PCS at week 24
- H10: SEC 150 mg is not different from placebo regimen with respect to the improvement (change) from baseline for SF-36 PCS at week 24
- H11: SEC 75 mg is not different from placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at week 24
- H12: SEC 150 mg is not different from placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at week 24
- H13: SEC 75 mg is not different from placebo regimen with respect to ACR50 response at week 24
- H14: SEC 150 mg is not different from placebo regimen with respect to ACR50 response at week 24
- H15: SEC pooled regimen (75 mg and 150 mg) is not different from placebo regimen with respect to structural damage (vdH-mTSS) at week 24
- H16: SEC pooled regimen (75 mg and 150 mg) is not different from placebo regimen with respect to presence of dactylitis at week 24 in the subset of patients who have dactylitis at baseline
- H17: SEC pooled regimen (75 mg and 150 mg) is not different from placebo regimen with respect to presence of enthesitis at week 24 in the subset of patients who have enthesitis at baseline
- H18: SEC 75 mg is not different from placebo regimen with respect to structural damage (vdH-mTSS) at week 24
- H19: SEC 150 mg is not different from placebo regimen with respect to structural damage (vdH-mTSS) at week 24.

For the FUTURE 2 trial, the type I error was set to $\alpha = 5\%$ and was controlled with the proposed hierarchical testing strategy. With this hierarchical testing approach, the hypotheses were separated into two families: hypotheses H1 to H21 were the first family, and hypotheses H22 and H23 were the second family. The second-family hypotheses were tested only when all hypotheses in the first family had been rejected. Each of the hypotheses (H1, H2, and H3) for the primary objective (based on ACR20 response at week 24) for each SEC regimen versus placebo were tested simultaneously at $\alpha/3 = 0.01666$. If at least one of H1 or H2 or H3 was rejected, then H4 or H5 or H6, respectively, was tested. If at least one of H4 or H5 or H6 was rejected, then H7 or H8 or H9, was tested, respectively. A similar process was applied until H19 to H21. Once all hypotheses within the first family for a SEC regimen were rejected, then the respective $\alpha/3$ could be passed on to the other regimen's hypotheses within the family, if they were not already rejected at $\alpha/3$. Only when all hypotheses H1 to H21 were rejected, the objective on the proportion of patients with dactylitis at week 24 for testing pooled SEC doses versus placebo (H22) was tested at α.

Primary objectives:

- H1: SEC 75 mg is not different from placebo regimen with respect to ACR20 response at week 24
- H2: SEC 150 mg is not different from placebo regimen with respect to ACR20 response at week 24
- H3: SEC 300 mg is not different from placebo regimen with respect to ACR20 response at week 24.

Secondary objectives:

- H4: SEC 75 mg is not different from placebo regimen with respect to PASI 75 response at week 24 in the subgroup of patients who have ≥ 3% skin involvement with psoriasis
- H5: SEC 150 mg is not different from placebo regimen with respect to PASI 75 response at week 24 in the subgroup of patients who have ≥ 3% skin involvement with psoriasis
- H6: SEC 300 mg is not different from placebo regimen with respect to PASI 75 response at week 24 in the subgroup of patients who have ≥ 3% skin involvement with psoriasis
- H7: SEC 75 mg is not different from placebo regimen with respect to PASI 90 response at week 24 in the subgroup of patients who have ≥ 3% skin involvement with psoriasis
- H8: SEC 150 mg is not different from placebo regimen with respect to PASI 90 response at week 24 in the subgroup of patients who have ≥ 3% skin involvement with psoriasis
- H9: SEC 300 mg is not different from placebo regimen with respect to PASI 90 response at week 24 in the subgroup of patients who have ≥ 3% skin involvement with psoriasis
- H10: SEC 75 mg is not different from placebo regimen with respect to the improvement (change) from baseline for DAS 28-CRP at week 24
- H11: SEC 150 mg is not different from placebo regimen with respect to the improvement (change) from baseline for DAS 28-CRP at week 24
- H12: SEC 300 mg is not different from placebo regimen with respect to the improvement (change) from baseline for DAS 28-CRP at week 24
- H13: SEC 75 mg SC is not different from placebo regimen with respect to the improvement (change) from baseline for SF-36 PCS at week 24
- H14: SEC 150 mg is not different from placebo regimen with respect to the improvement (change) from baseline for SF-36 PCS at week 24
- H15: SEC 300 mg is not different from placebo regimen with respect to the improvement (change) from baseline for SF-36 PCS at week 24
- H16: SEC 75 mg is not different from placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at week 24
- H17: SEC 150 mg is not different from placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at week 24
- H18: SEC 300 mg is not different from placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at week 24
- H19: SEC 75 mg is not different from placebo regimen with respect to ACR50 response at week 24
- H20: SEC 150 mg is not different from placebo regimen with respect to ACR50 response at week 24
- H21: SEC 300 mg is not different from placebo regimen with respect to ACR50 response at week 24
- H22: SEC pooled regimen (75 mg and 150 mg and 300 mg) is not different from placebo regimen with respect to presence of dactylitis at week 24 in the subset of patients who have dactylitis at baseline
- H23: SEC pooled regimen (75 mg and 150 mg and 300 mg) is not different from placebo regimen with respect to presence of enthesitis at week 24 in the subset of patients who have enthesitis at baseline.

The CDR protocol included subgroups by body weight at baseline, number of prior DMARDs and/or biologic response modifiers, patients using MTX as concomitant medication versus non-MTX, and disease severity (based on DAS 28). However, such subgroup analyses were not undertaken, with the exception of subgroup analyses according to previous anti-TNF use, which were conducted for the primary end point and secondary end points (pre-specified exploratory end points). Subgroup analyses with and without concomitant MTX therapy were done post hoc.

a) Analysis Populations

The analysis populations were defined in the same way in both trials.

The randomized set consisted of all patients who were randomized into the study at baseline.

The safety set consisted of all patients in the randomized set who took at least one dose of study medication. Patients were evaluated according to the treatment received.

The full analysis set consisted of all patients from the randomized set to whom study treatment had been assigned. Following the intention-to-treat principle, patients were analyzed according to the treatment assigned at randomization.

The per-protocol set consisted of all patients who had completed the study without a major protocol deviation.

3.3 Patient Disposition

Patient disposition is summarized in Table 7. In FUTURE 1, a total of 606 patients were randomized to SEC 150 mg, SEC 75 mg, or placebo at baseline. In FUTURE 2, 397 patients were randomized to SEC 300 mg, SEC 150 mg, SEC 75 mg, or placebo at baseline. Overall, the number of premature discontinuations at week 24 was higher in the placebo groups (10.2% to 13.9%) than in the SEC 150 mg group (5% to 6.4%) or the SEC 300 mg group (3%). The corresponding completion rates at week 24 were 93.6% to 95% in the SEC 150 mg group and 97% in the SEC 300 mg group versus 86.6% to 89.8% in the placebo group. Isolated cases of lack of efficacy, AEs, loss to follow-up, physician decision, and patient decision were reported as the causes of study discontinuation in the SEC groups and placebo groups. At week 16, 30.2% of patients in the placebo groups of the FUTURE 1 were assigned to SEC 150 mg treatment, and 28.6% and 27.6% of patients in the placebo groups of the FUTURE 2 were assigned to SEC 150 mg and SEC 300 mg treatment, respectively.

TABLE 7: PATIENT DISPOSITION

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg, then 150 mg	PL	SEC 300 mg	SEC 150 mg	PL
Screened, N	817		469		
Randomized, N	606		397		
Enrolled, N	202	202	100	100	98
Discontinued through week 16, N (%)		16 (7.9)			10 (10.2)
Adverse events		3 (1.5)			
Lack of efficacy		6 (3.0)			
Lost to follow-up		2 (1.0)			
Physician decision		1 (0.5)			
Patient/guardian decision		4 (2.0)			
Completed, week 16		186 (92.1)			88 (89.8)
Assigned to receive SEC 300 mg SC from week 16	NA	NA	NA	NA	28 (28.6)
Assigned to receive SEC 150 mg SC from week 16	NA	61 (30.2)	NA	NA	27 (27.6)

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg, then 150 mg	PL	SEC 300 mg	SEC 150 mg	PL
Assigned to receive SEC 75 mg SC from week 16	NA	62 (30.7)	NA	NA	NA
Discontinued through week 24, N (%)	13 (6.4)	28 (13.9)	3 (3)	5 (5)	[redacted]
Adverse events	4 (2.0)	8 (4.0)	2 (2)	0	[redacted]
Lack of efficacy	3 (1.5)	10 (5.0)	0	3 (3)	[redacted]
Lost to follow-up	1 (0.5)	3 (1.5)	0	0	[redacted]
Physician decision	2 (1.0)	1 (0.5)	0	1 (1)	[redacted]
Patient/guardian decision	3 (1.5)	6 (3.0)	1 (1)	1 (1)	[redacted]
Completed, week 24	189 (93.6)	175 (86.6)	97 (97)	95 (95)	88 (89.8)
Randomized set, N	202	202	100	100	98
Full analysis set, N	202	202	100	100	98
Safety set, N	202	202	100	100	98

NA = not applicable; PL = placebo; SC = subcutaneous injection; SEC = secukinumab.
Source: Clinical study reports.[6,7]

3.4 Exposure to Study Treatments

In the FUTURE 1 trial, the majority of the patients had three IV infusions at weeks 0, 2, and 4, [redacted]. Up to week 16, the majority of the patients had a total of [redacted] study visits with SC injections, [redacted] patients in the placebo group.

In the FUTURE 2 trial, [redacted] had 16 or more weeks of exposure to SEC 300 mg, SEC 150 mg, and placebo, respectively, and [redacted] had 24 or more weeks of exposure to SEC 300 mg, SEC 150 mg, and placebo, respectively. In addition, [redacted] patients in the SEC 300 mg, SEC 150 mg, and placebo groups, respectively, self-administered the study treatment by week 16.

3.5 Critical Appraisal

3.5.1 Internal Validity

FUTURE 1 was randomized and double-blinded up to week 24, and dose-blinded up to two years. Appropriate methods of randomization, blinding, and allocation concealment were reported. Entry into the early escape phase was blinded, which can help minimize bias. Patients were stratified at randomization according to whether they were TNF alpha inhibitor–naive or TNF alpha inhibitor–IR. Study treatments were administered by dedicated blinded trained site personnel. An independent, unblinded pharmacist, nurse, physician, or authorized personnel prepared the study treatment and made sure that no other person had access to the medication and drug-administration documentation.

In the FUTURE 2 trial, randomization was done by an electronic system (IRT) that concealed treatment assignment from patients and investigators. The same electronic system was used for re-randomizing placebo patients who were non-responders at week 16. Patients were stratified at randomization according to being TNF alpha inhibitor–naive or TNF alpha inhibitor–IR. FUTURE 2 trial was blinded; the identity of the treatments was concealed by the use of study treatments in the form of PFS for SC injection, filled with SEC or placebo that are identical in appearance. The FUTURE 2 trial included a double-dummy design in order to maintain the blinding, which was appropriately done. Blinding was

maintained throughout the trial, up to 52 weeks. Although patients were randomized, some baseline characteristics were still imbalanced: baseline PASI score, the proportion of patients with psoriasis of hands and feet, the proportion of patients with psoriasis of the nail, the proportion of female patients, patients with psoriasis affecting at least 3% of their body surface, and patients with dactylitis or enthesitis. However, the clinical expert noted that these imbalances were unlikely to have a significant impact on the study results.

A hierarchical test procedure for series-ranked primary and secondary outcomes was used in order to control the type I error rate (at 5%), which was divided by 2 ($\alpha/2 = 0.025$) in the FUTURE 1 trial for each SEC treatment group comparison with placebo and was not divided ($\alpha = 0.05$) in the pooled analysis of SEC groups versus placebo. In the FUTURE 2 trial, the type I error of 5% was divided by 3 ($\alpha/3 = 0.01666$) for each SEC treatment group comparison with placebo, but was not divided ($\alpha = 0.05$)in the pooled analysis of SEC groups versus placebo. Testing in the hierarchy was conditional on the first test being significant; the second hypothesis was tested with the same α level of significance. Statistical testing for the hypotheses was performed only if the previous null hypothesis in the hierarchy could be rejected. The limitation with this approach was that only certain outcomes were selected and, hence, the hierarchical approach did not take into consideration all outcomes measured in the study, including some of the patient-reported outcomes data (proportion of patients with improvements of 0.30 point or more in HAQ-DI, change from baseline in the MCS score of the SF-36, proportion of patients with improvement of 2.5 points or more in the MCS score and the PCS score of the SF-36, change from baseline in the PsAQoL, change from baseline in the DLQI, patient assessment of pain, and change from baseline in the FACIT–Fatigue). These outcomes were identified as exploratory variables in FUTURE 1 and FUTURE 2, although they were considered clinically important patient-reported outcomes for this review. These outcomes were not adjusted for multiplicity, and hence, given the large number of comparisons in the study, a statistically significant finding ($P < 0.05$) for the comparisons between SEC treatment groups and placebo for these outcomes may be attributable to an inflated type I error rate. In addition, no criteria were stated on how the outcomes that were included in the hierarchy were ranked and there was no rationale provided for which of the secondary outcomes were included in the hierarchy. Finally, in the FUTURE 2 trial, the *P* value for the comparison of the change from baseline in HAQ-DI at week 24 was 0.0278 for the comparison between SEC 150 mg and placebo, which is greater than the pre-specified level of significance (0.016). The statistical testing should have been stopped for the comparison between SEC 150 mg group and placebo group according to the pre-specified criteria in the study protocol; however, statistical testing continued for all of the remaining outcomes.

The Health Canada–approved indication is SEC 150 mg for TNF alpha inhibitor–naive and 300 mg for TNF alpha inhibitor–IR patients. Subgroup analyses according to previous anti-TNF use for the primary end point and secondary end points were pre-specified exploratory end points; however, these subgroup analyses were not adjusted for multiplicity, and hence a statistically significant finding ($P < 0.05$) for the comparisons between SEC treatment groups and placebo for these analyses must be interpreted with caution because of the risk of inflated type I error. Patients were stratified at randomization according to being TNF alpha inhibitor–naive or TNF alpha inhibitor–IR; hence, randomization was maintained in these subgroup analyses.

Subgroup analyses with and without concomitant MTX therapy were not pre-specified and were done post hoc; hence, results reported should be interpreted with caution.

In FUTURE 1 and FUTURE 2, 69% and 66% of placebo patients, respectively, discontinued randomized treatment before week 24 (either owing to early escape or because of treatment discontinuation). This

means that a substantial proportion of the outcomes data at week 24 had to be imputed based on an intention-to-treat (ITT) analysis. In addition, the imputation would have been differential (more imputed data in the placebo group than in the active treatment). Therefore, there is a high degree of uncertainty with respect to the findings of the studies beyond the week 16 time point. On the other hand, patients in the placebo group who were switched to active treatment at week 16 were imputed as non-responders in the analysis at week 24. However, given that the symptoms of PsA fluctuate over time, it is possible that a certain proportion of placebo-treated patients could have achieved ACR20 after week 16. Also, because the percentage escaping early at week 16 was different between placebo and SEC, this could likely bias the 24-week assessment and overestimate the effect of SEC. In addition, some of the placebo patients could have had a spontaneous improvement, but they were considered non-responders.

In the published articles for the trials,[20,21] it is indicated that SEC-treated patients who had no response at week 16 were imputed as non-responders at week 24. However, it was unclear from the protocol and clinical study report how data were handled/imputed for this time point for SEC-treated patients. In the clinical study report analyses of continuous outcomes, data collected after the patient was rescued were treated as missing for placebo patients who switched to SEC, and actual values were used for SEC patients; for binary outcomes, rescued patients were considered non-responders after the time of rescue.

Continuous outcomes were analyzed using an MMRM approach, with missing data assumed to be missing at random (MAR); however, the MAR assumption might not have been met. Generally, patients who drop out of trials are those who have poorer outcomes (lack of efficacy, AEs). Because of this, those who remain in the trial may have better HRQoL, leading to bias and more favourable results. In addition, no sensitivity analysis with an alternative imputation strategy, such as last observation carried forward (LOCF), was undertaken in order to compare results.

Patients knew that they were receiving active treatment after week 24, which potentially biased the results of patient-reported outcomes such as HRQoL, symptom and disability measures, as well as AEs.

Currently available outcome measures in PsA have largely been adopted from other conditions, such as rheumatoid arthritis and psoriasis. Hence, validity and reliability data specific to PsA are sparse, and some instruments lack an MCID.

In the responder analyses for the SF-36 PCS, an MCID of 2.5 was used, whereas an MCID of 3.74 was estimated for patients with PsA. Hence, it is not clear whether these patients should be considered responders.

PASI was assessed only in patients in whom psoriasis affected at least 3% of the body surface area at baseline. As a result of the small sample size and selected population , randomization may not have been maintained for this subgroup which appeared to be imbalanced.

Work productivity was assessed only in patients who work, so for the reasons explained above, randomization may also not have been maintained in this subset of patients.

In the analyses of DAS 28-CRP, more than [redacted] of data were missing in the placebo group at week 16 and week 24, respectively; [redacted] of data were missing in the placebo group at week 16 and

week 24, respectively; this large proportion of missing data in the placebo group makes results very uncertain, especially at week 24. In addition, randomization may not have been maintained.

In the analyses of DLQI and mNAPSI, only a subset of the patient population was included, and no definition was provided of who was included in such analyses. Less than [redacted] of patients were included in the analyses at week 16 in all treatment groups and less than [redacted] of patients in the placebo group were included in the analyses at week 24; [redacted] missing data in the placebo group makes results very uncertain, especially at week 24. In addition, randomization may not have been maintained.

3.5.2 External Validity

The loading dose used the FUTURE 1 trial (an IV loading infusion of SEC at a dose of 10 mg/kg at weeks 0, 2, and 4, followed by SEC 150 mg SC starting at week 8 and injected every four weeks) is different from and higher than the Health Canada–recommended loading dose (150 mg SC injection with initial dosing at weeks 0, 1, 2, and 3, followed by monthly maintenance dosing starting at week 4). In the clinical expert's opinion, the dose used in the FUTURE 1 trial would result in a rapid onset of efficacy for SEC, and reach a certain level and stay at that level, whereas it might take patients who receive the Health Canada–recommended dose longer to reach that level of efficacy.

Several outcomes measured in the trials have limitations, including a lack of clearly defined MCID in score change in patients with PsA (see APPENDIX 5).

Patients were excluded from the trials if they had underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, infectious, or gastrointestinal conditions. While this is a prudent approach, it limits the generalizability of harms results to clinical practice where patients who are at higher risk may be prescribed the drug.

PsA is a chronic disease, with patients expected to be on treatment for many years. Although long-term harms data were reported for up to 104 weeks in the FUTURE 1 trial and up to week 52 in the FUTURE 2 trial, the only placebo-controlled data available for SEC are up to week 24. However, these data are likely limited in their utility, given the aforementioned high proportion of patients who discontinued randomized treatment (either owing to early escape or because of treatment discontinuation) during the studies.

High-quality evidence for the use of MTX in PsA is lacking, although it is generally accepted in clinical practice as a therapeutic option. Because of the lack of evidence, appropriate dosing of MTX is unclear. In both studies, the median dose at baseline ranged from 14 mg to 18 mg/kg per week across studies and between-treatment groups, which is lower than recommended MTX doses used in rheumatoid arthritis (approximately 25 mg per week).

There is a lack of direct, head-to-head comparisons of SEC versus another active control, such as one of the biologics.

Patients who were using DMARDs other than MTX or TNF alpha inhibitors before enrolment in the trials were required to discontinue their medication; 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, there is unlikely to be a washout period.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are subsequently reported (section 2.2, Table 3). See *APPENDIX 4* for detailed efficacy data. The reviewer focused primarily on the results from the FUTURE 2 trial, which used the SC loading and maintenance dose, matching the Health Canada–recommended dose. The FUTURE 1 trial was also reviewed but more as supportive data, since it uses the IV loading dose, which is not the dosing regimen recommended by Health Canada. Only data associated with SEC 150 mg and SEC 300 mg are reported, as these are the Health Canada–approved dosages.

3.6.1 Outcomes Related to Psoriatic Arthritis Symptoms

a) ACR20, 50, 70

In the FUTURE 2 trial, a statistically significantly greater proportion of patients in the SEC 150 mg and SEC 300 mg treatment groups achieved an ACR20 response at week 16 compared with placebo (57% for SEC 300 mg versus 18.4% for placebo, $P < 0.0001$; 60% for SEC 150 mg versus 18.4% for placebo, $P < 0.0001$). Similarly, a statistically significantly greater proportion of patients in the SEC 300 mg and SEC 150 mg treatment groups achieved an ACR20 response at week 24 compared with the placebo group (54% for SEC 300 mg versus 15% for placebo, $P < 0.0001$; 51% for SEC 150 mg versus 15% for placebo, $P < 0.0001$) (Table 8).

In the FUTURE 2 trial, subgroup analyses by previous anti-TNF use at weeks 16 and 24 were performed for ACR20 and are presented in Table 8. [redacted] of TNF alpha inhibitor–naive patients in the SEC 150 mg treatment group achieved an ACR20 response at weeks 16 and 24 compared with the placebo group [redacted], and 63% for SEC 150 mg versus 16% for placebo, $P < 0.0001$ at week 24). A statistically significantly greater proportion of TNF alpha inhibitor–IR patients in the SEC 300 mg treatment group achieved an ACR20 response at weeks 16 and 24 compared with the placebo group [redacted], and 45% for the SEC 300 mg group versus 14% for the placebo group, $P = 0.0077$ at week 24). However, these subgroup analyses (at both weeks 16 and 24) were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error.

In the FUTURE 2 trial, subgroup analyses by concomitant MTX use and by weight (< 100 kg versus ≥ 100 kg) at weeks 16 and 24 were performed for ACR20 and are presented in Table 8. A statistically significantly greater proportion of patients in the SEC 150 mg and SEC 300 mg treatment groups achieved an ACR20 response at weeks 16 and 24 compared with placebo in all the analyses except in the subgroup analysis of body weight ≥ 100 kg for SEC 150 mg versus placebo at week 24, in which no statistically significant difference was found. This lack of a difference could be due to the small sample size of this subgroup. These subgroup analyses were post hoc in nature, and any result reported should be interpreted with caution.

In the FUTURE 1 trial, a [redacted] proportion of patients in the SEC 150 mg treatment group achieved an ACR20 response at weeks 16 and 24 compared with placebo [redacted] at week 16, and 50% for SEC 150 mg versus 17.3% for placebo, $P < 0.0001$ at week 24). Subgroup analyses by previous anti-TNF use at weeks 16 and 24 were performed for ACR20. A statistically significantly greater proportion of TNF alpha inhibitor–naive patients in the SEC 150 mg treatment group achieved an ACR20 response at weeks 16 and 24 compared with placebo ([redacted] at week 16, and 54.5% for SEC 150 mg versus 17.5% for placebo, $P < 0.0001$ at week 24). However, these subgroup analyses (at both weeks 16 and 24) were not included in the hierarchical statistical analysis approach and should be considered

exploratory in nature because of the potential for inflated type I error. Similarly, in the FUTURE 2 trial, a statistically significantly greater proportion of patients in the SEC 150 mg treatment group achieved an ACR20 response at weeks 16 and 24 compared with the placebo group in the subgroup analyses by concomitant MTX use; however, this subgroup analysis was post hoc in nature and any result reported should be interpreted with caution (Table 8).

TABLE 8: PROPORTION OF PATIENTS WITH ACR20 RESPONSE AT WEEK 16 AND WEEK 24 (USING NON-RESPONDER IMPUTATION)

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
ACR20 at week 16					
Full analysis set[a]					
n (%)	115 (56.9)	43 (21.3)	57 (57)	60 (60)	18 (18.4)
Odds ratio (95% CI)	5.31 (3.39 to 8.31)		6.14 (3.18 to 11.86)	7.76 (3.96 to 15.22)	
P value	< 0.0001		< 0.0001	< 0.0001	
TNF alpha inhibitor–inadequate responder[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Concomitant MTX use[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
No concomitant MTX treatment[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Weight (< 100 kg)[b]					
n/N (%)	NR	NR	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	NR	NR	[redacted]	[redacted]	
P value	NR		[redacted]	[redacted]	
Weight (≥ 100 kg)[b]					
n/N (%)	NR	NR	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	NR	NR	[redacted]	[redacted]	
P value	NR		[redacted]	[redacted]	

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
ACR20 at week 24					
Full analysis set[a]					
n (%)	101 (50.0)	35 (17.3)	54 (54)	51 (51)	15 (15)
Odds ratio (95% CI)	[redacted]		6.81 (3.42 to 13.56)	6.52 (3.25 to 13.08)	
P value	< 0.0001		< 0.0001	< 0.0001	
TNF alpha inhibitor–inadequate responder[b]					
n/N (%)	23/59 (39.0)	10/59 (16.9)	15/33 (45)	11/37 (30)	5/35 (14)
Odds ratio (95% CI)	[redacted]		4.97 (1.53 to 16.15)	2.55 (0.78 to 8.32)	
P value	0.0062		0.0077	0.1216	
TNF alpha inhibitor–naive patients[b]					
n/N (%)	78/143 (54.5)	25/143 (17.5)	39/67 (58)	40/63 (63)	10/63 (16)
Odds ratio (95% CI)	[redacted]		7.77 (3.36 to 17.98)	9.99 (4.22 to 23.66)	
P value	< 0.0001		< 0.0001	< 0.0001	
Concomitant MTX use[b]					
n/N (%)	63/121 (52.1)	24/125 (19.2)	24/44 (54·5)	21/44 (47·7)	10/50 (20·0)
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	< 0.0001		0·0007	0·0049	
No concomitant MTX treatment[b]					
n/N (%)	38/81 (46.9)	11/77 (14.3)	30/56 (53·6)	30/56 (53·6)	5/48 (10·4)
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	< 0.0001		< 0·0001	< 0·0001	
Weight (< 100 kg)[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Weight (≥ 100 kg)[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	

ACR = American College of Rheumatology; CI = confidence interval; MTX = methotrexate; NR = not reported; PL = placebo; SEC = secukinumab; TNF = tumour necrosis factor.

Note: n is the number of patients who are responders with corresponding imputation approach in the treatment group. Missing responses are considered non-responders. Rescued patients are also considered non-responders after the time of rescue. Discontinued patients are considered non-responders after the time of discontinuation.

[a] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment and randomization stratum (TNF alpha inhibitor–naive or –IR) as factors and baseline weight as a covariate.

[b] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment as the factor and baseline weight as a covariate.

Source: Clinical study reports.[6,7]

In the FUTURE 2 trial, a higher proportion of patients in the SEC 150 mg and SEC 300 mg treatment groups achieved an ACR50 and ACR70 response at weeks 16 and week 24 compared with placebo. However, claims of statistical significance can only be made for ACR50 at week 24 in the SEC 300 mg treatment group (Table 10). Claims of statistical significance could not be made for ACR50 at week 24 in the SEC 150 mg treatment group because the outcome assessed in the hierarchy (HAQ-DI) did not achieve statistical significance. Hence, the hierarchical testing was stopped before testing ACR50 in the SEC 150 mg treatment group. The analyses for ACR50 at week 16 and ACR70 at weeks 16 and 24 were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 11).

In the FUTURE 1 trial, a higher proportion of patients in the SEC 150 mg treatment group achieved an ACR50 and ACR70 response at weeks 16 and week 24 compared with placebo. A claim of statistical significance can be made for ACR50 at week 24 in the SEC 150 mg treatment group (Table 10). The analyses for ACR50 at week 16, and ACR70 at weeks 16 and 24 were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 11).

b) Minimal Disease Activity

In the FUTURE 2 trial, a higher proportion of patients in the SEC 150 mg and SEC 300 mg treatment groups achieved an MDA response at weeks 16 and week 24 compared with placebo; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 20).

In the FUTURE 1 trial, a higher proportion of patients in the SEC 150 mg treatment group achieved an MDA response at weeks 16 and week 24 compared with placebo; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 20).

c) Disease Activity Score 28–C-reactive Protein

In the FUTURE 2 trial, there was a statistically significantly greater reduction in DAS 28-CRP score in the SEC 150 mg and SEC 300 mg treatment groups compared with the placebo group at weeks 16 and 24. In the subgroup analysis by previous anti-TNF use at weeks 16 and 24, there was a statistically significantly greater reduction in DAS 28-CRP score in the SEC 150 mg and SEC 300 mg treatment groups compared with placebo at weeks 16 and week 24 in the subgroups of patients who were TNF alpha inhibitor–naive patients and TNF alpha inhibitor–IR. However, a claim of statistical significance could only be made for the all-population analysis at week 24, as it was part of the hierarchical statistical analysis, but the week 16 analysis and all other analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 14).

In the FUTURE 1 trial, there was a statistically significantly greater reduction in DAS 28-CRP score in the SEC 150 mg treatment group compared with placebo at weeks 16 and week 24. In the subgroup analysis by previous anti-TNF use at weeks 16 and 24, a statistically significantly greater reduction in DAS 28-CRP score in the SEC 150 mg treatment group compared with placebo at weeks 16 and week 24 were found in the subgroup of TNF alpha inhibitor–naive patients. However, a claim of statistical significance could only be made for the overall population analysis at week 24, as it was part of the hierarchical statistical analysis, but the week 16 analysis and all other analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 14).

In FUTURE 2 trial, the proportion of patients achieving DAS 28 EULAR response of "good" was higher in the SEC 150 mg and SEC 300 mg treatment groups compared with placebo at week 16, and it was only higher in treatment group SEC 300 mg at week 24; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 15).

In the FUTURE 1 trial, the proportion of patients achieving DAS 28 EULAR response of "good" was higher in the SEC 150 mg treatment group compared with placebo at weeks 16 and 24; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 15).

d) Health Assessment Questionnaire-Disability Index

In the FUTURE 2 trial, a statistically significantly greater reduction from baseline in HAQ-DI score was achieved in patients in the SEC 300 mg treatment group compared with placebo at week 24; however, the SEC 150 mg treatment group did not achieve a statistically significantly greater reduction from baseline in HAQ-DI score at week 24 (*P* = 0.0278), which was [redacted]. The difference in change from baseline between SEC 150 mg and the placebo group, and SEC 300 mg and placebo treatment groups at week 16 was [redacted] respectively, and it was respectively [redacted] at week 24. Hence, the difference between the mean score change from baseline exceeded the MCID for the HAQ-DI (estimated to range from 0.3 to 0.35) in the comparison between SEC 300 mg and placebo groups at week 16 (Table 17). The difference in change from baseline between SEC 150 mg and placebo groups in the subgroup of patients who were TNF alpha inhibitor–naive and in the subgroup of patients who were TNF alpha inhibitor–IR at weeks 16 and 24 did not exceed the MCID for the HAQ-DI. The difference in change from baseline between SEC 300 mg and placebo groups in the subgroup of patients who were TNF alpha inhibitor–IR at weeks 16 and 24 only exceeded the MCID for the HAQ-DI in the comparison at week 16 (Table 17).

In the FUTURE 2 trial, the proportion of patients achieving HAQ-DI improvements of at least 0.30 point at weeks 16 and 24 was statistically significant in favour of the SEC 150 mg and SEC 300 mg treatment groups in comparison with placebo treatment group. However, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 17).

In the FUTURE 1 trial, a statistically significantly greater reduction from baseline in HAQ-DI score was achieved in patients in the SEC 150 mg treatment group compared with placebo at week 24. However, the difference in change from baseline between the SEC 150 mg group and the placebo group at weeks 16 and 24 did not exceed the MCID for the HAQ-DI (Table 17). Similarly, in the subgroup of patients who were TNF alpha inhibitor–naive and the subgroup of patients who were TNF alpha inhibitor–IR, the difference in change from baseline between SEC 150 mg and placebo group at weeks 16 and 24 did not exceed the MCID for the HAQ-DI (estimated to range from 0.3 to 0.35) (Table 17). In the FUTURE 1 trial, the proportion of patients achieving HAQ-DI improvements of at least 0.30 point at weeks 16 and 24 were statistically significant in favour of the SEC 150 mg treatment group in comparison with the placebo treatment group. However, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 17).

e) Dactylitis

In the FUTURE 2 trial, resolution of dactylitis was evaluated in the subset of patients who had dactylitis at baseline. A lower percentage of patients with dactylitis is desirable, and resolution is defined as complete absence of the symptom in this analysis. The placebo groups had a greater percentage of patients without dactylitis resolution compared with SEC 150 and SEC 300 mg treatment groups at week 24. Overall, the percentage of patients without resolution of dactylitis at week 24 was [redacted] for SEC 150 mg, 300 mg, and placebo groups, respectively; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 19).

In the FUTURE 2 trial, there was no statistically significant difference in LDI change from baseline at week 24 when SEC 150 and SEC 300 mg treatment groups were compared with the placebo group, but there was a statistically significant difference when the SEC 300 mg group was compared with the placebo group at week 16; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 26).

In the FUTURE 1 trial, the placebo group had a greater percentage of patients without dactylitis resolution compared with the SEC 150 mg treatment group at week 24. Overall, the percentage of patients without resolution of dactylitis at week 24 was [redacted] for SEC 150 mg and placebo groups, respectively; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 19).

In the FUTURE 1 trial, there was a statistically significant difference in LDI change from baseline at weeks 16 and 24 when the SEC 150 treatment group was compared with placebo; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 26).

f) Enthesitis

In the FUTURE 2 trial, resolution of enthesitis was evaluated in the subset of patients who had enthesitis at baseline. A lower percentage of patients with enthesitis is desirable, and resolution is defined as complete absence of the symptom in this analysis. The placebo group had a greater percentage of patients without resolution of enthesitis compared with SEC 150 mg and SEC 300 mg treatment groups at week 24. Overall, the percentage of patients without resolution of enthesitis at week 24 was [redacted] for SEC 150 mg, 300 mg, and placebo groups, respectively; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 19).

In the FUTURE 1 trial, the placebo group had a greater percentage of patients without enthesitis resolution compared with the SEC 150 mg treatment group at week 24. Overall, the percentage of patients without resolution of enthesitis at week 24 was [redacted] for SEC 150 mg and placebo groups, respectively; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error (Table 19).

3.6.2 Health-Related Quality of Life and Other Patient-Reported Outcomes

a) SF-36

Results for the mean change from baseline in SF-36 PCS and MCS scores at week 16 and 24 are presented in Table 16.

In the FUTURE 2 trial, at week 16 the difference between the SEC 300 mg treatment group and the placebo group was 5.06, and the difference between the SEC 150 mg treatment group and the placebo group was 4.34. There was a statistically significant greater change from baseline in the SF-36 PCS score in the SEC treatment groups than in the placebo group at week 16; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error. At week 24 the difference between the SEC 300 mg treatment group and the placebo group was 5.30, and the difference between the SEC 150 mg treatment group and placebo was 4.44. There was a statistically significant greater change from baseline in the SF-36 PCS score in the SEC treatment groups than in the placebo group at week 24. The difference in the SF-36 PCS score between the SEC 300 mg treatment group and the placebo group in the subgroup of patients who were TNF alpha inhibitor–IR was 5.36 and 6.56 at weeks 16 and 24, respectively, and the difference in the SF-36 PCS score between the SEC 150 mg treatment group and placebo in the subgroup of patients who were TNF alpha inhibitor–naive was 4.70 and 5.83 at weeks 16 and 24, respectively (Table 16). These differences exceeded the MCID of 3.74 for the SF-36 PCS score. The proportion of patients achieving an improvement of 2.5 points or more in SF-36 PCS score was statistically significantly greater in the SEC 300 mg and SEC 150 mg treatment groups than in the placebo group at weeks 16 and 24. However, this outcome assessment was not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error.

In the FUTURE 1 trial, at week 16 the difference between the SEC 150 mg treatment group and the placebo group was 4.17, and this difference was statistically significant; however, this analysis was not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error. At week 24 the difference between the SEC 150 mg treatment group and the placebo group was 4.09. There was statistically significantly greater change from baseline in the SF-36 PCS score in the SEC treatment group than in the placebo group at week 24. The difference in the SF-36 PCS score between the SEC 150 mg treatment group and the placebo group in the subgroup of patients who were TNF alpha inhibitor–naive was 4.51 and 4.16 at weeks 16 and 24, respectively (Table 16). These differences exceeded the MCID of 3.74 for the SF-36 PCS score. The proportion of patients achieving an improvement 2.5 points or more in SF-36 PCS score was statistically significantly greater in the SEC 150 mg treatment group than in the placebo group at weeks 16 and 24. However, this outcome assessment was not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error.

In the FUTURE 2 trial, at week 16, the difference between the SEC 300 mg treatment group and the placebo group was [redacted], and the difference between the SEC 150 mg treatment group and the placebo group was [redacted]. These differences exceeded the MCID of 1.77 for the SF-36 MCS score. There was a statistically significantly greater change from baseline in the SF-36 MCS score only in the SEC 150 mg treatment group than in the placebo group at week 16. At week 24, the difference between the SEC 300 mg treatment group and the placebo group was 0.26, and the difference between the SEC 150 mg treatment group and the placebo group was 2.39. The difference between the SEC 150 mg treatment group and the placebo group exceeded the MCID of 1.77 for the SF-36 MCS score. There was no statistically significant difference in the change from baseline in the SF-36 MCS score between any of the SEC treatment groups and the placebo group at week 24. The difference in the SF-36 MCS score

between the SEC 300 mg treatment group and the placebo group in the subgroup of patients who were TNF alpha inhibitor–IR was [redacted] and 1.50 at weeks 16 and 24, respectively. This difference was not statistically significant and did not exceed the MCID of 1.77 for the SF-36 MCS score. The difference in the SF-36 MCS score between the SEC 150 mg treatment group and the placebo group in the subgroup of patients who were TNF alpha inhibitor–naive was [redacted] and 2.89 at weeks 16 and 24, respectively. These differences exceeded the MCID of 1.77 for the SF-36 MCS score but were statistically significant at week 16 only (Table 16). The proportion of patients achieving an improvement of 2.5 points or more in SF-36 MCS score was statistically significantly greater in the SEC 150 mg treatment group than in the placebo group at weeks 16 and 24, and it was statistically significantly greater in the SEC 300 mg treatment group than in the placebo group at week 24 only (Table 16). However, all outcomes assessed in this discussion were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error.

In the FUTURE1 trial, at week 16, the difference between the SEC 150 mg treatment group and the placebo group was [redacted] exceeding the MCID of 1.77 for the SF-36 MCS score, and this difference was statistically significant. At week 24, the difference between the SEC 150 mg treatment group and the placebo group was 3.27, exceeding the MCIDs of 1.77 for the SF-36 MCS score. There was a statistically significantly greater change from baseline in the SF-36 MCS score in the SEC treatment group than in the placebo group at week 24. The difference in the SF-36 MCS score between the SEC 150 mg treatment group and the placebo group in the subgroup of patients who were TNF alpha inhibitor–naive was [redacted] at weeks 16 and 24, respectively. This difference was statistically significant at weeks 16 and 24 and exceeding the MCID of 1.77 for the SF-36 MCS score (Table 16). The proportion of patients achieving an improvement of 2.5 points or more in SF-36 MCS score was statistically significantly greater in the SEC 150 mg treatment group than in the placebo group at weeks 16 and 24. However, all outcomes assessed in this discussion were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error.

b) Psoriatic Arthritis Quality of Life

In FUTURE 2, at weeks 16 and 24, the mean change in scores decreased (improved) from baseline for all treatment groups, including the placebo group. Both SEC 150 mg and SEC 300 mg groups had statistically significant greater improvement relative to the placebo group for mean score change at weeks 16 and 24 (Table 22). In FUTURE 1, at weeks 16 and 24, the mean change in scores decreased (improved) from baseline for SEC 150 mg and placebo groups. SEC 150 mg treatment group had statistically significant greater improvement relative to placebo for mean score change at weeks 16 and 24 (Table 22). However, in both trials this outcome assessment was not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error.

c) Dermatology Life Quality Index

In FUTURE 2, at weeks 16 and 24, the mean change in scores decreased (improved) from baseline for all treatment groups, including placebo. Both SEC 150 mg and SEC 300 mg groups had statistically significant greater improvement relative to the placebo group for mean score change at weeks 16 and 24 (Table 24). In FUTURE 1, at weeks 16 and 24, the mean change in scores decreased (improved) from baseline for SEC 150 mg and placebo groups. The SEC 150 mg treatment group had statistically significant greater improvement relative to placebo for mean score change at weeks 16 and 24 (Table 24). However, in both trials this outcome assessment was not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated

type I error. [redacted].

d) Patient's Assessment of Pain (VAS)

In FUTURE 2, at weeks 16 and 24, the mean change in scores decreased (improved) from baseline for all treatment groups, including the placebo group. Both SEC 150 mg and SEC 300 mg groups had statistically significant greater improvement relative to placebo for mean score change at weeks 16 and 24 (Table 21). In FUTURE 1, at weeks 16 and 24, the mean change in scores decreased (improved) from baseline for SEC 150 mg and placebo. SEC 150 mg treatment group had statistically significant greater improvement relative to placebo for mean score change at weeks 16 and 24 (Table 21). However, in both trials, this outcome assessment was not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error. [redacted].

e) Functional Assessment of Chronic Illness Therapy–Fatigue

In FUTURE 2, at weeks 16 and 24, the mean change in scores increased (improved) from baseline for all treatment groups, including placebo. Both SEC 150 mg and SEC 300 mg groups had statistically significant greater improvement relative to placebo for mean score change at weeks 16 and 24 (Table 23). In FUTURE 1, at weeks 16 and 24, the mean change in scores increased (improved) from baseline for SEC 150 mg and placebo groups. The SEC 150 mg treatment group had statistically significant greater improvement relative to the placebo group for mean score change at weeks 16 and 24 (Table 23). However, in both trials, this outcome assessment was not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error. [redacted].

3.6.3 Work Productivity

Numerically greater reductions in work or activity impairment because of disease, as measured by the WPAI-GH questionnaire, were observed in both studies (Table 27).

In FUTURE 1, at weeks 16 and 24, the mean change from baseline showed greater improvements for the SEC 150 mg group compared with the placebo group in categories pertaining to percentage of work time missed because of health [redacted], percentage of impairment while working because of health [redacted] percentage of overall work impairment because of health [redacted] and percentage of activity impairment because of health [redacted].

In FUTURE 2, at weeks 16 and 24, the mean change from baseline showed greater improvements for the SEC 300 mg and SEC 150 mg treatment groups compared with the placebo group in categories pertaining to percentage of work time missed because of health [redacted] percentage of impairment while working because of health [redacted], percentage of overall work impairment because of health [redacted]

[redacted]and percentage of activity impairment because of health [redacted]

Statistical comparisons between SEC and placebo groups were not reported.

3.6.4 Radiographic Changes

a) van der Heijde modified total Sharp score

Radiographic change was assessed only in the FUTURE 1 trial, using vdH-mTSS. Results for the change in vdH-mTSS at week 24 can be found in Table 18. The mean change from baseline in vdH-mTSS was statistically significantly lower in the SEC 150 mg treatment group (0.13 points) than in the placebo group (0.57), and the between-treatment difference estimate was –0.47 for SEC 150 mg versus placebo (*P* = 0.0212).

The mean change from baseline in vdH-mTSS was statistically significantly lower in the SEC 150 mg treatment group than in the placebo group in the subgroup analyses according to previous anti-TNF use and concomitant MTX therapy. However, these subgroup analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error.

3.6.5 Psoriatic Outcome Measures

a) Psoriasis Area and Severity Index (PASI)

PASI is a measure of the extent and severity of psoriasis lesions; absolute scores range from 0 to 72, with higher scores representing more severe psoriasis. PASI 75 responders are those with a 75% improvement from baseline and PASI 90 responders have a 90% improvement from baseline. Only patients with a body surface area involvement of 3% or more at baseline had a PASI assessment (approximately 54% of all randomized patients in FUTURE 1 and from 41% to 58% in FUTURE 2). In FUTURE 1, the proportion of patients achieving PASI 75 and PASI 90 response in the SEC 150 mg treatment group compared with the placebo group was statistically significantly higher at weeks 16 and 24. In FUTURE 2, a statistically significantly higher proportion of patients achieved PASI 75 and PASI 90 response in the SEC 150 mg and SEC 300 mg treatment groups compared with the placebo group at weeks 16 and 24 (Table 12 and Table 13). However, in both studies, only the analyses at week 24 were included in the hierarchical statistical analysis approach, while analyses at week 16 were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error.

b) Modified Nail Psoriasis Severity Index (mNAPSI)

In FUTURE 2, at weeks 16 and 24, the mean change in scores decreased (improved) from baseline for all treatment groups, including the placebo group. Both SEC 150 mg and SEC 300 mg groups had statistically significant greater improvement relative to placebo for mean score change at weeks 16 and 24 (Table 25). In FUTURE 1, at weeks 16 and 24, the mean change in scores decreased (improved) from baseline for SEC 150 mg and placebo. The SEC 150 mg treatment group had statistically significant greater improvement relative to placebo for mean score change at weeks 16 and 24 (Table 25). However, in both trials, this outcome assessment was not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error.

3.7 Harms

Only those harms identified in the review protocol (section 2.2.1, Protocol) are reported in this section. See Appendix 4, Table 28 for detailed harms data.

3.7.1 Adverse Events

In FUTURE 2, AEs were reported in 56% of patients in the SEC 300 mg group, 57% in the SEC 150 mg group, and 58% in the placebo group by week 16. Generally, the majority of AEs reported up to week 16 were mild or moderate in severity. The most frequently reported AEs during the first 16 weeks of treatment in any SEC group were upper respiratory tract infection, nasopharyngitis, headache, nausea, diarrhea, and urinary tract infection, with frequency comparable to those reported with placebo. Headache and oral herpes were reported in higher frequency on secukinumab 300 mg compared with placebo (7.0% versus 4.1% for headache; and 4.0% versus 2.0% for oral herpes) (Table 28).

In FUTURE 1, the overall incidence of AEs was higher in the SEC 150 mg group (64.9%) than in the placebo group (58.4%) by week 16. Nasopharyngitis, headache, upper respiratory tract infection, hypercholesterolemia, and nausea were the most frequently reported treatment-emergent AEs during the first 16 weeks of treatment (Table 28). The majority of AEs reported up to week 16 were mild or moderate in severity.

3.7.2 Serious Adverse Events

In FUTURE 2, higher rates of serious adverse events (SAEs) were reported in the SEC 300 mg treatment group (5%) compared with the placebo group (2%); however, the SEC 150 mg group had lower rates of SAEs than the placebo group (1%) (Table 9). None of the SAEs occurred in more than one patient.

In FUTURE 1, up to week 16, the incidence of SAEs was low and comparable between the SEC 150 mg group and the placebo group (4.5% for SEC 150 mg versus 5% for placebo) (Table 9).

3.7.3 Withdrawals Due to Adverse Events

In FUTURE 2, higher rates of discontinuations due to AEs were reported in the placebo group (3%) compared with the SEC 300 group (2%) and the SEC 150 mg group (0%) (Table 9).

In FUTURE 1, up to week 16, the proportion of patients discontinuing owing to an AE was low in the SEC group and the placebo group (1.5% for SEC 150 mg and 2.5% for placebo) (Table 9).

3.7.4 Mortality

There were no deaths in any of the studies after 16 weeks of therapy (Table 9).

3.7.5 Notable Harms

[redacted]

[redacted]

Table 9: Harms at Week 16

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
Deaths	0	0	0	0	0
SAEs, N (%)	9 (4.5)	10 (5.0)	5 (5)	1 (1)	2 (2)
WDAEs, N (%)	3 (1.5)	5 (2.5)	2 (2)	0	3 (3)
Patients with > 0 AEs, N (%)	131 (64.9)	118 (58.4)	56 (56)	57 (57)	57 (58)
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]			
[redacted]			[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			
[redacted]			[redacted]	[redacted]	[redacted]

AE = adverse event; PL = placebo; SAE = serious adverse event; SEC = secukinumab; WDAE = withdrawal due to adverse event.
Source: Clinical study reports.[6,7]

4. DISCUSSION

4.1 Summary of Available Evidence

Two manufacturer-sponsored, phase 3, multi-centre, randomized, double-blind, placebo-controlled trials, FUTURE 1 (N = 606) and FUTURE 2 (N = 397), met the inclusion criteria for this systematic review. The trials included patients who had symptoms of moderate to severe PsA for at least six months. Twenty-nine per cent of patients included in FUTURE 1 were TNF alpha inhibitor–IR, whereas 37% of patients included in the FUTURE 2 trial were TNF alpha inhibitor–IR. The FUTURE 1 trial was a three-group superiority study that evaluated the efficacy and safety of SEC 150 mg or SEC 75 mg SC every four weeks compared with placebo, and the FUTURE 2 trial was a four-group superiority trial that evaluated the efficacy and safety of SEC 300 mg, SEC 150 mg, or SEC 75 mg SC every four weeks compared with placebo. The primary efficacy end point in both included studies was the proportion of patients in each treatment group who achieved ACR20 response at week 24. No trials directly comparing SEC with other biologic response modifiers were found in the scientific literature. Both trials had an appropriate randomization strategy, with generally similar treatment groups at baseline. In FUTURE 1 and FUTURE 2, 69% and 66% of placebo patients, respectively, discontinued randomized treatment before week 24 (either owing to early escape or because of treatment discontinuation). This means that a substantial proportion of the outcome data at week 24 had to be imputed based on an ITT analysis. Therefore, there is a high degree of uncertainty with respect to the findings of the studies beyond the week 16 time point. Subgroup analyses for patients with previous anti-TNF use were performed. No subgroup analyses by disease severity were performed.

4.2 Interpretation of Results

4.2.1 Efficacy

The primary efficacy outcome in both trials was ACR20 response at week 24 (defined as an improvement of at least 20% in both SJC and TJC and at least three of five additional disease criteria). In the FUTURE 2 trial, both SEC treatment groups were statistically significantly superior to the placebo group for ACR20 response at week 24. The clinical expert involved in the review noted that the difference in ACR20 response compared with placebo at 16 and 24 weeks was clinically meaningful. Other clinical response outcomes (ACR50, ACR70, MDA, DAS 28-CRP, PASI 75, PASI 90, improvement in dactylitis and enthesitis, and mNAPSI) at weeks 16 and 24 also demonstrated a statistically significant and clinically meaningful difference favouring both SEC treatment groups compared with the placebo group. However, all clinical response outcomes at week 16, and outcomes ACR70, MDA, and mNAPSI at week 24, were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error. [redacted]. The clinical expert involved in the review noted that the proportion of patients with complete resolution of dactylitis and enthesitis versus placebo was clinically meaningful. Claims of statistical significance could not be made for ACR50 at week 24 in the SEC 150 mg treatment group because the outcome assessed in the hierarchy (HAQ-DI) did not achieve statistical significance; hence, the hierarchical testing was stopped before testing ACR50 in the SEC 150 mg treatment group. Results of the subgroup analyses, when undertaken for prior TNF alpha inhibitor–IR patients in the SEC 300 mg treatment group and TNF alpha inhibitor–naive patients in the SEC 150 mg treatment group, were generally in line with results from the overall population for these outcomes, especially at week 24. However, these analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error. The effectiveness of the two dosing regimens of SEC for the treatment of PsA patients appeared to be maintained up to

week 52, as reported in the extension study (Appendix 6). However, the lack of a comparator limits the conclusions that may be drawn from the dose-blind and extension phases. Overall, similar results were observedin the SEC 150 mg treatment groups in both the FUTURE 1 and FUTURE 2 trials.

Common themes seen as important in the patient group input were improvements in quality of life and work productivity (APPENDIX 1: PATIENT INPUT SUMMARY). In the FUTURE 1 and FUTURE 2 trials, SF-36 was used to assess HRQoL. In the FUTURE 2 trial, statistically significantly greater improvements were observed in the SF-36 PCS scores in both SEC treatment groups compared with those in the placebo group at week 24: the difference in change from baseline between the SEC 300 mg treatment group and the placebo group was 5.30, and the difference between the SEC 150 mg treatment group and the placebo group was 4.44, both of which exceeded the MCID 3.74 for the SF-36 PCS. In addition, the difference in the SF-36 PCS score between the SEC 300 mg treatment group and placebo in the subgroup of patients who were TNF alpha inhibitor–IR was [redacted] at weeks 16 and 24, respectively, and the difference in the SF-36 PCS score between the SEC 150 mg treatment group and the placebo group in the subgroup of patients who were TNF alpha inhibitor–naive was [redacted] at weeks 16 and 24, respectively; [redacted]. Also, statistically significantly more patients achieved improvements in HRQoL (change in SF-36 score of 2.5 points or more) in both SEC treatment groups compared with placebo. There were no statistically significant differences between both SEC treatment groups and the placebo group at weeks 24 in the SF-36 MCS scores. The difference in change from baseline between the SEC 300 mg treatment group and placebo was 0.26, and the difference between the SEC 150 mg treatment group and placebo was 2.39, which exceeded the MCID of 1.77 for the SF-36 MCS score. The difference in the SF-36 MCS score between the SEC 300 mg treatment group and placebo in the subgroup of patients who were TNF alpha inhibitor–IR was [redacted] at weeks 16 and 24, respectively. This difference was not statistically significant and [redacted]. The difference in the SF-36 MCS score between the SEC 150 mg treatment group and the placebo group in the subgroup of patients who were TNF alpha inhibitor–naive was [redacted] at weeks 16 and 24, respectively. These differences [redacted]. Overall, similar results were seen in the SEC 150 mg treatment groups in the FUTURE 1 trial and the FUTURE 2 trial for the SF-36. The PsAQoL, a quality-of-life instrument specific to psoriatic arthritis, indicated that both SEC 150 mg and SEC 300 mg groups in the FUTURE 2 trial had statistically significant greater improvement relative to the placebo group for mean score change at weeks 16 and 24. As well, in FUTURE 1, at weeks 16 and 24, the mean change in scores decreased (improved) from baseline for SEC 150 mg and placebo groups. There is no MCID specified for PsAQoL; hence, it is difficult to determine whether the difference in results between SEC regimens and placebo were clinically meaningful. The DLQI is a widely used dermatology-specific quality-of-life instrument. Results indicated that both SEC 150 mg and SEC 300 mg groups in the FUTURE 2 trial had a statistically significant greater improvement relative to placebo for mean DLQI score change at weeks 16 and 24, similar to results in the FUTURE 1 trial at weeks 16 and 24. In both trials, the difference in change from baseline between-treatment groups and the placebo group exceeded the established MCID (3.2) for DLQI in patients with psoriasis at weeks 16 and 24. The outcome measures MCS of the SF-36, PsAQoL, and DLQI were not part of the hierarchical analysis plan and therefore were not adjusted for multiple comparisons; hence, the level of significance is inflated and results should be interpreted with caution.

Arthritis pain in patients was evaluated using patient's assessment of pain according to a VAS of 100 mm. In the FUTURE 2 trial, both SEC 150 mg and SEC 300 mg groups had statistically significant greater improvement relative to the placebo group for mean score change at weeks 16 and 24. Similarly, in the FUTURE 1 trial, the SEC 150 mg treatment group had statistically significant greater improvement

relative to placebo for mean score change at weeks 16 and 24. In both trials, the difference in change from baseline between-treatment groups and placebo exceeded the established MCID of patient's assessment of pain, defined as an improvement (reduction) in pain of 10 mm at weeks 16 and 24. Fatigue in patients was assessed using FACIT–Fatigue. In both trials, the SEC treatment groups had statistically significantly greater improvement relative to placebo for mean score change at weeks 16 and 24; however, the difference in change from baseline between-treatment groups and the placebo group exceeded the established MCID (3.56) for FACIT–Fatigue in patients with rheumatoid arthritis at weeks 16 and 24 in the FUTURE 2 trial only. The outcome measures patient's assessment of pain; FACIT–Fatigue were not part of the hierarchical analysis plan and therefore were not adjusted for multiple comparisons. Hence, the level of significance is inflated and results should be interpreted with caution.

In addition to improvement in HRQoL in the FUTURE 2 trial, statistically significantly more patients achieved improvements in physical function (improvement in HAQ-DI score of 0.30 or more) in both SEC treatment groups compared with placebo at weeks 16 and 24. Also, a statistically significantly greater reduction from baseline in HAQ-DI score was achieved in patients in the SEC 300 mg treatment group compared with placebo at week 24; however, the SEC 150 mg treatment group did not achieve a statistically significantly greater reduction from baseline in HAQ-DI score at week 24 (P = 0.0278), which was [redacted]The difference in change from baseline between the SEC 150 mg and placebo groups and between SEC 300 mg and placebo treatment groups at week 16 was [redacted]respectively, and it was [redacted]at week 24; hence, the difference between the mean score change from baseline exceeded the MCID for the HAQ-DI (estimated to range from 0.3 to 0.35) in the comparison between SEC 300 mg and placebo groups at week 16. The difference in change from baseline between SEC 150 mg and placebo groups in the subgroup of patients who were TNF alpha inhibitor–naive and in the subgroup of patients who were TNF alpha inhibitor–IR at weeks 16 and 24 did not exceed the MCID for the HAQ-DI. The difference in change from baseline between SEC 300 mg and placebo groups in the subgroup of patients who were TNF alpha inhibitor–IR at weeks 16 and 24 only exceeded the MCID for the HAQ-DI in the comparison at week 16. Similar results were observed in FUTURE 1 trial in the SEC 150 mg treatment group when compared with placebo. The outcome measures improvement in HAQ-DI score of 0.30 or more and change from baseline in HAQ-DI score at week 16 were not part of the hierarchical analysis plan and therefore were not adjusted for multiple comparisons; hence, the level of significance is inflated and results should be interpreted with caution.

Work productivity in patients with PsA was identified as an important outcome in the research protocol, as well as in the patient input. Statistical inference for work productivity measures was not conducted; therefore, it is unclear whether the between-group differences were statistically significant.

Radiographic change was assessed only in the FUTURE 1 trial, using vdH-mTSS. The mean change from baseline in vdH-mTSS was statistically significantly lower in the SEC 150 mg treatment group (0.13 points) than in the placebo group (0.57); the between-treatment difference estimate was –0.47 for SEC 150 mg versus placebo (P = 0.0212). In addition, the mean change from baseline in vdH-mTSS was statistically significantly lower in the SEC 150 mg treatment group than in the placebo group in the subgroup analyses according to previous anti-TNF use. Inhibition of progression of structural damage was observed through week 52.[49] However, the results have uncertain clinical significance given that the difference between the SEC 150 mg treatment group and placebo was 0.47 on a scale that ranges from 0 to 528 and assessed following 24 weeks of treatment.

The improvements observed at week 24 were maintained or continued to improve through week 52 in the FUTURE 2 trial and through week 104 in the FUTURE 1 trial among patients in the SEC 150 mg (in the FUTURE 1 and FUTURE 2 trials) and SEC 300 mg (in the FUTURE 2 trial) treatment groups. Improvements in outcomes over 24 weeks were generally observed in ACR, PASI, DAS 28-CRP, MCS and PCS of the SF-36, HAQ-DI, PsAQoL, and FACIT–Fatigue across both studies. However, the longer-term phases of the trials, after 24 weeks, had limited clinical value for the following reasons:

- There were no control groups.
- There was no blinding because all patients received SEC at this time point in the trials. Open label assessment of patient-reported outcomes and subjective outcomes could be potentially biased.
- There was a lack of stopping criteria whereby early escapers at week 16, who were initially randomized to SEC, were allowed to remain on SEC during the long-term phases.
- It is likely that in clinical practice such non-responders would no longer continue to receive SEC.

In the absence of adequate data from head-to-head trials comparing SEC with other PsA treatments, the manufacturer conducted an indirect treatment comparison (IDC) based on a systematic review of RCTs to compare the efficacy of secukinumab with etanercept, infliximab, adalimumab, golimumab, ustekinumab, certolizumab, and apremilast. HRQoL data were not evaluated using the IDC methods; therefore, the comparative HRQoL data have yet to be fully evaluated. Despite the fact that the patient populations were somewhat heterogeneous and that there were certain potential methodological limitations, overall, SEC demonstrated treatment effect over placebo. No statistically significant difference was found for efficacy when compared with other treatments in terms of ACR in populations that were biologics-naive and inadequate responders to previous biologics. In addition, for PASI outcomes, SEC 150 mg and SEC 300 mg were statistically significantly better than all other therapies with the exception of infliximab, adalimumab, golimumab 100 mg, and ustekinumab 45/90 mg. It is uncertain whether this treatment effect is sustainable in the longer term.

4.2.2 Harms

By week 16, the frequency of SAEs was low and similar in the SEC and placebo treatment groups. Withdrawals due to AEs were also low in all treatment groups. Treatment-emergent AEs were relatively similar between-treatment groups, with the most common infectious AEs being nasopharyngitis in FUTURE1 and upper respiratory tract infection in FUTURE 2. The frequency of serious infections and injection site reactions was low. No deaths were reported in any of treatment groups included in this review.

The safety profile of SEC in PsA over 52 weeks in FUTURE 2 and 104 weeks in FUTURE 1 was consistent with that observed by week 16, with no new safety signals reported.

Harms were not analyzed in the IDC, and the comparative safety between SEC and other treatments for PsA is unknown.

4.3 Potential Place in Therapy

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

Currently, there are five biologic drugs approved for the treatment of PsA after an inadequate response to traditional DMARDs. All are TNF inhibitors, all are equally effective, and all share the same profile of

AEs.[4,22,50] SEC is an IL-17 inhibitor and the first biologic utilizing a different mechanism of action to improve arthritis, dactylitis, enthesitis, spondylitis, and skin disease.

IL-17 is considered to play a more central role than TNF in the pathogenesis of psoriatic disease. However, at the evaluated Health Canada–approved doses of SEC 150 mg and 300 mg, the ACR20/50/70 responses and other clinical responses appear similar to those reported for TNF inhibitors, according to the clinical expert involved in the review. The clinical expert also noted that the lack of a statistically significant response to SEC 150 mg compared with placebo among patients in subgroups of TNF alpha inhibitor–IR patients is disappointing (based on subgroup findings from FUTURE 2). However, ACR response to the SEC 300 mg dose in this subgroup appeared to be superior to placebo, and the clinical expert suggested this dosing regimen may be an effective approach, with an alternative mechanism of action, in this difficult-to-treat population.

Radiographic changes, efficacy in treating skin disease, and the safety profile would also influence the place in therapy for SEC. There are, however, no apparent radiographic or safety advantages of SEC compared with TNF inhibitors, according to the clinical expert consulted by CDR. The expert also noted that the PASI 75 skin response appears similar to the responses of most TNF inhibitors, but the PASI 90 response appears to be superior.

In summary, the clinical expert indicated that the place in therapy for SEC 150 mg is first-line therapy for PsA after failure of traditional DMARDS, making it the sixth (or seventh) drug (depending on the use of apremilast) in this type of patient population. However, based on the arthritis clinical responses, it would not fill a need currently unmet by TNF inhibitors. SEC would be an option at the 300 mg dose for patients with an inadequate response to TNF inhibitor treatment because SEC provides the first formal evaluation of responses in patients who are TNF inhibitor–IR.

5. CONCLUSIONS

Based on two double-blind, randomized controlled trials (FUTURE 1 and FUTURE 2) in patients with moderate to severe PsA, treatment with SEC 150 mg (in FUTURE 1 and FUTURE 2 trials) and SEC 300 mg (FUTURE 2 trial) resulted in statistically significant and clinically meaningful improvements in clinical response (ACR20, ACR50, ACR70, MDA, DAS 28-CRP, and PASI) at weeks 16 and 24 when compared with placebo. A statistically significant and clinically significant improvement was also seen in quality of life, physical function, pain, and fatigue at 16 and 24 weeks. However, except for ACR20, ACR50, DAS 28-CRP, PCS of the SF-36, and HAQ-DI, adjustment for multiplicity was not done for all other outcomes; hence, results for these outcomes should be interpreted with caution. In both studies, a very large proportion of placebo patients discontinued randomized treatment before week 24 (either owing to early escape or because of treatment discontinuation), so claims of efficacy at week 24 are uncertain.

Overall, the incidence of treatment-emergent AEs was similar to that in the placebo groups for both SEC groups, although the study was not designed to identify between-group differences in safety. Moreover, PsA is a chronic condition that will be treated over a lifetime, and therefore a 24-week controlled trial is a short duration to evaluate harms.

A manufacturer-submitted IDC suggested no statistically significant difference for efficacy when SEC was compared with other treatments in terms of ACR; as well, the results of PASI, SEC 150 mg and SEC 300 mg were statistically significantly better than all other therapies with the exception of infliximab, adalimumab, golimumab 100 mg, and ustekinumab 45/90 mg. Harms, health-related quality of life, and patient-reported outcomes were not analyzed in the IDC, and the comparative safety between SEC and other treatments for PsA is unknown.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups.

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

Four submissions from five patient groups — the Canadian Spondylitis Association (CSA), Arthritis Consumer Experts (ACE), the Canadian Arthritis Patient Alliance (CAPA), and a joint submission by the Canadian Skin Patient Alliance (CSPA) and The Arthritis Society — provided input for this review.

The CSA is a volunteer-run patient association to support, educate, and advocate for those living with spondyloarthritis (SpA). The association's membership comprises individuals from all provinces and territories who live with axial or peripheral SpA, which includes ankylosing spondylitis and psoriatic arthritis. The aims of CSA are to create awareness of SpA, with the objective of reducing the time from onset of disease until diagnosis; to provide information and education to those living with SpA including caregivers and family; to enable those living with SpA to better manage their disease; and to advocate for equal access to treatment options. CSA has received restricted educational and developmental grants from AbbVie, Amgen, and Janssen, and restricted travel grants from UCB Canada. The president, Michael Mallinson, has received honorariums from AbbVie (indirectly) and Novartis. CSA declared no conflicts of interest in the preparation of this submission.

The ACE is a national organization working to educate and empower individuals with arthritis to take control of their disease and improve their quality of life; to make evidence-based information more accessible to and interpretable by the general public, government, and media; and to train individuals with arthritis to be able to contribute meaningfully to research initiatives and governmental decision-making. ACE provides programs in both official languages. ACE receives unrestricted grants-in-aid from public- and private-sector organizations, as well as unsolicited funding from individual donors, including AbbVie, Amgen Canada, Arthritis Research Canada, BIOTECanada, the Canadian Institutes of Health Research, Celgene, Hoffman-La Roche Canada, Janssen, Pfizer Canada, Sanofi Canada, UCB Canada Inc., and the University of British Columbia. ACE declared no conflicts of interest in the preparation of this submission.

The CAPA is a patient-driven, independent, national organization with members across Canada. CAPA creates links among Canadians with arthritis. CAPA believes the first expert on arthritis is the person who lives with arthritis. CAPA has received grants and support in the last year from AbbVie, Amgen Canada, Hoffman-La Roche, Janssen, Novartis, and UCB Pharma. Additionally, CAPA has received support in the past from the Arthritis Alliance of Canada, The Arthritis Society, the Canadian Institutes for Health Research (Institute for Musculoskeletal Health and Arthritis), the Canadian Rheumatology Association, the Ontario Rheumatology Association, Pfizer Canada, Rx&D, Schering Canada, the Scleroderma Society, and STA Communications. However, CAPA declared no conflict of interest in the preparation of the submission.

The CSPA is a non-profit organization that serves patients with dermatological conditions, diseases, and traumas in Canada. CSPA focuses on education and advocacy for these patients as well as its more than 20 affiliate members, including the Canadian Association of Psoriasis Patients and the Canadian Psoriasis Network. The CSPA has a steady social media community as well as thousands of readers. The Arthritis Society is dedicated to a vision of living well while creating a future without arthritis. The Society is one

of Canada's principal health charities, providing education, programs, and support to the more than 4.6 million Canadians living with arthritis. Since it was founded in 1948, The Society has been the largest non-government funder of arthritis research in Canada, investing more than $190 million in projects that have led to breakthroughs in the diagnosis, treatment, and care of people with arthritis. The Arthritis Society is accredited under Imagine Canada's Standards Program. The website www.arthritis.ca provides more detailed information. The CSPA has received project-based and/or unrestricted funding from the following drug manufacturers over the past 12 months: AbbVie, Celgene, Galderma, GlaxoSmithKline, Janssen, Merck, and Novartis. Over the past 12 months The Arthritis Society has accepted funding from the following members of the pharmaceutical industry: AbbVie, Amgen, Bayer, Bristol-Myers Squibb, Celgene, Eli Lilly, Hospira, Janssen, Merck, Novartis, Pfizer, Purdue, Roche, and UCB. The CSPA and The Arthritis Society declared no conflicts of interest in the preparation of this submission.

2. Condition-Related Information

The CSA collected information from its members and its Board of Directors through patient forums, newsletters, and its Facebook page. ACE gathered information through a request for patient input from JointHealth™ members and subscribers sent via email and the JointHealth™ website, Facebook, and Twitter posts, as well as previous patient input responses. ACE also provided additional organizational comments to augment the information from individuals. The CAPA conducted a brief phone interview with a person who has lived with PsA for close to 30 years, who participated in a clinical trial for secukinumab, and who has remained on secukinumab for just over one year. Other information was obtained through personal experiences of the CAPA Board and its membership. CSPA collected data from a survey promoted via CSPA's social media channels to PsA patients or those with PsA-related symptoms (16 surveys received). The CSPA also reached out via email to the clinical dermatologists involved in the clinical trials to facilitate two patient connections. The Arthritis Society had contact with two patients through rheumatologists involved in the clinical trials. In addition, the CSPA and The Arthritis Society used social media (Twitter and Facebook) and online discussion boards (26 posts) to gather patient perspectives.

Psoriatic arthritis (PsA) is an autoimmune disease characterized by inflammation in the joints that destroys the lining of the joint and ultimately the surrounding bone, and which causes a scaly-type rash on the body, usually on the elbows, knees, and scalp. The disease affects patients' day-to-day life tremendously, causing them to constantly consider their ability to cope, think of ways of doing what they need to do, and assess how much help they need. Therefore, PsA patients pace and prioritize routine activities taken for granted by non-patients.

PsA patients experience joint pain, stiffness, fatigue, and loss of function. Some patients have difficulty sitting, using the stairs, bending to pick up objects, and getting in and out of the bathtub. Daily living activities such as vacuuming, cleaning, doing the dishes, and grocery shopping becomes challenging for some patients, causing them to require help from caregivers. Patients also experience skin sensitivity, redness, flaking, and pain from the plaque psoriasis. One patient group reported that PsA is "linked to the skin disease, psoriasis. In fact, psoriasis is considered to be a significant risk factor for developing psoriatic arthritis — up to 30% of people diagnosed with psoriasis go on to develop psoriatic arthritis." The group reported that a patient developed ischial bursitis, in which her tendons and ligaments are also affected. It provided the following quote from another patient: "I'm a patient suffering from rheumatoid arthritis and I take methotrexate injections, which caused plaque psoriasis to appear on my body, my scalp, and my ears." Of the 16 surveys received by the CSPA, 62% reported joint pain; when asked which parts of their body are most affected by PsA, 62% said fingers and hands, 38% said legs, and 30% said all

over. In addition, one patient indicated that on bad pain days she cannot be touched without crying out in pain, and that, when the pain gets bad, it usually triggers a seizure. A patient who has lived with PsA for over 30 years described it as follows: He could not socialize with people because he would "shed his skin. Now he can wear anything that he wants [after starting secukinumab]." He also indicated that he experienced psoriasis rashes from head to toe, with swollen and stiff fingers and hands, and that at any time his skin would rip and bleed, no matter how careful he was. Additionally, he would often lose fingernails due to infection, and furthermore, these infected nails would emit a horrible odour. At times, he could not work because of his PsA.

The impact of the disease goes beyond physical well-being, with some patients likely to stop social and creative activities because of limited time and energy, and increased pain. Furthermore, the acute awareness of skin lesions has a psychological impact. A patient group reported that, as a result of the symptoms of PsA, anxiety and depression is prominent among people in this disease group. According to a patient group, PsA patients whose conditions are not well-controlled find it difficult to participate in post-secondary education and to become and stay employed. Of the 16 surveys received by the CSPA, 50% of respondents reported their self-confidence dropped and 50% reported a decline in intimacy. One patient indicated that almost every aspect of her life has been greatly affected by PsA. Another patient indicated that "PsA is a horrible disease which can leave you disabled and mutates your body, had to stop many activities due to this disease." Another patient indicated that depression, anxiety, alcoholism, and weight gain all have made her life miserable, and that she has suffered from the pain and mental issues.

Caregivers of patients with PsA have indicated that time is always a concern for them. They need to arrange and plan their schedule to accommodate for sudden and emergency requests from the person living with PsA. They have to help with household chores when the patient is in extreme pain, as well as fulfill the patient's financial and household responsibilities. Of the 16 surveys received by CSPA, 58% of respondents reported that caring for loved ones was challenging, 26% of patients indicated that their caregiver's health is at risk because of all that they do to care for the patient and his or her disease, and 57% of patients indicated that their children have been greatly affected. Depression and isolation also mean that family members and caregivers live in a dysfunctional setting, one in which caregivers are often solely responsible to provide the help needed by the patient.

3. Current Therapy-Related Information

Current therapy includes biologic response modifiers, disease-modifying antirheumatic drugs (DMARDs), and nonsteroidal anti-inflammatory drugs (NSAIDs). There is a high degree of variability of disease, and there are currently no methods by which physicians can predict which patients will respond best to which therapies. Therefore, while some patients respond well to a drug for long periods, others will need to try many different drugs before they find the best treatment for their PsA. Even while responding well to their medication(s), PsA patients are aware of the potential for the drug to become ineffective over time. Therefore, patients believe that the more options there are, the better, as more options could mean better access to medication and a backup plan in case the current therapy treatment stops working. Of the 16 surveys received by CSPA, patients reported that they either have used or are still using the following treatment options: 76% NSAIDs, 58% methotrexate, 58% etanercept, 51% phototherapy, 20% ustekinumab, 20% apremilast, 20% sulfasalazine, 20% cyclosporine, and 17% secukinumab. When asked how effectively the current therapy controls the common aspects of this condition, 40% said it worked very well in dealing with overall pain, 50% said it worked somewhat in dealing with swelling, 50% said it worked very well in dealing with stiffness or pain in joints, 50% said

that the treatment was not convenient at all, 40% said they had issues with accessing the medication because of cost, and 56% said it worked very well in reducing psoriasis skin plaques and spots.

Psoriatic arthritis patients have concerns about adverse effects (which may include heartburn, dizziness, and increased blood sugar levels) over a prolonged period of drug use, cost, scheduling issues for infusions, and the need to take time off work or find someone to deal with family commitments. A commonly mentioned AE was gastrointestinal side effects associated with DMARDS and NSAIDS. One patient group mentioned that DMARDs and biologic response modifiers suppress the patients' immune systems, predisposing them to serious infections. Other AEs included vein scarring and scar tissues from numerous infusions and injections.

Infusion or injection treatments are disruptive and time-consuming. The cost of a biologic drug therapy is expensive. For those patients without a health insurance plan, a plan that only partially covers drug costs, or access only to their provincial health insurance, the cost can be demanding.

Caregiver experiences included having to give the patients their injections and taking on more family responsibilities while the patient is receiving his or her infusion or when the patient's conditions are very severe, keeping them from participating in daily activities. Caregiver burdens include inadequate time, as they need to arrange and plan their schedule to accommodate sudden and emergency requests from the person living with PsA. For some, caring for the patient deprives them of the time to engage in gainful employment, participate in recreational activities, and socialize with friends.

4. Expectations About the Drug Being Reviewed

Sources of information for this section are identical to that previously described in Section 2. CAPA conducted a brief phone interview with a person who has lived with PsA for close to 30 years, who participated in a clinical trial for secukinumab, and who has remained on secukinumab for slightly more than one year. Some of the patients who responded to the survey done by the CSPA had experience with secukinumab. The Arthritis Society had email contact with two patients in the clinical trial. The other two patient groups (ACE and the CSA) did not receive any input from anyone who has experience with the drug.

One patient who had used secukinumab for four months had his lesions completely cleared up, but he had a lot of problems with sinus and upper respiratory tract infections. One patient indicated that secukinumab has been amazing for him so far (he has been on secukinumab since October 2015). The results are incredible, his joints feel great, and he feels normal again. Another patient who had been on secukinumab for about two months indicated that he went from about 95% to about 10% (barely noticeable) body surface coverage. Also, the PsA in his ankle is gone. However, he indicated that he also gained about 20 pounds of fat, mostly in his stomach area, likely because of the drug. Another patient indicated that secukinumab was the first biologic that helped him at all, and did so without side effects. The patient also indicated that, at six months, it is already losing effectiveness. Another patient receiving secukinumab for PsA indicated that he is getting the dreaded fatigue/low mood affect, which feels like a head cold/fogginess. Another patient indicated that secukinumab was moderately effective for the psoriasis after a while, but when he started receiving secukinumab injections, it was amazing. Some patients noted redness at the injection site and feeling very sleepy following their treatment with secukinumab. Others reported weight gain, respiratory infections, and dark spots. Patients believe this treatment would have a positive impact on their lives. Another patient indicated that within two weeks of his starting secukinumab, his body rash was 90% cleared. While some rash remains on his scalp, since he was diagnosed with PsA, he has never been so rash-free or symptom-free. Additionally, he is now

able to do things he has not been able to do in a long time, from activities as simple as socializing without worrying about his skin flaking, to other more complex activities. Since secukinumab has decreased the swelling in his joints profoundly, he has been able to lower the amount of the nonsteroidal anti-inflammatory drug that he usually takes as well. He no longer experiences the stiffness and soreness that he previously did, and he has not experienced any side effects. Overall, this person's quality of life has been dramatically improved by secukinumab.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 18, 2016
Alerts:	Bi-weekly search updates until July 20 2016
Study Types:	No search filters were applied.
Limits:	No date or language limits were used. Conference abstracts were excluded.

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.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		
Line #	**Search Strategy**	**Results**
1	(cosentyx* or secukinumab* or zafrez* or ain 457 or ain457 or DLG4EML025 or BLA 125-504 or 1229022-83-6 or 875356-43-7 or 875356-44-8 or "1229022836" or "875356437" or "875356448").ti,ab,kf,ot,hw,rn,nm. use pmez	156
2	Arthritis, Psoriatic/ or exp spondylarthropathies/ use pmez	24143
3	(psoria* adj2 (arthrit* or arthro* or polyarthrit* or rheumat*)).ti,ab,kf. use pmez	7106
4	(alibert bazin* or Spondyloarthropath* or Spondylarthropath*).ti,ab,kf. use pmez	3082
5	2 or 3 or 4	28684
6	1 and 5	50
7	*secukinumab/ use oemezd	249
8	(cosentyx* or secukinumab* or zafrez* or ain 457 or ain457 or DLG4EML025 or BLA 125-504 or 1229022-83-6 or 875356-43-7 or 875356-44-8 or "1229022836" or "875356437" or "875356448").ti,ab,kw. use oemezd	374
9	7 or 8	385
10	psoriatic arthritis/ or spondyloarthropathy/ or arthritis, psoriatic/ use oemezd	22607
11	(psoria* adj2 (arthrit* or arthro* or polyarthrit* or rheumat*)).ti,ab,kw. use oemezd	12652
12	(alibert bazin* or Spondyloarthropath* or Spondylarthropath*).ti,ab,kw. use oemezd	4613
13	10 or 11 or 12	26600
14	9 and 13	126
15	conference abstract.pt.	2180083
16	14 not 15	63
17	16 or 6	113
18	remove duplicates from 17	76

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

Grey Literature

Dates for Search:	March 2016
Keywords:	Cosentyx (secukinumab), Psoriatic Arthritis
Limits:	No date or language limits used

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

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
McInnes[51]	Abstract only

APPENDIX 4: DETAILED OUTCOMES DATA

TABLE 10: PROPORTION OF PATIENTS WITH ACR50 RESPONSE AT WEEK 16 AND WEEK 24 (USING NON-RESPONDER IMPUTATION)

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
ACR50 at week 16					
Full analysis set[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Concomitant MTX use[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
No concomitant MTX treatment[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
ACR50 at week 24					
Full analysis set[a]					
n/N (%)	70/202 (34.7)	15/202 (7.4)	35/100 (35)	35/100 (35)	7/98 (7)
Odds ratio (95% CI)	[redacted]		7.15 (2.97 to 17.22)	7.54 (3.11 to 18.25)	
P value	< 0.0001		< 0.0001		
TNF alpha inhibitor–inadequate responder[b]					
n/N (%)	13/59 (22.0)	3/59 (5.1)	9/33 (27)	7/37 (19)	3/35 (9)
Odds ratio (95% CI)	[redacted]		4.37 (1.05 to 18.26)	2.39 (0.56 to 10.15)	
P value	0.0114		0.0431	0.2374	

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
TNF alpha inhibitor–naive patients[b]					
n/N (%)	57/143 (39.9)	12/143 (8.4)	26/67 (39)	28/63 (44)	4/63 (6)
Odds ratio (95% CI)	[redacted]		9.72 (3.14 to 30.09)	12.54 (4.03 to 39.05)	
P value	< 0.0001		< 0.0001	< 0.0001	
Concomitant MTX use[b]					
n/N (%)	[redacted]	[redacted]	17/44 (38·6)	14/44 (31·8)	4/50 (8·0)
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		0·0010	0.0058	
No concomitant MTX treatment[b]					
n/N (%)	[redacted]	[redacted]	18/56 (32·1)	21/56 (37·5)	3/48 (6·3)
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		0·0034	0·0007	

ACR = American College of Rheumatology; CI = confidence interval; MTX = methotrexate; PL = placebo; SEC = secukinumab; TNF = tumour necrosis factor.
Note: n is the number of patients who are responders with corresponding imputation approach in the treatment group. Missing responses were considered non-responders. Rescued patients were also considered non-responders after the time of rescue. Discontinued patients were considered non-responders after the time of discontinuation.
[a] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors and baseline weight as a covariate.
[b] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment as the factor and baseline weight as a covariate.
Source: Clinical study reports.[6,7]

TABLE 11: PROPORTION OF PATIENTS WITH ACR70 RESPONSE AT WEEK 16 AND WEEK 24 (USING NON-RESPONDER IMPUTATION)

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
ACR70 at week 16					
Full analysis set[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Concomitant MTX use[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
No concomitant MTX treatment[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
ACR70 at week 24					
Full analysis set[a]					
n/N (%)	38/202 (18.8)	4/202 (2.0)	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	< 0.0001		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n/N (%)	32/143 (22.4)	4/143 (2.8)	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	< 0.0001		[redacted]	[redacted]	
Concomitant MTX use[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
No concomitant MTX treatment[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	

ACR = American College of Rheumatology; CI = confidence interval; MTX = methotrexate; PL = placebo; SEC = secukinumab; TNF = tumour necrosis factor.

Note: n is the number of patients who are responders with corresponding imputation approach in the treatment group. Missing responses are considered non-responders. Rescued patients are also considered non-responders after the time of rescue. Discontinued patients are considered non-responders after the time of discontinuation

[a] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors and baseline weight as a covariate.

[b] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment as the factor and baseline weight as a covariate.

[c] *P* values are from a Fisher's exact test.

Source: Clinical study reports.[6,7]

TABLE 12: PROPORTION OF PATIENTS WITH PASI 75 RESPONSE AT WEEK 16 AND WEEK 24 IN PSORIASIS SUBSET (USING NON-RESPONDER IMPUTATION)

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
PASI 75 at week 16					
Full analysis set[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		NR	NR	
P value	[redacted]		NR	NR	
TNF alpha inhibitor–naive patients[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
PASI 75 at week 24					
Full analysis set[a]					
n/N (%)	66/108 (61.1)	9/109 (8.3)	26/41 (63)	28/58 (48)	7/43 (16)
Odds ratio (95% CI)	[redacted]		9.48 (3.33 to 27.00)	5.70 (2.12 to 15.34)	
P value	< 0.0001		< 0.0001	0.0006	
TNF alpha inhibitor–inadequate responder[b]					
n/N (%)	[redacted]	[redacted]	7/11 (64)	8/22 (36)	1/12 (8)
Odds ratio (95% CI)	[redacted]		19.29 (1.77 to 210.18)	6.17 (0.66 to 57.30)	
P value	[redacted]		0.0152	0.1094	
TNF alpha inhibitor–naive patients[b]					
n/N (%)	[redacted]	[redacted]	19/30 (63)	20/36 (56)	6/31 (19)
Odds ratio (95% CI)	[redacted]		7.96 (2.42 to 26.16)	6.33 (1.99 to 20.15)	
P value	[redacted]		0.0006	0.0018	

CI = confidence interval; PASI = Psoriasis Area and Severity Index; PL = placebo; NR = not reported; SEC = secukinumab; TNF = tumour necrosis factor.

Note: Missing responses are considered non-responders. Rescued patients are also considered non-responders after the time of rescue. Discontinued patients are considered non-responders after the time of discontinuation

[a] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors and baseline weight as a covariate.

[b] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment as the factor and baseline weight as a covariate.

Source: Clinical study reports.[6,7]

TABLE 13: PROPORTION OF PATIENTS WITH PASI 90 RESPONSE AT WEEK 16 AND WEEK 24 IN PSORIASIS SUBSET (USING NON-RESPONDER IMPUTATION)

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
PASI 90 at week 16					
Full analysis set[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		NR	NR	
P value	[redacted]		NR	NR	
TNF alpha inhibitor–naive patients[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
PASI 90 at week 24					
Full analysis set[a]					
n/N (%)	49/108 (45.4)	4/109 (3.7)	20/41 (49)	19/58 (33)	4/43 (9)
Odds ratio (95% CI)	[redacted]		10.74 (3.13 to 36.84)	6.36 (1.89 to 21.47)	
P value	< 0.0001		0.0002	0.0029	
TNF alpha inhibitor–inadequate responder[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	

CI = confidence interval; PASI = Psoriasis Area and Severity Index; PL = placebo; NR = not reported; SEC = secukinumab; TNF = tumour necrosis factor.

Note: Missing responses are considered non-responders. Rescued patients are also considered non-responders after the time of rescue. Discontinued patients are considered non-responders after the time of discontinuation.

[a] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors and baseline weight as a covariate.

[b] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment as the factor and baseline weight as a covariate.

Source: Clinical study reports.[6,7]

TABLE 14: CHANGE FROM BASELINE IN DISEASE ACTIVITY SCORE 28–C-REACTIVE PROTEIN AT WEEK 16 AND WEEK 24

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
At week 16					
Full analysis set[a]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder[b]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
At week 24					
Full analysis set[a]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	–1.62 (0.084)	–0.77 (0.123)	–1.61 (0.11)	–1.58 (0.11)	–0.96 (0.15)
LS mean difference vs. PL (95% CI)	–0.85 (–1.14 to –0.56)		–0.65 (–1.02 to –0.29)	–0.62 (–0.98 to –0.26)	
P value	< 0.0001		0.0004	0.0008	
TNF alpha inhibitor–inadequate responder[b]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	

CI = confidence interval; LS = least squares; PL = placebo; SD = standard deviation; SE = standard error; SEC = secukinumab; TNF = tumour necrosis factor; vs. = versus.
Note: n = number of patients with measurements at both baseline and the post-baseline visits. Data collected after the patients were rescued was treated as missing for placebo patients who switched to secukinumab, and the actual values were used for secukinumab patients.
[a] LS mean, 95% CI, and *P* value are from a mixed-effect model repeated measures (MMRM) with treatment regimen, analysis visit, and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure.
[b] LS mean, 95% CI, and *P* value are from an MMRM with treatment regimen, analysis visit as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure.
Source: Clinical study reports.[6,7]

TABLE 15: PROPORTION OF PATIENTS WITH DISEASE ACTIVITY SCORE 28–C-REACTIVE PROTEIN EULAR RESPONSE OF "GOOD" AT WEEK 16 AND WEEK 24

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
At week 16					
Full analysis set					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
At week 24					
Full analysis set					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	

CI = confidence interval; EULAR = European League Against Rheumatism; PL = placebo; SEC = secukinumab.
Note: *P* value is obtained from proportional odds regression model with treatment group and randomization strata as factors, weight and baseline Disease Activity Score 28 score as covariates.
Source: Clinical study reports.[6,7]

TABLE 16: CHANGE FROM BASELINE IN SHORT FORM (36) HEALTH SURVEY PHYSICAL COMPONENT SUMMARY AND MENTAL COMPONENT SUMMARY SCORES AND RESPONSE AT WEEK 16 AND WEEK 24

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
At week 16					
Change from baseline in SF-36 MCS					
Full analysis set[a]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
MCS responders (improvement of ≥ 2.5 points) using non-responder imputation					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Change from baseline in SF-36 PCS					
Full analysis set[a]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference	[redacted]		[redacted]	[redacted]	

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
PCS responders (improvement of ≥ 2.5 points) using non-responder imputation					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
At week 24					
Change from baseline in SF-36 MCS					
Full analysis set[a]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	5.66 (0.639)	2.39 (0.911)	3.94 (0.916)	6.07 (0.917)	3.69 (1.269)
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder[b]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
MCS responders (improvement of ≥ 2.5 points) using non-responder imputation[c]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Change from baseline in SF-36 PCS					
Full analysis set[a]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change	5.91 (0.525)	1.82 (0.715)	7.25 (0.74)	6.39 (0.73)	1.95

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
from baseline (SE)					(0.97)
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	< 0.0001		< 0.0001	0.0003	
TNF alpha inhibitor–inadequate responder[b]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. PL (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
PCS responders (improvement of ≥ 2.5 points) using non-responder imputation[c]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	

CI = confidence interval; LS = least squares; MCS = Mental Component Summary; PCS = physical component summary; PL = placebo; SD = standard deviation; SE = standard error; SEC = secukinumab; SF-36 = Short Form (36) Health Survey; TNF = tumour necrosis factor; vs. = versus.

Note: n = number of patients with measurements at both baseline and the post-baseline visits. Data collected after the patient was rescued were treated as missing for placebo patients who switched to secukinumab, and the actual values were used for secukinumab patients.

[a] LS mean, 95% CI, and *P* value are from a mixed-effect model repeated measures (MMRM) with treatment regimen, analysis visit and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure.

[b] LS mean, 95% CI, and *P* value are from an MMRM with treatment regimen, analysis visit as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure.

[c] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors and baseline score and weight as covariates. Missing responses are considered non-responders. Rescued patients are also considered non-responders after the time of rescue. Discontinued patients are considered non-responders after the time of discontinuation. For the non-responder imputation, n = the number of patients who are responders as per the corresponding imputation approach in the treatment group.

Source: Clinical study reports.[6,7]

TABLE 17: CHANGE FROM BASELINE IN DISABILITY ASSESSMENT (HEALTH ASSESSMENT QUESTIONNAIRE-DISABILITY INDEX SCORE) AND RESPONSE AT WEEK 16 AND WEEK 24

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
At week 16					
Change from baseline in HAQ-DI score					
Full analysis set[a]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder[b]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Proportion of patients achieving HAQ-DI improvements of at least 0.30 points using non-responder imputation[c]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
At week 24					
Change from baseline in HAQ-DI score					
Full analysis set[a]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	–0.40 (0.036)	–0.17 (0.047)	–0.56 (0.05)	–0.48 (0.05)	–0·31 (0·06)
LS mean difference (95% CI)	–0.23 (–0.35 to –0.12)		–0.25 (–0.40 to –0.10)	–0·17 (–0·32 to –0·02)	
P value	< 0.0001		0.0013	0.0278	
TNF alpha inhibitor–inadequate responder[b]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference, (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference, (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Proportion of patients achieving HAQ-DI improvements of at least 0.30 points using non-responder imputation[c]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	

CI = confidence interval; HAQ-DI = health assessment questionnaire-disability index; LS = least squares; PL = placebo; SD = standard deviation; SE = standard error; SEC = secukinumab; TNF = tumour necrosis factor.
Note: n = number of patients with measurements at both baseline and the post-baseline visits. Data collected after the patient was rescued were treated as missing for placebo patients who switched to secukinumab, and the actual values were used for secukinumab patients.
[a] LS mean, 95% CI, and *P* value are from a mixed-effect model repeated measures (MMRM) with treatment regimen, analysis visit, and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure.
[b] LS mean, 95% CI, and *P* value are from an MMRM with treatment regimen, analysis visit as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure.
[c] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors and baseline weight as a covariate. Missing responses are considered non-responders. Rescued patients are also considered non-responders after the time of rescue. Discontinued patients are considered non-responders after the time of discontinuation. For the non-responder imputation, n = the number of patients who are responders as per the corresponding imputation approach in the treatment group.Source: Clinical study reports.[6,7]

TABLE 18: CHANGE FROM BASELINE IN JOINT STRUCTURAL DAMAGE USING VAN DER HEIJDE MODIFIED TOTAL SHARP SCORE AT WEEK 24 IN FUTURE 1 TRIAL

	FUTURE 1	
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)
Full analysis set		
N	185	179
Mean change from baseline	0.13	0.57
Estimate for the difference in mean (SE)	–0.47 (0.20)	
P value	0.0212	
TNF alpha inhibitor–inadequate responder		
N	50	50
Mean change from baseline	0.10	0.58
Estimate for the difference in mean (SE)	[redacted]	
P value	[redacted]	
TNF alpha inhibitor–naive patients		
N	135	129
Mean change from baseline	0.15	0.57
Estimate for the difference in mean (SE)	[redacted]	
P value	[redacted]	
Concomitant MTX use		
N	111	114
Mean change from baseline	0.14	0.57
Estimate for the difference in mean (SE)	[redacted]	
P value	[redacted]	
No concomitant MTX treatment		
N	74	65
Mean change from baseline	0.12	0.58
Estimate for the difference in mean (SE)	[redacted]	
P value	[redacted]	

MTX = methotrexate; PL = placebo; SE = standard error; SEC = secukinumab; TNF = tumour necrosis factor.
Note: Baseline value is the last measurement before dosing, if available, or a value within 30 days post-dosing if no value available before dosing. N = number of patients in each treatment group. Estimate for the difference in mean, SE, and *P* value are from a non-parametric analysis of covariance (ANCOVA) model (Koch, 1998) with the change from baseline van der Heijde modified total Sharp score (or Erosion Score or Joint Space Narrowing Score) as the dependent variable, treatment, and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors, and weight and baseline van der Heijde total modified Sharp score (or Erosion Score or Joint Space Narrowing Score) as covariates.
Source: Clinical study reports.[6,7]

TABLE 19: PRESENCE OF DACTYLITIS AND ENTHESITIS USING NON-RESPONDER IMPUTATION AT WEEK 16 AND WEEK 24

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
Presence of dactylitis at week 16					
Full analysis set[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Presence of enthesitis at week 16					
Full analysis set[a]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Presence of dactylitis at week 24					
Full analysis set[a]					
n/N (%)	54/104 (51.9)	98/116 (84.5)	20/46 (43.5)	16/32 (50.0)	23/27 (85.2)
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder[b]					

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Presence of enthesitis at week 24					
Full analysis set[a]					
n/N (%)	68/126 (54.0)	102/117 (87.2)	29/56 (51.8)	37/64 (57.8)	51/65 (78.5)
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–inadequate responder[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
TNF alpha inhibitor–naive patients[b]					
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	

CI = confidence interval; PL = placebo; SEC = secukinumab; TNF = tumour necrosis factor.
Note: A responder means dactylitis was cleared for a patient with dactylitis at baseline. Missing responses are considered non-responders. Rescued patients are also considered non-responders after the time of rescue. Discontinued patients are considered non-responders after the time of discontinuation.
[a] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors and baseline weight as a covariate.
[b] Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment as the factor and baseline weight as a covariate.
Source: Clinical study reports.[6,7]

TABLE 20: MINIMAL DISEASE ACTIVITY RESPONSE USING NON-RESPONDER IMPUTATION AT WEEK 16 AND WEEK 24

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
At week 16					
Full analysis set					
n/N (%)	48/202 (23.8)	5/202 (2.5)	22/100 (22.0)	22/100 (22.0)	7/98 (7.1)
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
At week 24					
Full analysis set					
n/N (%)	43/202 (21.3)	4/202 (2.0)	22/100 (22.0)	19/100 (19.0)	3/98 (3.1)
Odds ratio (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	

CI = confidence interval; PL = placebo; SEC = secukinumab.
Note: Odds ratio, 95% confidence interval, and *P* value are from a logistic regression model with treatment and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors and baseline weight as a covariate. Missing responses are considered non-responders. Rescued patients are also considered non-responders after the time of rescue. Discontinued patients are considered non-responders after the time of discontinuation.
Source: Clinical study reports.[6,7]

TABLE 21: CHANGE FROM BASELINE IN PATIENT'S ASSESSMENT OF PSORIATIC ARTHRITIS PAIN (VISUAL ANALOGUE SCALE) AT WEEK 16 AND WEEK 24

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
At week 16					
Full analysis set					
n	190	182	96	100	86
Baseline, mean (SD)	54.8 (24.16)	56.8 (21.52)	58.2 (18.85)	58.9 (19.76)	54.5 (22.45)
LS mean change (SE)	–20.39 (1.587)	–4.95 (1.605)	[redacted]	[redacted]	[redacted]
LS mean difference, (95% CI)	–15.43 (–19.78 or –11.08)		[redacted]	[redacted]	
P value	< 0.0001		[redacted]	[redacted]	
At week 24					
Full analysis set					
n	188	58	95	94	33
LS mean change (SE)	–20.78 (1.645)	–6.66 (2.439)	–22.35 (2.260)	–23.39 (2.251)	–11.71 (3.176)

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
LS mean difference, (95% CI)	–14.11 (–19.83 or –8.40)		–10.64 (–18.27 or –3.01)	–11.68 (–19.31 or –4.05)	
P value	< 0.0001		0.0064	0.0028	

CI = confidence interval; LS = least squares; PL = placebo; SD = standard deviation; SE = standard error; SEC = secukinumab.
Note: N = Number of patients in each treatment group of the specified analysis set. LS mean, 95% CI, and *P* value are from a mixed-effect model repeated measures (MMRM) with treatment regimen, analysis visit, and randomization stratum (tumour necrosis factor alpha inhibitor –naive or –inadequate responder) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure. Data collected after the patient was rescued were treated as missing for placebo patients who switched to secukinumab, and the actual values were for secukinumab patients.
Source: Clinical study reports.[6,7]

TABLE 22: CHANGE FROM BASELINE IN PSORIATIC ARTHRITIS QUALITY OF LIFE AT WEEK 16 AND WEEK 24

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
At week 16					
Full analysis set					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	10.3 (5.9)	10.5 (5.9)	10.3 (5.5)	11.7 (5.4)	9.4 (5.6)
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
At week 24					
Full analysis set					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	–3.49 (0.365)	–0.36 (0.482)	–4.23 (0.491)	–4.51 (0.491)	–1.99 (0.606)
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	

CI = confidence interval; LS = least squares; PL = placebo; SD = standard deviation; SE = standard error; SEC = secukinumab.
Note: n = number of patients in each treatment group of the specified analysis set. LS mean, 95% CI, and *P* value are from a mixed-effect model repeated measures (MMRM) with treatment regimen, analysis visit, and randomization stratum (tumour necrosis factor alpha inhibitor –naive or –inadequate responder) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure. Data collected after the patient was rescued were treated as missing for placebo patients who switched to secukinumab, and the actual values were used for secukinumab patients.
Source: Clinical study reports.[6,7]

TABLE 23: CHANGE FROM BASELINE IN FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY–FATIGUE TOTAL SCORE AT WEEK 16 AND WEEK 24

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
At week 16					
Full analysis set					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	29.1 (10.9)	28.1 (11.3)	28.4 (12.6)	26.6 (11.6)	30.3 (11.6)
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
At week 24					
Full analysis set					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	6.74 (0.651)	4.00 (0.895)	5.97 (0.921)	7.97 (0.913)	1.63 (1.222)
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	0.0123		0.0045	< 0.0001	

CI = confidence interval; LS = least squares; PL = placebo; SD = standard deviation; SE = standard error; SEC = secukinumab.
Note: n = number of patients in each treatment group of the specified analysis set. LS mean, 95% CI, and *P* value are from a mixed-effect model repeated measures (MMRM) with treatment regimen, analysis visit, and randomization stratum (tumour necrosis factor alpha inhibitor–naive or –inadequate responder) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure. Data collected after the patient was rescued were treated as missing for placebo patients who switched to secukinumab, and the actual values were used for secukinumab patients.
Source: Clinical study reports.[6,7]

TABLE 24: CHANGE FROM BASELINE IN DERMATOLOGY LIFE QUALITY INDEX TOTAL SCORE AT WEEK 16 AND WEEK 24

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
At week 16					
Full analysis set					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	12.8 (7.7)	12.6 (7.1)	12.8 (8.4)	14.4 (7.6)	11.9 (7.6)
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
At week 24					
Full analysis set					

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	–8.80 (0.571)	0.70 (0.796)	–8.48 (0.890)	–8.77 (0.737)	–2.13 (1.196)
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	< 0.0001		< 0.0001	< 0.0001	

CI = confidence interval; LS = least squares; PL = placebo; SD = standard deviation; SE = standard error; SEC = secukinumab.
Note: n = number of patients in each treatment group of the specified analysis set. LS mean, 95% CI, and *P* value are from a mixed-effect model repeated measures (MMRM) with treatment regimen, analysis visit, and randomization stratum (tumour necrosis factor alpha inhibitor–naive or –inadequate responder) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure. Data collected after the patient was rescued were treated as missing for placebo patients who switched to secukinumab, and the actual values were used for secukinumab patients.
Source: Clinical study reports.[6,7]

TABLE 25: CHANGE FROM BASELINE IN MODIFIED NAIL PSORIASIS SEVERITY INDEX AT WEEK 16 AND WEEK 24

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
At week 16					
Full analysis set					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	19.8 (21.1)	18.1 (17.1)	15.7 (15.7)	18.6 (22.1)	18.8 (20.2)
LS mean change (SE)	–8.78 (0.831)	–3.09 (0.813)	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	–5.70 (–7.96 to –3.43)		[redacted]	[redacted]	
P value	< 0.0001		[redacted]	[redacted]	
At week 24					
Full analysis set					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	–10.93 (0.902)	–4.05 (1.165)	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	–6.89 (–9.77 to –4.00)		[redacted]	[redacted]	
P value	< 0.0001		[redacted]	[redacted]	

CI = confidence interval; LS = least squares; PL = placebo; SD = standard deviation; SE = standard error; SEC = secukinumab.
Note: n = number of patients in each treatment group of the specified analysis set. LS mean, 95% CI, and *P* value are from a mixed-effect model repeated measures (MMRM) with treatment regimen, analysis visit and randomization stratum (tumour necrosis factor alpha inhibitor–naive or –inadequate responder) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure. Data collected after the patient was rescued were treated as missing for placebo patients who switched to secukinumab, and the actual values were used for secukinumab patients.
Source: Clinical study reports.[6,7]

TABLE 26: CHANGE FROM BASELINE IN LEEDS DACTYLITIS INDEX AND DACTYLITIS COUNT AT WEEK 16 AND WEEK 24

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
At week 16					
LDI					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Dactylitis count					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
At week 24					
LDI					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	–18.21 (1.469)	–12.22 (2.228)	–15.13 (2.954)	–11.70 (2.921)	–10.19 (3.283)
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	0.0220		0.2602	0.7287	
Dactylitis count					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	–1.46 (0.091)	–0.88 (0.132)	–0.90 (0.161)	–0.85 (0.159)	–0.44 (0.191)
LS mean difference (95% CI)	[redacted]		[redacted]	[redacted]	
P value	0.0003		0.0659	0.1000	

CI = confidence interval; LDI = Leeds Dactylitis Index; LS = least squares; PL = placebo; SE = standard error; SEC = secukinumab.
Note: n = number of patients in each treatment group of the specified analysis set. LS mean, 95% CI, and *P* value are from a mixed-effect model repeated measures (MMRM) with treatment regimen, analysis visit, and randomization stratum (tumour necrosis factor alpha inhibitor–naive or –inadequate responder) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure. Data collected after the patient was rescued were treated as missing for placebo patients who switched to secukinumab, and the actual values were used for secukinumab patients.
Source: Clinical study reports.[6,7]

TABLE 27: WORK PRODUCTIVITY USING OBSERVED DATA AT WEEK 16 AND WEEK 24

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
WPAI-GH: percentage of work time missed because of health issues for those who were currently employed at week 16					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI-GH: percentage of work time missed because of health issues for those who were currently employed at week 24					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI-GH: percentage of impairment while working because of health issues at week 16					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI-GH: percentage impairment while working because of health issues at week 24					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI-GH: percentage overall work impairment because of health issues for those who were currently employed at week 16					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI-GH: percentage overall work impairment because of health issuesfor those who were currently employed at week 24					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI-GH: percentage activity impairment because of health issues at week 16					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI-GH: percentage activity impairment because of health issues at week 24					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LS = least squares; PL = placebo; SD = standard deviation; SEC = secukinumab; WPAI-GH = Work Productivity and Activity Impairment–General Health.
Source: Clinical study reports.[6,7]

TABLE 28: TREATMENT-EMERGENT ADVERSE EVENTS IN AT LEAST 2% OF PATIENTS IN THE SECUKINUMAB GROUPS UP TO WEEK 16

	FUTURE 1		FUTURE 2		
	SEC 10 mg/kg then 150 mg (N = 202)	PL (N = 202)	SEC 300 mg (N = 100)	SEC 150 mg (N = 100)	PL (N = 98)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			
[redacted]			[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]

PL = placebo; SEC = secukinumab.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- American College of Rheumatology (ACR) 20/50/70
- Minimal disease activity (MDA)
- Disease Activity Score in 28 joints (DAS 28) based on C-reactive protein (CRP)
- Health assessment questionnaire-disability index (HAQ-DI)
- Short Form (36) Health Survey (SF-36)
- Psoriatic Arthritis Quality of Life questionnaire (PsAQoL)
- Dermatology Life Quality Index (DLQI)
- Patient's assessment of pain–visual analogue scale (VAS)
- Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue
- Work Productivity and Activity Impairment–General Health questionnaire (WPAI-GH)
- Leeds Dactylitis Index (LDI)
- van der Heijde modified total Sharp score (vdH-mTSS)
- Psoriasis Area and Severity Index (PASI)
- Modified Nail Psoriasis Severity Index (mNAPSI)

TABLE 29: FINDINGS

Instrument	Type	Evidence of Validity	MCID	References
ACR20/50/70	Provide a composite measure of ≥ 20%, ≥ 50%, or ≥ 70% improvement in both swollen and tender joint counts and at least 3 of 5 additional disease criteria	Yes	ACR20	24,52-55
MDA	A composite outcome measure developed as a target of treatment for patients with PsA that encompasses the different aspects of disease domains	Yes	Unknown	26,56
DAS 28	Evaluates a patient's response to treatment based on assessment of 28 each of tender and swollen joints, along with a patient global assessment of well-being	Yes	Unknown	27,28
HAQ-DI	Assesses physical disability and pain in RA	Yes	0.13 to 0.35	30,31,57,58
SF-36	General health status instrument	Yes	Between 2.5 and 5 points	33-36,59
PsAQoL	Quality-of-life instrument specific to PsA	No	Unknown	38,60
DLQI	10-item, dermatology-specific quality-of-life questionnaire	Yes	3.2	39,61,62
Patient's assessment of arthritis pain (VAS)	Scored on a 0 to 100 mm horizontal line on which 0 represents "no pain," and the 100 mm mark represents "pain as severe as can be imagined"	Yes	10 mm	40
FACIT–Fatigue	Assesses both the physical and functional consequences of fatigue	Yes	3.56 for patients with rheumatoid arthritis	42-44

Instrument	Type	Evidence of Validity	MCID	References
WPAI-GH	Measures the impact of disease on productivity	No	Unknown	63,64
LDI	Evaluates for a ≥ 10% difference in the circumference of the digit compared with the opposite digit	Yes	Unknown	45,46
vdH-mTSS	Assesses two different aspects of joint damage: articular erosions and joint space narrowing	Yes	4.6	47,65-67
PASI	Numeric score ranging from 0 to 72, based on assessments of four body areas and severity of induration, erythema, and scaling	Yes	PASI 75	48,68-71
mNAPSI	Assesses psoriatic nail involvement in patients with PsA and nail psoriasis	Yes	Unknown	6,7,72

ACR = American College of Rheumatology; DAS 28 = Disease Activity Score in 28 joints (DAS 28); DLQI = Dermatology Life Quality Index; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = health assessment questionnaire-disability index; LDI = Leeds Dactylitis Index; MCID = minimal clinically important difference; MDA = minimal disease activity; mNAPSI = Modified Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PsAQoL = Psoriatic Arthritis Quality of Life; RA = rheumatoid arthritis; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale; vdH-mTSS = van der Heijde modified total Sharp score; WPAI-GH = Work Productivity and Activity Impairment–General Health.

American College of Rheumatology 20/50/70

The ACR criteria for assessing joint status were originally developed for patients with rheumatoid arthritis and provide a composite measure of 20% or more, 50% or more, or 70% or more improvement in both swollen and tender joint counts, and at least three of five additional disease criteria, including patient/physician global assessment of disease activity (10 cm VAS), HAQ, patient assessment of pain intensity, and levels of CRP or erythrocyte sedimentation rate.[24] The ACR joint count assesses 68 joints for tenderness and 66 joints for swelling. Assessment of the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints of the hands and feet (i.e., 78 joints for tenderness and 76 for swelling) is not typically included for psoriatic arthritis (PsA) because of difficulty distinguishing PIP and DIP joint inflammation in the toes.[52] The ACR has been shown to have good inter- and intra-observer reliability in PsA, [53,54]and to be a valid outcome measure in randomized controlled trials (RCTs).[55] The ACR20 is generally accepted as the minimally clinically important difference (MCID), indicating a response to treatment, whereas the ACR50 and 70 more likely reflect truly important change for the long-term management of arthropathy. The ACR is a general measure of clinical response of peripheral joint disease and does not include assessment of enthesitis, dactylitis, the spine, or the skin. Consequently, it represents only part of the clinical features of PsA; therefore, the use of additional assessment instruments to assess other clinical features is necessary.

Minimal Disease Activity

MDA is a composite outcome measure developed as a target of treatment for patients with PsA that encompasses the different aspects of disease domains.[25] Patients were considered as achieving MDA if they fulfilled five of seven outcome measures: a tender joint count of one or less, a swollen joint count of one or less, PASI of one or less or body surface area of 3% or less, patient pain-VAS 15 mm or less, patient global VAS 20 mm, HAQ-DI 0.5 or less, tender entheseal points of one or less.[26] These criteria for MDA were validated in patients with active PsA using interventional trial data.[26] In an observational PsA

cohort, it was found that patients who achieved sustained MDA (defined as achieving MDA on consecutive visits for a minimum duration of 12 months) had a reduction in joint damage progression and 69% of patients who achieved sustained MDA showed no progression of joint damage, compared with 51% in the control group. In addition, the mean change in damaged joint counts was 0.931 in the sustained MDA group and 2.245 in the controls ($P < 0.001$).[56]

Disease Activity Score 28 and C-Reactive Protein

The DAS 28 score evaluates a patient's response to treatment based on the assessment of 28 each of tender and swollen joints, along with a patient global assessment of well-being.[27,28] The score ranges from 0 to 9.4 and is calculated using either clinical values of erythrocyte sedimentation rate (ESR) or CRP. DAS 28 can be expressed as:

$$DAS\ 28 = 0.56(\sqrt{TJC28}) + 0.28(\sqrt{SJC28}) + 0.36Ln(CRP + 1) + 0.014(PGA)$$[27]

where TJC28 and SJC28 are the tender and swollen joint counts, respectively, and PGA is patient's global assessment.

The threshold values for DAS 28 are 2.6, 3.2, and 5.1, corresponding with remission, low disease activity, and high disease activity, respectively.[24] As with the ACR and other psoriatic arthritis response criteria, the DAS 28 is only a general assessment of clinical response.

The DAS components correlate well with each other and with the ACR,[27,73-75] and have been shown to be discriminant and responsive in trials.[76] However, the DAS 28 does not include assessment of DIP or lower extremity disease and, thus, may not describe the full extent of a patient's disease status. The DAS 28 using ESR is better established compared with DAS 28 using CRP, and it has been validated for use as an outcome measure in several rheumatoid arthritis trials.[24,27,55,77] Although DAS 28-ESR has shown the ability to discriminate between placebo and active treatment in PsA trials,[76] a formal validation in PsA has not yet been conducted. The DAS 28-CRP, which was used in trials included in this review, shows general agreement with the ESR equation in rheumatoid arthritis trials, and tends to yield better response criteria results than the DAS 28-ESR when disagreements occur between the two.[78-80] The CRP may be a more desirable clinical measurement than ESR because CRP levels are sensitive to short-term changes in disease activity, whereas ESR can be influenced by such factors as age, gender, or plasma proteins.[81]

EULAR Response

The European League Against Rheumatism (EULAR) response criteria classify patients as good or moderate responders, or as non-responders to treatment based on the individual patient's disease severity as measured on the current DAS 28 score, and changes in DAS 28 from baseline at the time of assessment.[29] The definition of a good or moderate EULAR response is presented in Table 30.

TABLE 30: EULAR RESPONDER CLASSIFICATION

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

DAS = Disease Activity Score; EULAR = European League Against Rheumatism.

Health Assessment Questionnaire

The HAQ was developed to assess physical disability and pain in rheumatoid arthritis[30] and has been used extensively in RCTs in arthritis, including for PsA. Patients assess and score the difficulty in performing activities in eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities) using a self-assessment questionnaire. The performance scores range from 0 (without any difficulty) to 3 (unable to do), and are adjusted for use of aids, devices, or persons who help with the activity. The summed score is then divided by the number of answered questions and reported. Scores are evaluated based on change from baseline. The MCID for the HAQ-DI has been estimated from a phase 3 trial of etanercept in PsA[31] to be 0.3 (unlike 0.22 for rheumatoid arthritis), which was estimated using a distribution-based method based on standard error of measurement. Mease et al.[58] have determined that the MCID for the HAQ-DI in PsA patients using anchor-based methods is 0.35, whereas Kwok and Pope[57] have estimated the MCID to be 0.13 in PsA patients using an anchor-based approach (equal bidirectional magnitudes for improvement and worsening).Blackmore et al. [82] have shown that the HAQ-DI adequately captures clinically important changes in functional status and pain in patients with PsA.[82] However, the HAQ-DI focuses on physical disability and may not adequately capture disability in patients with predominantly skin disease.[82] Modified versions of the HAQ to include spinal domains (HAQ-S) or skin disease assessment (HAQ-SK) have not proven to be significantly better in the assessment of health status in PsA than the original HAQ-DI.[82,83] The HAQ-SK has poor correlation with the PASI, although it does correlate with patient-assessed or physician-assessed severity of psoriasis.[83]

Medical Outcomes Study Short Form (36) Health Survey

The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[32] The SF-36 consists of eight health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[33] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries, the physical component summary (PCS) and the mental component summary (MCS), derived from aggregating the eight domains according to a scoring algorithm. The PCS and MCS scores range from 0 to 100, with higher scores indicating better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a standard deviation of 10 in the general US population. Therefore, all scores above/below 50 are considered above/below average for the general US population. Husted et al.[84] and Leung et al.[59] reported that the SF-36 is reliable and valid for the assessment of patients with PsA and could be used to distinguish PsA patients from patients without PsA. In addition, the PCS and MCS summary scores support the validity of the SF-36.[59] The SF-36 is at least as responsive as the HAQ instrument to short-term changes in perceived health status and inflammatory disease activity in patients with PsA.[85]

The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 and 5 points.[34-36] Leung et al.[37] reported MCIDs of 3.74 and 1.77 for the PCS and MCS subsections, respectively, in PsA patients treated with TNF alpha inhibitor drugs using an anchor-based approach. The MCS was observed in a phase 3 trial[37] to be weaker in differentiating drug and placebo effects. However, the trial was limited by its small sample size (n = 17).[37]

Psoriatic Arthritis Quality of Life

The PsAQoL is a quality-of-life instrument specific to psoriatic arthritis.[38] It comprises 20 items, so that the score ranges from 0 to 20, with higher scores indicating a worse HRQoL.[38] It has been used in clinical studies and trials to assess the impact of interventions for PsA. It is well-accepted by patients and has

acceptable scaling and psychometric properties.[38] Although HRQoL measures may provide valuable information about treatment benefits in patient well-being, it was observed that patient-reported outcomes, such PsAQoL, correlate very poorly with clinical outcomes in PsA. It indicated that patients who respond clinically do not necessarily report improvements to their HRQoL and vice versa.[60] No MCID for the PsAQoL was identified.

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.[6] These aspects are symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[6] 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).[61] The higher the score, the more quality of life is impaired. The meaning of the DLQI scores for a patient's life is as follows:[86]

- 0 to 1 = no effect
- 2 to 5 = small effect
- 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.[61] The estimated MCID for the DLQI in patients with psoriasis is 3.2.[39] Estimates of the minimal important difference (the smallest difference a patient would regard as beneficial) have ranged from 2.3 to 5.7.[62]

- A number of limitations of the DLQI have been identified: Concerns have been identified regarding unidimensionality and the behaviour of items of the DLQI in different psoriatic patient populations with respect to their age, gender, culture, etc.[86]
- The patient's emotional aspects may be underrepresented, and this may be one reason for unexpectedly low DLQI scores in patients with more emotionally disabling diseases such as vitiligo. To overcome this, it is suggested that the DLQI be combined with more emotionally oriented measures, such as the mental component of the SF-36 or hospital anxiety and depression (HAD) scales.[86]
- Benchmarks for the MCID of DLQI scores in general dermatological conditions are not available, although there have been some attempts to determine these differences for specific conditions such as psoriasis.[86]
- The DLQI may lack sensitivity in detecting change from mild to severe psoriasis.[87]

Patient's Assessment of Pain

Patients' assessment of pain was scored on a 0 to 100 mm horizontal line on which 0 represents "no pain," and the 100 mm mark represents "pain as severe as can be imagined."[40] Patients were asked to place a vertical line on the horizontal line to indicate the level of their arthritis pain on the day of the visit.[40] The MCID of patient's assessment of pain was defined as an improvement (reduction) in pain of 10 mm or more from baseline.[40] Patients' assessment of pain is part of the ACR core set of measures in arthritis.[41]

Functional Assessment of Chronic Illness Therapy –Fatigue

The FACIT–Fatigue scale is a self-administered questionnaire that assesses both the physical and functional consequences of fatigue.[42] The FACIT–Fatigue was validated in a Toronto PsA cohort study and was found to be well-correlated with the modified Fatigue Severity Scale, showing high internal consistency, test–retest reliability, as well as criterion and construct validity.[43] It is a 13-item questionnaire, with each question scored from 0 to 4 for a total score range of 0 to 52. Higher scores denote lower levels of fatigue. Therefore, higher FACIT–Fatigue scores are expected with greater improvements in a patient's PsA.[42] A validated MCID for improvement in the FACIT–Fatigue is not currently available in PsA patients. A validated FACIT–Fatigue MCID in rheumatoid arthritis patients is estimated to be 3.56.[44]

Work Productivity and Activity Impairment –General Health (WPAI-GH)

Work productivity was measured by WPAI-GH, a self-administered instrument used to measure the impact of disease on productivity. Four main outcomes can be generated from the WPAI-GH and expressed in percentages: 1) percentage of work time missed because of health issues for those who were currently employed; 2) percentage of impairment while working because of health issues for those who were currently employed and actually worked in the past seven days; 3) percentage of overall work impairment because of health issues for those who were currently employed; and 4) percentage of activity impairment because of health issues for all respondents. Greater scores indicate greater impairment. The recall period is two to seven days before the visit. This instrument has been validated in a variety of diseases including ankylosing spondylitis and rheumatoid arthritis, and it is found to be strongly correlated with health outcomes and disease status in previous studies;[63,64] however, this instrument is not validated in patients with PsA. The MCID of WPAI-GH is currently unknown.

Leeds Dactylitis Index

Dactylitis, the swelling of an entire digit related to articular and periarticular inflammation, is a characteristic of inflammatory spondyloarthropathies, including PsA. Presence of dactylitis was assessed using the LDI basic, which evaluates for a 10% difference or more in the circumference of the digit compared with the opposite digit.[45,46] No MCID for LDI was identified.

Modified Total Sharp Score

The Sharp scoring system, first developed in 1971, has undergone modifications over time and is now referred to as the modified Sharp. This method allows for the assessment of two different aspects of joint damage: articular erosions (representing direct invasion of cartilage and bone by the proliferating synovial pannus) and joint space narrowing (representing destruction of surface cartilage). Data on the progression of joint structural damage are obtained by radiography of specific joints (typically in the hands and feet) before treatment and at various points after treatment has been initiated.

The most recent modification of the Sharp scoring system was performed by van der Heijde.[66] Van der Heijde scores erosions are listed in the following table.

TABLE 31: VAN DER HEIJDE MODIFIED TOTAL SHARP SCORE[65]

Erosions	
0	Normal
1	Discrete erosions
2-3	Larger erosions according to surface area involved
4	Erosion extending over the middle of the bone
5	Complete collapse
Joint space narrowing	
0	Intact bony outlines and normal joint space
1	Erosion < 1 mm in diameter or joint space narrowing
2	One or several small erosions (diameter > 1 mm)
3	Marked erosions
4	Severe erosions (usually no joint space left and the original bony outlines are only partly preserved)
5	Mutilating changes (the original bony outlines have been destroyed)

The van der Heijde erosion score includes 16 joints from the hands and wrists (graded from 0 to 5) and six joints from the feet (graded from 0 to 10). The joint space narrowing score includes 15 areas from the hands and wrists (graded from 0 to 4) and six areas from the feet (also graded from 0 to 4). The maximum erosion score is 160 for hands and wrists and 120 for feet, while the maximum joint space narrowing score is 120 for hands and 48 for feet.[88] Maximum total scores for both erosion and joint space narrowing are shown, as follows:

Erosion = (32 joints in hands and wrists × 5) + (12 joints in feet × 10) = 280
Joint space narrowing = (30 joints in hands and wrists × 4) + (12 joints in feet × 4) = 168

The van der Heijde modification has become the most commonly used for a few reasons: it includes both hands and feet; it measures erosions and joint space narrowing; and it covers a broad spectrum of joints, providing sensitivity to change.[89]

In the early stages of rheumatoid arthritis, inflammation, rather than actual damage to joints, appears to be the main contributor to increased disability.[90,91] The relationship between radiological and functional changes has been studied. A reanalysis of published data performed by Welsing et al. found that patients must reach a certain amount of radiological damage before an increase in damage will affect disability.[92] The authors also found that changes in Sharp scores had a greater impact on disability with advancing age. A study by Sahin et al. found that radiological damage assessed by the van der Heijde method was highly correlated with HAQ scores in a population with a mean disease duration of seven years.[93] They also cited findings from another study, which found that Sharp scores became correlated with HAQ after six years' disease duration. At the other end of the spectrum, a study by Clarke et al. found that radiological scores assessed using the Genant method were positively correlated with HAQ in patients with 20 years' disease duration.[94] Therefore, radiological changes, assessed by Sharp scores, and functional changes, assessed by the HAQ, do not correlate with each other early in RA, but do so after several years of disease.

Several limitations exist with using radiographs to assess clinical status in rheumatoid arthritis. Radiographs tend to change slowly in rheumatoid arthritis, requiring at least six months to a year to detect changes in a single patient. Inter-rater and intra-rater reliability is also a concern, because of the subtle nature of changes and subjective interpretation. The images themselves can also vary between

samples, owing to positioning and quality. Radiographs should be read in random order to reduce the potential bias of interpretation at different time points.[95] Given these limitations, beginning in the early 1990s, the use of magnetic resonance imaging was being examined as an alternative for assessing disease progression.[96] However, the use of magnetic resonance imaging for assessing the clinical status of rheumatoid arthritis is limited because of cost and accessibility.

In a study by Bruynesteyn et al.,[47] a panel of experts determined an MCID of 4.6 units for the Sharp/van der Heijde method. They defined the MCID as a progression in radiological joint damage that makes a rheumatologist change therapy. This MCID was equal to, or slightly lower than, the smallest detectable difference for this scoring system. The smallest detectable difference represents the smallest change score that can be reliably discriminated from the measurement error of the scoring method.[67] The authors also note that, with improvements in disease-modifying therapies such as the biologics, the magnitude of progression will continue to shrink, requiring increasingly sensitive measures.

Psoriasis Area and Severity Index

The PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It produces a numeric score ranging from 0 to 72. In general, a PASI score of 5 to 10 is considered moderate disease, and a score 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 FDA.[48] PASI 75 is a dichotomous (yes/no) scale indicating whether a patient achieved an improvement of 75% or more from baseline PASI score.

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). These regions account for 10%, 20%, 30%, and 40% of the total body surface area (BSA), respectively.[70] 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). The 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:

$$PASI = 0.1 (Eh + Ih + Sh) Ah + 0.2 (Eu + Iu + Su) Au + 0.3 (Et + It + St) At + 0.4 (El + Il + Sl) Al$$[70]

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

A number of limitations of the PASI have been identified:

- The PASI has been criticized as not correlating the clinical extent of the disease with quality of life and the psychological stress caused by psoriasis. The patient's measure of quality of life is often worse than the physician's rated clinical severity.[97]

- There are significant inter-rater reliability issues regarding the measurement of body surface area.[68,69]
- The PASI often fails to predict severity as seen from the patient's perspective.[68,69]
- Improvements in PASI score are not linearly related to severity or improvements in psoriasis.[68,69] The extent of psoriatic involvement is measured using a scale of 1 to 6, and the areas corresponding to each score are non-linear.
- Some severe disease (clinically) may be scored low. For example, scores as low as 3 (on palms and soles) may represent psoriasis that disables a patient from work and other life activities.
- Most patients fall into a narrow band of scores, thereby decreasing the usefulness of the full range of scores (i.e., scores above 40 are rare).[68] Validity of this scale may be overrated, in part because of the skew toward lower scores.[71]
- There is little research on the reliability of the assessments for erythema, desquamation, and induration, together with overall PASI scores.[68]
- Criterion validity is restricted by the lack of a "gold standard" measure of psoriatic severity.[98]
- 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 percentage improvement in PASI (e.g., reduction of T cells, loss of K16 expression, and reduction in epidermal thickness).[48]
- Little work has been done to determine the clinical relevance of derived PASI scores.[68]

Modified Nail Psoriasis Severity Index

The mNAPSI is an instrument to assess psoriatic nail involvement in patients with PsA and nail psoriasis. For the evaluation of the mNAPSI, three features or groups of features (onycholysis and oil-drop dyschromia, pitting, and crumbling) of each fingernail are graded on a scale from 0 to 3. The mNAPSI scores range from 0 to 130 for all fingernails. The total mNAPSI score is calculated as the sum of all the scores from available nails.[6,7] The mNAPSI has been validated in patients with PsA, and it is found to be strongly correlated with global nail severity VAS scores.[72] The MCID of mNAPSI is currently unknown.

Conclusion

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

APPENDIX 6: SUMMARY OF EXTENDED DATA IN FUTURE 1 AND FUTURE 2

Aim

To summarize the efficacy and safety findings of FUTURE 1 and FUTURE 2 at week 52 and week 104.

Findings

Study and Baseline Disease Characteristics

The baseline study and disease characteristics are reported in the main text. Briefly, FUTURE 1 and FUTURE 2 were phase 3 double-blind randomized controlled trials (RCTs). In FUTURE 1, at week 16, patients were classified as responders (improvement of 20% or more from baseline in both tender and swollen joint counts) or non-responders. Patients who were randomized to placebo at baseline were re-randomized by the interactive response technology (IRT) to receive double-blind treatment up to 24 weeks, and dose-blind treatment up to two years, as follows: patients on placebo who were responders remained on placebo until week 24. At week 24, these patients were re-randomized (1:1) to receive either secukinumab (SEC) 75 mg or 150 mg by subcutaneous (SC) injection every four weeks. Patients on placebo who were non-responders were re-randomized (1:1) at week 16 to receive either SEC 75 mg or 150 mg SC every four weeks. In FUTURE 2, at week 16 patients were classified as responders (improvement of 20% or more from baseline in both tender and swollen joint counts) or non-responders and were re-randomized by the IRT to receive double-blind treatment up to 24 weeks, and dose-blind treatment up to 52 weeks, as follows: Patients on placebo who were non-responders were re-randomized to receive SEC 150 mg or 300 mg SC (1:1) every four weeks. Patients on placebo who were responders continued to receive placebo every four weeks until week 24. At week 24, these patients were re-randomized to receive SEC 150 mg or 300 mg SC (1:1) every four weeks regardless of responder status. In both studies, patients originally assigned to the SEC groups continued their treatment until the end of study (two years in FUTURE 1 and five years in FUTURE 2). Therefore, there were no patients in the placebo group after week 16 or week 24 in either study. The primary clinical outcomes were the ACR20 response at week 24. The long-term efficacy and safety were evaluated in FUTURE 1 and FUTURE 2. Outcomes measured included American College of Rheumatology ACR20/50/70, Psoriasis Area and Severity Index (PASI) 75/90, Disease Activity Score (DAS) 28–C-reactive protein (CRP), presence of dactylitis, presence of enthesitis, and van der Heijde modified total Sharp score (vdH-mTSS, for FUTURE 1 only). Patient-reported outcomes were also reported, including Short Form (36) Health Survey (SF-36) physical component summary (PCS) and mental component summary (MCS), fatigue, and disease-specific health-related quality of life (HRQoL). Safety data included all adverse events (AEs), and routine laboratory analyses were followed. At the time of the current review, efficacy and safety data up to week 104 were available in the FUTURE 1 trial and up to week 52 in the FUTURE 2 trial.

Patient Disposition

In FUTURE 1, a total of 606 patients were randomized at baseline. At week 104, 35 patients in the original SEC 150 mg group and 48 patients in the original placebo group discontinued the study. In FUTURE 2, 397 patients were randomized at baseline. At week 52, 14 patients in the original SEC 150 mg group, eight patients in the original SEC 300 mg group, and 16 patients in the original placebo group had discontinued the study.

TABLE 32: PATIENT DISPOSITION IN THE FUTURE 1 TRIAL UP TO WEEK 104

	FUTURE 1			
	SEC 10 mg/kg then 150 mg	PL	Placebo non-responder then SEC 150 mg	Placebo responder then SEC 150 mg
Randomized	202	202	61	33
Completed week 52, N (%)	180 (89.1)	161 (79.7)	51 (83.6)	28 (84.8)
Discontinued week 52, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]
Patient/guardian decision	[redacted]	[redacted]	[redacted]	[redacted]
Completed week 104	167 (82.7)	154 (76.2)	49 (80.3)	27 (81.8)
Discontinued week 104	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]
Patient/guardian decision	[redacted]	[redacted]	[redacted]	[redacted]
Randomized set, N	202	202	61	33
Full analysis set, N	202	202	61	33
Safety, N	202	202	61	33

PL = placebo; SEC = secukinumab.
Source: Clinical study reports.[6,99]

TABLE 33: PATIENT DISPOSITION IN THE FUTURE 2 TRIAL UP TO WEEK 52

	FUTURE 2					
	SEC 300 mg	SEC 150 mg	Placebo non-responder then SEC 150 mg	Placebo non-responder then SEC 300 mg	Placebo responder then SEC 150 mg	Placebo responder then SEC 300 mg
Randomized	100	100	27	28	16	17
Completed week 52, N (%)	92 (92.0)	86 (86.0)	26 (96.3)	24 (85.7)	15 (93.8)	17 (100.0)
Discontinued week 52, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-compliance with study treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient/guardian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	FUTURE 2					
	SEC 300 mg	SEC 150 mg	Placebo non-responder then SEC 150 mg	Placebo non-responder then SEC 300 mg	Placebo responder then SEC 150 mg	Placebo responder then SEC 300 mg
decision						
Randomized set, N	100	100	27	28	16	17
Full analysis set, N	100	100	27	28	16	17
Safety, N	100	100	27	28	16	17

SEC = secukinumab.
Source: Clinical study reports.[7,100]

Efficacy

In FUTURE 1, the responses in ACR20, ACR50, ACR70 and treatment effect on all other secondary efficacy variables observed at week 16 and week 24 in the SEC 150 mg dose group were sustained through week 52 and week 104 (Table 34). ACR20 response rates [redacted] observed for the original SEC 150 mg group at week 16 were maintained to week 52 (59.9%) and week 104 [redacted] For missing data and patients who escaped, a non-responder imputation was used in the analysis of ACR response criteria at week 52, whereas observed data were used at week 104. Similarly, improvements in ACR50, ACR70, DAS 28, PASI 75, and PASI 90 were maintained to week 52 and week 104. Compared with week 16/24, greater improvements in the patient-reported outcomes SF-36 MCS score, SF-36 PCS score, health assessment questionnaire-disability index (HAQ-DI) score, Psoriatic Arthritis Quality of Life (PsAQoL) score, and Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue total score were observed in the SEC 150 mg dose group. Patients originally randomized to placebo who escaped at either week 16 or at week 24 were subsequently re-randomized to SEC treatment (SEC 150 mg or SEC 75 mg every four weeks) and experienced improvements in ACR20/50/70 response rates, as well as in other outcomes following SEC treatment; these improvements were maintained through to week 52 of the study.

Similar to FUTURE 1, in FUTURE 2, the responses in ACR20, ACR50, ACR70, and treatment effect on all other secondary efficacy variables observed at week 16 in the SEC 150 mg dose group were sustained through week 52 (Table 35). ACR20 response rates observed for the original SEC 150 mg group (60%) and the original SEC 300 mg group (57%) at week 16 were maintained to week 52 (64%) in both SEC 150 mg and SEC 300 mg groups. For missing data and patients who escaped, a non-responder imputation was used in the analysis of ACR response criteria at week 52. Similarly, improvements in ACR50, ACR70, DAS 28, PASI 75, and PASI 90 were maintained to week 52. Improvements in the patient-reported outcomes SF-36 MCS score, SF-36 PCS score, HAQ-DI score, PsAQoL score, and FACIT–Fatigue total score observed at to week 16 or 24 were maintained until week 52 in both SEC 150 mg and SEC 300 mg groups. Patients originally randomized to placebo who escaped either at week 16 or at week 24 were subsequently re-randomized to SEC treatment (SEC 150 mg or SEC 300 mg every four weeks), experienced higher response rates in ACR20/50/70 as well as in other outcomes following SEC treatment; these improvements were maintained through to week 52 of the study.

TABLE 34: EFFICACY OF SECUKINUMAB IN THE FUTURE 1 TRIAL UP TO WEEK 104

	FUTURE 1		
	[redacted]	[redacted]	[redacted]
ACR20 response at week 52[a]	[redacted]	[redacted]	[redacted]
ACR20 response at week 52 in TNF alpha inhibitor–inadequate responder [a]	[redacted]	[redacted]	[redacted]
ACR20 response at week 52 in TNF alpha inhibitor–naive patients [a]	[redacted]	[redacted]	[redacted]
ACR20 response at week 104[b]	[redacted]	[redacted]	[redacted]
ACR20 response at week 104 in TNF alpha inhibitor–inadequate responder [b]	[redacted]	[redacted]	[redacted]
ACR20 response at week 104 in TNF alpha inhibitor–naive patients [a]	[redacted]	[redacted]	[redacted]
ACR50 response at week 52[a]	[redacted]	[redacted]	[redacted]
ACR50 response at week 104[b]	[redacted]	[redacted]	[redacted]
ACR70 response at week 52[a]	[redacted]	[redacted]	[redacted]
ACR70 response at week 104[b]	[redacted]	[redacted]	[redacted]
PASI 75 response at week 52[a]	[redacted]	[redacted]	[redacted]
PASI 75 response at week 104[b]	[redacted]	[redacted]	[redacted]
PASI 90 response at week 52[a]	[redacted]	[redacted]	[redacted]
PASI 90 response at week 104[b]	[redacted]	[redacted]	[redacted]
DAS 28-CRP change from baseline using MMRM at week 52[c]			
n	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]
DAS 28-CRP change from baseline at week 104[b]			
n	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
SF-36 MCS score change from baseline using MMRM at week 52[c]			
n	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]
SF-36 MCS score change from baseline at week 104[b]			
n	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
SF-36 PCS score change from baseline using MMRM at week 52[c]			
n	[redacted]	[redacted]	[redacted]

	FUTURE 1		
	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]
SF-36 PCS score change from baseline at week 104[b]			
n	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
MCS responders (improvement of ≥ 2.5 points) at week 52[b]	[redacted]	[redacted]	[redacted]
MCS responders (improvement of ≥ 2.5 points) at week 104[b]	[redacted]	[redacted]	[redacted]
PCS responders (improvement of ≥ 2.5 points) at week 52[b]	[redacted]	[redacted]	[redacted]
PCS responders (improvement of ≥ 2.5 points) at week 104[b]	[redacted]	[redacted]	[redacted]
HAQ-DI score change from baseline using MMRM at week 52[c]			
n	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]
HAQ-DI score change from baseline at week 104[b]			
n	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
HAQ-DI response (MCID = 0.3) at week 52[b]	[redacted]	[redacted]	[redacted]
HAQ-DI response (MCID = 0.3) at week 104[b]	[redacted]	[redacted]	[redacted]
PsAQoL score change from baseline at week 52[b]			
n	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
PsAQoL score change from baseline at week 104[b]			
n	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
FACIT–Fatigue total score change from baseline at week 52[b]			
n	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]

	FUTURE 1		
	[redacted]	[redacted]	[redacted]
FACIT–Fatigue total score change from baseline at week 104[b]			
n	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]

ACR = American College of Rheumatology; DAS 28-CRP = Disease Activity Score 28–C-reactive protein; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = health assessment questionnaire-disability index; LS = least squares; MCS = mental component summary; MMRM = mixed model-effect repeated measures; PASI = Psoriasis Area and Severity Index; PCS = physical component summary; PsAQoL = Psoriatic Arthritis Quality of Life; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; TNF = tumour necrosis factor.
[a] Using non-responder imputation.
[b] Using observed data.
[c] LS mean, 95% CI, and *P* value are from an MMRM with treatment regimen, analysis visit, and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure.
Source: Clinical study reports.[6,99]

TABLE 35: EFFICACY OF SECUKINUMAB IN THE FUTURE 2 TRIAL UP TO WEEK 52

	FUTURE 2					
	SEC 300 mg	SEC 150 mg	[redacted]	[redacted]	[redacted]	[redacted]
ACR20 response at week 52[a]	64/100 (64.0)	64/100 (64.0)	[redacted]	[redacted]	[redacted]	[redacted]
ACR20 response at week 52 in TNF alpha inhibitor–inadequate responder [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR20 response at week 52 in TNF alpha inhibitor–naive patients [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR50 response at week 52[a]	44/100 (44.0)	39/100 (39.0)	[redacted]	[redacted]	[redacted]	[redacted]
ACR70 response at week 52[a]	24/100 (24.0)	20/100 (20.0)	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75 response at week 52[a]	30/41 (73.2)	33/58 (56.9)	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90 response at week 52[a]	23/41 (56.1)	25/58 (43.1)	[redacted]	[redacted]	[redacted]	[redacted]
DAS 28-CRP change from baseline using MMRM at week 52[b]						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	4.8 (0.92)	4.8 (1.04)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	–1.78 (0.118)	–1.69 (0.118)	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 MCS score change from baseline using MMRM at week 52[b]						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	FUTURE 2					
	SEC 300 mg	SEC 150 mg				
Baseline, mean (SD)	43.5 (12.2)	40.3 (11.6)				
LS mean change (SE)	4.24 (0.879)	6.24 (0.900)				
SF-36 PCS score change from baseline using MMRM at week 52[b]						
n						
Baseline, mean (SD)	37.1 (7.9)	37.3 (7.6)				
LS mean change (SE)	7.70 (0.783)	6.65 (0.791)				
MCS responders (improvement of ≥ 2.5 points) at week 52[c]						
PCS responders (improvement of ≥ 2.5 points) at week 52[c]						
HAQ-DI score change from baseline using MMRM at week 52[b]						
n						
Baseline, mean (SD)	1.28 (0.59)	1.16 (0.59)				
LS mean change (SE)	–0.56 (0.052)	–0.47 (0.052)				
HAQ-DI response (MCID = 0.3) at week 52[a]						
PsAQoL score change from baseline at week 52[c]						
n						
Baseline, mean (SD)						
Mean change (SD)						
FACIT–Fatigue total score change from baseline at week 52						
n						
Baseline, mean (SD)						
Mean change (SD)						

ACR = American College of Rheumatology; DAS 28-CRP = Disease Activity Score 28–C-reactive protein (CRP); FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = health assessment questionnaire-disability index; LS = least squares; MCS = mental component summary; MMRM = mixed-effect model repeated measures; PASI = Psoriasis Area and Severity Index; PCS = physical component summary; PsAQoL = Psoriatic Arthritis Quality of Life; SD = standard deviation; SE = standard error; SEC = secukinumab; SF-36 = Short Form (36) Health Survey; TNF = tumour necrosis factor.

[a] Using non-responder imputation.

[b] LS mean, 95% CI, and *P* value are from an MMRM with treatment regimen, analysis visit and randomization stratum (TNF alpha inhibitor–naive or –inadequate responder) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure.

[c] Using observed data.

Source: Clinical study reports.[7,100]

Safety

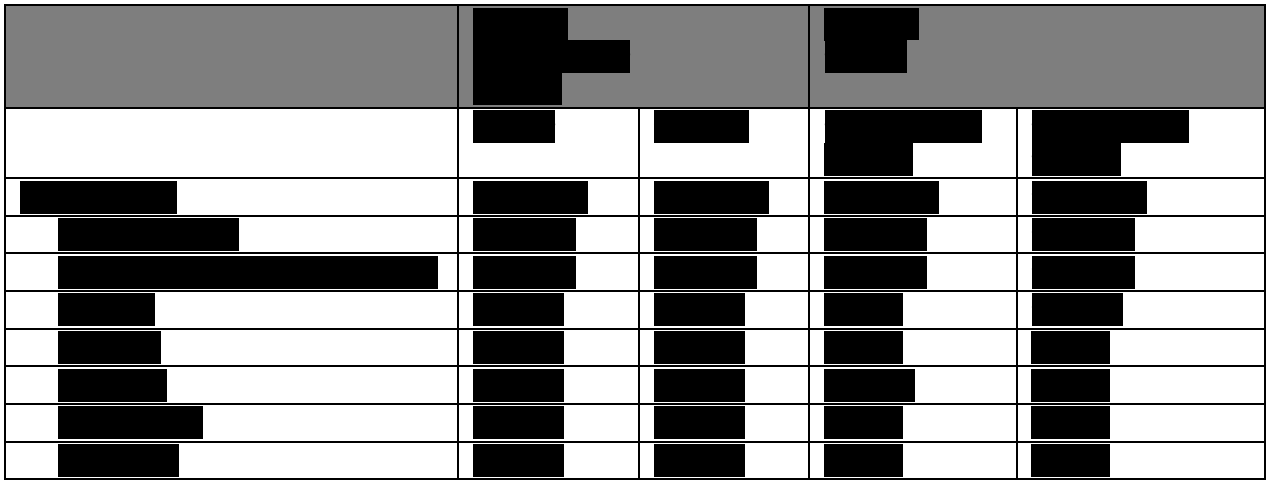
In FUTURE 1, safety data up to week 104 were reported. Due to the study design, less than one-third of patients remained on placebo past week 16 (63/202, 31%), and no patients remained on placebo after week 24. Thus, safety data were available for patients in the SEC groups only thereafter.

In all SEC 150 mg groups (including patients randomized at baseline to SEC 150 mg and placebo patients re-randomized to 150 mg SEC either at week 16 or week 24; N = 295), [redacted] of patients reported treatment-emergent AEs (TEAEs) at week 52. During the entire treatment period (week 104 for study completers, and up to 84 days after the last dose for those patients who discontinued early or who completed but did not enter the extension study), the total incidence of TEAEs was [redacted] in all SEC 150 mg groups, and the majority of AEs were mild or moderate in severity. Upper respiratory tract infection, nasopharyngitis, headache, back pain, and diarrhea were the most common AEs. The safety profile of SEC 150 mg at week 104 was similar to that observed at week 52. Two deaths in the SEC 75 mg group were reported: one occurred by week 52 and one occurred by week 104. No additional deaths were reported. In all SEC 150 mg groups, 10 patients (3.4%) discontinued the study treatment owing to AEs. At week 104, the rate of serious infections was 3.7% in all SEC 150 mg groups.

Similar findings were reported in FUTURE 2. Due to the study design, approximately one-third of patients remained on placebo past week 16 (33/98, 33.6%), and no patients remained on placebo after week 24. Thus, safety data were available for patients in the SEC groups only thereafter.

In all SEC 150 mg groups (including patients randomized at baseline to SEC 150 mg and placebo patients re-randomized to 150 mg SEC; N = 143), [redacted] of patients reported TEAEs at week 52. In all SEC 300 mg groups (including patients randomized at baseline to SEC 300 mg and placebo patients re-randomized to 300 mg SEC; N = 145), [redacted] of patients reported TEAEs at week 52. Upper respiratory tract infection, nasopharyngitis, headache, psoriatic arthropathy, and diarrhea were the most common AEs in the SEC 150 mg group; upper respiratory tract infection, nasopharyngitis, headache, sinusitis, pharyngitis, and diarrhea were the most common AEs in the SEC 300 mg group. No deaths were reported in any treatment group up until week 52. In all SEC 150 mg groups, four patients (2.8%) discontinued the study treatment because of AEs, whereas in all SEC 300 mg groups, three patients (2.1%) discontinued the study treatment because of AEs. The rate of serious infections was 1.4% in all SEC 150 mg groups and 2.8% in all SEC 300 mg groups.

TABLE 36: MOST FREQUENT TREATMENT-EMERGENT ADVERSE EVENTS (≥ 5% IN THE TREATMENT GROUPS)



NR = not reported; SAE = serious adverse event; SEC = secukinumab; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical study reports.[6,99,100]

Limitations

FUTURE 1 and FUTURE 2 were randomized, double-blinded (until week 24 in both trials; dose-blind until week 104 in the FUTURE 1 trial and dose-blind until week 52 in the FUTURE 2 trial). Patients knew that they were on active treatment after week 24. Since all patients were receiving SEC after week 24, this would bias the results of patient-reported outcomes such as HRQoL, symptom and disability measures, as well as AEs. The other limitation for the long-term findings at (week 52 and week 104) is the lack of placebo control. It is particularly problematic for the interpretation of patient-reported outcomes and subjective outcomes, as it is uncertain what the gain in HRQoL would be, above and beyond the effect of placebo. Results of patient-reported outcomes could be biased, because in both trials at week 52 [redacted] was used; however, the [redacted] assumption might not have been met because, generally, patients who drop out of trials are those who have poorer outcomes (lack of efficacy, AEs). Because of this, those who remain in the study may have better HRQoL, possibly leading to bias and more favourable results. In addition, no sensitivity analysis with an alternative imputation strategy, such as last observation carried forward (LOCF), was undertaken in order to compare results. In the responder analyses for PCS of the SF-36, an MCID of 2.5 was used, whereas an MCID of 3.74 was estimated for patients with PsA. Hence, it is not clear whether these patients should be considered responders. In FUTURE 1, the patient-reported outcomes data for more than 14% of patients were missing at week 52, and approximately 25% of data were missing at week 104. Also, in the FUTURE 1 trial results for week 104, observed data were used, which also might bias the results. Finally, the long-term safety outcomes were based on observed data.

Summary

The improvements in clinical response rates and patient-reported outcomes, which were observed over 16 or 24 weeks of FUTURE 1 in the SEC 150 mg regimen and in FUTURE 2 in the SEC 150 mg regimen and the SEC 300 mg regimen, were maintained throughout the dose-blind trial period to week 104 in FUTURE 1 and week 52 in FUTURE 2. The safety profile of SEC in PsA patients over 104 weeks was consistent with that observed at 16 weeks, with no new safety signals reported.

APPENDIX 7: SUMMARY OF INDIRECT COMPARISONS

Introduction

Background

The included clinical trials in this review did not provide direct evidence about the comparative efficacy and safety of secukinumab relative to disease-modifying antirheumatic drugs (DMARDS), small-molecule inhibitors of phosphodiesterase 4 (e.g., apremilast), or biological-response modifiers (biologics). The objective of this section is to summarize and critically appraise published and unpublished indirect evidence available for assessment of comparative efficacy and harms of secukinumab versus DMARDS, apremilast, and biologics. This summary will inform the pharmacoeconomic evaluation.

Methods

One indirect comparison (IDC) submitted by the manufacturer was reviewed in this section.[50] An information specialist conducted an independent literature search for published IDCs that compared secukinumab with other available drugs (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ustekinumab, and apremilast) when used for the treatment of PsA. We were able to identify two additional published articles containing indirect evidence.[101,102]

Description of IDCs Identified

Table 37 presents the population, interventions, comparisons, outcomes, and study design (PICOS) criteria for each IDC identified.

Review and Appraisal of Indirect Comparisons

Review of the Manufacturer-Submitted Indirect Comparison

Objectives and Rationale for Indirect Comparison Submitted by the Manufacturer

The objective of the IDC was to establish the short-term comparative efficacy of secukinumab relative to etanercept, infliximab, adalimumab, golimumab, ustekinumab, certolizumab, and apremilast for the treatment of active psoriatic arthritis (PsA) among adult patients for whom the response to previous DMARD therapy has been inadequate, based on currently available randomized controlled trial (RCT) evidence by means of a network meta-analysis (NMA). Specifically, the interest in this IDC was to identify how secukinumab compares to these other interventions with respect to American College of Rheumatology (ACR) scores and the Psoriasis Area and Severity Index (PASI) for the treatment of PsA.

TABLE 37: PICOS CRITERIA FOR STUDY INCLUSION

	Manufacturer-Submitted IDC	Ungprasert et al.[101]	Ungprasert et al.[102]
Population	Adults (aged ≥ 18 years) with active psoriatic arthritis for whom the response to previous DMARD therapy has been inadequate	Patients with active PsA who either failed to respond adequately to or could not tolerate TNF inhibitors	Patients with active PsA who either failed to respond adequately to DMARDs/NSAIDs or could not tolerate DMARDs/NSAIDs
Interventions	Either as monotherapy or in combination with MTX: SEC (150 mg/300 mg), etanercept (25 mg /50 mg), ustekinumab (45 mg /90 mg), adalimumab (40 mg), infliximab (5 mg/kg), golimumab (50 mg /100 mg), certolizumab (400 mg loading,	Non-TNF inhibitor biologic drugs	Biologic drugs

	Manufacturer-Submitted IDC	Ungprasert et al.[101]	Ungprasert et al.[102]
	then 200 mg /400 mg), or apremilast (20 mg /30 mg /40 mg)		
Comparisons	Placebo or any of the above-mentioned interventions	Placebo	
Outcomes	ACR20, ACR50, ACR70, PASI 75, PASI 90, PASI 100	ACR20	
Study Design	RCTs	RCTs	
Other	All languages Trials reporting at 12, 14, or 16 weeks	Duration of studies was greater than or equal to 12 weeks	

ACR = American College of Rheumatology; DMARD = disease-modifying antirheumatic drugs; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; RCT = randomized controlled trial; SEC = secukinumab.

Methods for Indirect Comparison Submitted by the Manufacturer

Study Eligibility and Selection Process

A systematic literature review was conducted in order to identify and select published RCTs evaluating the efficacy of biologics for the treatment of PsA up to September 12, 2014. Specific treatments included in this review were secukinumab, etanercept, infliximab, adalimumab, golimumab, ustekinumab, certolizumab, and apremilast. Inclusion criteria required that the RCTs enrol adult patients for whom the response to previous DMARD therapy had been inadequate. NMAs using the Bayesian framework were conducted for the efficacy outcomes ACR, psoriatic arthritis response criteria (PsARC), and PASI.

Study/Population Characteristics

The systematic literature review described previously, including data extraction, was conducted by a third party. The following baseline study design information was extracted: study design, study inclusion criteria, study exclusion criteria, study time period, active-treatment duration, follow-up period during randomized phase, outcomes, and sample size at baseline and follow-up by intervention. The following information was extracted regarding interventions: treatment dose, frequency of administration, duration, and concomitant/background therapies. Regarding baseline patient characteristics, the following variables were extracted and used to assess comparability of studies: age, gender, disease duration, PASI score, prior methotrexate use, prior biologic use, tender joint count, and swollen joint count. Information for the following efficacy measures was extracted for the reported populations or subgroups of interest: PsARC, ACR20, ACR50, ACR70, PASI50, PASI 75, PASI 90, and PASI 100. However, none of the patient characteristics extracted from the included trials were presented in the report. Overall, a total of 20 RCTs involving 6,021 adults with active PsA were identified.

Comparators

The identified trials spanned 56 treatment groups. Most treatments were compared with placebo and with other dosages of the same treatment. Two trials compared adalimumab with placebo, four studies compared apremilast with placebo, one trial compared etanercept with secukinumab, another trial compared ustekinumab with secukinumab, three other trials compared secukinumab with placebo, one trial compared golimumab with placebo, two trials compared infliximab with placebo, three trials compared etanercept with placebo, two trials compared ustekinumab with placebo, and one trial compared certolizumab with placebo. The evidence base was also restricted to two subpopulations: biologics-naive and biologics-experienced patients. The evidence base for biologics-naive patients was restricted to 12 trials comprising 3,339 patients. The evidence base for biologics-experienced patients was very limited, with only the ACR outcome reported in multiple trials (four trials and 480 patients). A

summary of the patient characteristics in the included studies was not provided in the IDC report provided by the manufacturer.

Outcomes

The reported outcomes included ACR and PASI, but not all studies included both of these measures. Table 38 provides a summary of the evaluated outcomes and the time points of outcome assessment. When multiple time points were available, 12-week results were favoured over 16-week results, and both of these were favoured over 14-week results. Sensitivity analyses restricting to specific time points were also conducted. Row data for the included outcomes were provided in the submissions. The IDC did not include any safety or harms outcomes, nor did it include health-related quality of life (HRQoL) data.

TABLE 38: STUDY CHARACTERISTICS

Direct Comparisons	Studies	Intervention and Comparators	Outcomes	Outcome Assessment
Secukinumab vs. placebo	FUTURE 1	• Secukinumab 150 mg (N = 202) • Placebo (N = 202)	• ACR (20, 50, 70) • PASI (50, 75, 90)	12 and 16 weeks
	FUTURE 2	• Secukinumab 150 mg (N = 100) • Secukinumab 300 (N = 100) • Placebo (N = 98)	• ACR (20, 50) • PASI 50	12 and 16 weeks
	ERASURE (subanalysis)	• Secukinumab 150 mg (N = 46) • Secukinumab 300 (N = 57) • Placebo (N = 68)	• PASI (75, 90)	12 weeks
Secukinumab or etanercept vs. placebo	FIXTURE (subanalysis)	• Secukinumab 150 mg (N = 49) • Secukinumab 300 (N = 50) • Etanercept 50 mg (N = 44) • Placebo (N = 47)	• PASI (75, 90)	12 weeks
Secukinumab vs. ustekinumab	CLEAR	• Secukinumab 300 mg (N = 69) • Ustekinumab 45 mg to 90 mg (N = 54)	• PASI 90	16 weeks
Apremilast vs. placebo	PALACE-1	• Apremilast 20 mg (N = 168) • Apremilast 30 mg (N = 168) • Placebo (N = 168)	• ACR (20, 50, 70) • PASI (50, 75)	16 weeks
	PALACE-2	• Apremilast 20 mg (N = 162) • Apremilast 30 mg (N = 163) • Placebo (N = 159)		
	PALACE-3	• Apremilast 20 mg (N = 169) • Apremilast 30 mg (N = 167) • Placebo (N = 169)		
	Schett et al. (2012)	• Apremilast 20 mg (N = 69) • Apremilast 40 mg (N = 67) • Placebo (N = 68)	• ACR (20, 50, 70)	12 weeks
Adalimumab vs. placebo	ADEPT	• Adalimumab 40 mg (N = 151) • Placebo (N = 162)	• ACR (20, 50, 70) • PASI (50, 75, 90)	12 and 16[a] weeks
	Genovese et al. 2007	• Adalimumab 40 mg (N = 51) • Placebo (N = 49)	• ACR (20, 50, 70)	12 weeks
	SPIRIT P1	• Adalimumab 40 mg (N = 101) • Placebo (N = 106)	• ACR (20, 50, 70) • PASI (75, 90)	12 weeks
Certolizumab vs. placebo	RAPID-PsA	• Certolizumab 200 mg (N = 138) • Certolizumab 400 mg (N = 135)	• ACR (20, 50, 70) • PASI (50, 75, 90)	12 and 16[b] weeks

Direct Comparisons	Studies	Intervention and Comparators	Outcomes	Outcome Assessment
		• Placebo (N = 136)		
Etanercept vs. placebo	Mease et al. 2000	• Etanercept 25 mg (N = 30) • Placebo (N = 30)	• ACR (20, 50, 70) • PASI (50, 75)	12 weeks
	Mease et al. 2004	• Etanercept 25 mg (N = 99) • Placebo (N = 97)	• ACR (20, 50, 70)	12 weeks
	PRESTA	• Etanercept 50 mg once weekly • Etanercept 50 mg twice weekly	• PASI 75)	12 weeks
Golimumab vs. placebo	GO-REVEAL	• Golimumab 50 mg (N = 146) • Golimumab 100 mg (N = 146) • Placebo (N = 113)	• ACR (20, 50, 70) • PASI (50, 75, 90)	12 and 16 weeks
Infliximab vs. placebo	IMPACT	• Infliximab 5 mg/kg (N = 52) • Placebo (N = 52)	• ACR (20, 50, 70) • PASI (50, 75, 90)	12[b] and 16 weeks
	IMPACT 2	• Infliximab 5 mg/kg (N = 100) • Placebo (N = 100)		12[b], 14[c] and 16[b] weeks
Ustekinumab vs. placebo	PSUMMT 1	• Ustekinumab 45 mg (N = 205) • Ustekinumab 90 mg (N = 204) • Placebo (N = 206)	• ACR20	12 and 16 weeks
	PSUMMT 2	• Ustekinumab 45 mg (N = 103) • Ustekinumab 90 mg (N = 105) • Placebo (N = 104)	• ACR20	12 and 16 weeks

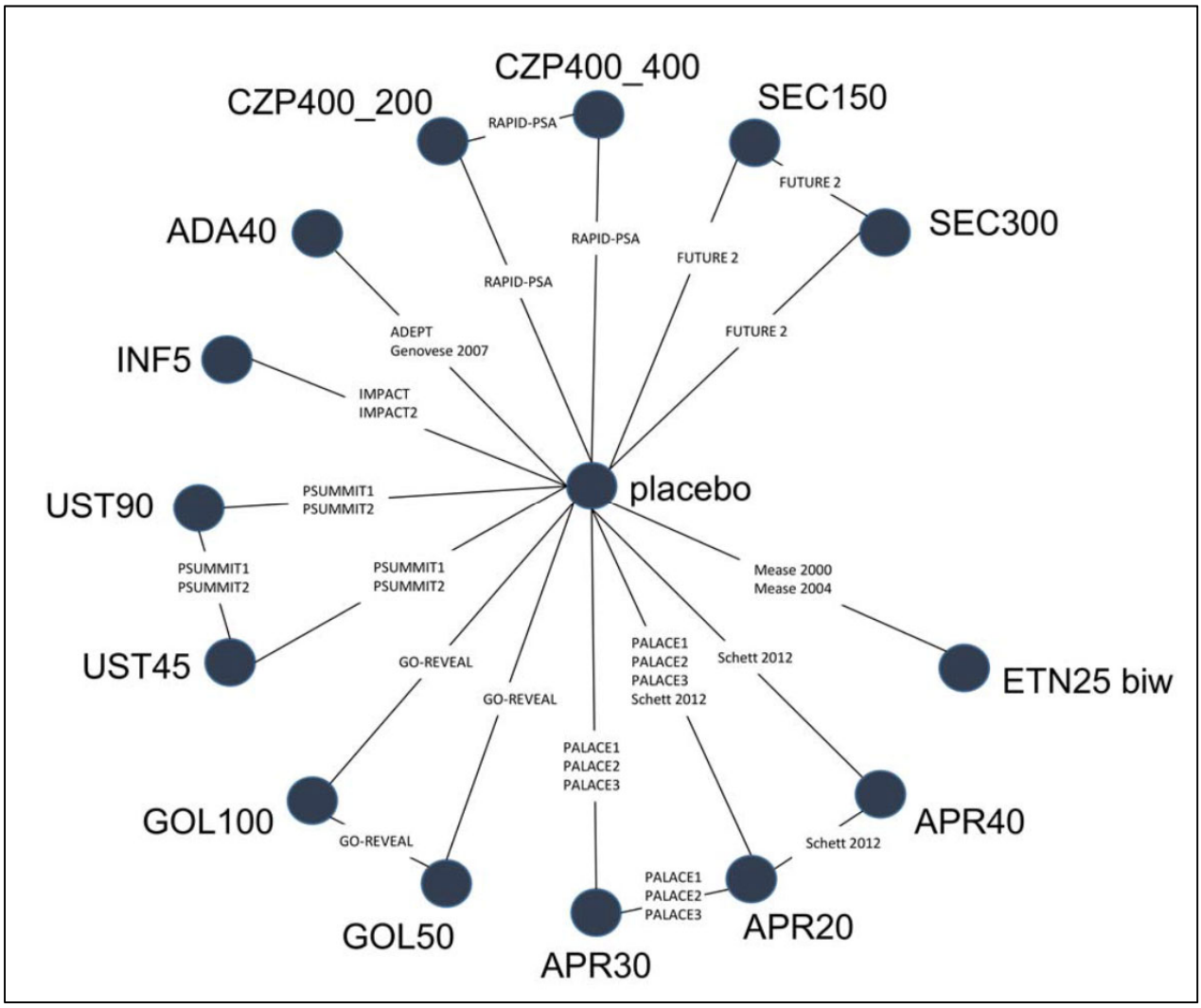
ACR = American College of Rheumatology; PASI = Psoriasis Area and Severity Index; vs. = versus.
Source: Manufacturer's submission.[50]
[a] Time point for ACR assessment only.
[b] Time point for ACR20 only.
[c] Time point for PASI assessment.

Quality Assessment of Included Studies

A quality assessment was conducted for each individual RCT using standards recommended by the UK National Institute for Health and Care Excellence (NICE). Quality assessment of RCTs included randomization, concealment of treatment allocation, groups' similarity at the outset of the study in terms of prognostic factors, blinding, imbalances in dropouts between groups, evidence to suggest that the authors measured more outcomes than they reported, inclusion of an intention-to-treat analysis, and the appropriateness of methods used to account for missing data.

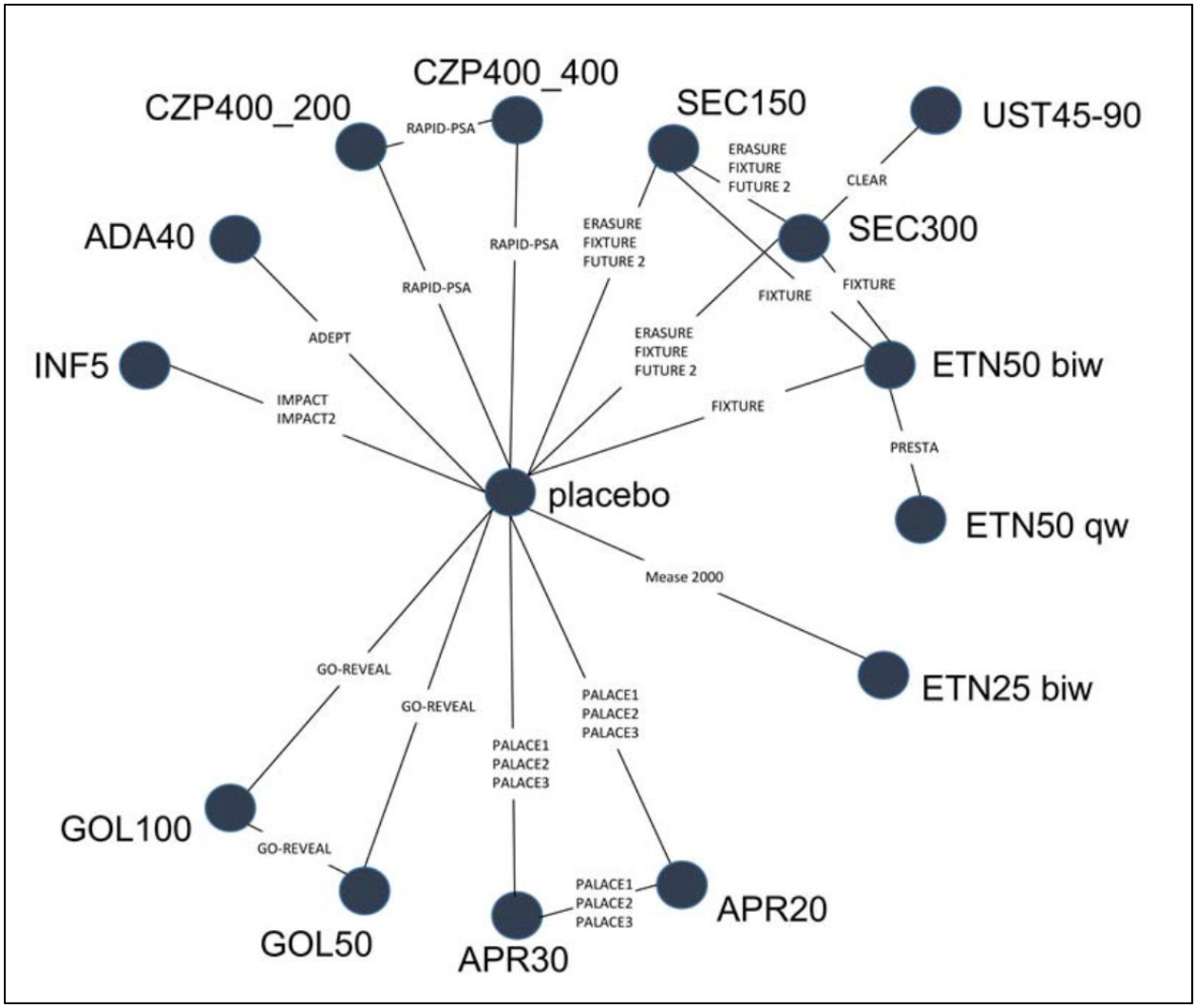
Evidence Network

FIGURE 4: EVIDENCE NETWORK FOR AMERICAN COLLEGE OF RHEUMATOLOGY SCORE



ADA = adalimumab; APR = apremilast; biw = twice weekly; CZP = certolizumab pegol; ETN = etanercept; INF = infliximab; GOL = golimumab; SEC = secukinumab; UST = ustekinumab.
Source: Manufacturer's submission.[50]

FIGURE 5: EVIDENCE NETWORK FOR PSORIASIS AREA AND SEVERITY INDEX



ADA = adalimumab; APR = apremilast; biw = twice weekly; CZP = certolizumab pegol; ETN = etanercept; INF = infliximab; GOL = golimumab; SEC = secukinumab; UST = ustekinumab.
Source: Manufacturer's submission.[50]

Indirect Comparison Methods

[redacted]

[redacted]

Results

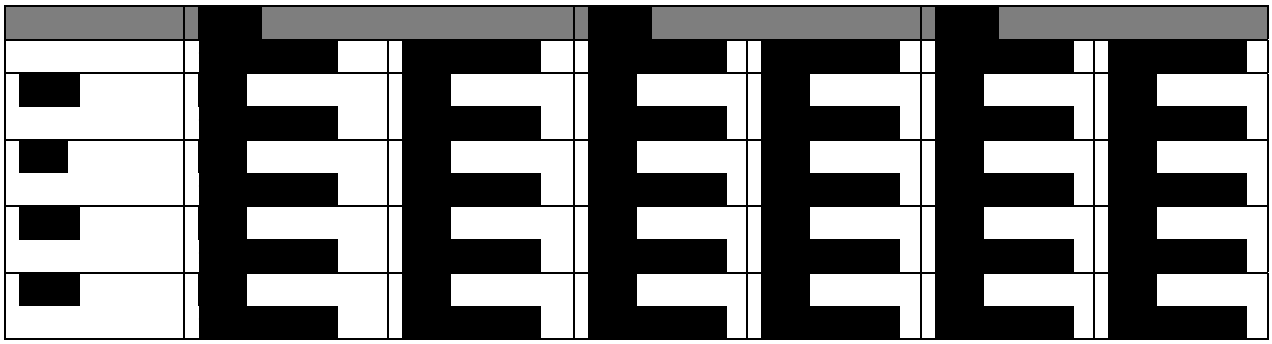
American College of Rheumatology

Fifteen trials informed the network of ACR response. For the ACR result at all time points, the random-effects model was selected as the best-fitting model.

For ACR20, all treatments demonstrated a higher likelihood of response than placebo (Table 39). There were no statistically significant differences in response when comparing secukinumab 150 mg and secukinumab 300 mg with all other treatments. The same patterns held for both ACR50 and ACR70. The probability of ACR20 response in the placebo group was estimated to be [redacted] and that for ACR50 and ACR70 was estimated to be [redacted] and [redacted], respectively.

TABLE 39: INDIRECT DRUG COMPARISON RESULTS FOR AMERICAN COLLEGE OF RHEUMATOLOGY SCORE: ALL-POPULATION ANALYSIS

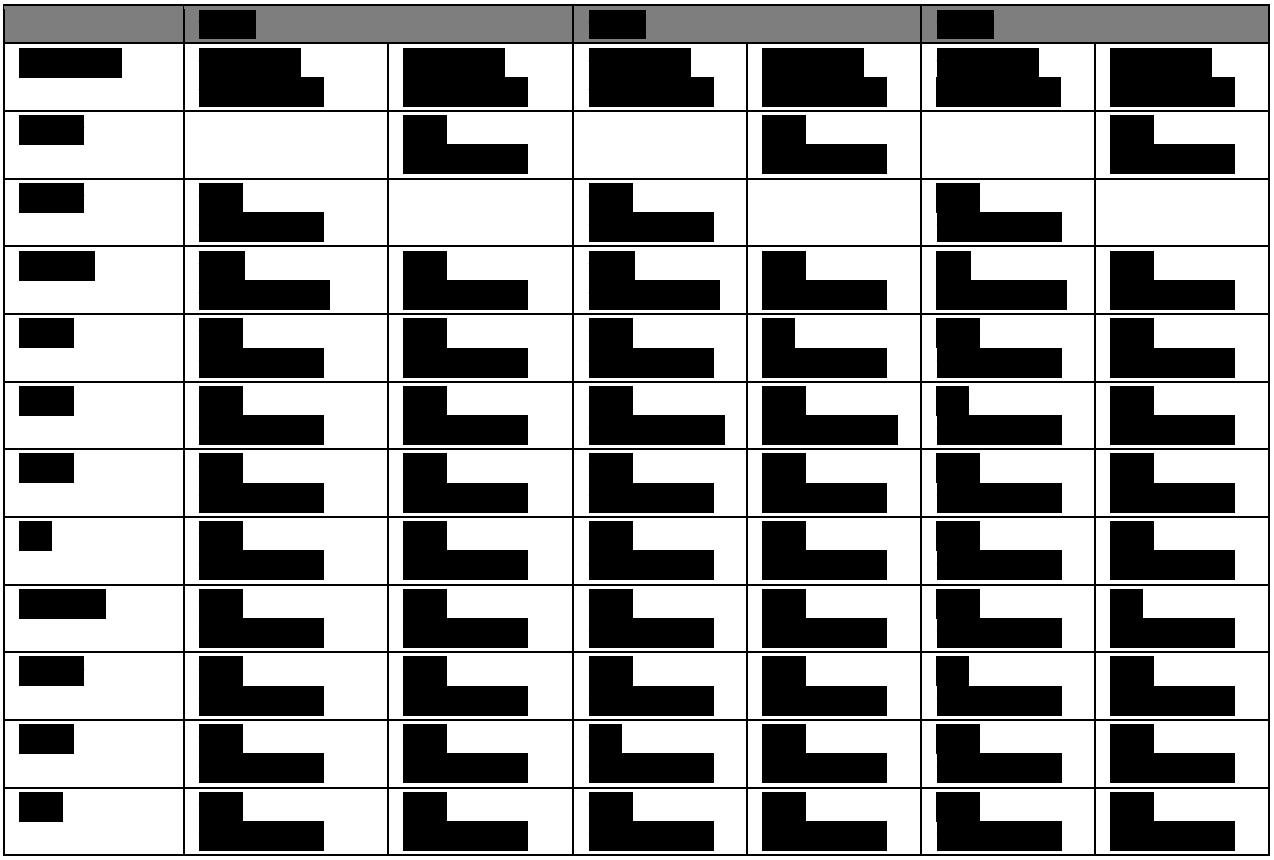
[redacted]



ACR = American College of Rheumatology score; ADA = adalimumab; APR = apremilast; BIW = twice weekly; CZP = certolizumab pegol; ETN = etanercept; INF = infliximab; GOL = golimumab; SEC = secukinumab; UST = ustekinumab.
Source: Manufacturer's submission.[50]

In the subgroup analysis of the biologics-naive population, 10 trials reported on ACR response. A random-effects model with an informative prior was used. In these analyses, the networks were sparser, and thus the credible intervals tended to be larger. Similar to the full analyses, all treatments in this network performed better than placebo for the outcomes ACR20, ACR50, and ACR70, with the exception of secukinumab 300 mg, apremilast 20 mg, apremilast 30 mg, certolizumab pegol, ustekinumab 45, and ustekinumab 90. Comparisons of secukinumab with other treatments showed no statistically significant differences (Table 40).

TABLE 40: INDIRECT DRUG COMPARISON RESULTS IN THE SUBGROUP ANALYSIS OF THE BIOLOGICS-NAIVE SUBPOPULATION FOR AMERICAN COLLEGE OF RHEUMATOLOGY SCORE: ALL-POPULATION ANALYSIS



ACR = American College of Rheumatology score; ADA = adalimumab; APR = apremilast; BIW = twice weekly; CZP = certolizumab pegol; ETN = etanercept; INF = infliximab; GOL = golimumab; SEC = secukinumab; UST = ustekinumab.
Source: Manufacturer's submission.[50]

TABLE 41: INDIRECT DRUG COMPARISON RESULTS IN THE SUBGROUP ANALYSIS OF THE BIOLOGICS-EXPERIENCED SUBPOPULATION FOR AMERICAN COLLEGE OF RHEUMATOLOGY SCORE: ALL-POPULATION ANALYSIS

ACR = American College of Rheumatology score; APR = apremilast; BIW = twice weekly; CZP = certolizumab pegol; SEC = secukinumab; UST = ustekinumab.
Source: Manufacturer's submission.[50]

[redacted]

Psoriasis Area and Severity Index

Fourteen trials informed the network of PASI response. There were five variations of the analysis performed for the principal analysis cohort: a fixed-effects model, a random-effects model, a random-effects model using informative priors, and fixed- and random-effects placebo-response adjusted models. These models all produced similar results and fit the data equally well. Given the similarities in model fit and the theoretical considerations, the random-effects model was chosen by the manufacturer to represent this outcome in the principal analysis.

For PASI 50, all treatments demonstrated statistically significantly improved responses versus placebo (Table 42). Compared with other treatments, both doses of secukinumab showed [redacted]. secukinumab 300 was [redacted]. The same results were observed for PASI 75 and 90 responses. [redacted]

TABLE 42: INDIRECT DRUG COMPARISON RESULTS FOR PSORIASIS AREA AND SEVERITY INDEX: ALL-POPULATION ANALYSIS

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

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

ADA = adalimumab; APR = apremilast; BIW = twice weekly; CZP = certolizumab pegol; ETN = etanercept; INF = infliximab; GOL = golimumab; PASI = Psoriasis Area Severity Index; SEC = secukinumab; UST = ustekinumab.
Source: Manufacturer's submission.[50]

[redacted] fixed-effects model was 44.44, and for the random-effects model with an informative prior the deviance information criterion(DIC) was 43.86. Results for the random-effects model with an informative prior were presented. Only treatments secukinumab 150 mg, secukinumab 300 mg, adalimumab 40 mg, golimumab 100 mg, golimumab 50 mg, and infliximab 5 mg were included in these analyses. [redacted] Comparisons between the treatments showed no statistically significant differences. Similar trends were seen at the PASI 75 and PASI 90 cutoffs, although the relative risks were larger and had wider credible intervals. The results from the naive population showed effect sizes that were very similar to those observed in the full analysis. There was a small reduction in the effect of both doses of secukinumab, while the other treatments showed effects that were roughly the same as those observed

in the full cohort analysis. This, along with widened credible intervals, results in the loss of the statistically significant difference when comparing secukinumab 300 mg with golimumab 50 mg.

Analyses with PASI for the treatment-experienced populations were not feasible.

[redacted]

Critical Appraisal

The literature search is dated, as it ended in September 12, 2014, more than one year 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 NMA.

[redacted]

Trials included in the evidence base employed different imputation strategies. The method by which discontinuations are handled by different trials represents an important potential source of heterogeneity. Trials used last observation carried forward (LOCF), non-responder imputation, or simply did not report on how these cases are addressed. Non-responder imputation is a technique in which dropouts are assumed to have failed treatment. By contrast, LOCF uses the last reported value before the patient drops out as the outcome measure. In cases such as this, the last observation reported may

be better than those that would have been observed had the patient continued in the trial. These differences in the method used to account for discontinuation cannot be controlled for analytically.

NMAs were conducted on results that were measured between 12 and 16 weeks after treatment initiation. PsA is a lifelong disease; hence, it is not clear how meaningful the comparisons are given the short duration of the studies, and the 12 to 16 weeks of placebo-controlled data or indirect evidence/comparison are insufficient.

Consistency was not evaluated in the submitted IDC; consistency testing is useful to validate the IDC results by comparing them with the available direct evidence. Direct comparative evidence was available for some of the treatments.

The IDC did not include any safety or harms outcomes, nor did it include HRQoL data.

Significant heterogeneity existed in the baseline patient characteristics across the included trials. Some had a mixed population, in that both TNF alpha inhibitor–naive patients and patients who had an inadequate response to previous TNF alpha inhibitors were enrolled, whereas others had TNF alpha inhibitor–naive patients only. Also, the definition of PsA differed between trials, there was considerable trial-design heterogeneity (e.g., end point assessments at 12 to 16 weeks or at 24 weeks), early escape criteria differed between trials, etc.; placebo responses also differed between trials based on the included patients; placebo withdrawal differed between trials owing to the escape design or other factors. In addition, the small network size and the differences among the trials made it challenging to establish reliable results.

Additional Evidence

Two articles that compared the efficacy of secukinumab relative to other treatments for the treatment of active PsA among adult patients were identified from the literature.[101,102] One article by Ungprasert et al.[102] conducted an IDC of the efficacy of biological drugs in patients with PsA with an inadequate response to traditional DMARDs or to NSAIDs. The second article by Ungprasert et al.[101] conducted an IDC of the efficacy of subsequent biological drugs in patients with PsA with an inadequate response to TNF inhibitors. In both of these articles, the Bucher method was used to conduct the IDCs. These IDCs were made through placebo group, which was the common comparator. If the *P* value for IDC for the efficacy of two biologic drugs was less than 0.05 or if the 95% CI did not contain one, then the two biologic drugs were considered significantly different. In Ungprasert et al.,[101] data analysis was performed using Review Manager software from the Cochrane Collaboration. If more than one RCT was available for a given biologic drug, then a random-effects, Mantel–Haenszel analysis was used to calculate the pooled odds ratio of achieving ACR20 response and 95% confidence interval (CI) across studies. Statistical heterogeneity of the ACR20 response rate was assessed using Cochran's Q test, which was complemented with the I^2 statistic. In Ungprasert et al.,[102] data analysis was performed using Review Manager software from the Cochrane Collaboration. If more than one RCT was available for a given biologic drug, then a random-effects, Mantel–Haenszel analysis was used to calculate the pooled risk ratio and 95% CI. Given the high likelihood of between-study variance, a random-effects model rather than a fixed-effects model was used. Statistical heterogeneity of the ACR20 response rate was assessed using Cochran's Q test, which was complemented with the I^2 statistic. Two investigators independently searched published studies indexed in MEDLINE, Cochrane Central, and Embase database. The Jadad scale was used to appraise the quality of the included RCTs.

Ungprasert et al.,[102] included 12 trials in the analysis: seven trials of older TNF inhibitors (etanercept, infliximab, adalimumab, and golimumab) (1,387 patients), two trials of ustekinumab (747 patients), one trial of apremilast (363 patients), one trial of certolizumab (409 patients), and another trial of secukinumab (258 patients). ACR20 was compared between these treatments. No significant differences were found in ACR20 between secukinumab 150 mg or 300 mg and all of the TNF inhibitors analyzed. A statistically significant difference in favour of secukinumab 150 mg was found when compared with apremilast 20 mg, apremilast 30 mg, ustekinumab 45 mg, and ustekinumab 90 mg for ACR20 response. Also, a statistically significant difference in favour of secukinumab 300 mg was found when compared with apremilast 20 mg, apremilast 30 mg, and ustekinumab 45 mg for ACR20 response.

Ungprasert et al.,[101] included five trials in the analysis: two trials of secukinumab (317 patients), one trial of ustekinumab (180 patients), one trial of apremilast (115 patients), and one trial of abatacept (63 patients). Ungprasert et al.[101] compared ACR20 between different treatments. No statistically significant difference was found when secukinumab 150 mg and secukinumab 300 mg were compared with apremilast 20 mg, apremilast 30 mg, ustekinumab 45 mg, ustekinumab 90 mg, abatacept 3 mg/kg, abatacept 10 mg/kg, and abatacept 30 mg/kg then 10 mg/kg.

Discussion

All of the trials that were identified in Ungprasert et al.[101] and Ungprasert et al.[102] were also included in the IDC submitted by the manufacturer, indicating that the literature search and study selection criteria in Ungprasert et al.[101] and Ungprasert et al.[102] and the manufacturer-submitted IDC were similar. The quality of Ungprasert et al.[101] and Ungprasert et al.[102] IDCs was good; however, the methods used in the indirect comparisons were based on the Bucher method. The Bucher method only compares two treatments against each other whenever there is a common comparator, using frequentist approach, while the NMA submitted by the manufacturer compared all treatments against each other using Bayesian NMA. This difference in methods used yielded slightly different results between the comparison submitted by the manufacturer and that done by Ungprasert et al.[102] The analysis conducted by Ungprasert et al.,[102] found that, for ACR20, secukinumab 150 mg was statistically significantly better than apremilast 20 mg, apremilast 30 mg, ustekinumab 45 mg, and ustekinumab 90 mg; as well, secukinumab 300 mg was statistically significantly better than apremilast 20 mg, apremilast 30 mg, and ustekinumab 45 mg. [redacted]. On the other hand, results from TNF treatment-experienced patients were similar between the IDC submitted by the manufacturer and that of Ungprasert et al.[101].

[redacted]

Conclusion

In the absence of adequate head-to-head trial data for secukinumab with other treatments, the manufacturer conducted an IDC analysis based on a systematic review of RCTs to compare the efficacy of secukinumab with adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ustekinumab, and apremilast. Safety outcomes and HRQoL data were not evaluated using the IDC methods; therefore, the comparative safety and HRQoL data of secukinumab with other treatments for PsA have yet to be fully evaluated. Although the patient populations and study designs were somewhat heterogeneous, with certain potential methodological limitations in the NMA, overall, secukinumab demonstrated treatment effect over placebo, and no statistically significant difference was found for efficacy when compared with other treatments in terms of ACR, in populations who were biologics-naive and who had inadequate response to previous biologics. In addition, for PASI, secukinumab 150 and secukinumab 300 were statistically significantly better than all other therapies with the exception of infliximab, adalimumab, golimumab 100 mg, and ustekinumab 45 mg and 90 mg. It is uncertain whether this treatment effect is sustainable in the longer term.

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