Common Drug Review
Clinical Review Report

August 2016

Drug	Secukinumab (Cosentyx)
Indication	For the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy.
Reimbursement request	[redacted]
Dosage form(s)	Sterile solution for injection in pre-filled syringe or Sensoready pen (150 mg/1 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

ACR	The American College of Rheumatology
AE	adverse event
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASQoL	ankylosing spondylitis quality of life
BASDAI	The Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BRM	biologic response modifier
CDEC	Canadian Drug Expert Committee
CI	confidence interval
CDR	CADTH Common Drug Review
CrI	credible interval
CRP	C-reactive protein
DB	double blind
DMARD	disease-modifying antirheumatic drugs
EQ-5D	EuroQol-5D
FACIT-Fatigue	The Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FAS	full analysis set
HRQoL	health-related quality of life
IV	intravenous
ITT	intention to treat
LS	least square
MCS	mental component summary
MRI	magnetic resonance imaging
mSASSS	modified Stoke Ankylosing Spondylitis Spinal Score
MTC	mixed treatment comparison
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PCS	physical component summary
PP	per-protocol
RASSS	Radiographic Ankylosing Spondylitis Spinal Score
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SEC	secukinumab
SF-36	Medical Outcomes Study Questionnaire Short Form 36
TNFi	tumour necrosis factor inhibitor
VAS	visual analogue scale
WDAE	withdrawal due to adverse event
WPAI-GH	Work Productivity and Activity Impairment-General Health

EXECUTIVE SUMMARY

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease primarily involving the spine and the sacroiliac joints. Patients suffer from back pain and progressive spinal stiffness, and may also suffer from non-arthritic manifestations such as uveitis, skin psoriasis, and inflammatory bowel disease. AS results in functional impairment, subsequent potential socioeconomic consequences, and disability — all of which negatively impact patients' health-related quality of life (HRQoL). Based on data collected from 1960 to 1993, the prevalence of AS worldwide ranged from 0.15% to 1.4% of the population. Canadian estimates suggest that AS affects approximately 150,000 to 300,000 Canadians, according to a report published in 2011.

Secukinumab (SEC) is a fully human IgG1k monoclonal antibody that selectively binds and neutralizes interleukin-17A (IL-17A), a naturally occurring cytokine involved in normal inflammatory and immune responses. Patients with AS have increased levels of IL-17A in the blood. SEC targets IL-17A and inhibits its interaction with the IL-17 receptor. SEC has been approved by Health Canada for the treatment of adult patients with active AS who have responded inadequately to conventional therapy.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of secukinumab (Cosentyx) at the Health Canada recommended dose for the treatment of adult patients with AS.

Included studies

MEASURE 1 and MEASURE 2 were phase 3, multicenter, randomized, double-blind, placebo-controlled trials that met the inclusion criteria for this systematic review. The study population included adult patients with moderate to severe AS (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥ 4 on a scale with scores ranging from 0 to 10; score for spinal pain of ≥ 4 cm on a 10 cm visual analogue scale) despite treatment with maximum doses of nonsteroidal anti-inflammatory drugs (NSAIDs). Both studies assessed the efficacy and safety of SEC 150 mg and 75 mg administered subcutaneously (SC) every four weeks compared with placebo SC injection every four weeks. SEC-treated patients in both studies received a loading dose of SEC, either through intravenous administration at weeks 0, 2 and 4 (MEASURE 1) or SC administration at weeks 0, 1, 2 and 3 (MEASURE 2). In MEASURE 1, patients in the placebo group who failed to achieve an Assessment of SpondyloArthritis International Society (ASAS) 20 response were re-randomized to either SEC 150 mg or SEC 75 mg at week 16. At week 24, all patients remaining in the placebo group, regardless of ASAS 20 response criteria, were re-randomized to receive either SEC 150 mg or SEC 75 mg. After re-randomization, patients were unblinded to active versus placebo treatment groups but remained dose-blinded until the end of treatment period (week 104). In MEASURE 2, all patients in the placebo group were re-randomized to SEC 150 mg or SEC 75 mg at week 16. The patients were dose-blinded until week 52; thereafter they received open-label treatment with SEC 150 mg or SEC 75 mg up to five years after the randomization. The primary outcome was the proportion of patients achieving ASAS 20 criteria at week 16. Other efficacy outcomes included health-related quality of life (HRQoL), disease activity and work productivity. Safety outcomes measured included adverse events (AEs), serious adverse events (SAEs) and withdrawal due to adverse events (WDAEs). A safety follow-up was performed for all patients, including those withdrawn from study treatment, 12 weeks after their last dose of study drug. Only data related to the Health Canada approved dose of 150 mg of SEC were presented in the this review.

The early escape design, while common in AS trials based on ethical considerations, potentially limits the interpretation and clinical relevance of trial data after week 16. After week 16, active versus placebo blinding was not maintained, and there was no control group to evaluate the relative treatment effect of SEC 150 mg compared withplacebo. Furthermore, a hierarchical testing procedure was used for selected efficacy outcomes (ASAS 20, ASAS 40, BASDAI, SF-36 physical component summary (PCS), and Ankylosing Spondylitis Quality of Life [ASQoL] at week 16). Thus, all other outcomes, as well as subgroup analyses, were not adjusted for multiplicity and, as such, the risk of making a type 1 error (erroneously finding a statistical difference) was not adequately controlled.

Efficacy

SEC 150 mg was superior to placebo in the proportion of patients achieving ASAS 20 response at week 16 in both studies (MEASURE 1 and MEASURE 2). At week 16, in MEASURE 1, statistically significantly higher ASAS 20 response rates were observed in the SEC 150 mg group (61%) compared with the placebo group (29%) (OR, 3.9; 95% CI, 2.3 to 6.7; $P < 0.0001$). In MEASURE 2, a higher proportion of patients treated with SEC 150 mg met the ASAS 20 response criteria compared with those treated with placebo at 61.1% versus 28.4%, respectively (OR, 4.4; 95% CI, 2.1 to 9.0; $P < 0.0001$). ASAS 40 response rates were also statistically significantly higher in the SEC 150 mg group compared with placebo at week 16 in both MEASURE 1 (41.6% versus 13.1%, respectively [OR, 4.9; 95% CI, 2.6 to 9.3; $P < 0.0001$]) and MEASURE 2 (36.1% versus 10.8%, respectively (OR, 5.1; 95% CI, 2.1 to 12.4; $P = 0.0008$)). Statistically significant improvements in HRQoL were also observed based on the SF-36 PCS and ASQoL changes from baseline to week 16 for patients in the SEC 150 mg group compared with the placebo group in both studies. In MEASURE 1 at week 16, the difference in the improvement in SF-36 PCS between SEC 150 mg and placebo was 4.6, favouring SEC 150 mg ($P < 0.0001$); in MEASURE 2, the difference in the improvement in SF-36 PCS score between SEC 150 mg and placebo was 4.1 ($P = 0.0002$). The difference in ASQoL improvement between the SEC 150 mg group and the placebo group was –2.5 ($P < 0.0001$) in MEASURE 1; in MEASURE 2, the difference in ASQoL was –2.6 ($P < 0.0001$). In MEASURE 1 at week 16, a statistically significant difference in improvement in total BASDAI score between SEC 150 mg and placebo was observed (–1.7, $P < 0.0001$); in MEASURE 2, the difference in total BASDAI score between SEC 150 mg group and placebo was statistically significant (–1.3, $P = 0.0002$). The between-group differences in HRQoL at week 16 were considered clinically important according to the corresponding minimum clinically important differences (MCIDs); changes in total BASDAI score between the SEC 150 mg group and placebo were not considered clinically meaningful. [redacted]

[redacted]

In the absence of head-to-head trial data comparing SEC 150 mg with other biologic response modifiers (BRMs), [redacted]

[redacted]

Harms

By week 16, in MEASURE 1, AEs were reported in 69.6% of patients in the SEC 150 mg group and 55.7% in the placebo group; in MEASURE 2, the number of AEs was similar between the SEC 150 mg group (65.3%) and the placebo group (63.5%). Nasopharyngitis was the most frequently reported AE. Risks of SAEs were low in both studies, ranging from 2.4% to 5.6% in the SEC 150 mg groups, and 4.1% in the placebo groups. Up to week 16 in MEASURE 1, higher rates of WDAEs were reported in the placebo group (4.9%) compared with the SEC 150 mg group (0.8%); in MEASURE 2, the proportion of patients discontinuing due to an AE was low and similar among the SEC and placebo groups (6.9% for SEC 150 mg and 5.4% for placebo). In MEASURE 1, there was one death reported up to week 16 in a placebo patient who suffered from depression and committed suicide, while no deaths were reported in MEASURE 2 during the study period.

Conclusions

Based on two double-blind randomized controlled trials in patients with moderate to severe AS (MEASURE 1 and MEASURE 2), treatment with SEC 150 mg every four weeks resulted in statistically significant improvements in clinical response (ASAS 20 and ASAS 40) at week 16 when compared with placebo. A statistically significant and clinically meaningful improvement in quality of life (SF-36 PCS, ASQoL), and a statistically significant improvement, but not clinically meaningful improvement in disease activity (BASDAI) was also found for patients receiving SEC 150 mg compared with placebo. Overall, the number of treatment-emergent adverse events was similar between SEC 150 mg and placebo in both studies. [redacted]

Results from a manufacturer-submitted mixed treatment comparison suggested that [redacted]

TABLE 1: SUMMARY OF RESULTS

	MEASURE 1		MEASURE 2	
	SEC 150 mg (N = 125)	**Placebo (N = 122)**	**SEC 150 mg (N = 72)**	**Placebo (N = 74)**
Efficacy (at week 16)				
% of patients meeting ASAS 20 criteria				
n (%)	76 (60.8)	35 (28.7)	44 (61.1)	21 (28.4)
OR (95% CI)	3.9 (2.3 to 6.7)		4.4 (2.1 to 9.0)	
P value	< 0.0001		< 0.0001	
% of patients meeting ASAS 40 criteria				
n (%)	52 (41.6)	16 (13.1)	26 (36.1)	8 (10.8)
OR (95% CI)	4.9 (2.6 to 9.3)		5.1 (2.1 to 12.4)	
P value	< 0.0001		0.0004	
Change in SF-36 PCS from baseline				
Baseline, mean (SD)	36.8 (6.8)	36.3 (6.4)	[redacted]	[redacted]
Change from baseline, mean (SE)	5.6 (0.6)	1.0 (0.6)	6.1 (0.8)	1.9 (0.8)
Between-group difference in LS mean (95% CI)	4.6 (3.0 to 6.2)		4.1 (2.0 to 6.3)	
P value	< 0.0001		0.0002	
Change in ASQoL score from baseline				
Baseline, mean (SD)	10.9 (4.7)	11.7 (4.2)	[redacted]	[redacted]
Change from baseline, mean (SE)	–3.6 (0.4)	–1.0 (0.4)	–4.0 (0.5)	–1.3 (0.5)
Between-group difference in LS mean (95% CI)	–2.5 (–3.7 to –1.4)		–2.6 (–4.1 to –1.2)	
P value	< 0.0001		0.0005	
Change in FACIT-Fatigue score from baseline				
Baseline, mean (SD)	25.6 (10.7)	24.5 (9.4)	[redacted]	[redacted]
Change from baseline, mean (SE)	6.8 (0.8)	2.5 (0.9)	[redacted]	[redacted]
Between-group difference in LS mean (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Change in EQ-5D (VAS) from baseline				
Baseline, mean (SD)	45.2 (19.9)	46.5 (20.5)	[redacted]	[redacted]
Change from baseline, mean (SE)	13.3 (1.9)	2.0 (2.0)	[redacted]	[redacted]
Between-group difference in LS mean (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Change in BASDAI total score from baseline				
Baseline, mean (SD)	6.4 (1.6)	6.5 (1.5)	6.6 (1.5)	6.8 (1.3)
Change from baseline, mean (SE)	–2.3 (0.2)	–0.6 (0.2)	–2.2 (0.2)	–0.9 (0.3)
Between-group difference in	–1.7 (–2.2 to –1.3)		–1.3 (–2.0 to –0.7)	

	MEASURE 1		MEASURE 2	
	SEC 150 mg (N = 125)	**Placebo (N = 122)**	**SEC 150 mg (N = 72)**	**Placebo (N = 74)**
LS mean (95% CI)				
P value	< 0.0001		0.0002	
Harms (at week 16)				
N	125	122	72	74
Deaths	0	1 (suicide)	0	0
AEs, n (%)	87 (69.6)	68 (55.7)	47 (65.3)	47 (63.5)
SAEs, n (%)	3 (2.4)	5 (4.1)	4 (5.6)	3 (4.1)
WDAEs, n (%)	1 (0.8)	6 (4.9)	6 (6.9)	4 (5.4)

AE = adverse event; ASAS = Assessment of SpondyloArthritis International Society; ASQoL = the Ankylosing Spondylitis Quality of Life scale; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = confidence interval; EQ-5D = EuroQoL-5D; FACIT-Fatigue = the Functional Assessment of Chronic Illness Therapy-Fatigue Scale; IR = inadequate responder; LS = least square; N/A = not applicable; OR = odds ratio; PCS = physical component summary; SAE = serious adverse event; SD = standard deviation; SE = standard error; SEC = secukinumab; SF-36 = Medical Outcomes Study Questionnaire Short Form 36; TNFi = tumour necrosis factor inhibitor; VAS = visual analogue scale; WDAE = withdrawal due to adverse event.

1. INTRODUCTION

1.1 Disease prevalence and incidence

Ankylosing spondylitis (AS) is a chronic inflammatory disease primarily involving the spine and the sacroiliac joints.[1,2] It usually begins in young adults with a peak age of onset between 20 to 30 years of age and is more common in men than in women. Patients suffer from back pain and progressive spinal stiffness, and may also suffer from non-arthritic manifestations such as uveitis, skin psoriasis, and inflammatory bowel disease. The AS symptoms and the rate of progression fluctuate with time and can vary substantially between patients. The disease results in functional impairment and subsequent potential socioeconomic consequences and disability; therefore, negatively affecting patients' health-related quality of life (HRQoL).[1,2] A diagnosis of AS can be made based on the clinical features, genetic testing, biological testing, and imaging examinations.[2] The modified New York classification criteria for AS have often been applied as a diagnostic instrument.[3,4] The prevalence of AS worldwide ranges from 0.15% to 1.4% of the population (data were collected from 1960 to 1993).[5] In a report published by the Arthritis Society in 2011, AS was estimated to affect approximately 150,000 to 300,000 Canadians (year of data collection was not specified), and a previous study showed that around 58% of Canadian patients have active disease, which is determined by a disease-specific test (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], a BASDAI score ≥ 4 indicates active disease).[6,7]

1.2 Standards of therapy

According to the practice guidelines developed by the American College of Rheumatology (ACR) in 2016, the goals of treatment for patients with AS are to reduce symptoms, maintain spinal flexibility and normal posture, reduce functional limitations, maintain work ability, and decrease disease complications.[8] Treatment decisions are made based on the degree of disease activity, functional disability, and HRQoL.

Several drug classes are employed in the pharmacologic therapy of AS. Nonsteroidal anti-inflammatory drugs (NSAIDs), including nonselective and selective cyclooxygenase-2 inhibitors, are the first choice of treatment for adult patients with active AS. The next line of treatment is the tumour necrosis factor inhibitors (TNFis), such as adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab, should NSAIDs fail or if there are contraindications to them (Table 2). Clinical evidence has shown that these drugs are associated with significant improvements in disease activity and function, and a higher proportion of patients meeting the Assessment of SpondyloArthritis International Society (ASAS) response criteria, as compared with placebo. After failure of the first TNFi, switching to a different TNFi is recommended for most patients.[1,8] However, the indiscriminate use of TNFi is discouraged because of cost concerns and a lack of long-term safety data. Other concerns related to the use of TNFi include rare sustained drug-free remissions and progressively increased dropout rates during treatment.[1] Disease-modifying antirheumatic drugs (DMARDs), for example, sulfasalazine, can be used in patients with AS and peripheral arthritis, when the patient has contraindications to TNFi or decline treatment with TNFi. In adults with active AS, systemic glucocorticoids are not recommended; however, locally administered parenteral glucocorticoids can be used in adults with AS with stable axial disease and active enthesitis or active peripheral arthritis.[8]

1.3 Drug

Secukinumab (SEC) is a fully human IgG1k monoclonal antibody that selectively binds and neutralizes interleukin-17A (IL-17A), a naturally occurring cytokine involved in normal inflammatory and immune responses. Patients with AS 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 treatment of adult patients with active AS who have responded inadequately to conventional therapy; moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy; and adult patients with active psoriatic arthritis when the response to previous DMARD therapy has been inadequate.[9,10] Tuberculosis (TB) 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.[10]

Indication under review
Treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy
Reimbursement criteria requested by sponsor
[redacted]

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

	Secukinumab	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab
Mechanism of Action	a fully human IgG1k monoclonal antibody that selectively binds and neutralizes the pro-inflammatory cytokine IL-17A	a recombinant human IgG1 monoclonal antibody that inhibits binding of TNF to TNF-alpha receptors; modulates biological responses that are induced or regulated by TNF.	a recombinant, humanized antibody Fab fragment inhibits binding of TNF to TNF- alpha receptors	a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p.75) TNF receptor linked to the Fc portion of human IgG1. Etanercept inhibits binding of TNF- alpha and TNF-beta to TNF receptors	a human IgG1 monoclonal antibody inhibits binding of TNF to TNF receptors	a chimeric IgG1 monoclonal antibody that inhibits binding of TNF to TNF receptors

	Secukinumab	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab
Indication[a]	Reduce the signs and symptoms of active AS. Other indications: PsA and Ps.	Reducing signs and symptoms in patients with active AS who have had an inadequate response to conventional therapy. Other indications: RA, polyarticular JIA, PsA, CD, UC, HS, Ps.	Reducing signs and symptoms in adult patients with active AS who have had an inadequate response to conventional therapy. Other indications: RA, PsA	Reducing signs and symptoms of active AS. Other indications: RA, polyarticular JIA, PsA, and Ps.	Reducing signs and symptoms in adult patients with active AS who have had an inadequate response to conventional therapies. Other indications: RA, PsA, UC	Reduction of signs and symptoms and improvement in physical function in patients with active AS who have responded inadequately, or are intolerant to, conventional therapies. Other indications: RA, CD, UC, PsA and Ps.
Route of administration	SC					IV
Recommended Dose	Loading dose at weeks 0, 1, 2 and 3, followed by a monthly maintenance dose of 150 mg SC starting at week 4	40 mg administered every other week as a 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 by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.
Serious Side Effects / Safety issues	Infections (tuberculosis and serious infection in particular), hypersensitivity reactions and inflammatory bowel disease (exacerbations or new onset)	Serious infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic infections Malignancies Hypersensitivity reactions (allergic reactions and injection site reactions)				

AS = ankylosing spondylitis; CD = Crohn disease; HS = hidradenitis suppurativa; IgG1 = immunoglobin G1; IV = intravenous injection; JIA = juvenile idiopathic arthritis; MTX = methotrexate; Ps = plaque psoriasis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SC = subcutaneous injection; TNF = tumour necrosis factor; UC = ulcerative colitis.

[a] Health Canada indication.

Source: Health Canada product monographs.[10-15]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of secukinumab (Cosentyx) at the recommended dose for the treatment of adult patients with active AS.

2.2 Methods

Studies selected for the systematic review included the pivotal studies provided in the manufacturer's submission to 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 ankylosing spondylitis who have responded inadequately to conventional therapy. **Subgroups of interest:** • Duration of disease • Previous use of BRMs versus no previous use of BRMs • Response versus no response to previous treatment • Levels of serologic markers of inflammation (C-reactive protein or erythrocyte sedimentation rate) • Body weight at baseline	
Intervention	Secukinumab: initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing (150 mg SC) starting at week 4	
Comparators	Currently approved BRMs for AS: • Certolizumab pegol • Infliximab • Golimumab • Adalimumab • Etanercept	
Outcomes	**Key efficacy outcomes:** • Clinical response (e.g., ASAS 20 and ASAS 40 response criteria) • Measures of AS symptoms (e.g., VAS)[a] • Measures of function and disability (e.g., BASFI, VAS)[a] • Health-related quality of life (generic and disease-specific)[a] • Work productivity[a] **Other efficacy outcomes:** • Disease activity (e.g., BASDAI)[a] • Patient global assessment (e.g., VAS) • Radiographic changes	**Harms outcomes:** • Mortality • SAEs[a] • AEs[a] • WDAEs • Notable harms: serious infections (including tuberculosis), malignancies, heart failure, injection and hypersensitivity reactions and hematologic effects (such as anemia and/or pancytopenia)
Study Design	Published and unpublished Phase 3 RCTs	

AEs = adverse events; AS = ankylosing spondylitis; ASAS = Assessment of Ankylosing Spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BRM = biologic response modifier; RCT = randomized controlled trial; SAEs = serious adverse events; SC = subcutaneously; VAS = visual analogue scale; WDAE = withdrawal due to adverse events.

[a] Outcomes that were considered important by the patient groups.

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 through Ovid; Embase (1974-) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Cosentyx (secukinumab) and Ankylosing Spondylitis.

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 18, 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); and an 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 0.

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.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

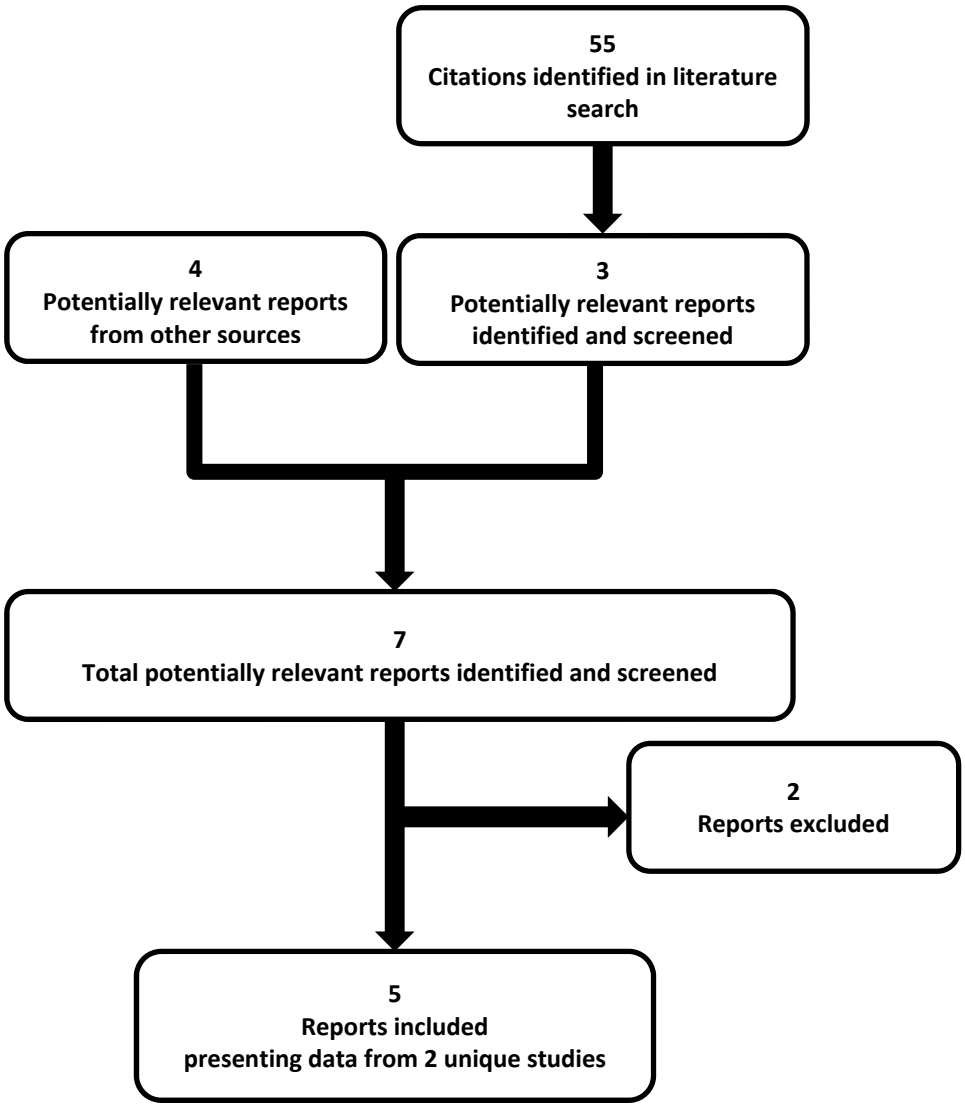


TABLE 4: DETAILS OF INCLUDED STUDIES

		MEASURE 1	MEASURE 2
DESIGNS AND POPULATIONS	**Study Design**	DB RCT, phase 3	
	Locations	65 centres across Asia, Europe, North America, and South America	52 centres across Asia, Europe, and North America
	Randomized (N)	371	219
	Inclusion Criteria	• ≥ 18 years of age. • Diagnosis of moderate to severe AS with prior documented radiologic evidence. • BASDAI score ≥ 4 and score for spinal pain of ≥ 4 cm on a 10 cm VAS despite. treatment with maximum doses of NSAIDs. • Taking NSAIDs at the highest recommended dose for ≥ 3 months with inadequate response, or < 3 months if withdrew due to drug toxicity. • Patients who were taking TNFi (only 1 previous TNFi drug was allowed) must have experienced inadequate response to previous or current treatment for ≥ 3 months or have been intolerant to ≥ 1 administration. • Patients had 4 to 10 weeks washout period for previous TNFi prior to randomization.	
	Exclusion Criteria	• Total spinal ankylosis. • Evidence of ongoing infection or malignance on chest X-ray. • Previous exposure to secukinumab or any other biologic drug targeting IL-17 or IL-17 receptor; previous treatment with cell-depleting therapies or biological immunomodulating drugs other than TNFi. • Active ongoing inflammatory diseases other than AS (e.g., inflammatory bowel disease or uveitis) that might confound the evaluation of the benefit of secukinumab. • Active tuberculosis or any active systemic infection < 2 weeks before baseline. • Underlying conditions that immunocompromised the patient and/or placed the patient at unacceptable risk for participation in an immunomodulatory therapy. • Pregnant or nursing women. • Significant medical problems such as uncontrolled hypertension or congestive heart failure, or very poor functional status.	
DRUGS	**Intervention**	SEC in vial: loading doses of 10 mg/kg IV at baseline, week 2 and week 4, followed by 75 mg SC every four weeks starting at week 8. SEC in vial: loading doses of 10 mg/kg IV at baseline, week 2 and week 4, followed by 150 mg SC every four weeks starting at week 8.	SEC in pre-filled syringe: loading dose of 75 mg SC at baseline, week 1, week 2 and week 3, followed by 75 mg SC every four weeks starting at week 4. SEC in pre-filled syringe: loading dose of 150 mg SC at baseline, week 1, week 2 and week 3, followed by 150 mg SC every four weeks starting at week 4.
	Comparator(s)	Placebo[a]	Placebo[a]

		MEASURE 1	MEASURE 2
DURATION	**Phase**		
	Run-in	4 weeks screening	4 to 10 weeks screening
	Double-blind	• 16 weeks for the DB treatment with SEC or placebo. • Starting at week 16, placebo-nonresponders received dose-blinding treatment with 1 of the 2 SEC doses up to 2 years. • Starting at week 24, placebo-responders received dose-blinding treatment with 1 of the 2 SEC doses up to 2 years.	• 16 weeks for the DB treatment with SEC or placebo. • From 16 to 52 weeks for the dose-blinding treatment with 1 of the 2 SEC doses. • After the week 52 analysis, patients continued to receive same active dose of SEC but as open-label treatment until week 256.
	Follow-up	12 weeks	12 weeks
OUTCOMES	**Primary End Point**	% of patients achieved ASAS 20 at week 16	% of patients achieved ASAS 20 at week 16
	Other End Points	• ASAS 20 response at time points other than week 16: ○ MEASURE 1: weeks 1, 2, 4, 8, 12, 20, 24, 28, 32, 40, 52, 60, 68, 76, 84, 92, and 104. ○ MEASURE 2: weeks 1, 2, 3, 4, 8, 12, 20, 24, 28, 32, 40, 52, 60, 68, 76, 84, 92, 100, 104, 116, 128, 140, 156, 168, 180, 192, 208, 220, 232, 244, and 260. • ASAS 40 response at week 16 and other time points. • HRQoL (measured by change from baseline in SF-36 PCS/EQ-5D/FACIT-Fatigue/ASQoL) at week 16 and other time points. • Function (as measured by BASFI and patient's global assessment by VAS) at week 16 and other time points. • Disease activity: ○ change from baseline in total BASDAI score ○ patient's global assessment by VAS at week 16 and other time points. • Work productivity: WPAI-GH at week 16 and other time points (this outcome was evaluated in MEASURE 1 only). • Radiographic changes: ○ MRI in a subgroup of TNFi-naive patients at selected sites at week 16 ○ X-rays of cervical, thoracic, and lumbar spine at 2 years of treatment. • Safety outcomes including AEs, SAEs, and WDAEs.	
NOTES	**Publications**	Baeten 2015[16] and supplementary appendix[17]	

AE = adverse event; ASAS = the Assessment of SpondyloArthritis International Society; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = the Bath Ankylosing Spondylitis Disease Activity Index; DB = double-blind; FACIT-Fatigue = the Functional Assessment of Chronic Illness Therapy-Fatigue Scale; HRQoL = health-related quality of life; hsCRP = high sensitivity C-reactive protein; IV = intravenous; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; PCS = physical component summary, SAE=serious adverse event; SC = subcutaneous; SEC = secukinumab; SF-36 = Medical Outcomes Study Questionnaire Short Form 36; TNFi = tumour necrosis factor inhibitor; VAS = visual analogue scale; WDAE = withdrawal due to adverse event; WPAI-GH = Work Productivity and Activity Impairment — General Health

[a] In MEASURE 1, patients in the placebo group switched to SEC therapy at weeks 16 and 24, depending on the treatment response; in MEASURE 2, all patients in the placebo group switched to SEC therapy at week 16.

Note: 2 additional reports were included: the CADTH Common Drug Review submission[18] and the European Medicines Agency report.[19]

Source: Clinical Study Reports.[20,21]

3.2 Included studies

3.2.1 Description of studies

Two phase 3, multicenter, double-blind, placebo-controlled RCTs met the inclusion criteria for this systematic review.[20,21]

The study design of MEASURE 1 and MEASURE 2 are shown in Figure 2.

MEASURE 1 (N = 371), a three-arm 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 duration of two years. A screening period running four weeks before randomization was used to assess participants' eligibility. Their medical history and current medical condition were assessed. Physical exams, laboratory tests (including tuberculosis skin test), and relevant radiographic examinations were performed. After the screening phase, eligible participants were randomized to one of the SEC therapy or placebo. Patients in both SEC groups received an intravenous (IV) loading infusion of SEC at a dose of 10 mg/kg at week 0 (baseline), week 2 and week 4, followed by maintenance SEC therapy SC every four weeks starting from week 8. Patients in the placebo group received IV infusion at week 0 (baseline), weeks 2 and 4, then maintenance placebo SC every four weeks starting from week 8. Patients in the placebo group who did not meet the ASAS 20 response criteria (i.e., improvement of ≥ 20% and absolute improvement of ≥ 1 unit on a 10-unit scale in at least 3 of the 4 main ASAS domains with no worsening by ≥ 20% in the remaining domain) at week 16 were defined as non-responders, and were re-randomized in a 1:1 ratio to receive SEC 150 mg or 75 mg SC every four weeks. Placebo-treated patients who were responders to placebo (met the ASAS 20 response criteria) at week 16 remained on placebo, and then were re-randomized in a 1:1 ratio to receive SEC 150 mg or 75 mg SC every four weeks from week 24. Therefore, there were no patients on placebo after week 24. From the time of randomization, patients, investigators, persons performing the assessments, and data analysts remained blinded to the identity of the treatment. After re-randomization (from week 16 or week 24 onward), all patients and the investigators were aware that active treatment was administrated, although the assigned SEC dose remained double-blinded until the end of treatment period (week 104). Data analysts remained blinded to the identity of the treatment from the time of randomization until the week 52 analysis. In this study, SEC 150 mg powder for solution for SC injection or IV infusion was provided in glass vials each containing 150 mg SEC as lyophilized cake. Unblinded pharmacists were needed to prepare the study medications, and then the prepared SC injection or IV infusion was administered to the patients by blinded site personnel.

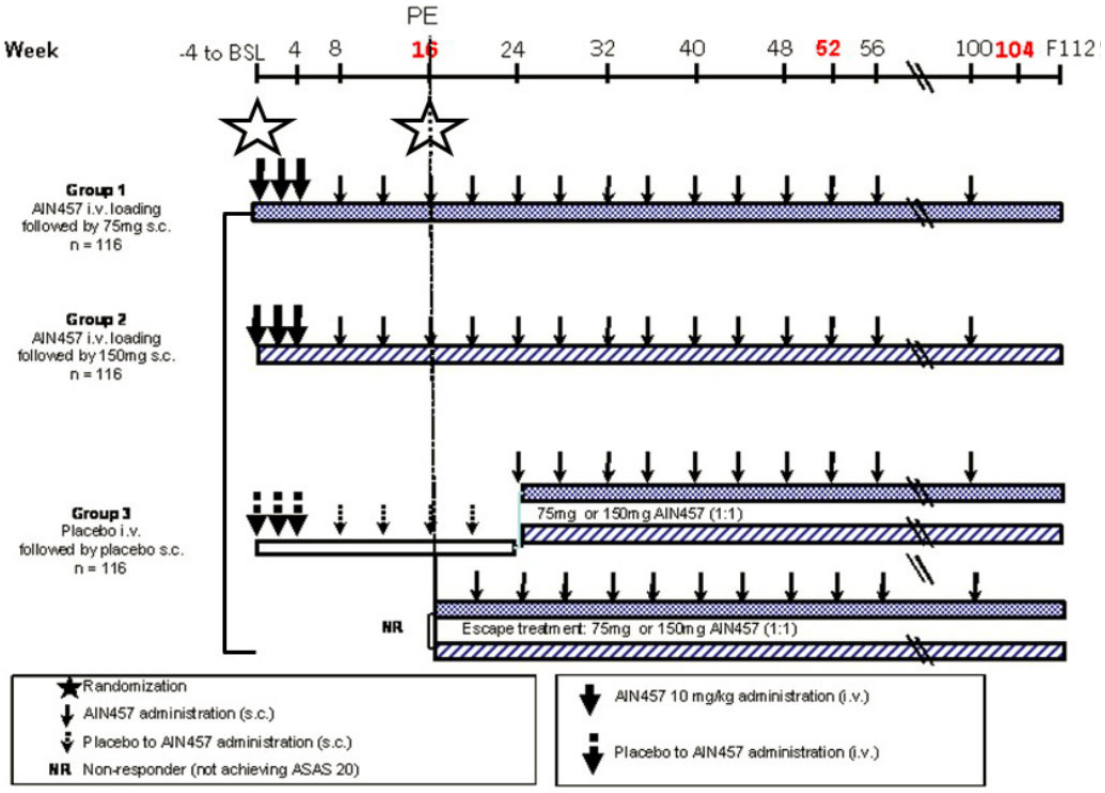
MEASURE 2 (N = 219) was a three-arm, double-blind, double dummy superiority study evaluating the efficacy and safety of SEC 150 mg SC every four weeks or SEC 75 mg SC every four weeks compared with placebo. Similar to MEASURE 1, a screening period (running 4 to 10 weeks) before randomization was used to assess participants' eligibility. Their medical history and current medical condition were assessed. Physical exams, laboratory tests (including tuberculosis skin test) and relevant radiographic examinations were performed. The study did not specify why a longer screening period was required. After the screening phase, eligible patients were randomized to one of the SEC groups or placebo. Patients in the SEC groups received an SC loading injection of SEC 150 mg plus placebo 75 mg or SEC 75 mg plus placebo 150 mg at baseline (week 0), week 1, 2 and 3, followed by respective maintenance therapy (SEC 150 mg or 75 mg, respectively) every four weeks starting from week 4. Patients randomized to placebo received placebo 75 mg plus placebo 150 mg once weekly at baseline, weeks 1, 2, 3 and 4, followed by placebo SC every four weeks starting at week 4. Starting at week 16, patients originally randomized to placebo were re-randomized in a 1:1 ratio to receive SEC 150 mg SC or SEC 75 mg SC every four weeks until the end of study regardless of treatment response. The study duration

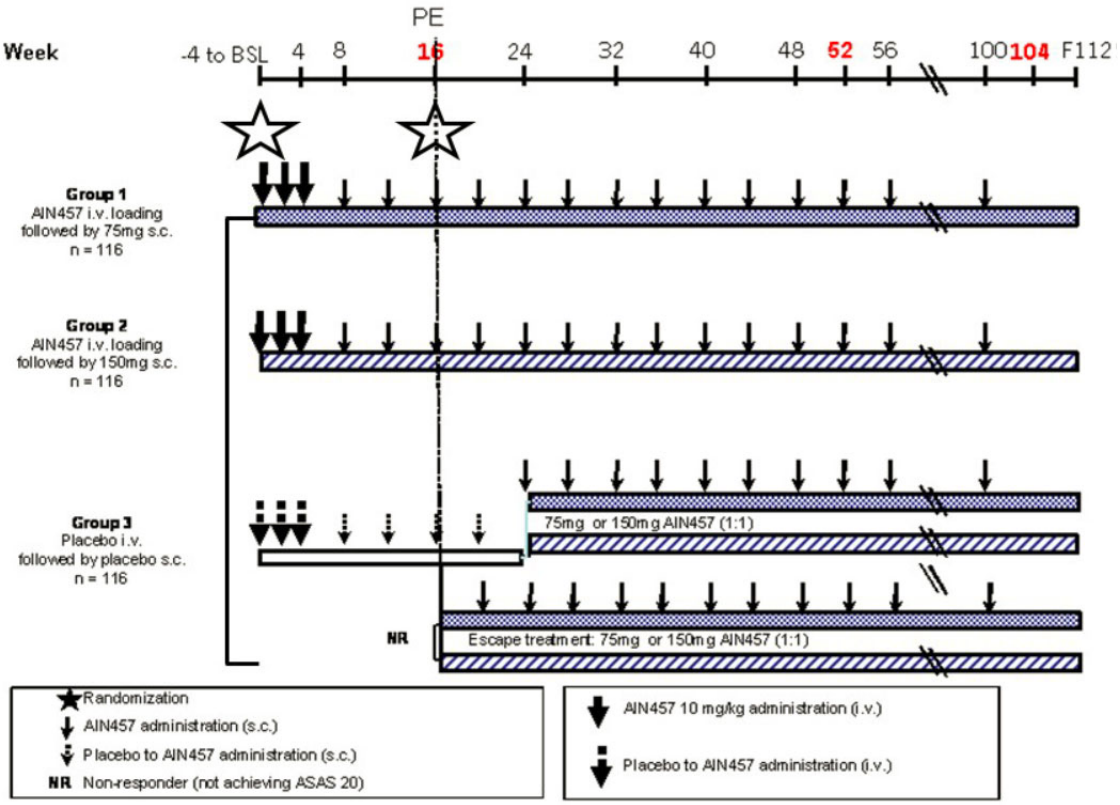
of MEASURE 2 was five years. From the time of randomization, patients, investigators, and persons performing the assessments remained blinded to the identity of the treatment until the week 52 analysis. Data analysts remained blinded until week 16 database lock. After the week 52 analysis had been conducted, site personnel and the patients were unblinded to the treatment arms and the patients continued receiving the same SEC dose as open-label treatment until week 256. In this study, SEC 75 mg or 150 mg were provided in 0.5 mL or 1.0 mL pre-filled syringes for SC injection. Therefore, a pharmacist was not required to prepare the study medications. Patients were trained to self-administer the study drug at the time of randomization. Self-injection took place under the supervision of a site staff member, and the site staff administered the injection only to those who were not able to self-administer the pre-filled syringe.

In both studies, randomization at baseline and re-randomization at week 16 or week 24 were conducted by the Interactive Response Technology (IRT). The patients were stratified by prior exposure to TNFi (TNFi-naive patients versus inadequate responders to TNFi). 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.

The Health Canada–approved dose for SEC is 150 mg, and as such, only data associated with this dose are reported in this review.

FIGURE 2: STUDY DESIGN FOR MEASURE 1 (TOP) AND MEASURE 2 (BOTTOM)





Sources: Clinical Study Reports,[20,21]

3.2.2 Populations

a) Inclusion and exclusion criteria

MEASURE 1 and MEASURE 2 used the same selection criteria. To be eligible, patients were required to be at least 18 years of age and had a diagnosis of moderate to severe active AS with prior documented X-ray evidence fulfilling the modified New York criteria for AS. The patients should have had a BASDAI score of 4 or higher (on a 0 to 10 scale with higher score indicating more severe disease activity) or a spinal pain score of 4 cm or greater on a 10 cm visual analogue scale (VAS) (higher score indicating greater disease activity) at baseline. Previous use of DMARDs and TNFi drugs was allowed but washout periods for these drugs, other than sulfasalazine and methotrexate, were required before initiation of the study treatment. Patients previously treated with not more than one TNFi drug were eligible if they had an inadequate response to an approved dose for three months or more or had unacceptable side effects. Continuous use of sulfasalazine, methotrexate, prednisone or equivalent, and NSAIDs at a stable dose was allowed.

Patients were excluded if they had total spinal ankylosis, had ongoing infection (including active tuberculosis or any active systemic infection less than two weeks before study baseline) or malignance, had active ongoing inflammatory diseases other than AS, or had previous exposure to secukinumab or any other biologic drug targeting IL-17 or IL-17 receptor. Patients with significant medical problems such as uncontrolled hypertension, congestive heart failure, or very functional status were also ineligible.

b) Baseline characteristics

In general, the baseline demographic and disease characteristics of patients in the SEC 150 mg and the placebo group in MEASURE 1 and MEASURE 2 were similar; however, some differences across treatment groups were observed. Patients in the SEC 150 mg groups (40.1 to 41.9 years on average) were younger compared with the placebo group (43.1 to 43.6 years on average) at baseline. The majority of patients were white (60.7% to 95.2%, when the proportion of white patients was higher in MEASURE 2 compared to MEASURE 1, and in MEASURE 1, more white patients were included in the placebo arm) and male (63.9% to 75.7%; in MEASURE 2, the proportion of male patients was 12% higher in the placebo group compared to the SEC 150 mg group). The mean total BASDAI score ranged from 6.4 to 6.8. In MEASURE 1, there were 26.4% and 27.0% of patients had prior TNFi exposure in the SEC 150 mg group and the placebo group, respectively. The level of C-reactive protein (CRP) was balanced between the two treatment groups in MEASURE 1; however in MEASURE 2, it was higher in the SEC 150 mg group (25.8 mg/L on average) compared to the placebo group (15.7 mg/L on average). In MEASURE 2, there were 38.9% and 39.2% of patients had prior TNFi exposure in the SEC 150 mg group and the placebo group, respectively. In MEASURE 1, patients on SEC 150 mg had shorter duration of disease (mean time since diagnosis of AS: 6.5 years) compared with placebo (mean time since diagnosis of AS: 8.3 years). In MEASURE 2, the mean time since diagnosis of AS was similar between SEC 150 mg and placebo, 7.0 years versus 6.4 years, respectively. In addition, the proportion of patients with previous use of methotrexate (ranged from 11.1% to 13.6% in MEASURE 1 and MEASURE 2) or sulfasalazine (ranged from 33.6% to 34.4% in MEASURE 1 and from 12.2% to 13.9% in MEASURE 2) was similar across the treatment groups (Table 5). In MEASURE 1, the background and disease characteristics of the re-randomized placebo non-responder and responder groups were similar to those of the originally randomized treatment groups (data not shown).

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

	MEASURE 1		MEASURE 2	
	SEC 150 mg (N = 125)	**Placebo (N = 122)**	**SEC 150 mg (N = 72)**	**Placebo (N = 74)**
Age, mean years (SD)	40.1 (11.6)	43.1 (12.4)	41.9 (12.5)	43.6 (13.2)
Age, range	[redacted]	[redacted]	[redacted]	[redacted]
Male, n (%)	84 (67.2)	85 (69.7)	46 (63.9)	56 (75.7)
Race, n (%)				
White	69 (55.2)	81 (66.4)	69 (95.8)	70 (94.6)
Asian	21 (16.8)	19 (15.6)	2 (2.8)	4 (5.4)
Other	35 (28.0)	22 (18.0)	1 (1.4)	0
Weight, mean kg (SD)	74.7 (16.2)	76.7 (14.4)	82.3 (18.0)	80.3 (15.2)
Global assessment of disease activity on VAS (0 to 100 mm), mean (SD)	64.0 (19.4)	66.3 (18.6)	67.5 (16.8)	70.5 (15.8)
Total back pain (0-100 mm), mean (SD)	64.0 (18.6)	66.7 (16.5)	66.2 (16.7)	69.2 (18.8)
BASFI, mean (SD)	5.6 (2.2)	5.8 (2.0)	6.2 (2.1)	6.1 (2.0)
BASDAI, mean (SD)	6.4 (1.6)	6.5 (1.5)	6.6 (1.5)	6.8 (1.3)
C-reactive protein, mean mg/L (SD)	17.0 (22.2)	16.9 (22.3)	25.8 (50.1)	15.7 (18.5)
Erythrocyte sedimentation rate, mean mm/h (SD)	33.7 (26.0)	31.2 (24.2)	33.9 (24.8)	29.5 (17.8)
Prior TNFi, n (%)				
0	92 (73.6)	89 (73.0)	44 (61.1)	45 (60.8)
1	30 (24.0)	33 (27.0)	27 (37.5)	29 (39.2)
≥ 2	3 (2.4)	0	1 (1.4)	0
Time since first diagnosis of AS, mean years (SD)	6.5 (6.9)	8.3 (8.9)	7.0 (8.2)	6.4 (8.9)
Methotrexate use at randomization, n (%)	17 (13.6)	16 (13.1)	8 (11.1)	9 (12.2)
Sulfasalazine use at randomization, n (%)	42 (33.6)	42 (34.4)	10 (13.9)	9 (12.2)

AS = ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; SEC = secukinumab; SD = standard deviation; TNFi = tumour necrosis factor inhibitor; VAS = visual analogue scale.
Source: Clinical Study Reports.[20,21]

3.2.3 Interventions

In MEASURE 1, patients randomized to receive SEC received loading SEC IV infusion at a dose of 10 mg/kg at weeks 0, 2 and 4. Starting at week 8, maintenance dose of secukinumab 150 mg or 75 mg was administered SC every four weeks. At week 16, patients in the placebo group who did not respond well to the treatment (called "non-responders" based on ASAS 20 improvement criteria) were re-randomized to receive SEC 75 mg or 150 mg SC injection. Patients who were responders in the placebo

group remained on placebo until week 24, and were re-randomized to either SEC group at week 24, up to two years. At week 16 (for non-responders) or week 24 (for responders) all patients originally treated with placebo were aware they were receiving active treatment as mandated by the protocol, although the assigned SEC dose remains double-blinded. SEC SC and IV injection were supplied in glass vials containing SEC 150 mg powder for solution. Placebo injection contained 100 mL 0.9% sodium chloride solution. Rescue medications referred to any new therapeutic intervention or a significant change to ongoing therapy because the patient was experiencing either no benefit from participation in the trial or worsening/exacerbation of their disease. Rescue medications were not allowed before week 16.

In MEASURE 2, patients randomized to the SEC groups received an SC loading injection of SEC at a dose of 150 mg or 75 mg at week 0 (baseline), week 1, week 2 and week 3, followed by maintenance therapy every four weeks starting from week 4. Starting at week 16, patients originally randomized to placebo were re-randomized in a 1:1 ratio to receive either SEC 150 mg SC or SEC 75 mg SC every four weeks until the end of study (week 256), in a double-blind fashion. After the week 52 analysis was conducted, the patients continued to receive the same active dose of SEC as open-label treatment until week 256, and they no longer received the placebo pre-filled syringe, which had been administered to maintain the dose double-blind. SEC SC and IV injection and placebo were supplied in pre-filled syringes (SEC 150 mg/ 75 mg in 1.0 mL/0.5 mL). Rescue medications were not allowed before week 20.

In both studies, SEC and placebo solutions were identical in appearance.

NSAIDs, acetaminophen/paracetamol, DMARDs (sulfasalazine, MTX, or leflunomide washout with cholestyramine), and systemic corticosteroids were permitted during the study.

3.2.4 Outcomes

a) Assessment of SpondyloArthritis International Society (ASAS) criteria

The primary efficacy outcome in MEASURE 1 and MEASURE 2 was the proportion of patients who met ASAS 20 response criteria at week 16. The ASAS 40 response criteria at week 16 were the secondary outcome in MEASURE 1 and MEASURE 2. ASAS 20 and ASAS 40 are composite measures containing four main domains: patient's global assessment of disease activity on a 100 mm VAS ranging from not severe to very severe; assessment of back pain intensity with a 100 mm VAS ranging from no pain to unbearable pain; function represented by Bath Ankylosing Spondylitis Functional Index (BASFI), measure by a 100 mm VAS; and inflammation represented by mean duration and severity of morning stiffness (measured by the average scores from the last two questions on BASDAI, using a scale of 0 to 10). Two additional domains are: spinal mobility represented by Bath Ankylosing Spondylitis Metrology Index (BASMI) lateral spinal flexion assessment; and CRP. ASAS 20 response is defined as an improvement of ≥ 20% and ≥ 1 unit on a scale of 10 in at least 3 of the 4 main domains and no worsening of ≥ 20% and ≥ 1 unit on a scale of 10 in the remaining domain; ASAS 40 response is defined as an improvement of ≥ 40% and ≥ 2 units on a scale of 10 in at least 3 of the 4 main domains and no worsening in the remaining domain.

b) Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI was assessed as a secondary efficacy outcome at week 16 in MEASURE 1 and MEASURE 2, and contains six questions pertaining to the 5 major symptoms of AS: fatigue, spinal pain, joint pain/swelling, areas of localized tenderness (inflammation of tendons and ligaments), morning stiffness duration, and morning stiffness severity. A continuous VAS scale of 0 to 10 is used to measure these disease activities, where 0 indicates no problem and 10 indicates the worst problem. Scores of four or greater suggest suboptimal control of disease, and patients with scores of four or greater are usually

good candidates for either a change in their medical therapy or for enrolment in clinical trials evaluating new drug therapies directed at AS.[22] The MCID for the BASDAI has been determined as a change of −1.96 on the 10-point BASDAI scale. [23]

c) Health-Related Quality of Life (HRQoL)

Medical Outcomes Study Short Form-36 (SF-36)

The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas. The SF-36 consists of 8 health domains: physical functioning, role-physical, bodily pain, general health (GH), vitality, social functioning, role-emotional, and mental health. The 8 domains are aggregated to create two component summaries: the physical component summary (PCS) and the mental component summary (MCS), with scores ranging from 0 to 100 with higher scores indicating better health status. The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 and 5.0 points.[24] Leung et al. reported MCIDs of 3.74 and 1.77 in psoriatic arthritis (PsA) patients treated with TNFi drugs for the PCS and MCS subsections, respectively.[25] In MEASURE 1 and MEASURE 2, SF-36 PCS was assessed as a secondary efficacy end point at week 16, and a patient was considered a PCS responder if there was an increase of ≥ 2.5 points from baseline. [redacted]

Ankylosing Spondylitis Quality of Life (ASQoL)

The purpose of the ASQoL is to assess the disease-specific HRQoL of patients with AS. The ASQoL was assessed as a secondary efficacy outcome at week 16 in MEASURE 1 and MEASURE 2, and is a self-administered questionnaire containing 18 items with a dichotomous yes/no response option. Items in the ASQoL include an assessment of mobility/energy, self-care and mood/emotion. A single point is assigned for each "yes" response and no points for each "no" response resulting in overall scores that range from 0 (least severity) to 18 (highest severity). Therefore, a lower score indicates better quality of life. The minimum clinically important difference (MCID) of the ASQoL has been identified as a change of −1.8 on the 18-point ASQoL scale.[26] [redacted]

FACIT-Fatigue

The FACIT-Fatigue is a 13-item self-reported questionnaire that assesses the impact of fatigue on daily activities and function in patients with AS, as an exploratory efficacy end point in MEASURE 1 and MEASURE 2. It has been validated in the general population as well as in patients with different diseases such as cancer, PsA, RA, and inflammatory bowel disease.[27] Scores of FACIT-Fatigue range from 0 to 52, with lower scores representing greater fatigue. A difference of three to 4 units is considered a MCID.[27]

EQ-5D

The EQ-5D is a widely used, self-administered questionnaire designed to assess health status in adults, and was assessed as an exploratory efficacy end point in MEASURE 1 and MEASURE 2. The measure is divided into two distinct sections. The first section includes one item addressing each of 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Patients rate each of these items as "no problem," "some problem," or "extreme problem." A composite health index is then defined by combining the levels for each dimension using a multi-attribute utility function. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented VAS where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. [redacted]

d) Patient's global assessment on health status

The patient's global assessment on health status was not assessed in any of the included studies.

e) Work productivity

In MEASURE 1 and MEASURE 2, work productivity was measured as an exploratory efficacy end point using the Work Productivity and Activity Impairment-General Health (WPAI-GH) that measures absenteeism, presenteeism, as well as the impairments in unpaid activity because of health problem during the previous seven days. Four main outcomes can be generated from the WPAI-GH and expressed in percentages: percentage of work time missed due to health for those who were currently employed; percentage of impairment while working due to health for those who were currently employed and actually worked in the past seven days; percentage of overall work impairment due to health for those who were currently employed; and percentage of activity impairment due to health for all respondents. [redacted]

f) Radiographic changes

In MEASURE 1, magnetic resonance imaging (MRI) examination of the spine and sacroiliac joints was performed in a subgroup of TNFi-naive patients (38 patients in the SEC 150 mg group and 33 patients in the placebo group) at selected clinical sites. Only the sites qualified to conduct MRI assessments (adequate imaging equipment, training in standardized imaging techniques, and test transfers of MRI images from the site to the imaging vendor) were allowed to provide MRI assessments in the study.[28] X-rays of the cervical, thoracic, and lumbar spine were assessed at baseline and week 104, according to the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) and Radiographic Ankylosing Spondylitis Spinal Score (RASSS). Increases in mSASSS and RASSS scores indicate worsening structural progression. The mSASSS has been validated in patients with ankylosing spondylitis.[29,30]

g) Safety

Adverse events (AEs), serious adverse events (SAEs), and their severity and relationship to the treatment, as well as withdrawals due to AEs (WDAEs) and notable harms were evaluated in MEASURE 1 and MEASURE 2. All laboratory tests were conducted at the central laboratory except for erythocite seditmentation rate and urinalysis/urine pregnancy tests.

h) Statistical analysis

In MEASURE 1, patients were stratified according to being TNFi-inadequate responders (TNFi-IR) or TNFi-naive patients at randomization. It was anticipated that a sample size of at least 39 patients for each treatment group was needed for 90% power to detect statistically significant differences in the proportion of patients achieving ASAS 20 between SEC 150 mg and SEC 75 mg groups and placebo at week 16, assuming a response rate of 20% in the placebo group (indicated by previous research) and 60% in the SEC groups. In order to collect additional safety information on the use of SEC in the study population, 348 patients were planned to be equally allocated to the three treatment groups (116 patients in each treatment group), including at least 70% TNFi-naive patients.

In MEASURE 2, patients were stratified at randomization according to TNFi-naive patients (132 patients planned) or TNFi-IR patients (90 patients planned). It was anticipated that a sample size of at least 39 patients for each treatment group was needed to detect statistically significant differences in the proportion of patients achieving ASAS 20 between SEC 150 mg or 75 mg groups and placebo at week 16 with 90% power, assuming a response rate of 20% in the placebo group (indicated in previous research) and 60% in the SEC groups. In order to collect additional safety information on the use of SEC in the study population, 222 patients were planned to be equally allocated to the 3 treatment groups (74

patients in each treatment group), including at least 60% TNFi-naive patients. The power of the test for the primary end point based on 74 patients per group was over 99%.

In both studies, the analysis of the primary outcome (ASAS 20) and other binary outcomes was conducted using logistic regression with treatment group and TNFi response status as independent variables, and body weight as a covariate, based on the full analysis set (FAS). Missing values, including those due to discontinuation of the study treatment, were imputed as non-responders. Between-group differences in continuous outcomes (i.e., BASDAI score) were analyzed using a mixed-model repeated-measure (MMRM) approach, with missing data assumed to be missing at random and with treatment group, assessment visit, and TNFi response status as factors, weight, and baseline values of the outcome were included in the model as continuous covariates. The primary and key secondary efficacy outcomes were assessed using a hierarchical testing procedure in order to control the type 1 error rate. Continued testing was conditional on the first test being significant and the second hypothesis was tested with the same alpha level of 5%. Statistical testing for the hypotheses was performed only if the previous null hypothesis in the hierarchy could be rejected:

Primary objectives:
H1: SEC 75 mg: no difference versus placebo for ASAS 20 response at week 16
H2: SEC 150 mg: no difference versus placebo for ASAS 20 response at week 16.

Secondary objectives:
H3: SEC 75 mg: no difference versus placebo for ASAS 40 response at week 16
H4: SEC 150 mg: no difference versus placebo for ASAS 40 response at week 16
H5: SEC 75 mg: no difference versus placebo for high sensitivity C-reative protein (hsCRP) at week 16
H6: SEC 150 mg: no difference versus placebo for hsCRP at week 16
H7: SEC 75 mg: no difference versus placebo for ASAS 5 out of 6 domains (ASAS 5/6) response at week 16
H8: SEC 150 mg: no difference versus placebo for ASAS 5/6 response at week 16
H9: SEC 75 mg: no difference versus placebo for total BASDAI at week 16
H10: SEC 150 mg: no difference versus placebo for total BASDAI at week 16
H11: SEC 75 mg: no difference versus placebo for SF-36 PCS at week 16
H12: SEC 150 mg: no difference versus placebo for SF-36 PCS at week 16
H13: SEC 75 mg: no difference versus placebo for ASQoL at week 16
H14: SEC 150 mg: no difference versus placebo for ASQoL at week 16
H15: SEC 75 mg: no difference versus placebo for ASAS partial remission at week 16
H16: SEC 150 mg: no difference versus placebo for ASAS partial remission at week 16.

The CDR protocol included subgroups by duration of disease, previous use of biologic response modifiers (BRM), response to previous treatment, and levels of serologic markers of inflammation and body weight at baseline; however, such subgroup analyses were not undertaken except for the previous use and response of TNFi.

i) Analysis populations

The analysis populations were defined the same in MEASURE 1 and MEASURE 2.

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

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

The FAS consisted of all patients from the RS to whom study treatment was assigned. Following the intent-to-treat principle, patients were evaluated according to the treatment assigned to at randomization. If the actual stratum was different to the assigned stratum in IRT, the actual stratum was used in analysis.

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

3.3 Patient disposition

Patient disposition at week 16 is summarized in Table 6. Patient disposition beyond week 16 can be found in 0. In MEASURE 1, a total of 371 patients were randomized to SEC 150 mg, SEC 75 mg, or placebo at baseline. In MEASURE 2, 219 patients were randomized to SEC 150 mg, SEC 75 mg or placebo at baseline. Overall, the number of premature discontinuations at week 16 was higher in the placebo groups (8.2% to 10.8%) than in the SEC 150 mg group (3.2% to 8.3%). The corresponding completion rates at week 16 were 91.8% to 96.8% in the SEC 150 mg group versus 89.2% to 91.7% in the placebo group. Isolated cases of lack of efficacy, adverse event, technical problems and consent withdrawal were reported as the causes of study discontinuation in the SEC groups and placebo group. One patient in the placebo group died before week 16 in MEASURE 1.

TABLE 6: PATIENT DISPOSITION UP TO WEEK 16

	MEASURE 1		MEASURE 2	
	SEC 150 mg	**Placebo**	**SEC 150 mg**	**Placebo**
Screened, N	448		253	
Randomized, N	125	122	72	74
Discontinued by week 16, N (%)	4 (3.2)	10 (8.2)	6 (8.3)	8 (10.8)
Lack of efficacy	1 (0.8)	-	-	1 (1.4)
Adverse event	1 (0.8)	5 (4.1)	5 (6.9)	4 (5.4)
Lost to follow-up	-	1 (0.8)	-	-
Technical problems	1 (0.8)	-	-	-
Death	-	1 (0.8)	-	-
Withdrew	1 (0.8)	3 (2.5)	1 (1.4)	3 (4.1)
FAS, N (%)	125 (100)	122 (100)	72 (100)	74 (100)
PP, N (%)	105 (84)	105 (86)	67 (93)	71 (96)
Safety, N (%)	125 (100)	122 (100)	72 (100)	74 (100)

FAS = full analysis set; PP = per-protocol; SEC = secukinumab.
Source: Clinical Study Reports,[20,21] Baeten et al. 2015.[16]

3.4 Exposure to study treatments

In MEASURE 1, [redacted] in each group received all three loading doses by week 16, [redacted] in the 150 mg group and [redacted] in the placebo group. The study drugs were administered by investigators or site personnel. [redacted] in each group received three loading IV injections and two maintenance SC injections at week 8 and week 12, [redacted] in the 150 mg group and [redacted] in the placebo group. Up to week 52, [redacted] of patients randomized or re-randomized to

any 150 mg SEC group (including patients randomized to 150 mg at baseline and placebo patents re-randomized to 150 mg SEC either at week 16 for non-responders or week 24 for responders) received all 12 SC injections. Up to week 16, the mean (standard deviation [SD]) treatment duration was [redacted] days in the SEC 150 mg group and [redacted] days in the placebo group.

In MEASURE 2, patients were trained in how to self-administer the SC injection using the pre-filled syringe pen formulation at the time of randomization. Each injection was administered into an appropriate injection site of the body. For the first 24 months of the study (up to week 104), all injections were performed at the study site. After 24 months the patients were allowed to self-administer the study medication at home or continue to do so at monthly intervals at the study site, based on their preference and the investigator's judgment. By week 16, [redacted] patients in the SEC 150 mg and placebo groups respectively, self-administered the study treatment. By week 52, [redacted] patients in the SEC 150 mg and placebo groups respectively, self-administered the study treatment.

3.5 Critical appraisal

3.5.1 Internal validity

MEASURE 1 and MEASURE 2 were double-blind, randomized, placebo-controlled trials up to week 16. MEASURE 1 was dose-blinded up to two years, and in MEASURE 2 the dose was blinded up to one year. Appropriate methods of randomization, blinding and allocation concealment were reported. Entry into the early escape phase was blinded, which can help minimize bias. Emergency unblinding was only to be undertaken when it was essential to treat the patient safely and efficaciously. In general, patients' baseline demographic and disease characteristics were similar between treatment groups in MEASURE 1 and MEASURE 2; however, some differences between the SEC 150 mg group and the placebo group were noted. For example, patients in the SEC 150 mg groups were younger than those in the placebo group in both studies; in MEASURE 2, patients in the SEC 150 mg group had a higher level of CRP compared with those in the placebo group; and in MEASURE 1, patients in the SEC 150 mg group had a shorter duration of disease compared with placebo. It is unclear whether this imbalance would have had an impact on the study results. Randomization was stratified by prior TNF inhibitor exposure and response. In MEASURE 1, study treatments were prepared by unblinded pharmacists, but were administered to patients by blinded site personnel.

A hierarchical test procedure for series that ranked primary and secondary outcomes was used in both studies in order to control the type 1 error rate (at 5%). Statistical testing was conditional on the first test being significant, and the second hypothesis was tested with the same alpha level of 5%. 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 HRQoL data (FACIT-Fatigue, EQ-5D), work productivity, or radiographic change. These outcomes were identified as exploratory variables in MEASURE 1 and MEASURE 2, even though HRQoL and work productivity were identified by patient groups as important outcomes. These outcomes were not adjusted for multiplicity and 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 1 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 the selection of which of the secondary outcomes were included in the hierarchy. In MEASURE 1 and MEASURE 2, all outcomes in the statistical testing hierarchy were statistically significant compared with placebo at week 16.

Between-group differences in continuous outcomes (i.e., BASDAI score and SF-36 PCS) were analyzed using a mixed-model repeated-measure (MMRM) approach, with missing data assumed to be missing at random. However, this may not be an appropriate assumption because reasons for patient dropout may be due to differences in the treatment effects between the two groups. Sensitivity analyses were conducted using different forms of imputation, including multiple imputation and observed data analysis. The results of these sensitivity analyses were consistent with the results from the primary analysis at week 16.

Seventy-seven patients (63.1%) in the placebo group in MEASURE 1 and 66 patients (89.2%) of patients in the placebo group in MEASURE 2 changed their assigned treatment at week 16 after meeting the criteria for early escape and were re-randomized to treatment with SEC 150 mg or SEC 75 mg. Patients who remained in the placebo group at week 16 (determined to have responded to placebo at week 16) in MEASURE 1 switched to SEC 150 mg or SEC 75 mg treatment at week 24 regardless of response. This early escape design, although common in rheumatological clinical trials, limits the ability to interpret the safety and efficacy of SEC 150 mg compared with placebo beyond the primary end point of the study (at week 16). Rescue medications were also allowed after week 16 in MEASURE 1, and after week 20 in MEASURE 2, further limiting the interpretation of the clinical efficacy of SEC 150 mg after these end points.

Subgroup analyses based on prior TNFi exposure were performed for ASAS response rates, [redacted]. When interpreting these results, consideration should be given to a number of limitations including the potential for inadequate power given the small sample sizes (less precise estimates) and the lack of adjustment for multiplicity. TNFi exposure was a stratification variable, so the randomization would have been maintained.

Radiographic progression is an important outcome in AS trials, and was assessed in a subset of patients in MEASURE 1. It was unclear which patients were selected for this exam, and the clinical expert consulted for this review noted that the MRI measures have not been validated.

3.5.2 External validity

Patients enrolled in MEASURE 1 and MEASURE 2 had moderate to severe AS based on the baseline BASDAI score. Exclusion of patients with total spinal ankyloses and exclusion of patients at increased risk of TNFi-associated AEs limits the generalizability of results to clinical practice. According to the clinical expert involved in the review, the patients' baseline characteristics were consistent with what can be seen in clinical practice and in other AS trials.

Even though the loading dose administered to patients in MEASURE 1 was different from the Health Canada product monograph, the clinical expert indicated that variations in the loading dose provided to patients were unlikely to affect the generalizability of the results. The loading dose in MEASURE 2 was consistent with that recommended in the product monograph.

Longer-term data (up to week 104) were available for MEASURE 1 and MEASURE 2; however, the interpretation of these results is limited by the open-label design and lack of a comparator group.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See 0 for efficacy data beyond week 16.

3.6.1 Clinical Response

a) ASAS 20

The primary analysis was conducted on the FAS using logistic regression with treatment and TNFi status as factors and body weight as a covariate. Details of the results of ASAS 20 are presented in Table 7.

At week 16, in MEASURE 1, statistically significantly higher ASAS 20 response rates were observed in the SEC 150 mg group (61%) compared with the placebo group (29%), (OR, 3.9; 95% CI, 2.3 to 6.7; $P < 0.0001$). A subgroup analysis based on prior TNFi treatment was conducted. The ASAS 20 response was 66.3% in the SEC 150 mg group and 32.6% in the placebo group in patients without prior TNFi (TNFi-naive), and was 45.5% for SEC 150 mg versus 18.2% for placebo in patients who had inadequate response to prior TNFi treatment (TNFi-IR). [redacted]

At week 16, in MEASURE 2, a higher proportion of patients treated with SEC 150 mg met the ASAS 20 response criteria compared with those treated with placebo at, 61.1% versus 28.4%, respectively (OR, 4.4; 95% CI, 2.1 to 9.0; $P < 0.0001$). The results of subgroup analysis based on prior TNFi treatment suggested that SEC-treated patients reported [redacted] ASAS 20 response rates compared with placebo-treated patients, in both TNFi-naive patients (68.2% for SEC 150 mg versus 31.1% for placebo, [redacted]) and TNFi-IR patients (50.0% for SEC 150 mg versus 24.1% for placebo, [redacted]).

b) ASAS 40

In MEASURE 1, ASAS 40 response rates were statistically significantly higher in the SEC 150 mg group compared with the placebo group at week 16, 41.6% versus 13.1%, respectively (OR, 4.9; 95% CI 2.6 to 9.3; $P < 0.0001$). [redacted]

In MEASURE 2, ASAS 40 response rate at week 16 was statistically significantly higher for SEC 150 mg (36.1%) compared with placebo (10.8%): OR, 5.1; 95% CI, 2.1 to 12.4; $P = 0.0008$. [redacted]

TABLE 7: EFFICACY OUTCOME — CLINICAL RESPONSE RATES

	MEASURE 1		MEASURE 2	
	SEC 150 mg (N = 125)	**Placebo (N = 122)**	**SEC 150 mg (N = 72)**	**Placebo (N = 74)**
ASAS 20 at week 16				
n (%)	76 (60.8)	35 (28.7)	44 (61.1)	21 (28.4)
OR (95% CI)	3.9 (2.3 to 6.7)		4.4 (2.1 to 9.0)	
P value	< 0.0001		< 0.0001	
Subgroup				
TNFi-naive, n/N (%)	61/92 (66.3)	29/89 (32.6)	30/44 (68.2)	14/45 (31.1)
OR (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
TNFi-IR, n/N (%)	15/33 (45.5)	6/33 (18.2)	14/28 (50.0)	7/29 (24.1)
OR (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
ASAS 40 at week 16				
n (%)	52 (41.6)	16 (13.1)	26 (36.1)	8 (10.8)
OR (95% CI)	4.9 (2.6 to 9.3)		5.1 (2.1 to 12.4)	
P value	< 0.0001		0.0004	
Subgroup				
TNFi-naive, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
TNFi-IR, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

ASAS = Assessment of SpondyloArthritis International Society; CI = confidence interval; IR = inadequate responder; OR = odds ratio; SEC = secukinumab; TNFi = tumour necrosis factor inhibitor.
Sources: Clinical Study Reports.[20,21]

3.6.2 Measures of AS symptoms

Changes in AS symptoms data (such as spinal pain and BASMI) were captured as part of the ASAS response criteria and therefore were not reported separately in this report.

3.6.3 Measures of function and disability

Function and disability (BASFI) data were captured as part of the ASAS response criteria and therefore were not reported separately in this report.

3.6.4 Health-related quality of life

Changes in HRQoL data are reported in Table 8. With the exception of SF-36 PCS and ASQoL, all HRQoL outcomes were considered exploratory and were not adjusted for multiple statistical testing.

a) SF-36 PCS

In MEASURE 1 there was a statistically and clinically (2.5 points) significant improvement in mean SF-36 PCS scores from baseline to week 16 for patients in the SEC 150 mg group compared with the placebo group (difference in LS mean change from baseline of 4.6, 95% CI, 3.0 to 6.2; *P* < 0.0001). [redacted]

[redacted]

In MEASURE 2, there was a statistically and clinically (2.5 points) significant improvement in mean SF-36 PCS scores from baseline to week 16 for patients in the SEC 150 mg group compared with the placebo group (difference in LS mean change from baseline of 4.1, 95% CI, 2.0 to 6.3; *P* = 0.0002. [redacted]

b) ASQoL

In MEASURE 1, there was a statistically and clinically (–1.8 points) significant improvement in ASQoL scores from baseline to week 16 in the SEC 150 mg group compared with the placebo group (difference in LS mean change from baseline of –2.5, 95% CI, –3.7 to –1.4, *P* < 0.0001). [redacted]

In MEASURE 2, there was a statistically and clinically (–1.8 points) significant improvement in ASQoL scores from baseline to week 16 in the SEC 150 mg group compared with the placebo group (difference in LS mean change from baseline of –2.6; 95% CI, –4.1 to –1.2; *P* = 0.0005). [redacted]

c) FACIT-Fatigue

In MEASURE 1 and MEASURE 2 [redacted] The MCID for FACIT-Fatigue was three to four units.

d) EQ-5D

In MEASURE 1 [redacted]

In MEASURE 2 [redacted]

TABLE 8: EFFICACY OUTCOME — HEALTH-RELATED QUALITY OF LIFE

	MEASURE 1		MEASURE 2	
	SEC 150 mg (N = 125)	**Placebo (N = 122)**	**SEC 150 mg (N = 72)**	**Placebo (N = 74)**
SF-36 PCS at week 16				
Baseline, mean (SD)	36.8 (6.8)	36.3 (6.4)	[redacted]	[redacted]
Change from baseline, mean (SE)	5.6 (0.6) n = 122	1.0 (0.6) n =111	6.1 (0.8) n = 67	1.9 (0.8) n = 66
Between-group difference in LS mean (95% CI)	4.6 (3.0 to 6.2)		4.1 (2.0 to 6.3)	
P value	< 0.0001		0.0002	
Subgroup				
TNFi-naive, change from baseline, mean (SE)	6.9 (0.6) [redacted]	1.3 (0.7) [redacted]	[redacted]	[redacted]
Between-group difference (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
TNFi-IR, change from baseline, mean (SE)	3.6 (1.2) [redacted]	2.0 (1.3) [redacted]	[redacted]	[redacted]
Between-group difference (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
ASQoL at week 16				
Baseline, mean (SD)	10.9 (4.7)	11.7 (4.2)	[redacted]	[redacted]
Change from baseline, mean (SE)	–3.6 (0.4) N = 121	–1.0 (0.4) N = 111	–4.0 (0.5) N = 66	–1.3 (0.5) N = 66
Between-group difference in LS mean (95% CI)	–2.5 (–3.7 to –1.4)		–2.6 (–4.1 to –1.2)	
P value	< 0.0001		0.0005	
Subgroup				
TNFi-naive, change from baseline, mean (SE)	–4.4 (0.5) [redacted]	–1.3 (0.5) [redacted]	[redacted]	[redacted]
Between-group difference (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
TNFi-IR, change from baseline, mean (SE)	–1.9 (0.9) [redacted]	–1.0 (0.9) [redacted]	[redacted]	[redacted]
Between-group difference (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
FACIT-Fatigue at week 16				
Baseline, mean (SD)	25.6 (10.7)	24.5 (9.4)	[redacted]	[redacted]

	MEASURE 1		MEASURE 2	
	SEC 150 mg (N = 125)	**Placebo (N = 122)**	**SEC 150 mg (N = 72)**	**Placebo (N = 74)**
Change from baseline, mean (SE)	6.8 (0.8) [redacted]	2.5 (0.9) [redacted]	[redacted]	[redacted]
Between-group difference in LS mean (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
EQ-5D (VAS) at week 16				
Baseline, mean (SD)	45.2 (19.9)	46.5 (20.5)	[redacted]	[redacted]
Change from baseline, mean (SE)	13.3 (1.9) [redacted]	2.0 (2.0) [redacted]	[redacted]	[redacted]
Between-group difference in LS mean (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

ASQoL = the Ankylosing Spondylitis Quality of Life scale; CI = confidence interval; EQ-5D = EuroQoL-5D; FACIT-Fatigue = the Functional Assessment of Chronic Illness Therapy-Fatigue Scale; IR = inadequate responder; LS = least square; PCS = physical component summary; SD = standard deviation; SE = standard error; SEC = secukinumab; SF-36 = Medical Outcomes Study Questionnaire Short Form 36; TNFi = tumour necrosis factor inhibitor; VAS = visual analogue scale.
Sources: Clinical Study Reports.[20,21]

3.6.5 Work productivity

There were [redacted] in work or activity impairment due to disease as measured by the WPAI-GH questionnaire observed in both studies (**Error! Reference source not found.**). [redacted]

In MEASURE 1, at week 16, [redacted] for patients in the SEC 150 mg group compared with patients in the placebo group in categories pertaining to the per cent of work time missed due to health [redacted], per cent impairment while working due to health [redacted], per cent overall work impairment due to health [redacted], and per cent activity impairment due to health [redacted].

In MEASURE 2, at week 16, [redacted] for patients in the SEC 150 mg group compared with patients in the placebo group in categories pertaining to per cent impairment while working due to health [redacted], per cent overall work impairment due to health [redacted], and per cent activity impairment due to health [redacted]. The difference in percentage work time missed due to health [redacted].

TABLE 9: [redacted]

	MEASURE 1		MEASURE 2	
	SEC 150 mg (N = 125)	**Placebo (N = 122)**	**SEC 150 mg (N = 72)**	**Placebo (N = 74)**
[redacted]				

SEC = secukinumab.
Sources: Clinical Study Reports.[20,21]

3.6.6 Disease activity

Details of change in disease activity are presented in Table 10.

a) BASDAI, change from baseline

In MEASURE 1, there was a statistically significant improvement in BASDAI scores from baseline to week 16 in the SEC 150 mg group compared with the placebo group (difference in LS mean change from baseline of –1.7; 95% CI,–2.2 to –1.3; $P < 0.0001$). The between-group difference was not considered clinically meaningful based on an MCID of two points. [redacted]

[redacted]

In MEASURE 2, there was a statistically significant improvement in BASDAI scores from baseline to week 16 in the SEC 150 mg group compared with the placebo group (difference in LS mean change from baseline of –1.3; 95% CI, –2.0 to –0.7; *P*= 0.0002). This difference was not considered clinically meaningful based on an MCID of two points. [redacted]

TABLE 10: EFFICACY OUTCOME — DISEASE ACTIVITY

	MEASURE 1		MEASURE 2	
	SEC 150 mg (N = 125)	**Placebo (N = 122)**	**SEC 150 mg (N = 72)**	**Placebo (N = 74)**
BASDAI total score change from baseline at week 16, mean (SD)				
Baseline	6.4 (1.6)	6.5 (1.5)	6.6 (1.5)	6.8 (1.3)
Change from baseline, mean (SE)	–2.3 (SE 0.2)	–0.6 (SE 0.2)	–2.2 (0.2)	–0.9 (0.3)
Between-group difference in LS mean (95% CI)	–1.7 (–2.2 to –1.3)		–1.3 (–2.0 to –0.7)	
P value	< 0.0001		0.0002	
Subgroup				
TNFi-naive, change from baseline, mean (SE)	–2.7 (0.2)	–0.7 (0.2)	[redacted]	[redacted]
Between-group difference (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
TNFi-IR, change from baseline, mean (SE)	–1.7 (0.3)	–0.7 (0.3)	[redacted]	[redacted]
Between-group difference (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = confidence interval; IR = inadequate responder; LS = least square; SD = standard deviation; SE = standard error; SEC = secukinumab; TNFi = tumour necrosis factor inhibitor.
Source: Clinical Study Reports.[20,21]

3.6.7 Patient's global assessment

No outcomes were reported in MEASURE 1 or MEASURE 2 related to a patient's global health status.

3.6.8 Radiographic changes

In MEASURE 1, MRIs of the spine and sacroiliac joints performed in a subset of TNFi-naive patients at selected study sites (38 patients in the SEC 150 mg group and 33 patients in the placebo group) showed statistically significantly greater reductions in the sacroiliac joint edema score for SEC 150 mg compared with placebo at week 16 ($P < 0.05$). Radiographic change results were not available in MEASURE 2.

3.7 Harms

Only those harms identified in the review protocol are reported in this document (see Table 3). Details of the harm outcomes are presented in Table 11. Reported harms beyond week 16 in MEASURE 1 and MEASURE 2 are reported in 0.

3.7.1 Adverse events

In MEASURE 1, AEs were reported in 69.6% of patients in the SEC 150 mg group and 55.7% in the placebo group (Table 11). Generally, the majority of AEs reported up to week 16 were mild or moderate in severity. Nasopharyngitis, dyslipidemia, headache and nausea were the most frequently reported treatment-emergent AEs (TEAEs) during the first 16 weeks of treatment, and each was more prevalent in the SEC 150 mg group compared with placebo.

In MEASURE 2, the overall incidence of AEs was comparable between the SEC 150 mg group (65.3%) and the placebo group (63.5%) up to week 16. Nasopharyngitis, headache, influenza, oropharyngeal pain, and upper respiratory tract infection were the most frequently reported TEAEs during the first 16 weeks of treatment. The majority of AEs reported up to week 16 were mild or moderate in severity.

3.7.2 Serious adverse events

In MEASURE 1, slightly higher rates of SAEs were reported in the placebo group (4.1%) compared with the SEC 150 mg group (2.4%). SAEs reported in this treatment group included uveitis, tonsillitis, and respiratory failure.

In MEASURE 2 up to week 16, the incidence of SAEs was low and comparable between the SEC 150 mg group and placebo (5.6% for SEC 150 mg versus 4.1% for placebo).

3.7.3 Withdrawals due to adverse events

In MEASURE 1, higher rates of discontinuations due to AEs were reported in the placebo group (4.9%) compared with SEC 150 mg group (0.8%).

In MEASURE 2, up to week 16, the proportion of patients discontinuing due to an AE was low and similar between the SEC 150 mg group and placebo (6.9% for SEC 150 mg and 5.4% for placebo).

3.7.4 Mortality

In MEASURE 1, there was one death reported up to week 16 in a placebo patient who suffered from depression and committed suicide (on Day 80, 10 days after last dose of placebo). No death was reported in the SEC 150 mg group by week 16. No deaths were reported in MEASURE 2.

3.7.5 Notable harms

By week 16 in MEASURE 1, one case of tonsillitis was reported in the SEC 150 mg group. No serious infections were reported in MEASURE 2 up to week 16.

TABLE 11: HARMS UP TO WEEK 16

	MEASURE 1		MEASURE 2	
	SEC 150 mg (N = 125)	Placebo (N = 122)	SEC 150 mg (N = 72)	Placebo (N = 74)
AEs				
Patients with > 0 AEs, N (%)	87 (69.6)	68 (55.7)	47 (65.3)	47 (63.5)
Most common AEs[a]				
Nasopharyngitis	17 (13.6)	9 (7.4)	8 (11.1)	3 (4.1)
Dyslipidemia	9 (7.2)	6 (4.9)	-	-
Headache	21 (11.6)	7 (5.7)	3 (4.2)	6 (8.1)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Abdominal pain upper	7 (3.9)	0	-	-
[redacted]				
Pain in extremity	-	-	3 (4.2)	1 (1.4)
Injection site pain	-	-	4 (5.6)	1 (1.4)
Fatigue	-	-	1 (1.4)	5 (6.8)
SAEs				
Patients with > 0 SAEs, N (%)	3 (2.4)	5 (4.1)	4 (5.6)	3 (4.1)
Most common SAEs	1 uveitis, 1 tonsillitis, 1 respiratory failure.	1 anemia, 1 vertigo, 1 adverse drug reaction, 1 lymphoma, 1 vocal cord paresis, 1 depression and resulted in suicide.	1 hepatic enzyme increased, 1 brain abnormal (nuclear magnetic resonance imaging), 1 costochondritis, 1 malignant melanoma.	1 concussion, 1 arthritis, 1 intervertebral disc protrusion, 1 depression.
WDAEs				
N (%)	1 (0.8)	6 (4.9)	5 (6.9)	4 (5.4)

	MEASURE 1		MEASURE 2	
	SEC 150 mg (N = 125)	Placebo (N = 122)	SEC 150 mg (N = 72)	Placebo (N = 74)
Most common reasons	1 hyperhidrosis	1 anemia, 1 adverse drug reaction, 1 ankylosing spondylitis, 1 spondylitis (worsening), 1 lymphoma, 1 completed suicide.	1 colitis, 1 hepatic enzyme increased, 1 NMR imaging brain abnormal, 1 malignant melanoma, 1 polyneuropathy, 1 dyspnea.	1 hepatitis toxic, 1 arthritis, 1 depression, 1 psoriasis.

AE = adverse event; SAE = serious adverse events; SEC = secukinumab; WDAEs = withdrawal due to adverse events.
Source: Clinical Study Reports.[20,21]
[a] Frequency > 3%.

4. DISCUSSION

4.1 Summary of available evidence

Two manufacturer-sponsored, phase 3, double-blind RCTs, MEASURE 1 (N = 371) and MEASURE 2 (N = 219) were included in this review. The studies evaluated the efficacy and safety of SEC 150 mg and SEC 75 mg compared with placebo every four weeks in patients with moderate to severe AS who did not respond well to previous treatment. The studies differed with respect to the administration of loading doses and the timing of treatment unblinding. The primary outcome in both trials was the proportion of patients meeting the ASAS 20 response criteria at week 16.

In the absence of head-to-head trial data comparing SEC 150 mg with other active treatments, the manufacturer submitted an indirect treatment comparison analysis to evaluate the comparative efficacy of SEC 150 mg to other BRMs in patients with active AS.

4.2 Interpretation of results

4.2.1 Efficacy

At week 16, there was a statistically significant improvement in clinical response rates (ASAS 20 and ASAS 40), HRQoL (SF-36 and ASQoL), and disease activity (BASDAI) for patients receiving SEC 150 mg compared with placebo in both studies (MEASURE 1 and MEASURE 2). The differences between the SEC 150 mg group and the placebo group were clinically meaningful for the quality of life measures — SF-36 and ASQoL at week 16 in both studies. Patients treated with SEC 150 mg were more likely to report AEs compared with the patients in the placebo group in MEASURE 1, while the incidence of AEs were similar between groups in MEASURE 2.

A hierarchical statistical testing procedure for series ranking primary and secondary outcomes was used in both studies to control the type 1 error rate. The hierarchical approach did not take into consideration all outcomes measured in the study, including some of the HRQoL data (FACIT-Fatigue, EQ-5D), work productivity, or radiographic change. These outcomes were identified as exploratory outcomes in MEASURE 1 and MEASURE 2, even though HRQoL and work productivity were identified by patient groups as important outcomes. These outcomes were not adjusted for multiplicity and given the large number of comparisons in the study, a statistically significant finding ($P < 0.05$) for the comparisons

between SEC 150 mg treatment group and placebo for these outcomes may be attributable to an inflated type 1 error rate. Radiographic outcome assessments (MRI scans) were planned for a subset of patients (approximately 25% of the study participants) in MEASURE 1. Improvement in MRI results was observed in one of the three MRI measures. The clinical expert consulted for this review noted that the MRI outcome measures have not been validated. Therefore, it is difficult to assess the effect of SEC 150 mg on radiographic outcomes in the study population.

Subgroup analyses were conducted to assess the results according to previous exposure to TNFis for some outcomes of interest. [redacted] Given the lack of adjustment for multiple statistical testing (risk of inflated type 1 error) and small sample sizes for some outcomes (less precise estimates) the results of the subgroup analyses should be interpreted with caution.

The primary outcome in MEASURE 1 and MEASURE 2 was the proportion of patients achieving ASAS 20 criteria at week 16. After this time point, patients originally randomized to the placebo group were switched to one of the SEC treatment groups due to ethical considerations. This early escape design, although common in rheumatological clinical trials, limits the ability to interpret the safety and efficacy of SEC 150 mg compared with placebo beyond the primary end point of the study (i.e., beyond week 16). AS is a remitting and relapsing disease that can often flare unexpectedly. In the long-term, the disease is associated with impaired function and disability. [redacted]

In the absence of head-to-head trial data for SEC, being compared with other BRMs, the manufacturer conducted a Bayesian MTC analysis based on a systematic review of RCTs to compare the efficacy of SEC with adalimumab, etanercept, goliumumab, infliximab, and certolizumab pegol. The systematic review and the MTC were found to demonstrate some methodological rigour based on International Society for Pharmacoeconimics and Outcomes Research (ISPOR) criteria. Despite the fact that the patient populations were somewhat heterogeneous and had some potential methodological limitations, overall, SEC demonstrated similar efficacy compared with other BRMs in terms of ASAS response rates and improvements in disease activity in AS patients in the short-term.

4.2.2 Harms

By week 16, the frequency of SAEs and WDAEs were similar between the SEC 150 mg group and the placebo group. TEAEs were generally similar between treatment groups with nasopharyngitis being the most commonly reported. In MEASURE 1, two deaths occurred during the double-blind period, one in the placebo group (on day 80), and one in the SEC 75 mg group (on day 706); neither were considered to be study drug-related. [redacted]

Harms outcomes were not assessed in the manufacturer-submitted MTC.

4.3 Potential place in therapy[1]

The decision to treat a patient with AS is based on clinical presentation and does not require any special tests. Some patients respond well to physical therapy alone or consider their symptoms not severe enough to take medicinal treatment. When inflammatory back pain is significant, treatment includes NSAIDs and TNFis. Traditional DMARDs are ineffective and not recommended, and chronic steroid therapy is not recommended because of the potential for harm.[8] In Canada, the step from NSAIDs to a TNFi requires failure of two or three NSAIDs, each used for two or three weeks. There are currently five TNFis marketed in Canada.

Secukinumab is an IL-17 inhibitor and is the first biologic drug with a different mechanism of action approved by Health Canada for the treatment of AS.[10] No direct evidence is available comparing secukinumab with TNFisl; however, based on a manufacturer-submitted MTC [redacted]

According to the clinical expert consulted for this review, there may be some differences in the harms reported for patients receiving secukinumab (for example, higher rates of non-serious *Candida* yeast infections), but in general, the harms appear to be similar to those reported for patients receiving TNFis. Further, the use of secukinumab requires the same attention to tuberculosis screening and other pre-treatment issues as a TNFi. [redacted]

The place in therapy of secukinumab in the treatment of AS was not discussed in the 2015 ACR recommendations.[8] Based on the current evidence, the clinical expert indicated that the availability of secukinumab does not appear to meet a need that is not provided by the TNFis; however, it could be considered as an alternative to TNFis in NSAID inadequate responders, and as an alternative to switching to another TNFi when a patient has failed a TNFi.

5. CONCLUSIONS

Based on two double-blind RCTs in patients with moderate to severe AS, treatment with SEC 150 mg every four weeks resulted in statistically significant improvements in clinical response (ASAS 20 and ASAS 40) at week 16 when compared with placebo. A statistically significant and clinically meaningful improvement in quality of life (SF-36 PCS, ASQoL); and a statistically significant improvement, but not clinically meaningful improvement in disease activity (BASDAI) was also found for patients receiving SEC 150 mg compared with placebo. Overall, the number of TEAEs was similar between SEC 150 mg and placebo in both studies. [redacted]

Results from a manufacturer-submitted MTC suggested that [redacted]

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

APPENDIX 1: PATIENT INPUT SUMMARY

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

1. Brief description of patient group(s) supplying input

Three patient groups submitted input for this review.

The Arthritis Consumer Expert (ACE) group provides science-based information, education and support programs in both official languages to help people with arthritis take control of their disease and improve their quality of life. The ACE group receives unrestricted grants-in-aid from AbbVie Corporation, Amgen Canada, BIOTECanada, Celgene Inc., Hoffmann-La Roche Canada Ltd., Janssen Inc., Pfizer Canada, Sanofi Canada, and UCB Canada Inc., as well as from public sector organizations. According to ACE, it was solely the staff and advisory board of the organization that aided in the compilation of the patient input they submitted and there was no conflict of interest reported with respect to compiling the patient input information.

The Canadian Arthritis Patient Alliance (CAPA) provides education and creates links between Canadians with arthritis to assist them to become more effective advocates and to improve their quality of life. In the last year, CAPA received grants and support from AbbVie, Amgen Canada, Hoffmann-La Roche, Janssen, Novartis, and UCB Pharma. In the past, CAPA received support from Pfizer Canada, Rx&D, Schering Canada, as well as from several non-pharmaceutical industry sources. CAPA declared no conflict of interest with respect to compiling the patient input information that was submitted.

The Canadian Spondylitis Association (CSA) is a volunteer-run patient organization that creates awareness of spondyloarthritis, and provides information and education to patients with spondyloarthritis and their caregivers and family. CSA also facilitates discussion among its members and support for each other through the use of social media. Members of CSA include patients with ankylosing spondylitis (AS) and psoriatic arthritis. CSA has received restricted educational and developmental grants from AbbVie, Amgen and Janssen, and restricted travel grants from UCB Canada. The president of CSA (who compiled this patient input information) received honoraria from AbbVie (indirectly) and Novartis. CSA declared there was no conflict of interest in respect of compiling the patient input information.

2. Condition related information

Patient input information from the three patient groups was collected from responses to requests for patient input sent via email, Facebook, or from the conversations among the patient group members who live with spondyloarthritis. In addition, one group (ACE) posted on the JointHealth website and provided organizational comments to augment the individual pieces of information from their group.

AS is a serious, debilitating, autoimmune disease characterized by inflammation in the joints of the spine. Patients typically suffer pain (in the back, neck, hips, legs, shoulders, eyes, and feet) and stiffness (particularly in the morning). Limited motion due to stiffness and fusing of the vertebrae is often reported. One individual with AS described: “I have difficulty looking up or down, left or right, without turning my whole body or leaning at precarious and slightly odd angles.”

Fatigue, stress, depression, anxiety and feelings of social isolation are common. AS negatively impacts patients’ day-to-day life, including daily routines (for example, dressing, cooking, and participating in

post-secondary education), sports, and work. Disability is present in severely affected patients and can force them to leave the work force. Depending on a patient's ability to cope with activities of daily living and their ability to stay employed, caregivers of people living with AS are relied upon in varying capacities, including assisting with simple tasks such as bathing, getting in and out of bed, using the toilet, giving the patient their injection, or taking over family responsibilities while the patient is receiving their infusion.

3. Current therapy related information

AS is a chronic and incurable condition that the patient may live with from the onset of symptoms (late teens or early 20s) until death. Treatment of AS is aimed at alleviating symptoms and delaying disease progression. For patients with more severe disease and where NSAIDs and analgesics are insufficient, TNF-inhibitors (TNFis) are prescribed. Individual patients respond differently to these medications. According to the patient groups, any one TNFi is effective in approximately 70% of AS patients and allows them a relatively normal life. However, the efficacy of any individual TNFi can wear off after a period, ranging from months to years, in an individual patient. This means that any particular TNFi will become ineffective in 30% of patients; for the 70% of patients who respond well on TNFi, some will not experience lasting efficacy. Therefore, patients may need to be exposed to many different drugs over their lifetime to achieve the best treatment for their AS. Since biologics suppress the patient's immune system, severe infections are a major concern for patients on biologics. Infections, cold-like symptoms and dizziness, as well as injection site allergic reactions were noted as side effects of TNFi. One patient reported the onset of cancer (follicular lymphoma) while on a biologic.

Patients also expressed concerns related to vein scarring and scar tissues from numerous infusions and injections over a prolonged period of drug use, scheduling issues for infusions, cost, and the need to take time off work or find someone to deal with family commitments. Patients expressed that they need medications that can lessen their AS pain and allow them to perform day-to-day activities, and pose the least chance of adverse effects.

Biologics are costly. Patients have access to the drugs through private and public drug plans, manufacturers' support programs, or find their own financial assistance. Depending on the province, only four or five TNFis are listed for use in AS. When patients do not have drug coverage options, the burden of disease is significant for them and their spouse (as a caregiver) as well. 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 treatment stops working. The best treatment is one that has the fewest side effects.

4. Expectations about the drug being reviewed

Different from the currently available biologics for AS, which are all anti-TNF drugs, secukinumab targets IL-17A. Therefore it is possible that when patients no longer respond to the current biologic therapy, they may still have a chance to benefit from secukinumab. In addition, the monthly treatment regimen of secukinumab would reduce the required amount of time on infusions.

The patient groups did not receive responses from patients who have been taking secukinumab to treat their AS. Given the information that has been made available about secukinumab and data from the clinical trials, it is estimated that this drug will be more efficacious than TNFi therapy, as safe, and possibly cheaper and hopefully effective in AS patients who have had inadequate response to TNFi. If patients' overall well-being improves (reduction in pain, stiffness, fatigue and depression; improvement

in quality of life; and return to more normal activities) for most of the time after they are on the drug, they will be willing to experience the side effects related to the drug.

The ACE group also indicated that "ACE advocates for evidence- and experience-based reimbursement recommendations. Doing so appropriately offers more medication options and creates an environment for the physician and patient to practice 'personalized medicine' and possibly achieve disease remission," and it believes that "clinical trials are extremely important to advancing research into new and effective treatments… patients across the country who are refractory to current therapies rely on the emerging treatments being tested in clinical trials and post-marketing studies."

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 19 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	exp spondylarthropathies/ or exp Ankylosis/ use pmez	27578
3	((Spondyloarthr* or Spondylarthr* or Spondylit* or spondilit* or spine or spinal or vertebrae or vertebraes or vertebral) adj3 (Ankylopoietica* or Ankylos* or ankylat* or ankylot* or Rheumat*)).ti,ab,kf. use pmez	12855
4	(Marie Struempell* or Bechterew* or Becterev or Spondyloarthropath* or Spondylarthropath*).ti,ab,kf. use pmez	3635
5	2 or 3 or 4	31959
6	1 and 5	37
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	exp ankylosing spondylitis/	35280
11	exp spondyloarthropathy/	24509
12	10 or 11	45898
13	12 use oemezd	25784
14	((Spondyloarthr* or Spondylarthr* or Spondylit* or spondilit* or spine or spinal or vertebrae or vertebraes or vertebral) adj3 (Ankylopoietica* or Ankylos* or ankylat* or ankylot* or Rheumat*)).ti,ab,kw. use oemezd	19378
15	(Marie Struempell* or Bechterew* or Becterev* or Spondyloarthropath* or Spondylarthropath*).ti,ab,kw. use oemezd	5319
16	13 or 14 or 15	29952
17	9 and 16	77
18	6 or 17	114
19	conference abstract.pt.	2180083
20	18 not 19	80
21	remove duplicates from 20	52

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, ankylosing spondylitis
Limits:	No date or language limits used

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

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Baeten D, Baraliakos X, Braun J. Erratum: Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. The Lancet 2013; 382:1705-13. The Lancet. 014;383(9928):1548.	Abstract
Baeten D, Baraliakos X, Braun J, Sieper J, Emery P, van der HD, et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2013 Nov 23;382(9906):1705-13.	Intervention not of interest

APPENDIX 4: VALIDITY OF OUTCOME MEASURES

Aim

The purpose of this section is to provide an overview of the characteristics, validity, and clinically important differences of the scales measured in trials included in the CADTH Common Drug Review systematic review. These scales include the Assessment of SpondyloArthritis International Society (ASAS) response criteria, the Ankylosing Spondylitis Quality of Life (ASQoL), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), SF-36, the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue), and the Work Productivity and Activity Impairment — General Health (WPAI-GH).

Findings

Table 12: Summary of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
ASAS response criteria	A composite set of response criteria which are commonly used in AS trials, contains 6 domains.	Yes	Unestablished	[31-36]
ASQoL	Self-administered disease-specific questionnaire, 18 items, scores ranging from 0 to 18.	Yes	–1.8	[26,37,38]
BASDAI	Self-administered disease-specific questionnaire, a composite index containing 6 questions related to 5 major symptoms of AS, scores ranging from 0 to 10.	Yes	2 units	[23,39-43]
SF-36	A 36-items generic health state instrument contains 8 domains and 2 component summaries on physical and mental health. Domain scores and summary scores ranging from 0 to 100.	Yes	2.5 to 5 points	[24,25,44]
FACIT-Fatigue	A 13-item self-reported questionnaire, scores ranging from 0 to 52.	Yes	3 to 4 units	[27,45]
WPAI-GH	Self-administered instrument used to measure the impact of disease on productivity.	Yes	Unestablished	[23,46,47]

ASAS = Assessment of SpondyloArthritis International Society; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; MCID = mimimum clinically important difference; SF-36 = Medical Outcomes Study Questionnaire Short Form 36; WPAI-GH = Work Productivity and Activity Impairment-General Health.

Assessment of Ankylosing Spondylitis Response criteria

The ASAS working group developed a composite set of response criteria that is commonly used in AS clinical trials. The ASAS working group is an international group of rheumatologists, epidemiologists, patients with AS, and pharmaceutical industry representatives from more than 21 countries.[31,32]

The ASAS international working group has defined a core set of six domains that are important in assessing "symptomatic" outcomes in AS. These domains include: measures of physical function, pain, patient's global assessment of disease activity, spinal mobility, spinal stiffness/ inflammation, and fatigue.[33,34] For each domain, one or more assessment instruments are recommended and are represented in the following table.

ASAS Core set of Domains and Instruments for Assessing Signs and Symptoms for each Domain[a]

Table 13: ASAS Core Set of Domains and Instruments for Assessing Signs and Symptoms for Each Domain

Domain	Recommended Instrument
Physical function	BASFI, VAS; DFI
Pain	2 separate questions: total pain in the spine due to AS and pain in the spine at night due to AS.
Patient's global assessment of disease activity	Patient's global VAS score.
Spinal mobility	Four instruments: occiput-to-wall distance; chest expansion; modified Schober test; lateral lumbar flexion or BASMI.
Spinal stiffness/ inflammation	Average of morning stiffness duration and intensity (BASDAI — questions 5 and 6)
Fatigue	Fatigue question from BASDAI

AS = ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; DFI = Dougados Functional Index; VAS = visual analogue scale.
[a]Adapted from van de Heijde 2005.[34]

It should be noted that the ASAS international working group has further designated other domains that should be assessed in addition to the six domains of the symptom-modifying core set for therapies assessed to have proposed disease-modifying properties. These additional domains include: acute-phase reactants (erythrocyte sedimentation rate or C-reactive protein level), number of swollen peripheral joints based on a 44-joint count, and enthesitis (assessed on a validated enthesitis score).[34]

The ASAS response criteria was developed to establish a uniform minimum core set of variables for inclusion in all research projects that may help prevent dilemmas such as AS studies that may have employed inconsistent and excessive numbers of assessment methods. This approach is hoped to help prevent such dilemmas by ensuring: change occurrences of statistically significant differences between groups are minimized; investigators do not introduce bias by selectively publishing only favourable variables; and comparisons can be made between studies including meta-analyses.[35]

ASAS 20 and ASAS 40

ASAS 20 response criteria is defined as an improvement of ≥ 20% and ≥ 1 unit on a scale of 10 in at least 3 of the 4 main domains and no worsening of ≥ 20% and ≥ 1 unit on a scale of 10 in the remaining domain. ASAS 40 response is defined as an improvement of ≥ 40% and ≥ 2 units on a scale of 10 in at least 3 of the 4 main domains and no worsening at all in the remaining domain. The validity, reliability, and responsiveness of the ASAS improvement criteria have been demonstrated in previous studies.[36]

Ankylosing Spondylitis Quality of Life

The purpose of the ASQoL is to assess the disease-specific HRQoL of patients with AS. The ASQoL is a validated self-administered questionnaire containing 18 items with a dichotomous yes/no response option. A single point is assigned for each "yes" response and no points for each "no" response resulting in overall scores that range from 0 (least severity) to 18 (highest severity). Therefore, lower score indicates better quality of life. Items in the ASQoL include an assessment of mobility/energy, self-care, and mood/emotion.

The validity of the ASQoL has been demonstrated in patients with axial spondyloarthritis.[37] In a New Zealand population (N = 63) with axial spondyloarthritis (SpA), the ASQoL had good internal consistency in the sample (alpha = 0.854). A positive correlation was found between the ASQoL and the BASFI (P = 0.635, P < 0.001), BASDAI (P = 0.521, P < 0.001) and patient global assessment VAS (P = 0.546, P < 0.001), providing evidence that the ASQoL has convergent validity among patients with SpA in New Zealand. Test-retest reliability was good over 16 weeks (rho = 0.730, P < 0.001). Test-retest reliability and Cronbach's alpha coefficients were high in the US-English version (0.85 and 0.85, respectively) and Canadian-English version (0.87 and 0.86, respectively).[38] In a survey conducted in the United Kingdom, the acceptability, data quality, and measurement properties of four patient-assessed measures of health outcome in patients with AS, including ASQoL, was conducted. In this survey, the minimum clinically important difference (MCID) of the ASQoL has been identified as a change of −1.8 on the 18-point ASQoL scale, which means that patients meeting this criterion are "quality of life responders."[26] The recall period for ASQoL in MEASURE 1 and MEASURE 2 was "at the moment."

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The most common and widely used validated measure of inflammatory activity of AS is the BASDAI.[22] This instrument for disease activity is a self-administered patient questionnaire. The BASDAI is a composite index that records patients' responses to major symptoms of AS. It includes six questions addressing five major symptoms: fatigue, axial (spinal) pain, peripheral joint pain, localized tenderness, and morning stiffness (both degree of stiffness and length of time for which stiffness persists).[39,40] Patients' responses for each question are recorded on a 10 cm VAS. The final BASDAI score has a range from 0 to 10. The higher the score, the greater the measured degree of disease activity. A reduction in the BASDAI score is considered improvement. The 2005 International ASAS consensus statement for the use of TNFi drugs in patients with AS recommends following the BASDAI after initiation of treatment. The definition of treatment response includes a change in the BASDAI value defined as 2 units (on a 0 to 10 scale) of the BASDAI.[41] The recall period for BASDAI is "past week." The MCID for the BASDAI has been determined as a change of −1.96 on the 10-point BASDAI scale.[23]

In previous research, the BASDAI has been shown to have good test-retest reliability, validity, and responsiveness in patients with AS.[40,42,43] Content and face validity were assessed through an appraisal of item content, while external construct validity required comparison of instrument scores with those for other measures of health, clinical, sociodemographic, and health service use variables.[42] In addition, the BASDAI was found to be quick and simple to complete, and appeared to be sensitive to change in disease activity.[39]

Medical Outcomes Study Short Form-36 (SF-36)

The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas. The SF-36 consists of eight health domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The eight domains are aggregated to create two component summaries: the physical component summary (PCS) and the mental component summary (MCS), with scores ranging from 0 to 100, with higher scores

indicating better health status. The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 and 5 points.[24] Leung et al. reported MCIDs of 3.74 and 1.77 in patients with PsA who were treated with TNFi drugs for the PCS and MCS subsections, respectively.[25] Husted et al.[44] and Leung et al.[25] reported that the SF-36 is reliable and valid for assessment of patients with PsA, and could be used to distinguish patients with PsA from patients without PsA. In addition, the PCS and MCS summary scores support the SF-36 validity.[25]

In MEASURE 1 and MEASURE 2, a patient was considered a PCS or MCS responder if the patient had an increase of ≥ 2.5 points from baseline. In MEASURE 1 and MEASURE 2, the outcome of SF-36 PCS had a one-week recall period.

Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue)
The FACIT-Fatigue is a 13-item self-reported questionnaire that assesses the impact of fatigue on daily activities and function in patients with cancer and other chronic diseases.[27] It has been validated in the general population as well as in patients with different diseases such as cancer, PsA, rheumatoid arthritis, and inflammatory bowel disease.[27,45] The responses to the 13 items on the FACIT-Fatigue questionnaire are each measured on a 4-point Likert scale. Thus, the total score ranges from 0 to 52. High scores represent less fatigue. A difference of 3 to 4 units is considered a MCID.[27]

In 135 patients with PsA, Cronbach's alpha (to measure internal consistency of the 13 items on FACIT-Fatigue) was 0.96. Repeat questionnaires were returned by 54% of patients. The test-retest reliability was high (the intraclass correlation coefficient for first and repeat FACIT-Fatigue scores was 0.95).[45]

Work Productivity and Activity Impairment — General Health (WPAI-GH)
Work productivity was measured by WPAI-GH, a self-administered instrument used to examine the extent of absenteeism, presenteeism, and impairment in daily activities attributable to general health.[47] Four main outcomes can be generated from the WPAI-GH and expressed in percentages: percentage o work time missed due to health for those who were currently employed; percentage of impairment while working due to health for those who were currently employed and actually worked in the past seven days; percentage of overall work impairment due to health for those who were currently employed; and percentage of activity impairment due to health for all respondents. For all four outcomes, greater scores (range 0% to 100%) indicate greater impact on health. The recall period was seven days before the visit. This instrument has been validated in a variety of diseases including AS and rheumatoid arthritis, and it is found to be strongly correlated with the health outcomes and disease status in previous studies.[23,46] The MCID of WPAI-GH is currently unknown.[47]

Conclusion

ASAS response criteria, ASQoL, BASDAI, SF-36, FACIT-Fatigue, and WPAI-GH are all validated instruments that can be used to measure disease activity, patient response to the treatment, change in quality of life associated with AS, and the impact of disease on work productivity in patients with AS. However, limitations exist in the use of these instruments. MCIDs are not always available to help determine the clinical relevance of a change in the health status. Some instruments have not been validated in patients with AS.

APPENDIX 5: SUMMARY OF OUTCOMES FOR MEASURE 1 AND MEASURE 2 AFTER THE PLACEBO-CONTROLLED PERIOD

Aim

To summarize the efficacy and safety data for MEASURE 1 and MEASURE 2 after the placebo-controlled period.

Findings

Study and baseline disease characteristics

The baseline study and disease characteristics are reported in the main text. Briefly, MEASURE 1 and MEASURE 2 are phase 3, double-blind, randomized controlled trials. In MEASURE 1, patients in the placebo group were re-randomized to SEC 150 mg or SEC 75 mg at week 16 or week 24 depending on their response to placebo (as measured by ASAS 20 criteria). In MEASURE 2, all patients originally randomized to placebo were re-randomized to SEC 150 mg or SEC 75 mg at week 16. Patients were aware that they were to receive active treatment after re-randomization but were blinded to the treatment dose. In MEASURE 1, patients remained dose-blinded until the end of the two-year treatment period (week 104), while in MEASURE 2, patients remained dose-blinded until week 52, and an additional four years open-label treatment were planned thereafter. In both studies, patients originally randomized to the SEC 150 mg or SEC 75 mg groups continued their treatment until the end of study (two years in MEASURE 1 and five years in MEASURE 2). Therefore, there were no patients receiving placebo treatment after week 16 or week 24 in either study. The primary clinical outcome was the ASAS 20 response rate at week 16 in MEASURE 1 and MEASURE 2. Other outcome measures included ASAS 40 response rate, total BASDAI score and HRQoL including the SF-36 PCS, fatigue and disease-specific HRQoL. Safety data included all AEs and routine laboratory analyses were followed. At the time of the current review, efficacy and safety data up to week 104 were available for both studies.

Patient disposition

At baseline, a total of 371 patients were randomized in MEASURE 1, and 219 patients were randomized In MEASURE 2. At week 16, 31.1% (MEASUARE 1) and 45.9% (MEASURE 2) of patients in the placebo groups escaped to the SEC 150 mg group; 32.0% (MEASUARE 1) and 43.2% (MEASURE 2) of patients in the placebo groups escaped to the SEC 75 mg group. At week 52, the completion rates were similar across treatment groups (ranging from 81.1% to 84.8%). At week 104 in MEASURE 1, 28 patients in the original SEC 150 mg group and 32 patients in the original placebo group discontinued the study; in MEASURE 2, 12 patients in the original SEC 150 mg group and 17 patients in the original placebo group discontinued the study.

TABLE 14: PATIENT DISPOSITION UP TO WEEK 104 IN MEASURE 1 AND MEASURE 2

	MEASURE 1		MEASURE 2	
	SEC 150 mg	**Placebo[a]**	**SEC 150 mg**	**Placebo[b]**
Screened, N	448[c]		253[d]	
Randomized, N	125	122	72	74
Discontinued by week 16, N (%)	4 (3.2)	10 (8.2)	6 (8.3)	8 (10.8)
Escaped to SEC 150 mg at week 16	N/A	38 (31.1, placebo-nonresponders)	N/A	34 (45.9)
Escaped to SEC 75 mg at week 16, N (%)		39 (32.0, placebo-nonresponders)		32 (43.2)
Escaped to SEC 150 mg at week 24		18 (14.8, placebo-responders)		N/A
Escaped to SEC 75 mg at week 24, N (%)		17 (13.9)		
Discontinued during week 17 to 52, N (%)	15	10[e]	5	6[f]
Lack of efficacy	5	4	3	5
Adverse event	6	2	1	
Lost to follow-up			-	-
Non-compliance with study treatment	1	1	-	-
Pregnancy	1	-	-	-
Withdrew	2	3	1	1
Completed, week 52, N (%)	106 (84.8)	102 (83.6): • 50 in SEC 75 mg group • 52 in SEC 150 mg group.	61 (84.7)	60 (81.1): • 28 in SEC 75 mg group • 32 in SEC 150 mg group.
Discontinued during week 53 to 104, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Subject/guardian decision	[redacted]	[redacted]	[redacted]	[redacted]
Completed, week 104	[redacted]	[redacted]	[redacted]	[redacted]

	MEASURE 1		MEASURE 2	
	SEC 150 mg	**Placebo[a]**	**SEC 150 mg**	**Placebo[a]**
FAS, N (%)	125 (100)	122 (100)	72 (100)	74 (100)
PP, N (%)	105 (84)	105 (86)	67 (93)	71 (96)
Safety, N (%)	125 (100)	122 (100)	72 (100)	74 (100)

FAS = full analysis set; IV = intravenously; N/A = not applicable; PP = per-protocol; SEC = secukinumab SC = subcutanously.
[a] After week 16, 38 placebo non-responders were re-randomized to receive SEC 150 mg or 75 mg SC; after week 24, 18 placebo-responders were re-randomized to receive SEC 150 mg or 75 mg SC. This resulted in 111 placebo patients treated with SEC after re-randomization.
[b] After week 16, patient in the placebo group were re-randomized to receive SEC 150 mg or 75 mg SC.
[c] Included patients who were randomized to SEC 10 mg/kg IV as loading dose and 75 mg SC as maintenance dose.
[d] Included patients who were randomized to SEC 150 mg SC as loading dose and 150 mg SC as maintenance dose.
[e] Included 6 patients who were re-randomized to receive SEC 75 mg SC.
[f] Included 4 patients who were re-randomized to receive SEC 75 mg SC.
Source: Clinical Study Reports.[20,21]

Efficacy

In MEASURE 1, ASAS 20, ASAS 40 response rates, and effect measures for all other secondary efficacy outcomes observed at week 16 in the SEC 150 mg dose group were sustained through week 52 (Table 15 and Table 16). Improvements in ASAS 20 (60.8%) observed for the original SEC 150 mg group at week 16, were maintained up to week 52 (63.2%). Non-responder imputation was used in the analysis of ASAS response criteria. Similar findings were reported for ASAS 40 (51.2%) and patient-reported HRQoL outcomes. Patients originally randomized to placebo that either escaped at week 16 or escaped at week 24 and were subsequently re-randomized to treatment with SEC 150 mg or SEC 75 mg every four weeks, experienced improvements in ASAS 20 and ASAS 40 response rates following treatment with SEC 150 mg; these improvements were maintained through to week 52 of the study.

Similar to MEASURE 1, in MEASURE 2, ASAS 20 and ASAS 40 response rates, and effect measures for all other secondary efficacy outcomes observed at week 16 in the SEC 150 mg dose group were sustained through week 52 (Table 15 and Table 16). Improvements in ASAS 20 (61.1%) observed for the original SEC 150 mg group at week 16, were maintained to week 52 (62.5%). Non-responder imputation was used in the analysis of ASAS response criteria. Similar findings were reported for ASAS 40 (48.6% at week 52) and patient-reported HRQoL outcomes. Patients originally randomized to placebo who escaped at week 16 and were subsequently re-randomized to SEC treatment (SEC 150 mg or SEC 75 mg every 4 weeks), experienced improvements in ASAS 20 and ASAS 40 response rates following SEC 150 mg treatment; these improvements were maintained through to week 52 of the study.

TABLE 15: [redacted]

	MEASURE 1			MEASURE 2	
	Original SEC 150 mg (N = 125)	**Placebo to SEC 150 mg at week 16 (N = 38)**	**Placebo to SEC 150 mg at week 24 (N = 18)**	**Original SEC 150 mg (N = 72)**	**Placebo to SEC 150 mg at week 16 (N = 34)**
Clinical Response					
ASAS 20, n/N (%)[a]	[redacted]				
ASAS 40, n/N (%)[a]	[redacted]				
HRQoL					
SF-36 PCS score change from baseline (LS mean, SE)[b]	[redacted]				
ASQoL change from baseline (LS mean, SE)[b]	[redacted]				
FACIT-Fatigue change from baseline (mean, SD)[c]	[redacted]				
EQ-5D VAS change from baseline (mean, SD)[c]	[redacted]				
Disease Activity					
Total BASDAI score change from baseline (LS mean change, SE)[b]	[redacted]				
Work Productivity: WPAI-GH					
% work time missed due to health (mean, SD)[c]	[redacted]				
% impairment while working due to health	[redacted]				
% overall work impairment due to health	[redacted]				
% activity impairment due to health	[redacted]				

ASAS = Assessment of Ankylosing Spondylitis; ASQoL = the Ankylosing Spondylitis Quality of Life scale; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = confidence interval; FACIT-Fatigue = the Functional Assessment of Chronic Illness Therapy-Fatigue Scale; IR = inadequate responder; LS = least square; N/A = not applicable; NR = not reported; OR = odds ratio; PCS = physical component summary; SD = standard deviation; SE = standard error; SEC = secukinumab; SF-36 = Medical Outcomes Study Questionnaire Short Form 36; VAS = visual analogue scale; WPAI-GH = Work Productivity and Activity Impairment-General Health.

[redacted]

Source: Clinical Study Reports.[20,21]

TABLE 16: TREATMENT EFFECT OF SEC AT WEEK 52

	MEASURE 1			MEASURE 2	
	Original SEC 150 mg (N = 125)	**Placebo to SEC 150 mg at week 16 (N = 38)**	**Placebo to SEC 150 mg at week 24 (N = 18)**	**Original SEC 150 mg (N = 72)**	**Placebo to SEC 150 mg at week 16 (N = 3 4)**
Clinical Response					
ASAS 20, n/N (%)[a]	79/125 (63.2)	[redacted]	[redacted]	45/72 (62.5)	[redacted]
ASAS 40, n/N (%)[a]	64/125 (51.2)	[redacted]	[redacted]	35/72 (48.6)	[redacted]
Health-Related Quality of Life					
SF-36 PCS score change from baseline (LS mean, SE)[b]	6.65 (0.62) N = 110	[redacted]	[redacted]	6.82 (0.90) N = 62	[redacted]
ASQoL change from baseline (LS mean, SE)[b]	–4.35 (0.42) N = 109	[redacted]	[redacted]	–4.80 (0.58) N = 61	[redacted]
FACIT-Fatigue change from baseline (mean, SD)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D VAS change from baseline (mean, SD)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease Activity					
Total BASDAI score change from baseline (LS mean change, SE)[b]	–2.79 (0.18) N = 103	[redacted]	[redacted]	–2.85 (0.26) N = 61	[redacted]
Work Productivity: WPAI-GH					
% work time missed due to health (mean, SD)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% impairment while working due to health	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% overall work impairment due to health	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% activity impairment due to health	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ASAS = Assessment of Ankylosing Spondylitis; ASQoL = the Ankylosing Spondylitis Quality of Life scale; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = confidence interval; FACIT-Fatigue = the Functional Assessment of Chronic Illness Therapy-Fatigue Scale; IR = inadequate responder; LS = least square; N/A = not applicable; NR = not reported; OR = odds ratio; PCS = physical component summary; SD = standard deviation; SE = standard error; SEC = secukinumab; SF-36 = Medical Outcomes Study Questionnaire Short Form 36; VAS = visual analogue scale; WPAI – GH = Work Productivity and Activity Impairment - General Health.

[a] Using non-responder imputation; Odds ratio, 95% CI, and *P* value were from a logistic regression model with treatment and TNFi status as the factors and baseline weight as a covariate.

[b] LS Mean, SE, 95% CI and *P* value were from mixed-effect model repeated measures (MMRM) with treatment sequence, visit, TNFi status as factors, baseline weight as covariates, treatment sequence by visit and baseline by visit as interaction terms.

[C] Using observed data, only subjects with a value at both baseline and week 52 were included.

Source: Clinical Study Reports.[20,21]

[redacted] (Table 17). X-rays of the cervical, thoracic, and lumbar spine were performed at baseline and week 104. In MEASURE 1, a summary of mSASSS and RASSS and change from baseline for the overall population (including originally randomized SEC dose groups and the placebo patients who switched to the SEC groups). [redacted]

TABLE 17: [redacted]

	MEASURE 1	MEASURE 2
	Original SEC 150 mg (N = 125)	**Original SEC 150 mg (N = 72)**
Clinical Response		
ASAS 20, n/N (%)[a]	[redacted]	[redacted]
ASAS 40, n/N (%)[a]	[redacted]	[redacted]
Health-Related Quality of Life		
SF-36 PCS score change from baseline (mean, SD)[a]	[redacted]	[redacted]
ASQoL change from baseline (LS mean, SE)[a]	[redacted]	[redacted]
Disease Activity		
Total BASDAI score change from baseline (mean, SD)[a]	[redacted]	[redacted]
Radiographic Progression		
mSASSS change from baseline (mean, SD)	[redacted]	[redacted]
RASSS change from baseline (mean, SD)	[redacted]	[redacted]

ASAS = Assessment of Ankylosing Spondylitis; ASQoL = the Ankylosing Spondylitis Quality of Life scale; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = confidence interval; FACIT-Fatigue = the Functional Assessment of Chronic Illness Therapy-Fatigue Scale; IR = inadequate responder; LS = least square; mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score; OR = odds ratio; PCS = physical component summary; RASSS=Radiographic Ankylosing Spondylitis Spinal Score; SD = standard deviation; SE = standard error; SEC = secukinumab; SF-36 = Medical Outcomes Study Questionnaire Short Form 36; VAS = visual analogue scale; WPAI – GH = Work Productivity and Activity Impairment — General Health.

[a] Using observed data, only patients with a value at both baseline and week 104 were included.

[b] Included patients originally randomized to the SEC groups and placebo patients who switched to SEC treatment; only patients with paired X-ray data at both baseline and week 104 were analyzed.

Source: Clinical Study Reports.[20,21]

Safety

In MEASURE 1, safety data up to week 104 were reported. Due to the study design, a minor proportion of patients remained on placebo past week 16 (35 of 122; 29%), and no patients remained on placebo after week 24. Thus, safety data were only available for patients in the SEC groups after week 24.

In the any SEC 150 mg group (included 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 = 181); 85.1% of patients reported TEAEs at week 52. [redacted]

[redacted]. Nasopharyngitis, diarrhea, headache, and pharyngitis were the most common AEs. The safety profile of SEC 150 mg maintenance therapy at week 104 was similar to that observed at week 52. Two deaths (one in the SEC 75 mg group and one in the placebo group) occurred by week 52. [redacted].

Similar findings were reported in MEASURE 2. Due to the study design, no patients remained on placebo after week 16. Thus, safety data were only available for patients in the SEC groups after week 16.

In the any SEC 150 mg group (included patients randomized at baseline to SEC 150 mg, and placebo patients re-randomized to 150 mg SEC; N = 106), 82.1% of patients reported 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), the total incidence of TEAEs was 84.9% in the any 150 mg group, and the majority of AEs were mild or moderate in severity. Nasopharyngitis, diarrhea, headache, and upper respiratory tract infection were the most common AEs. The safety profile of SEC 150 mg maintenance therapy at week 104 was similar to that observed at week 52. [redacted]

TABLE 18: [redacted]

	MEASURE 1 [redacted]		MEASURE 2 [redacted]	
	week 52	**week 104**	**week 52**	**week 104**
TEAE > 0, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Dyslipidemia	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
WDAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]

SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports.[20,21]

Limitations

The main limitations of the longer-term outcomes reported at week 52 and week 104 was the lack of a comparator group and the open-label trial design after week 24. These limitations are particularly important to note for the interpretation of patient-reported outcomes and subjective outcomes. In both studies, the analysis the binary outcomes (such as the ASAS response rate) was conducted using logistic regression with treatment group and TNFi response status as independent variables, and body weight as a covariate, based on the full analysis set. Missing values, including those due to discontinuation of the study treatment, were imputed as non-responders. Between-group differences in continuous outcomes (such as the total BASDAI score) were analyzed using a mixed-model repeated-measure (MMRM) approach, with treatment group, assessment visit, and TNFi response status as factors; weight and baseline values of the outcome were included in the model as continuous covariates. Missing data were assumed to be missing at random; however, this assumption may not be appropriate. In general, lack of efficacy and AEs are main reasons for patients dropping out of trials, and therefore more favourable HRQoL outcomes may have been reported for those patients who remained in the trial. [redacted] No sensitivity analyses were conducted with alternative imputation strategies to test the robustness of the missing-at-random assumption. Long-term safety outcomes were based on observed data, and no radiographic data or work productivity outcomes were reported beyond week 52.

Summary

The improvements in clinical response rates and patient-reported outcomes, which were observed over 16 weeks of MEASURE 1 and MEASURE 2 in the SEC 150 mg regimen, were maintained throughout the dose-blind trial period and the open-label period up to 104 weeks. The safety profile observed in patients with active AS receiving SEC 150 mg over 104 weeks was consistent with that observed during the double-blind, placebo-controlled phase of the trial (up to 16 weeks), with no new safety signals reported.

APPENDIX 6: SUMMARY OF INDIRECT COMPARISONS

Introduction

Background

The clinical trials included in this review did not provide direct evidence regarding the comparative efficacy and safety of secukinumab (SEC) relative to currently available TNFis. The aim of this section was to provide an overview and critical appraisal of the published and unpublished indirect evidence available for the assessment of the comparative efficacy and harms of SEC 150 mg with the available biologic response modifiers and their respective biosimilars in patients with active AS.

Methods

[redacted]

Description of the MTC identified

[redacted]

TABLE 19: [redacted]

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

[redacted]

Review of the manufacturer-submitted MTC

[redacted]

Methods for the manufacturer-submitted MTC

[redacted]

[redacted]

[redacted]

FIGURE 3: [redacted]

[redacted]

Indirect comparison methods

[redacted]

[redacted]

Results

[redacted]

TABLE 20: [redacted]

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

[redacted]

[redacted]

[redacted]

TABLE 21: [redacted]

[redacted]										
[redacted]										

[redacted]

TABLE 22: [redacted]

[redacted]				
[redacted]				

[redacted]

[redacted]

TABLE 23: [redacted]

[redacted]								
[redacted]								

[redacted]

TABLE 24: [redacted]

[redacted]				
[redacted]				

TABLE 25:

TABLE 26:

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

[redacted]

Critical appraisal

[redacted]

[redacted]

[redacted]

[redacted]

Conclusion

[redacted]

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