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CADTH COMMON DRUG REVIEW

Clinical Review Report

IXEKIZUMAB (Taltz)

(Eli Lilly Canada Inc.)

Indication: For the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to, or are intolerant to conventional therapy.

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Abbreviations

ACE	Arthritis Consumer Experts
ACR	The American College of Rheumatology
AE	adverse event
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
ASAS	The Assessment of Spondyloarthritis International Society
ASAS HI	Assessment of Spondyloarthritis International Society Health Index
ASDAS	Ankylosing Spondylitis Disease Activity Score
axSpA	axial spondyloarthritis
BASDAI	The Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASRI	Bath Ankylosing Spondylitis Radiology Index
bDMARD	biological disease-modifying antirheumatic drug
CDEC	CADTH Canadian Drug Expert Committee
cDMARD	conventional disease-modifying antirheumatic drug
CAPA	Canadian Arthritis Patient Alliance
CI	confidence interval
CRP	C-reactive protein
CSA	Canadian Spondylitis Association
DB	double blind
DFI	Douglas Functional Index
DMARD	disease-modifying antirheumatic drug
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
HLA	human leukocyte antigen
HRQoL	health-related quality of life
ICC	intraclass correlation coefficient
IgG	immunoglobulin G
IL	interleukin
ITC	indirect comparison
ITT	intention to treat

IXE	ixekizumab
JSEQ	Jenkins Sleep Evaluation Questionnaire
LOCF	last observation carried forward
LSM	least squares mean
mSASSS	Modified Stoke Ankylosing Spondylitis Score
mBOCF	modified baseline observation carried forward
MID	minimal important difference
MMRM	mixed-effects model of repeated measures
MS	Multiple sclerosis
NMA	network meta-analysis
NRI	nonresponder imputation
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug
OCA	observed case analysis
OR	odds ratio
PGA	Patient Global Assessment
PCS	Physical Component Summary
PP	plaque psoriasis
PsA	psoriatic arthritis
QIDS-SR16	Quick Inventory of Depressive Symptomatology–Self Report 16 items
rad-axSpA	radiographic axial spondyloarthritis; also called ankylosing spondylitis (AS)
RASSS	Radiographic Ankylosing Spondylitis Spinal Score
RCT	randomized controlled trial
ROC	receiver operating characteristic
RR	relative risk
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SEC	secukinumab
SF-36	Short Form (36) Health Survey

SIJ	sacroiliac joint
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
TEAE	treatment-emergent adverse event
TNFi	tumour necrosis factor inhibitor
VAS	visual analogue scale
WDAE	withdrawal due to adverse event
WPAI-SpA	Work Productivity Activity Impairment–Spondyloarthritis

Drug	Ixekizumab (Taltz)
Indication	Treatment of adult patients with active ankylosing spondylitis who have responded inadequately to, or are intolerant to conventional therapy
Reimbursement request	As per indication
Dosage form(s) and route of administration/strength(s)	Solution for subcutaneous Injection (SC) 80 mg / 1.0 mL
NOC date	February 4, 2020
Sponsor	Eli Lilly Canada Inc.

Executive Summary

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease primarily involving the spine and the sacroiliac joints (SIJ).[1,2] It usually begins in young adults (< 45 years old). AS is more common among men.[1] Patients with AS exhibit radiographic abnormalities consistent with sacroiliitis. Patients experience back pain and progressive spinal stiffness and may also suffer from non-arthritic manifestations such as uveitis, skin psoriasis, and inflammatory bowel disease. AS symptoms and the rate of progression fluctuate with time, which results in functional impairment and subsequent potential socioeconomic consequences and disability; therefore, the disease negatively impacts patients' health-related quality of life (HRQoL).[1-3] A diagnosis of AS can be made based on the clinical features, genetic testing, biological testing, and imaging examinations of the disease.[2] The modified New York classification criteria for AS have often been applied as a diagnostic instrument.[4,5] In the 2009 to 2010 National Health and Nutrition Examination Survey (NHANES) of the general population in the US, the prevalence of AS was 0.55%.[1] In a report published by the Arthritis Society in 2011, AS was estimated to affect approximately 150,000 to 300,000 Canadians and approximately 58% of Canadian patients have active disease, as determined by a disease-specific test (the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]; a BASDAI score ≥ 4 indicates active disease).[6,7]

The goals of treatment for patients with AS are to reduce symptoms, maintain spinal flexibility, reduce functional limitations, maintain work ability, and decrease disease complications.[8] 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. Second-line treatment is the tumour necrosis factor inhibitors (TNFis), such as adalimumab, certolizumab, etanercept, golimumab, and infliximab, should NSAIDs fail or if there are contraindications. Secukinumab (SEC, an interleukin 17 [IL-17] inhibitor) has been approved for treatment for patients with AS in Canada. Treatment recommendations for AS and non-radiographic axial spondyloarthritis (SpA) are similar.[8]

Ixekizumab (IXE), as known by the brand name Taltz, is a humanized immunoglobulin G4 (IgG4) monoclonal antibody that selectively binds and neutralizes the pro-inflammatory cytokine IL-17A. IXE inhibits the release of pro-inflammatory cytokines and chemokines. IXE is supplied as solution for subcutaneous injection (SC) at a concentration of 80 mg/1.0 mL. IXE targets IL-17A and inhibits its interaction with the IL-17 receptor. In Canada, Health

Canada's approved indications for IXE include treatment of adult patients with moderate to severe plaque psoriasis (PP) who are candidates for systemic therapy or phototherapy, and treatment of adult patients with active psoriatic arthritis (PsA) who have responded inadequately to or are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). IXE has been previously reviewed by CADTH for the treatment of adult patients with PP and patients with PsA. The CADTH Canadian Drug Expert Committee (CDEC) has recommended that IXE be reimbursed for the treatment of patients with moderate to severe PP and adult patients with active PsA who have responded inadequately to, or are intolerant to one or more DMARD.

Currently, the new Health Canada-approved indication for IXE is for treatment of adult patients with active AS who have responded inadequately to, or are intolerant to conventional therapy.[9] The Health Canada-recommended dose of IXE for treatment of AS is 80 mg SC once every four weeks. Limited data suggests that some TNFi-experienced patients with AS may benefit from a 160 mg SC starting dose. Conventional DMARDs (cDMARDs) (e.g., sulfasalazine), corticosteroids, NSAIDs, and/or analgesics may be continued during treatment with IXE.[9]

The objective of this review is to perform a systematic review of the beneficial and harmful effects of IXE (solution for SC injection, 80 mg/1.0 mL) for the treatment of adult patients with active AS who have responded inadequately to, or are intolerant to conventional therapy.

Stakeholder Engagement

Patient Input

Three patient input submissions were received for this review from the Canadian Spondylitis Association (CSA), Arthritis Consumer Experts (ACE), and the Canadian Arthritis Patient Alliance (CAPA) and the Arthritis Society (via joint submission). The information was gathered mainly through online surveys (website, Facebook, and Twitter) or surveys distributed via email. Patient groups indicated that common symptoms of AS that have the greatest impact on patients' day-to-day lives and daily activities included spinal pain, mobility, fatigue, and sleep. Patients are also faced with several psychological consequences. Patient groups emphasized that AS impacts lives in many ways, such as making it difficult or impossible to do simple things such as caring for or spending time with family and friends, participating in leisure activities, driving, working, and parenting. Consequently, the HRQoL of patients with AS was negatively affected.

Patients with AS desire more treatment options that can reduce pain, fatigue, joint stiffness, and swelling, slow down the disease progression, improve function, and reduce disability. They expect new treatments can increase their ability to work and be productive at work, as well as improve quality of life with less medication side effects.

Clinician Input

The following input is a summary of information provided by one clinical specialist with expertise in the diagnosis and management of AS:

There is an unmet need for the treatment of patients with active AS for the following reasons: not all patients respond to available treatments; some patients become refractory to current treatments; some treatments are not tolerated or are toxic; some treatments associated with

poor compliance; and many treatments are not convenient for the patient. Therefore, there remains a need for ongoing drug development in AS.

NSAIDs are first-line pharmacotherapeutic treatment for AS and failure of NSAIDs lead to the use of TNFis. Current treatment regimens permit ongoing treatment with NSAIDs. IL-17 inhibitors are available as treatment after failure of NSAIDs and as treatment after failure of a TNFi. IXE is the second IL-17 inhibitor to be approved by Health Canada for use in AS and joins five TNFis and their biosimilars in this therapeutic area. The 2019 American College of Rheumatology (ACR) guidelines on treatment of AS [8] indicated that TNFis are recommended over SEC or IXE as first-line biologics. SEC or IXE is recommended over a second TNFi in patients with a primary non-response to the first TNFi.

According to current CDR-participating plans reimbursement criteria, at this time, the singular basis for initiation of treatment of biologic DMARDs (bDMARDs) is the level of BASDAI. A BASDAI score of greater than four, despite treatment with NSAIDs, allows application for a biologic. There are no well-studied predictors of response to treatment. In the randomized controlled trials (RCTs) included for this review, patients with total ankylosis of the spine were excluded. However, the clinical expert indicated that, in real life, such patients may well demonstrate considerable decreases in pain, stiffness, and fatigue, and meaningful improvements in quality of life.

Currently, a pre-symptomatic state of AS is not recognized. There are no studies to consider prevention of disease in patients at high risk, for example a human leukocyte antigen B27 (HLA-B27) positive individual with a parent or sibling with definite AS. In patients with known inflammatory bowel disease, IL-17 inhibitors are not an optimal choice because of the risk of increased flares of bowel disease when IL-17 is inhibited. However, patients with inactive bowel or eye disease can be treated with proper vigilance. In contrast, IL-17 inhibition would be considered first-line therapy in patients with a personal or family history of multiple sclerosis (MS) because TNFis are associated with exacerbations of MS. At this time, it is not possible to identify those patients who are most likely to exhibit a response to treatment with IXE.

Co-administration of methotrexate with a TNFi is not recommended, nor is a treat-to-target strategy, discontinuation, or tapering of biologics in patients with stable disease recommended.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two pivotal studies (COAST-V and COAST-W) are included in this review. The COAST-V study (N = 341) was a phase III, multi-centre, randomized, double-blind, placebo-controlled trial with an active reference arm (adalimumab), examining the efficacy and safety of two IXE dosing regimens (IXE 80 mg SC every two weeks and IXE 80 mg SC every four weeks), as compared to placebo (SC) in adult patients with active AS who were bDMARD-naive during a double-blind, 16-week treatment period. Starting doses of 80 mg and 160 mg were evaluated for each IXE regimen. Adalimumab was selected as the active reference for comparison with placebo (see Figure 2). The COAST-W study (N = 316) was also a phase III, randomized, double-blind, placebo-controlled trial in adult patients with active AS, who had an inadequate response to, or intolerance of one or two TNFis. The objective of COAST-

W was to examine the efficacy and safety of two IXE dosing regimens (IXE 80 mg SC every two weeks and IXE 80 mg SC every four weeks) with placebo (with an 80 mg or 160 mg starting dose). The primary outcomes in both studies were Assessment of Spondyloarthritis International Society criteria (ASAS 40) assessed at week 16. An ASAS 40 response is defined as a 40% or greater improvement and an absolute improvement from baseline of two or greater units (range = 0 to 10) in three or more of four main domains (i.e., Patient Global, Spinal Pain, Function, and Inflammation), without any worsening in the remaining domain. The key secondary outcomes were: ASAS 20 (defined as a 20% or greater improvement and an absolute improvement from baseline of one or more units [range = 0 to 10] in three or more of four main domains, without any worsening in 20% or greater and one or more units [range = 0 to 10] in the remaining domain); Bath Ankylosing Spondylitis Functional Index (BASFI), which assesses the physical function in patients with AS; Medical Outcomes Study Questionnaire Short Form (36) Health Survey, Physical Component Summary (SF-36 PCS); BASDAI, which measures the inflammatory activity of AS; and Spondyloarthritis Research Consortium of Canada spinal magnetic resonance imaging (MRI Spine SPARCC), which measures bone marrow edema in patients with AS.

Both of the COAST-V and COAST-W studies included four periods (see Figure 2 and Figure 3); a screening period, a blinded treatment dosing period (16 weeks), an extended treatment period (to week 52), and a post-treatment follow-up period (up to 24 weeks).

Both COAST-V and COAST-W were conducted in multiple countries including Canada, the US, South America, and European and Asian countries (see Table 4).

Since the Health Canada-recommended dose of IXE for AS is 80 mg SC every four weeks, the results for the IXE 80 mg every two weeks treatment groups are not presented in this report.

Efficacy Results

Key efficacy and safety results are summarized in Table 1.

Clinical response (i.e., ASAS 40): In COAST-V at week 16, the proportion of patients who achieved ASAS 40 was 48.1% and 18.4% in the IXE 80 mg SC every four weeks and placebo groups, respectively. The mean between-group difference (IXE versus placebo) was 29.8% (95% CI, 16.2% to 43.3%; P < 0.001). In COAST-W, the proportion of patients who achieved ASAS 40 was 25.4% and 12.5% in the IXE 80 mg SC every four weeks and placebo groups, respectively. The mean between-group difference (IXE versus placebo) was 12.9% (95% CI, 2.7% to 23.2%; P = 0.017). According to the clinical expert CADTH consulted for this review, ASAS 20 at week 12 has been considered an acceptable clinical response for the bDMARDs trials in AS. Therefore, ASAS 40 at week 16 may be considered a major clinical improvement.

HRQoL (i.e., SF-36 PCS): In COAST-V, at week 16, the least squares mean (LSM) changes from baseline for SF-36 PCS were 7.69 and 3.64 in the IXE 80 mg SC every four weeks and placebo groups, respectively and the between-group LSM difference (IXE versus placebo) was 4.05 (95% CI, 1.94 to 6.16; P < 0.001). In COAST-W, at week 16, the LSM changes from baseline for SF-36 PCS were 6.58 and 1.36 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was 5.21 (95% CI, 3.02 to 7.41; P < 0.001). These results are shown in Table 1. A statistically and clinically significant greater improvement (minimal important difference [MID]: 2.5 to 5.0) was observed in patients receiving IXE 80 mg SC every four weeks compared with placebo treatment in both COAST-V and COAST-W.

Disease activity reduction (i.e., BASDAI, Ankylosing Spondylitis Disease Activity Score [ASDAS]): In COAST-V, the proportion of patients who achieved BASDAI 50 was reported as 42.0% and 17.2% in the IXE 80 mg SC every four weeks and placebo groups, respectively. The mean between-group difference (IXE versus placebo) was 24.7% (95% CI, 11.4% to 38.1%; P < 0.001). The LSM changes from baseline for ASDAS score were –1.43 and –0.46 in the IXE 80 mg SC every four weeks and placebo groups, respectively, and the between-group LSM difference (IXE versus placebo) was –0.97 (95% CI, –1.25 to –0.70; P < 0.001). The proportion of patients who achieved ASDAS Inactive Disease (< 1.3) was 16.0% and 2.3% in the IXE 80 mg SC every four weeks and placebo treatment groups, respectively. The mean between-group difference (IXE versus placebo) was 13.8% (95% CI, 5.2% to 22.3%; P = 0.007). In COAST-W, at week 16, the LSM changes from baseline for BASDAI scores was –2.17 and –0.92 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was –1.24 (95% CI, –1.81 to –0.67; P < 0.001). The LSM changes from baseline for ASDAS were –1.16 and –0.11 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was –1.05 (95% CI, –1.32 to –0.79; P < 0.001). The proportion of patients who achieved ASDAS low activity disease (< 2.1) were reported to be 17.5% and 4.8% in the IXE 80 mg SC every four weeks and placebo treatment groups, respectively. The mean between-group difference (IXE versus placebo) was 12.7% (95% CI, 4.6% to 20.8%; P = 0.006). A statistically significant greater reduction in disease activity was reported in patients receiving IXE 80 mg SC every four weeks compared with placebo treatment in terms of BASDAI and ASDAS in both COAST-V and COAST-W.

MRI Spine SPARCC Score: In COAST-V, at week 16, the LSM changes from baseline for MRI Spine SPARCC Score were –11.02 and –1.51 in the IXE 80 mg SC every four weeks and placebo groups, respectively, and the between-group LSM difference (IXE versus placebo) was –9.51 (95% CI, –12.6 to –6.4; P < 0.001). In COAST-W, at week 16, the LSM changes from baseline for MRI Spine SPARCC Score change from baseline were –2.99 and 3.29 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was –6.29 (95% CI, –10.0 to –2.5; P = 0.001). Statistically and clinically significant greater improvements in MRI Spine SPARCC Score were observed in both COAST-V and COAST-W.

Overall, the magnitude of treatment response to IXE was less in TNFi-experienced patients in COAST-W compared with bDMARD-naive patients in COAST-V, which reflects the fact that patients included in COAST-W who inadequately responded to, or were intolerant to TNFis were more difficult to treat.

Harms Results

The overall incidence of patients with treatment emergent adverse events (TEAEs) in patients treated with IXE 80 mg SC every four weeks was comparable to that in the placebo group in COAST-V (42.0% versus 39.5%) by week 16; however, it was relatively higher than in the placebo group in COAST-W (64.0% versus 49.0%). The most common TEAEs (> 5% of patients in either of the treatment groups) were nasopharyngitis (7.4% versus 7.0% and [redacted] for COAST-V and COAST-W, respectively) and upper respiratory tract infections (8.6% versus 4.7% and 7.9% versus 2.9%, for COAST-V and COAST-W, respectively), which appeared more in the IXE 80 mg SC every four weeks group than the placebo group, particularly for patients in COAST-W.

The percentage of patients experiencing a serious adverse event (SAE) by week 16 in the IXE 80 mg SC every four weeks and placebo groups was 1.2% versus 0% and 3.5% versus

4.8% in COAST-V and COAST-W respectively. It was noted that no patients withdrew due to adverse events (AEs) in COAST-V.

However, in COAST-W, more patients (8.8%) in the IXE 80 mg SC every four weeks group withdrew due to AEs than in the placebo group (1.9%). No deaths were reported in either of the studies. Furthermore, it appeared that a numerically higher percentage of patients in COAST-W reported notable harms including infections (19.8% versus 15.1% and 29.8% versus 9.6% in COAST-V versus COAST-W, respectively), inflammatory bowel disease, injection site reactions, hypersensitivity, and hepatotoxicity.

Table 1: Summary of Key Results From Pivotal and Protocol Selected Studies (At Week 16)

At week 16	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w. (N = 114)	PBO (N = 104)
Efficacy					
ASAS 40 (NRI, ITT)					
Response, n (%)	39 (48.1)	16 (18.4)	32 (35.6)	29 (25.4)	13 (12.5)
% Diff vs. PBO (95% CI)	29.8 (16.2 to 43.3)		17.2 (4.4 to 30.0)	12.9 (2.7 to 23.2)	
P value vs. PBO	< 0.001		0.005	0.017	
SF-36 PCS at week 16					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16 mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline LSM (SE)	7.69 (0.78)	3.64 (0.75)	6.90 (0.73)	6.58 (0.78)	1.36 (0.81)
Between-group LSM diff (95% CI)	4.05 (1.94 to 6.16)		3.26 (1.20 to 5.31)	5.21 (3.02 to 7.41)	
P value	< 0.001		0.002	< 0.001	
BASDAI 50 (NRI, ITT), n (%)	34 (42.0)	15 (17.2)	29 (32.2)	25 (21.9)	10 (9.6)
% Diff vs. PBO (95% CI)	24.7 (11.4 to 38.1)		15.0 (2.5 to 27.5)	[redacted]	
P value vs. PBO	< 0.001		0.012	[redacted]	
BASDAI CFB (MMRM, ITT)					
Week 16 (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	6.75 (1.32)	6.79 (1.23)	[redacted]	7.54 (1.34)	7.32 (1.26)
Week 16 mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE)	–2.92 (0.22)	–1.39 (0.22)	[redacted]	–2.17 (0.20)	–0.92 (0.21)
Between-group LSM diff (95% CI)	[redacted]		[redacted]	–1.24 (–1.81 to –0.67)	
P value	[redacted]		[redacted]	< 0.001	
ASDAS CFB					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	3.71 (0.738)	3.88 (0.739)	[redacted]	4.15 (0.858)	4.05 (0.811)
Week 16 mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE), (MMRM, ITT)	–1.43 (0.102)	–0.46 (0.099)	–1.30 (0.096)	–1.16 (0.094)	–0.11 (0.099)
Between-group LSM diff (95% CI)	–0.97 (–1.25 to –0.70)		–0.84 (–1.11 to –0.57)	–1.05 (–1.32 to –0.79)	
P value	< 0.001		< 0.001	< 0.001	

At week 16	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w. (N = 114)	PBO (N = 104)
ASDAS (< 1.3) (NRI, ITT) n, (%)	13 (16.0)	2 (2.3)	14 (15.6)	[redacted]	[redacted]
% Diff vs. PBO[b] (95% CI)	13.8 (5.2, 22.3)		13.3 (5.1, 21.4)	[redacted]	
P value vs. PBO[a]	0.007		0.009	[redacted]	
ASDAS (< 2.1) (NRI, ITT), n (%)	35 (43.2)	11 (12.6)	34 (37.8)	20 (17.5)	5 (4.8)
% Diff vs. PBO[b] (95% CI)	30.6 (17.72 to 43.42)		25.1 (12.92 to 7.34)	12.7 (4.6 to 20.8)	
P value vs. PBO	< 0.001		< 0.001	0.006	
MRI Spine SPARCC Score					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	14.53 (20.56)	15.80 (21.19)	[redacted]	8.30 (16.00)	6.37 (10.25)
Week 16 (mean)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE) OCA, (ANCOVA)	–11.02 (1.16)	–1.51 (1.15)	–11.57 (1.11)	–2.99 (1.38)	3.29 (1.40)
Between-group LSM diff (95% CI)	–9.51 (–12.6 to –6.4)		–10.07 (–13.2 to –6.9)	–6.29 (–10.0 to –2.5)	
P value	< 0.001		< 0.001	0.001	
Harms					
Patients with ≥ 1 TEAE, n (%)	34 (42.0)	34 (39.5)	44 (48.9)	73 (64.0)	51 (49.0)
Nasopharyngitis	6 (7.4)	6 (7.0)	6 (6.7)	[redacted]	[redacted]
Upper respiratory tract infection	7 (8.6)	4 (4.7)	2 (2.2)	9 (7.9)	3 (2.9)
Patients with ≥ 1 SAE, n (%)	1 (1.2)	0	3 (3.3)	4 (3.5)	5 (4.8)
WDAE, n (%)	0	0	1 (1.1)	10 (8.8)	2 (1.9)
Death, n (%)	0	0	0	0	0

ADA 40 q.2.w. = adalimumab 40 mg every 2 weeks; ANCOVA = analysis of covariance; ASAS 40 = Assessment of Spondyloarthritis International Society 40% improvement; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI 50 = Bath Ankylosing Spondylitis Disease Activity Index, 50% improvement; CFB = Change from baseline; CI = confidence interval; diff = difference; ITT = intention to treat; IXE 80 q.4.w. = ixekizumab 80 mg every fourweeks; LSM = least square mean; MMRM = mixed-effects model of repeated measures; MRI Spine SPARCC = magnetic resonance imaging of spine Spondyloarthritis Research Consortium of Canada score; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = nonresponder imputation; OCA = observed case analysis; PBO = placebo; SAE = serious adverse events; SD = standard deviation; SE = standard error; SF-36 PCS = Short-Form (36) Health Survey, Physical Component Summary; TEAE = treatment emergent adverse event; WDAE = withdrawal due to adverse events including death.

Note: BASDAI 50 response at week 16 was analyzed with multiplicity adjustment as a major secondary outcome in COAST-V, but not in COAST-W; BASDAI change from baseline at week 16 was analyzed with multiplicity adjustment as a major secondary outcome in COAST-W, but not in COAST-V.

Source: Clinical Study Report.[10,11]

Critical Appraisal

The multiplicity adjustment was done for the primary and major secondary outcomes at week 16. However, no multiplicity adjustment was performed for other secondary outcomes such as ASAS 5/6, ASAS partial remission, symptom measurement scale (i.e., spinal pain), fatigue severity numerical rating scale (NRS), Jenkins Sleep Evaluation Questionnaire (JSEQ), Quick Inventory of Depressive Symptomatology – Self Report 16 items (QIDS-SR16), HRQoL (EQ-5D- 5L, SF-36 Mental Component Summary); Work Productivity Activity Impairment–Spondyloarthritis (WPAI-SpA), BASDAI 50 in COAST-W, BASDAI Change from baseline in COAST-V, ASDAS < 1.3 in COAST-W, ASDAS < 2.1 in COAST-V and Patient Global Assessment (PGA). Given the large number of comparisons in the study, a statistically significant finding (P < 0.05) for the comparisons between IXE 80 mg SC every four weeks and placebo for these above-mentioned outcomes without multiplicity adjustment

may suffer from an inflated type I error rate. Therefore, the statistical significance reported for those outcomes remains uncertain.

One limitation was that both COAST-V and COAST-W were not designed for assessing the comparative efficacy and safety between IXE and the existing bDMARDs marketed in Canada (i.e., TNFis and SEC) in the treatment of AS, although adalimumab was included in COAST-V as an active reference only. Therefore, the direct comparative efficacy and safety evidence comparing IXE with other bDMARDs remains unknown.

The study duration was 16 weeks and there is no direct evidence beyond 16 weeks. The findings at week 52 in the extension phase were limited by the lack of any placebo or active control comparators.

Exclusion of patients with total spinal ankylosis may limit the generalizability of results to these patients with total ankylosis in clinical practice. However, the clinical expert CADTH consulted for this review indicated that in clinical practice, patients with total ankylosis may well demonstrate considerable improvements in pain, stiffness, and fatigue, and meaningful improvements in quality of life. Overall, according to the clinical expert involved in the review, in both COAST-V and COAST-W, the patients included in the trial are similar to those seen in Canadian clinical settings, with the exception that those with total AS would also be treated in a clinical setting. There is little concern about the generalizability of the findings from both COAST-V and COAST-W to patients in Canada.

Indirect Comparisons

Description of Studies

One indirect treatment comparison (ITC) was reviewed. This ITC was provided by the sponsor. The sponsor submitted an ITC that compared the efficacy and safety of IXE with SEC, adalimumab, etanercept, and golimumab in adult patients active AS.[12]

Efficacy Results

Findings from the ITC in biologic-naive populations suggest that there was no difference between IXE and other biologic drugs for the efficacy outcomes ASAS 20, ASAS 40, BASDAI 50, ASDAS 2.0 responses, or in change from baseline in ASDAS C-reactive protein (CRP), BASDAI, or BASFI. However, golimumab was favoured for SF-36 mental component summary (MCS) over each comparator explored, including IXE.

Analyses in TNFi-experienced populations showed no difference between IXE and SEC for the efficacy outcomes assessed (ASAS 20, ASAS 40, and BASDAI).

Harms Results

There were no differences in likelihood of short-term AEs, SAEs, or treatment discontinuation due to AEs in biologic-naive and TNFi-experienced populations. However, IXE was found to have a higher incidence of AEs and treatment discontinuation due to AEs relative to placebo in TNFi-experienced patients.

Critical Appraisal

There was insufficient information about the individual trials in the ITC, limiting the ability to assess clinical heterogeneity of the included studies. The ITC also failed to be updated by including more recent studies. In fact, the data included in the network as shown is relatively sparse. Therefore, whether IXE is comparable in efficacy and safety to its biologic

comparators remains somewhat uncertain, particularly in the long term. In addition, the comparative efficacy and safety of IXE to certolizumab pegol and infliximab is unknown.

Other Relevant Evidence

Description of Studies

Both included studies (COAST-V and COAST-W) included a long-term extension phase from week 16 to week 52.[13,14] The objective of the extension periods was to determine if the effect of either IXE dosing regimen (IXE 80 mg SC every two weeks or IXE 80 mg SC every four weeks) was maintained up to week 52 for patients with active AS who were bDMARD-naive or had an inadequate response to, or intolerance to TNFis. In the COAST-V extension period, patients in the two IXE arms continued their assigned treatment; patients in the placebo and adalimumab arms were re-randomized in a 1:1 ratio to either IXE 80 mg SC every two weeks or IXE 80 mg SC every four weeks, with patients originally in the placebo arm given a starting dose of IXE 160 mg. Patients who had been in the adalimumab arm in the first 16 weeks had a 6-week washout period before starting treatment with IXE on week 20. In COAST-W, similar to the COAST-V extension, patients in the two IXE arms continued their assigned treatment, and patients in the placebo arm were re-randomized in a 1:1 ratio to either IXE 80 mg SC every two weeks or IXE 80 mg SC every four weeks with all patients originally in the placebo arm given a starting dose of IXE 160 mg.

Efficacy Results

Overall, in the extension phase at week 52 of both COAST-V and COAST-W, all efficacy results (e.g., ASAS 40, SF-36 PCS, BASDAI, and MRI Spine SPARCC score) for patients treated with IXE 80 mg SC every four weeks were aligned with those reported at week 16.

Harms Results

No new safety signals arose over the course of the extension phase in either COAST-V or COAST-W.

Critical Appraisal

The results of the extension phase at week 52 were limited by the lack of a comparator.

Conclusions

Based on the two double-blind, randomized, controlled trials of patients with active AS, one of which was conducted in bDMARD-naive patients and the other in patients with inadequate response to, or intolerance to one or two TNFis, IXE 80 mg SC every four weeks consistently showed a clinically significant benefit as demonstrated by clinical response (i.e., ASAS 40), HRQoL (i.e., SF-36 PCS), disease activity reduction (i.e., BASDAI, ASDAS) and MRI Spine SPARCC change at week 16 compared with placebo. The magnitude of benefit appeared to be less in TNFi-experienced patients compared with bDMARD-naive patients for the primary outcome (ASAS 40). The incidence of AEs was similar between IXE 80 mg SC every four weeks and placebo in the two trials up to week 16. The efficacy achieved at week 16 appeared to be sustained at 52 weeks, and no new safety signals were identified in weeks 16 to 52. A sponsor-provided ITC suggested no difference was observed in terms of efficacy and safety comparing IXE 80 mg SC every four weeks with bDMARDs marketed in Canada. However, due to its various limitations, whether IXE is comparable in efficacy and safety to its biologic comparators remains somewhat uncertain, particularly over the long term.

Introduction

Disease Background

Ankylosing spondylitis, also referred to as radiographic axial spondyloarthritis (rad-axSpA), is a chronic inflammatory disease primarily involving the spine and the SIJ.[1,2] It usually begins in young adults (< 45 years old) with a peak age of onset between 20 to 30 years of age. AS is more common among men than in women.[1] Patients with AS exhibit radiographic abnormalities consistent with sacroiliitis. Patients experience back pain and progressive spinal stiffness and may also suffer non-arthritic manifestations such as uveitis, skin psoriasis, and inflammatory bowel disease. AS symptoms and the rate of progression fluctuate with time and can vary substantially between patients. It results in functional impairment and subsequent potential socioeconomic consequences and disability; therefore, AS negatively impacts patients' HRQoL.[1-3] A diagnosis of AS can be made based on clinical features, genetic testing, biological testing, and imaging examinations of the disease.[2] The modified New York classification criteria for AS have often been applied as a diagnostic instrument.[4,5] In the 2009 to 2010 National Health and Nutrition Examination Survey (NHANES) of the general population in the US, the prevalence of AS was 0.55%.[1] In a report published by the Arthritis Society in 2011, AS was estimated to affect approximately 150,000 to 300,000 Canadians, and a previous study showed that approximately 58% of Canadian patients have active disease as determined by a disease-specific test such as BASDAI, where a score of four or more indicates active disease.[6,7] According to American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations (2019),[8] active AS was defined as disease causing symptoms at an unacceptably bothersome level to the patient and judged by the examining clinician to be due to inflammation. Stable disease was defined as asymptomatic or causing symptoms but at an acceptable level as reported by the patient. A minimum of six months was required to qualify as clinically stable.[8]

Standards of Therapy

According to the practice guidelines developed by the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network in 2019,[8] 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.[8]

Several drug classes are used in the pharmacologic therapy of AS. 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 TNFis, such as adalimumab, certolizumab, etanercept, golimumab, and infliximab, should NSAIDs fail or if there are contraindications (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 ASAS response criteria, as compared to placebo. After failure of the first TNFi, switching to a different TNFi is recommended for most patients.[1,8,15] However, the indiscriminate use of TNFis is discouraged because of cost concerns and a lack of long-term safety data. Other concerns related to the use of TNFis include rare, sustained drug-free remissions and progressively increased dropout rates during treatment.[15] In addition to TNFis, SEC, an IL-17A inhibitor, has been approved for the treatment of AS. DMARDs, such

as sulfasalazine, can also be used in patients with AS and peripheral arthritis, when patients have contraindications to TNFis or decline treatment with TNFis.[8,15] 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.[8,15] The treatment recommendations for AS and non-radiographic axial SpA are similar.[8]

Drug

IXE is a humanized IgG4 monoclonal antibody that selectively binds and neutralizes the pro-inflammatory cytokine IL-17A. IXE inhibits the release of pro-inflammatory cytokines and chemokines, and is supplied as solution for SC injection, at a concentration of 80 mg/1.0 mL. Patients with AS have increased levels of IL-17A in their blood. IXE targets IL-17A and inhibits its interaction with the IL-17 receptor. In Canada, Health Canada's approved indications for IXE include treatment of adult patients with moderate to severe PP who are candidates for systemic therapy or phototherapy, and treatment of adult patients with active PsA who have responded inadequately to, or are intolerant to one or more DMARDs. IXE has been previously reviewed by CADTH for the treatment of adult patients with PP and patients with PsA. CDEC has recommended that IXE be reimbursed for the treatment of patients with moderate to severe PP and adult patients with active PsA who have responded inadequately to, or are intolerant to one or more DMARDs.

Currently, the new Health Canada-approved indication for IXE is for treatment of adult patients with active AS who have responded inadequately to, or are intolerant to conventional therapy.[9] The recommended dose of IXE for the treatment of AS is 80 mg SC every four weeks. Limited data suggests that some TNFi-experienced patients with AS may benefit from a 160 mg starting dose. cDMARDs, such as sulfasalazine, or corticosteroids, NSAIDs, and/or analgesics may be continued during treatment with IXE.[9]

The sponsor's reimbursement request for this review is the same as the indication.

Table 2: Key Characteristics of IXE, SEC, Adalimumab, Certolizumab Pegol, Etanercept, Golimumab, and Infliximab

	IXE[9]	SEC[16]	Adalimumab[17]	Certolizumab pegol [18]	Etanercept[19]	Golimumab[20]	Infliximab[21]
Mechanism of action	A humanized IgG4 monoclonal antibody that selectively binds and neutralizes the pro-inflammatory cytokine IL-17A. IXE inhibits the release of pro-inflammatory cytokines and chemokines.	A fully human IgG1k monoclonal antibody that selectively binds and neutralizes the pro-inflammatory cytokine IL-17A. SEC inhibits the release of pro-inflammatory cytokines and chemokines.	A recombinant human IgG1 monoclonal antibody that inhibits binding of TNF to TNF-alpha receptors. Adalimumab modulates biological responses that are induced or regulated by TNF.	A recombinant, humanized antibody Fab fragment. Certolizumab pegol 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. Golimumab inhibits binding of TNF to TNF receptors.	A chimeric IgG1 monoclonal antibody. Infliximab inhibits binding of TNF to TNF receptors.
Indication[a]	Treatment of adult patients with active AS who have responded inadequately to, or are intolerant to conventional therapy Other indications: PP, PsA	Reduction of signs and symptoms of active AS Other indications: PsA and PP	Reduction of 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, and PP	Reduction of signs and symptoms in adult patients with active AS who have had an inadequate response to conventional therapy Other indications: RA, PsA, and non-radiographic axSpA	Reduction of signs and symptoms of active AS Other indications: RA, polyarticular JIA, PsA, and PP	Reduction of signs and symptoms in adult patients with active AS who have had an inadequate response to conventional therapies Other indications: RA, PsA, UC, and non-radiographic axSpA	Reduction of signs and symptoms and improvement in physical function in patients with active AS who have responded inadequately to, or are intolerant to conventional therapies Other indications: RA, CD, UC, PsA ,and PP
Route of administration	SC						IV

	IXE[9]	SEC[16]	Adalimumab[17]	Certolizumab pegol [18]	Etanercept[19]	Golimumab[20]	Infliximab[21]
Recommended Dose	80 mg SC q.4.w. For patients with inadequate response or intolerance to at least 1 TNF inhibitor: 160 mg SC at Week 0, followed by 80 mg q.4.w. may be considered. cDMARD) (e.g., sulfasalazine), corticosteroids, NSAIDs, and/or analgesics may be continued during treatment with IXE	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 q.2.w. or 400 mg q.4.w.	50 mg per week in 1 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 (TB 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; axSpA = axial spondyloarthritis; CD = Crohn's disease; cDMARD = conventional disease-modifying antirheumatic drug; HS = hidradenitis suppurativa; IgG = immunoglobin G; IL = interleukin; IXE = ixekizumab; JIA = juvenile idiopathic arthritis; NSAIDs = nonsteroidal anti-inflammatory drugs; PP = plaque psoriasis; PsA = psoriatic arthritis; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; RA = rheumatoid arthritis; SC = subcutaneous injection; SEC = secukinumab; TB = tuberculosis; TNF = tumour necrosis factor; UC = ulcerative colitis.

[a] Health Canada indication.

Source: Health Canada Product Monograph. [9,16-21]

Stakeholder Engagement

Patient Group Input

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

About the patient groups and information gathered:

Three patient input submissions were received for this review from the CSA, ACE, and CAPA and the Arthritis Society (via joint submission).

The CSA is a national not-for-profit organization that provides advocacy, education, programs, and support to Canadians living with various forms of spondyloarthritis, including AS. The CSA gathered information for the submission through an independent survey distributed via email and social media channels (website, Facebook, and Twitter). The survey was open from August 8, 2019 until September 15, 2019. The CSA shared survey results with the Arthritis Society and CAPA, although none of the input from the Arthritis Society and CAPA is contained in the CSA patient submission. The CSA survey yielded 52 Canadian respondents. Of the 52 responses, 60% were female, ages ranged from over 18 to over 65 years of age with the majority (42%) being between 36 to 50 years.

ACE is a non-profit national arthritis patient organization, which serves people living with all forms of arthritis by helping them take control of their disease and improve their quality of life through education and empowerment. ACE also advocates on arthritis health policy issues, through ACE's JointHealth family of programs and the Arthritis Broadcast Network, directly to consumers and patients, media, and government. ACE gathered information using an online survey through the ACE Survey Monkey platform from August to September 2019.

CAPA and the Arthritis Society provided patient input through a joint submission. CAPA is a grassroots, patient-driven, independent, national education and advocacy organization with members and supporters across Canada. CAPA creates links between Canadians with arthritis to assist them in becoming advocates and to improve their quality of life. The Arthritis Society is dedicated to a vision of living in a world where people are free from the devastating effects that arthritis has on the lives of Canadians. The Arthritis Society is Canada's principal health charity providing education, programs, and support to six million Canadians living with arthritis. The Arthritis Society has invested more than $200 million in projects that have led to breakthroughs in the diagnosis, treatment, and care of people with arthritis. CAPA and the Arthritis Society collaboratively developed a survey that was shared via emails and social media (CAPA and Arthritis Society Facebook and Twitter accounts) to their Canadian networks and communities. The survey was open from August 9, 2019 to September 9, 2019. The Arthritis Society and CAPA shared survey results with the CSA, and some of the patient input for this submission was derived from the CSA survey. The CAPA and the Arthritis Society survey yielded 10 respondents, with four of these individuals responding to demographic questions indicating an age range of 31 to 49 years.

Disease experience:

AS is a chronic, progressive, painful form of inflammatory arthritis, which affects mainly the spine and SIJs. The bone erodes at these sites and the body tries to repair itself by forming new bone. The bones of the spine begin to fuse, or grow together, causing the spine to become stiff, inflexible, and painful. AS can also cause pain and stiffness in peripheral joints (hips and shoulders), tendons, and ligaments.

Many patients report living with symptoms for many years before being diagnosed. The CSA survey reported that 30% of patients lived with symptoms for 5 to 10 years prior to diagnosis, and 21% of patients reported a duration of 10 to 20 years.

AS impacts lives in many ways; daily tasks that many well individuals take for granted may become difficult or too exhausting to complete. Common symptoms that were reported to have the greatest impact on patients' day-to-day lives and daily activities included issues with joint pain, mobility, fatigue, and sleep. In addition to the physical impact of AS, patients are also faced with several psychological consequences. Many patients reported that it is difficult or impossible to do simple things like caring for or spending time with family and friends, participating in leisure activities, driving, working, and parenting.

"I cannot walk! So I am largely housebound. Cannot turn over in bed. Big impact on social life. Had to retire early because of it which has impacted on my retirement income."

"I can't work. Have had to stop activities I loved. Find I am becoming more housebound due to tiredness and pain. Sleep is affected due to pain."

"Fighting to get through every day with some level of normalcy, limited to what I can get achieved, makes work harder. Family life has changed considerably."

The burden of AS impacts patients' lives and relationships with their loved ones and caregivers.

"My kids are 9 and 12 and they know that certain days that are high pain days I just can't do as much in these days. They know I need more help with things around the house. My husband has shed tears watching me go through days, weeks, and months of intense pain. There are days I just can't do what I used too. I feel that I don't have the stamina or strength that I used to."

"Well, I lost my career, my home, my family, and my marriage fell apart. At this point, I have no family to impact with my daily routine, and I think it's best to keep it that way? I can barely manage to keep in regular contact with my brothers through Skype."

Experience with treatment:

There is no cure for AS. Pharmacologic medications for AS are intended to slow progression of the disease and help manage pain and other symptoms. Treatment options are based on trial and error and the effectiveness varies between patients. Some medications make a significant difference for people and allow them to continue doing all the things they love , and for others some medications simply help them to get through the day. For some, the medication may work well very quickly while for others it may take time. Some patients find sustained symptom relief and can stay on a medication for a long time (several years), while others have shorter bouts of symptom relief, or experience no relief, before needing to move to a different option.

"NSAID drugs have not made much difference and carry the risk of liver damage. They are not effective. Cosentyx is effective but a monthly dose is not enough to stay pain free. It only lasts 2 to 3 weeks before the pain returns full force. It is also cost prohibitive without a drug plan. Fatigue is improved with this drug, but again the results do not last."

Treatments used to manage AS include nonsteroidal anti-inflammatory drugs, corticosteroids, and DMARDs such as methotrexate, sulfasalazine, and biologics. Each treatment is associated with different benefits and side effects. Currently available treatments

can be difficult to tolerate and manage, with many survey respondents citing side effects that commonly included stomach issues, fatigue following injection, and weight gain. Side effects associated with long-term use of corticosteroids includes osteoporosis, glaucoma and cataracts, osteonecrosis, skin changes, heart disease, and stroke. Side effects associated with biologics include injection site irritation, increased risk of upper respiratory infections, pneumonia, urinary tract infections, and skin infections.

"I have been on biological therapy for 9 months and I believe there is a heightened effect on my bowels. My stomach also hurts (sharp stabbing pain) for one week after the injection."

"The side effects of treatment were the main reason that I do not use daily treatment."

Non-pharmacologic treatments such as physiotherapy, occupational therapy, massage therapy, and chiropractic therapy play an important role in managing symptoms of AS such as stiffness, pain, fatigue, and mental health. Unfortunately, availability and affordability issues prevent access to non-pharmacologic treatments for some patients.

"Cannabis is by far the most effective acute treatment. Pain killers are 100% ineffective and do not allow areas of my back to relax. Cannabis combined with yoga is very very effective at improving mobility — the cannabis reduces pain and allows areas which tend to tighten up (back and hips) to relax, thereby allowing for effective stretching and strengthening."

None of the patients surveyed in any of the three submissions had experience with the drug under review.

Improved outcomes:

People with AS desire more treatment options that improve the following outcomes:

- reduction in pain and fatigue
- reduction in disease progression
- reduction in stiffness and swelling
- increased mobility
- ability to work and be productive at work
- ability to carry out activities of daily living
- decrease in medication side effects.

"I would like pain-free days and the ability to exercise more, less doctor appointments for nerve blocks"

"Not willing to experience serious side effects. I would need to be pain free with a return of physical strength and significantly reduced fatigue to consider it effective. This would allow me to complete normal daily tasks without hinderance."

Clinician Input

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

Description of the current treatment paradigm for the disease:

The treatment of AS aims to alleviate symptoms of back pain and stiffness. Some patients manage with no pharmacological treatment, preferring exercise and activity to minimize pain and stiffness. Physiotherapy can be a useful adjunct, especially when directed at preservation of posture and spinal range of motion. In a specific patient, the rate of progression of AS is unpredictable and symptom intensity itself is not necessarily a harbinger of a poor outcome of total spinal ankylosis.

NSAIDs are the first-line pharmacologic treatment. There are numerous RCTs of NSAIDs in AS, demonstrating not only symptom relief but also inhibition of radiographic progression. However, some of the most effective NSAIDs such as selective cyclooxygenase-2 inhibitors including rofecoxib (Vioxx) and etoricoxib (Arcoxia) are no longer available in Canada due to increased cardiovascular events. Another NSAID, phenylbutazone was also withdrawn due to hematologic AEs. The remaining available NSAIDs are associated with other significant morbidities such as neurologic, renal, gastrointestinal, cardiac, and hepatic toxicity. AS is a spinal disease and studies, including RCTs, of conventional DMARDs (MTX, sulfasalazine, leflunomide) have not shown efficacy in managing AS.

Failure of NSAIDs lead to the use of TNF inhibition, which is effective in controlling symptoms and inhibiting radiographic progression. Access to TNFis (and their biosimilar equivalents) require—depending on province or country—failure of two or three NSAIDs administered for two to four weeks, and a level of disease activity usually defined as a BASDAI score greater than four. All Canadian insurers, including provincial formularies, provide access to TNFis. Most recently, IL-17 inhibition by SEC (Cosentyx) has been shown to be effective in AS. IXE is the second IL-17 inhibitor seeking approval from Health Canada for the treatment of AS.

The Janus kinase (JAK) inhibitor tofacitinib (Xeljanz) has a single phase II study showing efficacy in AS and is currently under evaluation in a Phase III RCT. It is expected that manufacturers of JAKs such as baricitinib and upadacitinib will evaluate their products in AS.

Other biologic drugs such as IL-6 inhibitors (abatacept and rituximab) and IL-23 inhibitors (apremilast) are not currently used for AS and are NOT likely to be tried off label, in some instances because of data showing lack of effectiveness, and in other instances because the sponsor has decided not to pursue development of their drug for the AS market.

Treatment Goals

Treatment reduces the severity of symptoms and prevents ankylosis (fusion) of the spine and nearby joints. Effective treatment could allow less exposure to NSAIDs, and their associated AEs, and steroids, which for many years were the only drug therapy available when symptoms could not be managed by NSAIDs alone. The relief of symptoms improves function and quality of life and should manifest in fewer days lost from work and the enjoyment of life. Prevention of ankylosis has additional implications, among them allowing the cervical spine to turn to check blind spots while driving, and maintaining pulmonary function. Because hips and shoulders can be involved in AS, it is expected that control of AS should reduce the future need for hip and shoulder replacements. Complications of untreated AS such as aortic insufficiency, pulmonary fibrosis, and renal amyloidosis causing kidney failure are expected to disappear.

Unmet Needs

There remains an ongoing need for drug development in AS for many reasons including; non-responsiveness of some patients to all available treatments; the development of treatment-refractory response in some patients; treatment intolerance and associated poor compliance; and lack of convenience of available treatments.

Place In Therapy

Current treatment regimens permit ongoing treatment with NSAIDs, but there is no reason to think that IL-17 inhibitors will be combined with TNFis or JAK inhibitors in the future. AS can occur in patients with psoriatic disease and inflammatory bowel disease, and in patients with psoriatic disease IL-17 inhibitors carry the advantage of controlling skin disease in addition to the spine and peripheral joints. In patients with psoriatic disease and peripheral joint arthritis, IXE can be combined with conventional DMARDs such as methotrexate. In patients with known inflammatory bowel disease, IL-17 inhibitors are not an optimal choice because of the risk of increased flares of bowel disease when IL-17 is inhibited. In the two IXE trials that comprise this report, patients with inactive inflammatory bowel disease were not excluded and four cases of inflammatory bowel disease were seen with IXE compared to one case with placebo.

IXE is the second IL-17 inhibitor to be approved in AS and joins five TNFis and their biosimilars in this therapeutic area. Most likely to arrive soon will be the JAKs, with three currently on the market and more to arrive. IXE will be available as treatment after failure of NSAIDs and as treatment after failure of a TNFi. There is no data regarding whether failure on the other IL-17 inhibitor, SEC, will predict success or equal failure on IXE. IXE is not expected to shift current treatment algorithms until there is data to show superior efficacy or safety compared to other available therapies.

The 2019 ACR guidelines on the treatment of AS[8] state: TNFis are recommended over SEC or IXE as the biologics of first choice. SEC or IXE is recommended over a second TNFi in patients with a primary non-response to the first TNFi. Co-administration of methotrexate with a TNFi is not recommended, nor is it recommended to use a treat-to-target strategy, to discontinue, or taper biologics in patients with stable disease.

These recommendations represent the state of therapy likely to be followed by Canadian rheumatologists. However, tapering strategies have not been well studied and in clinical practice, many patients take less medication. Full discontinuation of a biologic is discouraged, but appropriate studies are required before rheumatologists have the data to support such a strategy.

Patient Population

According to current reimbursement criteria of plans which participate in the CADTH Common Drug Review (CDR), at this time the singular basis for initiation of treatment is the BASDAI score. The BASDAI is a six-question instrument ranging from 0 to 10 and a BASDAI score of greater than four, despite treatment with NSAIDs, allows application for a biologic. There are no well-studied predictors of response to treatment. In the RCTs, patients with total ankylosis of the spine are excluded, but in the opinion of the clinical specialist consulted by CADTH, this is a “clinical trial strategy” predicated on excluding patients that are not likely to demonstrate changes in numerous outcome measures. In reality, such patients may well demonstrate considerable decreases in pain, stiffness, and fatigue and meaningful improvements in quality of life. Because most payers base reimbursement criteria on the

inclusion or exclusion criteria used in RCTs, such patients who may well benefit from treatment may be declared ineligible.

The RCTs were conducted on patients with unequivocal AS on X-ray, defined as Grade II or higher bilateral sacroiliitis or Grade III or IV unilateral sacroiliitis. Thus, the diagnosis of AS must be quite definitive and is usually easily established by a qualified radiologist or rheumatologist. Defined in this way, patients with AS are easily identified using simple and relatively inexpensive methods. Over-diagnosis of AS is unlikely but under-diagnosis can occur. The presence of sacroiliitis in the Canadian context almost always means AS. However, infections such as tuberculosis and brucellosis, and tumours, particularly sarcomas, can also cause "sacroiliitis" and on occasion need to be considered by the treating rheumatologist.

Under-diagnosis of AS occurs. At this time payers will likely exclude patients with non-radiographic AS, an accepted clinical entity diagnosed usually by MRI and eligible for treatment with TNFis. An RCT in such patients may be required to obtain reimbursement for MRI positive, non-radiographic AS with IXE. Other patients with symptoms of inflammatory low back pain but negative X-ray and MRI have been identified in research studies by biopsy of the SIJ. These patients do not meet current eligibility criteria for TNFis or IL-17 inhibition.

Currently, a pre-symptomatic state of AS is not recognized. There are no studies to consider prevention of disease in patients at high risk, for example an HLA-B27 positive individual with a parent or sibling with definite AS.

Patients with AS and active inflammatory bowel disease and/or uveitis are less suited for IL-17 inhibitors as there is a possibility of exacerbation of their bowel or eye disease. Patients with inactive bowel or eye disease can be treated with proper vigilance. In contrast, IL-17 inhibition would be considered first-line therapy in patients with a personal or family history of MS because TNFis are associated with exacerbations of MS.

At this time, it is not possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review.

Assessing Response To Treatment

The BASDAI is currently used to determine eligibility for treatment. A reduction of BASDAI by 50% and/or an absolute decrease in two units of the 10-point scale is necessary for drug renewal. Other outcomes exist but are not required to determine eligibility or renewal.

The reduction in BASDAI of 50% and/or two units on the 10-point scale is considered a clinically meaningful response to treatment. Other outcomes are important to the patient but not considered when it comes to approving ongoing treatment.

The initial treatment response should be evident by three months and an application for a change in therapy will be made between three and six months. Renewals are yearly or less often, depending on the province or insurer.

Discontinuing Treatment

Lack or loss of clinical response or drug toxicity determine discontinuation of treatment by the physician. Patient-related causes include loss of insurance, depression, and fear or distrust of the medication.

Prescribing Conditions

IXE is self-administered as a subcutaneous injection at home. A rheumatologist usually makes the diagnosis and initiates treatment. As there are "hard" criteria for diagnosis of AS, and for eligibility for initiation and renewal of treatment (i.e., self-administered BASDAI questionnaire), ongoing management of AS managed by a family doctor or nurse practitioner.

Clinical Evidence

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

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of IXE, a solution SC injection, with a concentration of 80 mg/1.0 mL, every 4 weeks, for the treatment of adult patients with active AS who have responded inadequately to, or are intolerant to conventional therapy.

Methods

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

This systematic review protocol was established prior to the granting of Notice of Compliance from Health Canada for IXE for AS.

Table 3: Inclusion Criteria for the Systematic Review

Patient population	Adult patients with active AS who have responded inadequately to, or are intolerant to conventional therapy. Subgroups of interest: • Baseline disease activity • Previous use of bDMARDs vs. no previous use of bDMARDs • Response to bDMARDs vs. no response to previous bDMARDs
Intervention	80 mg SC q.4.w. For patients with inadequate response or intolerance to at least 1 TNFi, 160 mg (2 doses of 80 mg) SC, at week 0, followed by 80 mg q.4.w. may be considered cDMARDs (e.g., sulfasalazine), corticosteroids, NSAIDs, and/or analgesics may be continued during treatment with IXE

Comparators	Currently approved bDMARDS for AS in Canada: • SEC • Certolizumab pegol • Infliximab • Golimumab • Adalimumab • Etanercept
Outcomes	**Efficacy outcomes:** • Clinical response (e.g., ASAS 40) • Measures of AS symptoms (e.g., pain, fatigue)[a] • Measures of function and disability (e.g., BASFI)[a] • Health-related quality of life (generic and disease-specific [e.g., SF-36, ASAS HI])[a] • Work productivity (e.g., WPAI-SpA) [a] • Disease activity (e.g., BASDAI, ASDAS)[a] • Patient Global Assessment • Radiographic changes (e.g., MRI Spine SPARCC) **Harms outcomes:** • Mortality • SAEs[a] • AEs[a] • WDAEs • Notable harms: serious infections (including tuberculosis and fungal infection), IBD, malignancies, MACE, injection site reactions, hypersensitivity, hepatotoxicity, and hematologic toxicity (such as anemia and/or pancytopenia)
Study design	Published and unpublished Phase III and IV RCTs

AE = adverse event; AS = ankylosing spondylitis; ASAS = Assessment of Spondyloarthritis International Society; ASAS HI = ASAS Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biological disease -modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; IBD = inflammatory bowel disease; IXE = ixekizumab; MACE = major adverse cerebrocardiovascular event; MRI Spine SPARCC = magnetic resonance imaging of spine Spondyloarthritis Research Consortium of Canada score; NSAID = nonsteroidal anti-inflammatory drug; q.4.w. = every 4 weeks; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous injection; SEC = secukinumab; SF-36 = Short-Form (36) Health Survey; TNFi = tumour necrosis factor inhibitor; WDAE = withdrawal due to adverse event; WPAI-SpA = Work Productivity Activity Impairment–Spondyloarthritis.

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

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist (https://www.cadth.ca/resources/finding-evidence/press).[22]

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

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on October 24, 2019. Regular alerts updated the search until the meeting of CDEC on February 19, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters: A Practical Tool for Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters)[23]:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trials registries
- databases (free).

Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Two 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.

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. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

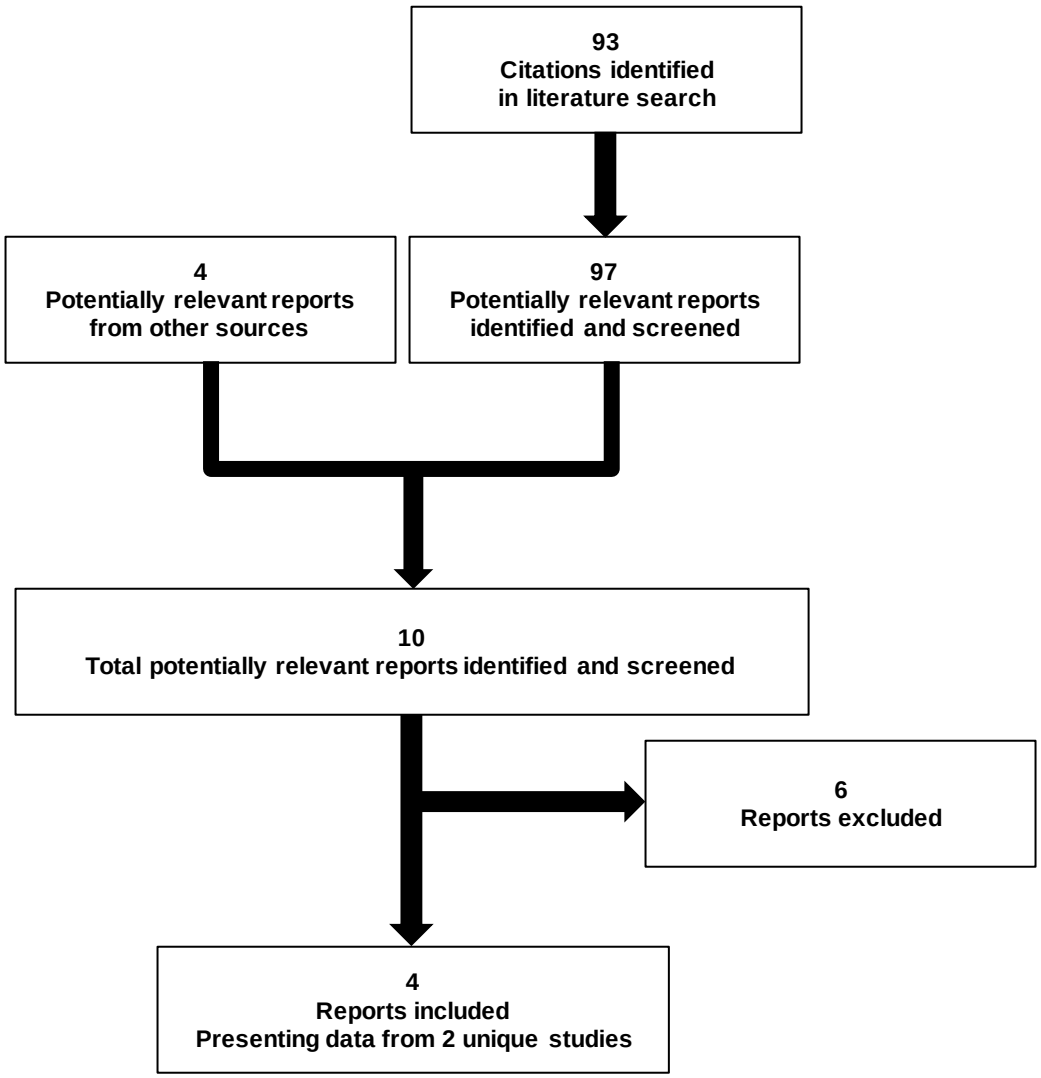


Table 4: Details of Included Studies

		COAST-V[11]	COAST-W[10]
Designs and Populations	**Study design**	Multi-centre, DB PBO-controlled RCT,[a] Phase III	Multi-centre, DB PBO-controlled RCT, Phase III
	Locations	84 sites in 12 countries, including Canada, the US, European, and Asian countries (the Czech Republic, Germany, Hungary, the Netherlands, Poland, Russia, Japan, South Korea, Mexico, and Taiwan)	106 sites in 15 countries including Canada, the US, Mexico, and South American, European, and Asian countries (Germany, the Netherlands, Poland, South Korea, Argentina, Brazil, Finland, France, Israel, Italy, Spain, and the UK)
	Randomized (N)	341	316
	Inclusion criteria	• Adult patients (≥ 18 years old) • Patients with a diagnosis of AS (rad-axSpA with sacroiliitis defined radiographically according to the mNY criteria based on central reading): sacroiliitis grade ≥ 2 bilaterally or grades 3 to 4 unilaterally and at least 1 SpA feature, according to ASAS criteria • Had a history of back pain ≥ 3 months with age at onset < 45 years • Active AS defined as BASDAI ≥ 4 and total back pain ≥ 4 on a numeric rating scale at screening and baseline • Must have had an inadequate response, as determined by the investigator, to 2 or more NSAIDs at the therapeutic dose range for a total duration of at least 4 weeks or have a history of intolerance to NSAIDs • Patients must have a history of prior therapy for axSpA of at least 12 weeks prior to screening	• Adult patients (≥ 18 years old) • Patients with a diagnosis of AS (rad-axSpA with sacroiliitis defined radiographically based on central reading, according to the mNY criteria and at least 1 SpA feature according to ASAS criteria) • TNFi-experienced (i.e., had prior treatment with 1 to 2 TNFis and discontinued at least 1 TNFi due to intolerance or inadequate response) • Had a history of back pain ≥ 3 months with age at onset < 45 years • Active AS defined as BASDAI ≥ 4 and spinal pain ≥ 4 on a numeric rating scale at screening and baseline • Had an inadequate response to ≥ 2 NSAIDs or a history of intolerance to NSAIDs and had a history of prior therapy for axSpA of at least 12 weeks prior to screening
	Exclusion criteria	• Total spinal ankylosis • Patients who had a serious infection in the past 12 weeks prior to baseline randomization • Currently exposure to IXE in a clinical trial or any other biologic drug (e.g., JAKi, TNFis, IL-1, IL-6, IL-23 , IL-17 [including IXE], IL-17R, T cell, or B cell targeted therapies) • Have received cDMARDs and/or other therapies such as but not limited to gold salts, cyclosporine, azathioprine, dapsone, 6-mercaptopurine, mycophenolate mofetil, or any other immunosuppressive drugs within 4 weeks prior to baseline randomization (exception: MTX [oral or parenteral up to 25 mg/week], SSZ [up to 3 g/day], or hydroxychloroquine [up to 400 mg/day] may	• Total ankylosis of the spine • History of other systemic inflammatory diseases: active Crohn's disease or active ulcerative colitis within 6 months prior to baseline; evidence of active anterior uveitis within 4 weeks prior to baseline • Active ongoing inflammatory diseases other than AS (e.g., IBD or uveitis) • Serious infections • Presence or history of a known immunodeficiency or of being immunocompromised • Prior/concurrent therapy or clinical trial experience: cDMARDs and/or any other immunosuppressive drugs within 4 weeks prior

		COAST-V[11]	COAST-W[10]
		be allowed if at stable dose for at least 4 weeks prior to baseline randomization) • Active ongoing inflammatory diseases other than AS (e.g., IBD or uveitis) • Active tuberculosis or any active systemic infection < 2 weeks before baseline • Underlying conditions which immunocompromised the patient and/or placed the patient at unacceptable risk for participation in an immunomodulatory therapy • Pregnant or nursing women • Presence of any significant comorbidity	to baseline (exceptions include MTX, SSZ, and hydroxychloroquine); oral corticosteroids > 10 mg/day; concurrent or prior use of biologic or other immunomodulatory drugs (note: previous TNFi therapy was permitted) • Concurrent or recent use of denosumab; parenteral glucocorticoid administration within 6 weeks prior to baseline or anticipated administration during Period 2 of the study
DRUGS	**Intervention**	IXE Starting dose: 80 mg or 160mg SC, followed up with IXE 80 mg SC q.2.w. or q.4w.	
	Comparator(s)	Placebo SC q.2.w. ADA[a] 40 mg SC q.2.w.	Placebo SC q.2.w.
DURATION	**Phase**		
	Run-in	NA	
	Screen	42 days	
	Double-blind	16 weeks	
	Extended Tx	36 weeks (to week 52)	
	Follow-up (post-Tx)	12 weeks to 24 weeks[b]	
OUTCOMES	**Primary end point**	ASAS 40 response at week 16	
	Secondary and exploratory end points	**Secondary:** • ASAS 20 • ASAS 5/6 • ASAS Partial Remission • ASAS Individual Components (Patient Global, Assessment of Disease Activity, Spinal Pain, C-Reactive Protein) • BASDAI 50 and BASDAI change from baseline[C] • ASDAS change from baseline, ASDAS < 1.3[d] , ASDAS < 2.1[e] • BASFI • MRI Spine and SIJ SPARCC score **Health Outcomes Measures:** • SF-36 • ASAS HI • EQ-5D-5L • Fatigue Severity Numeric Rating Scale • WPAI-SpA • JSEQ • QIDS-SR16 Safety outcomes including AEs, SAEs, and WDAEs	

		COAST-V[11]	COAST-W[10]
NOTES	**Publications**	van der Heijde et al. (2018)[24]	Deodhar et al. (2019)[25]

ADA= adalimumab; AE = adverse event; AS = ankylosing spondylitis; ASAS = Assessment of Spondyloarthritis International Society; ASAS HI = ASAS Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; axSpA = axial spondylarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; cDMARD = conventional disease-modifying antirheumatic drug; DB = double blind; EQ-5D-5L = European quality of life – 5 dimensions 5 level; IBD = inflammatory bowel disease; IL = interleukin; IXE = ixekizumab;

JAKi = Janus kinase inhibitors; JSEQ = Jenkins Sleep Evaluation Questionnaire; mNY = modified New York criteria; MRI Spine SPARCC = magnetic resonance imaging of spine Spondyloarthritis Research Consortium of Canada score; MTX = methotrexate; NA = not applicable; NSAID = nonsteroidal anti-inflammatory drug; PBO = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self Report 16 items; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous injection; SF-36 PCS = Medical Outcomes Study 36-Item Short Form Health Survey Physical Component Summary; SIJ = sacroiliac joints; SpA = spondyloarthritis; SSZ = sulfasalazine; TNFi = tumour necrosis factor inhibitor; Tx = treatment; WDAE = withdrawal due to adverse event; WPAI-SpA = Work Productivity Activity Impairment–Spondyloarthritis.

[a] Adalimumab 40 mg q.2.w., the approved dose for AS, was the active reference for comparison with placebo. All doses were administered via SC injection.

[b] The results of the Periods 4 were not available and not provided by the sponsor at the request from CADTH.

[c] BASDAI 50 was a major secondary outcomes and multiplicity was adjusted in Study COAST-V but not in Study COAST-W; BASDAI change from baseline was a major secondary outcomes and multiplicity was adjusted in Study COAST-W, but not in Study COAST-V.

[d] ASDAS < 1.3 was a major secondary outcomes and multiplicity adjustment was performed in Study COAST-V but not in Study COAST-W.

[e] ASDAS < 2.1 was a major secondary outcome and multiplicity adjustment was performed in Study COAST-W, but not in Study COAST- V.

Source: CSR[10,11]

Description of Studies

Two phase III trials (COAST-V[11] and COAST-W[10]) are included for this review. The COAST-V study (N = 341) was a multi-centre, randomized, double-blind, placebo-controlled trial, with an active reference arm (adalimumab), examining the efficacy and safety of two IXE dosing regimens (IXE 80 mg SC every two weeks and IXE 80 mg SC every four weeks), as compared to SC placebo in patients with active AS who were bDMARD-naive during a double-blind, 16-week treatment period. Starting doses of 80 mg and 160 mg (at week 0) were evaluated for each IXE regimen. Adalimumab was selected as the active reference for comparison with placebo. (see Figure 2). The study consisted of four periods:

- Period 1: screening period (lasting up to 42 days prior to Period 2); determined patient eligibility
- Period 2: blinded treatment dosing period, from week 0 (baseline) to week 16 inclusive; evaluated the efficacy and safety of two IXE dosing regimens compared to placebo
- Period 3: extended treatment period, after week 16 to week 52 inclusive; assessed long-term efficacy and safety of IXE
- Period 4: post-treatment follow-up period, occurring from last treatment or early termination visit to a minimum of 12 weeks following that visit (up to 24 weeks); data for period 4 is not available at the time of this review. Patients who completed Study COAST-V were eligible to enrol into a long-term study (COAST-Y) for up to two additional years. Results of COAST-Y is not available at the time of the review. The COAST-V study was conducted in 84 sites in 12 countries, including Canada, the US, European, and Asian countries.

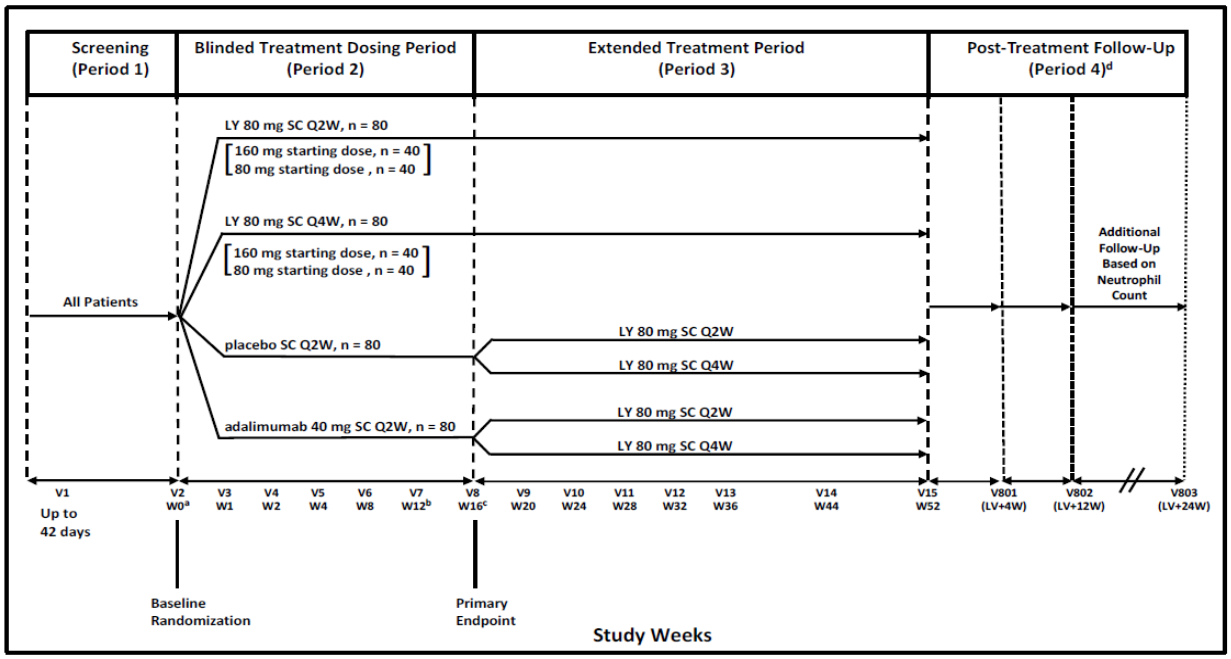
The COAST-W study (N = 316) was also a phase III, randomized, double-blind, placebo-controlled trial in adult patients with active AS, who had an inadequate response to, or intolerance of one or two TNFis. The objective of COAST-W was to examine the efficacy and safety of two IXE dosing regimens (IXE 80 mg SC every two weeks and IXE 80 mg SC every

four weeks) with placebo (with an 80- mg or 160 mg starting dose). Similar to COAST-V, the COAST-W study included four periods (see Figure 3).

- Period 1: screening period (lasting up to 42 days prior to period 2); determined patient eligibility.
- Period 2: blinded treatment dosing period, from week 0 (baseline) to week 16 inclusive; evaluated the efficacy and safety of two IXE dosing regimens compared to placebo.
- Period 3: extended treatment period, after week 16 to week 52 inclusive; assessed long-term efficacy and safety of IXE.
- Period 4: post-treatment follow-up period, occurring from last treatment or early termination visit to a minimum of 12 weeks following that visit (up to 24 weeks). The COAST-W study was conducted in 106 sites in 15 countries including Canada, the US, Mexico, South American, European, and Asian countries.

Since the Health Canada-recommended dose of IXE for AS is IXE 80 mg SC every four weeks, the results for the IXE 80 mg SC every two weeks treatment groups are not presented in this report.

Figure 2: COAST-V Study Design



ETV = early termination visit; LV = last visit; LY = ixekizumab; n = number of patients in the specified category; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; V = visit; W = week.

[a] All patients received 3 injections at baseline. Patients randomized to an ixekizumab treatment group were randomized to a 160 mg or 80 mg starting dose at a 1:1 ratio (within each ixekizumab treatment group).

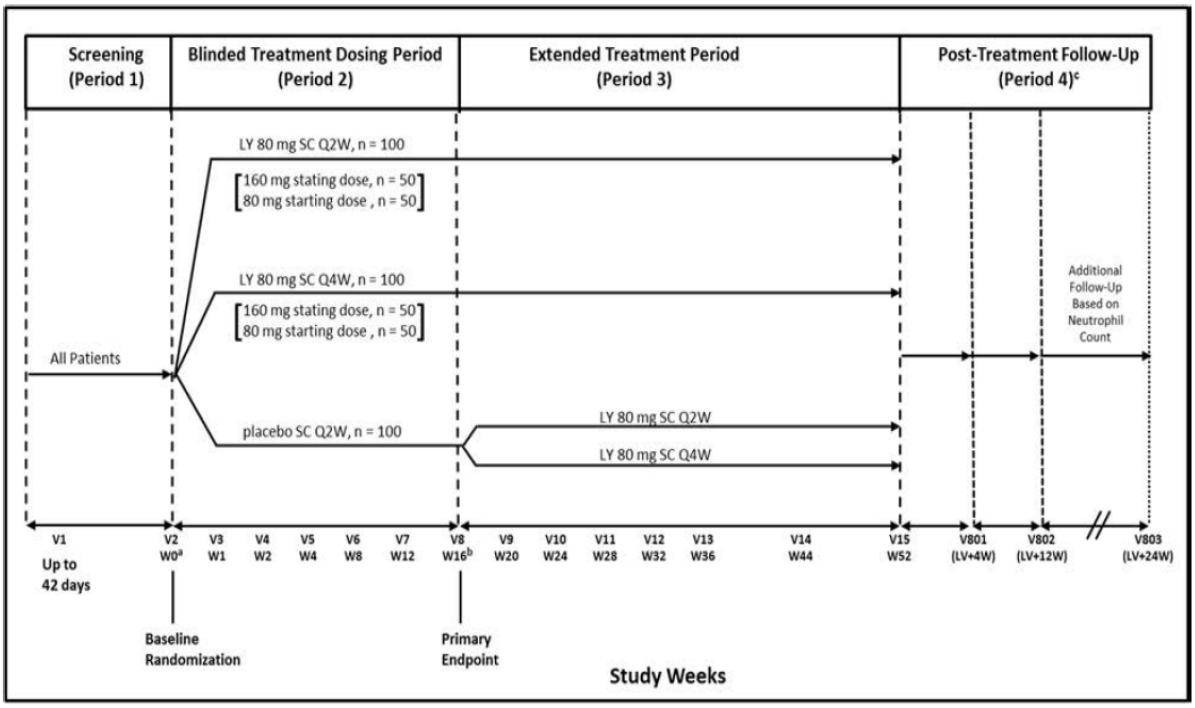
[b] Patients in the adalimumab treatment group were re-randomized at week 16 to ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W. They received their last adalimumab dose at week 14. Following a 6-week washout period, patients received their first ixekizumab dose at week 20.

[c] All patients received 2 injections at week 16. Patients randomized to placebo at week 0 began ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W at week 16 with a 160 mg starting dose.

[d] Patients who discontinued the study drug for any reason and who received at least 1 dose of study drug continued to the ETV before entering the post-treatment follow-up period. V801 and V802 were required for all patients; V803 may have been needed depending on neutrophil counts.

Source: CSR[11]

Figure 3: COAST-W Study Design



ETV = early termination visit; LV = last visit; LY = ixekizumab; n = number of patients in the specified category; PTFU = post-treatment follow-up; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; V = visit; W = week.

[a] All patients received 2 injections at baseline. Patients randomized to an ixekizumab treatment group were randomized to a 160 mg or 80 mg starting dose at a 1:1 ratio (within each ixekizumab treatment group).

[b] All patients received 2 injections at week 16. Patients randomized to placebo at week 0 began ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W at week 16 with a 160 mg starting dose.

[c] Patients who discontinued the study drug for any reason and who received at least 1 dose of study drug continued to the ETV before entering the PTFU Period. V801 and V802 were required for all patients; V803 may have been needed depending on neutrophil counts.

Source: CSR[10]

Populations

Inclusion and Exclusion Criteria

In COAST-V, the main selection criteria included patients who were at least 18 years of age and had a diagnosis of active AS, based on the modified New York criteria for AS, with a BASDAI score of four or greater on a 0 to 10 scale, with a higher score indicating more severe disease activity, and a total back pain score of four or more on the numeric rating scale (NRS) at screening and baseline. Patient must have had an inadequate response, as determined by the investigator, to two or more NSAIDs at the therapeutic dose range for a total duration of at least four weeks or have a history of intolerance to NSAIDs. Patients must have had a history of prior therapy for AS of at least 12 weeks prior to screening. The key exclusion criteria were patients with:

- Total spinal ankylosis or active ongoing inflammatory diseases other than AS (e.g., inflammatory bowel disease or uveitis)
- A history of a serious infection in the past 12 weeks prior to baseline

- Current exposure to IXE or any other biologic drug in a clinical trial and who had received cDMARDs and/or other therapies such as, but not limited to, gold salts, cyclosporine, azathioprine, dapsone, 6-mercaptopurine, mycophenolate mofetil, or any other immunosuppressive drugs within four weeks prior to baseline randomization. Exceptions to this were methotrexate (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day). These drugs may be allowed if the patient had been taking a stable dose for at least four weeks prior to baseline randomization (see Table 4).

In COAST-W, in addition to the main selection criteria in COAST-V, the patient with active AS must have had prior treatment with one or two TNFis and had discontinued at least one TNFi due to intolerance or inadequate response. The exclusion criteria were similar to that in COAST-V, with the exception that previous TNFi therapy was permitted (see Table 4). Compared with patients included in COAST-V, patients in COAST-W had a numerically longer disease duration of AS, older age, and higher baseline C-reactive protein (CRP) level.

Baseline Characteristics

The demographics and baseline characteristics in the intention-to-treat (ITT) population for COAST-V and COAST-W are presented in Table 5.

In COAST-V, overall, the baseline characteristics were balanced across treatment groups. The mean age of patients ranged from 41.0 to 42.7 years across the treatment groups; the majority of patients were male (81.1% to 84.0%) and white (60.5% to 64.2%). The mean age at onset of AS was 26.1 years ([redacted]). The mean duration of AS symptoms was 16.0 years ([redacted]), and mean time since AS diagnosis was 7.7 years ([redacted]). The mean total BASDAI score ranged from 6.65 to 6.81. The baseline ASDAS score ranged from 3.68 to 3.89. In addition, the proportion of patients with previous use of methotrexate ranged from 8.9% to 11.1%, and sulfasalazine ranged from 26.7% to 29.6%. The baseline NSAID/cyclooxygenase-2 inhibitor use ranged from 88.9% to 92.2%. The mean MRI Spine SPARCC score ranged from 14.53 to 19.98. The proportion of patients HLA-B27 positive ranged from 89.4% to 92.6%.

In COAST-W, overall, the baseline characteristics were balanced across treatment groups. The mean age of patients ranged from 46.6 to 47.4 years across the treatment groups; the majority of patients were male (79.8% to 87.3%) and white (80.5% to 81.7%). The mean age at onset of AS was 27.1 to 28.9 years in the IXE 80 mg SC every four weeks group and placebo group, respectively. The mean duration of AS symptoms was 18.8 to 19.9 years. The mean time since AS diagnosis was 10.1 to 13 years. The mean total BASDAI score ranged from 7.3 to 7.5. The baseline ASDAS score ranged from 4.1 to 4.2. In addition, 59.6% to 61% patients had used one TNFi and 38.6% to 40.4% had used two TNFis. The proportion of patients with previous use of methotrexate ranged from 12% to 20%, and sulfasalazine ranged from 13% to 17%. The baseline NSAID/cyclooxygenase-2 inhibitor use ranged from 75.4% to 80.8%. The mean MRI Spine SPARCC score ranged from 6.5 to 8.3. The proportion of patients HLA-B27 positive ranged from [redacted]

Table 5: Summary of Baseline Characteristics

	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w. (N = 114)	PBO (N = 104)
Age (years)					
Mean (SD)	41.0 (12.1)	42.7 (12.0)	41.8 (11.4)	47.4 (13.36)	46.6 (12.72)
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male, n (%)	68 (84.0)	71 (82.6)	73 (81.1)	91 (79.8)	87 (83.7)
Race, n (%)					
Asian	25 (30.9)	28 (32.6)	29 (32.2)	14 (12.4)	13 (12.5)
White	52 (64.2)	52 (60.5)	57 (63.3)	91 (80.5)	85 (81.7)
Other	4 (5)	6 (7)	4 (4)	[redacted]	[redacted]
Weight (kg), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age of onset of axSpA (years)					
Mean (SD)	25.4 (7.7)	26.4 (8.4)	26.5 (8.6)	28.9 (9.58)	27.1 (8.78)
Duration of symptoms since axSpA onset (years)					
Mean (SD)	15.82 (10.6)	16.59 (10.1)	15.61 (9.3)	18.80 (11.61)	19.85 (11.63)
Duration of disease since axSpA diagnosis (years), mean (SD)	8.31 (9.6)	6.84 (7.6)	7.54 (7.5)	10.1 (7.8)	13.0 (10.5)
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CRP level (mg/L), mean (SD)	12.19 (13.3)	15.97 (21.0)	12.46 (17.6)	20.2 (34.3)	16 (22.3)
Baseline ASDAS score, mean (SD)	3.71 (0.74)	3.89 (0.74)	3.68 (0.85)	4.2 (0.9)	4.1 (0.8)
Baseline BASDAI score, mean (SD)	6.75 (1.32)	6.81(1.22)	6.65 (1.46)	7.5 (1.3)	7.3 (1.3)
Baseline PGA of disease activity (NRS), mean (SD)	6.9 (1.52)	7.1 (1.61)	7.1 (1.71)	[redacted]	[redacted]
Baseline BASFI score, mean (SD)	6.06 (1.79)	6.35 (1.89)	6.06 (2.08)	7.4 (1.8)	7.0 (1.7)
Baseline ASAS Health Index (ASAS HI), mean (SD)	7.48 (3.34)	8.12 (3.50)	8.22 (3.74)	10.0 (3.7)	9.0 (3.5)
Baseline DMARDs use, n (%)					
Methotrexate	9 (11.1)	8 (9.3)	8 (8.9)	12 (10.5)	20 (19.2)
Sulfasalazine	24 (29.6)	23 (26.7)	25 (27.8)	17 (14.9)	13 (12.5)
Prior TNFi use					
1 TNFi	NA	NA	NA	70 (61.4)	62 (59.6)
2 TNFi	NA	NA	NA	44 (38.6)	42 (40.4)
Baseline NSAID/COX-2 inhibitor use, n (%)	72 (88.9)	78 (90.7)	83 (92.2)	86 (75.4)	84 (80.8)
MRI of spine SPARCC score, mean (SD)	14.53 (20.55)	15.80 (21.19)	19.98 (28.43)	8.3 (16)	6.4 (10.2)

	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w. (N = 114)	PBO (N = 104)
Human leukocyte antigen B27 positive, n (%)					
Yes	75 (92.6)	76 (89.4)	82 (91.1)	[redacted]	[redacted]
No	6 (7.4)	9 (10.6)	8 (8.9)	[redacted]	[redacted]

ADA 40 q.2.w. = adalimumab 40 mg every 2 weeks; ASAS = Assessment of Spondyloarthritis International Society; ASAS HI = ASAS Health Index; ASDAS = Assessment of Disease Activity; axSpA = axial spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; COX-2 = cyclooxygenase-2; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug; IXE 80 q.4.w. = ixekizumab 80 mg every 4 weeks; IXE 80 q.2.w. = ixekizumab 80 mg every 2 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; NA = not applicable; NRS = numeric rating scale; NSAID = nonsteroidal anti-inflammatory drug; PBO = placebo; PGA = Patient Global Assessment; SD = standard deviation; SPARCC = Spondyloarthritis Research Consortium of Canada; TNFi = tumour necrosis factor inhibitor.

Source: CSR[10,11]

Interventions

In COAST-V, patients were allocated to treatment by a computer-generated random sequence with stratification by country and results of a CRP screen (≤ 5 mg/L or > 5 mg/L). Patients were randomized (1:1:1:1) to receive 80 mg IXE every two weeks, 80 mg IXE every four weeks, 40 mg adalimumab every two weeks, or matching placebo every two weeks. All treatments were administered by SC injection. Patients in IXE treatment regimens were randomly assigned (1:1 ratio) to receive a starting dose of either 80 mg IXE or 160 mg IXE (two 80 mg injections) for the first dose at week 0. COAST-V was a double-dummy design in which each active treatment had its own matched placebo to preserve the blind. At week 16, patients entered an extended treatment period (weeks 16 to 52), during which time patients in the IXE treatment groups remained on their assigned treatment and patients in the placebo or adalimumab groups were re-randomized to receive one of the two IXE dosing regimens, while maintaining masking of treatment allocation. All patients continued to receive masked treatment until week 52.

In COAST-W, patients were also allocated to treatment by a computer-generated random sequence with stratification by country and results of a CRP screen (≤ 5 mg/L or > 5 mg/L) and the number of prior TNFis taken (one or two). Patients were randomized (1:1:1) to receive IXE 80 mg SC every two weeks, IXE 80 mg SC every four weeks, or matched placebo from week 0 to week 16. Patients randomized to the IXE treatment regimens were randomized (1:1) to receive either an 80 mg or 160 mg starting dose of IXE at week 0 during the double-blinded treatment period (weeks 0–16). At week 16, patients entered the extended treatment period (weeks 16–52). Patients who were initially assigned to the placebo group were, for the extended treatment period, re-randomized at week 16 to IXE 80 mg SC every two weeks or IXE 80 mg SC every four weeks with a 160 mg starting dose. Patients already receiving IXE remained on their assigned treatment regimens through week 52.

In both COAST-V and COAST-W, use of NSAIDs and analgesics, cDMARDs, and corticosteroids was permitted to continue during the study. Patients taking concomitant medications were to be on stable doses at the time of baseline through week 16. Up to week 16, patients should not have started new medications or made any changes to concomitant medications unless changes needed to be made for an AE or for safety reasons.

In COAST-V, adalimumab was used as the active reference for comparison with placebo to provide internal evidence of assay sensitivity. The adalimumab group was not used to show equivalence or noninferiority with IXE; no statistical comparisons were performed between IXE and adalimumab. Therefore, the data of adalimumab reported in this review is for active internal reference only. No interpretation and discussion on the comparative efficacy and safety outcomes between IXE and adalimumab was made.

Outcomes

Assessment of Spondyloarthritis International Society Criteria

ASAS 40 and ASAS 20

The primary efficacy outcome in COAST-V and COAST-W was the proportion of patients who met ASAS 40 response criteria at week 16. An ASAS 40 response is defined as a 40% or greater improvement and an absolute improvement from baseline of two or greater units (range 0 to 10) in three or more of four main domains (i.e., Patient Global, Spinal Pain, Function, and Inflammation), without any worsening in the remaining domain. ASAS 20 was assessed as a major secondary outcome (i.e., analyzed with multiplicity adjustment) in both COAST-V and COASDT-W. ASAS 20 response is defined as a 20% or greater improvement and an absolute improvement from baseline of one or more unit (range 0 to 10) in three or more of four main domains, without any worsening in 20% or greater and one or more units (range 0 to 10) in the remaining domain.

ASAS 40 and ASAS 20 are composite measures containing four main domains: 1) patient's global assessment of disease activity on a NRS, with scores ranging from 0 (not active) to 10 (very active); 2) assessment of back pain intensity with an NRS, with scores ranging from 0 (not active) to 10 (very active); 3) function represented by BASFI, measured by an NRS, with scores ranging from 0 (not active) to 10 (very active); and 4) 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: 1) spinal mobility represented by Bath Ankylosing Spondylitis Metrology Index (BASMI) lateral spinal flexion assessment; and 2) CRP.

ASAS 5/6 and ASAS Partial Remission

The ASAS 5/6 and ASAS partial remission were assessed as other secondary outcomes (i.e., analyzed without multiplicity adjustment) in both COAST-V and COAST-W. The ASAS 5/6 includes assessments of all six individual ASAS domains and represents improvement of 20% or more in at least five domains. An ASAS partial remission response is defined as a value not above two units (range 0 to 10, NRS) in each of the following four main domains: Patient Global, Spinal Pain, Function, and Inflammation.

Symptom Measurement

In both COAST-V and COAST-W, spinal pain, fatigue, sleep, and depression were assessed as other secondary outcomes in both studies. Spinal pain was one of the four main components of ASAS criteria. Fatigue was assessed with the Fatigue Severity NRS; sleep disturbance was assessed with Jenkins Sleep Evaluation Questionnaire (JSEQ), and depression was assessed with Quick Inventory of Depressive Symptomatology–Self Report 16 items (QIDS-SR16).

Spinal Pain NRS Scale

In both COAST-V and COAST-W, the patient was asked to respond to the following two questions (based on average during the last week): 1. "How much pain of your spine due to ankylosing spondylitis do you have?" 2. "How much pain of your spine due to ankylosing spondylitis do you have at night?" The answers were recorded on an NRS and were each rated between "0" (no pain) and "10" (most severe pain). The first question was one of the four main components in ASAS responses.[10,11]

Fatigue Severity Numeric Rating Scale

The Fatigue Severity NRS is a single-item, patient-reported, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no fatigue" and 10 representing "as bad as you can imagine." Patients rated their fatigue ("feeling tired or worn out") by circling the one number that described their worst level of fatigue during the previous 24 hours. Validity, reliability, and information of a minimal important difference (MID) was not identified for this outcome.

Jenkins Sleep Evaluation Questionnaire

The Jenkins Sleep Evaluation Questionnaire (JSEQ) is a four-item, patient-reported instrument designed to estimate sleep problems in clinical research. The JSEQ assesses the frequency of sleep disturbance in four categories: 1) trouble falling asleep, 2) waking up several times during the night, 3) having trouble staying asleep (including waking up far too early), and 4) waking up after the usual amount of sleep feeling tired and worn out. Patients report the number of days they experience each of these problems in the past month on a six-point Likert scale ranging from 0 = "no days" to 5 = "22 to 30 days." The total JSEQ score ranges from 0 to 20, with higher scores indicating greater sleep disturbance. No MID was identified in the literature.

Quick Inventory of Depressive Symptomatology – Self Report 16 items

The QIDS-SR16 is a self-administered, 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Patients were asked to consider each statement as it relates to the way they have felt for the past seven days. There is a four-point scale for each item ranging from 0 to 3. The 16 items corresponding to nine depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. The domains assessed by the instrument are sad mood, concentration, self-criticism, suicidal ideation, interest, energy/fatigue, sleep disturbance (initial, middle, and late insomnia or hypersomnia), decrease/increase in appetite/weight, and psychomotor agitation/retardation. A minimal important difference (MID) was not identified in the literature. In both studies, QIDS-SR16 was assessed as an other secondary outcome (i.e., the no multiplicity was adjusted in the analysis).

Bath Ankylosing Spondylitis Functional Index

The Bath Ankylosing Spondylitis Functional Index (BASFI) is one of the four main components of ASAS criteria. The BASFI is a validated, patient self-administered, composite instrument widely used in AS to assess physical function. The BASFI consists of eight specific questions regarding function in AS and two questions reflecting the patient's ability to cope with everyday life. Each question is answered on a 10 cm horizontal visual analogue scale (VAS) or a numeric response scale (0 to 10), the mean of which gives the BASFI score

(on a scale of 0 to 10). The higher the BASFI score, the greater the degree of functional impairment with reductions from baseline indicating improvement. The MID was 0.6 units on a 10-unit scale. In both studies, BASFI was assessed as a major secondary outcome.

Health-Related Quality of Life

Short-Form (36) Health Survey

The Short Form (36) item Health Survey (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, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems. For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries, the physical component summaries (PCS) and the mental component summary (MCS). The PCS and MCS scores range from 0 to 100 with higher scores indicating better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a SD of 10 in the general US population. Therefore, all scores above or below 50 are considered to be above or below average for the general US population. Changes between 2.5 to 5.0 points in the physical and mental component scores of the SF-36 are considered to be clinically relevant, as are changes of 5 to 10 points in the domain scores. In both COAST-V and COAST-W, SF-36 PCS was assessed as major secondary outcome. However, SF-36-MCS, was assessed as an other secondary outcome in both studies.

ASAS HI

The ASAS HI is an axSpA-specific 17-item patient-reported instrument designed to assess functioning, disability, and health. The ASAS HI has scores ranging from 0 (good health) to 17 (poor health). Each item consists of one question that the patient needed to respond to with either "I agree" (score of 1) or "I do not agree" (score of 0). A score of "1" was given where the item was affirmed, indicating adverse health. A higher score indicates a poor health quality. All item scores are summed to give a total score or index.

A MID for ASAS HI was not identified in the literature. In both COAST-V and COAST-W, ASAS HI was assessed as a major secondary outcome.

EQ-5D

The European Quality of Life Scale is a generic quality of life instrument that may be applied to a wide range of health conditions and treatments. The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥1 2 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five possible levels of response (no problems, slight problems, moderate problems, severe problems, or extreme problems). Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights. The second part is a 20 cm visual analogue scale (EQ-VAS) that has endpoints labelled 0 and 100, with respective anchors of 'worst imaginable health state' and 'best imaginable health state.' Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS which best represents their health on that day. The EQ-5D index score is generated by applying a multi-attribute utility function to the

descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states 'dead' and 'perfect health,' respectively. Reported MIDs for this scale have ranged from 0.033 to 0.074. In both COAST-V and COAST-W, EQ-5D was assessed as an other secondary outcome.

WPAI-SpA

Work Productivity and Activity Impairment Questionnaire-Spondyloarthritis (WPAI-SpA) is a six-item, patient-reported instrument designed to assess the impact of SpA on work productivity and activity impairment. Four scores are derived: Percentage of Absenteeism, percentage of presenteeism, an overall work impairment score that combines absenteeism and presenteeism, and percentage of impairment in activities performed outside of work. Greater scores indicate greater impairment. No MID was identified in the literature. In both studies, EQ-5D was assessed as an other secondary outcome.

Bath Ankylosing Spondylitis Disease Activity Index

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is the most common and widely used validated measure of inflammatory activity of AS. BASDAI 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) and peripheral joint pain, localized tenderness, and morning stiffness (both degree of stiffness and length of time for which stiffness persists). Patients' responses are recorded on a 10-unit horizontal NRS or 10 cm VAS or a numeric response scale (1 to 10). The scores for questions 5 and 6 (severity and duration of morning stiffness) are averaged; the result is then averaged with the remaining four question scores. 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 an improvement. The definition of treatment response (i.e., MID) includes a change in the BASDAI value defined as two units (on a 0 to 10 scale) of the BASDAI. BASDAI 50, which reflects an improvement of 50%, was assessed as a major secondary outcome in COAST-V but was assessed as an other secondary outcome in COAST-W. In contrast, BASDAI score change from baseline, was assessed as a major secondary outcome in COAST-W, and was assessed as an other secondary outcome in COAST-V.

Ankylosing Spondylitis Disease Activity Score

Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite index to assess disease activity in AS. The parameters used for the ASDAS (with CRP as the acute phase reactant) are the following: total back pain (BASDAI question 2); Patient Global (individual ASAS domain); peripheral pain/swelling (BASDAI question 3); duration of morning stiffness (BASDAI question 6); CRP in mg/L. The ASDAS CRP is calculated with the following equation: 0.121 × total back pain + 0.110 × Patient Global + 0.073 × peripheral pain/swelling + 0.058 × duration of morning stiffness + 0.579 × Ln(CRP + 1). Four disease activity states have been defined by ASAS consensus as below:

- ASDAS less than 1.3 defines inactive disease;

- ASDAS 1.3 or greater or less than 2.1 defines low disease activity;
- ASDAS 2.1 or greater or less than 3.5 defines high disease activity; and
- ASDAS greater than 3.5 defines very high disease activity.

The clinically important improvement is defined as a change of 1.1 units or greater, and major improvement is defined as a change of 2.0 units or greater.[10,11] At the 2018 ASAS annual meeting, the nomenclature for the ASDAS low disease activity cut-off was updated. 'Moderate disease activity' was replaced by 'low disease activity' to better reflect what ASDAS values of ASDAS 1.3 or greater or less than 2.1 represent, in the opinion of patients and physicians.[10,11]

Inactive AS (i.e., ASDAS < 1.3) was assessed as a major secondary outcome in COAST-V, but it was assessed as an other secondary outcome in COAST-W. In contrast, low disease activity AS (i.e., ASDAS < 2.1) was assessed as a major secondary outcome in COAST-W, but it was assessed as an other secondary outcome in COAST-V.

Patient's Global Assessment

The Patient Global Assessment (PGA) of Disease Activity relates to a single specific ASAS domain based on an NRS. For this assessment, the patient was asked to respond to the following question: "How active was your spondylitis on average during the last week?" The answer was recorded on an NRS and was rated between "0" (not active) and "10" (very active). Additionally, an international validation study on the ASAS HI assessed PGA of disease activity using cut-off values of less than three and greater than six on NRS to distinguish between "good" and "poor" health status. While a MID for PGA was not identified in the literature, the minimum change that should be considered detectable would be approximately two to three units on a scale of 0 to 10.[26] The PGA was assessed as an other secondary outcome in both COAST-V and COAST-W.

MRI SPARCC Index

MRI Spine SPARCC Index

The Spondyloarthritis Research Consortium of Canada MRI Index (MRI SPARCC index) for spine is a MRI-based scoring system that assesses the presence, three-dimensional extent, and signal intensity of active inflammatory lesions represented by bone marrow edema in the spine of affected patients. In the spine, the scoring system measures bone marrow edema in the bone marrow of discovertebral units (DVU), with each unit representing the region between two imaginary lines drawn through the middle of adjacent vertebrae. All 23 discovertebral units of the spine (from C2 to S1) were scored for bone marrow edema. A single DVU has a scoring range of 0 to 18, bringing the maximum total score to 414, with higher scores reflecting worse disease. A MID of 5.0 units for the SPARCC MRI score for the spine has been identified. MRI Spine SPARCC Index was assessed as a major secondary outcome (the multiplicity was adjusted in the analysis) in both COAST-V and COAST-W.

MRI SIJ SPARCC Index

The MRI SPARCC score for sacroiliac joints (MRI SJI SPARCC) is a scoring method based on the assessment of increased signal denoting bone marrow edema on T2-weighted STIR sequences. All signal changes within the iliac bone and sacrum up to the sacral foramina are scored on six consecutive slices through the sacroiliac (SI) joint. Each SI joint is divided into four quadrants: upper iliac, lower iliac, upper sacral, and lower sacral. The presence of an increased signal on STIR in each of these four quadrants was scored on a dichotomous

basis, where one indicated an increased signal and zero indicated a normal signal. Total SIJ SPARCC scores can range from 0 to 72, with higher scores reflecting worse disease. An MID of 2.5 units for the SPARCC MRI score for SIJ has been identified. MRI SIJ SPARCC Index was assessed as an other secondary outcome (the multiplicity was not adjusted in the analysis) in COAST-V. MRI SIJ SPARCC Index was not reported in COAST-W.

Safety Outcomes

In both trials, safety data are presented as AE, SAE, death, withdrawals due to AEs, and notable AEs. All AE data presented in this review report are for TEAEs, defined as an AE that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the double blind (DB) period (with week 16).

Statistical Analysis

In COAST-V, approximately 320 patients were planned to be randomized at a 1:1:1:1 ratio in the DB phase to IXE 80 mg SC every two weeks, IXE 80 mg SC every four weeks, adalimumab 40 mg SC every two weeks, and placebo. With 80 patients per treatment group, COAST-V was planned to have approximately 96% power to test the superiority of IXE 80 mg SC every two weeks compared to placebo for ASAS 40 response at week 16. The following assumptions were used for the power calculations for ASAS 40 response at week 16 regardless of starting dose: 44% for the IXE 80 mg SC every two weeks group and 16% for the placebo group. A two-sided Fisher's exact test at an alpha level of 0.05 was assumed. These assumptions were based on a review of historical bDMARDS clinical studies in AS patients who were TNFi-naive.[11]

In COAST-W, approximately 300 patients were planned to be randomized at a 1:1:1 ratio in the DB phase to IXE 80 mg SC every two weeks, IXE 80 mg SC every four weeks, and placebo. With 100 patients per treatment group, COAST-W was planned to have approximately 96% power to test the superiority of IXE 80 mg SC every two weeks compared to placebo for ASAS 40 response rate at week 16. The following assumptions were used for the power calculations for ASAS 40 response at week 16 regardless of starting dose: 27% for the IXE 80 mg SC every two weeks group and 7% for the placebo group. A two-sided Fisher's exact test at an alpha level of 0.05 was assumed. These assumptions were based on a review of historical bDMARDS clinical studies in AS patients who were TNFi-experienced. [10]

In both COAST-V and COAST-W, the primary analysis method for treatment comparisons of categorical efficacy outcomes was made using a logistic regression analysis with treatment, geographic region (Europe and non-Europe), and baseline CRP status used in the model using PROC Logistic with a Wald test. In addition, in COAST-W, the number of prior TNFis used was also used in the model using PROC Logistic with a Wald test. As a secondary analysis for the primary and major secondary categorical efficacy measures, a categorical, pseudo-likelihood based mixed-effects model of repeated measures (categorical MMRM), estimating the percentage of patients achieving response across post-baseline visits, was used. The model included treatment, geographic region, baseline CRP status (non-elevated or elevated where elevated was defined as > 5.00 mg/L), visit, and treatment-by-visit as fixed factors.

In both COAST-V and COAST-W, the primary analyses for continuous efficacy outcomes were made using MMRM. The primary analyses for MRI SPARCC score were made based on observed case using analysis of covariance (ANCOVA). A secondary analysis for

continuous efficacy outcomes was made using ANCOVA with the modified baseline observation carried forward (mBOCF) method and the last observation carried forward (LOCF) method was also used for major and other secondary outcomes. When MMRM was used, the model included treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors. In addition, in COAST-W, the number of prior TNFi use was also used in the MMRM model.

Type III tests for the least squares (LS) means were used for the statistical comparison.

In both COAST-V and COAST-W, the impact of the IXE starting dose of 160 mg versus 80 mg on treatment response was evaluated for patients randomized to IXE 80 mg SC every four weeks treatment groups. For response analysis, starting dose comparisons within IXE 80 mg SC every four weeks treatment groups were based on a logistic regression model with treatment, starting dose, and treatment-by-starting-dose interaction. For mean change analysis, starting dose comparisons within IXE 80 mg SC every four weeks dosing regimens were based on the MMRM model with treatment, starting dose, baseline value, visit, baseline value-by-visit, treatment-by-visit, treatment-by-starting-dose, starting-dose-by-visit, and treatment-by-starting-dose-by-visit interactions as fixed factors. In general, in both studies, when MMRM was used for analyses, baseline value and baseline-by-visit interactions were included as covariates; when ANCOVA was used for analyses, baseline value was included as a covariate.

Analysis Populations

Unless otherwise specified, efficacy and health outcomes analyses were conducted on the ITT population, defined as all randomized patients, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Patients were analyzed according to the treatment group to which they were assigned. In addition, the primary analysis for the primary outcome was repeated using the per-protocol set. Patients were analyzed according to the treatment to which they were assigned. Safety analyses for the double-blind phase were conducted on the safety population (defined as all randomized patients who received at least one dose of study drug). Patients were analyzed according to the treatment group to which they were assigned.

The following methods for imputation of missing data were used for analyses for the DB phase:

Nonresponder Imputation (NRI): Analysis of categorical efficacy outcomes were assessed using a NRI method. Patients were considered non-responders for the NRI analysis if they did not meet the clinical response criteria, without at least one post-baseline observation, had missing clinical response data at week 16, or discontinued the study drug at any time prior to week 16 for any reason.

mBOCF and LOCF: In both COAST-V and COAST-W, mBOCF and LOCF analysis were performed on continuous efficacy outcomes in the major and other secondary outcomes. mBOCF and LOCF were identical approaches except for patients discontinuing the study drug because of an AE. The baseline observation was carried forward for evaluation in mBOCF, but the last non-missing observation before discontinuation was carried forward for evaluation in LOCF. Randomized patients without any post-baseline observations were not included for evaluation.

Multiplicity adjustment: A graphical multiple testing procedure was used to control the family-wise type I error rate at a two-sided alpha level of 0.05. According to the sponsor, the graphical approach was a closed testing procedure, therefore, it was considered that the

family-wise type I error rate was well controlled.[10,11] The following are the primary and major secondary outcomes that were tested for both the IXE 80 mg SC every two weeks and IXE 80 mg SC every four weeks treatment groups at week 16:

- Primary outcome – ASAS 40
- Secondary outcome 1 – ASAS 20
- Secondary outcome 2 – ASDAS
- Secondary outcome 3 – BASDAI 50 (in COAST-V only) and BASDAI change from baseline (in COAST-W only)
- Secondary outcome 4 – BASFI
- Secondary outcome 5 – ASDAS inactive disease (1.3 or less, [in COAST-V only]) and ASDAS low disease activity (2.1 or less [in COAST-W only])
- Secondary outcome 6 – MRI Spine SPARCC
- Secondary outcome 7 – SF-36 PCS score
- Secondary outcome 8 – ASAS HI.

There was no multiplicity adjustments for other outcomes (e.g., ASAS 5/6, ASAS partial remission, spinal pain, Fatigue Severity NRS, JSEQ, QIDS-SR16, SF-36 MCS, EQ-5D-5L, WPAI-SpA, and MRI SIJ SPARCC).

Results

Patient Disposition

Patient disposition for COAST-V and COAST-W are presented in Table 6. In COAST-V, 781 patients were screened and a total of 341 were randomized. Of the 341 randomized patients, 81 patients, 87 patients, and 90 patients received IXE 80 mg SC every four weeks, placebo, or adalimumab 40 mg SC every two weeks respectively (i.e., ITT population). In addition, 83 patients received IXE 80 mg SC every two weeks, which is not reported in this review since it is not aligned with the Health Canada-recommended dose regimen. Of the ITT population, 96.3%, 98.9%, and 97.8% patients completed the study in the IXE 80 mg SC every four weeks group, placebo, and adalimumab 40 mg every two weeks group respectively, and 3.7%, 1.1%, and 2.2% discontinued from the study (or treatment), respectively. The reasons for discontinuation were due to patient consent (1.1 to 2.4%), lack of efficacy (1.2%), adverse events (1.1%), and exclusion due to allocation error (1.1%) across treatment groups (Table 6).

In COAST-W, 610 patients were screened and a total of 316 were randomized. Of the 316 randomized patients, 114 patients and 104 patients received IXE 80 mg SC every four weeks and placebo respectively (i.e., ITT population). In addition, 98 patients received IXE 80 mg SC every two weeks, which is not reported in this review since it is not aligned with the Health Canada-recommended dose regimen. Of the ITT population, 86.8%, and 89.4% patients completed the study in the IXE 80 mg SC every four week group and placebo, respectively, and 14.4%, and 9.7% discontinued from the study (or treatment), respectively. The reasons for discontinuation were due to patient consent (2.9 to 6.1%), lack of efficacy (0.9 to 1.8%), adverse events (1.8 to 8.7%), and by physician (0.9%) across treatment groups.

Table 6: Patient Disposition

	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w. (N = 114)	PBO (N = 104)
Screened, n		781			610
Randomized, n	81	87	90	114	104
Completed at week 16, n (%)	78 (96.3)	86 (98.9)	88 (97.8)	99 (86.8)	93 (89.4)
Discontinued, n (%) at week 16	3 (3.7)	1 (1.1)	2 (2.2)	15 (14.4)	11 (9.7)
Reason for discontinuation, n (%)					
Lack of efficacy	1 (1.2)			1 (0.9)	2 (1.8)
Adverse events			1 (1.1)	9 (8.7)	2 (1.8)
Excluded due to allocation error		1 (1.1)			
By consent	2 (2.4)		1 (1.1)	3 (2.9)	7 (6.1)
By physician				1 (0.9)	
ITT, N	81	87	90	114	104
PP, N	79	75	73	80	88
Safety, N	81	86	90	114	104

ADA 40 q.2.w. = adalimumab 40 mg every 2 weeks; ITT = intent-to-treat; IXE 80 q.4.w.= ixekizumab 80 mg every 4 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; PP = per protocol.

Note: In addition, 83 patients in COAST-V and 98 patients in COAST-W received ixekizumab 80 mg every 2 weeks, which is not reported in this review since it is not aligned with the Health Canada-recommended dose regimen.

Source: CSR [10,11]

Exposure to Study Treatments

In COAST-V, the extent of exposure in the IXE 80 mg SC every four weeks groups and the placebo group (mean duration/total patient years) were [redacted].[11] In COAST-W, the extent of exposure in the IXE 80 mg SC every four weeks groups and the placebo group (mean duration/total patient years) were [redacted].[10] [redacted]

Efficacy

Only those efficacy outcomes (assessed at week 16) and analyses of subgroups identified in the review protocol are reported below. See Appendix 3 for detailed efficacy data. The results from the IXE 80 mg SC every two weeks dosing regimen was not reported in this review since it is not aligned with the Health Canada-recommended dose regimen. The results from adalimumab in COAST-V was presented for active reference only in this review. The results from week 16 to 52 (extension period) are presented in the section of long-term extension studies.

Clinical Response

ASAS 40: The primary outcome in both COAST-V and COAST-W was ASAS 40 at week 16. The results of ASAS 40 are presented in Table 7.

In COAST-V, in the ITT analysis, the proportion of patients who achieved ASAS 40 were reported as 48.1% and 18.4% in the IXE 80 mg SC every four weeks and placebo group,

respectively. The mean between-group difference (IXE versus placebo) was 29.8% (95% CI, 16.2% to 43.3%; P < 0.001). In per-protocol analysis, the ASAS 40, the mean between-group difference (IXE versus placebo) was 32.3% (95% CI, 18.2% to 46.3%, P < 0.001), which was consistent with the results of the primary analysis with the ITT population (Table 7). The additional secondary analysis (i.e., categorical MMRM) for ASAS 40 were also reportedly consistent with results of the primary analysis (i.e., ITT, NRI).

In COAST-W, in the ITT analysis, the proportion of patients who achieved ASAS 40 were reported as 25.4% and 12.5% in the IXE 80 mg SC every four weeks and placebo group, respectively. The mean between-group difference (IXE versus placebo) was 12.9% (95% CI, 2.7% to 23.2%; P = 0.017). In the per-protocol analysis, the ASAS 40 mean between-group difference (IXE versus placebo) was 11.4% (95% C, 0.1% to 22.6%; P = 0.049), which was consistent with the results of the primary analysis with the ITT population (see Table 7). The additional secondary analysis (i.e., categorical MMRM) for ASAS 40 were also consistent with the results of the primary analysis (ITT, NRI).

Table 7: ASAS 40 Response at Week 16 (NRI, ITT)

ASAS 40 at week 16	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w. (N = 141)	PBO (N = 104)
ASAS 40, (NRI, ITT)					
Response, n (%)	39 (48.1)	16 (18.4)	32 (35.6)	29 (25.4)	13 (12.5)
% Diff vs. PBO[b] (95% CI)	29.8 (16.2 to 43.3)		17.2 (4.4 to 30.0)	12.9 (2.7 to 23.2)	
P value vs. PBO[a]	< 0.001		0.005	0.017	
ASAS 40, (NRI, PP)	N = 79	N = 75	N = 73	[redacted]	[redacted]
Response, n (%)	38 (50.0)	14 (17.7)	29 (38.2)	[redacted]	[redacted]
% Diff vs. PBO[b] (95% CI)	32.3 (18.2 to 46.3)		20.4 (6.6 to 34.2)	[redacted]	
P value vs. PBO[a]	< 0.001		0.003	[redacted]	

ADA 40 q.2.w. = adalimumab 40 mg every 2 weeks; ASAS 40 = Assessment of Spondyloarthritis International Society 40% improvement; CI = confidence interval; Diff = difference; ITT = intent-to-treat; IXE 80 q.4.w. = ixekizumab 80 mg every 4 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = nonresponder imputation; PBO = placebo; PP = per protocol.

[a] In COAST-V, logistic regression analysis with treatment, geographic region, and baseline CRP status in the model. In COAST-W, logistic regression analysis with treatment, geographic region, and baseline CRP status and the number of prior TNFi in the model.

[b] Confidence intervals are constructed using the simple asymptotic method, without continuity correction (i.e., normal approximation to the binomial distribution).

Source: CSR.[10,11]

ASAS 20

ASAS 20 response was reported as a major secondary outcome in both COAST-V and COAST-W. The results of ASAS 20 are presented in Table 8.

In COAST-V, in the ITT analysis, the proportion of patients who achieved ASAS 20 were reported as 64.2% and 40.2% in the IXE 80 mg SC every four weeks and placebo group, respectively. The mean between-group difference (IXE versus placebo) was 24.0 % (95% CI 9.3% to 38.6%; P < 0.001). In per-protocol analysis, the ASAS 20 mean between-group difference (IXE versus placebo) was 27.9% (95% CI 12.8% to 42.9%; P < 0.001), which was consistent with the results of the primary analysis with the ITT population (see Table 8). The

additional secondary analysis (i.e., categorical MMRM) for ASAS 20 were also consistent with results of the primary analysis (ITT, NRI).

In COAST-W, in the ITT analysis, the proportion of patients who achieved ASAS 20 were reported as 48.2% and 29.8% in the IXE 80 mg SC every four weeks and placebo group, respectively. The mean between-group difference (IXE versus placebo) was 18.4 % (95% CI, 5.7% to 31.1%; P = 0.006). In the per-protocol analysis, the ASAS 20 mean between-group difference (IXE versus placebo) was 19.2% (95% CI, 5.3% to 33.2%; P = 0.008), which was consistent with the results of the primary analysis with the ITT population (Table 8). The additional secondary analysis (i.e., categorical MMRM) for ASAS 20 were also reportedly consistent with results of the primary analysis.

Table 8: ASAS 20 Response at Week 16 (NRI, ITT)

ASAS 20 at Week 16	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 40 q.4.w. (N = 114)	PBO (N = 104)
ASAS 20 (NRI, ITT)					
Response, n (%)	52 (64.2)	35 (40.2)	53 (58.9)	55 (48.2)	31 (29.8)
% Diff (95% CI) vs. PBO[b]	24.0 (9.3 to 38.6)		18.7 (4.2 to 33.1)	18.4 (5.7 to 31.1)	
P value vs. PBO[a]	0.001		0.007	0.006	
ASAS 20 (NRI, PP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Diff (95% CI) vs. PBO[b]	[redacted]		[redacted]	[redacted]	
P value vs. PBO[a]	[redacted]		[redacted]	[redacted]	

ADA 40 q.2.w. = adalimumab 40 mg every 2 weeks; ADA 40 q.4.w. = adalimumab 40 mg every 4 weeks; ASAS 20 = Assessment of Spondyloarthritis International Society 20% improvement; CI = confidence interval; Diff = difference; ITT = intent-to-treat; IXE 40 q.4.w. = ixekizumab 40 mg every 4 weeks; IXE 80 q.4.w. = ixekizumab 80 mg every 4 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = nonresponder imputation; PBO = placebo; PP = per protocol.

[a] In COAST-V, logistic regression analysis with treatment, geographic region, and baseline CRP status in the model. In COAST-W, logistic regression analysis with treatment, geographic region, and baseline CRP status and the number of prior TNFi in the model.

[b] Confidence intervals are constructed using the simple asymptotic method, without continuity correction (i.e., normal approximation to the binomial distribution).

Source: CSR.[10,11]

No subgroup analysis based on the baseline disease activity (e.g., BASDAI) was conducted in either COAST-V or COAST-W.

Efficacy Starting Dose Analyses: The ASAS 40 and ASAS 20 responses based on the IXE starting dose (160 mg or 80 mg at week 0) are presented in Table 28 in Appendix 3. In COAST-V, the ASAS 40 were [redacted] in the 160 mg and 80 mg groups, respectively. The mean between-group difference (IXE 160 mg versus IXE 80 mg) was [redacted] The ASAS 20 responses were [redacted] in the 160 mg and 80 mg groups, respectively. The mean between-group difference (IXE 160 mg versus IXE 80 mg) was [redacted] (Table 28).

In COAST-W, the ASAS 40 responses were [redacted] in the 160 mg and 80 mg group respectively. The mean between-group difference (IXE 160 mg versus IXE 80 mg) was [redacted] The ASAS 20 responses were [redacted] in the 160 mg and 80 mg groups, respectively and the mean between-group difference (IXE 160 mg versus IXE 80 mg) was [redacted] (Table 28).

ASAS 5/6

The ASAS 5/6 responses at week 16 are presented in Table 29. In COAST-V, at week 16, the proportion of patients who achieved the ASAS 5/6 were [redacted] in the IXE 80 mg SC every four weeks and placebo groups, respectively. The mean between-group difference (IXE versus placebo) was [redacted]. In COAST-W, at week 16, the proportion of patients who achieved the ASAS 5/6 were [redacted] in the IXE 80 mg SC every four weeks and placebo groups, respectively. The mean between-group difference (IXE versus placebo) was [redacted] (Table 29).

ASAS Partial Remission

The ASAS partial remission at week 16 results are presented in Table 30. In COAST-V, at week 16, the proportion of patients who achieved the ASAS partial remission were [redacted] in the IXE 80 mg SC every four weeks and placebo groups, respectively. The mean between-group difference (IXE versus placebo) was [redacted] In COAST-W, at week 16, the proportion of patients who achieved ASAS partial remission were [redacted] in the IXE 80 mg SC every four weeks and placebo groups, respectively. The mean between-group difference (IXE versus placebo) was [redacted] (Table 30).

Measures of AS Symptoms

The results of the AS symptom measures (i.e., spinal pain, Fatigue Severity NRS, JSEQ, and QIDS-SR16) are presented in Table 31 in Appendix 4.

Spinal pain: The spinal pain assessment is one of the six ASAS criteria components. In COAST-V, at week 16, the LSM changes from baseline for spinal pain were –3.2 and –1.7 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted]. In COAST-W, at week 16, the LSM changes from baseline for spinal pain were –2.4 and –1.0 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted] (Table 31).

Fatigue Severity NRS: In COAST-V, at week 16, the LSM changes from baseline for Fatigue Severity NRS were –2.5 and –1.4 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted]. In COAST-W, at week 16, the LSM changes from baseline for Fatigue Severity NRS were –2.0 and –0.7 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted] (Table 31).

JSEQ: The frequency of sleep disturbance was assessed with the JSEQ.

In COAST-V, at week 16, the LSM changes from baseline for JSEQ were –2.5 and –1.5 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted]. In COAST-W, at week 16, the LSM changes from baseline for JSEQ were –3.0 and –1.8 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted] (Table 31).

QIDS-SR16

Depression symptoms were assessed with Quick Inventory of Depressive Symptomatology–Self Report 16 items (QIDS-SR16). In COAST-V, at week 16, the LSM changes from baseline for QIDS-SR16 were [redacted] in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted]. In COAST-W, at week 16, the LSM changes from baseline for QIDS-SR16 were [redacted] in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted] (Table 31).

Function and Disability

Function and disability were assessed with the BASF,, which is one of the six components of the ASAS response criteria. The results of BASFI is presented in Table 9.

In COAST-V, at week 16, the LSM changes from baseline for BASFI were –2.39 and –1.16 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was –1.22 (95% CI, –1.83 to –0.62; P < 0.001). In COAST-W, at week 16, the LSM changes from baseline for BASFI were –1.69 and –0.64 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was –1.05 (95% CI, –1.63 to –0.47; P < 0.001) (Table 9). In both COAST-V and COAST-W, the results of the analyses by ANCOVA with the mBOCF or LOCF methods were reportedly consistent with the results of the analysis by MMRM.

Table 9: BASFI Score at week 16 (MMRM, ITT)

BASFI	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w. (N = 114)	PBO (N = 104)
BASFI					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	*6.06(1.79)*	*6.349 (1.88)*	[redacted]	*7.35 (1.78)*	*7.01 (1.73)*
Week 16, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE)	-2.39 (0.22)	-1.16 (0.22)	-2.14 (0.21)	-1.69 (0.21)	-0.64 (0.22)
Between-group LSM diff (95% CI)	-1.22 (-1.83, -0.62)		-0.97 (-1.56, -0.39)	-1.05 (-1.63, -0.47)	
P value	<0.001		0.001	<0.001	

ADA 40 q.2.w. = adalimumab 40 mg every two weeks; ANCOVA= analysis of covariance; BASFI = Bath Ankylosing Spondylitis Functional Index; CFB = change from baseline; CI = confidence interval; Diff = difference; ITT = Intent-to-Treat; IXE 80 q.4.w. = ixekizumab 80 mg every four weeks; LSM = least squares mean; mBOCF= modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = Placebo; SD = Standard of deviation; SE = standard error.

Source: CSRs.[10,11]

Health-related Quality of Life

SF-36 PCS and ASAS HI were analyzed as major secondary outcomes. The results of SF-36 PCS and ASAS HI are presented in Table 10. SF-36 MCS and EQ-5D-5L were analyzed as other outcomes and the results of SF-36 MCS and EQ-5D-5L are presented in Table 32 in Appendix 4.

SF-36

SF-36 PCS: In COAST-V, at week 16, the LSM changes from baseline for SF-36 PCS were 7.69 and 3.64 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was 4.05 (95% CI, 1.94 to 6.16; P < 0.001). In COAST-W, at week 16, the LSM changes from baseline for SF-36 PCS were 6.58 and 1.36 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was 5.21 (95% CI, 3.02 to 7.41; P < 0.001) (Table 10). In both COAST-V and COAST-W, the results of the analyses by ANCOVA with the mBOCF or LOCF methods were reportedly consistent with the results of the analysis by MMRM.

SF-36 MCS: In COAST-V, at week 16, the LSM changes from baseline for SF-36 MCS were [redacted] in the IXE 80 mg SC every four weeks and placebo group respectively. The between-group LSM difference (IXE versus placebo) was [redacted]. In COAST-W, at week 16, the LSM changes from baseline for SF-36 MCS were [redacted] in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted] (Table 32).

ASAS HI: In COAST-V, at week 16, the LSM changes from baseline for ASAS HI were –2.36 and –1.25 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was 1.11 (95% CI, –1.95 to –0.27; P < 0.01). In COAST-W, at week 16, the LSM changes from baseline for ASAS HI were –1.92 and –0.89 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was –1.03 (95% CI, –1.94 to –0.13; P < 0.026) (Table 10). In both COAST-V and COAST-W, the results of the analyses by ANCOVA with the mBOCF or LOCF methods were reportedly consistent with the results of the analysis by MMRM.

EQ-5D-5L: In COAST-V, at week 16, the LSM changes from baseline for EQ-5D-5L VAS were [redacted] in the IXE 80 mg SC every four weeks and placebo groups, respectively. The EQ-5D-5L VAS between-group LSM difference (IXE versus placebo) was [redacted]. The LSM changes from baseline for the EQ-5D-5L UK population-based Index score were [redacted] in the IXE 80 mg SC every four weeks and placebo groups, respectively. The EQ-5D-5L index between-group LSM difference (IXE versus placebo) was [redacted] (Table 32).

In COAST-W, at week 16, the LSM changes from baseline for EQ-5D-5L VAS were [redacted] in the IXE 80 mg SC every four weeks and placebo groups, respectively. The EQ-5D-5L VAS between-group LSM difference (IXE versus placebo) was [redacted]. The LSM changes from baseline for the EQ-5D-5L UK population-based Index score were [redacted] in the IXE 80 mg SC every four weeks and placebo groups, respectively. The EQ-5D-5L index between-group LSM difference (IXE versus placebo) was [redacted] (Table 32).

Table 10: HRQoL at Week 16 (MMRM, ITT)

HRQoL	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w. (N = 114)	PBO (N = 104)
SF-36 PCS at week 16					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline LSM (SE)	7.69 (0.78)	3.64 (0.75)	6.90 (0.73)	6.58(0.78)	1.36 (0.81)
Between-group LSM diff. (95% CI)	4.05 (1.94 to 6.16)		3.26 (1.20 to 5.31)	5.21 (3.02 to 7.41)	
P value	< 0.001		0.002	< 0.001	
ASAS HI at week 16					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline LSM (SE)	-2.36 (0.31)	-1.25 (0.300)	-2.30 (0.290)	-1.92 (0.32)	-0.89 (0.34)
Between-group LSM diff. (95% CI)	-1.11 (-1.95 to -0.27)		-1.05 (-1.87 to -0.23)	-1.03 (-1.94 to -0.13)	
P value	0.010		0.012	0.026	

ADA 40 q.2.w. = adalimumab 40 mg every two weeks; ANCOVA= analysis of covariance; ASAS HI = Assessment of Spondyloarthritis International Society Health Index; CFB = change from baseline; CI = confidence interval; Diff = difference; EQ-5D-5L= European Quality of Life – 5 Dimensions 5 Levels; HRQoL= Health-related quality of life; ITT = Intent-to-Treat; IXE 80 q.4.w. = ixekizumab 80 mg every four weeks; LSM = least squares mean; mBOCF= modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = Placebo; SD = Standard of deviation; SE = standard error; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; SF-36-MCS = SF-36 mental component summary; SF-36-PCS= SF-36 physical component summary.

[a]ANCOVA model includes treatment, geographic region, baseline CRP status, and baseline value.

Source: CSRs[10,11]

Work Productivity

Work productivity was assessed with the Work Productivity Activity Impairment–Spondyloarthritis (WPAI-SpA) Score. The results of WPAI-SpA (Percentage of Absenteeism, presentisms, overall work impairment score, and percentage of activity impairment) at week 16 are presented in Table 33 in Appendix 4.

Percentage of Absenteeism Change From Baseline: In COAST-V, at week 16, the LSM changes from baseline for Percentage of Absenteeism were 1.23 and –1.26 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted]. In COAST-W, at week 16, the LSM changes from baseline for Percentage of Absenteeism were –4.74 and –1.17 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted] (Table 33).

Percentage of Presentisms Change From Baseline: In COAST-V, at week 16, the LSM changes from baseline for Percentage of Presentisms were –22.7 and –17.7 in the IXE 80

mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted]. In COAST-W, at week 16, the LSM changes from baseline for Percentage of Presentisms were –19.5 and –8.9 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted] (Table 33).

Overall Work Impairment Score Change From Baseline: In COAST-V, at week 16, the LSM changes from baseline for overall work impairment score were –21.36 and 17.82 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted]. In COAST-W, at week 16, the LSM changes from baseline for overall work impairment score were –20.97 and –9.84 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted] (Table 33).

Percentage of Activity Impairment Change From Baseline: In COAST-V, at week 16, the LSM changes from baseline for Percentage of Activity Impairment were –23.0 and –14.1 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted]. In COAST-W, at week 16, the LSM changes from baseline for Percentage of Activity Impairment were –16.5 and –10.1 in the IXE 80 mg SC every four weeks and placebo group respectively. The between-group LSM difference (IXE versus placebo) was [redacted] (Table 33).

Disease Activity

The Disease Activity (i.e., BASDAI, ASDAS) results are presented in Table 11.

BASDAI 50: BASDAI 50 was assessed as a major secondary outcome in COAST-V; however, BASDAI 50 was assessed as an other secondary outcome in COAST-W. In COAST-V, in the ITT analysis, the proportion of patients who achieved BASDAI 50 were reported as 42.0% and 17.2% in the IXE 80 mg SC every four weeks and placebo groups, respectively. The mean between-group difference (IXE versus placebo) was 24.7% (95% CI, 11.4% to 38.1%; P < 0.001) (Table 11).

In COAST-W, in the ITT analysis, the proportion of patients who achieved BASDAI 50 were reported as 21.9% and 9.6% in the IXE 80 mg SC every four weeks and placebo groups, respectively. The mean between-group difference (IXE versus placebo) was: [redacted]

In both COAST-V and COAST-W, the additional secondary analysis (by categorical MMRM) for BASDAI 50 was reportedly consistent with results of the primary analysis by NRI.

BASDAI Change From Baseline: BASDAI change from baseline at week 16 was analyzed as a major secondary outcome in COAST-W, but was assessed as an other secondary outcome in COAST-V. In COAST-V, at week 16, the LSM changes from baseline for BASDAI score were –2.92 and –1.39 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was [redacted] (Table 11). In COAST-W, at week 16, the LSM changes from baseline for BASDAI score were –2.17 and –0.92 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was –1.24 (95% CI, –1.81 to –0.67; P <0.001). In both COAST-V and COAST-W, the results of

the analyses by ANCOVA with the mBOCF or LOCF methods were reportedly consistent with the results of the analysis by MMRM.

ASDAS Change From Baseline: ASDAS change from baseline at week 16 was assessed as a major secondary outcome in both COAST-V and COAST-W. In COAST-V, at week 16, the LSM changes from baseline for ASDAS were –1.43 and –0.46 in the IXE 80 mg SC every four weeks and placebo group respectively. The between-group LSM difference (IXE versus placebo) was –0.97 (95% CI, –1.25 to –0.70; P < 0.001) (Table 11). In COAST-W, at week 16, the LSM changes from baseline for ASDAS were –1.16 and –0.11 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus placebo) was –1.05 (95% CI, –1.32 to –0.79; P < 0.001) (Table 11). In both COAST-V and COAST-W, the results of the analyses by ANCOVA with the mBOCF or LOCF methods were reportedly consistent with the results of the analysis by MMRM.

ASDAS Inactive Disease (<1.3) response at week 16 was analyzed as a major secondary efficacy in COAST-V, and was analyzed as an other secondary outcome in COAST-W. In COAST-V, in the ITT population (NRI), the proportion of patients who achieved ASDAS Inactive Disease (< 1.3) were reported as 16.0% and 2.3% in the IXE 80 mg SC every four weeks and placebo treatment groups, respectively. The mean between-group difference (IXE versus placebo) was 13.8% (95% CI; 5.2% to 22.3%; P = 0.007) (Table 11). Additional secondary analysis by categorical MMRM was performed and it was reported that due to the low ASDAS-inactive disease response rates, the model did not converge and does not provide additional information.

In COAST-W, in the ITT population, the proportion of patients who achieved ASDAS Inactive Disease (<1.3) were reported in [redacted] the IXE 80 mg SC every four weeks and placebo treatment groups, respectively. The mean between-group difference (IXE versus placebo) was [redacted] (Table 11) [redacted].

ASDAS Low Activity Disease (< 2.1) response at week 16 was analyzed as a major secondary efficacy in COAST-W, and was analyzed as an other secondary outcome in COAST-V. The results of ASDAS Low Activity Disease (< 2.1) are presented in Table 11. In COAST-V, in the ITT population (NRI), the proportion of patients who achieved ASDAS low activity disease (<2.1) was reported as 43.2% and 12.6% in the IXE 80 mg SC every four weeks and placebo treatment groups, respectively. The mean between-group difference (IXE versus placebo) was 30.6% (95% CI, 17.72% to 43.42%; P < 0.001) (Table 11). The additional secondary analysis (by categorical MMRM) was performed, but due to the low ASDAS inactive disease response rates, the model did not converge and does not add additional information.

In COAST-W, in the ITT population, the proportion of patients who achieved ASDAS low activity disease (2.1) were reported as 17.5% and 4.8% in the IXE 80 mg SC every four weeks and placebo treatment groups, respectively. The mean between-group difference (IXE versus placebo) was 12.7% (95% CI, 4.6% to 20.8%; P = 0.006) (Table 11). Results of the additional secondary analysis (by categorical MMRM) were reportedly consistent with the results of the analysis by logistic regression with NRI.

Table 11: Disease Activity (BASDAI, ASDAS) at Week 16 (NRI, ITT)

Disease activity	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w. (N = 114)	PBO (N = 104)
BASDAI 50 (NRI, ITT), n (%)	34 (42.0)	15 (17.2)	29 (32.2)	25 (21.9)	10 (9.6)
% Diff (95% CI) vs. PBO*b	24.7 (11.4, 38.1)		15.0 (2.5, 27.5)	[redacted]	
P value, vs. PBO[a]	<0.001		0.012	[redacted]	
BASDAI CFB (MMRM, ITT)					
Week 16 (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean, (SD)	6.75 (1.32)	6.79 (1.23)	[redacted]	7.54 (1.34)	7.32 (1.26)
Week 16, mean, (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE)	-2.92 (0.22)	-1.39 (0.22)	[redacted]	-2.17 (0.20)	-0.92 (0.21)
Between-group LSM diff. (95% CI)	[redacted]		[redacted]	-1.24 (-1.81, -0.67)	
P value	[redacted]		[redacted]	<0.001	
ASDAS CFB					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, Mean(SD)	3.71 (0.738)	3.88 (0.739)	[redacted]	*4.15 (0.858)*	*4.05(0.811)*
Week 16, Mean(SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE), (MMRM, ITT)	-1.43 (0.102)	-0.46 (0.099)	-1.30 (0.096)	-1.16 (0.094)	-0.11 (0.099)
Between-group LSM diff. (95% CI)	-0.97 (-1.25, -0.70)		-0.84 (-1.11, -0.57)	-1.05 (-1.32, -0.79)	
P value	<0.001		<0.001	<0.001	
ASDAS (< 1.3) (NRI, ITT) n, (%)	*13 (16.0)*	*2 (2.3)*	*14 (15.6)*	[redacted]	[redacted]
% Diff (95% CI) vs. PBO[b]	*13.8 (5.2, 22.3)*		*13.3 (5.1, 21.4)*	[redacted]	
P value vs. PBO[a]	*0.007*		*0.009*	[redacted]	
ASDAS (< 2.1) (NRI, ITT), n (%)	*35 (43.2)*	*11 (12.6)*	*34 (37.8)*	*20 (17.5)*	*5 (4.8)*
% Diff (95% CI) vs. PBO[b]	*30.6 (17.72, 43.42)*		*25.1 (12.92, 7.34)*	12.7 (4.6, 20.8)	
P value vs. PBO	*<0.001*		*<0.001*	0.006	

ADA 40 q.2.w. = adalimumab 40 mg every two weeks; ANCOVA= analysis of covariance; ASDAS = Ankylosing Spondylitis Disease Activity Score; CFB = change from baseline; CI = confidence interval; Diff = difference; ITT = Intent-to-Treat; IXE 80 q.4.w. = ixekizumab 80 mg every four weeks; LSM = least squares mean; mBOCF= modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; N = number of patients in the analysis population; n = number of patients in the specified category; NRI= nonresponder; OR = odds ratio; PBO = Placebo; SD = standard of deviation; SE = standard error;

Note: ASDAS Inactive disease (<1.3) response at week 16 was analyzed as a major secondary outcome in COAST-V, but not in COAST-W; ASDAS low disease activity (< 2.1) response at week 16 was analyzed as a major secondary outcome in COAST-W, but not in COAST-V.

Note: BASDAI 50 response at week 16 was analyzed as a major secondary outcome in COAST-V, but not in COAST-W; BASDAI change from baseline at week 16 was analyzed as a major secondary outcome in COAST-W, but not in COAST-V.

a. In COAST-V, Logistic regression analysis with treatment, geographic region, and baseline CRP status in the model; In COAST-W; Logistic regression analysis with treatment, geographic region, and baseline CRP status, and the number of prior TNFi in the model.

b. Confidence intervals are constructed using the simple asymptotic method, without continuity correction (that is, normal approximation to the binomial distribution).

Source: CSRs[10,11]

Patient Global Assessment

The Patient's Global Assessment (PGA) on health status was the first component in ASAS criteria. PGA was analyzed as an other secondary outcome in both COAST-V and COAST-

W. The results of PGA are presented in Table 34. In COAST-V, at week 16, the LSM changes from baseline for PGA were –2.5 and –1.4 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus PBO) was [redacted] In COAST-W, at week 16, the LSM changes from baseline for PGA were –2.4 and –0.7 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus PBO) was [redacted] (Table 34). In both COAST-V and COAST-W, the results of the secondary analyses by ANCOVA with the mBOCF methods were reportedly consistent with the results of the analysis by MMRM.

MRI SPARCC Index

MRI Spine SPARCC Score was a major secondary outcome in both COAST-V and COAST-W. The results of MRI Spine and SIJ SPARCC at week 16 are presented in Table 12.

In COAST-V, at week 16, the LSM changes from baseline for MRI Spine SPARCC Score were –11.02 and –1.51 in the IXE 80 mg SC every four weeks and placebo group respectively. The between-group LSM difference (IXE versus PBO) was –9.51 (95% CI, –12.6 to –6.4; P < 0.001) (Table 12). In COAST-W, at week 16, the LSM changes from baseline for MRI Spine SPARCC Score change from baseline were –2.99 and 3.29 in the IXE 80 mg SC every four weeks and placebo groups, respectively. The between-group LSM difference (IXE versus PBO) was –6.29 (95% CI, –10.0 to –2.5; P = 0.001) (Table 12). In both COAST-V and COAST-W, the results of the secondary analyses by ANCOVA with the mBOCF or LOCF methods were reportedly consistent with the results of the observed case analysis by ANCOVA.

MRI SIJ SPARCC Score was reported only in COAST-V. It was not reported in COAST-W. MRI SIJ SPARCC Score was analyzed as an other secondary outcome. In COAST-V, at week 16, the LSM changes from baseline for MRI SIJ SPARCC Score were –3.97 and 0.92 in the IXE 80 mg SC every four weeks and placebo group respectively. The between-group LSM difference (IXE versus PBO) was –4.89 (95% CI, –6.5 to –3.3; P < 0.001) (Table 12). Results of the secondary analyses by ANCOVA with the mBOCF method were reportedly consistent with the results of the observed case analysis by ANCOVA.

Table 12: MRI Spine and SIJ SPARCC Score at Week 16 (ANCOVA, OCA)

MRI Spine and SIJ SPARCC	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w. (N = 114)	PBO (N = 104)
MRI Spine SPARCC Score					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	14.53 (20.56)	15.80 (21.19)	[redacted]	8.30(16.00)	6.37 (10.25)
Week 16 (Mean)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE) at week 16	-11.02 (1.16)	-1.51 (1.15)	-11.57 (1.11)	-2.99 (1.38)	3.29 (1.40)
Between-group LSM diff (95% CI)	-9.51 (-12.6, -6.4)		-10.07 (-13.2, -6.9)	-6.29 (-10.0, -2.5)	
P value	<0.001		<0.001	0.001	
MRI SIJ SPARCC Score				NR	NR
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MRI Spine and SIJ SPARCC	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w. (N = 114)	PBO (N = 104)
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16 mean, (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE)	–3.97 (0.59)	0.92 (0.58)	–4.21 (0.56)	NR	NR
Between-group LSM diff (95% CI)	–4.89 (-6.5, –3.3)		–5.13 (–6.7 to –3.5)	NR	NR
P value	< 0.001		< 0.001	NR	NR

ADA 40 q.2.w. = adalimumab 40 mg every two weeks; ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; Diff = difference; ITT = intent-to-treat; IXE 80 q.4.w. = ixekizumab 80 mg every four weeks; LSM = least squares mean; N = number of patients in the analysis population; n = number of patients in the specified category; OCA = Observed Case Analysis; PBO = placebo; SD = standard of deviation; SE = standard error. SIJ = sacroiliac joint; SPARCC = Spondyloarthritis Research Consortium of Canada.

Source: CSRs[10,11]

Harms

Only those harms identified in the review protocol are reported below. Detailed harms results are presented in Table 13.

Adverse Events

In the COAST-V, overall TEAEs were reported as 42.0% and 39.5% of patients in the IXE 80 mg SC every four weeks and placebo groups, respectively. The most common TEAEs (> 5% in either of the treatment groups) were nasopharyngitis (7.4% versus 7.0%) and upper respiratory tract infection (8.6% and 4.7%) reported in patients in the IXE 80 mg SC every four weeks and placebo groups, respectively (Table 13).

In the COAST-W, overall TEAEs were reported as 64.0% and 49.0% of patients in the IXE 80 mg SC every four weeks and placebo groups, respectively. The most common TEAEs (> 5% in either of the treatment groups) were upper respiratory tract infection (7.9% and 2.9%), [redacted] and [redacted] reported in patients in the IXE 80 mg SC every four weeks and placebo groups, respectively (Table 13).

Serious Adverse Events: In the COAST-V, SAEs (e.g., urinary tract infection) occurred in one patient (1.2%) in the IXE 80 mg SC every four weeks and 0% in placebo group (Table 13). In the COAST-W, SAEs occurred in four patients (3.5%) in the IXE 80 mg SC every four weeks and five patients (4.8%) in the placebo group, respectively (Table 13). In the IXE 80 mg SC every four weeks group, the SAEs were [redacted] (Table 13).

Withdrawal Due to Adverse Events (WDAE): In the COAST-V, no patients withdrew due to adverse events (WDAE) in either groups. In the COAST-W, WDAE occurred in 10 (8.8%) patients in the IXE 80 mg SC every four weeks and two (1.9%) of patients in placebo group respectively (Table 13).

Mortality: No deaths were reported in either the COAST-V or COAST-W studies (Table 13).

Notable Harms

Notable harms identified in this review are serious infections (including tuberculosis and fungal infection), inflammatory bowel disease, malignancies, major adverse

cerebrocardiovascular event, injection site reactions, hypersensitivity, hepatotoxicity, and hematologic toxicity (such as anemia and/or pancytopenia). The notable harms reported in the COAST-V and COAST-W studies are presented in Table 13.

In COAST-V, the most common (> 3% in either arm) notable harms were infections, allergic reactions or hypersensitivities, and injection site reactions. Infections occurred in 16 (19.8%) patients in the IXE 80 mg SC every four weeks and 13 (15.1%) patients in the placebo group, respectively. Allergic reactions or hypersensitivities occurred in 3 (3.7%) patients in the IXE 80 mg SC every four weeks and one (1.2%) patient in the placebo group respectively. Injection site reactions occurred in three (3.7%) patients in the IXE 80 mg SC every four weeks and four (4.7%) patients in the placebo group, respectively. No patients reported inflammatory bowel disease, malignancy, fungal skin infection, or potential anaphylaxis in COAST-V (Table 13).

In COAST-W, the most common (> 3% in either arm) notable harms were infections, injection site reactions, and hepatic events. Infections occurred in 34 (29.8%) patients in the IXE 80 mg SC every four weeks and 10 (9.6%) patients in the placebo group, respectively. Injection-site reactions occurred in nine (7.9%) patients in the IXE 80 mg SC every four weeks and six (5.8%) patients in the placebo group, respectively. Hepatic events occurred in five (4.4%) patients in the IXE 80 mg SC every four weeks and two (1.9%) patients in the placebo group respectively. Inflammatory bowel disease was reported in three (2.6%) of patients in the IXE 80 mg SC every four weeks and one (1.0%) of patients in the placebo group respectively. Fungal skin infection was reported in three (2.6%) of patients in the IXE 80 mg SC every four weeks and zero patients in the placebo group, respectively. One patient (0.9%) in the IXE 80 mg SC every four weeks group reported a malignancy (Table 13).

Table 13: Harms (Safety Population)

Harms	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 86)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w. (N = 114)	PBO, n (%)(N = 104)
Patients with ≥1 TEAE, n (%)	34 (42.0)	34 (39.5)	44 (48.9)	73 (64.0)	51 (49.0)
Most common TEAEs (Patients with ≥ 2 TEAE), n (%)					
Nasopharyngitis	6 (7.4)	6 (7.0)	6 (6.7)	[redacted]	[redacted]
Upper respiratory tract infection	7 (8.6)	4 (4.7)	2 (2.2)	9 (7.9)	3 (2.9)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Harms	COAST-V			COAST-W	
	IXE 80 q.4.w. (N = 81)	PBO (N = 86)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w. (N = 114)	PBO, n (%)(N = 104)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
Depression	0	0	1 (1.1)	0	5 (4.8)
[redacted]					
[redacted]					
Death, n (%)	0	0	0	0	0
SAE, n (%)	1 (1.2)	0	3 (3.3)	4 (3.5)	5 (4.8)
WDAE (including death) , n (%)	0	0	1 (1.1)	10 (8.8)	2 (1.9)
Notable harms					
Hepatic events	1 (1.2)	1 (1.2)	2 (2.2)	5 (4.4)	2 (1.9)
Cytopenias	[redacted]	[redacted]	[redacted]	0	0
Infections	16 (19.8)	13 (15.1)	19 (21.1)	34 (29.8)	10 (9.6)
Allergies/ hypersensitivities	3 (3.7)	1 (1.2)	4 (4.4)	3 (2.6)	1 (1.0)
Potential Anaphylaxis	0	0	0	0	0
Injection-site reactions	3 (3.7)	4 (4.7)	7 (7.8)	9 (7.9)	6 (5.8)
CCA events	1 (1.2)	0	0	0	1 (1.0)
Malignancies	0	0	0	1 (0.9)	0
Inflammatory bowel disease	0	0	0	3 (2.6)	1 (1.0)
[redacted]					

AAT= Alanine aminotransferase increased (Hepatic enzyme increased); ADA 40 q.2.w. = adalimumab 40 mg every two weeks; AE = adverse events; CCA = confirmed cerebrocardiovascular events, n = number of patients with event; IXE 80 q.4.w. = ixekizumab 80 mg every four weeks; N = total number of patients included in the analysis; PBO = placebo; SAE = serious adverse events; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse events including death.

Note: A treatment emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the study period.

Source: CSRs[10,11]

Critical Appraisal

Internal Validity

Both COAST-V and COAST-W were double-blind (double-dummy design), randomized, placebo-controlled trials for a duration of 16 weeks. In addition, COAST-V also included adalimumab as an active control group. Appropriate methods of randomization, blinding, and allocation concealment were reported. Randomization was done by a computer-generated random sequence in both studies. Furthermore, to achieve between-group comparability, in both COAST-V and COAST-W, the randomization was stratified by country and results of a CRP screen (≤ 5 mg/L or > 5 mg/L). In COAST-W, randomization was also stratified by the number of prior TNFis taken. In general, important patient baseline demographic and disease characteristics (including baseline scores of BASDAI, ASDAS, and SF-36-PCS,

duration of the disease, and baseline medication use) were similar between treatment groups in both COAST-V and COAST-W. Concomitant medications used during the trial were balanced across the treatment groups in each of the two studies. However, some differences between the IXE 80 mg SC every four weeks and the placebo group were noted. For example, baseline CRP level (mg/L) was lower in the IXE 80 mg SC every four weeks group than in the placebo group in COAST-V, but it was higher in the IXE 80 mg SC every four weeks group than in the placebo group in COAST-W. According to the clinical expert consulted for this review, this imbalance would unlikely have had an impact on the study results.

In both COAST-V and COAST-W, the primary outcome was ASAS 40 response at week 16. According to the clinical expert CADTH consulted for this review, ASAS 20 at week 12 is considered a clinically meaningful response and has been commonly used in previous bDMARDS trials for AS. Therefore, ASAS 40 may be considered a major clinical improvement, representing a more stringent outcome than ASAS 20, although the duration of the COAST trials (16 weeks) was longer than other completed trials for bDMARDS in the treatment of AS to allow for time to achieve a greater degree of improvement.

Multiplicity adjustment was used for the primary and major secondary outcomes to control the family-wise type I error rate at a two-sided alpha level of 0.05. However, no multiplicity adjustment was performed for other secondary outcomes, such as ASAS 5/6, symptom measurement scales (i.e., spinal pain, Fatigue Severity NRS, JSEQ, QIDS-SR16), QoL (EQ-5D- 5L, SF-36 MCS), WPAI-SpA, BASDAI 50 in COAST-W, BASDAI Change from baseline in COAST-V, ASDAS <1.3 in COAST-W, ASDAS low disease activity < 2.1 in COAST-V and PGA.

Given the large number of comparisons in the study, a statistically significant finding ($P < 0.05$) for the comparisons between IXE 80 mg every four weeks and placebo groups for these above-mentioned outcomes without multiplicity adjustment may be suffering an inflated type I error rate. Therefore, the statistical significance (P value) reported for those outcomes without multiplicity adjustment remains uncertain.

Both COAST-V and COAST-W were designed to have approximately 96% power to test the superiority of IXE 80 mg every two weeks compared to placebo groups for ASAS 40 response rate at week 16. It can be assumed that it was a more conservative and stringent design for the Health Canada-recommended IXE dose regimen (i.e., IXE 80 mg SC every four weeks).

The primary analysis method for treatment group difference of categorical efficacy outcomes was conducted using a logistic regression analysis. An important strength of these analyses was use of the most conservative nonresponder imputation (NRI) method. To examine the robustness of the results for the primary and major secondary categorical efficacy outcomes, a categorical, mixed-effects model of repeated measures (categorical MMRM, as secondary analysis) was used to estimate response across post-baseline visits.

The primary analysis for between treatment group differences in all major secondary continuous efficacy outcomes except MRI SPARCC were analyzed using an MMRM approach. It was reported that MMRM analysis is a superior method in controlling type I error rates and minimizing biases, as compared to LOCF ANCOVA analysis.[27] The potential number of patients with missing data were low and comparable between treatment groups although the information of missing data were not clearly reported and described in the clinical study report. To examine the robustness of the results for major secondary

continuous outcomes, additional secondary analysis was performed using mBOCF and LOCF methods in both COAST-V and COAST-W.

Radiographic progression is an important outcome in AS trials. It was assessed with MRI SPARCC in both COAST-V and COAST-W. However, in COAST-V, both MRI spine and SIJ SPARCC were reported. In COAST-W, only MRI Spine SPARCC was assessed. No rationale was provided for not including MRI SIJ SPARCC in COAST-W. The primary analyses for MRI SPARCC were conducted using ANCOVA based on observed case analysis (OCA). It was unclear how patients were selected for this assessment. Since only a few patients were not included in OCA, this OCA approach was unlikely to have an impact on the results. Furthermore, additional secondary analysis was conducted using ANCOVA with mBOCF method or LOCF. Results of the analyses by ANCOVA with the mBOCF or LOCF methods were reportedly consistent with the results of the OCA by ANCOVA, which ensured the robustness of the findings of the MRI SPARCC.

With respect to the starting dosing, patients randomized to the IXE treatment group were also randomized to a 160 mg or 80 mg starting dose at a 1:1 ratio (within each IXE treatment group). No statistically significant difference between the two initial doses was found in ASAS 40 and major secondary outcomes at week 16.

One limitation was that both COAST-V and COAST-W were not designed for assessing the comparative efficacy and safety between IXE and the existing bDMARDs marketed in Canada (i.e., TNFis and SEC) in the treatment of AS, although adalimumab was included in COAST-V as an active reference only. Therefore, the direct comparative efficacy and safety evidence comparing IXE with other bDMARDs remains unknown.

As the study duration was 16 weeks, there was no direct evidence beyond 16 weeks. The findings at week 52 in the extension phase were limited by the lack of any placebo or active control comparators.

Regarding to the sponsor-submitted ITC, there was insufficient information about the individual trials, which limits the ability to assess clinical heterogeneity of the included studies and thus the credibility of findings is uncertain. In addition, the comparative efficacy and safety of IXE to certolizumab pegol and infliximab is unknown, and the comparative efficacy and safety of IXE to other biologics beyond 16 weeks is unknown.

External Validity

Patients enrolled in COAST-V and COAST-W had very high AS disease activity based on the baseline ASDAS and BASDAI score. Exclusion of patients with total spinal ankylosis may limit the generalizability of results to those patients with total ankylosis in clinical practice. The clinical expert CADTH consulted for this review indicated that exclusion of patients with total ankylosis of the spine in the trials was a “clinical trial strategy” to exclude patients that were not likely to demonstrate changes in numerous outcome measures. In clinical practice, it is possible that patients with total ankylosis may demonstrate decreases in pain, stiffness, and fatigue and meaningful improvements in quality of life.

Both COAST-V and COAST-W included a patient population that was predominantly male (80 to 84% across the groups) and most patients were white (61% to 82% across the groups). According to the clinical expert CADTH consulted in the review, the data in male patients will be applicable to female patients.

Overall, according to the clinical expert involved in the review, in both COAST-V and COAST-W, the patients included in the trial are close to those seen in Canadian clinical settings, except that those AS patients with total ankylosis of the spine would also be treated in clinic. There is little concern about the generalizability in Canada of the findings from both COAST-V and COAST-W.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

The treatment groups of the studies included in this review included IXE 80 mg SC every two weeks, IXE 80 mg SC every four weeks, and placebo. COAST-V study also included a group that received adalimumab 40 mg every two weeks, but this study was not designed to make statistical comparisons between IXE and adalimumab. Due to the lack of direct evidence that compared IXE to other biologic drugs for the treatment of adult patients with active AS, ITCs may provide information on the comparative effectiveness and safety of IXE versus existing therapies. The objective of this section was to summarize and critically appraise available indirect evidence comparing IXE with relevant treatment regimens (as specified in CDR review protocol) for adult patients with active AS.

The sponsor submitted one ITC[28] which was reviewed, summarized, and critically appraised. CDR conducted an independent literature search for published ITCs that compared IXE with other relevant comparators for the treatment of adult patients with active AS. MEDLINE, Embase, and PubMed were searched. No relevant publications were identified in the literature.

Description of Indirect Comparison

The sponsor submitted an ITC that compared the efficacy and safety of IXE with SEC, adalimumab, etanercept, golimumab, infliximab, and certolizumab pegol in adult patients active AS.[28]

The population, intervention, comparators, outcomes, and design of the studies included in the sponsor's ITC are provided in Table 14.

Table 14: Study Selection Criteria and Methods for the Sponsor-Submitted ITC

	Sponsor-Submitted ITC
Population	Adult patients with AS (analysis was conducted separately on biologic-naive population and TNFi-experienced population)
Intervention	Ixekizumab 80 mg q.2.w. and Ixekizumab 80 mg q.4.w.
Comparator	Adalimumab 40 mg SC q.2.w. Certolizumab pegol 200 mg Q2W or 400 mg SC q.4.w. Etanercept 25 mg b.i.d. or 50 mg SC q.1.w. Golimumab 50 mg SC q.4.w. Infliximab 5mg/kg IV followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks Secukinumab 150 mg q.4.w. SC (with and without SC loading dose) Placebo
Outcome	Proportion of patients achieving ASAS 20 Proportion of patients achieving ASAS 40 Proportion of patients achieving BASDAI 50

	Sponsor-Submitted ITC
	Mean change from baseline to end point (12 to 18 weeks) in BASDAI Mean change from baseline to end point (12 to 18 weeks) in BASFI Proportion of patients with ASDAS improvement ≥ 2 from baseline (ASDAS 2.0) Mean change from baseline to end point (12 to 18 weeks) in ASDAS – CRP Mean change from baseline to end point (12 to 18 weeks) SF-36 MCS AEs Treatment discontinuation due to AE SAE
Study design	RCTs
Publication characteristics	Publication in English
Exclusion criteria	Studies reporting mixed patient populations of AS (in which there is no stratification of results between biologic-naive population and TNFi-experienced population) Comparator in the trials was not in the list of comparators Non-randomized studies (except when specified as extension studies of RCTs) Maximum tolerated dose studies/ dose escalation studies Dose-limiting toxicity studies Pharmacokinetic/ treatment mechanism studies Case studies and case series that are not designed to compare clinical effectiveness Commentaries Cytological studies
Databases searched	MEDLINE, MEDLINE In-process, E-pubs ahead of print, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL)
Selection process	Two reviewers independently assessed the full text of the articles. Any disagreement was referred to a third reviewer and a consensus was reached
Data extraction process	NR
Quality assessment	NR

AEs = adverse events; AS = ankylosing spondylitis; ASAS = Ankylosing Spondylitis Disease Activity Score; ASDAS = assessment of disease activity; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; b.i.d. = twice weekly; MCS = mental component scores; q.1.w. = once weekly; NR = not reported; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; RCTs = randomized controlled trials; SAE = serious adverse event; SC = subcutaneous injection; SF-36 = Short Form (36) Health Survey; TNFi = tumour necrosis factor.

Source: Sponsor-submitted ITC.[28]

Methods of the Sponsor-Submitted ITC

Objectives

The objective of the ITC was to assess the relative efficacy and safety of IXE 80 mg SC every two weeks and every four weeks versus other approved biologic treatments for the treatment of adult patients with active AS. Comparators selected for this network meta-analysis were IXE, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and SEC. Study populations included both biologic-naive patients and patients with prior exposure to biologics. Given the Health Canada-recommended dose, only the results for IXE 80 mg every four weeks were included in this summary.

Study Selection Methods

Multiple electronic databases such as MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched on November 25, 2016. Search filters to identify RCTs were applied in MEDLINE and Embase. Conference abstracts were also searched. In addition, ClinicalTrials.gov and International Clinical Trials Registry Platform (ICTRP) Search Portal were searched in order to identify ongoing studies on November 25, 2016.

Studies were included if they were RCTs that reported the outcomes of interest. Studies were excluded if they reported mixed patient populations of spondyloarthropies (in which there is no stratification of results), were not published in English, or did not include the treatment of interest. Also, studies of non-randomized design (except when specified as extension studies of RCTs), maximum tolerated dose studies, dose-limiting toxicity studies, pharmacokinetic or treatment mechanism studies, case studies and case series that were not designed to compare clinical effectiveness, commentaries, and cytological studies were excluded.

All abstracts were reviewed according to the eligibility criteria by two reviewers. Full papers retrieved from the initial searches were screened independently by two reviewers, and in case of disagreement about any studies, a decision was made after discussion with a third reviewer.

It is not reported how data extraction was conducted and whether more than one reviewer was involved in data extraction. No quality assessment of included studies was reported.

The efficacy outcomes assessed were the proportion of patients achieving ASAS 20, proportion of patients achieving ASAS 40, proportion of patients achieving BASDAI 50, mean change from baseline to end point (12 to 18 weeks) in BASDAI, mean change from baseline to end point (12 to 18 weeks) in BASFI, proportion of patients with ASDAS improvement of two or more from baseline (ASDAS 2.0), mean change from baseline to end point (12 to 18 weeks) in ASDAS CRP, and mean change from baseline to end point (12 to 18 weeks) in SF-36 MCS. The safety outcomes assessed were AEs, treatment discontinuation due to AEs, and SAEs.

ITC Analysis Methods

A two-stage analytical approach was used for this network meta-analysis (NMA) where frequentist meta-analysis (MA) was conducted to assess heterogeneity and understand the data. Then, an NMA was conducted using Bayesian mixed treatment comparisons as described in the National Institute for Health Care and Excellence Decision Support Unit (NICE-DSU) Technical Support Documents. In this method, if the Bayesian model does not converge, a frequentist model NMA based on the method proposed by Rücker et al[29] is conducted as part of the sensitivity analysis. If heterogeneity is observed, studies that may cause this were considered to be removed as part of sensitivity analyses.

The NMA was performed in both a Bayesian and frequentist framework using Eli Lilly inhouse-developed tools called BATMAN and CHEETAH. The models included in the BATMAN tool were based on those presented in the NICE Technical Support Document (NICE TSD).[30] The information technology validation of this tool has been conducted per Eli Lilly Standard Operating Procedures. The statistical validation was done by using the same models found in a series of NICE submission documents and comparing the results produced by BATMAN. For the sensitivity analysis, a frequentist approach was adopted using the CHEETAH tool which uses the NETMETA function in R, and uses the method proposed by Rücker et al.[29]

The assumptions of homogeneity and transitivity were assessed by adjusting for treatment effect modifiers through a meta-regression. The meta-regression fitted the following baseline covariates as separate models; baseline risk (placebo response), CRP mean level, gender, and year of publication. Both fixed and random-effects models were assessed for the analysis. In addition, the networks were conducted separately for biologic-naive and TNFi-

experienced populations in this analysis, in an aim to define networks with comparable patient populations and adjust for differences between studies regarding those covariates.

Non-informative prior distributions were used for all model parameters. For the random-effects model, the prior for the heterogeneity parameter used was uniform (0, 2). If the model appeared to be sensitive to the choice of vague priors, i.e., if unstable (wide) credible intervals were observed, informative priors could be used. However, it was not clear what informative priors were used and in which analysis.

The first 53,000 iterations were discarded as "burn-in" and results were based on an additional 53,000 iterations using three chains. Convergence was assessed using the Brooks-Gelman-Rubin convergence diagnostics. Both fixed and random-effects models were assessed for each network where feasible. Goodness of fit statistics were compared between the fixed and random-effects models, to determine improvement in model fit. These statistics comprised the deviance, residual deviance, and deviance information criterion. Based on these criteria, the fixed effects models were presented in the sponsor ITC. The consistency assumption was not checked due to the rarity of closed loops.

Heterogeneity was assessed visually by inspecting the magnitude and variability of the study results within each forest plot of MA. In addition, heterogeneity was assessed by evaluating I^2, the between-study variance (tau^2), and the heterogeneity statistic Q. In addition, the difference between fixed and random effects in treatment estimates was assessed by visual inspection.

Separate models were developed in the base case for biologic-naive patients and TNFi-experienced patients. The base case included IXE data at 16 weeks, and the time points of either 12 weeks or 18 weeks were considered for the comparators.

A series of sensitivity analyses were performed depending on the availability of data within the networks and chosen base-case analysis. The following sensitivity analyses were conducted separately for the biologic-naive and TNFi-experienced population:

- Sensitivity 1 (removal of studies from base case with < 100% or unclear percentage of patients having BASDAI ≥ 4 at baseline, to align with reimbursement criteria for biologics)
- Sensitivity 2 (addition of studies with unclear or mixed populations that do not provide any biologic-naive subgroup data to the base case, to account for the effect of studies that were excluded in the base-case analysis)
- Sensitivity 3 (addition of studies that are open label, pilot, phase I, or phase II to the base case, to account for the effect of studies that were excluded in the base-case analysis)
- Sensitivity 4 (inclusion of TNF-alpha inhibitors from base case only)
- Sensitivity 5 (removal of studies from any analysis of high heterogeneity [I^2 > 60%])
- Sensitivity 6 (removal of studies from base case due to inconsistency [based on node splitting])
- Sensitivity 7 (removal of studies from base case with digitized data)

All sensitivity analyses were conducted on the best fitting model (either fixed or random effects) determined by comparing deviance information criterion values. Meta-regression was conducted only for the base case.

Additional sensitivity analysis was performed to support the expected Canadian label for IXE in AS patients which mentions that the recommended dose is 80 mg by SC injection every four weeks. For patients who have had an inadequate response or are intolerant to at least

one TNFi, a dose of 160 mg (two 80 mg injections) by SC at week 0, followed by 80 mg every four weeks may be considered. The following additional analysis were conducted for biologic-naive patients:

- Sensitivity 8 (base case with inclusion of trial COAST-V patients with 80 mg loading dose only) for ASAS 20, ASAS 40
- Sensitivity 10 (sensitivity 8 with data from mixed population for MEASURE2 trial) for BASDAI 50.

And in TNFi-experienced patients:

- Sensitivity 8 (base case with inclusion of trial COAST-W patients with 80 mg loading dose only) for ASAS 20 and ASAS 40
- Sensitivity 9 (base case with inclusion of trial COAST-W patients with 160 mg loading dose only) for ASAS 20 and ASAS 40
- Sensitivity 10 (sensitivity 8 with data from mixed population for MEASURE2 trial) for BASDAI 50
- Sensitivity 11 (sensitivity 9 with data from mixed population for MEASURE2 trial) for BASDAI 50.

Table 15 below presents a summary of the methods used for the ITC.

Table 15: ITC Analysis Methods

	Ramachandran et al.
ITC methods	network meta-analysis
Priors	uniform (0, 2)
Assessment of model fit	The model selected was chosen based on residual deviance and DIC
Assessment of consistency	Not conducted, given that there were no closed loops
Assessment of convergence	Brooks-Gelman-Rubin convergence diagnostics
Follow-up timepoints	12 to 18 weeks
Sensitivity analyses	• Several sensitivity analyses were conducted
Subgroup analysis	• Biologic-naive patients • TNFi-experienced patients

DIC = deviance information criterion; ITC = indirect treatment comparison; TNFi= tumour necrosis factor inhibitor.

Source: Sponsor-submitted ITC.[28]

Results of the Sponsor-Submitted ITC

Summary of Included Studies

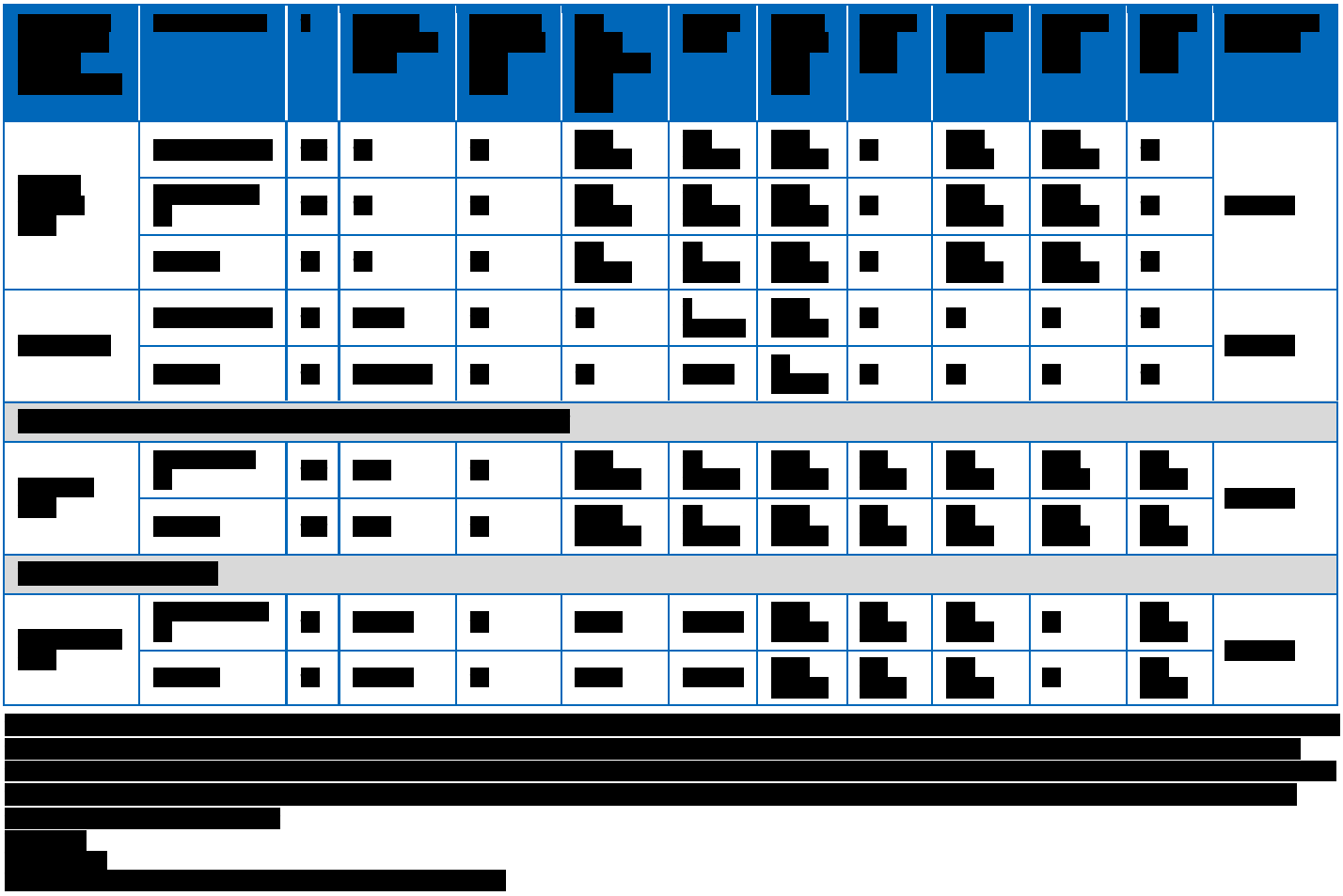
[redacted] Table 16. [redacted]

[redacted]

[redacted]

Table 16: Baseline Demographic and Disease Activity Characteristics for the Trials Included in the Base-Case Analyses

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



Source: Sponsor-submitted ITC.[28]

Results

Figure 4, Figure 5, Figure 7, Figure 8, Figure 9, and Figure 10 . Figure 6 Figure 11

Figure 4: Network of Studies Included in the Biologic-Naive Analysis for ASAS 40

Figure 4 contained confidential information and was removed at the request of the sponsor.

Source: Sponsor-submitted ITC.[28]

Figure 5: Network of Studies Included in the Biologic-Naive Analysis for ASAS 20

Figure 5 contained confidential information and was removed at the request of the sponsor.

Source: Sponsor-submitted ITC.[28]

Figure 6: Network of Studies Included in the Biologic-Naive Analysis for ASDAS CRP, BASFI, ASDAS 2.0

Figure 6 contained confidential information and was removed at the request of the sponsor.

Source: Sponsor-submitted ITC.[28]

Figure 7: Network of Studies Included in the Biologic-Naive Analysis for BASDAI

Figure 7 contained confidential information and was removed at the request of the sponsor.

Source: Sponsor-submitted ITC.[28]

Figure 8: Network of Studies Included in the Biologic-Naive Analysis for BASDAI 50

Figure 8 contained confidential information and was removed at the request of the sponsor.

Source: Sponsor-submitted ITC.[28]

Figure 9: Network of Studies Included in the Biologic-Naive Analysis for SF-36 MCS

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

Source: Sponsor-submitted ITC.[28]

Figure 10: Network of Studies Included in the Biologic-Naive Analysis for AE

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

Source: Sponsor-submitted ITC.[28]

Figure 11: Network of Studies Included in the TNFi-Experienced Analysis for ASAS 40, ASAS 20, BASDAI, AE, SAE, and Treatment Discontinuation Due to AE

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

Source: Sponsor-submitted ITC.[28]

[redacted]

[redacted]

[redacted] (Table 17, Table 18, Table 20).

[redacted] (Table 17).

[redacted] (Table 18).

[redacted] (Table 18).

[redacted] (Table 18).

[redacted] (Table 19).

[redacted] (Table 20).

[redacted]

[redacted]

[redacted]

Table 17: Network Meta-Analysis Results for ASAS 40, ASAS 20, and AE in Biologic-Naive Patients

[redacted]

Source: Sponsor-submitted ITC.[28]

Table 18: Network Meta-Analysis Results for ASDAS CRP, BASDAI, BASFI, ASDAS 2.0, and SF-36 MCS, in Biologic-Naive Patients

[redacted]

Source: Sponsor-submitted ITC.[28]

Table 19: Network Meta-Analysis Results for AE in Biologic-Naive Patients

[redacted]

Source: Sponsor-submitted ITC.[28]

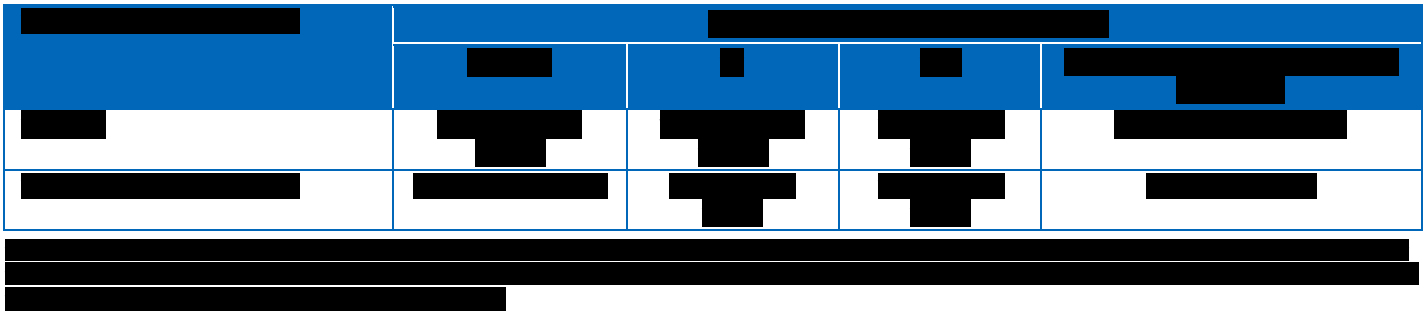
Table 20: Network Meta-Analysis Results for SAE, and Treatment Discontinuation due to AE in Biologic-Naive Patients

Source: Sponsor-submitted ITC.[28]

(Table 21 and Table 22).

(Table 21).

Table 21: Network Meta-Analysis Results for ASAS 20, and AE, SAE, and Treatment discontinuation Due to AE in TNFi-Experienced Patients



Source: Sponsor-submitted ITC.[28]

Table 22: Network Meta-Analysis Results for ASAS 40 and BASDAI in TNFi-Experienced Patients

Source: Sponsor-submitted ITC.[28]

Critical Appraisal of the Sponsor-Submitted ITC

There was insufficient information provided in the report to assess the level of similarity or heterogeneity among the included studies. This limits the ability to assess the appropriateness of the meta-analyses and the generalizability of the results.

A significant limitation is the lack of quality assessment of the included trials and the fact that quality was not considered in the analyses.

The number of studies in each network was generally small, particularly for the biologic-experienced networks. Often there was only one study per pairwise comparison of treatments. In fact, the wide 95% CrI as observed across all the comparisons was highly likely due to the lack of data in the network, leading to increased uncertainty (lack of precision) of the findings.

Moreover, the literature search was conducted on November 25, 2016, more than three years ago. Since then, there may have been new trials published which would have not been included in the analysis, potentially impacting the conclusions of the NMA.

There are reporting issues, which have also compromised our assessment of the ITC results. For example, the citation for the included trials was not reported hence it was not possible to validate the included studies.

It was not reported whether data extraction was undertaken by more than one reviewer and whether quality checking by a second reviewer was undertaken.

The authors did not perform consistency assessments because lack of closed loops in the networks. However, there was a closed loop in the networks for the IXE studies, but this was not assessed for consistency.

All of the outcomes of interest in the NMA were also outcomes of interest in the protocol for this CDR report.

The analyses use relatively short timepoints (e.g., 12 to 16 weeks) and do not reflect the durability of relative response over the length of time that patients are likely to be using these biologics. In addition, given that the assessment of outcome in IXE studies were reported at week 16, while those of etanercept were reported at week 12, it is not clear whether results were biased in favour of IXE given this additional 4 weeks of treatment.

Studies for certolizumab pegol and infliximab had no subgroup results available for treatment-naive and TNFi-experienced patients, hence there were no results for the comparison between IXE and these two biologics.

While AEs were analyzed as a binary outcome with OR and 95% CrI, for SAE and WDAE, a frequentist normal model was applied, and instead of OR, a median treatment difference was reported on those two outcomes. However, it is unclear what is the implications of such an analysis.

The software used for the indirect comparisons was developed and validated by the sponsor, however, given the lack of information about the software used and how it was validated, it is uncertain whether results reported would be similar to what would be generated by using other software such as Winbugs and R language.

It is not clear when a vague prior or an informative prior was used, and what values and distributions were used for the informative priors.

Several sensitivity analyses were conducted, however for most of the analyses only results against placebo were reported, hence CDR reviewers being unable to comment on the impact of these sensitivity analyses.

Summary

In the absence of head-to-head trials, the sponsor conducted an ITC analysis based on a systematic review of RCTs and compared the efficacy and safety of IXE with adalimumab, golimumab, etanercept, and SEC in biologic-naive patients, and compared IXE with SEC in TNFi-experienced patients over a 12 to 16-week period.

Overall, there was no difference in the efficacy outcomes between IXE and other biologic drugs in biologic-naive patients. Nor was there a difference in TNFi-experienced patients.

Similarly, no difference was found in AEs, SAEs, or treatment discontinuation due to AEs in biologic-naive and TNFi-experienced populations. However, IXE had a higher incidence of AEs and treatment discontinuation due to AEs relative to placebo in TNFi-experienced patients.

Of note, there was insufficient information about the individual trials in the ITC, limiting the ability to assess clinical heterogeneity of the included studies. The ITC also failed to be

updated by including perhaps more recent studies. In fact, the data included in the network as shown is relatively sparse. Therefore, whether IXE is comparable in efficacy and safety to its biologic comparators remains somewhat uncertain, particularly in the long-term. In addition, the comparative efficacy and safety of IXE to certolizumab pegol and infliximab is unknown.

Other Relevant Studies

Long-Term Extension Studies

This section of the report includes a summary and critical appraisal of the long-term extension periods for COAST-V[14] and COAST-W.[13] The Health Canada-indicated dose of IXE 80 mg every four weeks will be the focus of this review.[31] The data pertaining to IXE 80 mg every two weeks is not reported in this summary and appraisal.

Methods

COAST-V[14] and COAST-W[13] included a long-term extension phase from week 16 to week 52. The extension periods provide information on the long-term efficacy and safety of IXE 80 mg for the treatment of adult patients with active AS who have responded inadequately to or are intolerant to conventional therapy (e.g., NSAIDs).

The objective of the extension periods was to determine if the effect of either IXE dosing regimen (80 mg every two weeks; 80 mg every four weeks) is maintained up to week 52.

In the 16-week period, COAST-V patients were assigned to one of four treatment arms (IXE 80 mg SC every two weeks, IXE 80 mg SC every four weeks, placebo or adalimumab 40 mg), and patients randomized to IXE received a starting dose of either 80 mg or 160 mg. In the extension period, patients in the two IXE arms continued their assigned treatment and patients in the placebo and adalimumab arms were re-randomized in a 1:1 ratio to either IXE 80 mg SC every two weeks or IXE 80 mg SC every four weeks with patients originally in the placebo arm given a starting dose of IXE 160 mg. Patients who had been in the adalimumab arm in the first 16 weeks had a six week washout period before starting treatment with IXE on week 20.

In the 16-week period of COAST-W, patients were assigned to one of three treatment arms (IXE 80 mg SC every two weeks, IXE 80 mg SC every four weeks, or placebo). Similar to the COAST-V extension, patients in the two IXE arms continued their assigned treatment, and patients in the placebo arm were re-randomized in a 1:1 ratio to either IXE 80 mg SC every two weeks or IXE 80 mg SC every four weeks with all patients originally in the placebo arm given a starting dose of IXE 160 mg.

Populations

Patients who entered the COAST-V and COAST-W 16-week trials were eligible to be included in the extension studies. No additional eligibility criteria specific to the extension period were identified. Inclusion and exclusion criteria for COAST-V and COAST-W can be found in the Populations section of the main report.

Generally, the baseline characteristics were balanced between treatment arms in both COAST-V and COAST-W. The mean age of patients was between [redacted] in COAST-V. In COAST-W the mean age was approximately [redacted].

[redacted] In COAST-W, [redacted] In COAST-W [redacted] In COAST-V [redacted] in COAST-W. [redacted]. The duration of disease since diagnosis was [redacted]

Table 23: Summary of Baseline Characteristics

	COAST-V			COAST-W	
	IXE 80 q.4.w./IXE 80 q.4.w. (N = 78)	PBO/IXE 80 q.4.w. [redacted]	ADA 40 q.4.w./IXE 80 q.4.w. [redacted]	IXE 80 q.4.w./IXE 80 q.4.w. (N = 98)	PBO/IXE 80 q.4.w. [redacted]
Age, years (SD)	40.8 (11.77)	[redacted]	[redacted]	47.1 (13.25)	[redacted]
Male, n (%)	65 (83.3)	[redacted]	[redacted]	81 (82.7)	[redacted]
Geographic region, n (%)					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age of onset of axSpA, mean years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of symptoms since axSpA onset					
Mean years (SD)	15.82 (11.035)	[redacted]	[redacted]	18.21 (11.132)	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of disease since AxSpA diagnosis, mean years (SD)	8.25 (9.464)	[redacted]	[redacted]	9.66 (7.953)	[redacted]

ADA 40 q.4.w. = adalimumab 40 mg every four weeks; axSpA = axial spondyloarthritis; IXE 80 q.4.w. = ixekizumab 80 mg every four weeks; NA = not applicable; SD = standard deviation; q.4.w = every 4 weeks.

Source: Clinical Study Reports for COAST-V[14] and COAST-W[13], Dougados et al., 2019[32].

Interventions

In COAST-V, patients previously assigned to IXE 80 mg SC every two weeks or IXE 80 mg SC every four weeks during weeks 0 to 16 continued their assigned dose throughout the extension period. Patients previously assigned to placebo received a starting dose of IXE 160 mg and were re-randomized in a 1:1 ratio to either IXE 80 mg SC every two weeks or IXE 80 mg SC every four weeks. Similarly, patients previously assigned to the adalimumab arm were re-randomized in a 1:1 ratio to either IXE 80 mg SC every two weeks or IXE 80 mg SC every four weeks after a 6-week washout period.

In COAST-W, patients previously assigned to IXE 80 mg SC every two weeks or IXE 80 mg SC every four weeks during weeks 0 to 16 continued their assigned dose throughout the extension period. Patients previously assigned to placebo received a starting dose of IXE

160 mg and were re-randomized in a 1:1 ratio to either IXE 80 mg SC every two weeks or IXE 80 mg SC every four weeks.

In both trials, all doses were administered via SC injection at approximately the same time each day.

Outcomes

The outcomes assessed in the extension studies were consistent with those assessed in the 16-week period of COAST-V and COAST-W. Efficacy and health outcomes relevant to the review included the following: ASAS 40, ASAS 20, ASAS 5/6, ASAS Partial Remission, BASFI, BASDAI, BASDAI 50, ASDAS, SPARCC MRI for spine and SIJ (COAST-V only), and SF-36, ASAS Patient Global, ASAS HI, Fatigue Severity NRS Score, JSEQ, and QIDS-SR16. Detailed descriptions of these outcomes can be found in the Outcomes section of the main report.

Harms outcomes assessed included AEs, SAEs, and patients who stopped treatment due to AEs and deaths.

Statistical Analysis

Statistical analysis was performed using SAS Version 9.2 or later versions. Continuous data were summarized in terms of the number of observations, mean, SD, minimum, median, and maximum. Categorical data were summarized in terms of the number of patients in the analysis population, the number of patients providing data at the relevant time point, frequency counts, and the percentages corresponding to the appropriate method. All confidence intervals were two-sided unless otherwise specified. The baseline for efficacy outcomes were defined as the last available value before the first injection in the 16-week blinded treatment dosing period.

Missing data from continuous efficacy were imputed using mBOCF. Missing data for categorical efficacy outcomes were imputed using NRI.

No adjustments to the analysis were made based on country or region. Neither study was powered to detect responses at week 52.

Efficacy results for all treatment arms are available for the "extended treatment period population." Patients in this analysis set were defined as all patients who received at least one dose of IXE treatment during the period extension period. Note, efficacy data for the ITT population were only available for the IXE 80 mg every four weeks arm and is not presented in this summary.

Patient Disposition

In COAST-V, a total of 78 patients who were originally assigned to IXE 80 mg SC every four weeks (and continued this dose to week 52) entered the extension phase. By week 52, six patients (7.7%) discontinued the extension phase due to patient withdrawal or AEs. A total of 42 patients who were originally assigned to placebo and then switched to IXE 80 mg once every four weeks entered the extension phase; none of these patients discontinued the study during the extension phase. A total of 44 patients who were originally assigned to adalimumab 40 mg and then switched to IXE 80 mg SC every four weeks entered the extension phase. In this arm there were two patients who discontinued the extension phase of COAST-V.

In COAST-W, 98 patients who were originally assigned to IXE 80 mg SC every four weeks (and continued this dose to week 52) entered the extension phase. By week 52, nine patients (9.2%) discontinued the extension phase, with most discontinuations attributed to AEs. A total of 46 patients who were originally assigned to placebo and then switched to IXE 80 mg SC every four weeks entered the extension phase. In this arm seven patients discontinued the trial in the extension phase with most discontinuations attributed to lack of efficacy (10.9%).

Table 24: Patient Disposition

	COAST-V			COAST-W	
	IXE 80 mg q.4.w./IXE 80 mg q.4.w.	PBO/IXE 80 mg q.4.w.	ADA 40/IXE 80 mg q.4.w.	IXE 80 mg q.4.w./IXE 80 mg q.4.w.	PBO/IXE 80 mg q.4.w.
Randomized at week 0, n	81	87	90	114	104
Entered extension at week 52, n	78	42	44	98	46
Completed extension at week 52, n (%)	72 (92.3)	42 (48.3)	42 (46.7)	89 (90.8)	39 (37.5)
Discontinued extension by week 52, n (%)	6 (7.7)	0	2 (4.8)	9 (9.2)	7 (15.2)
Patient withdrew	5 (6.4)	NA	0	2 (2.0)	1 (2.2)
Adverse event	1 (1.3)	NA	1 (2.4)	4 (4.1)	1 (2.2)
Lack of efficacy	0	NA	1 (2.4)	2 (2.0)	5 (10.9)
Physician decision	0	NA	0	1 (1.0)	0
Intent-to-treat population	81	NA	NA	114	NA
Extended treatment period population	78	42	44	98	46

ADA 40 q.4.w. = adalimumab 40 mg every four weeks; IXE 80 q.4.w. = Ixekizumab 80 mg every four weeks; NA = not applicable; q.4.w. = every 4 weeks.

Source: Clinical Study Reports for COAST-V[14] and COAST-W[13], Dougados et al., 2019[32].

Exposure to Study Treatments

In COAST-V, the mean days of exposure was [redacted].

In COAST-W, the mean days of exposure was [redacted].

Efficacy

The focus of this review is on the subset of patients in COAST-V and COAST-W who were treated with IXE 80 mg SC every four weeks in the extension phase of the trials regardless of their treatment assignment in the first 16 weeks of the trials. Results for efficacy outcomes based on the extended treatment period population are presented in Table 25.

ASAS 40

[redacted]

ASAS 20

[redacted]

ASAS 5/6

[redacted]

ASAS Partial Remission

[redacted]

BASFI Score

[redacted]

[redacted]

[redacted]

BASDAI 50

[redacted]

[redacted]

BASDAI Score

[redacted]

[redacted]

ASDAS Score

[redacted]

[redacted]

SPARCC Score for Spine

[redacted]

[redacted]

SPARCC Score for Sacroiliac Joints

[redacted]

SF-36 PCS Score

[redacted]

SF-36 MCS Score

[redacted]

ASAS Patient Global Assessment of Disease

[redacted]

ASAS HI

[redacted]

Fatigue Severity NRS Score

[redacted]

[redacted]

JSEQ

[redacted]

[redacted]

QIDS-SR16

[redacted]

[redacted]

Table 25: Efficacy Outcomes (Extended Treatment Period Population)

	COAST-V			COAST-W	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					

	COAST-V			COAST-W	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					

	COAST-V			COAST-W	
[redacted]					

Source: Clinical Study Reports for COAST-V[14] and COAST-W[13], Dougados et al., 2019[32]

Harms

In COAST-V, AEs were experienced by 64.1% of patients in the IXE 80 mg every four weeks arm, [redacted] (Table 26). The most common AEs were attributed to [redacted] Severe adverse events were experienced by 5.1% of patients in the IXE 80 mg every four weeks arm, [redacted]. No deaths occurred during the 52-week period.

In COAST-W, adverse events were experienced by 70.4% of patients in the IXE 80 mg every four weeks arm [redacted] (Table 26). The most common AEs were attributed to [redacted]. Severe AEs were experienced by 2.0% of patients in the IXE 80 mg every four weeks arm, [redacted]. No deaths occurred during the 52-week period.

Table 26: Harms Outcomes (Extended Treatment Period Populations)

	COAST-V			COAST-W	
	IXE 80 mg q.4.w./IXE 80 mg q.4.w. (N = 78)	PBO/IXE 80 mg q.4.w. [redacted]	ADA 40/IXE 80 mg q.4.w. [redacted]	IXE 80 mg q.4.w./IXE 80 mg q.4.w. (N = 98)	PBO/IXE 80 mg q.4.w. [redacted]
Patients with ≥ 1 adverse event					
n (%)	**50 (64.1)**	[redacted]	[redacted]	**69 (70.4)**	[redacted]
Most common events[a]					
Nasopharyngitis	**8 (10.3)**	[redacted]	[redacted]	**3 (3.1)**	[redacted]
Injection site reaction	**3 (3.8)**	[redacted]	[redacted]	**NA**	[redacted]
Upper respiratory tract infection	**4 (5.1)**	[redacted]	[redacted]	**4 (4.1)**	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 SAE, n (%)	**4 (5.1)**	[redacted]	[redacted]	**2 (2.0)**	[redacted]
Patients who stopped treatment due to adverse events, n (%)	**1 (1.3)**	[redacted]	[redacted]	**4 (4.1)**	[redacted]
Deaths, n (%)	**0**	[redacted]	[redacted]	**0**	[redacted]
Notable harms, n (%)					
Hepatic	**3 (3.8)**	[redacted]	[redacted]	**2 (2.0)**	[redacted]
Tuberculosis	**NR**	[redacted]	[redacted]		
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inflammatory bowel disease	**1 (1.3)**	[redacted]	[redacted]	**0**	[redacted]
Malignancies	**0**	[redacted]	[redacted]	**0**	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reactions	**5 (6.4)**	[redacted]	[redacted]	**3 (3.1)**	**2 (4.3)**
Hypersensitivity	**4 (5.1)**	[redacted]	[redacted]	**6 (6.1)**	**1 (2.2)**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Frequency > 5%.

ADA 40 q.4.w. = adalimumab 40 mg every four weeks; IXE 80 q.4.w. = Ixekizumab 80 mg every four weeks; N = number of patients in the analysis population; n = number of patients in the specified category; NA = not applicable; NR = not reported; PBO = Placebo; SAE = serious adverse event

Note: As a notable AE, injection site reactions included injection site reaction: 3 (3.8%) and injection site erythema: 2 (2.6%).

Source: Clinical Study Reports for COAST-V[14] and COAST-W[13], Dougados et al., 2019[32]

Critical Appraisal

The extension phases of COAST-V and COAST-W provided evidence of efficacy and safety of IXE in patients with AS who were bDMARD-naive or had an inadequate response to, or intolerance to TNFis up to 52 weeks. No additional eligibility criteria specific to the extension

period were specified for patients to enter the extension phase of the studies. Blinding of patients was maintained throughout the extension phases with specific safeguards in place at week 16 to maintain blinding during the transition from the first phase of the study to the extension phase (i.e., at week 16 all patients received two injections regardless of treatment group). Patients originally in the adalimumab arm had a washout period of sufficient duration (6 weeks) prior to beginning treatment with IXE thereby preventing any carryover effect. Missing data in the extension phase of each trial was minimal (less than 5% for most outcomes) and not a concern.

Patient characteristics for those in COAST-V and COAST-W were generally reflective of the patients that would be seen in the Canadian clinical setting, however one exclusion criterion related to patients with total spinal ankylosis does reduce the external validity of the studies.

Summary of COAST-V and COAST-W Long-Term Extension Phase

COAST-V[14] and COAST-W[13] included a long-term extension phase from week 16 to week 52. The objective of the extension periods was to determine if the effect of either IXE dosing regimen (80 mg every two weeks or 80 mg every four weeks) is maintained up to week 52 for patients with active AS who were bDMARD-naive or had an inadequate response to, or intolerance to TNFis. The extension phase of COAST-V and COAST-W was generally well designed with no additional eligibility criteria specified for patients to enter the extension and maintenance of blinding throughout the studies. The studies were limited by exclusion of patients with total spinal ankylosis. Results of the COAST-V and COAST-W extension phase suggest that the effect of treatment with IXE is maintained over a 52-week period based on the assessment of numerous efficacy and health-related outcomes. Improvements in disease activity were also observed for patients previously treated with placebo who were switched to IXE. Overall, efficacy results for patients treated with IXE are aligned with those of the 16-week trials. No new safety signals arose over the course of the extension phase of the COAST studies.

Discussion

Summary of Available Evidence

Two phase III, double-blind RCTs (16 weeks), COAST-V (N = 341) and COAST-W (N = 316), are included in this review. The two trials evaluated the efficacy and safety of IXE 80 mg SC every four weeks compared to placebo in patients with active AS. COAST-V was conducted in patients with AS who were bDMARD-naive and COAST-W was conducted in patients with AS who inadequately responded to, or were intolerant to one or two TNFis. In both trials, the initial IXE dose was IXE 80 mg or IXE 160 mg. The primary outcome in both trials was the proportion of patients meeting the ASAS 40 response criteria at week 16.

Results of the extension phase at week 52 of the above two studies (COAST-V and COAST-W) are also presented in this report.

In addition, due to lack of head-to-head trials comparing IXE 80 mg SC every four weeks to other active bDMARDS treatments for AS, a summary of the sponsor-submitted ITC analysis is also presented that evaluated the comparative efficacy and safety of IXE 80 mg SC every four weeks to other bDMARDS in the treatment of patients with active AS.

Interpretation of Results

Efficacy

Results at 16 Weeks

Clinical response (i.e., ASAS 40 and ASAS 20): At week 16, in both COAST-V and COAST-W, it was reported that a statistically and clinically significant greater proportion of patients treated with IXE 80 mg SC every four weeks achieved ASAS 40 and ASAS 20 than patients with placebo treatment. Twenty-eight percent more patients in the IXE group in COAST-V and 19% more patients in COAST-W achieved ASAS 40 than those in the placebo group, respectively. According to the clinical expert CADTH consulted for this review, ASAS 20 at week 12 is considered an acceptable clinical response for the bDMARDs trial in AS; therefore, ASAS 40 at week 16 was considered as a major clinical improvement. The response rates of ASAS 40 and ASAS 20 reported in both COAST-V and COAST-W are considered clinically meaningful. It is also noted that the ASAS 40 and ASAS 20 response to the IXE treatment were greater in the COAST-V than that in COAST-W, which reflects that patients included in COAST-W who responded to, or were intolerant to TNFis were more difficult to treatment.

Symptoms reduction: In both COAST-V and COAST-W, patients treated with IXE compared with placebo appeared to have a numerically greater reduction in spinal pain and greater improvement in fatigue (measured with fatigue NRS); IXE treatment also showed some benefit in improving sleep and depression. Since these individual symptom measurements were analyzed with no multiplicity adjustment, the statistical significance (P value) remains uncertain. In addition, no MID was identified for these symptom measurement scales. However, the most important symptom, spinal pain, is a main component of ASAS criteria. It is therefore reasonable to believe that the observed difference of spinal pain between IXE treatment and placebo maybe clinically meaningful.

Function and disability improvement (i.e., BASFI): It was observed that there were statistically and clinically significant greater improvement in BASFI in patients receiving IXE

80 mg SC every four weeks than in patients with placebo based on the MID for BASFI (MID = 0.6 units on a 10-unit scale).

Quality of life improvement: In terms of quality of life measured by SF-36 PCS in both COAST-V and COAST-W, a statistically and clinically significant greater improvement was observed in patients receiving IXE 80 mg SC every four weeks than in patients with placebo based on the MID of SF-36 (MID = 2.5 to 5 points). In terms EQ-5D-5L, a notable difference between IXE treatment and placebo in favour of IXE treatment was also observed. As EQ-5D-5L was analyzed with no multiplicity adjustment, the statistical significance for EQ-5D-5L remains uncertain. [redacted] Therefore, the benefit of IXE 80 mg SC every four weeks treatment compared with placebo in terms of EQ-5D-5L may still be considered clinically meaningful. As to ASAS HI, a statistically significant greater improvement was observed in patients treated with IXE 80 mg SC every four weeks than patients with placebo. Since there are no MID identified for ASAS HI, whether or not the between-group difference of ASAS HI is clinical meaningful remains unknown.

Work productivity (i.e., WPAI-SpA Score): Some numerical benefit was also observed in favour of IXE treatment compared with placebo. However, since the WPAI-SpA was analyzed with no multiplicity adjustment, the statistical significance remains uncertain. In addition, no MID was identified for WPAI-SpA, therefore, whether or not the between-group difference of the WPAI-SpA score between IXE and placebo is clinically meaningful remains unclear.

Disease activity reduction: A statistically and clinically significant greater reduction in disease activity was reported in patients receiving IXE 80 mg SC every four weeks than in patients receiving placebo in terms of BASDAI 50 in COAST-V. ASDAS change from baseline in both COAST-V and COAST-W was based on respective MID. The MID was two units for BASDAI and 1.1 for ASDAS, respectively. A statistically significant BASDAI change from baseline in the IXE group compared with placebo was observed in COAST-W.

A notable treatment difference with respect to PGA was also observed in favour of IXE treatment compared with placebo. However, since PGA were analyzed with no multiplicity adjustment, the statistical significance remains uncertain. In addition, no MID was identified for PGA. However, PGA is a main component of ASAS criteria. Therefore, it is reasonable to conclude that the observed difference of PGA between IXE treatment and placebo may be clinically meaningful.

MRI Spine SPARCC score: In both COAST-V and COAST-W, compared with placebo, treatment with IXE showed a statistically and clinically significant greater improvement based on MID, with MID being five units for MRI Spine SPARCC).

Overall, the magnitude of treatment response to IXE was less in TNFi-experienced patients in COAST-W compared with bDMARD-naive patients in COAST-V, which reflects that patients included in COAST-W who inadequately responded to, or were intolerant to TNFis were more difficult to treat.

Results at 52 Weeks

Based on the 52-week extension phase in both COAST-V and COAST-W, the effectiveness of IXE 80 mg SC every four weeks for the treatment of AS patients appeared to be sustained up to week 52. However, the results were limited due to the lack of a comparator in the extension phase at week 52; therefore, no statistical inference could be made.

Indirect Comparison Results

A sponsor-submitted ITC analysis suggested there was no difference in all efficacy outcomes comparing IXE with adalimumab, golimumab, etanercept, and SEC in biologic-naive patients, as well as no difference in terms of efficacy and safety comparing IXE with SEC in TNFi-experienced patients with AS.

Harms

The overall frequency of TEAEs in patients treated with IXE 80 mg SC every four weeks appeared to be low and similar to that in the placebo group in COAST-V (42% versus 40%) by week 16. COAST-W showed a higher proportion of TEAEs in patients treated with IXE 80 mg SC every four weeks than in the placebo group (64% versus 49%). The most common TEAEs (> 5% of patients in either of the treatment groups) were nasopharyngitis and upper respiratory tract infection, which appeared in more patients in the IXE 80 mg SC every four weeks group than in the placebo group in both studies. Overall frequency of patients with SAEs seemed to be very low in both studies by week 16. It was noted that no patients withdrew due to adverse events in COAST-V. However, in COAST-W more patients (8.8%) in the IXE 80 mg SC every four weeks group withdrew due to adverse events than in the placebo group (1.9%). No deaths were reported in either of the studies. Furthermore, although the incidence was very low, it appeared that a numerically higher percentage of patients reported notable harms including infections, inflammatory bowel disease, injection site reactions, hypersensitivity, and hepatotoxicity in COAST-W. Based on the clinical expert CADTH consulted for this review, the TEAEs reported in both COAST-V and COAST-W were similar to the TEAEs observed in other IXE clinical trials for psoriasis and PsA. There were no significant findings with respect to notable harms. The higher rates of infection in COAST-W in the IXE 80 mg SC every four weeks group compared with placebo was expected. The lower rate in the placebo group was anticipated and these infections were minor.

The safety profile of IXE 80 mg SC every four weeks in AS through week 52 was consistent with that observed by week 16, with no new safety signals reported.

A sponsor-submitted ITC analysis suggested that there was no difference in terms of safety profile comparing IXE 80 mg SC every four weeks with adalimumab, golimumab, etanercept, and SEC in biologic-naive patients. However, IXE has a higher likelihood of AEs and treatment discontinuation due to AEs relative to placebo in TNFi-experienced patients.

Conclusions

Based on the two double-blind RCTs of patients with active AS, one of which was conducted in bDMARD-naive patients and the other in patients with an inadequate response to, or intolerance to one or two TNFis, IXE 80 mg SC every four weeks consistently showed a clinically significant benefit as demonstrated by clinical response (i.e., ASAS 40), HRQoL (i.e., SF-36 PCS), disease activity reduction (i.e., BASDAI, ASDAS) and MRI Spine SPARCC change at week 16 compared with placebo. The magnitude of benefit appeared to be less in TNFi-experienced patients compared with bDMARD-naive patients for the primary outcome (ASAS 40). The incidence of AEs was similar between the IXE 80 mg SC every four weeks and placebo groups in the two trials up to week 16. The efficacy achieved at week 16 appeared to be sustained at 52 weeks, and no new safety signals were identified in weeks 16 to 52. A sponsor-submitted ITC suggested no difference was observed in terms of efficacy and safety comparing IXE 80 mg every four weeks with bDMARDS marketed in Canada. However, due to its various limitations, whether IXE is comparable in efficacy and safety to its biologic comparators remains somewhat uncertain, particularly in the long term.

Appendix 1: 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:	October 24, 2019
Alerts:	Weekly search updates until February 19, 2020
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#	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
1. (taltz* or ixekizumab* or LY2439821 or LY-2439821or BTY153760O or BTY-153760O).ti,ot,ab,kf,rn,hw,nm.
2. exp spondylarthropathies/
3. exp spondylitis, ankylosing/
4. (Spondyloarthr* or Spondylarthr* or Spondylit* or spondilit* or spine or spinal or vertebrae or vertebraes or vertebral).ti,ab,kf.
5. (Marie Struempell* or Bechterew* or Becterev* or Bekhterev* or Spondyloarthropath* or Spondylarthropath*).ti,ab,kf.
6. 2 or 3 or 4 or 5
7. 1 and 6
8. 7 use medall
9. (taltz* or ixekizumab* or LY2439821 or LY-2439821or BTY153760O or BTY-153760O).ti,ab,kw,dq.
10. *ixekizumab/
11. exp ankylosing spondylitis/
12. (Spondyloarthr* or Spondylarthr* or Spondylit* or spondilit* or spine or spinal or vertebrae or vertebraes or vertebral).ti,ab,kw,dq.
13. (Marie Struempell* or Bechterew* or Becterev* or Bekhterev* or Spondyloarthropath* or Spondylarthropath*).ti,ab,kw,dq.
14. conference abstract.pt.
15. conference review.pt.
16. 14 or 15
17. 9 or 10
18. 11 or 12 or 13
19. 17 and 18
20. 19 not 16
21. 20 use oemezd
22. 8 OR 21
23. remove duplicates

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:	October 2019
Keywords:	Taltz (ixekizumab)
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 2: Excluded Studies

Table 27: Excluded Studies

Reference	Reason for Exclusion
Wendling D et al.[33]	Review article
Papp K et al.[34]	Study design (Not RCT, comparator not of interest)
Torgutalp M et al.[35]	Review article
So A et al.[36]	Review article
Paine A et al.[37]	Review article
Mease P et al.[38]	Review article

Appendix 3: Detailed Outcome Data

Table 28: ASAS 40 and ASAS 20 Response at Week 16 by Ixekizumab Starting Dose (NRI, ITT)

	COAST-V		COAST-W	
	IXE 80 q.4.w./160S [redacted]	IXE 80 q.4.w./80S [redacted]	IXE 80 q.4.w./160S [redacted]	IXE 80 q.4.w./80S [redacted]
ASAS 40 week 16 (NRI)				
Response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
% Diff. (95% CI) vs. 80S*c	[redacted]		[redacted]	
P value, 160S vs. 80S*b	[redacted]		[redacted]	
ASAS 20 week 16 (NRI)				
Response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
% Diff (95%, CI) 160S vs. 80S [b]	[redacted]		[redacted]	
P value, 160S vs. 80S[a]	[redacted]		[redacted]	

80S = 80 mg starting dose; 160S = 160 mg starting; ADA 40 q.2.w. = adalimumab 40 mg every two weeks; ASAS 40 = Assessment of Spondyloarthritis International Society 40% improvement; ASAS 20 = Assessment of Spondyloarthritis International Society 20% improvement; CI = confidence interval; Diff. = difference; ITT = Intent-to-Treat; IXE 80 q.4.w. = ixekizumab 80 mg every four weeks; Diff = difference; N = number of patients in the analysis population; n = number of patients in the specified category; NRI= nonresponder imputation; n = number of patients in the specified category; OR = Odds Ratio; PBO = Placebo.

a. [redacted]

b. [redacted]

Source: CSRs[10,11]

Table 29: ASAS 5/6 at Week 16 (NRI, ITT)

ASAS 5/6	COAST-V			COAST-W	
	IXE 80 q.4.w [redacted]	PBO [redacted]	ADA 40 q.4.w. [redacted]	IXE 80 q.4.w [redacted]	PBO [redacted]
Week 16 (NRI)					
Response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Diff (95% CI) vs. PBO [b]	[redacted]		[redacted]	[redacted]	
P value vs. PBO[a]	[redacted]		[redacted]	[redacted]	

ADA 40 q.2.w. = adalimumab 40 mg every two weeks; ASAS 20 = Assessment of Spondyloarthritis International Society 20% improvement; CI = confidence interval; Diff = difference; ITT = Intent-to-Treat; IXE 80 q.4.w. = ixekizumab 80 mg every four weeks; N = number of patients in the analysis population; n = number of patients in the specified category; NRI= nonresponder imputation; n = number of patients in the specified category; OR = odds Ratio; PBO = placebo; PP= per protocol; vs. = versus

a. [redacted]

b. [redacted]

Source: CSRs[10,11]

Table 30: ASAS Partial Remission at Week 16 (NRI, ITT)

ASAS partial remission	COAST-V			COAST-W	
	IXE 80 q.4.w [redacted]	PBO [redacted]	ADA 40 q.2.w. [redacted]	*IXE 80 q.4.w* [redacted]	PBO [redacted]
Week 16 (NRI)					
Response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Diff. (95% CI) vs. PBO [b]	[redacted]		[redacted]	[redacted]	
P value vs. PBO[a]	[redacted]		[redacted]	[redacted]	

ADA 40 q.2.w = adalimumab 40 mg every two weeks; ASAS 20 = Assessment of Spondyloarthritis International Society 20% improvement; CI = confidence interval; Diff = difference; ITT = intent-to-treat; IXE 80 q.4.w. = ixekizumab 80 mg every four weeks; N = number of patients in the analysis population; NRI= nonresponder imputation; n = number of patients in the specified category; OR = odds ratio; PBO = placebo; PP= per protocol.

a. [redacted]

b. [redacted]

Source: CSRs[10,11]

Table 31: Measures of AS symptoms CFB at Week 16 (MMRM, ITT)

	COAST-V			COAST-W	
Symptoms	IXE 80 q.4.w (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	*IXE 80 q.4.w* (N = 114)	PBO (N = 104)
Spinal Pain Change from Baseline					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, Mean (SD)	*7.2 (1.33)*	*7.4 (1.45)*	[redacted]	*7.9(1.48)*	*7.8 (1.35)*
Week 16, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE)	–3.2 (0.25)	*–1.7 (0.24)*	–2.7 (0.23)	–2.4 (0.23)	–1.0 (0.24)
Between-group LSM diff (95%)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
Fatigue Severity NRS					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE)	–2.5 (0.24)	*–1.4 (0.23)*	–2.2 (0.23)	–2.0 (0.23)	*–0.7 (0.24)*
Between-group LSM diff (95%)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
JSEQ					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE)	–2.5 (0.43)	–1.5 (0.41)	–2.7 (0.40)	–3.0 (0.48)	*–1.8 (0.50)*
Between-group LSM diff (95%)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	

Symptoms	COAST-V			COAST-W	
	IXE 80 q.4.w (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	*IXE 80 q.4.w* (N = 114)	PBO (N = 104)
QIDS-SR16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16 (mBOCF, ANCOVA), n					
Baseline, Mean(SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16 Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-group LSM diff (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	

ADA 40 q.2.w. = adalimumab 40 mg every two weeks; ANCOVA= analysis of covariance; CFB = change from baseline; CI = confidence interval; Diff = difference; NRS = numeric rating scale; ITT = Intent-to-Treat; IXE 80 q.4.w. = ixekizumab 80 mg every four weeks; JSEQ = Jenkins Sleep Evaluation Questionnaire; LSM = least squares mean; mBOCF= modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = Placebo; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self Report 16 items; SD = Standard of deviation; SE = standard error.

Source: CSRs[10,11]

Table 32: HRQoL at Week 16 (MMRM, ITT)

HRQoL	COAST-V			COAST-W	
	IXE 80 q.4.w (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w (N = 114)	PBO (N = 104)
SF-36 MCS					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-group LSM diff (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	
EQ-5D-5L VAS					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE) week 16 (mBOCF, ANCOVA)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-group LSM diff (95% CI)	[redacted]		[redacted]	[redacted]	
P value[a]	[redacted]		[redacted]	[redacted]	
EQ-5D-5L UK Index Score					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, Mean(SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HRQoL	COAST-V			COAST-W	
	IXE 80 q.4.w (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w (N = 114)	PBO (N = 104)
CFB LSM (SE) (mBOCF, ANCOVA)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-group LSM diff (95% CI)	[redacted]		[redacted]	[redacted]	
P value[a]	[redacted]		[redacted]	[redacted]	

ADA 40 q.2.w. = adalimumab 40 mg every two weeks; ANCOVA= analysis of covariance; ASAS HI = Assessment of Spondyloarthritis International Society Health Index; CFB = change from baseline; CI = confidence interval; Diff = difference; EQ-5D-5L= European Quality of Life – 5 Dimensions 5 Levels; HRQoL= Health-related quality of life; ITT = Intent-to-Treat; IXE 80 q.4.w. = ixekizumab 80 mg every four weeks; LSM = least squares mean; mBOCF= modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = Placebo; SD = Standard of deviation; SE = standard error; SF-36-MCS = Medical Outcomes Study 36-Item Short Form Health Survey mental component summary; VAS = Visual analogue scale.

[a] [redacted].

Source: CSRs[10,11]

Table 33: WPAI-SpA Score at Week 16 (ANCOVA, mBOCF, ITT)

WPAI-SpA	COAST-V			COAST-W	
	IXE 80 q.4.w (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w (N = 114)	PBO (N = 104)
Percentage of Absenteeism CFB					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE) week 16	1.23 (2.18)	–1.26 (2.35)	–1.22 (2.03)	–4.74 (2.93)	–1.17 (2.75)
Between-group LSM diff (95% CI)	[redacted]		[redacted]	[redacted]	
P value [a]	[redacted]		[redacted]	[redacted]	
Percentage of Presentisms CFB					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE)	–22.7 (2.91)	–17.7 (3.09)	–20.9 (2.77)	–19.5 (3.90)	–8.9 (3.62)
Between-group LSM diff (95% CI)	[redacted]		[redacted]	[redacted]	
P value [a]	[redacted]		[redacted]	[redacted]	
Overall Work Impairment CFB					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE)	–21.36 (3.06)	–17.82 (3.25)	–21.44 (2.92)	–20.97 (4.02)	–9.84 (3.73)
Between-group LSM diff (95% CI)	[redacted]		[redacted]	[redacted]	
P value [a]	[redacted]		[redacted]	[redacted]	

WPAI-SpA	COAST-V			COAST-W	
	IXE 80 q.4.w (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w (N = 114)	PBO (N = 104)
Percentage of Activity Impairment CFB					
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16 mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE)	–23.0 (2.35)	–14.1 (2.28)	–21.1 (2.22)	–16.5 (2.44)	–10.1 (2.60)
Between-group LSM diff (95% CI)	[redacted]		[redacted]	[redacted]	
P value [a]	[redacted]		[redacted]	[redacted]	

ADA 40 q.2.w. = adalimumab 40 mg every two weeks; ANCOVA= analysis of covariance; CFB = change from baseline; CI = confidence interval; Diff = difference; ITT = Intent-to-Treat; IXE 80 q.4.w. = ixekizumab 80 mg every four weeks; LSM = least squares mean; mBOCF= modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = Placebo; SD = Standard of deviation; SE = standard error;

[a] [redacted].

Source: CSRs[10,11]

Table 34: Patient Global, CFB at Week 16 (MMRM, ITT)

PGA	COAST-V			COAST-W	
	IXE 80 q.4.w (N = 81)	PBO (N = 87)	ADA 40 q.2.w. (N = 90)	IXE 80 q.4.w (N = 114)	PBO (N = 104)
Week 16, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB LSM (SE)	–2.5 (0.25)	–1.4 (0.24)	–2.6 (0.24)	–2.4 (0.22)	*–0.7 (0.23)*
Between-group LSM diff (95% CI)	[redacted]		[redacted]	[redacted]	
P value	[redacted]		[redacted]	[redacted]	

ADA 40 q.2.w. = adalimumab 40 mg every two weeks; ANCOVA= analysis of covariance; PGA = Patient Global Assessment; CFB = change from baseline; CI = confidence interval; Diff = difference; ITT = intent to treat; IXE 80 q.4.w. = ixekizumab 80 mg every four weeks; LSM = least squares mean; MMRM = mixed-effects model of repeated measures; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; SD = standard of deviation; SE = standard error.

Source: CSRs[10,11]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures (Table 35) and review their measurement properties (validity, reliability, responsiveness to change, and MID) (Table 36):

Table 35: Outcome Measures Included in Each Study

Outcome Measure	Study 001	Study 002
ASAS response		
• ASAS 40	Primary	Primary
• ASAS 20	Major Secondary	Major Secondary
• ASAS 5/6	Other Secondary	Other Secondary
• ASAS Partial Remission	Other Secondary	Other Secondary
• ASAS HI	Major Secondary	Major Secondary
• Patient Global ASAS (individual component)	Other Secondary	Other Secondary
BASDAI	Major Secondary	Major Secondary
BASFI	Major Secondary	Major Secondary
ASDAS	Major Secondary	Major Secondary
Spine SPARCC	Major Secondary	Major Secondary
SIJ SPARCC	Other Secondary	Other Secondary
SF-36	Major Secondary	Major Secondary
EQ-5D-5L	Health Outcome	Health Outcome
Fatigue Severity Numeric Rating Scale	Health Outcome	Health Outcome
WPAI-SpA	Health Outcome	Health Outcome
JSEQ	Health Outcome	Health Outcome
QIDS-SR16	Health Outcome	Health Outcome

ASAS = Assessment of Spondyloarthritis International Society; ASAS HI = Assessment of Spondyloarthritis International Society - Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; EQ-5D = EuroQol 5 dimension; JSEQ = Jenkins Sleep Evaluation Questionnaire; MRI = magnetic resonance imaging; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self Report 16 items; SF-36 = 36-item Short Form survey; SIJ = sacroiliac joints; SPARCC = Spondyloarthritis Research Consortium of Canada; WPAI-SpA = Work Productivity Activity Impairment–Spondyloarthritis.

Findings

Table 36: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
ASAS response	A composite set of response criteria which are commonly used in AS trials, contains 6 domains.	See ASAS variations below	None identified
ASAS 40	40% improvement and absolute improvement from baseline of ≥ 2 units (range 0 to 10) in ≥ 3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), without any worsening in the remaining domain.	The ASAS 40 was determined to have a chi-square = 26.5 (95% CI, 13.3 to 41.1) and a low placebo response rate of 5.7%, this indicated good discriminating capacity between treatment (with infliximab) and placebo.[39] Using a combined data set using data from an infliximab and an etanercept trial, it was determined that most of the best-performing ASAS criteria (including ASAS 40) from the infliximab data set also had the highest chi-square values in the combined data set indicating good reliability of the ASAS 40.[39]	NA
ASAS 20	≥ 20% improvement and an absolute improvement from baseline of ≥ 1 units (range 0 to 10) in ≥3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), without any worsening of ≥ 20% and ≥ 1 unit (range 0 to 10) in the remaining domain.	The criteria for the ASAS 20 was identified as the best-performing criteria out of 20 different ASAS-based criteria based on its chi-square value = 36.4% (P < 0.001), and a placebo response rate that did not exceed 25%.[26] This finding was validated using the remaining one-third of data from the three NSAID trials which found very similar results.[26]	NA
ASAS 5/6	The ASAS 5/6 includes assessments of all 6 individual ASAS domains and represents improvement of ≥ 20% in at least 5 domains.	ASAS 5/6 was determined to have a chi-square = 31.9 (95% CI, 18.0 to 46.9) and a low placebo response rate of 2.9%, this indicated good discriminating capacity between treatment (with infliximab) and placebo. [39] Using a combined data set using data from an infliximab and an etanercept trial it was determined that most of the best-performing ASAS criteria (including ASAS 5/6) from the infliximab data set also had the highest chi-square values in the combined data set indicating good reliability of the ASAS 5/6.[39]	NA
ASAS Partial Remission	A value not above 2 units (range 0 to 10; NRS) in each of the following 4 ASAS domains: Patient Global, Spinal Pain, Function, and Inflammation.	None identified.	NA
ASAS HI	The ASAS HI is an axSpA-specific 17-item patient-reported instrument designed to assess functioning, disability, and health. The ASAS HI has scores ranging from 0 (good health) to 17 (poor health).	The sum score of the 17 items correlated significantly with BASDAI and total back pain (r = 0.6) as well as with Bath AS Functional Index and Bath AS—Patient Global Score (r = 0.7), (all P < 0.0001). [40] Construct validity showed a Spearman correlation coefficient ranging from moderate (WPAI absenteeism: 0.38) to high (BASFI: 0.71 or SF-36	None identified

Outcome measure	Type	Conclusions about measurement properties	MID
	All item scores are summed to give a total score or index.	PSC 0.73).[41] Internal consistency was high (Cronbach's-alpha = 0.93). The reliability among 578 patients was good (ICC = 0.87; 95% CI, 0.84 to 0.89).[41] Responsiveness among 246 patients was moderate to large (SRM = –0.44 for NSAIDs, –0.69 for cDMARD, and –0.85 for TNFi).[41]	
Patient Global Assessment of Disease Activity (ASAS individual component)	The Patient Global Assessment of Disease Activity relates to a single specific ASAS domain based on a NRS. For this assessment, the patient was asked to respond to the following question: "How active was your spondylitis on average during the last week?" The answer was recorded on an NRS and was rated between "0" (not active) and "10" (very active).	The Patient Global Assessment of Disease Activity is moderately correlated with the ASAS HI (r = 0.57). [41]	None identified
BASDAI	Self-administered disease-specific questionnaire, 18 items, scores ranging from 0-18.	Test-retest results were significantly intercorrelated with r (s) = 0.90 for BASDAI.[42] BASDAI appeared to be sensitive to change, reflecting a 16% (mean) improvement in inpatient scores after three weeks of intensive physiotherapy treatment.[43]	2 units[44]
BASFI	Self-administered 8-question instrument addressing physical function and patient's ability to cope with everyday life on 10 cm visual analogue scales.	Test-retest results showed significant intercorrelation with r (s) = 0.92 for BASFI. [42] BASFI is one of 3 AS assessment instruments with the most extensive evidence for validity through comparison with instruments that measure similar or related constructs, and/or with measures of mobility.[45]	7 mm on VAS or 17.5% of the baseline score[46] Or 0.6 units on a 10 unit scale.[47]
ASDAS	The ASDAS is a composite index to assess disease activity in rad-axSpA that include the following parameters: Total back pain (BASDAI Question 2); Patient Global Assessment of Disease Activity (individual ASAS domain); Peripheral pain/swelling (BASDAI Question 3); Duration of morning stiffness (BASDAI Question 6); CRP in mg/L.	The ASDAS is correlated with other measures including the BASDAI (concordance coefficients = 0.81[48]; 0.76[49]), ASAS HI (correlation coefficient = 0.56)[50], C-reactive protein (correlation coefficient = 0.79)[49], MRI sacroiliac joints inflammation (correlation coefficient = 0.46)[49] and MRI total inflammation scores (correlation coefficient = 0.34)[49] patient's global assessment (correlation coefficient = 0.71)[51] and physician's global assessment (correlation coefficient =0.65)[51].	≥ 1.1 units[52]
Spine SPARCC Score	A MRI-based scoring system that assesses the presence, 3-dimensional extent, and signal	When assessing the 6 most affected units, the overall intra-observer reproducibility was excellent (ICC 0.93 to 0.98) for the three readers, and the	5.0 units[54]

Outcome measure	Type	Conclusions about measurement properties	MID
	intensity of active inflammatory lesions represented by bone marrow edema, in the spine of affected patients.	mean percentage intra-observer concordance for the selection of affected discovertebral units was 78.8%, 87.9%, and 80.3% for the 3 readers. [53]	
SIJ SPARCC Score	A MRI-based scoring method that assesses increased signal denoting bone marrow edema on T2-weighted STIR sequences.	The intra-observer reproducibility of the total score based on three readers was excellent (ICC = 0.90 to 0.98) while the ICC for change (in MRI activity) scores was lower (ICC 0.53). [55] In another study assessing inter-reader reliability, the SPARCC showed an ICC for the total status score of 0.55 and 0.52 for the change score. The SPARCC MRI score for SIJ has been shown to be correlated with the ASDAS (pre-treatment, $R^2 = 0.2038$). [56]	2.5 units[54]
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 0-100.	The SF-36 had a strong correlation with the Mander Enthesitis Index and the BASDAI. [52] The internal consistency, construct validity and responsiveness to change of SF-36 has been assessed in two RCTs comparing adalimumab with placebo for the treatment of AS. SF-36 had a good internal consistency (alpha = 0.74-0.92). [57]	2.5 to 5 points for the component scores[58]
EQ-5D	The EQ-5D is a generic QoL instrument consisting of 5 dimensions of health (mobility, self care, usual activities, pain/discomfort, and anxiety/depression) and a VAS for rating health today. Weighted scoring produces an EQ-5D index score.	When compared to the Short Form 6-dimensions (SF-6D) and the well-being rating scale (RS) in AS patients, the ICCs indicated moderate agreement (0.46 to 0.55). [59] Instruments correlated equally with disease activity, functioning, and quality of life. Compared with EQ-5D and RS, SF-6D showed smaller average differences in utility between patients with better and worse disease.[59]	0.033 to 0.074 for general population[60]
Fatigue Severity Numeric Rating Scale	A single-item, patient-reported, 11-point horizontal scale anchored at 0 and 10, with 0 representing “no fatigue” and 10 representing “as bad as you can imagine.”	None identified	None identified
WPAI-SpA	A 6-item, patient-reported instrument designed to assess the impact of SpA on work productivity and activity impairment.	Construct validity was demonstrated using median scores of other measures including the BASDAI and SF-36. Patients with AS of the worst severity (BASDAI > median) demonstrated significantly greater overall work impairment (difference = –14.5, $P < 0.001$), presenteeism (difference = –20.3, $P < 0.001$) and daily activity impairment (difference = –19.5, $P < 0.001$) based on the WPAI-SpA.[61]	None identified
JSEQ	A 4-item, patient-reported instrument designed to estimate sleep problems in clinical research.	The Turkish version of the JSEQ has good internal consistency (Cronbach’s alpha = 0.83), was strongly correlated with the Pittsburgh Sleep Quality Index (rho = 0.75) and a moderate correlation with the BASDAI (rho = 0.57) when assessed in patients with AS.[62]	None identified

Outcome measure	Type	Conclusions about measurement properties	MID
QIDS-SR16	A self-administered,16-item instrument intended to assess the existence and severity of symptoms of depression.	Evidence of validation of the QIDS-SR16 in the AS patient population was not identified in the literature search.	None identified
mSASSS	Score obtained by assessing anterior sites of the lumbar(L1-L5) and cervical spine (C2-T1) on a lateral view. Each site gets a score from 0 (normal) to 3 (bridging syndesmophytes), which gives a total score range of 0 to 72.	Interobserver correlations of the lumbar and cervical spine scores were good (r > 0.95).[63]	None identified

AS = ankylosing spondylitis; ASAS = Assessment of Spondyloarthritis International Society; ASAS HI = Assessment of Spondyloarthritis International Society - Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; cDMARD = conventional disease-modifying antirheumatic drug; EQ-5D = EuroQol 5 dimension; JSEQ = Jenkins Sleep Evaluation Questionnaire; mSASSS = modified Stoke Ankylosing Spondylitis Spine Score; MID = minimal important difference; MRI = magnetic resonance imaging; NA = not applicable; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self Report 16 items; QoL = quality of life; SF-36 = 36-item Short Form survey; SIJ = sacroiliac joints; SPARCC = Spondyloarthritis Research Consortium of Canada.

Assessment in Ankylosing Spondylitis (ASAS) Response

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.[64,65]

The ASAS International Working Group has defined core domains that are important in assessing the ASAS 20, ASAS 40, and ASAS 5/6. These domains include: PGA of disease activity, spinal pain, function, inflammation (mean of BASDAI question 5 and 6), CRP, and spinal mobility (lateral spinal flexion).[10,11]

Patient global assessment of disease activity is described below. Spinal pain is assessed based on the ASAS Handbook through the following questions: "How much pain of your spine due to ankylosing spondylitis do you have?", and "How much pain of your spine due to ankylosing spondylitis do you have at night?" The responses are assessed using an NRS from 0 (no pain) to 10 (most severe pain).[66] Function is assessed using the BASFI (described subsequently). Inflammation is assessed using the mean of BASDAI questions 5 and 6 which relate to intensity and duration of morning stiffness (described subsequently). CRP, a measure of acute phase reactant, is measured using high-sensitivity assay at the central laboratory.[10,11] Spinal mobility is assessed using the BASMI, a combined index of the following measurements: lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober test), maximal intermalleolar distance, and cervical rotation.[66]

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.[67]

ASAS 40

The ASAS 40 is derived from patient-reported assessments.[39] An ASAS 40 response is defined as a 40% or greater improvement and an absolute improvement from baseline of two or more units (range 0 to 10) in three or more of four domains (Patient Global, Spinal Pain, Function, and Inflammation), without any worsening in the remaining domain.[10,11] The ASAS 40 has been identified as advantageous as it sets a high threshold for efficacy, although it is restricted to the patient-reported outcomes.[39]

Using data derived from two RCTs (n = 99), the criteria for the ASAS 40 was identified out of 50 different ASAS criteria as one of the two best-performing criteria (the ASAS 5/6 is the other best-performing criteria, although neither of these two criteria is clearly superior on statistical grounds).[39] The ASAS 40 was determined using Boolean type criteria. The power of different criteria were evaluated using chi-square values with 95% CIs calculated using bootstrap methods. Based on the data from an infliximab trial, the ASAS 40 was determined to have a chi-square = 26.5 (95% CI, 13.3 to 41.1) and a low placebo response rate of 5.7%. This indicated good discriminating capacity between treatment (with infliximab) and placebo.[39] Using a combined data set using data from an infliximab and an etanercept trial, it was determined that most of the best-performing ASAS criteria (including ASAS 40) from the infliximab data set also had the highest chi-square values in the combined data set indicating good reliability of the ASAS 40.[39]

ASAS 20

The ASAS 20 is derived from patient-reported assessments. An ASAS 20 response is defined as a 20% or greater improvement and an absolute improvement from baseline of one or more units (range 0 to 10) in three or more of four domains (Patient Global, Spinal Pain, Function, and Inflammation), without any worsening of 20% or more and one or more units (range 0 to 10) in the remaining domain.[10,11]

Using a random subset of two-thirds of the data from three NSAID trials (n = 923) the criteria for the ASAS 20 was identified as the best-performing criteria out of 20 different ASAS-based criteria based on its chi-square value of 36.4% ($P < 0.001$), and a placebo response rate that did not exceed 25%.[26] This finding was validated using the remaining one-third of data from the three NSAID trials which found very similar results.[26]

ASAS 5/6

The ASAS 5/6 includes assessments of all six individual ASAS domains and represents improvement of 20% or more in at least five domains.[10,11,39] The ASAS 5/6 has been identified as advantageous as it includes the objective domains of spinal mobility and acute phase reactants, but only requires a 20% improvement.[39]

The ASAS 5/6 was evaluated in the same study as the ASAS 40 using methods described above.[39] The criteria for the ASAS 5/6 was identified out of 50 different ASAS criteria as one of two best-performing criteria (the ASAS 40 is the other best-performing criteria).[39] Based on the data from an infliximab trial, the ASAS 5/6 was determined to have a chi-square of 31.9 (95% CI, 18.0 to 46.9) and a low placebo response rate of 2.9%. This indicated good discriminating capacity between treatment (with infliximab) and placebo.[39] Using a combined data set using data from an infliximab and an etanercept trial it was determined that most of the best-performing ASAS criteria (including ASAS 5/6) from the infliximab data set also had

the highest chi-square values in the combined data set indicating good reliability of the ASAS 5/6.[39]

ASAS Partial Remission

The ASAS partial remission is derived from patient-reported assessments. An ASAS partial remission response is defined as a value not above two units (range 0 to 10; NRS) in each of the following four domains: Patient Global, Spinal Pain, Function, and Inflammation.[10,11,66] Validity and reliability assessments were not identified in the literature.

ASAS HI

The ASAS HI is an axSpA-specific 17-item, patient-reported instrument designed to assess functioning, disability, and health.[10,11,40] The ASAS HI has scores ranging from 0 (good health) to 17 (poor health). Each item consists of one question that the patient needed to respond to with either "I agree" (score of 1) or "I do not agree" (score of 0). A score of "1" was given where the item was affirmed, indicating adverse health. All item scores are summed to give a total score or index.[10,11,40]

The 17 items on the ASAS HI were selected from an item pool of 251 items that had been selected to cover all categories of the International Classification of Functioning, Disability, and Health core set. The final 17 items cover most of the core set and showed the best representation of the health status of patients with AS.[40]

The 251-item pool was reduced to 17 items that showed the best reliability and fit to the Rasch model, no residual correlation, and absence of consistent differential item function and a Person Separation Index of 0.82.[40] The sum score of the 17 items correlated significantly with BASDAI and total back pain ($r = 0.6$) as well as with Bath AS Functional Index and Bath AS—Patient Global Score ($r = 0.7$; all $P < 0.0001$).[40]

The ASAS HI was assessed in an international validation study that included translations of the ASAS HI in 23 countries.[41] Construct validity showed a Spearman correlation coefficient ranging from moderate (WPAI absenteeism: 0.38) to high (BASFI: 0.71 or SF-36 PSC 0.73). Internal consistency was high (Cronbach's-alpha = 0.93). The reliability among 578 patients was good (intraclass correlation coefficient [ICC] = 0.87; 95% CI, 0.84 to 0.89). Responsiveness among 246 patients was moderate to large (SRM = –0.44 for NSAIDs, –0.69 for cDMARDs, and –0.85 for TNFis).[41]

An MID was not identified in the literature and the smallest detectable change was identified at 3.0 units.[41] The threshold of ASAS HI which differentiated patients with "good/very good" health from those with "moderate" state of health, was identified as being 5.0. The most clinically relevant threshold of ASAS HI for "moderate" versus "poor/very poor" health was identified as a score of 12.0 or above.[41]

Patient Global Assessment of Disease Activity (Individual ASAS Domain)

The Patient Global Assessment of Disease Activity relates to a single specific ASAS domain based on an NRS. For this assessment, the patient was asked to respond to the following question: "How active was your spondylitis on average during the last week?" The answer was recorded on an NRS and was rated between "0" (not active) and "10" (very active).

The Patient Global Assessment of Disease Activity is moderately correlated with the ASAS HI ($r = 0.57$).[41] While an MID was not identified in the literature, a validation study determined that for individual domains on the ASAS (e.g., Patient Global Assessment of Disease

Activity), the minimum change that should be considered detectable would be approximately two to three units on a scale of 0 to 10.[26] Additionally, an international validation study on the ASAS HI assessed Patient Global Assessment of Disease Activity using cut-off values of less than three and greater than six on NRS to distinguish between "good" and "poor" health status.[41]

BASDAI

The most common and widely used validated measure of inflammatory activity of AS is the BASDAI.[68] 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 was designed by a multidisciplinary team (rheumatologists, physiotherapists, and research associates) with input from patients. It includes six questions addressing five major symptoms: fatigue, axial (spinal) and peripheral joint pain, localized tenderness, and morning stiffness (both degree of stiffness and length of time for which stiffness persists).[43] Patients' responses are recorded on a 10-unit horizontal NRS or 10 cm VAS, or a numeric response scale (1 to 10). The scores for questions 5 and 6 (severity and duration of morning stiffness) are averaged; the result is then averaged with the remaining four question scores. The final BASDAI score has a range from 0 to 10: the higher the score, the greater the measured degree of disease activity.

BASDAI 20, 50, 70 and 90 reflect an improvement of 20%, 50%, 70%, and 90%, or more, respectively over an initial assessment at a given point in time of treatment of an AS patient.

The 2005 International ASAS consensus statement for the use of anti-TNFi drugs in patients with AS recommends the BASDAI follow after initiation of treatment. The recognized MID/treatment response is a change in the BASDAI of two units (on a 0 to 10 scale) of the BASDAI.[44]

Garrett and colleagues developed and evaluated this instrument through analysis of user friendliness, reliability (consistency), score distribution, sensitivity to change and comparisons to a previous Bath Disease Activity Index and the Newcastle Enthesitis Index.[43] In this assessment, the BASDAI was completed by 154 patients receiving three weeks of intensive physiotherapy (inpatients and outpatients). It was found by patients to be relatively quick (mean 67 seconds, range 30 to 120 seconds) and simple to complete. BASDAI appeared to be sensitive to change, reflecting a 16% (mean) improvement in inpatient scores after three weeks of intensive physiotherapy treatment. [43]

Haywood et al. completed a structured review of the measurement properties for all disease-specific, multi-item, patient-assessed health instruments in patients with AS including BASDAI.[45] In this investigation, systematic literature searches were made to identify instruments using pre-defined criteria relating to reliability (measurement stability over time), validity (instrument measures, what is intended, content and face), responsiveness (ability of an instrument to measure clinically important change) and precision.[45] The investigators reported strong evidence for the reliability, validity, and responsiveness of the BASDAI.[45]

Maravic et al. also evaluated the psychometric properties of different translated versions of the BASDAI available (English, Turkish, French, Swedish, and Spanish) including assessing face validity, content validity, construct validity (factorial analysis, convergent and divergent validity), reliability (test-retest, Cronbach's coefficient α which indicates the degree of relatedness between items) and responsiveness.[69] Face validity was validated in all versions. The authors outline that no version initially defined the dimensions for content validity and construct validity was partially studied and validated in English, French, and

Spanish. Reliability was validated in English, French, and Turkish. Responsiveness was demonstrated in all versions except for French.

Calin et al. set out to answer the question of whether the composite index is an accurate reflection of the component parts or whether weighting would provide increased accuracy of assessment. Four hundred and seventy-three patients with AS randomly received placebo or NSAID therapy for six weeks. Disease activity was assessed using BASDAI and the individual components of BASDAI relating to morning stiffness, pain, fatigue, and discomfort were analyzed separately. A principal component analysis was used to explore the best combination of variable and to assess whether a simple sum, as is currently used for the BASDAI index, or a weighted index, would best define disease activity. The BASDAI as a simple sum of its components was found to have excellent content validity.[70]

Madsen et al. examined the reproducibility of BASDAI in anti-TNFi-treated SpA patients already familiar with the use of the indice.[42] Testing was performed twice on two different days (median interval 7 days, range 4 to 10 days) under standardized conditions in 26 outpatient clinic patients with a median age of 39 years (range 22 to 56 years). Limits of agreement were calculated as the 95% likely range for the difference between paired scores. Test-retest results were significantly intercorrelated with an r(s) of 0.90 for BASDAI. Limit of agreement for BASDAI was plus or minus 1.8. Internal consistency reliability and construct validity of BASDAI was deemed acceptable by the authors. The authors concluded that, in a sample of anti-TNF-treated patients experienced with the use of BASDAI, random measurement errors of BASDAI were not negligible.[42]

Pavy et al. investigated the MID of BASDAI and BASFI.[46] They administered both questionnaires to 125 patients with AS at baseline and two weeks after an intensive physiotherapy program. Along with the final assessment, a global validated 15-point rating scale was used to examine each domain. Receiver operating characteristic (ROC) curves were used to determine the score change that most accurately classified patients with respect to a clinically meaningful change. According to analyses of ROC curves, the MID was 10 mm or 22.5% for BASDAI with a sensitivity of 0.65 and a specificity of 0.82. Regression analysis showed that MID values were independent of the patients' baseline scores.[24] These results were similar to a study by Kviatkovsky et al. (2016) that identified the minimally clinically important improvement to be 1.1 units on a 10 unit scale.[47]

Cohen et al. conducted a survey of patients' perceptions about current disease control.[71] One thousand questionnaires were mailed to members of a spondyloarthropathic organization for patients to estimate the best BASDAI cut-off for discriminating between poor and well-controlled groups, from a patient's perspective. A proportion of 55.3% perceived inadequate control of their disease. The mean BASDAI in the overall population was 43.5 +/–22.9, 30.4 +/–19.9 in the well-controlled group, and 54 +/- 19.4 in the poorly controlled group ($P < 0.001$). From the ROC curve, the best BASDAI cut-off for discriminating between patients in the two groups was found to be 39 (sensitivity 74.6% and specificity 72.4%). According to gender, the best cut-off was 44 for women and 36 for men.[71]

BASFI

The BASFI is a validated, patient self-administered, composite instrument widely used in AS to assess physical function. The BASFI consists of eight specific questions regarding function in AS and two questions reflecting the patient's ability to cope with every day life.[72] Each question is answered on a 10 cm horizontal VAS or a numeric response scale (0 to 10), the mean of which gives the BASFI score (on a scale of 0 to 10). The higher the BASFI

score, the greater the degree of functional impairment with reductions from baseline indicating improvement.

Calin and colleagues (1994) developed the BASFI and evaluated it in comparison to the published Douglas Functional Index (DFI). [72] In this investigation, the questionnaire was completed 257 times in total; once by 116 outpatients and on three occasions by 47 inpatients over a three-week intensive physiotherapy course. The BASFI was analyzed in terms of all validity criteria and compared with the DFI. Patient scores covered 95% of the BASFI range, producing a normal distribution of results. Sensitivity results of the BASDAI in comparison to DFI were reported.[72] Over the three-week period of inpatient treatment, the BASFI revealed a significant improvement in function (20%, P = 0.004) while there was less change in the DFI (6%, P = 0.03).

Spoorenberg et al. (1999) conducted a comparative study of the usefulness of BASFI and the DFI in assessment of AS in 191 outpatients in Europe.[73] The external criterion for disease activity was both patient and physician assessment on a VAS and the BASDAI. The external criterion for damage was two radiological scores of the spine (Bath AS Radiology Index spine [BASRI-s]) and a modified Stoke AS Spine Score (mSASSS). Both BASFI and DFI appeared to correlate equally well with disease activity and damage. The average correlation with disease activity variables was 0.42 for BASFI and 0.41 for DFI. The correlation for both BASFI and DFI with BASRI-s was 0.42 and with mSASSS 0.36. Sensitivity for the BASFI and DFI was between 76% and 94% for distinguishing between patients with high and low disease activity, while specificity was between 66% and 87%.[73]

The study carried out by Madsen et al. (2010) also examined the reproducibility of BASFI in anti-TNFi-treated SpA patients.[42] With the same study population and protocol that have been mentioned for BASDAI, test-retest results showed significant intercorrelation with r(s) equal to 0.92 for BASFI. [42] Limit of agreement for BASFI was +/- 1.4. Internal consistency reliability and construct validity of BASFI was deemed acceptable by the authors, but they also mentioned that random measurement error of BASFI was not negligible.[42]

In a review of AS instruments, Haywood et al. (2005) reported on 70 published instrument evaluations for BASFI following completion by patients with AS.[45] The authors comment that BASFI is one of three AS assessment instruments with the most extensive evidence for validity through comparison with instruments that measure similar or related constructs, and/or with measures of mobility.[45]

As mentioned for BASDAI, Pavy et al. investigated the MID of BASFI in 125 AS patients undergoing an intensive physiotherapy program.[46] Using that protocol and according to analyses of ROC curves, the MID was 7 mm or 17.5% for BASFI with a sensitivity equal to 0.60 and a specificity equal to 0.85. As shown by regression analysis, MID values were independent of the patients' baseline scores. These results were similar to a study by Kviatkovsky et al. that identified the minimally clinically important improvement to be 0.6 units on a 10 unit scale.[47]

Ankylosing Spondylitis Disease Activity Score

The ASDAS is a composite index to assess disease activity in rad-axSpA that includes the following parameters:[74]

- Total back pain (BASDAI Question 2)
- Patient Global Assessment of Disease Activity (individual ASAS domain)
- Peripheral pain/swelling (BASDAI Question 3)

- Duration of morning stiffness (BASDAI Question 6)
- CRP in mg/L (acute phase reactant).

The ASDAS CRP is calculated with the following equation: 0.121 × total back pain + 0.110 × Patient Global + 0.073 × peripheral pain/swelling + 0.058 × duration of morning stiffness + 0.579 × Ln(CRP+1).[74,75]

Four disease activity states have been defined by ASAS consensus:[52,76]

- ASDAS less than 1.3 defines inactive disease;
- ASDAS 1.3 or greater or less than 2.1 defines low disease activity;
- ASDAS 2.1 or greater or less than 3.5 defines high disease activity; and
- ASDAS greater than 3.5 defines very high disease activity.

The ASDAS is correlated with other measures including the BASDAI (concordance coefficients = 0.81[48]; 0.76[49]), ASAA HI (correlation coefficient = 0.56)[50], CRP (correlation coefficient = 0.79)[49], MRI SIJ inflammation (correlation coefficient = 0.46)[49] and MRI total inflammation scores (correlation coefficient = 0.34)[49], PGA (correlation coefficient = 0.71)[51] and Physician's Global Assessment (correlation coefficient = 0.65)[51].

Clinically important improvement based on the ASDAS is defined as change 1.1 or more units, and major improvement is defined as a change of 2.0 or more units or achieving the minimum ASDAS score of 0.6361 at post-baseline visit.[52] Conclusions by the ASAS consensus defined clinically important worsening as an increase in ASDAS of at least 0.9 points.[77]

The Spondyloarthritis Research Consortium of Canada MRI Index for Spine

The SPARCC MRI index for spine is an MRI-based scoring system that assesses the presence, three-dimensional extent, and signal intensity of active inflammatory lesions represented by bone marrow edema, in the spine of affected patients.[54] In the spine, the scoring system measures bone marrow edema in the bone marrow of discovertebral units, with each unit representing the region between two imaginary lines drawn through the middle of adjacent vertebrae.[54]

All 23 discovertebral units of the spine (from C2 to S1) were scored for bone marrow edema. A single unit has a scoring range of 0 to 18, bringing the maximum total score to 414, with higher scores reflecting worse disease.[53]

When assessing the six most affected units, the overall intra-observer reproducibility was excellent (ICC 0.93 to 0.98) for the three readers, and the mean percentage intra-observer concordance for the selection of affected discovertebral units was 78.8%, 87.9%, and 80.3% for the three readers.[53] The average ICC for the interobserver reproducibility of change (in MRI activity) scores was 0.82.[53] An MIC of 5.0 units for the SPARCC MRI score for the spine has been identified.[54]

The SPARCC MRI Score for Sacroiliac Joints

The SPARCC MRI score for SIJ is a scoring method based on the assessment of increased signal denoting bone marrow edema on T2-weighted STIR sequences. All signal changes within the iliac bone and sacrum up to the sacral foramina are scored on six consecutive slices through the SIJ. Each SIJ is divided into four quadrants: upper iliac, lower iliac, upper sacral, and lower sacral. The presence of increased signal on STIR in each of these four

quadrants was scored on a dichotomous basis, where one indicated on increased signal and zero indicated a normal signal. Total SIJ SPARCC scores can range from 0 to 72, with higher scores reflecting worse disease.[55]

The intra-observer reproducibility of the total score based on three readers was excellent (ICC = 0.90 to 0.98) while the ICC for change (in MRI activity) scores was lower (ICC 0.53).[55] In another study assessing inter-reader reliability, the SPARCC showed an ICC for the total status score of 0.55 and 0.52 for the change score.[56] The SPARCC MRI score for SIJ has been shown to be correlated with the ASDAS (pre-treatment, R2 = 0.2038).[2] A MIC of 2.5 units for the SPARCC MRI score for SIJ has been identified.[54]

Short Form 36-item Health Survey

The Short Form 36-item health survey (SF-36) is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[78] The SF-36 consists of eight health domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems.[79] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries, the PCS and the MCS. The PCS and MCS scores range from 0 to 100 with higher scores indicating better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a SD of 10 in the general US population. Therefore, all scores above or below 50 are considered to be above or below average for the general US population. Changes between 2.5 to 5.0 points in the physical and mental component scores of the SF-36 are considered to be clinically relevant, as are changes of 5 to 10 points in the domain scores.[58]

Turan and colleagues[80] reported that the SF-36 had a strong correlation with the Mander Enthesitis Index, and the BASDAI in 46 AS patients in an study conducted to investigate which parameters of disease activity, functional condition, and other clinical parameters had a greater effect on quality of life.[52] The internal consistency, construct validity and responsiveness to change of SF-36 has been assessed in two RCTs comparing adalimumab with placebo for the treatment of AS.[57] SF-36 had a good internal consistency (alpha = 0.74 to 0.92). At baseline, the SF-36 score correlated with AS quality of life scores (r = –0.36 to –0.66; P < 0.0001). SF-36 scores varied by indicators of clinical severity, with greater impairment observed for more severe degrees of clinical activity (P < 0.0001 for all).

European Quality of Life Scale

The European Quality of Life Scale is a generic quality of life instrument that may be applied to a wide range of health conditions and treatments.[81,82] The first of two parts of the EQ-5D-5L is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five possible levels of response (no problems, slight problems, moderate problems, severe problems, or extreme problems). Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights [81,82] The second part is a 20 cm EQ-VAS that has endpoints labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS which best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

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

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., the US or the UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported MIDs for this scale have ranged from 0.033 to 0.074.[60]

The validity of EQ-5D-5L was compared with the Short Form 6-dimensions (SF-6D) and the well-being rating scale in 254 AS patients (134 patients from an observational cohort and 120 from a RCT).[59] The median score was 0.69 (range; −0.08 to 1.00) for the EQ-5D-5L. Intraclass correlation coefficients were of moderate agreement (0.46 to 0.55). Instruments correlated equally with disease activity, functioning, and quality of life. Compared with EQ-5D and the well-being rating scale, SF-6D showed smaller average differences in utility between patients with better and worse disease. The smallest detectable differences in the control group of RCT were 0.36, 0.17, and 0.33 for EQ-5D-5L, SF-6D, and the rating scale, respectively. The ability to detect treatment effect in the intervention trial showed standardized effect sizes that were moderate for EQ-5D-5L and SF-6D (0.63 and 0.64) and low for the rating scale (0.23).[59]

Fatigue Severity Numeric Rating Scale

The Fatigue Severity NRS is a single-item, patient-reported, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no fatigue" and 10 representing "as bad as you can imagine."[10,11,83] Patients rated their fatigue ("feeling tired or worn out") by circling the one number that described their worst level of fatigue during the previous 24 hours.[10,11,83] Validity, reliability, and MID information was not identified for this outcome.

Work Productivity and Activity Impairment Questionnaire-Spondyloarthritis

The WPAI-SpA is a 6-item, patient-reported instrument designed to assess the impact of SpA on work productivity and activity impairment.[61] Four scores are derived: Percentage of Absenteeism, percentage of presenteeism, an overall work impairment score that combines absenteeism and presenteeism, and percentage of impairment in activities performed outside of work. Greater scores indicate greater impairment.[61]

Construct validity was demonstrated using median scores of other measures including the BASDAI and SF-36. Patients with AS of the worst severity (BASDAI > median) demonstrated significantly greater overall work impairment (difference = –14.5, $P < 0.001$), presenteeism (difference = –20.3, $P < 0.001$) and daily activity impairment (difference = –19.5, $P < 0.001$) based on the WPAI-SpA.[61] Similar results were found when patients with the worst health was defined by the median SF-36 PCS and MCS values.[61] No MID was identified in the literature.

Jenkins Sleep Evaluation Questionnaire

The JSEQ is a 4-item, patient-reported instrument designed to estimate sleep problems in clinical research. The JSEQ assesses the frequency of sleep disturbance in four categories:

- trouble falling asleep
- waking up several times during the night
- having trouble staying asleep (including waking up far too early)
- waking up after the usual amount of sleep feeling tired and worn out

Patients report the number of days they experience each of these problems in the past month on a six-point Likert scale ranging from zero, indicating "no days" to five, indicating "22 to 30 days." The total JSEQ score ranges from 0 to 20, with higher scores indicating greater sleep disturbance.[10,11,62]

The Turkish version of the JSEQ has good internal consistency (Cronbach's alpha = 0.83), was strongly correlated with the Pittsburgh Sleep Quality Index (rho = 0.75), and a moderate correlation with BASDAI (rho = 0.57) when assessed in patients with AS.[62] No MID was identified in the literature.

Quick Inventory of Depressive Symptomatology–Self Report 16 items

The QIDS-SR16 is a self-administered, 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Patients were asked to consider each statement as it relates to the way they have felt for the past seven days. There is a four-point scale for each item ranging from 0 to 3. The 16 items corresponding to nine depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. The domains assessed by the instrument are sad mood, concentration, self-criticism, suicidal ideation, interest, energy/fatigue, sleep disturbance (initial, middle, and late insomnia or hypersomnia), decrease/increase in appetite/weight, and psychomotor agitation/retardation.

Evidence of validation of the QIDS-SR16 in the AS patient population was not identified in the literature search. In a validation study based on patients with major depressive disorder, the QIDS-SR16 is highly correlated with the Hamilton Rating Scale for Depression (Cronbach's alpha = 0.86).[84] A MID was not identified in the literature.

mSASSS

In AS, radiographic findings include erosions, sclerosis, syndesmophyte formation, and ankylosis of the SIJs and vertebrae. MRI is used to visualize inflammation of the SIJs and the spine and for structural damage whereas ultrasound is used for enthesitis, synovitis, and occasionally boney changes. Conventional radiographs are also used in clinical practice. In general, progression in AS is slow. After two years up to 46% of AS patients showed progression of structural damage and after four years, the number increased to 56%. The ASAS recommends radiographs once every two years.[85]

MRI has an advantage over radiographs because it can detect abnormalities earlier than conventional radiographs and can also access the thoracic spine, which is frequently involved in AS and difficult to access with conventional radiographs. In research, MRI is the tool of choice for monitoring AS progression. [85]

For study purposes, several scoring systems have been developed. In AS, the mSASSS[33] is preferred by the ASAS for use in clinical trials.[85] The mSASSS score is obtained by assessing anterior sites of the lumbar (L1-L5) and cervical spine (C2-T1) on a lateral view. Each site gets a score from 0 (normal) to 3 (bridging syndesmophytes), which gives a total score range of 0 to 72. It does not score the thoracic spine.

A 48-week NSAID study of 57 patients was used to evaluate the validity of this scale. In this study, interobserver correlations of the lumbar and cervical spine scores were good ($r > 0.95$). This study concludes that the mSASSS is useful for assessing extensive radiographic damage in AS and it was reliable, detected changes over 48 weeks, and showed a satisfactory face and construct validity.[63]

Salaffi et al. compared the mSASSS scoring method with the BASRI using two observers on 95 AS patients.[86] mSASSS showed better intra- and interobserver correlation coefficients, a better correlation with BASFI and a more sensitive to change score than BASRI. Similarly, Ramiro et al. compared mSASSS with the Radiographic AS Spinal Score (RASSS) on 195 AS patients using two independent readers.[87] Results showed that RASSS was found to be frequently impossible to determine. The contribution of the vertebral corners in the RASSS were found to be negligible. Therefore, the use of mSASSS remains justified.

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