CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

Ixekizumab (Taltz)

(Eli Lilly Canada Inc.)

Indication: Treatment of adult patients with active psoriatic arthritis who have responded inadequately to, or are intolerant to one or more disease-modifying antirheumatic drugs (DMARD). Taltz can be used alone or in combination with a conventional DMARD (e.g., methotrexate).

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Table of Contents

Abbreviations 7
Executive Summary 8
Introduction 8
Results and Interpretation 9
Potential Place in Therapy 13
Conclusions 14
Introduction 17
Disease Prevalence and Incidence 17
Standards of Therapy 17
Drug 18
Objectives and Methods 22
Objectives 22
Methods 22
Results 24
Findings From the Literature 24
Included Studies 27
Exposure to Study Treatments 42
Critical Appraisal 42
Efficacy 44
Harms 52
Discussion 56
Summary of Available Evidence 56
Interpretation of Results 56
Conclusions 60
Appendix 1: Patient Input Summary 61
Appendix 2: Literature Search Strategy 64
Appendix 3: Excluded Studies 66
Appendix 4: Detailed Outcome Data 67
Appendix 5: Validity of Outcome Measures 75
Appendix 6: Summary of Findings of 52-Week Extension Period in Study SPIRIT-P1 84
Appendix 7: Summary of Indirect Comparisons 92
References 107

Tables

Table 1: Summary of Results (Intention-to-Treat Population) 15
Table 2: Key Characteristics of Ixekinumab, Secukinumab, Ustekinumab, Adalimumab, Certolizumab Pegol, Etanercept, Golimumab, Infliximab, and Apremilast 19
Table 3: Inclusion Criteria for the Systematic Review 22
Table 4: Details of Included Studies 25
Table 5: Summary of Baseline Characteristics (Intention-to-Treat Population) 31
Table 6: Patient Disposition 41
Table 7: Proportion of Patients With ACR20 Response at Week 12 and Week 24 (Using NRI, ITT Population, and Subgroups) 46
Table 8: Proportion of Patients Achieving Minimum Disease Activity at Week 24 (Using NRI, ITT Population) 47
Table 9: Change From Baseline in HAQ-DI Score at Week 24 (Using MMRM, ITT Population) 48
Table 10: Change From Baseline in PASI 75 at Week 12 and Week 24 (Using NRI, ITT Population With Baseline Psoriatic Lesions Involving ≥ 3% Body Surface Area) 50
Table 11: Improvement in LEI at Week 12 (SPIRIT-P1, Using MMRM) and Week 24 (SPIRIT-P2, Using NRI), [redacted] 51
Table 12: Change From Baseline in mTSS at Week 24 (Using MMRM, ITT Population) 52
Table 13: Harms 54
Table 14: Excluded Studies 66
Table 15: Proportion of Patients With ACR50/70 Response at Week 24 (Using NRI, ITT Population) 67
Table 16: Proportion of Patients Achieving PsARC Response at Week 24 (Using NRI, ITT Population) 68
Table 17: Change From Baseline in WPAI-SHP Scores at Week 24 (Using MMRM, ITT Population) 69
Table 18: Change From Baseline in Patient's Assessment of Pain-VAS Score at Week 24 (Using MMRM, ITT Population) 71
Table 19: Change From Baseline in Fatigue Severity Numeric Rating Scale at Week 24 (Using MMRM, ITT Population) 71
Table 20: Change From Baseline in SF-36 Physical and Mental Component Summaries at Week 24 (Using MMRM, ITT Population) 72
Table 21: Change From Baseline in EQ-5D-5L at Week 24 (Using MMRM, ITT Population) 72
Table 22: Change From Baseline in LDI-B at Week 24 (Using MMRM, ITT Population) 73
Table 23: Change From Baseline in BASDAI Score at Week 24 (Using MMRM, ITT Population) 74
Table 24: Characteristics of Outcome Measures in the Included Studies 75

Table 25: Baseline Characteristics (Extension-Period Population, at Week 0) 85
Table 26: Efficacy Results at Week 52 (Extension-Period Population) 88
Table 27: Adverse Events Reported During the Extension Period (EPP, Weeks 24 to 52)..... 90
Table 28: PICOS Criteria for Study Inclusion 92
Table 29: Network Meta-Analyses Performed by the Manufacturer 94
Table 30: Study Characteristics 95
Table 31: Available Outcome Data by Treatment..... 97
Table 32: [redacted] .. 99
Table 33: [redacted] 99
Table 34: [redacted] 99
Table 35: [redacted] 99
Table 36: [redacted] 100
Table 37: [redacted] 100
Table 38: [redacted] 101
Table 39: [redacted] 101
Table 40: [redacted] ... 101
Table 41: [redacted] 101
Table 42: [redacted] 102
Table 43: [redacted] 102
Table 44: [redacted] 103

Figures

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies 24
Figure 2: Study Design of SPIRIT-P1 28
Figure 3: Study Design of SPIRIT-P2 29
Figure 4: Evidence Network for ACR, Biologic-Naive Analysis (Base Case A) 97
Figure 5: Evidence Network for ACR, Biologic-Experienced Analysis (Base Case B) 97

Abbreviations

ACR	American College of Rheumatology
AE	adverse event
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
CRP	C-reactive protein
DMARD	disease-modifying antirheumatic drug
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels questionnaire
EPP	extension-period population
FSNRS	Fatigue Severity Numeric Rating Scale
HAQ-DI	Health Assessment Questionnaire–Disability Index
HRQoL	health-related quality of life
INRS	Itch Numeric Rating Scale
IL	interleukin
ITT	intention-to-treat population
LDI-B	Leeds Dactylitis Index–Basic
LEI	Leeds Enthesitis Index
MCID	minimal clinically important difference
MDA	minimum disease activity
mTSS	modified Total Sharp Score
NSAID	nonsteroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form (36) Health Survey
sPGA	static physician global assessment of psoriasis
SJC	swollen joint count
TJC	tender joint count
TNF	tumour necrosis factor
VAS	visual analogue scale
WDAE	withdrawal due to adverse event
WPAI-SHP	Work Productivity and Activity Impairment–Specific Health Problem

Drug	Ixekizumab (Taltz)
Indication	Treatment of adult patients with active psoriatic arthritis who have responded inadequately to, or are intolerant to one or more disease-modifying antirheumatic drugs (DMARD). Taltz can be used alone or in combination with a conventional DMARD (e.g., methotrexate).
Reimbursement Request	To be reimbursed for the treatment of adult patients with active psoriatic arthritis, used alone or in combination with methotrexate, when the response to previous conventional DMARDs therapy has been inadequate.
Dosage Form	Pre-filled syringe or autoinjector, 80 mg/mL
NOC Date	March 29, 2018
Manufacturer	Eli Lilly Canada Inc.

Executive Summary

Introduction

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. The patients suffer not only from the chronic inflammatory peripheral arthritis, but may also suffer from skin and nail disease, axial disease, dactylitis, and enthesitis. Diagnosis of PsA is based on clinical judgment: specific patterns of joint inflammation together with the absence of rheumatoid factor (91% to 94%) and the presence of psoriasis skin lesions. X-rays can aid diagnosis and show the extent and location of joint damage. The prevalence of PsA is approximately 1 to 2 per 1,000 in the general population, while among patients with psoriasis, the estimated prevalence of PsA varies considerably from 8% to > 40%. PsA results in significant disease burden, functional impairment, increased comorbidity and mortality, and poor health-related quality of life (HRQoL). Several drug classes are employed in the pharmacologic treatment of PsA, including nonsteroidal anti-inflammatory drugs (NSAIDs), conventional disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs, and the small-molecule inhibitor of phosphodiesterase 4 (i.e., apremilast). Conventional DMARDs such as methotrexate are recommended to be used as the primary treatment after NSAIDs in many instances. For patients in whom conventional DMARD treatment has been unsuccessful, biologic DMARDs (including tumour necrosis factor [TNF] inhibitors, interleukin [IL]-12/23 inhibitors and IL-17 inhibitors) or apremilast are strongly recommended. In the case of biologic drug treatment failure, due to either lack of efficacy or adverse events (AEs), switching either to an alternative biologic drug within a drug class or to a drug with a different mode of action is recommended in treatment guidelines.

Ixekizumab is a humanized IgG4 monoclonal antibody with neutralizing activity against IL-17A, a naturally occurring proinflammatory cytokine. It inhibits the release of proinflammatory cytokines and chemokines. A Notice of Compliance for Taltz, for the treatment of adult patients with active PsA who have responded inadequately to or are intolerant to one or more DMARDs, was granted by Health Canada on March 29, 2018.[1] Ixekizumab can be used alone or in combination with a conventional DMARD (e.g., methotrexate). Ixekizumab is also indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Tuberculosis infection should be ruled out before initiating treatment with ixekizumab. The Health Canada–recommended dose for adult PsA patients or PsA patients with coexistent mild plaque psoriasis is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg every 4 weeks. For PsA patients with coexistent moderate to severe plaque psoriasis, the dosing regimen for plaque psoriasis is to be used (160 mg by subcutaneous injection [two 80 mg injections] at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, and then 80 mg every four weeks).

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

Results and Interpretation

Included Studies

Two multi-centre, phase III, randomized, double-blind, placebo-controlled superiority trials, SPIRIT-P1 (N = 417) and SPIRIT-P2 (N = 363), met the inclusion criteria for this systematic review. The studies included adult patients with an established diagnosis of PsA. Patients in SPIRIT-P1 were biologic DMARD-naive, while those in SPIRIT-P2 were conventional DMARD-experienced and had received previous TNF inhibitor therapy, but the TNF inhibitor was discontinued due to inadequate response or intolerance to the treatment. Efficacy and safety of ixekizumab 80 mg every two weeks and ixekizumab 80 mg every four weeks were compared with placebo in both studies. In SPIRIT-P1, eligible participants were randomized at a 1:1:1:1 ratio to one of four treatment groups: ixekizumab 80 mg every two weeks (with a starting dose of 160 mg at week 0), ixekizumab 80 mg every four weeks (with a starting dose of 160 mg at week 0), adalimumab 40 mg every two weeks, and placebo. Adalimumab 40 mg was compared with placebo in this study for the purpose of providing internal evidence of assay sensitivity. At week 16, inadequate responders receiving adalimumab or placebo were re-randomized to either ixekizumab 80 mg every two weeks or ixekizumab 80 mg every four weeks and received rescue therapy; inadequate responders who were already assigned to ixekizumab at baseline continued their ixekizumab and received rescue therapy after week 16. Rescue therapy referred to modifications made to the patient's background therapy, e.g., conventional DMARDs, NSAIDs, analgesics, and/or corticosteroids. In SPIRIT-P2, eligible participants were randomized at a 1:1:1 ratio to one of three treatment groups: ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo (with starting doses of 160 mg at week 0 for those randomized to ixekizumab). Similar to SPIRIT-P1, inadequate responders receiving placebo were re-randomized to either ixekizumab 80 mg every two weeks or 80 mg every four weeks and received rescue therapy at week 16; inadequate responders receiving either ixekizumab dosage at week 16 continued their ixekizumab and received rescue therapy. In both studies, responders at week 16 in all treatment groups remained on their initially assigned treatment until week 24. It is noteworthy that the doses of ixekizumab in the every-two-weeks arms of SPIRIT-P1 and SPIRIT-P2 are not consistent with the Health Canada–recommended dose. The Health Canada–approved product monograph for ixekizumab recommends that patients with PsA with coexistent moderate to severe plaque psoriasis receive the dosing regimen for plaque psoriasis, which is 160 mg at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, and then 80 mg every four weeks. Thus, continuance of the ixekizumab every-two-weeks dosing beyond week 12 in SPIRIT-P1 and SPIRIT-P2 is inconsistent with Health Canada–recommended dosing.

The primary efficacy end point in SPIRIT-P1 and SPIRIT-P2 was the proportion of patients in each treatment group who achieved 20% American College of Rheumatology response (ACR20, defined as an improvement of at least 20% in both swollen and tender joint counts and at least three of five additional disease criteria) at week 24. Both studies had an appropriate randomization strategy, with generally similar treatment groups at baseline. In SPIRIT-P1 and SPIRIT-P2, 39.6% and 47.5% of patients in the placebo groups, respectively, discontinued the originally assigned treatment before week 24 (either due to early escape at week 16 or because of treatment discontinuation). This means that a substantial proportion of the outcome data at week 24 had to be imputed based on an intention-to-treat population (ITT) analysis. Therefore, there is a high degree of uncertainty with respect to the study findings for the primary end point. The primary and major secondary efficacy outcomes were assessed using a hierarchical testing procedure to control the familywise type I error rate to ≤ 5%. The major secondary efficacy outcomes included change from baseline to week 24 in Health Assessment Questionnaire–Disability Index (HAQ-DI) (both studies), change from baseline to week 24 in the modified Total Sharp Score (mTSS) (SPIRIT-P1 only), proportion of patients achieving ACR20 response at week 12 (both studies), proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 response at week 12 (both studies), proportion of patients achieving minimum disease activity (MDA) criteria at week 24 (SPIRIT-P2 only), change from baseline to week 12 in the Leeds Enthesitis Index (LEI) (SPIRIT-P1 only), proportion of patients achieving complete resolution in enthesitis as assessed by the LEI at week 24 (SPIRIT-P2 only), and change from baseline to week 12 in Itch Numeric Rating Scale (INRS) (SPIRIT-P1 only).

Efficacy

Results of the primary outcome, major secondary efficacy outcomes, and those considered important by patient groups are reported. Results of any other efficacy outcomes that were not included in the multiplicity-controlled analyses are described, however they are considered inconclusive because of the potential for inflated type I error.

Clinical Responses to Psoriatic Arthritis Symptoms

For the primary efficacy outcome, ACR20 response at week 24, both ixekizumab treatment groups were statistically significantly superior to placebo for ACR20 response: in SPIRIT-P1, 62.1%, 57.9%, and 30.2% of patients treated with ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo achieved ACR20 response, respectively; in SPIRIT-P2, 48.0%, 53.3%, and 19.5% of patients treated with ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo achieved ACR20 response, respectively; all *P* values for ixekizumab versus placebo < 0.001. The findings for ACR20 responses also favoured the two ixekizumab groups at week 12: in SPIRIT-P1, 60.2%, 57.0%, and 31.1% of patients treated with ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo achieved ACR20 response, respectively; in SPIRIT-P2, 48.0%, 50.0%, and 22.0% of patients treated with ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo achieved ACR20 response, respectively; all *P* values for ixekizumab versus placebo < 0.001. In SPIRIT-P2, results of the subgroup analyses by disease severity at baseline were in line with results from the overall population for ACR20 response; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered as exploratory in nature because of the potential for inflated type I error. The clinical expert consulted for this review noted that the differences in ACR20 responses compared with placebo were clinically meaningful. For clinical responses measured with the MDA criteria, patients treated with the

two ixekizumab dosage groups had higher response rates compared with placebo at week 24 in SPIRIT-P1; the between-group differences were statistically significant in SPIRIT-P2 (23.6% for ixekizumab 80 mg every two weeks, 27.9% for ixekizumab 80 mg every four weeks, and 3.4% for placebo at week 24; both *P* values < 0.001).

Measurement of Function and Disability

The improvement in physical function at week 24 as measured with HAQ-DI was statistically and clinically significant. The differences in change from baseline between ixekizumab 80 mg every two weeks and placebo and between ixekizumab 80 mg every four weeks and placebo were −0.3 and −0.4, respectively, in SPIRIT-P2 (both *P* values < 0.001) and −0.32 and −0.26, respectively, in SPIRIT-P1 (both *P* values < 0.001).

Work productivity was measured by the Work Prodictivity and Activity Impairment–Specific Health Problem (WPAI-SHP) questionnaire in a portion of study participants in SPIRIT-P1 and SPIRIT-P2. Numerically greater reductions in work or activity impairment due to disease were observed for the ixekizumab groups compared with placebo at week 24. This was identified as an important outcome by the patient groups, but in both SPIRIT-P1 and SPIRIT-P2 it was an exploratory variable and was not included in the multiplicity-controlled analyses. Therefore, the results should be interpreted with caution.

Measurement of Psoriatic Arthritis Symptoms

PsA symptoms such as fatigue and arthritis pain were reported in both studies. At week 24, greater improvements in mean score change for these patient-reported efficacy outcomes were observed for patients treated with ixekizumab compared with those in the placebo group. The outcome measures of patient's assessment of pain and Fatigue Severity Numeric Rating Scale (FSNRS) were not part of the hierarchical analysis plan and therefore were not adjusted for multiple comparisons; hence, the level of significance is inflated and results should be interpreted with caution.

Health-Related Quality of Life

HRQoL was measured by the Short Form (36) Health Survey (SF-36) in SPIRIT-P1 and SPIRIT-P2. Greater improvements were observed in the physical component summary scores of the SF-36 among both ixekizumab treatment groups compared with those in the placebo group at week 24 in both SPIRIT-P1 and SPIRIT-P2. Improvements were also observed in the mental component summary scores of the SF-36 between the ixekizumab treatment regimens and placebo in both SPIRIT-P1 and SPIRIT-P2; however, the magnitudes of the changes were smaller than those for the physical component summary. The results suggested that treatment with ixekizumab was associated with improved HRQoL, in particular for the patient's physical well-being domain. Even though HRQoL was identified as an important outcome by the patient groups, the outcome measures of physical and mental component summaries of the SF-36 were not part of the hierarchical analysis plan and therefore were not adjusted for multiple comparisons; hence, the level of significance is inflated and results should be interpreted with caution.

Measurement of Skin Disease and Other Musculoskeletal Disease

Only patients with a body surface area involvement ≥ 3% at baseline had a PASI assessment. In SPIRIT-P1, the proportion of patients achieving PASI 75 response in each of the ixekizumab treatment groups compared with placebo was statistically significantly higher at week 12: 69.5% for ixekizumab 80 mg every two weeks, 75.3% for ixekizumab 80 mg every four weeks, and 7.5% for placebo (both *P* values < 0.001). In SPIRIT-P2, the

proportion of patients achieving PASI 75 response in each of the ixekizumab treatment groups compared with placebo was also statistically significantly higher at week 12: 61.8% for ixekizumab 80 mg every two weeks, 57.4% for ixekizumab 80 mg every four weeks, and 10.4% for placebo (both *P* values < 0.001). The clinical expert consulted for this review indicated that the between-group differences in PASI 75 were considered clinically relevant.

For patients with enthesitis at baseline, improvement in enthesitis (assessed with LEI) was not statistically significant for all comparisons between ixekizumab groups and placebo at week 24 in SPIRIT-P1 and SPIRIT-P2.

Radiographic Changes

Radiographic change was assessed only in SPIRIT-P1, using mTSS. The between-treatment difference in mean change from baseline in mTSS was −0.41 for ixekizumab 80 mg every two weeks versus placebo (*P* < 0.001) and −0.33 for ixekizumab 80 mg every four weeks versus placebo (*P* = 0.004) at week 24. The clinical expert consulted for this review noted that it is difficult to observe meaningful radiographic changes within 24 weeks in the study population.

Findings From Extension Study

Results of the extension phase of SPIRIT-P1 suggested that the improvements in clinical and patient-reported outcomes observed at week 24 were maintained throughout the 52-week extension period, in both ixekizumab every two weeks and ixekizumab every four weeks dosing regimens. Patients re-randomized to ixekizumab every four weeks or ixekizumab every two weeks from placebo or adalimumab also showed improvements of clinical and patient-reported outcomes at week 52 that were similar to the efficacy achieved by the groups that remained on ixekizumab from baseline to week 52. However, the longer term phases of the study had limited clinical value for the following reasons: there were no control groups, and the background therapies were allowed to be modified. As a result, it is impossible to disentangle the drug effect from the changes in the background therapies on the reported outcomes. Furthermore, given that all patients were aware that they were receiving ixekizumab, results for patient-reported and subjective outcomes may be subject to bias.

Findings From Indirect Treatment Comparison

In the absence of sufficient head-to-head trial data comparing ixekizumab with other biologic drugs to treat PsA, the manufacturer conducted an indirect treatment comparison analysis based on a systematic review of randomized controlled trials and compared the efficacy and safety of ixekizumab with adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab. Efficacy (based on ACR responses, Psoriatic Arthritis Response Criteria [PsARC], HAQ-DI, and PASI scores) and safety outcomes were evaluated, but no HRQoL data were assessed. There was insufficient information about the individual trials, limiting the ability to assess clinical heterogeneity of the included studies. Based on data from 12 weeks (up to 16 weeks), analyses in biologic-naive populations showed that ixekizumab tended to perform better in the PASI analyses and not as favourably in the ACR, PsARC, and HAQ-DI analyses relative to other biologics. Analyses in biologic-experienced populations showed no difference between ixekizumab and other biologic drugs for efficacy outcomes.

Harms

By week 24, the frequency of serious adverse events (SAEs) was low and isolated cases of SAEs were reported for the ixekizumab and the placebo treatment groups. In SPIRIT-P1, the rates of SAE were 2.9%, 5.6% and 1.9% for ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo, respectively. In SPIRIT-P2, the rates of SAE were 6.5%, 2.5%, and 3.4% for ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo, respectively. Withdrawals due to adverse events (WDAEs) were also low in all treatment groups. In SPIRIT-P1, the rates of WDAEs were 3.9%, 1.9%, and 1.9% for ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo, respectively. In SPIRIT-P2, the rates of WDAEs were 6.5%, 4.1%, and 5.1% for ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo, respectively. Patients treated with either ixekizumab therapy were associated with higher risk of AEs compared with those in the placebo group, with the most common AEs being infections, hypersensitivity, and injection site reactions. No death was reported in any of the treatment groups included in this review.

The safety profile of ixekizumab over 52 weeks was consistent with that observed during the 24-week double-blind period, with no unexpected safety signals reported. Findings from the indirect comparison submitted by the manufacturer suggested that there were no differences in likelihood of AEs or SAEs between ixekizumab and other biologics in the mixed biologic-naive and biologic-experienced population based on data from 12 weeks (up to 16 weeks).

Potential Place in Therapy[1]

At this date, ixekizumab will be the second IL-17 inhibitor for treatment of psoriasis and PsA. The following comments are specific to PsA only.

Ixekizumab joins a crowded biologic marketplace in PsA. It will compete with the five original TNF inhibitors, at least two biosimilar TNF inhibitors, apremilast, and the IL-17 inhibitor secukinumab. Shortly, the IL-17 inhibitors gesulkumab and brodalumab may join the marketplace, and in the near future one or more Janus kinase inhibitors. Informal comparisons of all the drugs available to treat PsA do not discern obvious differences in efficacy, substantiated by a formal network meta-analysis provided by the manufacturer.[2] Therefore, it is difficult to say that there is an unmet need for ixekizumab in PsA. Further, there is no reason to think that ixekizumab is likely to be more effective for PsA patients with enthesitis, dactylitis, sacroiliitis, or spondylitis.

Compared with TNF inhibitors (except etanercept), IL-17 inhibitors are at a disadvantage in the treatment of PsA patients who have a history of uveitis or inflammatory bowel disease. The role of IL-17 inhibitors in precipitating inflammatory bowel disease or uveitis in patients without a history remains a topic of interest to be fully defined. Measurement of fecal calprotectin, traditional colonoscopy, and video capsule endoscopy to identify patients in whom *not* to use an IL-17 inhibitor are under consideration, but are costly and have some risk. Based on these concerns, TNF inhibitors will probably be the first-line therapy for PsA patients.

Ixekizumab may have an advantage over secukinumab in PsA patients who have failed or have been intolerant to a TNF inhibitor. There is no direct comparison. Secukinumab was not assessed in a study dedicated to patients who were TNF exposed, although in the

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

FUTURE-2 study of secukinumab administered by the subcutaneous route, 35% of patients had been exposed to a TNF inhibitor. The 150 mg dose of secukinumab was barely effective. The 300 mg dose was associated with an ACR20 response of 45.5% compared with 58.2% in TNF-naive patients. This magnitude of diminished activity is seen commonly in TNF inadequate responders. In contrast, when ixekizumab was studied in TNF inadequate responders, there was not a large drop in the ACR20 response in the lower dose (administered every four weeks), which suggests a benefit for ixekizumab based on both efficacy and cost.

Conclusions

Based on two double-blind randomized controlled trials (SPIRIT-P1 and SPIRIT-P2) in adult patients with active PsA and either biologics-naive or TNF inhibitor–experienced respectively, treatment with ixekizumab 80 mg every two weeks and ixekizumab 80 mg every four weeks is associated with statistically significant and clinically meaningful improvements in the primary efficacy outcome: ACR20 response at week 12 and week 24. Statistically significant changes were also reported for other outcomes related to the clinical response, such as MDA at week 24 favouring treatment with ixekizumab. Greater improvement was seen in quality of life, physical function, fatigue, and pain at week 24 in the ixekizumab groups compared with the placebo group. Except for ACR20, MDA, HAQ-DI, radiographic changes measured with mTSS, change in skin disease measured with PASI, and change in enthesitis measured with LEI, adjustment for multiplicity was not done for all other outcomes; hence, results for these outcomes are considered inconclusive. In both studies, a very large proportion of placebo patients discontinued randomized treatment before week 24 (either due to early escape or because of treatment discontinuation), so claims of efficacy at week 24 are uncertain.

Overall, the incidence of treatment-emergent AEs was higher than with placebo for both ixekizumab groups in patients who were biologic-naive or TNF inibitor–experienced. Infections, hypersensitivity and injection site reactions were common AEs. Moreover, PsA is a chronic condition that will be treated over a lifetime, and therefore a 24-week controlled trial is a short duration to evaluate harms.

Findings of the extension phase of SPIRIT-P1 suggested that the improvements in clinical and patient-reported outcomes observed at week 24 were maintained throughout the 52-week extension period. The safety profile of ixekizumab over 52 weeks was consistent with that observed during the 24-week double-blind period, with no unexpected safety signals reported. Based on the short-term data provided in a manufacturer-submitted network meta-analysis, in biologic-naive populations, ixekizumab tended to perform better in the PASI analyses and not as favourably in the ACR, PsARC, and HAQ-DI analyses relative to other biologics. Analyses in biologic-experienced populations showed no difference between ixekizumab and other biologic drugs for efficacy outcomes. In addition, there were no differences in likelihood of AEs or SAEs between ixekizumab and other biologics in the mixed biologic-naive and biologic-experienced population.

Table 1: Summary of Results (Intention-to-Treat Population)

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
EFFICACY							
% of Patients Who Achieved ACR20 at Week 12							
n (%)	62 (60.2)	61 (57.0)	52 (51.5)	33 (31.1)	59 (48.0)	61 (50.0)	26 (22.0)
Odds ratio (95% CI vs. PL)	3.32 (1.88 to 5.89)	2.92 (1.66 to 5.14)	2.36 (1.34 to 4.17)		3.28 (1.85 to 5.79)	3.56 (2.02 to 6.26)	
P value vs. PL	< 0.001	< 0.001	0.003		< 0.001	< 0.001	
% of Patients Who Achieved ACR20 at Week 24							
n (%)	64 (62.1)	62 (57.9)	58 (57.4)	32 (30.2)	59 (48.0)	65 (53.3)	23 (19.5)
Odds ratio (95% CI vs. PL)	3.88 (2.18 to 6.91)	3.24 (1.84 to 5.72)	3.16 (1.78 to 5.60)		3.79 (2.12 to 6.78)	4.74 (2.65 to 8.48)	
P value vs. PL	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	
% of Patients Who Achieved MDA at Week 24							
n (%)	42 (40.8)	32 (29.9)	32 (31.7)	16 (15.1)	29 (23.6)	34 (27.9)	4 (3.4)
Odds ratio (95% CI vs. PL)	3.93 (2.03 to 7.64)	2.42 (1.23 to 4.75)	2.61 (1.32 to 5.14)		8.89 (3.01 to 26.27)	11.58 (3.91 to 34.30)	
P value vs. PL	< 0.001	0.010	0.006		< 0.001	< 0.001	
Change From Baseline in HAQ-DI Score at Week 24							
n	84	83	85	63	91	95	64
LS mean difference (95% CI vs. PL)	−0.32 (−0.46 to −0.18)	−0.26 (−0.40 to −0.12)	−0.19 (−0.33 to −0.05)		−0.3 (−0.4 to −0.1)	−0.4 (−0.5 to −0.3)	
P value vs. PL	< 0.001	< 0.001	0.007		< 0.001	< 0.001	
% of Patients Who Achieved PASI 75 at Week 12							
n/N (%)	41/59 (69.5)	55/73 (75.3)	23/68 (33.8)	5/67 (7.5)	42/68 (61.8)	39/68 (57.4)	7/67 (10.4)
Odds ratio (95% CI vs. PL)	29.06 (9.87 to 85.53)	38.80 (13.36 to 112.72)	6.29 (2.20 to 17.95)		16.67 (6.28 to 44.24)	14.03 (5.28 to 37.27)	
P value vs. PL	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	
Improvement in Baseline Enthesitis	**Change From Baseline at Week 12**				**% of Complete Resolution at Week 24**		
	LS mean Δ (SE): −1.5 (0.24)	LS mean Δ (SE): −0.9 (0.21)	LS mean Δ (SE): −0.8 (0.24)	LS mean Δ (SE): −0.8 (0.24)	n/N (%): 30/95 (31.6)	n/N (%): 27/89 (30.3)	n/N (%): 18/82 (22.0)
	LS mean diff (95% CI vs. PL): −0.7 (−1.32 to −0.04)	LS mean diff (95% CI vs. PL): 0 (−0.65 to 0.56)	LS mean diff (95% CI vs. PL): 0 (−0.59 to 0.69)		Odds ratio (95% CI vs. PL): 1.68 (0.84 to 3.38)	Odds ratio (95% CI vs. PL): 1.55 (0.77 to 3.13)	
	P = 0.038	*P* = 0.884	*P* = 0.879		*P* = 0.142	*P* = 0.218	

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
Change From Baseline in mTSS at Week 24							
n	85	82	83	61	NR		
LS mean difference (95% CI vs. PL)	−0.41 (−0.63 to −0.19)	−0.33 (−0.55 to −0.10)	−0.39 (−0.61 to −0.16)				
P value vs. PL	< 0.001	0.004	< 0.001				
HARMS							
Patients With ≥ 1 AE, n (%)	67 (65.7)	71 (66.4)	65 (64.4)	50 (47.2)	90 (73.2)	83 (68.0)	76 (64.4)
Patients With ≥ 1 SAE, n (%)	3 (2.9)	6 (5.6)	5 (5.0)	2 (1.9)	8 (6.5)	3 (2.5)	4 (3.4)
Patients With ≥ 1 WDAE, n (%)	4 (3.9)	2 (1.9)	2 (2.0)	2 (1.9)	8 (6.5)	5 (4.1)	6 (5.1)
Death	0	0	0	0	0	0	0

ACR20 = American College of Rheumatology 20% response; ADA = adalimumab; AE = adverse event; CI = confidence interval; HAQ-DI = Health Assessment Questionnaire–Disability Index; ITT = intention-to-treat; IXE = ixekizumab; LS = least squares; MDA = minimum disease activity; MMRM = mixed-effects model for repeated measures; mTSS = modified Total Sharp Score; NR = not reported; PASI = Psoriasis Area and Severity Index; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SAE = serious adverse event; SE = standard error; vs. = versus; WDAE = withdrawal due to adverse event.

[a] In Study SPIRIT-P1, odds ratio, CI, and *P* value are from a logistic regression model using Wald test with treatment, region, and baseline conventional DMARD experience as factors; LS mean, LS mean difference, CI and *P* value are from an MMRM with treatment, region, baseline conventional DMARD experience, visit, and treatment-by-visit interaction as fixed factors, and baseline as covariate.

[b] In Study SPIRIT-P2, odds ratio, CI, and *P* value are from a logistic regression model using Wald test with treatment, geographic region, and TNF inhibitor experience in the model; LS mean, SE, 95% CI, and *P* value are based on an MMRM model that includes treatment, visit, geographic region, TNF inhibitor experience (inadequate responder to 1 TNF inhibitor, inadequate responder to 2 TNF inhibitors, or intolerance to a TNF inhibitor), treatment-by-visit interaction, geographic region–by-visit interaction, and TNF inhibitor experience–by-visit interaction as well as the continuous, fixed covariates of baseline value and baseline value–by-visit interaction, with variance-covariance structure set to unstructured (for change from baseline).

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Introduction

Disease Prevalence and Incidence

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis.[5] It is a heterogeneous disease associated with multiple and variable clinical features. The patients suffer not only from the chronic inflammatory peripheral arthritis but may also suffer from skin and nail disease, axial disease, dactylitis, and enthesitis.[6,7] Diagnosis of PsA is based on clinical judgment: specific patterns of joint inflammation together with the absence of rheumatoid factor (91% to 94%) and the presence of psoriasis skin lesions. There are no tests for particular biomarkers to confirm the diagnosis, but X-rays can aid diagnosis and show the extent and location of joint damage.[8] The prevalence of PsA is approximately 1 to 2 per 1,000 in the general population, while among patients with psoriasis, the estimated prevalence of PsA varies considerably from 8% to > 40%.[5,9] PsA results in significant disease burden, functional impairment, increased comorbidity and mortality, and poor health-related quality of life (HRQoL).[7,10,11]

Standards of Therapy

Treatment goals for patients with PsA include:

- to achieve the lowest possible level of disease activity in all domains of disease
- to optimize functional status, improve quality of life and well-being, and prevent structural damage to the greatest extent possible
- to avoid or minimize complications, both from untreated active disease and from therapy.[12]

This disease impacts on more than just the joints of the patient; therefore, treatment effects need to be assessed in different areas, such as the musculoskeletal condition and the skin condition. Several drug classes are employed in the pharmacologic treatment of PsA, including nonsteroidal anti-inflammatory drugs (NSAIDs), conventional disease-modifying antirheumatic drugs (DMARDs, i.e., methotrexate, sulfasalazine, and leflunamide), biologic DMARDs (i.e., tumour necrosis factor alpha [TNF] inhibitors, and interleukin [IL] inhibitors), and the small-molecule inhibitor of phosphodiesterase 4 (i.e., apremilast).

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for PsA indicate that despite the lack of evidence from randomized controlled trials, conventional DMARDs such as methotrexate are recommended to be used as the primary treatment after NSAIDs in many instances. These recommendations were based on data from observational studies, the low costs and universal access of the conventional DMARDs, and the lack of evidence that a short time delay in the introduction of more effective therapies would impact long-term function and quality of life.[12,13] In recent years, the clinical benefits of biologic DMARDs such as TNF inhibitors and IL inhibitors have been confirmed in numerous clinical trials, and no major safety signals are identified.[14] The Group's recommendations also indicate that for patients in whom conventional DMARD treatment has been unsuccessful, biologic DMARDs (including TNF inhibitors and IL-12/23 inhibitors) or apremilast are strongly recommended; in addition, a conditional recommendation was given for IL-17 inhibitors (phase III data for IL-17 inhibitors were available only in abstract form at the time of guideline development). In the case of biologic drug treatment failure, due to either lack of efficacy or adverse events (AEs), switching either

to an alternative biologic drug within a drug class or to a drug with a different mode of action was recommeded in the Group's guideline.[12,15]

Although there is no Canadian treatment guideline aimed specifically at management of PsA, the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada Treatment Recommendations for the Management of Spondyloarthritis[16] include the following recommendations:

- Methotrexate, sulfasalazine, and leflunomide may be considered in patients with peripheral spondyloarthritis; however these treatments have only minimal to moderate evidence of efficacy.
- Combination therapy with DMARDs should be considered in peripheral spondyloarthritis, particularly in patients with moderate to high disease activity, poor prognostic features, or recent-onset disease, and combination therapy should also be considered in patients with inadequate response to monotherapy.
- TNF inhibitors should be offered to those with persistent inflammation despite a trial of NSAIDs and one conventional DMARD in patients with predominantly peripheral spondyloarthritis.
- TNF inhibitors should be offered to patients with refractory enthesitis or dactylitis accompanied by persistent inflammation.

The recommendations on the use of conventional DMARDs and TNF inhibitors in peripheral spondyloarthritis were based on PsA data.

Drug

Ixekizumab is a humanized IgG4 monoclonal antibody with neutralizing activity against IL-17A, a naturally occurring proinflammatory cytokine. Elevated levels of IL-17A have been implicated in the pathogenesis of a variety of autoimmune diseases. Ixekizumab inhibits the release of proinflammatory cytokines and chemokines.[17] A Notice of Compliance for Taltz, for the treatment of adult patients with active PsA who have responded inadequately to or are intolerant to one or more DMARDs, was granted by Health Canada on March 29, 2018.[1] Ixekizumab can be used alone or in combination with a conventional DMARD (e.g., methotrexate).[17] Ixekizumab is also indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[17] Tuberculosis infection should be ruled out before initiating treatment with ixekizumab. The Health Canada–recommended dose for adult PsA patients or PsA patients with coexistent mild plaque psoriasis is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg every four weeks. For PsA patients with coexistent moderate to severe plaque psoriasis, the dosing regimen for plaque psoriasis is to be used (160 mg by subcutaneous injection [two 80 mg injections] at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, and then 80 mg every four weeks).[17]

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

Table 2: Key Characteristics of Ixekinumab, Secukinumab, Ustekinumab, Adalimumab, Certolizumab Pegol, Etanercept, Golimumab, Infliximab, and Apremilast

	Ixekinumab	Secukinumab	Ustekinumab	Adalimumab	Certolizumab Pegol	Etanercept	Golimumab	Infliximab	Apremilast
Mechanism of Action	Humanized IgG4 monoclonal antibody that selectively binds and neutralizes the proinflammatory cytokine IL-17A	Fully human IgG1k monoclonal antibody that selectively binds and neutralizes the proinflammatory cytokine IL-17A	Fully human IgG1k monoclonal antibody that inhibits the bioactivity of IL-12 and IL-23	TNF inhibitor; recombinant human monoclonal antibody	TNF inhibitor; recombinant, humanized antibody Fab' fragment	TNF inhibitor; fusion protein	TNF inhibitor; human monoclonal antibody	TNF inhibitor; chimeric monoclonal antibody	PDE-4 inhibitor
Indication[a]	Treatment of adult patients with active PsA who have responded inadequately to or are intolerant to one or more DMARDs. It can be used alone or in combination with a conventional DMARD, e.g., MTX.	Treatment of adult patients with active PsA when the response to previous DMARD therapy has been inadequate. It can be used alone or in combination with MTX.	Treatment of adult patients with active PsA. It can be used alone or in combination with MTX.	Reducing the signs and symptoms of active arthritis and inhibiting the progression of structural damage and improving the physical function in adult PsA patients. It can be used in combination with MTX in patients who do not respond adequately to MTX alone.	Reducing signs and symptoms and inhibiting the progression of structural damage, as assessed by X-ray, in adult patients with moderately to severely active PsA who have failed one or more DMARDs. It can be used alone or in combination with MTX.	Reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in adult patients with PsA. It can be used in combination with MTX in adult patients who do not respond adequately to MTX alone.	Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active PsA. It can be used in combination with MTX in patients who do not respond adequately to MTX alone.	Reduction of signs and symptoms, induction of major clinical response, inhibition of the progression of structural damage of active arthritis, and improvement in physical function in patients with PsA.	Treatment of active PsA in adult patients who have had an inadequate response, intolerance, or contraindication to a prior DMARD.

	Ixekinumab	Secukinumab	Ustekinumab	Adalimumab	Certolizumab Pegol	Etanercept	Golimumab	Infliximab	Apremilast
Route of Administration	SC			SC				IV	oral
Recommended Dose	For PsA or PsA with coexistent mild PP: 80 mg × 2 at week 0, followed by 80 mg q.4.w. For PsA with coexistent moderate to severe PP: 80 mg × 2 at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg q.4.w.	150 mg at weeks 0, 1, 2, and 3, followed by monthly maintenance dosing starting at week 4. For PsA patients with coexistent moderate to severe PP: 300 mg at weeks 0, 1, 2, and 3, followed by monthly maintenance dosing starting at week 4 Patients with PsA who are anti-TNF alpha inadequate responders and continue to have active PsA: 300 mg dose should be considered	45 mg administered at weeks 0 and 4, then every 12 weeks thereafter Alternately, 90 mg may be used in patients with a body weight > 100 kg	40 mg administered every other week	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 SC q.w. in 1 injection, or as SC 25 mg × 2 on the same day q.w. or 3 or 4 days apart	50 mg SC once a month on same date each month	5 mg/kg given as an IV infusion followed with additional similar doses at 2 and 6 weeks after the first infusion, then q.8.w. thereafter	30 mg b.i.d.

	Ixekinumab	Secukinumab	Ustekinumab	Adalimumab	Certolizumab Pegol	Etanercept	Golimumab	Infliximab	Apremilast
Serious Side Effects / Safety Issues	Infections (tuberculosis and serious infection in particular), hypersensitivity reactions, and inflammatory bowel disease (exacerbations or new onset)		Infections and reactivate latent infections, injection site reactions, malignancies, RPLS	Serious infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic infections Malignancies Hypersensitivity reactions (allergic reactions and injection site reactions)					Clinically significant: weight loss Common adverse events: nausea and diarrhea

b.i.d. = twice a day; DMARD = disease-modifying antirheumatic drug; IgG = immunoglobin G; IL = interleukin; IV = intravenous injection; MTX = methotrexate; PDE-4 = phosphodiesterase 4; PP = plaque psoriasis; PsA = psoriatic arthritis; q.w. = once weekly; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.8.w. = every 8 weeks; RPLS = reversible posterior leukoencephalopathy syndrome; SC = subcutaneous injection; TNF = tumour necrosis factor.
[a] Health Canada indication.
Source: Health Canada product monographs.[17-24]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of ixekizumab subcutaneous injection (Taltz) at recommended doses for the treatment of active PsA in adult patients.

Methods

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

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adult patients with active PsA who have responded inadequately to or are intolerant to one or more DMARDs; used alone or in combination with a conventional DMARD (e.g., MTX) **Subgroups of interest:** • Severity of baseline PsA (e.g., DAS28, HAQ-DI, tender joint count, swollen joint count) • Biologics-naive vs. biologics-experienced • Concomitant DMARD vs. no concomitant DMARD
Intervention	Ixekizumab alone or in combination with a conventional DMARD at the Health Canada–approved dosing regimen: • PsA with no or mild coexistent plaque psoriasis: 160 mg SC at week 0, followed by 80 mg every 4 weeks • PsA with coexistent moderate to severe plaque psoriasis: 160 mg SC at week 0, followed by 80 mg every 2 weeks until week 12, then 80 mg SC every 4 weeks
Comparators	Individual or combination therapy with: • Biologic response modifiers (e.g., infliximab, etanercept, adalimumab, golimumab, certolizumab pegol, ustekinumab and secukinumab) • Small-molecule inhibitor of phosphodiesterase 4 (e.g., apremilast) • DMARDs including MTX
Outcomes	**Key efficacy outcomes:** • Clinical response in PsA symptoms (e.g., ACR20/50/70, DAS28, PsARC, MDA) • Measure of function and disability[a] (e.g., HAQ-DI and work productivity) • Measure of PsA symptoms[a] (e.g., pain and fatigue) • Health-related quality of life[a] (e.g., SF-36 and PsAQoL) **Other efficacy outcomes:** • Measure of skin disease (e.g., PASI 75/90) • Measure of other musculoskeletal disease (e.g., dactylitis, enthesitis, axial arthritis) • Radiographic changes **Harms outcomes:** Mortality, SAEs,[a] AEs,[a] WDAEs Notable harms: Serious infections (including tuberculosis and fungal infection), inflammatory bowel disease, injection site reactions, hypersensitivity, hepatotoxicity, and hematologic toxicity (such as anemia or pancytopenia)
Study Design	Published and unpublished RCTs, phase III or phase IV

ACR20/50/70 = American College of Rheumatology 20%/50%/70% response; AE = adverse event; DAS28 = Disease Activity Score (28-joint); DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire–Disability Index; MDA = minimum disease activity; MTX = methotrexate; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PsARC = PsA Response Criteria; PsAQoL = Psoriatic Arthritis Quality of Life; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous injection; vs. = versus; WDAE = withdrawal due to adverse event.
[a] Outcomes that were considered important by the patients groups.

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

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

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

The initial search was completed on March 19, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on July 18, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases, and Internet search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

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

Results

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.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

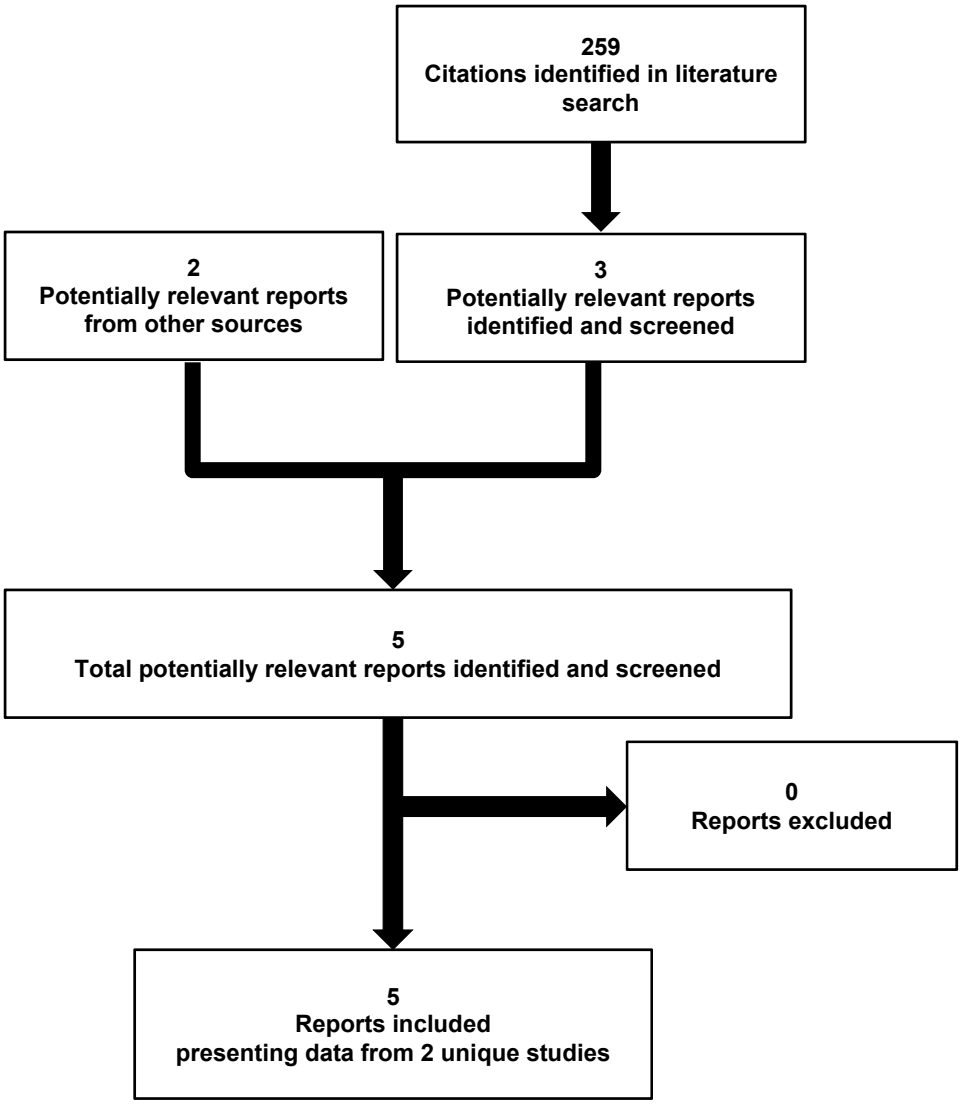


Table 4: Details of Included Studies

		SPIRIT-P1	SPIRIT-P2
Designs & Populations	**Study Design**	Phase III, DB, multi-centre, active and PL-controlled RCT	Phase III, DB, multi-centre, PL-controlled RCT
	Locations	15 countries in North America (including 7 patients from Canada), Europe, and Asia	10 countries in North America (no patients from Canada), Europe, and Asia
	Randomized (N)	417	363
	Inclusion Criteria	Patients ≥ 18 years who were biologic DMARD-naive and had an established diagnosis of PsA ≥ 6 months, had ≥ 3/68 tender and 3/66 swollen joints, had ≥ 1 disease-related hand or foot joint erosion or CRP > 6 mg/L at screening, and had active psoriatic skin lesions (plaques) or a documented history of plaque psoriasis	Patients ≥ 18 years who were conventional DMARD-experienced, were previously treated with ≥ 1 TNF inhibitor (discontinued due to inadequate response or intolerance), had an established diagnosis of PsA ≥ 6 months, had ≥ 3/68 tender and 3/66 swollen joints, and had active psoriatic skin lesions (plaques) or a documented history of plaque psoriasis
	Exclusion Criteria	Receiving or had received medication or therapy that could confound the interpretation of the study results or be a safety risk if taken concomitantly with the study drug, e.g., any biologic DMARD therapy for PsA or biologic therapy for psoriasis, including investigational therapies; used conventional DMARDs other than MTX, leflunomide, sulfasalazine, or hydroxychloroquine in the 8 weeks prior to baseline, or concurrently used > 1 conventional DMARD at entry to the study	Receiving or had received medication or therapy that could confound the interpretation of the study results or be a safety risk if taken concomitantly with the study drug, e.g., any biologic or small-molecule therapy for PsA or psoriasis, or had previously completed or withdrawn from this study or any other study investigating IXE or other IL-17 inhibitors
		A history of drug-induced psoriasis	
Drugs	**Intervention**	IXE 80 mg SC q.2.w., with starting dose of 160 mg at week 0 IXE 80 mg SC q.4.w., with starting dose of 160 mg at week 0	IXE 80 mg SC q.2.w., with starting dose of 160 mg at week 0 IXE 80 mg SC q.4.w., with starting dose of 160 mg at week 0
	Comparator(s)	ADA 40 mg SC q.2.w. PL	PL
Duration	**Phase**		
	Screening	4 to 30 days	
	Double-blind	24 weeks	
	Extension	Extension period: After week 24 to week 52, inclusive Long-term extension period: After week 52 to week 156, inclusive	After week 24 to week 156, inclusive
	Follow-up	From last treatment period visit or early termination visit to a minimum of 12 weeks following that visit	

		SPIRIT-P1	SPIRIT-P2
Outcomes	**Primary End Point**	ACR20 at week 24	
	Major Secondary End Points	• Change from baseline in HAQ-DI scores at week 24 • Change from baseline in mTSS on hand and foot X-rays at week 24 • % of patients achieving ACR20 response at week 12 • % of patients achieving PASI 75 response at week 12 • Change from baseline in LEI at week 12 • Change from baseline to week 12 in INRS	• Change from baseline in HAQ-DI scores at week 24 • % of patients achieving ACR20 response at week 12 • % of patients achieving PASI 75 response at week 12[a] • % of patients achieving MDA at week 24 • % of patients achieving complete resolution in enthesitis as assessed by LEI at week 24
	Other End Points	• Change from baseline in HAQ-DI scores at weeks 12 and over the 24-week period • Change from baseline in mTSS on hand and foot X-rays at week 24 • % of patients achieving ACR50/70 response at weeks 12 and 24 and over the 24-week period • Change from baseline in individual components of the ACR core set at weeks 12 and 24 and over the 24-week period • Change from baseline in LEI at week 12, week 24 and over the 24-week period • Change from baseline in DAS28-CRP at weeks 12 and 24 and over the 24-week period • % of patients meeting the PsARC at weeks 12 and 24 and over the 24-week period • Change from baseline in LDI-B at weeks 12 and 24 and over the 24-week period • Change from baseline in BASDAI at weeks 12 and 24 and over the 24-week period • Change from baseline in FSNRS at weeks 12 and 24 and over the 24-week period • Change from baseline in SF-36 summary scores at weeks 12 and 24 and over the 24-week period • WPAI-SHP[a] • Safety	• % of patients achieving ACR50/70 response at weeks 12 and 24 and over the 24-week period • Change from baseline in individual components of the ACR core set at weeks 12 and 24 and over the 24-week period • Change from baseline in DAS28-CRP[a] • % of patients meeting the PsARC[a] • Change from baseline in LDI-B[a] • Change from baseline in BASDAI at weeks 12 and 24 and over the 24-week period • Change from baseline in FSNRS at weeks 12 and 24 and over the 24-week period • Change from baseline in SF-36 summary scores at weeks 12 and 24 and over the 24-week period • WPAI-SHP[a] • Safety
Notes	**Publications**	Mease 2014[25] Coates 2017[26]	Nash 2017[27]
Duration			

ACR20/50/70 = American College of Rheumatology 20%/50%/70% response; ADA = adalimumab; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein; DAS28-CRP = 28-joint Disease Activity Score using C-reactive protein; DB = double-blind; DMARD = disease-modifying antirheumatic drug; FSNRS = Fatigue Severity Numeric Rating Scale; HAQ-DI = Health Assessment Questionnaire–Disability Index; IL = interleukin; INRS = Itch Numeric Rating Scale; IXE = ixekizumab; LDI-B = Leeds Dactylitis Index–Basic; LEI = Leeds Enthesitis Index; MDA = minimum disease activity; mTSS = modified Total Sharp Score; MTX = methotrexate; PASI = Psoriasis Area and Severity Index; PL = placebo; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; RCT = randomized controlled trial; SC = subcutaneous injection; SF-36 = Short Form (36) Health Survey; TNF inhibitor = tumour necrosis factor inhibitor; WPAI-SHP = Work Productivity and Activity Impairment–Specific Health Problem.

Note: Two additional reports were included (CDR submission,[28] Health Canada Reviewer's Report[29]).

[a] Exploratory variables in the included studies.

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Included Studies

Description of Studies

Two phase III, multi-centre, double-blind randomized controlled trials met the inclusion criteria for this systematic review.[3,4] The study designs of SPIRIT-P1 and SPIRIT-P2 are shown in Figure 2 and Figure 3, respectively.

SPIRIT-P1 (N = 417), a four-arm superiority study, evaluated the efficacy and safety of ixekizumab 80 mg subcutaneous injection every two weeks or ixekizumab 80 mg subcutaneous every four weeks compared with placebo subcutaneous injection over a double-blind period of 24 weeks in biologic DMARD-naive patients with active PsA. In addition, adalimumab at the Health Canada–approved dose and regimen was selected as the active control for comparison with placebo to provide internal evidence of assay sensitivity; it was not used to show equivalence or noninferiority with ixekizumab. A screening period running 4 to 30 days before randomization was used to assess participants' eligibility, where their medical history, treatment history, and current medical condition including disease severity were assessed and relevant laboratory tests including tuberculosis skin test and radiographic examinations were performed. After the screening phase, eligible participants were randomized at a 1:1:1:1 ratio to one of four treatment groups: ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, adalimumab 40 mg every two weeks, and placebo. Patients assigned to the ixekizumab groups received a starting dose of 160 mg at week 0. A computer-generated random sequence was obtained using an interactive voice response system. Patients, study site personnel, and sponsor study team were blinded to the study drug, including re-randomizations at week 16 and week 24, until all patients completed week 24 or had discontinued from the study and the reporting database through week 24 had been locked. At week 16, inadequate responders (defined as patients who failed to meet defined criteria for improvement in tender and swollen joints at week 16 and were administered rescue therapy [referred to modification to the background therapy, e.g., conventional DMARDs, NSAIDs, analgesics, and/or corticosteroids]; however, no explicit definition for inadequate responder was provided by the manufacturer) receiving adalimumab or placebo were re-randomized to either ixekizumab 80 mg every two weeks or ixekizumab 80 mg every four weeks and received rescue therapy; inadequate responders who were already assigned to ixekizumab at baseline continued their ixekizumab and received rescue therapy after week 16. Responders at week 16 in all treatment groups remained on their initially assigned treatment until week 24.

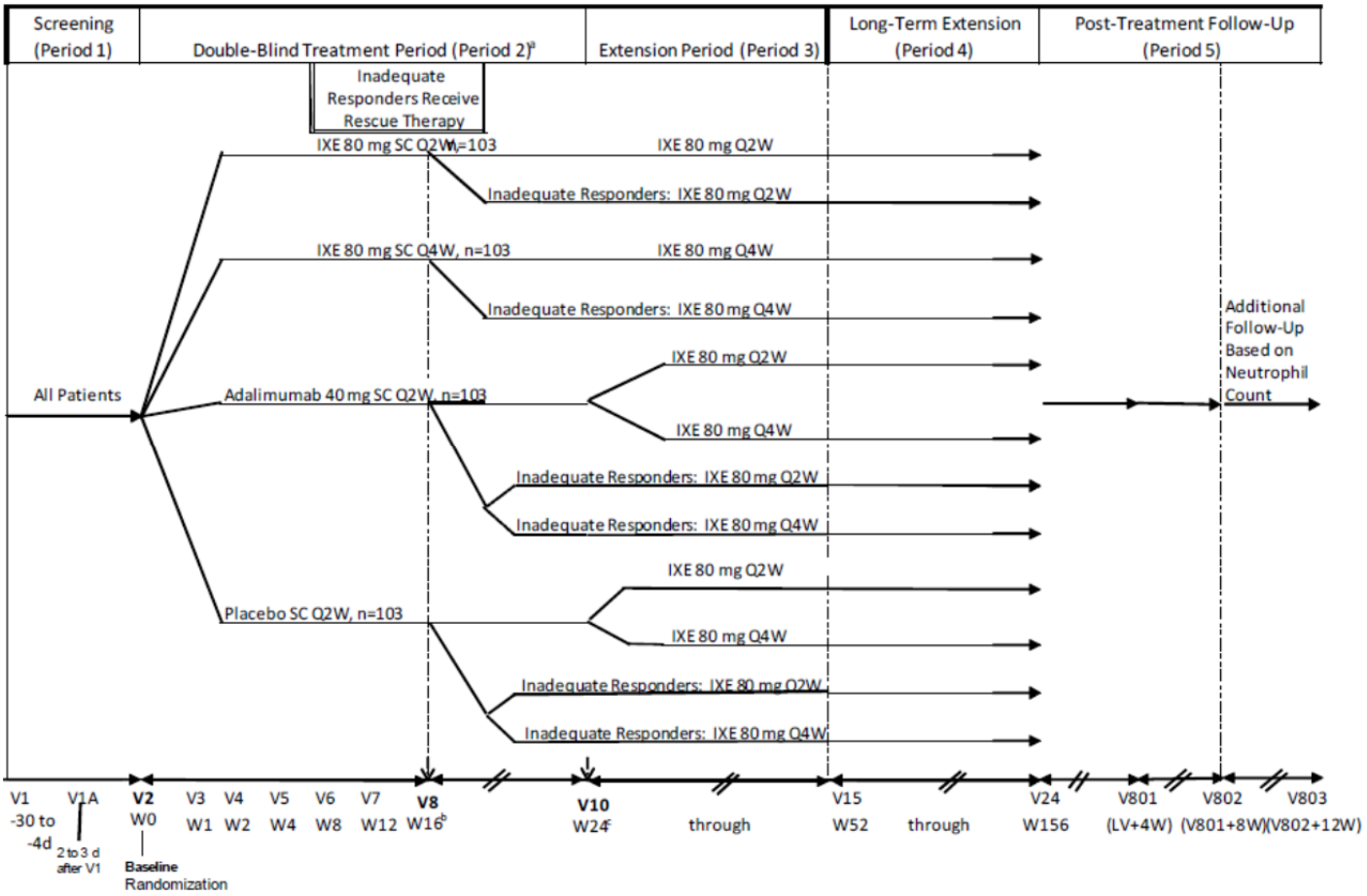
SPIRIT-P2 (N = 363), a three-arm superiority study, evaluated the efficacy and safety of ixekizumab 80 mg subcutaneous every two weeks or ixekizumab 80 mg subcutaneous every four weeks compared with placebo subcutaneous injection over a double-blind period of 24 weeks in TNF inhibitor–experienced patients with active PsA. A screening period running 4 to 30 days before randomization was used to assess participants' eligibility according to their medical history, treatment history, current medical condition including disease severity, relevant laboratory tests including tuberculosis skin test, and radiographic examinations. Eligible participants were randomized at a 1:1:1 ratio to one of three treatment groups: ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo. Patients assigned to the ixekizumab groups received a starting dose of 160 mg at week 0. A computer-generated random sequence was obtained using an interactive Web response system. Patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments, including re-randomizations at week 16 and week 24, until all patients completed week 24 or had

discontinued from the study and the clinical trial database through week 24 had been locked. At week 16, inadequate responders receiving placebo were re-randomized to either ixekizumab 80 mg every two weeks or ixekizumab 80 mg every four weeks and received rescue therapy; inadequate responders receiving either ixekizumab dosage at week 16 continued their ixekizumab and received rescue therapy. Responders at week 16 in all treatment groups remained on their initially assigned treatment until week 24.

In both studies, the primary efficacy end point was the 20% American College of Rheumatology response (ACR20, defined as an improvement of at least 20% in both swollen joint counts (SJC) and tender joint counts (TJC) and at least three of five additional disease criteria) at week 24. Joint assessments were performed by an independent, blinded assessor to minimize bias.

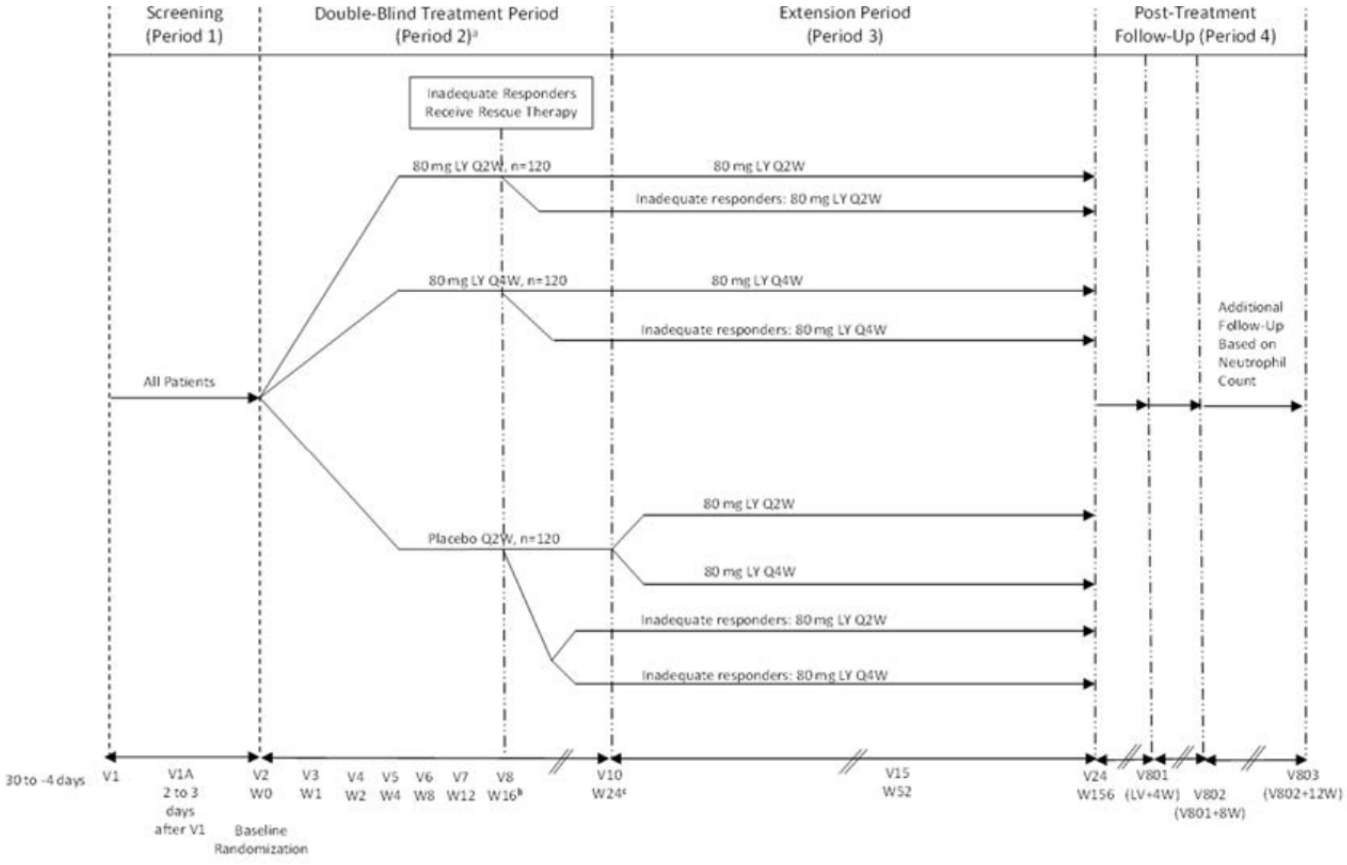
In both studies, the long-term efficacy and safety of ixekizumab in the study population were evaluated for up to three years.

Figure 2: Study Design of SPIRIT-P1



IXE = ixekizumab; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SC = subcutaneous.
Source: Clinical Study Report of SPIRIT-P1.[3]

Figure 3: Study Design of SPIRIT-P2



LY = ixekizumab; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SC = subcutaneous.
Source: Clinical Study Report of SPIRIT-P2.[4]

Populations

Inclusion and Exclusion Criteria

In SPIRIT-P1 and SPIRIT-P2, to be eligible, patients were required to be at least 18 years of age and have an established diagnosis of PsA with at least three tender joints and at least three swollen joints. The patients should have had active psoriatic skin lesions (plaques) at baseline or a documented history of plaque psoriasis. Patients in SPIRIT-P1 were biologic DMARD-naive. Patients in SPIRIT-P2 were all conventional DMARD-experienced and had been previously treated with at least one TNF inhibitor that had been discontinued due to inadequate responses or treatment intolerance.

Patients were excluded if they had a history of drug-induced psoriasis and were receiving or had received medication or therapy that could confound the interpretation of the study results or be a safety risk if taken concomitantly with the study drug. In SPIRIT-P1, the prohibited therapies included treatment with any biologic DMARD therapy for PsA or biologic therapy for psoriasis (such as a TNF inhibitor or any biologic drug targeting IL-1, IL-6, IL-12/23p40, T cell, or B cell), or conventional DMARD other than methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine eight weeks prior to baseline, or

concurrently used more than one conventional DMARD at study entry. In SPIRIT-P2, the prohibited therapies were any biologic or small-molecule therapy for PsA or psoriasis, or previous completion or withdrawal from this study or any other studies investigating ixekizumab or other IL-17 inhibitors; concurrent or recent use of any biologic drug within the following washout periods: etanercept < 28 days; infliximab, adalimumab, certolizumab pegol, or alefacept < 60 days; golimumab < 90 days; rituximab < 12 months; or any other biologic drug or small molecule < 5 half-lives prior to baseline.

Baseline Characteristics

Across both studies, the mean age ranged from 49 to 53 years and the majority of patients were Not Hispanic or Latino. The mean time since PsA diagnosis ranged from 6.2 to 7.2 years in SPIRIT-P1 and from 9.2 to 11.0 years in SPIRIT-P2. In SPIRIT-P1, 12% to 17% of patients never received conventional DMARD, 20% to 23% had previous use of conventional DMARD, and 61% to 66% were receiving conventional DMARD at baseline. In SPIRIT-P2, all patients had past or current use of conventional DMARD and had been treated with TNF inhibitor (53% to 58% had inadequate response to one TNF inhibitor, 34% to 37% had inadequate response to two TNF inhibitors, and 8% to 10% were intolerant to TNF inhibitor). The mean TJC was 19 to 22 in SPIRIT-P1 and 22 to 25 in SPIRIT-P2. The mean SJC was 10 to 12 in SPIRIT-P1 and 10 to 13 in SPIRIT-P2. The proportion of patients with a C-reactive protein (CRP) level of > 6 mg/L was higher in SPIRIT-P1 (52% to 65%) compared with that in SPIRIT-P2 (43% to 50%). The vast majority of the patients (92% to 97%) in both studies had plaque psoriasis at baseline. Enthesitis at baseline was reported in 54% to 65% of patients in SPIRIT-P1 and 72% to 81% of patients in SPIRIT-P2, while dactylitis at baseline was reported in 23% to 51% of patients in SPIRIT-P1 and 17% to 31% of patients in SPIRIT-P2. In general, the baseline demographic and disease characteristics were similar across the study groups in SPIRIT-P1 and SPIRIT-P2, although the proportions of male and female patients and body weight were somewhat imbalanced across the treatment groups in the two studies (Table 5). Other discrepancies are noted. For example, in SPIRIT-P1, compared with the placebo group, fewer patients in the ixekizumab 80 mg every-two-weeks group had a CRP level of > 6 mg/L, and the proportion of patients with dactylitis at baseline was higher in the ixekizumab 80 mg every-four-weeks group; in SPIRIT-P2, more patients in the ixekizumab 80 mg every-two-weeks group were receiving methotrexate at baseline compared with placebo, and the proportions of patients having enthesitis or dactylitis at baseline were higher in the ixekizumab groups compared with placebo.

The clinical expert consulted in this review indicated that the study populations in SPIRIT-P1 and SPIRIT-P2 represent a typical PsA patient group in Canadian practice.

Table 5: Summary of Baseline Characteristics (Intention-to-Treat Population)

	SPIRIT-P1				SPIRIT-P2		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
Age (Years), Mean (SD)							
	49.79 (12.62)	49.07 (10.07)	48.58 (12.43)	50.60 (12.32)	51.7 (11.85)	52.6 (13.57)	51.5 (10.39)
Gender, n (%)							
Male	48 (46.6)	45 (42.1)	51 (50.5)	48 (45.3)	50 (40.7)	63 (51.6)	56 (47.5)
Female	55 (53.4)	62 (57.9)	50 (49.5)	58 (54.7)	73 (59.3)	59 (48.4)	62 (52.5)
Ethnicity, n (%)							
Hispanic or Latino	4 (3.9)	5 (4.7)	5 (5.0)	6 (5.7)	13 (10.6)	11 (9.0)	11 (9.3)
Not Hispanic or Latino	87 (84.5)	94 (87.9)	83 (82.2)	92 (86.8)	109 (88.6)	109 (89.3)	106 (89.8)
Not applicable	12 (11.7)	8 (7.5)	13 (12.9)	8 (7.5)	1 (0.8)	2 (1.6)	1 (0.8)
Weight (kg), Mean (SD)							
	81.64 (17.47)	85.48 (22.97)	91.58 (21.93)	83.78 (19.62)	85.24 (20.65)	89.89 (22.04)	91.02 (22.11)
Body Mass Index (kg/m^2), Mean (SD)							
	28.58 (6.56)	30.21 (8.38)	32.05 (11.37)	29.18 (6.34)	30.0862 (6.77)	30.9120 (7.14)	31.5708 (7.58)
Background Therapy, n (%)							
cDMARD-naive	17 (16.5)	17 (15.9)	14 (13.9)	13 (12.3)	0	0	0
cDMARD past use	23 (22.3)	22 (20.6)	20 (19.8)	24 (22.6)	50 (40.7)	62 (50.8)	66 (55.9)
cDMARD current use	63 (61.2)	68 (63.6)	67 (66.3)	69 (65.1)	73 (59.3)	60 (49.2)	52 (44.1)
IR to 1 TNFi	NA				65 (52.8)	71 (58.2)	68 (57.6)
IR to 2 TNFi					46 (37.4)	41 (33.6)	41 (34.7)
Intolerance to a TNFi					12 (9.8)	10 (8.2)	9 (7.6)
MTX Use, n (%)							
Yes	53 (51.5)	57 (53.3)	57 (56.4)	59 (55.7)	61 (49.6)	48 (39.3)	40 (33.9)
No	50 (48.5)	50 (46.7)	44 (43.6)	47 (44.3)	62 (50.4)	74 (60.7)	78 (66.1)
CASPAR Total Score, Mean (SD)							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time Since PsA Onset (Years), Mean (SD)							
	10.82 (10.80)	9.98 (9.51)	9.15 (7.93)	10.37 (8.82)	11.5491 (7.46)	13.8197 (10.63)	11.1425 (8.45)
Time Since PsA Diagnosis (Years), Mean (SD)							
	7.21 (8.04)	6.22 (6.42)	6.88 (7.54)	6.34 (6.86)	9.9236 (7.39)	10.9697 (9.63)	9.2051 (7.30)
Baseline Tender Joint Count, Mean (SD)							
	21.51 (14.08)	20.50 (13.68)	19. 26 (12.97)	19.19 (12.98)	25.0 (17.28)	22.0 (14.08)	23.0 (16.24)
Baseline Swollen Joint Count, Mean (SD)							
	12.06 (7.23)	11.43 (8.21)	9.91 (6.481)	10.58 (7.26)	13.5 (11.50)	13.1 (11.16)	10.3 (7.35)
Patient's Assessment of Joint Pain (mm), Mean (SD)							
	58.40 (21.66)	60.11 (19.42)	58.67 (19.732)	58.51 (22.96)	62.7 (20.87)	63.9 (21.40)	63.9 (20.11)

	SPIRIT-P1				SPIRIT-P2		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
HAQ-DI Total Score, Mean (SD)							
	1.17 (0.57)	1.24 (0.54)	1.13 (0.59)	1.15 (0.60)	1.20 (0.64)	1.18 (0.62)	1.23 (0.67)
[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DAS28-CRP, Mean (SD)							
	4.97 (1.06)	4.98 (1.00)	4.85 (0.98)	4.86 (1.04)	5.14 (1.13)	5.10 (1.06)	4.99 (1.09)
mTSS, Mean (SD)							
	15.18 (28.86)	19.18 (32.68)	15.91 (27.37)	17.58 (28.62)	NR		
Current Psoriasis, n (%)							
	95 (92.2)	100 (93.5)	97 (96.0)	102 (96.2)	113 (91.9)	118 (96.7)	108 (91.5)
PASI Total Score, Mean (SD)							
	5.98 (7.04)	6.90 (6.61)	5.46 (6.46)	6.15 (7.52)	6.16 (8.75)	6.44 (7.88)	5.15 (6.25)
BASDAI Score, Mean (SD)							
	5.54 (2.05)	5.83 (1.80)	5.54 (2.02)	5.40 (1.96)	6.65 (1.37)	6.50 (1.37)	6.78 (1.35)
Current Enthesitis, n (%)							
	59 (57.3)	70 (65.4)	56 (55.4)	57 (53.8)	99 (80.5)	89 (73.0)	85 (72.0)
LEI, Mean (SD)							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current Dactylitis, n (%)							
	41 (39.8)	54 (50.5)	23 (22.8)	39 (36.8)	28 (22.8)	38 (31.1)	20 (16.9)
LDI-B, Mean (SD)							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 PCS, Mean (SD)							
	34.23 (8.68)	32.44 (10.09)	33.87 (8.85)	34.01 (8.33)	34.30 (9.10)	34.80 (8.78)	33.86 (8.96)
SF-36 MCS, Mean (SD)							
	48.01 (9.77)	46.53 (13.38)	46.62 (11.74)	47.41 (12.46)	49.05 (11.51)	49.58 (11.35)	48.03 (13.08)
[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI-SHP Score, Mean (SD)[a]							
	NR				38.83 (26.55)	46.93 (26.71)	41.55 (29.64)

ADA = adalimumab; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CASPAR = Classification of Psoriatic Arthritis; CRP = C-reactive protein; DAS28-CRP = 28-joint Disease Activity Score using C-reactive protein; FSNRS = Fatigue Severity Numeric Rating Scale; HAQ-DI = Health Assessment Questionnaire–Disability Index; IR = inadequate responder; ITT = intention-to-treat; IXE = ixekizumab; LDI-B = Leeds Dactylitis Index–Basic; LEI = Leeds Enthesitis Index; mTSS = modified Total Sharp Score; MTX = methotrexate; NA = not applicable; NR = not reported; PASI = Psoriasis Area and Severity Index; PL = placebo; PsA = psoriatic arthritis; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation; SF-36 MCS = Short Form (36) Health Survey, mental component summary; SF-36 PCS = Short Form (36) Health Survey, physical component summary; TNFi = tumour necrosis factor inhibitor; WPAI-SHP = Work Productivity and Activity Impairment–Specific Health Problem.

[a] WPAI-SHP that combines presenteeism and absenteeism.

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Interventions

In SPIRIT-P1, at the beginning of the 24-week double-blind treatment period, patients were randomized to one of four treatment groups: ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, placebo, or adalimumab 40 mg every two weeks. Patients assigned to the ixekizumab groups received a starting dose of 160 mg at week 0. Patients in each treatment group who were inadequate responders at week 16 received rescue therapy (modifications to the patient's background therapy [e.g., conventional DMARDs, NSAIDs, analgesics, and/or corticosteroids] were made and maintained for the remainder of the double-blind treatment period without further adjustments unless required due to safety reasons). In addition, inadequate responders at week 16 who had been assigned to placebo or adalimumab were re-randomized to receive ixekizumab 80 mg every two weeks or ixekizumab 80 mg every four weeks (those who were originally randomized to adalimumab went through a blinded placebo washout phase for eight weeks, from after week 16 until week 24, before starting ixekizumab). Inadequate responders at week 16 who received either ixekizumab 80 mg every two weeks or ixekizumab 80 mg every four weeks remained on ixekizumab. During the extension period from week 24 to week 52, all patients (including those who remained on placebo or adalimumab at the end of the double-blind treatment period) were re-randomized to receive one of two ixekizumab regimens, beginning with a starting dose of 160 mg at week 24. From week 53 to week 156, patients remained on the ixekizumab therapy and continued to receive one blinded injection at two-week intervals. Ixekizumab and placebo to match ixekizumab were supplied as an injectable solution in 1 mL (designed to deliver ixekizumab 80 mg), single-dose, pre-filled, disposable manual syringes. Adalimumab and placebo to match adalimumab were supplied as an injectable solution in single-dose, pre-filled, disposable manual syringes. Each syringe of adalimumab was designed to deliver adalimumab 40 mg.

In SPIRIT-P2, patients were randomized to receive ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, or placebo during the 24-week double-blind treatment period. Patients assigned to the ixekizumab groups received a starting dose of 160 mg at week 0. Similar to SPIRIT-P1, at week 16, patients in the placebo group who were considered inadequate responders were re-randomized to ixekizumab 80 mg every two weeks or 80 mg every four weeks; and those receiving either ixekizumab regimen at week 16 continued their original ixekizumab treatment. Rescue therapy (modification to the patient's background therapy) was allowed in SPIRIT-P2. During the extension period from week 24 to week 156, patients who received an ixekizumab regimen by the completion of double-blind treatment remained on the same dose regimen; patients who remained on placebo at the end of the double-blind treatment period were re-randomized to receive ixekizumab 80 mg every two weeks or ixekizumab 80 mg every four weeks, beginning with a starting dose of 160 mg at week 24. Patients were blinded to the dose of the study drug. Ixekizumab and placebo to match were supplied as an injectable solution in 1 mL (designed to deliver ixekizumab 80 mg), single-dose, pre-filled, disposable manual syringes.

In both studies, the syringes and contents containing either ixekizumab or matching placebo were visibly indistinguishable from each other. In SPIRIT-P1, the syringes and contents containing either adalimumab or placebo to match adalimumab were visibly indistinguishable from each other and visibly different from ixekizumab and its matching placebo. Analgesics and NSAIDs were allowed during the course of the study. During the double-blind treatment period, any dose adjustment, changes of NSAIDs, or introduction of a new NSAID were not permitted unless required for safety reasons or for rescue therapy for inadequate responders at week 16.

Outcomes

Details of outcome measures are provided in Appendix 5.

American College of Rheumatology 20/50/70

The ACR criteria for assessing joint status provide a composite measure of ≥ 20%, ≥ 50%, or ≥ 70% improvement in both swollen and TJCs and at least three of five additional disease criteria including patient/physician global assessment of disease activity (10 cm visual analogue scale [VAS]), Health Assessment Questionnaire–Disability Index (HAQ-DI), patient assessment of pain intensity, and levels of CRP or erythrocyte sedimentation rate. The ACR20 is generally accepted as the minimal clinically important difference (MCID) indicating a response to treatment, while the ACR50 and ACR70 more likely reflect truly important change for the long-term management of arthropathy. The ACR is a general measure of clinical response of peripheral joint disease and does not include assessment of enthesitis, dactylitis, the spine, or the skin. ACR20 at week 24 was the primary outcome in both SPIRIT-P1 and SPIRIT-P2 and was tested in the multiplicity-controlled analyses. ACR50/70 at various time points were secondary end points in SPIRIT-P1 and SPIRIT-P2, but they were not major secondary end points and were not included in the multiplicity-controlled analyses.

Psoriatic Arthritis Response Criteria

Psoriatic arthritis response criteria (PsARC) measures signs and symptoms of PsA assessed by tender or SJC, physician global assessment (0 to 5 Likert scale), and patient global assessment (0 to 5 Likert scale). To be a PsARC responder, a patient must have at least a 30% reduction in tender or SJC as well as a 1-point reduction on the 5-point patient or physician global assessment scales and no worsening on any score. PsARC has been shown to be a responsive and discriminate outcome instrument in PsA randomized controlled trials. PsARC does not account for psoriasis severity and is only a general assessment of clinical status. The MCID for PsARC is unknown. In both studies, the PsARC response was modified by using the physician's global assessment and the patient's global assessment on a 100 mm VAS instead of a 5-point Likert scale in the original criteria. This was a secondary outcome in SPIRIT-P1 and SPIRIT-P2 and was not included in the multiplicity-controlled analyses.

Minimum Disease Activity

Minimum disease activity (MDA) is a composite outcome measure that was developed as a target of treatment for patients with PsA that encompasses different aspects of disease domains. Various criteria were developed specifically for PsA.

In SPIRIT-P1, MDA was measured as follows:

- MDA_{PASI}: Patients were considered as achieving MDA if they fulfilled five of seven outcome measures: TJC ≤ 1, SJC ≤ 1, Psoriasis Area and Severity Index (PASI) total score ≤ 1 or body surface area ≤ 3%, patient's assessment of pain-VAS score ≤ 15, patient's global assessment of disease activity–VAS score ≤ 20, HAQ-DI ≤ 0.5, or tender entheseal points ≤ 1 based on Leeds Enthesitis Index (LEI).
- MDA_{sPGA}: Patients were considered as achieving MDA if they fulfilled five of seven outcome measures: TJC ≤ 1, SJC ≤ 1, static physician global assessment of psoriasis (sPGA) 0 or 1 or body surface area ≤ 3%, patient's assessment of pain-VAS score ≤ 15,

patient's global assessment of disease activity–VAS score ≤ 20, HAQ-DI ≤ 0.5, or tender entheseal points ≤ 1 based on LEI.

In SPIRIT-P2, MDA was measured as follows:

- Coates criteria for MDA (six entheseal points): Patients were considered as achieving MDA if they fulfilled five of seven outcome measures: TJC ≤ 1, SJC ≤ 1, PASI total score ≤ 1 or body surface area ≤ 3%, patient's assessment of pain-VAS score of ≤ 15, patient global disease activity–VAS score of ≤ 20, HAQ-DI score ≤ 0.5, and tender entheseal points ≤ 1 based on LEI.
- Coates criteria for MDA (18 entheseal points): For modification of the MDA described previously, tender entheseal points are assessed based on LEI and Spondyloarthritis Research Consortium of Canada criteria.
- Modified Coates criteria for MDA (six entheseal points): For modification of the Coates criteria for MDA for six entheseal points described previously, PASI ≤ 1 is substituted with sPGA "Clear" or "Almost clear" as $MDA_{sPGA}(0,1)$.
- Modified Coates criteria for MDA (18 entheseal points): For modification of the Coates criteria for MDA for 18 entheseal points described previously, PASI ≤ 1 is substituted with sPGA "Clear" or "Almost clear" as MDA_{sPGA} (0,1).

MDA response for six entheseal points at week 24 was a major secondary end point in SPIRIT-P2 and therefore was included in the multiplicity-controlled analyses.

Health Assessment Questionnaire–Disability Index

The HAQ-DI was developed to assess physical disability and pain in rheumatoid arthritis and has been used extensively in arthritis randomized controlled trials, including PsA. Through a self-assessed questionnaire of eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities), a patient's difficulty in performing these activities is scored from 0 (without any difficulty) to 3 (unable to do). The MCID for the HAQ-DI ranges from 0.3 to 0.35. Change from baseline in the HAQ-DI score at week 24 was a major secondary end point in SPIRIT-P1 and SPIRIT-P2 and therefore was included in the multiplicity-controlled analyses.

Work Productivity and Activity Impairment

Work productivity was measured by Work Productivity and Activity Impairment–Specific Health Problem (WPAI-SHP). This is a self-administered instrument used to measure the impact of disease on productivity. The WPAI-SHP consists of six questions to determine employment status, hours missed from work due to PsA, hours missed from work for other reasons, hours actually worked, the degree to which PsA affected work productivity while at work, and the degree to which PsA affected activities outside of work. Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), 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. This instrument is not validated in patients with PsA. It is unclear how the questions are scored, the range of scores for the four scores, and the range for the overall score. The MCID of WPAI-SHP is currently unknown. This is an exploratory variable in both SPIRIT-P1 and SPIRIT-P2 and was not included in the multiplicity-controlled analyses.

Patient's Assessment of Pain–Visual Analogue Scale

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

Fatigue Severity Numeric Rating Scale

The Fatigue Severity Numeric Rating Scale (FSNRS) is a validated, patient-administered, single-item 11-point scale, consisting of numerals from 0 to 10 on a horizontal line, with 0 representing "no fatigue" and 10 representing "fatigue as bad as you can imagine." Patients were asked to rate their fatigue (weariness, tiredness) during the past week on the scale, choosing a single number from 0 to 10. A 1-point decrease from baseline was suggested as MCID for FSNRS. This outcome was not included in the multiplicity-controlled analyses.

Short Form (36) Health Survey

The Short Form (36) Health Survey (SF-36) is a 36-item, generic health status instrument that has been used extensively in clinical trials in many disease areas. It consists of eight health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The eight domains are aggregated to create two component summaries: the physical component summary and the mental component summary, with scores ranging from zero to 100 with higher scores indicating better health status. The MCID for either the physical component summary or mental component summary of the SF-36 for the change from baseline is typically between 2.5 and five points. Leung et al. reported MCIDs of change scores of 3.74 and 1.77 in PsA patients treated with TNF inhibitor drugs for the physical and mental component summary, respectively. This outcome was not included in the multiplicity-controlled analyses.

EuroQol 5-Dimensions Questionnaire

The EuroQol 5-Dimensions questionnaire (EQ-5D) is a generic instrument for HRQoL evaluation. It has been validated in a diverse patient population in six countries; however, no studies specifically validating EQ-5D in patients with PsA were identified. It may be applied to a wide range of health conditions and treatments. The EQ-5D 5-Levels (EQ-5D-5L) consists of an EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with five levels that level 1 response represents "no problems" and level 5 "extreme problems" or "unable to perform." Results from the EQ-5D-5L descriptive system can be converted into a single index score. A score of 0 represents the health state "dead" and 1.0 reflects "perfect health." Negative scores are also possible for those health states that society (not the individual patient) considers to be "worse than dead." The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the end points are labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). The EQ-5D index and VAS scores can be summarized and analyzed as continuous data. The MCID estimates for the index score in Canadian population have a summarized mean (standard deviation [SD]) of 0.056 (0.011), and a summarized median of 0.056 (interquartile range 0.049 to 0.063). This

was an exploratory variable in both SPIRIT-P1 and SPIRIT-P2 and was not included in the multiplicity-controlled analyses.

Psoriasis Area and Severity Index

PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It produces a numeric score ranging from 0 to 72. In general, a PASI score of 5 to 10 is considered moderate disease and a score more than 10 is considered severe. A 75% reduction in the PASI score (PASI 75) is the current benchmark for most clinical trials in psoriasis and the criterion for efficacy of new psoriasis treatments approved by the FDA. The proportion of patients achieving PASI 75 response at week 12 (restricted to patients with baseline psoriatic lesions involving ≥ 3% body surface area) was one of the major secondary end points in both SPIRIT-P1 and SPIRIT-P2; therefore, it was included in the multiplicity-controlled analyses.

Leeds Enthesitis Index

The LEI was developed specifically for use in PsA. It measures enthesitis at six sites: lateral epicondyle, left and right; medial femoral condyle, left and right; and Achilles tendon insertion, left and right). Each site is assigned a score of 0 (absent) or 1 (present); the results from each site are then added to produce a total score ranging from 0 to 6. Change from baseline in LEI score at week 12 (SPIRIT-P1) and proportion of patients achieving complete resolution in enthesitis as assessed by LEI at week 24 (SPIRIT-P2) were major secondary efficacy outcomes for patients with enthesitis at baseline and were therefore included in the multiplicity-controlled analyses in SPIRIT-P2. An MCID was not identified from the literature.

Leeds Dactylitis Index–Basic

Presence of dactylitis was assessed using the Leeds Dactylitis Index–Basic (LDI-B) which evaluates for a ≥ 10% difference in the circumference of the digit compared with the opposite digit. No MCID for LDI-B was identified. Change from baseline in LDI-B at various time points was a secondary efficacy outcome in SPIRIT-P1 and SPIRIT-P2 and was assessed in patients with dactylitis at baseline. It was not included in the multiplicity-controlled analyses. A formula was used to calculate an LDI-B total score (see Appendix 5: Validity of Outcome Measures). An MCID was not identified from the literature.

Bath Ankylosing Spondylitis Disease Activity Index

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) contains six questions pertaining to the five major symptoms of axial activity: fatigue, neck/back/hip pain, joint pain/swelling other than neck/back/hips, areas of localized tenderness, overall level of morning stiffness, and duration of morning stiffness. A continuous VAS scale of 0 to 10 is used to measure these disease activities, where 0 indicates no problem and 10 indicates the worst problem. Scores of 4 or greater suggest suboptimal control of disease, and patients with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrolment in clinical trials evaluating new drug therapies directed at ankylosing spondylitis. The MCID for the BASDAI has been determined as a change of −1.96 on the 10-point BASDAI scale. The BASDAI was assessed as a secondary efficacy outcome at various time points in SPIRIT-P1 and SPIRIT-P2. This outcome was not included in the multiplicity-controlled analyses.

Modified Total Sharp Score

The Sharp scoring system allows for the assessment of two different aspects of joint damage: articular erosions and joint space narrowing. The van der Heijde erosion score includes 16 joints from the hands and wrists (graded from 0 to 5) and six joints from the feet (graded from 0 to 10). The joint space narrowing score includes 15 areas from the hands and wrists (graded from 0 to 4) and six areas from the feet (also graded from 0 to 4). The modified Total Sharp Score (mTSS) was modified for PsA by addition of hand distal interphalangeal joints. The maximum possible scores were 320 for erosions, 208 for joint space narrowing, and 528 for the total score. An MCID of mTSS is unknown in patients with PsA. Only SPIRIT-P1 assessed radiographic changes from baseline to week 24. This was a major secondary efficacy outcome in SPIRIT-P1 and was included in the multiplicity-controlled analyses.

Safety

In both studies, AEs, serious AEs (SAEs), AEs of special interest, and withdrawals due to AEs (WDAEs) were recorded.

Statistical Analysis

In SPIRIT-P1, patients were stratified by country and conventional DMARD experience at baseline. It was anticipated that a sample size of 412 patients (with 103 per treatment group) was needed to detect statistically significant differences in the proportion of patients who achieved ACR20 response between ixekizumab treatment groups and placebo at week 24 with 90% power, assuming a response rate of 48% for each ixekizumab group and 15% for the placebo group, at a two-sided significance level of 0.025. Treatment comparisons of categorical efficacy variables (e.g., ACR20/50/70) were performed using a logistic regression analysis with treatment, geographic region (Europe and Rest of the World), and conventional DMARD experience at baseline (naive, past use, and current use) in the model. The proportions and 95% confidence interval were reported. The primary analyses for all continuous efficacy variables (e.g., HAQ-DI scores) at the specified time points as included in the multiplicity adjustment plan were based on the mixed-effects model for repeated measures analysis method. The model included treatment, geographic region (Europe and Rest of the World), baseline score, conventional DMARD experience at baseline (naive, past use, and current use), visit, and the interaction of treatment-by-visit as fixed factors.

In SPIRIT-P2, patients were stratified by country and TNF inhibitor experience at baseline. Assumptions and inputs to determine sample size included a two-sided Fisher's exact test at the 0.025 level to maintain an overall type I error rate of 0.05 across the two ixekizumab doses tested in the primary objective. With 120 patients per treatment arm and assuming the ACR20 response rates of 35% for ixekizumab 80 mg every two weeks and 15% for placebo at week 24, the power was approximately 90%. The primary analysis of categorical efficacy variables used a logistic regression analysis with treatment, geographic region, and TNF inhibitor experience (inadequate responder to one TNF inhibitor, inadequate responder to two TNF inhibitors, or intolerance to a TNF inhibitor) in the model. Secondary analysis was conducted using a Fisher's exact test. The primary analyses for all continuous efficacy variables were based on the mixed-effects model for repeated measures analysis method. The model included treatment, visit, geographic region, TNF inhibitor experience (inadequate responder to one TNF inhibitor, inadequate responder to two TNF inhibitors, or intolerance to a TNF inhibitor), treatment-by-visit interaction, geographic region–by-visit

interaction, and TNF inhibitor experience–by-visit interaction as well as the continuous, fixed covariates of baseline value and baseline value–by-visit interaction.

For SPIRIT-P1 and SPIRIT-P2, all efficacy analyses were conducted in the intention-to-treat (ITT) population. The primary efficacy analysis was the proportion of patients with ACR20 at week 24 using nonresponder imputation for missing values. Patients who did not meet the clinical response criteria for categorical responses (e.g., ACR20/50/70, PASI 75, etc.), who were missing categorical response data at a time point of interest, or who discontinued the study drug at any time before that time point for any reason were defined as nonresponders for the nonresponder imputation analysis. Patients who were eligible for rescue therapy at week 16 were analyzed as nonresponders after week 16 and onward. Randomized patients without at least one post-baseline observation were also defined as nonresponders for the nonresponder imputation analysis. Other approaches for missing data imputation included the linear extrapolation method for analysis of the structural progression end point, modified baseline observation carried forward for continuous efficacy and health outcomes, the last observation carried forward for continuous efficacy and health outcomes, and the placebo multiple imputation for major continuous efficacy outcomes at week 24. In both studies, for patients who were identified as inadequate responders at week 16, only data up to the week 16 injection were included in the double-blind, placebo-controlled treatment analyses.

The primary and major secondary efficacy outcomes were assessed using a hierarchical testing procedure to control the familywise type I error rate to ≤ 5%: First, all the primary and pre-specified major secondary end points within an ixekizumab dose regimen were tested in a sequential manner; the statistical significance of each secondary end point was investigated only if the previous end point was significant. Second, if all the hypotheses for a dose regimen were rejected at alpha/2 (or 0.025 level) then the hypotheses related to other dose regimens could be tested at level alpha (or 0.05 level). A sequentially rejective Bonferroni multiple testing procedure was used in these multiplicity-controlled analyses.

The sequence of the primary and major secondary outcomes tested for each ixekizumab dose regimen compared with placebo in SPIRIT-P1 was as follows:

- Primary (test 1): proportion of patients achieving ACR20 response at week 24
- Major secondary 1 (test 2): change from baseline to week 24 in HAQ-DI
- Major secondary 2 (test 3): change from baseline to week 24 in mTSS
- Major secondary 3 (test 4): proportion of patients achieving ACR20 response at week 12
- Major secondary 4 (test 5): proportion of patients achieving PASI 75 response at week 12 (restricted to patients with baseline psoriatic lesion[s] involving ≥ 3% body surface area)
- Major secondary 5 (test 6): change from baseline to week 12 in LEI in patients with enthesitis at baseline
- Major secondary 6 (test 7): change from baseline to week 12 in Itch Numeric Rating Scale (INRS) (restricted to patients with baseline psoriatic lesion[s] involving ≥ 3% body surface area).

The sequence of the primary and major secondary outcomes tested for each ixekizumab dose regimen compared with placebo in SPIRIT-P2 was as follows:

- Primary (test 1): proportion of patients achieving ACR20 response at week 24

- Major secondary 1 (test 2): change from baseline to week 24 in HAQ-DI
- Major secondary 2 (test 3): proportion of patients achieving ACR20 response at week 12
- Major secondary 3 (test 4): proportion of patients achieving PASI 75 response at week 12 (restricted to patients with baseline psoriatic lesion[s] involving ≥ 3% body surface area)
- Major secondary 4 (test 5): proportion of patients achieving Coates criteria for MDA at week 24 (using LEI [six entheseal points] to assess enthesitis)
- Major secondary 5 (test 6): proportion of patients achieving complete resolution in enthesitis as assessed by the LEI at week 24 in patients with enthesitis at baseline.

In each study, these statistical tests were grouped into two parallel branches, one for tests of ixekizumab 80 mg every four weeks versus placebo and another branch for tests of ixekizumab 80 mg every two weeks versus placebo. Test 2 was to be performed at a dose regimen only if test 1 at that dose regimen was significant. Similarly, each test for a particular dose was to be performed only if all prior tests at that dose were significant. For each dose regimen, if a test was not significant, all subsequent tests were not performed and were treated as not significant.

The CDR protocol included subgroups by severity of baseline PsA, biologics treatment experience (treatment-naive versus treatment-experienced) and concomitant use of DMARDs (current use versus past use). In SPIRIT-P1 and SPIRIT-P2, for ACR20 response analyses, the treatment-by-subgroup interaction was tested at the significance level of 0.10. At week 24, only the subgroup of baseline disease severity based on the level of CRP (≤ 6 mg/L versus > 6 mg/L) from SPIRIT-P2 showed statistically significant treatment-by-subgroup interaction, and therefore the results associated with this subgroup on ACR20 response are summarized in this review. Inclusion criteria for SPIRIT-P1 and SPIRIT-P2 allowed examination of treatment effects separately for biologic-naive (SPIRIT-P1) and biologic-experienced (SPIRIT-P2) patients. Neither study provided subgroup data based on whether patients were taking conventional DMARDs concomitantly.

Analysis Populations

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

The ITT population consisted of all randomized patients, even if the patient did not take the assigned treatment, did not receive the correct treatment, did not receive any medication, or otherwise did not follow the protocol. Patients were analyzed according to the treatment to which they were assigned at baseline.

The per-protocol set was defined as all randomized patients who were compliant with therapy, who did not have significant protocol violations, and whose study site did not have significant Good Clinical Practice issues that occurred during the double-blind treatment period and would require reporting to regulatory agencies.

The safety set was defined as all randomized patients who received at least one dose of study drug. Patients were analyzed according to the treatment to which they were assigned at baseline.

Patient Disposition

Patient disposition is summarized in Table 6. In SPIRIT-P1, a total of 417 patients were randomized to ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, adalimumab 40 mg every two weeks, or placebo at baseline. In SPIRIT-P2, 363 patients were randomized to ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, or placebo at baseline.

Overall, the number of premature discontinuations at week 24 was higher in the placebo groups (14% and 20%) than in the ixekizumab 80 mg every-two-weeks group (6% and 11%), and ixekizumab 80 mg every-four-weeks group (9%). Isolated cases of lack of efficacy, AE, lost to follow-up, sponsor decision, and patient decision were reported as the causes of study discontinuation in the ixekizumab groups and placebo groups. At week 16, 25.5% of patients in the placebo group of SPIRIT-P1 escaped to one of the two ixekizumab treatment arms, and 27.1% of patients in the placebo group of SPIRIT-P2 escaped to one of the two ixekizumab treatment arms.

Table 6: Patient Disposition

	SPIRIT-P1				SPIRIT-P2		
	IXE 80 mg q.2.w.	**IXE 80 mg q.4.w.**	**ADA 40 mg q.2.w.**	**PL**	**IXE 80 mg q.2.w.**	**IXE 80 mg q.4.w.**	**PL**
Screened, N	719				474		
Randomized, N	417				363		
	103	107	101	106	123	122	118
IRs at Week 16, n (%)	10 (9.7)	11 (10.3)	9 (8.9)	27 (25.5)	17 (13.8)	15 (12.3)	32 (27.1)
IRs Reassigned to Receive IXE 80 mg SC q.2.w. From Week 16, n (%)	NA	NA	4 (4.0)	14 (13.2)	NA	NA	16 (13.6)
IRs Reassigned to Receive IXE 80 mg SC q.4.w. From Week 16, n (%)	NA	NA	5 (5.0)	13 (12.3)	NA	NA	16 (13.6)
Discontinued Through Week 24, n (%)	6 (5.8)	10 (9.3)	4 (4.0)	15 (14.2)	14 (11.4)	11 (9.0)	24 (20.3)
Entry criteria not met	3	3	1	1	0	1	1
Adverse events	3	2	2	2	7	5	5
Lack of efficacy	0	2	0	4	4	2	9
Lost to follow-up	0	1	0	1	1	1	2
Patient decision	0	1	1	3	2	2	7
Sponsor decision	0	1	0	3	0	0	0
Protocol violation	0	0	0	1	0	0	0
Death	0	0	0	0	0	0	0
Completed, Week 24, n (%)	97 (94.2)	97 (90.7)	97 (96.0)	91 (85.8)	109 (88.6)	111 (91.0)	94 (80.0)
ITT, n (%)	103 (100.0)	107 (100.0)	101 (100.0)	106 (100.0)	123 (100.0)	122 (100.0)	118 (100.0)
PP, n (%)	91 (88.3)	89 (83.2)	83 (82.2)	80 (75.5)	100 (81.3)	91 (74.6)	91 (77.1)
Safety, n (%)	102 (99.0)	107 (100.0)	101 (100.0)	106 (100.0)	123 (100.0)	122 (100.0)	118 (100.0)

ADA = adalimumab; IR = inadequate responder; ITT = intention-to-treat population; IXE = ixekizumab; NA = not applicable; NR = not reported; PL = placebo; PP = per-protocol population; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SC = subcutaneous injection.
Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Exposure to Study Treatments

In SPIRIT-P1, the mean duration of exposure during the double-blind treatment period was similar in the two ixekizumab groups (159.3 ± SD 26.9 days for ixekizumab 80 mg every two weeks; 155.6 ± SD 34.3 days for ixekizumab 80 mg every four weeks) and longer than the placebo group (142.4 ± SD 38.2 days). The mean dose of ixekizumab was 967.8 mg in the every-two-weeks group and 512.9 mg in the every-four-weeks group.

In SPIRIT-P2, the mean duration of exposure during the double-blind treatment period was similar in the two ixekizumab groups (151 ± SD 37.7 days for ixekizumab 80 mg every two weeks; 156.7 ± SD 35.1 days for ixekizumab 80 mg every four weeks) and longer than the placebo group (137.3 ± SD 43.9 days).The mean dose of ixekizumab was 910.6 mg in the every-two-weeks group and 508.9 mg in the every-four-weeks group.

Critical Appraisal

Internal Validity

SPIRIT-P1 and SPIRIT-P2 were randomized and double-blinded up to week 24. Appropriate methods of randomization, blinding, and allocation concealment were reported. Entry into the early escape phase was blinded, which can help minimize bias. Patients were stratified at randomization according to their geographic region, previous experience with DMARDs, and prior TNF inhibitor exposure and response. All clinical laboratory safety tests (including chemistry, hematology, and urinalysis panels) were to be analyzed by a central laboratory. In addition, images taken at screening were reviewed and assessed centrally by qualified readers, and the readers had no knowledge of the true chronologic order, patient identity, or treatment group. In general, patients' baseline demographic and disease characteristics were similar between treatment groups in SPIRIT-P1 and SPIRIT-P2; however, some differences between the ixekizumab groups and the placebo group were noted. For example, in SPIRIT-P1, fewer patients in the ixekizumab 80 mg every-two-weeks group had a CRP level of > 6 mg/L, and the proportion of patients with dactylitis at baseline was higher in the ixekizumab 80 mg every-four-weeks group than in the placebo group; in SPIRIT-P2, more patients in the ixekizumab 80 mg every-two-weeks group were receiving methotrexate at baseline compared with the placebo group, and the proportions of patients having enthesitis or dactylitis at baseline were higher in the ixekizumab groups compared with the placebo group. This suggests that the randomization may not have achieved full balance. The clinical expert indicated that these imbalances were unlikely to have a significant impact on the study results.

Multiplicity-controlled analyses using a hierarchical test procedure for series-ranked primary and secondary efficacy outcomes was used in both studies in order to control the overall type I error rate at 5%. Statistical testing was conditional on the first test being significant, and the second hypothesis was tested with the same alpha level. Statistical testing for the hypotheses was performed only if the previous null hypothesis in the hierarchy could be rejected. The limitation with this approach was that only certain outcomes were selected, and hence the hierarchical approach did not take into consideration all outcomes measured in the study, including some of the HRQoL data (i.e., FSNRS, SF-36, and EQ-5D) or work productivity. These outcomes were identified as exploratory variables or not major secondary efficacy variables in SPIRIT-P1 and SPIRIT-P2, even though HRQoL and work productivity were identified by patient groups as important outcomes. These outcomes were not adjusted for multiplicity, and, given the large number of comparisons in the study, a statistically significant finding ($P < 0.05$) for the comparisons between ixekizumab treatment

groups and placebo groups for these outcomes may be attributable to an inflated type I error. In addition, no criteria were stated on how the outcomes that were included in the hierarchy were ranked, and there was no rationale provided for which of the secondary outcomes were included in the hierarchy. In SPIRIT-P1 and SPIRIT-P2, all outcomes in the statistical testing hierarchy were statistically significant compared with placebo at week 24, except for the outcomes related to enthesitis assessment (i.e., LEI).

Missing data are a particular concern in the analyses of patient-reported outcomes, such as HAQ-DI, SF-36, patient's assessment of pain, FSNRS, and EQ-5D, where more than 10% to 40% of data were missing in the placebo group at week 24. The large proportion of missing data in the placebo group makes results very uncertain; in addition, randomization may not be maintained. Furthermore, given that the HAQ-DI was a major secondary variable and was included early in the hierarchical testing, the > 20% missing data within the groups could have significantly biased the results obtained. Sensitivity analyses were conducted using different forms of imputation, including last observation carried forward, modified baseline observation carried forward, and placebo multiple imputation for continuous efficacy outcomes, or using different populations. The results of these sensitivity analyses were consistent with the results from the primary analysis. However, all approaches make major assumptions with regard to the missing data (e.g., partially or completely missing at random), which is unlikely to hold true in these studies. As a result, the validity of these alternative approaches is also questionable.

In SPIRIT-P1 and SPIRIT-P2, 39.6% (42/106) and 47.5% (56/118) of patients in the placebo groups, respectively, discontinued their originally assigned treatment before week 24 (either due to early escape or because of treatment discontinuation). This means that a substantial proportion of the outcome data at week 24 had to be imputed based on an ITT analysis. In addition, the imputation would have been differential (more imputed data in the placebo group than active treatment). Therefore, there is a high degree of uncertainty with respect to the findings of the studies beyond the week 16 time point. These patients were less likely to have achieved ACR20 in an ITT analysis. Given that more patients in the placebo group were coded as nonresponders due to discontinuations in the ITT analysis, the ITT analysis could bias the results in favour of the ixekizumab groups. Moreover, given that PsA is a condition where the symptoms fluctuate over time, it is possible that a certain proportion of patients in the placebo group would have achieved ACR20 after week 16. Because the proportion of patients entering early escape at week 16 is greater in the placebo group than in the ixekizumab groups, this could bias the week 24 assessment and overestimate the effect of ixekizumab, because placebo-treated participants may have spontaneously improved but they were considered as nonresponders in the studies.

After week 24, patients knew that they were on active treatment, since all patients were receiving ixekizumab after week 24. Also, changes in background therapy were allowed, and it is difficult to establish the effects of the drugs versus changes in background therapy on the outcomes observed after week 24, making interpretation of results challenging. This would bias the results of patient-reported outcomes such as HRQoL, symptoms, and disability measures, as well as AEs, in the long term.

Currently available outcome measures in PsA have largely been adopted from other conditions, such as rheumatoid arthritis and psoriasis. Hence, validity and reliability data specific to PsA are sparse, and some instruments lack a known MCID exclusively for patients with PsA, for instance SF-36, EQ-5D-5L, LEI, and LDI-B.

Subgroup analysis by disease severity (measured with level of CRP) was performed in SPIRIT-P2. The results should be interpreted with caution, due to the small subgroup sizes

and no control for type I error. PASI was assessed only in patients in whom psoriasis affected at least 3% of the body surface area at baseline; hence, randomization was broken and not maintained for this subgroup as it is a subset of patients and appeared to be imbalanced. Similarly, LEI and LDI-B were evaluated in patients with enthesitis or dactylitis at baseline. Only a subset of this population (58% of patients in SPIRIT-P1 and 75% in SPIRIT-P2 had enthesitis at baseline; 38% in SPIRIT-P1 and 24% in SPIRIT-P2 had dactylitis at baseline) was assessed. Work productivity was assessed in the subset of patients who work, so randomization was broken and not maintained. Therefore, as neither variable was included as a stratification variable in the randomization process, randomization was not maintained for these subgroups, and thus imbalance may be expected between the subgroups.

External Validity

The included studies were multi-centre trials enrolling patients from different countries; however only a small percentage of patients (7 patients [1.6%] in SPIRIT-P1; none in SPIRIT-P2) were recruited from Canada. According to the clinical expert involved in the review, the patients' baseline characteristics were consistent with what can be seen in Canadian clinical practice and in other PsA trials; therefore the study results are likely generalizable to the Canadian patient population.

Several outcomes measured in the trials have limitations, including not being validated in a PsA population and lack of clearly defined MCID in score change in PsA patients (see Appendix 5).

The doses of ixekizumab every two weeks in SPIRIT-P1 and SPIRIT-P2 are not consistent with the Health Canada–recommended dose. Health Canada recommends that patients with PsA with coexistent moderate to severe plaque psoriasis receive the dosing regimen for plaque psoriasis, which is 160 mg at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, and then 80 mg every four weeks. Thus, continuance of the ixekizumab every-two-weeks dosing beyond week 12 in SPIRIT-P1 and SPIRIT-P2 is inconsistent with Health Canada–recommended dosing.

The treatment duration of SPIRIT-P1 and SPIRIT-P2 was three years. Although long-term data were reported for up to week 52 in SPIRIT-P1, the only placebo-controlled data that exist for ixekizumab are up to week 24; moreover, these data are likely limited in their utility given the high proportion of patients who discontinued randomized treatment (either due to early escape or because of treatment discontinuation) during the studies. The interpretation of results after week 24 is limited by the lack of a comparator group and the allowance for changes in background therapies within the groups.

The doses of ixekizumab (80 mg every two weeks and every four weeks) and adalimumab (40 mg every two weeks) were consistent with Canadian practice. However, there is a lack of direct, head-to-head comparisons of ixekizumab with another active control, particularly non-TNF inhibitor biologics, in the population of patients who have demonstrated inadequate response to TNF inhibitors.

Efficacy

Only those efficacy outcomes identified in the review protocol (Table 3), those included in the multiplicity-controlled analyses (primary and major secondary efficacy outcomes), and those indicated as important outcomes by patient groups are presented. See Appendix 4 for detailed efficacy data.

In the multiplicity-controlled analyses of SPIRIT-P1, statistically significant differences for the comparisons between ixekizumab 80 mg every two weeks and placebo and between ixekizumab 80 mg every four weeks and placebo were observed for the primary end point of ACR20 response rate at week 24 and all major secondary end points. with the exception of change from baseline to week 12 in LEI and change from baseline to week 12 in INRS (not tested because of the multiplicity control strategy).

In the multiplicity-controlled analyses of SPIRIT-P2, statistically significant differences for the comparisons between ixekizumab 80 mg every two weeks and placebo and between ixekizumab 80 mg every four weeks and placebo were observed for the primary end point of ACR20 response rate at week 24 and all major secondary end points, with the exception of the resolution of enthesitis as assessed by LEI at week 24.

Clinical Responses in PsA Symptoms

American College of Rheumatology 20/50/70

The proportion of patients achieving ACR20 at week 24 was the primary end point in both SPIRIT-P1 and SPIRIT-P2.

In SPIRIT-P1, a statistically significantly greater proportion of biologic DMARD-naive patients in both ixekizumab treatment groups achieved an ACR20 response at week 24 compared with placebo (62.1% for ixekizumab 80 mg every two weeks versus 30.2% for placebo, $P < 0.001$; 57.9% for ixekizumab 80 mg every four weeks versus 30.2% for placebo, $P < 0.001$). Similarly, a statistically significantly greater proportion of patients in both ixekizumab treatment groups achieved an ACR20 response at week 12 compared with placebo (60.2% for ixekizumab 80 mg every two weeks versus 31.1% for placebo, $P < 0.001$; 57.0% for ixekizumab 80 mg every four weeks versus 31.1% for placebo, $P < 0.001$) (Table 7).

In SPIRIT-P2, a statistically significantly greater proportion of patients in both ixekizumab treatment groups achieved an ACR20 response at week 24 compared with placebo (48.0% for ixekizumab 80 mg every two weeks versus 19.5% for placebo, $P < 0.001$; 53.3% for ixekizumab 80 mg every four weeks versus 19.5% for placebo, $P < 0.001$). Similarly a statistically significantly greater proportion of TNF inhibitor–experienced patients in both ixekizumab treatment groups achieved an ACR20 response at week 12 compared with placebo (48.0% for ixekizumab 80 mg every two weeks versus 22.0% for placebo, $P < 0.001$; 50.0% for ixekizumab 80 mg every four weeks versus 22.0% for placebo, $P < 0.001$).

A subgroup analysis by disease severity (based on CRP levels at baseline) was also performed for ACR20 at week 24. Statistically significant treatment-by-subgroup interaction was observed for the subgroup of baseline disease severity ($P = 0.083$). However, TNF inhibitor–experienced patients in both ixekizumab treatment groups had higher ACR20 response rates at week 24 compared with placebo at the CRP levels ≤ 6 mg/L and > 6 mg/L, which is consistent with the main analysis (Table 7).Further, this subgroup analysis was not included in the hierarchical statistical analysis approach and should be considered inconclusive because of the potential for inflated type I error.

According to the clinical expert consulted for this review, the between-group differences in ACR20 in the ITT population in SPIRIT-P1 and SPIRIT-P2 are considered clinically important.

Table 7: Proportion of Patients With ACR20 Response at Week 12 and Week 24 (Using NRI, ITT Population, and Subgroups)

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
ACR20 at Week 12							
ITT population							
n (%)	62 (60.2)	61 (57.0)	52 (51.5)	33 (31.1)	59 (48.0)	61 (50.0)	26 (22.0)
Odds ratio (95% CI vs. PL)	3.32 (1.88 to 5.89)	2.92 (1.66 to 5.14)	2.36 (1.34 to 4.17)		3.28 (1.85 to 5.79)	3.56 (2.02 to 6.26)	
P value vs. PL	< 0.001	< 0.001	0.003		< 0.001	< 0.001	
ACR20 at Week 24							
ITT population							
n (%)	64 (62.1)	62 (57.9)	58 (57.4)	32 (30.2)	59 (48.0)	65 (53.3)	23 (19.5)
Odds ratio (95% CI vs. PL)	3.88 (2.18 to 6.91)	3.24 (1.84 to 5.72)	3.16 (1.78 to 5.60)		3.79 (2.12 to 6.78)	4.74 (2.65 to 8.48)	
P value vs. PL	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	
Subgroups (week 24)							
[redacted]							

ACR20 = American College of Rheumatology 20% response; ADA = adalimumab; CI = confidence interval; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug; IR = inadequate responder; ITT = intention-to-treat; IXE = ixekizumab; NRI = nonresponder imputation; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; TNF = tumour necrosis factor; vs. = versus.

[a] NRI is applied for inadequate responders at week 16 and patients who discontinued on or before week 24. Odds ratio, CI, and *P* value are from a logistic regression model using Wald test with treatment, region, and baseline conventional DMARD experience as factors.

[b] NRI is applied for inadequate responders at week 16 and patients who discontinued on or before week 24. Odds ratio, CI, and *P* value are from a logistic regression model using Wald test with treatment, geographic region, and TNF inhibitor experience in the model.

[c] *P* value from Fisher's exact test.

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

In SPIRIT-P1 and SPIRIT-P2, higher proportions of patients in the ixekizumab 80 mg every-two-weeks group and ixekizumab 80 mg every-four-weeks group achieved an ACR50 and ACR70 response at week 24 compared with placebo. The analyses for ACR50/70 at week 24 were not included in the hierarchical statistical analysis approach and should be considered as inconclusive because of the potential for inflated type I error (Appendix 4, Table 15).

Psoriatic Arthritis Response Criteria

In SPIRIT-P1, a higher proportion of patients in the ixekizumab 80 mg every-two-weeks and ixekizumab 80 mg every-four-weeks treatment groups achieved PsARC response at week 24 compared with placebo: 66% for ixekizumab 80 mg every two weeks, 57.9% for ixekizumab 80 mg every four weeks, and 32.1% for placebo. In SPIRIT-P2, a higher proportion of patients in ixekizumab 80 mg every-two-weeks and ixekizumab 80 mg every-four-weeks treatment groups achieved PsARC response at week 24 compared with placebo: 47.2% for ixekizumab 80 mg every two weeks, 55.7% for ixekizumab 80 mg every four weeks, and 20.3% for placebo. These analyses were not included in the hierarchical statistical analysis approach and should be considered as inconclusive because of the potential for inflated type I error (Appendix 4,Table 16).

Minimum Disease Activity

In SPIRIT-P1, a higher proportion of patients in the ixekizumab 80 mg every-two-weeks and ixekizumab 80 mg every-four-weeks treatment groups achieved MDA response (based on PASI) at week 24 compared with placebo: 40.8% for ixekizumab 80 mg every two weeks, 29.9% for ixekizumab 80 mg every four weeks, and 15.1% for placebo. However, these analyses were not included in the hierarchical statistical analysis (Table 8).

In SPIRIT-P2 at week 24, a statistically significantly higher proportion of patients in the ixekizumab 80 mg every-two-weeks and ixekizumab 80 mg every-four-weeks treatment groups achieved MDA response based on Coates criteria (six entheseal points) compared with placebo: 23.6% for ixekizumab 80 mg every two weeks, 27.9% for ixekizumab 80 mg every four weeks, and 3.4% for placebo, both *P* values < 0.001 (Table 8).

Table 8: Proportion of Patients Achieving Minimum Disease Activity at Week 24 (Using NRI, ITT Population)

	SPIRIT-P1[a] (Based on PASI)				SPIRIT-P2[b] (Based on PASI)		
	IXE 80 mg q.2.w. (N = 103)	**IXE 80 mg q.4.w. (N = 107)**	**ADA 40 mg q.2.w. (N = 101)**	**PL (N = 106)**	**IXE 80 mg q.2.w. (N = 123)**	**IXE 80 mg q.4.w. (N = 122)**	**PL (N = 118)**
n (%)	42 (40.8)	32 (29.9)	32 (31.7)	16 (15.1)	29 (23.6)	34 (27.9)	4 (3.4)
Odds ratio (95% CI vs. PL)	3.93 (2.03 to 7.64)	2.42 (1.23 to 4.75)	2.61 (1.32 to 5.14)		8.89 (3.01 to 26.27)	11.58 (3.91 to 34.30)	
P value vs. PL	< 0.001	0.010	0.006		< 0.001	< 0.001	

ADA = adalimumab; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ITT = intention-to-treat; IXE = ixekizumab; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; TNF = tumour necrosis factor; vs. = versus.

[a] NRI is applied for inadequate responders at week 16 and patients who discontinued on or before week 24.Odds ratio, CI, and *P* value are from a logistic regression model using Wald test with treatment, region, and baseline conventional DMARD experience as factors.

[b] NRI is applied for inadequate responders at week 16 and patients who discontinued on or before week 24. Odds ratio, CI, and *P* value are from a logistic regression model using Wald test with treatment, geographic region, and TNF inhibitor experience in the model.

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Measurement of Function and Disability

Health Assessment Questionnaire–Disability Index

In SPIRIT-P1, a statistically significantly greater reduction from baseline in the HAQ-DI score was achieved in biologic-naive patients in both ixekizumab treatment groups compared with placebo at week 24. The differences in change from baseline between ixekizumab 80 mg every two weeks and placebo and between ixekizumab 80 mg every four weeks and placebo were −0.32 and −0.26, respectively (both *P* values < 0.001).

In SPIRIT-P2, a statistically significantly greater reduction from baseline in the HAQ-DI score was achieved in TNF inhibitor–experienced patients in both ixekizumab treatment groups compared with placebo at week 24. The differences in change from baseline between ixekizumab 80 mg every two weeks and placebo and between ixekizumab 80 mg every four weeks and placebo were −0.3 and −0.4, respectively (both *P* values < 0.001).

Hence, the between-group differences in improvement in the HAQ-DI score were within the range of the MCID for HAQ-DI (0.13 to 0.35) in the comparisons between each ixekizumab group and placebo at week 24 (Table 9). The clinical expert consulted for this review indicated that the between-group differences were considered clinically relevant.

Table 9: Change From Baseline in HAQ-DI Score at Week 24 (Using MMRM, ITT Population)

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
n	84	83	85	63	91	95	64
Baseline, mean (SD)	1.17 (0.57)	1.24 (0.54)	1.13 (0.59)	1.15 (0.60)	1.20 (0.64)	1.18 (0.62)	1.23 (0.67)
LS mean change (SE)	−0.50 (0.05)	−0.44 (0.05)	−0.37 (0.05)	−0.18 (0.05)	−0.4 (0.07)	−0.6 (0.07)	−0.2 (0.08)
LS mean difference (95% CI vs. PL)	−0.32 (−0.46 to −0.18)	−0.26 (−0.40 to −0.12)	−0.19 (−0.33 to −0.05)		−0.3 (−0.4 to −0.1)	−0.4 (−0.5 to −0.3)	
P value vs. PL	< 0.001	< 0.001	0.007		< 0.001	< 0.001	

ADA = adalimumab; CI = confidence interval; HAQ-DI = Health Assessment Questionnaire–Disability Index; ITT = intention-to-treat; IXE = ixekizumab; LS = least squares; MMRM = mixed-effects model for repeated measures; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation; SE = standard error; TNF = tumour necrosis factor; vs. = versus.

[a] LS mean, LS mean difference, SE, CI, and *P* value are from an MMRM with treatment, region, baseline conventional DMARD experience, visit, and treatment-by-visit interaction as fixed factors, and baseline as covariate.

[b] LS mean, SE, 95% CI, and *P* value are based on an MMRM model which includes treatment, visit, geographic region, TNF inhibitor experience (inadequate responder to 1 TNF inhibitor, inadequate responder to 2 TNF inhibitors, or intolerance to a TNF inhibitor), treatment-by-visit interaction, geographic region–by-visit interaction, and TNF inhibitor experience–by-visit interaction as well as the continuous, fixed covariates of baseline value and baseline value-by-visit interaction, with variance-covariance structure set to unstructured (for change from baseline).

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Work Productivity

In SPIRIT-P1 and SPIRIT-P2, numerically greater reductions in work or activity impairment due to disease as measured by the WPAI-SHP questionnaire were observed for the ixekizumab groups compared with placebo at week 24 (Appendix 4, Table 17). The proportion of patients who had completed the questionnaire ranged from 25% to 91% in

SPIRIT-P1 and from 21% to 90% in SPIRIT-P2. This was an exploratory variable in both studies and was not included in the multiplicity-controlled analyses.

Measurement of Psoriatic Arthritis Symptoms

Pain

In SPIRIT-P1 and SPIRIT-P2 at week 24, the mean change in patient's assessment of pain-VAS scores decreased (improved) from baseline to week 24 for all treatment arms, including placebo (Appendix 4, Table 18). Neither trial included this outcome in the statistical hierarchy.

Fatigue

In both SPIRIT-P1 and SPIRIT-P2 at week 24, the mean change in FSNRS scores decreased (improved) from baseline to week 24 for all treatment arms, including placebo (Appendix 4,Table 19). Neither trial included this outcome in the statistical hierarchy.

Health-Related Quality of Life

Short Form (36) Health Survey

In SPIRIT-P1 at week 24, patients in both ixekizumab groups reported higher SF-36 physical component summary scores compared with placebo. The least squares mean differences were 5.29 for ixekizumab 80 mg every two weeks versus placebo and 4.51 for ixekizumab 80 mg every four weeks versus placebo. The differences versus placebo were more modest for the mental component summary than for the physical component summary: 0.72 for ixekizumab 80 mg every two weeks versus placebo and 2.19 for ixekizumab 80 mg every four weeks versus placebo (Appendix 4, Table 20).

In SPIRIT-P2 at week 24, patients in both ixekizumab groups reported higher SF-36 physical component summary scores compared with placebo. The least squares mean differences were 4.9 for ixekizumab 80 mg every two weeks versus placebo and 5.6 for ixekizumab 80 mg every four weeks versus placebo. The differences versus placebo were more modest for the mental component summary than for the physical component summary: 3.1 for ixekizumab 80 mg every two weeks versus placebo and 2.7 for ixekizumab 80 mg every four weeks versus placebo (Appendix 4, Table 20).

However, analyses of these data were not included in the hierarchical statistical analysis approach and should be considered inconclusive because of the potential for inflated type I error.

EuroQol 5-Dimensions 5-Levels

In SPIRIT-P1, there were greater improvements in the EQ-5D-5L health state index and the VAS scores from baseline to week 24 in both ixekizumab groups compared with the placebo group. The least squares mean differences in the health state index were 0.10 for ixekizumab 80 mg every two weeks versus placebo and 0.08 for ixekizumab 80 mg every four weeks versus placebo. The least squares mean differences in the VAS score were 9.3 for ixekizumab 80 mg every two weeks versus placebo and 8.1for ixekizumab 80 mg every four weeks versus placebo (Appendix 4, Table 21)

In SPIRIT-P2, there were greater improvements in the EQ-5D-5L health state index and the VAS scores from baseline to week 24 in both ixekizumab groups compared with the placebo group. The least squares mean differences in the health state index were 0.1 for

ixekizumab 80 mg every two weeks versus placebo and 0.1 for ixekizumab 80 mg every four weeks versus placebo. The least squares mean differences in the VAS score were 11.0 for ixekizumab 80 mg every two weeks versus placebo and 13.5 for ixekizumab 80 mg every four weeks versus placebo (Appendix 4, Table 21)

Measurement of Skin Disease

Psoriasis Area and Severity Index 75

PASI 75 responders are those with a 75% improvement from baseline scores. Only patients with a body surface area involvement ≥ 3% at baseline had a PASI assessment.

In SPIRIT-P1, the proportion of patients achieving PASI 75 response in each of the ixekizumab treatment groups compared with placebo was statistically significantly higher at week 12: 69.5% for ixekizumab 80 mg every two weeks, 75.3% for ixekizumab 80 mg every four weeks, and 7.5% for placebo (both *P* values < 0.001) (Table 10).

In SPIRIT-P2, the proportion of patients achieving PASI 75 response in each of the ixekizumab treatment groups compared with placebo was also statistically significantly higher at week 12: 61.8% for ixekizumab 80 mg every two weeks, 57.4% for ixekizumab 80 mg every four weeks, and 10.4% for placebo (both *P* values < 0.001) (Table 10).

The clinical expert consulted for this review considered that the between-group differences in PASI 75 were clinically relevant.

Table 10: Change From Baseline in PASI 75 at Week 12 and Week 24 (Using NRI, ITT Population With Baseline Psoriatic Lesions Involving ≥ 3% Body Surface Area)

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	**IXE 80 mg q.4.w. (N = 107)**	**ADA 40 mg q.2.w. (N = 101)**	**PL (N = 106)**	**IXE 80 mg q.2.w. (N = 123)**	**IXE 80 mg q.4.w. (N = 122)**	**PL (N = 118)**
PASI 75 at Week 12							
n/N (%)	41/59 (69.5)	55/73 (75.3)	23/68 (33.8)	5/67 (7.5)	42/68 (61.8)	39/68 (57.4)	7/67 (10.4)
Odds ratio (95% CI vs. PL)	29.06 (9.87 to 85.53)	38.80 (13.36 to 112.72)	6.29 (2.20 to 17.95)		16.67 (6.28 to 44.24)	14.03 (5.28 to 37.27)	
P value vs. PL	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	
PASI 75 at Week 24							
n/N (%)	47/59 (79.7)	52/73 (71.2)	37/68 (54.4)	7/67 (10.4)	41/68 (60.3)	38/68 (55.9)	10/67 (14.9)
Odds ratio (95% CI vs. PL)	33.94 (12.30 to 93.69)	21.18 (8.29 to 54.11)	10.25 (4.07 to 25.82)		9.90 (4.17 to 23.54)	7.70 (3.30 to 17.98)	
P value vs. PL	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	

ADA = adalimumab; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ITT = intention-to-treat; IXE = ixekizumab; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation; SE = standard error; TNF = tumour necrosis factor; vs. = versus.

[a] NRI is applied for inadequate responders at week 16 and patients who discontinued on or before week 24. Odds ratio, CI, and *P* value are from a logistic regression model using Wald test with treatment, region, and baseline conventional DMARD experience as factors.

[b] Odds ratio, CI, and *P* value are from a logistic regression model using Wald test with treatment, geographic region, and TNF inhibitor experience in the model.

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Measurement of Other Musculoskeletal Disease

Enthesitis

This outcome was included in the hierarchical statistical analysis. Using multiplicity-controlled analyses, in SPIRIT-P1 there were no statistically significant differences for both ixekizumab groups compared with the placebo group for the change from baseline to week 12 in LEI, and in SPIRIT-P2 there were no statistically significant differences for both ixekizumab groups compared with the placebo group for complete resolution of enthesitis as measured by LEI (LEI score = 0) at week 24 (Table 11)

Table 11: Improvement in LEI at Week 12 (SPIRIT-P1, Using MMRM) and Week 24 (SPIRIT-P2, Using NRI), [redacted]

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
Change From Baseline at Week 12							
n	54	70	53	53			
Baseline, mean (SD)	3.07 (1.776)	2.72 (1.614)	3.02 (1.624)	2.93 (1.678)			
LS mean change (SE)	−1.5 (0.24)	−0.9 (0.21)	−0.8 (0.24)	−0.8 (0.24)			
LS mean difference (95% CI vs. PL)	−0.7 (−1.32 to −0.04)	0 (−0.65 to 0.56)	0 (−0.59 to 0.69)				
P value vs. PL	0.038	0.884	0.879				
Complete Resolution at Week 24							
n/N (%)					30/95 (31.6%)	27/89 (30.3%)	18/82 (22.0%)
Odds ratio (95% CI vs. PL)					1.68 (0.84 to 3.38)	1.55 (0.77 to 3.13)	
P value vs. PL					0.142	0.218	

ADA = adalimumab; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ITT = intention-to-treat; IXE = ixekizumab; LEI = Leeds Enthesitis Index; LS = least squares; MMRM = mixed-effects model for repeated measures; NRI = nonresponder imputation; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation; SE = standard error; TNF = tumour necrosis factor; vs. = versus.

[a] LS mean, LS mean difference, SE, CI, and *P* value are from an MMRM with treatment, region, baseline conventional DMARD experience, visit, and treatment-by-visit interaction as fixed factors, and response value at baseline as a covariate.

[b] Odds ratio, CI, and *P* value were from a logistic regression model using Wald test with treatment, geographic region, and TNF inhibitor experience in the model.

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Dactylitis

In SPIRIT-P1, reductions in the mean LDI-B scores from baseline at week 24 were greater for ixekizumab 80 every two weeks and ixekizumab 80 mg every four weeks than for placebo in patients with dactylitis at baseline (Appendix 4, Table 22). In SPIRIT-P2, differences between ixekizumab 80 every two weeks and ixekizumab 80 mg every four weeks and placebo were negligible for change from baseline in LDI-B scores at week 24. This outcome was not included in the hierarchical statistical analysis approach and should be considered inconclusive because of the potential for inflated type I error (Appendix 4, Table 22)

Axial Arthritis

In SPIRIT-P1 and SPIRIT-P2, change in axial disease was assessed in patients with BASDAI score great than 4 at baseline. Greater improvement in BASDAI scores from baseline to week 24 were observed in each of the ixekizumab groups when compared with the placebo group. This outcome assessment was not included in the hierarchical statistical analysis approach and should be considered inconclusive because of the potential for inflated type I error (Appendix 4, Table 23).

Radiographic Changes

Modified Total Sharp Score

Radiographic change using mTSS was only assessed in SPIRIT-P1. At week 24, the differences in mean change from baseline in mTSS were statistically significant for ixekizumab 80 mg every two weeks versus placebo (−0.41, $P < 0.001$) and for ixekizumab 80 mg every four weeks versus placebo (−0.33, $P = 0.004$) (Table 12). An MCID for mTSS in patients with PsA is unknown.

Table 12: Change From Baseline in mTSS at Week 24 (Using MMRM, ITT Population)

	SPIRIT-P1[a]				SPIRIT-P2		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
n	85	82	83	61	NR		
Baseline, mean (SD)	15.18 (28.855)	19.18 (32.677)	15.91 (27.369)	17.58 (28.616)			
LS mean change (SE)	0.08 (0.083)	0.17 (0.082)	0.10 (0.085)	0.49 (0.086)			
LS mean difference (95% CI vs. PL)	−0.41 −0.63 to −0.19)	−0.33 (−0.55 to −0.10)	−0.39 (−0.61 to −0.16)				
P value vs. PL	< 0.001	0.004	< 0.001				

ADA = adalimumab; CI = confidence interval; ITT = intention-to-treat population; IXE = ixekizumab; LS = least squares; MMRM = mixed-effects model for repeated measures; mTSS = modified Total Sharp Score; NR = not reported; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation; SE = standard error; vs. = versus.

[a] LS mean, LS mean difference, SE, CI, and *P* value are from an MMRM with treatment, region, baseline conventional DMARD experience, visit, and treatment-by-visit interaction as fixed factors, and response value at baseline as a covariate.

Source: Clinical Study Report for SPIRIT-P1.[3]

Harms

Only those harms identified in the review protocol are reported in this section.

Adverse Events

In SPIRIT-P1, AEs were reported in 66% of patients in each of the ixekizumab groups and 47% in the placebo group during the double-blind treatment period. In SPIRIT-P2, the overall incidence of AEs was higher in the ixekizumab 80 mg every-two-weeks group (73.2%) and ixekizumab 80 mg every-four-weeks group (68%) than in the placebo group (64.4%) during the double-blind treatment period. Generally, the majority of AEs were mild

or moderate in severity in both studies. The most frequently reported AEs were infections and injection site reactions (Table 13)

Serious Adverse Events

In SPIRIT-P1, higher rates of SAEs were reported in the ixekizumab 80 mg every-two-weeks group (2.9%) and ixekizumab 80 mg every-four-weeks group (5.6%) than in the placebo group (1.9%). In SPIRIT-P2, patients in the ixekizumab 80 mg every-two-weeks group (6.5%) had a higher risk of SAEs; however, the ixekizumab 80 every-four-weeks group (2.5%) had a lower rate of SAEs than the placebo group (3.4%). Details of the reported SAEs are presented in Table 13.

Withdrawals Due to Adverse Events

In SPIRIT-P1 and SPIRIT-P2, isolated cases of WDAEs during the double-blind treatment period were reported across the treatment groups. Details of the reported WDAEs are presented in Table 13.

Mortality

There were no deaths in any of the studies during the double-blind treatment period.

Notable Harms

In SPIRIT-P1, 23.5%, 28%, and 25.5% of patients with ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo experienced infections during the double-blind period, respectively. Upper respiratory tract infection, nasopharyngitis, and bronchitis were the commonly reported infections. Injection site reactions were another commonly reported AE associated with the use of ixekizumab. The proportions of patients reporting injection site reactions were 26.5%, 24.3%, and 4.7% in the ixekizumab 80 mg every-two-weeks group, ixekizumab 80 mg every-four-weeks group, and placebo group, respectively. Hepatotoxicity occurred in 8.8%, 4.7%, and 6.6% of patients from the aforementioned treatment groups, respectively. Eleven cases of cytopenias occurred in the ixekizumab groups and placebo group: four in the ixekizumab 80 mg every-two-weeks group, one in the ixekizumab 80 mg every-four-weeks group, and six in the placebo group. No cases of inflammatory bowel disease were reported.

In SPIRIT-P2, 38.2%, 38.5%, and 29.7% of patients with ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo experienced infections during the double-blind period, respectively. Upper respiratory tract infection and sinusitis were the commonly reported infections. Hypersensitivity and injection site reactions were also commonly reported AEs associated with the use of ixekizumab in the study population. The proportions of patients reporting injection site reactions were 23.6%, 11.5%, and 4.2% in the ixekizumab 80 mg every-two-weeks group, ixekizumab 80 mg every-four-weeks group, and placebo group, respectively. Hypersensitivity was reported in 11.4%, 10.7%, and 5.1% of the patients in these three groups, respectively. Hepatotoxicity occurred in 4.1%, 1.6%, and 1.7% of patients from the aforementioned three treatment groups, respectively. Cytopenias or inflammatory bowel disease were not reported in this study.

Table 13: Harms

	SPIRIT-P1				SPIRIT-P2		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
AEs							
Patients with ≥ 1 AE, n (%)	67 (65.7)	71 (66.4)	65 (64.4)	50 (47.2)	90 (73.2)	83 (68.0)	76 (64.4)
Most common AEs[a]							
Infections	24 (23.5)	30 (28.0)	26 (25.7)	27 (25.5)	47 (38.2)	47 (38.5)	35 (29.7)
Allergic reactions/ hypersensitivities	5 (4.9)	2 (1.9)	5 (5.0)	3 (2.8)	14 (11.4)	13 (10.7)	6 (5.1)
Injection site reactions	27 (26.5)	26 (24.3)	6 (5.9)	5 (4.7)	29 (23.6)	14 (11.5)	5 (4.2)
Hepatic events	9 (8.8)	5 (4.7)	13 (12.9)	7 (6.6)	5 (4.1)	2 (1.6)	2 (1.7)
Diarrhea	5 (4.9)	2 (1.9)	3 (3.0)	3 (2.8)			
SAEs							
Patients with ≥ 1 SAE, n (%)	3 (2.9)	6 (5.6)	5 (5.0)	2 (1.9)	8 (6.5)	3 (2.5)	4 (3.4)
	Herpes zoster 1, esophageal candidiasis 1, impaired gastric emptying, cervical myelopathy 1, acquired phimosis 1	Gastroenter-itis 1, pancreatitis acute 1, post-traumatic headache 1, uterine polyp 1, cholelithiasis 1, fall 1, fibula fracture 1, lumber spinal stenosis 1	Cellulitis 1, pneumonia mycoplasmal 1, gastric ulcer 1, esophagitis 1, carotid artery occlusion 1, metrorrhagia 1	Bartholin's cyst 1, ↑ hepatic enzyme 1	Abscess jaw 1, anal abscess 1, perirectal abscess 1, iron deficiency anemia 1, anal fistula 1, fall 1, foot fracture 1, diabetes 1, abortion spontaneous 1, uterine prolapse 1	Vertigo 1, myofascial pain syndrome 1, cervicobrach-ial syndrome 1, prostate cancer 1	Abdominal pain 1, femoral neck fracture 1, tendon rupture 1, adnexa uteri cyst 1, peripheral arterial occlusive 1
WDAEs							
Patients with ≥ 1 WDAE, n (%)	4 (3.9)	2 (1.9)	2 (2.0)	2 (1.9)	8 (6.5)	5 (4.1)	6 (5.1)
	Injection site hypersensitivit y 1, injection site reaction 1, interferon gamma	Interferon gamma release assay (+) 1, hypersensitivity 1	Injection site reaction 1, hypersensitivity 1	Asthenia 1, injection site pain 1	Injection site rash 1, folliculitis 1, abdominal pain 1, hypertransamin	Injection site reaction 1, subcutaneous abscess 1, urinary tract infection 1,	Edema 1, lower respiratory tract infection 1, hepatitis 1, pruritus generalized 1,

	SPIRIT-P1				SPIRIT-P2		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
	release assay (+) 1, depression 1				asaemia 1, diabetes 1, abortion spontaneous 1, nasal necrosis 1	prostate cancer 1, rash pruritic 1	psoriatic arthropathy 1, adnexa uteri cyst 1
Deaths							
Number of deaths, n (%)	0	0	0	0	0	0	0
Notable Harms							
Infections	24 (23.5)	30 (28.0)	26 (25.7)	27 (25.5)	47 (38.2)	47 (38.5)	35 (29.7)
Upper respiratory tract infection	3 (2.9)	5 (4.7)	5 (5.0)	7 (6.6)	12 (9.8)	11 (9.0)	9 (7.6)
Nasopharyngitis	3 (2.9)	7 (6.5)	7 (6.9)	5 (4.7)	4 (3.3)	8 (6.6)	4 (3.4)
Sinusitis	1 (1.0)	1 (0.9)	2 (2.0)	3 (2.8)	5 (9.8)	7 (13.4)	2 (4.5)
Urinary tract infection	0	2 (1.9)	4 (4.0)	2 (1.9)	4 (3.3)	6 (4.9)	3 (2.5)
Bronchitis	3 (2.9)	3 (2.8)	4 (4.0)	3 (2.8)	4 (3.3)	1 (0.8)	4 (3.4)
Oral candidiasis					4 (3.3)	0	0
Tonsillitis	0	1 (0.9)	0	0	0	4 (3.3)	0
Vulvovaginal candidiasis	NR				2 (2.7)	0	0
Hypersensitivities	5 (4.9)	2 (1.9)	5 (5.0)	3 (2.8)	14 (11.4)	13 (10.7)	6 (5.1)
Injection site reactions	27 (26.5)	26 (24.3)	6 (5.9)	5 (4.7)	29 (23.6)	14 (11.5)	5 (4.2)
Hepatotoxicity	9 (8.8)	5 (4.7)	13 (12.9)	7 (6.6)	5 (4.1)	2 (1.6)	2 (1.7)
Elevated AST	3 (2.9)	2 (1.9)	2 (2.0)	0	2 (1.6)	1 (0.8)	1 (0.8)
Elevated ALT	4 (3.9)	3 (2.8)	3 (3.0)	0	NR		
Cytopenias	4 (3.9)	1 (0.9)	4 (4.0)	6 (5.7)	0	0	0
Inflammatory bowel disease	0	0	0	0	0	0	0

ADA = adalimumab; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; IXE = ixekizumab; NR = not reported; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: Clinical Study Reports of SPIRIT-P1[3] and SPIRIT-P2.[4]

Discussion

Summary of Available Evidence

Two multi-centre, phase III, randomized, double-blind, placebo-controlled superiority trials, SPIRIT-P1 (N = 417) and SPIRIT-P2 (N = 363), met the inclusion criteria for this systematic review. The studies included adult patients with an established diagnosis of PsA. Patients in SPIRIT-P1 were biologic DMARD-naive, while those in SPIRIT-P2 were conventional DMARD-experienced and had received previous TNF inhibitor therapy, but the TNF inhibitor was discontinued due to inadequate response or intolerance to the treatment. The efficacy and safety of ixekizumab 80 mg every two weeks and ixekizumab 80 mg every four weeks were compared with placebo in both studies. In addition, adalimumab 40 mg every two weeks was included in SPIRIT-P1 for the purpose of providing internal evidence of assay sensitivity. At week 16, patients who were inadequate responders to the randomized treatment (placebo or adalimumab) were re-randomized to either ixekizumab regimen. The primary end point in SPIRIT-P1 and SPIRIT-P2 was the proportion of patients in each treatment group who achieved ACR20 response at week 24. Both studies had an appropriate randomization strategy, with generally similar treatment groups at baseline. In SPIRIT-P1 and SPIRIT-P2, 39.6% and 47.5% of patients in the placebo groups, respectively, discontinued the originally assigned treatment before week 24 (either due to early escape at week 16 or because of treatment discontinuation). This means that a substantial proportion of the outcome data at week 24 had to be imputed based on an ITT analysis. Therefore, there is a high degree of uncertainty with respect to the findings of the studies beyond the week 16 time point. Subgroup analysis by disease severity was performed in SPIRIT-P2. Furthermore, the doses of ixekizumab every two weeks in SPIRIT-P1 and SPIRIT-P2 are not consistent with the Health Canada–recommended dose. Health Canada recommends that patients with PsA with coexistent moderate to severe plaque psoriasis receive the dosing regimen for plaque psoriasis, which is 160 mg at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, and then 80 mg every four weeks. Thus, continuance of the ixekizumab every-two-weeks dosing beyond week 12 in SPIRIT-P1 and SPIRIT-P2 is inconsistent with Health Canada–recommended dosing.

Interpretation of Results

Efficacy

For the primary efficacy outcome, ACR20 response at week 24, both ixekizumab treatment groups were statistically significantly superior to placebo: in SPIRIT-P1, 62.1%, 57.9%, and 30.2% of patients treated with ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo achieved ACR20 response, respectively; in SPIRIT-P2, 48.0%, 53.3%, and 19.5% of patients treated with ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo achieved ACR20 response, respectively (all *P* values for ixekizumab versus placebo < 0.001). The findings for ACR20 responses also favoured the two ixekizumab groups at week 12. While the week 24 data are potentially biased due to differential rescue/withdrawal, the week 12 data do not suffer this limitation and were similar to the week 24 data, which supports the validity of the treatment effect of ixekizumab.

Results of the subgroup analyses by disease severity at baseline were in line with results from the overall population for ACR20 response; however, these analyses were not included in the hierarchical statistical analysis approach and should be considered

inconclusive because of the potential for inflated type I error. The clinical expert consulted for this review noted that the differences in ACR20 response compared with placebo were clinically meaningful. Treatment with ixekizumab was found to be superior to placebo in achieving MDA responses at week 24 in the study population. The improvement in physical function as measured with HAQ-DI was statistically and clinically significant. For the subset of patients with enthesitis at baseline, improvement in enthesitis was uncertain at week 24. Claim of statistical significance could not be made for change from baseline in LEI in either ixekizumab group because the outcome assessed in the hierarchy [LEI] did not achieve statistical significance. The small number of patients in this subset may explain the statistically nonsignificant difference between ixekizumab and placebo. For patients with dactylitis at baseline, improvement in dactylitis was uncertain between ixekizumab and placebo at week 24 in both studies, because change in dactylitis (measured with LDI-B) was not included in the multiplicity-controlled analysis; therefore, the results should be considered inconclusive. Common themes seen as important in the patient group input were improvements in quality of life and work productivity (Appendix 1). In SPIRIT-P1 and SPIRIT-P2, SF-36 was used to assess HRQoL. In both SPIRIT-P1 and SPIRIT-P2, greater improvements were observed in the physical component summary scores of the SF-36 among both ixekizumab treatment groups compared with those in the placebo group at week 24, while the differences between both ixekizumab treatment groups and placebo in the mental component summaries were more modest. The results suggested that treatment with ixekizumab was associated with improved HRQoL, in particular for patient's physical well-being domain. However, the SF-36 physical and mental component summaries were not part of the hierarchical analysis plan and therefore were not adjusted for multiple comparisons, hence the level of significance is inflated and results should be interpreted with caution. Work productivity was assessed in a portion of study participants in SPIRIT-P1 and SPIRIT-P2. Although the results implied that there was improvement from baseline in various aspects of work productivity as measured with WPAI-SHP, it is challenging to interpret the data when this outcome was not included in the hierarchical statistical analysis approach. PsA symptoms such as fatigue and arthritis pain were reported in both studies. At week 24, the between-group differences in the mean score change from baseline for these patient-reported outcomes favoured ixekizumab compared with placebo. The outcome measures of patient's assessment of pain and FSNRS were not part of the hierarchical analysis plan and therefore were not adjusted for multiple comparisons, hence the level of significance is inflated and results should be interpreted with caution. Radiographic change using mTSS was assessed only in SPIRIT-P1. The between-treatment difference in mean change from baseline in mTSS was statistically significantly lower (better) than that in the placebo group at week 24. The clinical expert consulted for this review noted that it is difficult to observe meaningful radiographic changes within 24 weeks in the study population.

Results of the extension phase of SPIRIT-P1 suggested that the improvements in clinical and patient-reported outcomes observed at week 24 were maintained throughout the 52-week extension period in both the ixekizumab every-two-weeks and ixekizumab every-four-weeks dosing regimens. Patients re-randomized to ixekizumab every four weeks or ixekizumab every two weeks from placebo or adalimumab also showed improvements of clinical and patient-reported outcomes at week 52 that were similar to the efficacy achieved by the groups remaining on ixekizumab from baseline to week 52. However, the longer term phases of the study had limited clinical value for the following reasons: there were no control groups, and the background therapies were allowed to be modified. As a result, it is impossible to disentangle the drug effect from the changes in the background therapies on the reported outcomes. Furthermore, given that all patients were aware that they were

receiving ixekizumab, results for patient-reported and subjective outcomes may be subject to bias (see Appendix 6).

In the absence of sufficient head-to-head trial data for ixekizumab with other biologic drugs to treat PsA, the manufacturer conducted an indirect analysis based on a systematic review of randomized controlled trials and compared the efficacy and safety of ixekizumab with adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab (Appendix 7). Efficacy and safety outcomes were evaluated, but no HRQoL data were assessed. There was insufficient information about the individual trials, limiting the ability to assess clinical heterogeneity of the included studies. Based on data from 12 weeks (up to 16 weeks), analyses in biologic-naive populations suggest that ixekizumab tended to perform better in the PASI analyses and not as favourably in the ACR, PsARC, and HAQ-DI analyses relative to other biologics. Analyses in biologic-experienced populations suggest no difference between ixekizumab and other biologic drugs for efficacy outcomes.

Harms

By week 24, the frequency of SAEs was low, and isolated cases of SAEs were reported for the ixekizumab and placebo treatment groups. WDAEs were also low in all treatment groups. Patients treated with either ixekizumab therapy had a higher risk of treatment-emergent AEs compared with those in the placebo group, with the most common AEs being infections, hypersensitivity, and injection site reactions. No death was reported in any of the treatment groups included in this review.

The safety profile of ixekizumab over 52 weeks was consistent with that observed during the 24-week double-blind period, with no unexpected safety signals reported. Findings from the indirect comparison submitted by the manufacturer suggested that there were no differences in likelihood of AEs or SAEs between ixekizumab and other biologics in the mixed biologic-naive and biologic-experienced population, based on data from 12 weeks (up to 16 weeks).

Potential Place in Therapy[2]

At this date, ixekizumab will be the second IL-17 inhibitor for the treatment of psoriasis and PsA. The following comments are specific to PsA only.

Ixekizumab joins a crowded biologic marketplace in PsA. It will compete with the five original TNF inhibitors, at least two biosimilar TNF inhibitors, apremilast, and the IL-17 inhibitor secukinumab. Shortly, the IL-17 inhibitors gesulkumab and brodalumab may join the marketplace, and in the near future one or more Janus kinase inhibitors. Informal comparisons of all the drugs available to treat PsA do not discern obvious differences in efficacy, substantiated by a formal network meta-analysis provided by the manufacturer.[2] Therefore it is difficult to say that there is an unmet need for ixekizumab in PsA. Further, there is no reason to think that ixekizumab is likely to be more effective for PsA patients with enthesitis, dactylitis, sacroiliitis, or spondylitis.

Compared with TNF inhibitors (except etanercept), IL-17 inhibitors are at a disadvantage in the treatment of PsA patients who have a history of uveitis or inflammatory bowel disease. The role of IL-17 inhibitors in precipitating inflammatory bowel disease or uveitis in patients without a history remains a topic of interest to be fully defined. Measurement of fecal calprotectin, traditional colonoscopy, and video capsule endoscopy to identify patients in

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

whom *not* to use an IL-17 inhibitor are under consideration, but are costly and with some risk.[30] Based on these concerns, TNF inhibitors will probably be the first-line therapy for PsA patients.

Ixekizumab may have an advantage over secukinumab in PsA patients who have failed or have been intolerant to a TNF inhibitor. There is no direct comparison. Secukinumab was not assessed in a study dedicated to patients who were TNF exposed, although in the FUTURE 2 study of secukinumab administered by the subcutaneous route, 35% of patients had been exposed to a TNF inhibitor.[18,31] The 150 mg dose of secukinumab was barely effective. The 300 mg dose was associated with an ACR20 response of 45.5% compared with 58.2% in TNF-naive patients. This magnitude of diminished activity is seen commonly in TNF inadequate responders. In contrast, when ixekizumab was studied in TNF inadequate responders there was not a large drop in the ACR20 response in TNF inadequate responders in the lower dose (administered every four weeks), which suggests a benefit for ixekizumab based on both efficacy and cost.

Conclusions

Based on two double-blind randomized controlled trials (SPIRIT-P1 and SPIRIT-P2) in adult patients with active PsA and who were either biologics-naive or TNF inhibitor–experienced, respectively, treatment with ixekizumab 80 mg every two weeks and ixekizumab 80 mg every four weeks is associated with statistically significant and clinically meaningful improvements in the primary efficacy outcome, ACR20 response at weeks 12 and 24. Statistically significant changes were also reported for other outcomes related to the clinical response, such as MDA at week 24 favouring treatment with ixekizumab. Greater improvement was seen in quality of life, physical function, fatigue, and pain at week 24 in the ixekizumab groups compared with the placebo groups. Except for ACR20, MDA, HAQ-DI, radiographic changes measured with mTSS, change in skin disease measured with PASI, and change in enthesitis measured with LEI, adjustment for multiplicity was not done for all other outcomes; hence, results for these outcomes are considered inconclusive. In both studies, a very large proportion of placebo patients discontinued randomized treatment before week 24 (either due to early escape or because of treatment discontinuation), so claims of efficacy at week 24 are uncertain.

Overall, the incidence of treatment-emergent AEs was higher than placebo with both ixekizumab groups in patients who were biologic-naive or TNF inhibitor–experienced. Infections, hypersensitivity, and injection site reactions were common AEs. Moreover, PsA is a chronic condition that will be treated over a lifetime, and therefore a 24-week controlled trial is a short duration to evaluate harms.

Findings of the extension phase of SPIRIT-P1 suggested that the improvements in clinical and patient-reported outcomes observed at week 24 were maintained throughout the 52-week extension period. The safety profile of ixekizumab over 52 weeks was consistent with that observed during the 24-week double-blind period, with no unexpected safety signals reported. Based on the short-term data provided in a manufacturer-submitted network meta-analysis, in biologic-naive populations, ixekizumab tended to perform better in the PASI analyses and not as favourably in the ACR, PsARC, and HAQ-DI analyses relative to other biologics. Analyses in biologic-experienced populations showed no difference between ixekizumab and other biologic drugs for efficacy outcomes. In addition, there were no differences in likelihood of AEs or SAEs between ixekizumab and other biologics in the mixed biologic-naive and biologic-experienced population.

Appendix 1: Patient Input Summary

This section was summarized by CADTH staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

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

Four inputs were received from the following seven patient groups: Arthritis Consumer Experts, The Arthritis Society, the Canadian Arthritis Patient Alliance, The Canadian Spondylitis Association, the Canadian Skin Patient Alliance, the Canadian Association of Psoriasis Patients, and the Canadian Psoriasis Network.

Arthritis Consumer Experts is a national patient-led organization that provides science-based information, education and support programs to people with all forms of arthritis. The submission was expressly researched and written by Arthritis Consumer Experts and was free from advice or influence from any outside individual, group, or company. Over the past two years, Arthritis Consumer Experts received grants-in-aid from Eli Lilly Canada.

The Arthritis Society is Canada's principal health charity providing education, programs, and support to Canadians living with arthritis. The Canadian Arthritis Patient Alliance is a grassroots, patient-driven, independent, national education and advocacy organization with members and supporters across Canada. The submission, which was jointly prepared by the Society and the Alliance, was not influenced by any outside party. The Arthritis Society and the Canadian Arthritis Patient Alliance have received financial support from AbbVie, Amgen, Celgene, Eli Lilly, GSK, IMC, Janssen, Manulife, Merck, Novartis, Pfizer (including Pfizer Hospira), Purdue, Roche, Sandoz, Sanofi, and UCB.

The Canadian Spondylitis Association is a volunteer-run patient association to support, educate, and advocate for those living with spondyloarthritis.[32] The Association's submission was prepared by the Association without influence from any outside party. The Canadian Spondylitis Association has received financial support from AbbVie, Amgen, Eli Lilly, Janssen, Merck, Novartis, Pfizer, and UCB.

The Canadian Skin Patient Alliance, a national non-profit organization dedicated to advocating for, educating, and supporting Canadians living with skin diseases, conditions, and traumas,[33] worked in collaboration with the Canadian Association of Psoriasis Patients as well as the Canadian Psoriasis Network on this submission. The Canadian Association of Psoriasis Patients is a subsidiary of the Canadian Skin Patient Alliance and was formed to serve the needs of psoriasis patients across the country.[34] The Canadian Psoriasis Network is a national non-profit organization dedicated to improving the quality of life of all Canadians who are living with psoriasis and psoriatic arthritis (PsA) while vigorously pursuing a cure. The submission jointly prepared by these three groups was not influenced by any outside party. The Canadian Skin Patient Alliance, the Canadian Association of Psoriasis Patients, and the Canadian Psoriasis Network received financial support from AbbVie Canada, Amgen, Celgene, Eli Lilly, Janssen Canada, Leo Pharma, Novartis, and Pfizer Canada over the past two years.

2. Condition-Related Information

Information was gathered through a call for patient input, day-to-day interactions with people living with PsA, discussions with consumers and scientific members of the patient groups, patients' inputs for a previous submission for PsA, researchers, survey, or information gathered from patient websites and online disease discussion. Patient groups highlighted that PsA negatively impacts all aspects of a person's life, including the ability to

work. A patient's overall quality of life is significantly affected, and social activities, such as going out with friends and caring for grandchildren, are rare due to physical limitations. Symptoms having the greatest impact on their day-to-day life include significant pain, stiffness, fatigue, and limited range of motion in the joints. People also indicated that the skin sensitivity, redness, flaking, and pain from plaque psoriasis that accompanies PsA had considerable impact. Depression and mental health issues can be associated with PsA as well. A period of very active disease is called a flare, and for some people, flares can be incapacitating. Flares are not predictable in terms of how bad they will be or how long they will last. Caregivers of patients with PsA have indicated that time is always a concern for them. They have to arrange their day according to the person living with PsA. When patients are in pain, caregivers have to help with house chores. Some quotations from patients are provided here:

> "My life went from waking up and going about my day to planning, struggling, and having to be careful of what I do, where I go, and the unpredictability of the disease."

> "Pain/stiffness/swelling especially in the morning and late evening make activity difficult. The fatigue is especially difficult to manage…"

> "My caregivers have been stretched over the years but they are very supportive. PsA has impacted my caregivers just as negatively as me."

3. Current Therapy–Related Information

Current treatments for PsA range from naproxen, methotrexate, folic acid, and medical cannabis to disease-modifying antirheumatic drugs (DMARDs) and biologics. Patients react differently to these treatments in terms of benefits and side effects. The Arthritis Society and the Canadian Arthritis Patient Alliance indicated that there is currently no way to predict how a person's PsA will respond to any type of medication. In some cases, the body may develop a resistance to medication requiring changes in the treatment plan. Some quotations from patients with respect to the effect of currently available treatment regimens are presented here:

> "Current available treatments have advanced but my body has so much damage that surgeries are part of my treatment. With the ups and downs of surgery, managing my disease is still a struggle."

> "Medications I have used include Enbrel, Humira, and Stelara. I currently take Cosentyx, methotrexate, naproxen, prednisone, and leflunomide. I had early success with Enbrel and Humira and eventually these became ineffective after a few years… I am experiencing slight success with Cosentyx, but it is not 100%..."

> "I would like more energy."

> "I just want less intense flare-ups and fewer of them. On Humira they were much less frequent and intense."

> (With the treatment) "Don't have to think about stiffness. Few side effects of drug. Fix the fatigue."

4. Expectations About the Drug Being Reviewed

There is no cure for PsA, which means that patients need to go on medications for life. As a result, it is essential for patients to have access to an array of medications, including DMARDs (such as methotrexate) and a combination of biologics and DMARDs, in order to provide options to allow for individualized approaches to disease management. It is

important to know that people will often go through many different treatments over the course of their lifetime. It is also an anxious and stressful experience if medications cost thousands of dollars out of pocket. Patients want new treatments that can control or stop the symptoms of PsA and improve their quality of life, and they believe that the best treatment is the one that has the fewest side effects.

Of the patient groups that provided input, only one patient who responded to the survey of the Arthritis Society and the Canadian Arthritis Patient Alliance had experience using ixekizumab (Taltz) to treat PsA. This patient said, “I have participated in a clinical trial on a volunteer basis. My psoriasis is under control and more than 90% of it has ‘disappeared.’ Arthritis pains: a 50% to 60% improvement, having gone from 9.5/10 to now being 3 or 4/10. No adverse reaction or side effect. It is easy to use, and to self-inject. In only three months, it has positively changed — and will change — my health status and condition. I am convinced this medication can stabilize my health condition in the long term. I can now do my job better (as a building inspector)” (translated from the original quotation in French).

Other quotations related to the use of ixekizumab for PsA were gathered from the patient websites and online disease discussion boards:

> “I have severe PsA and have tried everything. I am on Taltz now, which is helping to a degree. The pain was a lot worse before I started it, however I am still in pain on and off most of the day.”
>
> “I have been on Taltz since January and it cleared ALL of my psoriasis, however I also have arthritis and it has done nothing to help it.”

Although only one respondent had experience on ixekizumab, all patients groups expected to see another option available to Canadians. Patients believe that new therapies provide hope for those who have not found a medication that works for them and relief to know there are more options available.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE ALL 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 19, 2018
Alerts:	Bi-weekly search updates until July 18, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.nm	Name of substance word
.pt	Publication type
.rn	Case Registry/EC number/Name of substance
medall	Ovid database code; MEDLINE ALL (1946-)
oemezd	Ovid database code; Embase 1974 to present, updated daily
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title

MULTI-DATABASE STRATEGY	
Line #	**Search String**
1	(taltz* or ixekizumab* or LY2439821 or LY 2439821 or BTY153760O or BTY 153760O).ti,ot,ab,kf,rn,hw,nm.
2	1 use medall
3	*ixekizumab/ or (taltz* or ixekizumab* or LY2439821 or LY 2439821).ti,ab,kw.
4	3 not conference abstract.pt.
5	4 use oemezd
6	2 or 5
7	remove duplicates from 6

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

Grey Literature

Dates for Search:	March 2018
Keywords:	Taltz, ixekizumab, psoriatic arthritis
Limits:	No date or language limits used

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

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

Appendix 3: Excluded Studies

Table 14: Excluded Studies

Reference	Reason for Exclusion
No studies were excluded from the study selection process.	

Appendix 4: Detailed Outcome Data

Table 15: Proportion of Patients With ACR50/70 Response at Week 24 (Using NRI, ITT Population)

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
ACR50							
n (%)	48 (46.6)	43 (40.2)	39 (38.6)	16 (15.1)	41 (33.3)	43 (35.2)	6 (5.1)
Odds ratio (95% CI vs. PL)	4.98 (2.573 to 9.638)	3.82 (1.974 to 7.379)	3.56 (1.828 to 6.942)		9.31 (3.75 to 23.13)	10.83 (4.31 to 27.23)	
P value vs. PL	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	
ACR70							
n (%)	35 (34.0)	25 (23.4)	26 (25.7)	6 (5.7)	15 (12.2)	27 (22.1)	0
Odds ratio (95% CI vs. PL)	8.68 (3.458 to 21.801)	5.12 (2.003 to 13.094)	5.79 (2.269 to 14.793)		NA from a logistic regression model	NA from a logistic regression model	
P value vs. PL	< 0.001	< 0.001	< 0.001		NA from a logistic regression model; < 0.001 based on Fisher's exact test	NA from a logistic regression model; < 0.001 based on Fisher's exact test	

ACR50/70 = American College of Rheumatology 50%/70% response; ADA = adalimumab; CI = confidence interval; DMARD = disease-modifying antirheumatic drugs; ITT = intention-to-treat; IXE = ixekizumab; NA = not applicable; NRI = nonresponder imputation; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; TNF = tumour necrosis factor; vs. = versus.

[a] NRI is applied for inadequate responders at week 16 and patients who discontinued on or before week 24. Odds ratio, CI, and *P* value are from a logistic regression model using Wald test with treatment, region, and baseline conventional DMARD experience as factors.

[b] NRI is applied for inadequate responders at week 16 and patients who discontinued on or before week 24. Odds ratio, CI, and *P* value are from a logistic regression model using Wald test with treatment, geographic region, and TNF inhibitor experience in the model.

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Table 16: Proportion of Patients Achieving PsARC Response at Week 24 (Using NRI, ITT Population)

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
n (%)	68 (66.0)	62 (57.9)	59 (58.4)	34 (32.1)	58 (47.2)	68 (55.7)	24 (20.3)
Odds ratio (95% CI vs. PL)	4.23 (2.36 to 7.57)	2.97 (1.69 to 5.22)	3.02 (1.70 to 5.35)		3.55 (1.99 to 6.32)	5.00 (2.81 to 8.90)	
P value vs. PL	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	

ADA = adalimumab; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ITT = intention-to-treat; IXE = ixekizumab; NRI = nonresponder imputation; PL = placebo; PsARC = Psoriatic Arthritis Response Criteria; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; TNF = tumour necrosis factor; vs. = versus.

[a] NRI is applied for patients who discontinued on or before week 24. Odds ratio, CI, and *P* value are from a logistic regression model using Wald test with treatment, region, and baseline conventional DMARD experience as factors.

[b] NRI is applied for inadequate responders at week 16 and patients who discontinued on or before week 24. Odds ratio, CI, and *P* value are from a logistic regression model using Wald test with treatment, geographic region, and TNF inhibitor experience in the model.

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Table 17: Change From Baseline in WPAI-SHP Scores at Week 24 (Using MMRM, ITT Population)

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
Absenteeism Score Change From Baseline							
n	39	46	50	28	NR		
Baseline, mean (SD)	NR						
LS mean change (SE)	0.9 (2.76)	−5.5 (2.57)	−0.5 (2.52)	−0.2 (3.19)			
LS mean difference (95% CI vs. PL)	1.0 (−7.13 to 9.21)	−5.4 (−13.26 to 2.56)	−0.3 (−8.13 to 7.52)				
P value vs. PL	0.802	0.183	0.938				
Presenteeism Score Change From Baseline							
n	37	45	47	27	NR		
Baseline, mean (SD)	NR						
LS mean change (SE)	−22.1 (2.83)	−19.4 (2.62)	−13.2 (2.69)	−6.8 (3.15)			
LS mean difference (95% CI vs. PL)	−15.2 (−23.21 to −7.28)	−12.6 (−20.25 to −4.94)	−6.3 (−14.01 to 1.31)				
P value vs. PL	< 0.001	0.001	0.104				
Work Productivity Score Change From Baseline							
n	37	45	47	27	NR		
Baseline, mean (SD)	NR						
LS mean change (SE)	−20.7 (3.15)	−20.6 (2.91)	−13.4 (2.97)	−8.3 (3.52)			
LS mean difference (95% CI vs. PL)	−12.3 (−21.23 to −3.39)	−12.3 (−20.85 to −3.71)	−5.1 (−13.68 to 3.48)				
P value vs. PL	0.007	0.005	0.242				
Activity Impairment Score Change From Baseline							
n	84	83	85	62	NR		
Baseline, mean (SD)	NR						
LS mean change (SE)	−26.1 (2.31)	−22.6 (2.31)	−16.3 (2.32)	−8.1 (2.50)			
LS mean difference (95% CI vs. PL)	−18.0 (−24.42 to −11.63)	−14.6 (−20.95 to −8.18)	−8.2 (−14.58 to −1.83)				
P value vs. PL	< 0.001	< 0.001	0.012				
Overall Work Impairment Score							
n	NR				41	43	25
Baseline, mean (SD)					38.8 (26.55)	46.9 (26.71)	41.5 (29.64)
LS mean change (SE)					−17.6 (4.57)	−23.2 (4.73)	−4.5 (5.43)
LS mean difference (95% CI vs. PL)					−13.0 (−23.4 to −2.7)	−18.6 (−28.9 to −8.4)	

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
P value vs. PL					0.014	< 0.001	
Percentage of Absenteeism							
n	NR				43	45	27
Baseline, mean (SD)					8.8 (23.21)	11.6 (26.63)	11.9 (28.12)
LS mean change (SE)					9.4 (4.40)	3.7 (4.55)	4.5 (4.97)
LS mean difference (95% CI vs. PL)					4.9 (−4.9 to 14.7)	−0.8 (−10.5 to 8.9)	
P value vs. PL					0.326	0.869	
Percentage of Presenteeism (Reduced Productivity While at Work)							
n	NR				41	43	25
Baseline, mean (SD)					36.9 (25.00)	45.0 (25.74)	40.4 (28.78)
LS mean change (SE)					−24.0 (4.13)	−26.6 (4.28)	−7.2 (4.87)
LS mean difference (95% CI vs. PL)					−16.8 (−26.2 to −7.4)	−19.4 (−28.6 to −10.1)	
P value vs. PL					< 0.001	< 0.001	
Percentage of Impairment in Activities Performed Outside of Work							
n	NR				90	93	64
Baseline, mean (SD)					49.3 (26.51)	53.9 (24.91)	54.0 (25.80)
LS mean change (SE)					−26.2 (3.73)	−30.2 (3.88)	−14.8 (4.12)
LS mean difference (95% CI vs. PL)					−11.4 (−18.7 to −4.1)	−15.4 (−22.7 to −8.2)	
P value vs. PL					0.002	< 0.001	

ADA = adalimumab; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ITT = intention-to-treat; IXE = ixekizumab; LS = least squares; MMRM = mixed-effects model for repeated measures; NR = not reported; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation; SE = standard error; TNF = tumour necrosis factor; vs. = versus; WPAI-SHP = Work Productivity and Activity Impairment–Specific Health Problem.

[a] LS mean, LS mean difference, SE, CI, and *P* value are from an MMRM with treatment, region, baseline conventional DMARD experience, visit, and treatment-by-visit interaction as fixed factors, and response value at baseline as a covariate.

[b] LS mean, SE, 95% CI, and *P* value are based on an MMRM model that includes treatment, visit, geographic region, TNF inhibitor experience (inadequate responder to 1 TNF inhibitor, inadequate responder to 2 TNF inhibitors, or intolerance to a TNF inhibitor), treatment-by-visit interaction, geographic region–by-visit interaction, and TNF inhibitor experience–by-visit interaction as well as the continuous, fixed covariates of baseline value and baseline value–by-visit interaction, with variance-covariance structure set as follows: overall work impairment score — unstructured (for change from baseline); percentage of absenteeism — unstructured (for change from baseline); percentage of presenteeism (reduced productivity while at work) — unstructured (for change from baseline); and percentage of impairment in activities performed outside of work — unstructured (for change from baseline).

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Table 18: Change From Baseline in Patient's Assessment of Pain-VAS Score at Week 24 (Using MMRM, ITT Population)

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
n	84	83	87	63	91	95	64
Baseline, mean (SD)	58.40 (21.66)	60.11 (19.42)	58.67 (19.73)	58.51 (22.96)	62.7 (20.87)	63.9 (21.40)	63.9 (20.11)
LS mean change (SE)	−31.6 (2.54)	−29.6 (2.51)	−30.0 (2.52)	−14.0 (2.68)	−33.5 (3.58)	−36.9 (3.74)	−21.4 (3.97)
LS mean difference (95% CI vs. PL)	−17.6 (−24.64 to −10.56)	−15.6 (−22.63 to −8.63)	−16.0 (−22.99 to −9.01)		−12.0 (−19.0 to −5.0)	−15.5 (−22.4 to −8.5)	
P value vs. PL	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	

ADA = adalimumab; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ITT = intention-to-treat; IXE = ixekizumab; LS = least squares; MMRM = mixed-effects model for repeated measures; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation; SE = standard error; TNF = tumour necrosis factor; VAS = visual analogue scale; vs. = versus.

[a] LS mean, LS mean difference, SE, CI, and *P* value are from an MMRM with treatment, region, baseline conventional DMARD experience, visit, and treatment-by-visit interaction as fixed factors, and response value at baseline as a covariate.

[b] LS mean, SE, 95% CI, and *P* value are based on an MMRM model that includes treatment, visit, geographic region, TNF inhibitor experience (inadequate responder to 1 TNF inhibitor, inadequate responder to 2 TNF inhibitors, or intolerance to a TNF inhibitor), treatment-by-visit interaction, geographic region–by-visit interaction, and TNF inhibitor experience–by-visit interaction as well as the continuous, fixed covariates of baseline value and baseline value–by-visit interaction, with variance-covariance structure set to unstructured (for change from baseline) and unstructured (for per cent improvement).

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Table 19: Change From Baseline in Fatigue Severity Numeric Rating Scale at Week 24 (Using MMRM, ITT Population)

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
n							
Baseline, mean (SD)							
LS mean change (SE)							
LS mean difference (95% CI vs. PL)							
P value vs. PL							

ADA = adalimumab; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ITT = intention-to-treat; IXE = ixekizumab; LS = least squares; MMRM = mixed-effects model for repeated measures; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation; SE = standard error; TNF = tumour necrosis factor; vs. = versus.

[a] LS mean, LS mean difference, SE, CI, and *P* value are from an MMRM with treatment, region, baseline conventional DMARD experience, visit, and treatment-by-visit interaction as fixed factors, and response value at baseline as a covariate.

[b] LS mean, SE, 95% CI, and *P* value are based on an MMRM model that includes treatment, visit, geographic region, TNF inhibitor experience (inadequate responder to 1 TNF inhibitor, inadequate responder to 2 TNF inhibitors, or intolerance to a TNF inhibitor), treatment-by-visit interaction, geographic region–by-visit interaction, and TNF inhibitor experience–by-visit interaction as well as the continuous, fixed covariates of baseline value and baseline value–by-visit interaction, with variance-covariance structure set to unstructured (for change from baseline).

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Table 20: Change From Baseline in SF-36 Physical and Mental Component Summaries at Week 24 (Using MMRM, ITT Population)

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
SF-36 PCS							
n	84	83	85	61	90	94	64
Baseline, mean (SD)	34.23 (8.68)	32.44 (10.09)	33.87 (8.85)	34.01 (8.33)	34.30 (9.10)	34.80 (8.78)	33.86 (8.96)
LS mean change (SE)	8.24 (0.90)	7.45 (0.89)	6.78 (0.90)	2.94 (0.958)	8.2 (1.23)	8.9 (1.29)	3.3 (1.36)
LS mean difference (95% CI vs. PL)	5.29 (2.83 to 7.76)	4.51 (2.08 to 6.98)	3.84 (1.38 to 6.31)		4.9 (2.5 to 7.3)	5.6 (3.2 to 8.0)	
P value vs. PL	< 0.001	< 0.001	0.002		< 0.001	< 0.001	
SF-36 MCS							
n	84	83	85	61	90	94	64
Baseline, mean (SD)	48.01 (9.77)	46.53 (13.38)	46.62 (11.74)	47.41 (12.46)	49.05 (11.51)	49.58 (11.35)	48.03 (13.08)
LS mean change (SE)	3.39 (0.94)	4.86 (0.93)	4.22 (0.94)	2.67 (1.01)	4.0 (1.18)	3.6 (1.24)	0.9 (1.32)
LS mean difference (95% CI vs. PL)	0.72 (−1.86 to 3.31)	2.19 (−0.39 to 4.77)	1.56 (−1.02 to 4.13)		3.1 (0.8 to 5.4)	2.7 (0.4 to 5.0)	
P value vs. PL	0.581	0.096	0.236		0.009	0.023	

ADA = adalimumab; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ITT = intention-to-treat; IXE = ixekizumab; LS = least squares; MCS = mental component summary; MMRM = mixed-effects model for repeated measures; PCS = physical component summary; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; TNF = tumour necrosis factor; vs. = versus.

[a] LS mean, LS mean difference, SE, CI, and *P* value are from an MMRM with treatment, region, baseline conventional DMARD experience, visit, and treatment-by-visit interaction as fixed factors, and response value at baseline as a covariate.

[b] LS mean, SE, 95% CI, and *P* value are based on an MMRM model that includes treatment, visit, geographic region, TNF inhibitor experience (inadequate responder to 1 TNF inhibitor, inadequate responder to 2 TNF inhibitors, or intolerance to a TNF inhibitor), treatment-by-visit interaction, geographic region–by-visit interaction, and TNF inhibitor experience–by-visit interaction as well as the continuous, fixed covariates of baseline value and baseline value–by-visit interaction, with variance-covariance structure set as follows: MCS — unstructured (for change from baseline); PCS — unstructured (for change from baseline).

Source: Clinical Study Reports for SPIRIT-P1[3]and SPIRIT-P2.[4]

Table 21: Change From Baseline in EQ-5D-5L at Week 24 (Using MMRM, ITT Population)

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
Health State Index							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]				[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI vs. PL)	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	
P value vs. PL	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
VAS Score							
n	82	82	85	62	90	94	64
Baseline, mean (SD)	NR				53.9 (19.70)	53.9 (22.40)	53.6 (20.03)
LS mean change (SE)	13.1	11.9	10.3	3.8	12.8 (3.02)	15.3 (3.15)	1.8 (3.35)
LS mean difference (95% CI vs. PL)	9.3 (3.12 to 15.50)	8.1 (1.92 to 14.26)	6.5 (0.38 to 12.66)		11.0 (5.1 to 17.0)	13.5 (7.6 to 19.4)	
P value vs. PL	0.003	0.010	0.038		< 0.001	< 0.001	

ADA = adalimumab; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; ITT = intention-to-treat; IXE = ixekizumab; LS = least squares; MMRM = mixed-effects model for repeated measures; NR = not reported; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation; SE = standard error; TNF = tumour necrosis factor; VAS = visual analogue scale; vs. = versus.

[a] LS mean, LS mean difference, SE, CI, and *P* value are from an MMRM with treatment, region, baseline conventional DMARD experience, visit, and treatment-by-visit interaction as fixed factors, and response value at baseline as a covariate.

[b] LS mean, SE, 95% CI, and *P* value are based on an MMRM model that includes treatment, visit, geographic region, TNF inhibitor experience (inadequate responder to 1 TNF inhibitor, inadequate responder to 2 TNF inhibitors, or intolerance to a TNF inhibitor), treatment-by-visit interaction, geographic region–by-visit interaction, and TNF inhibitor experience–by-visit interaction as well as the continuous, fixed covariates of baseline value and baseline value–by-visit interaction, with variance-covariance structure set as follows: EQ-5D-5L health state index — unstructured (for change from baseline); EQ VAS score — unstructured (for change from baseline).

Source: Manufacturer-provided additional information of EQ-5D-5L data,[35] Clinical Study Report of SPIRIT-P2.[4]

Table 22: Change From Baseline in LDI-B at Week 24 (Using MMRM, ITT Population)

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	IXE 80 mg q.4.w. (N = 107)	ADA 40 mg q.2.w. (N = 101)	PL (N = 106)	IXE 80 mg q.2.w. (N = 123)	IXE 80 mg q.4.w. (N = 122)	PL (N = 118)
n	31	38	20	21	14	22	7
Baseline, mean (SD)	40.55 (54.57)	58.08 (96.70)	93.86 (111.90)	46.20 (65.47)	53.91 (37.62)	31.54 (33.80)	37.26 (25.19)
LS mean change (SE)	−48.3 (6.31)	−57.1 (5.67)	−57.1 (7.84)	−25.4 (6.53)	−32.1 (6.66)	−34.7 (6.67)	−36.2 (8.43)
LS mean difference (95% CI vs. PL)	−22.9 (−39.07 to −6.72)	−31.7 (−47.08 to −16.27)	−31.7 (−50.64 to −12.74)		4.0 (−14.0 to 22.1)	1.5 (−15.0 to 18.0)	
P value vs. PL	0.006	< 0.001	0.001		0.652	0.854	

ADA = adalimumab; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ITT = intention-to-treat; IXE = ixekizumab; LDI-B = Leeds Dactylitis Index–Basic; LS = least squares; MMRM = mixed-effects model for repeated measures; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation; SE = standard error; TNF = tumour necrosis factor; vs. = versus.

[a] LS mean, LS mean difference, SE, CI, and *P* value are from an MMRM with treatment, region, baseline conventional DMARD experience, visit, and treatment-by-visit interaction as fixed factors, and response value at baseline as a covariate.

[b] LS mean, SE, 95% CI, and *P* value are based on an MMRM model that includes treatment, visit, geographic region, TNF inhibitor experience (inadequate responder to 1 TNF inhibitor, inadequate responder to 2 TNF inhibitors, or intolerance to a TNF inhibitor), treatment-by-visit interaction, geographic region–by-visit interaction, and TNF inhibitor experience–by-visit interaction as well as the continuous, fixed covariates of baseline value and baseline value–by-visit interaction, with variance-covariance structure set to unstructured (for change from baseline).

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Table 23: Change From Baseline in BASDAI Score at Week 24 (Using MMRM, ITT Population)

	SPIRIT-P1[a]				SPIRIT-P2[b]		
	IXE 80 mg q.2.w. (N = 103)	**IXE 80 mg q.4.w. (N = 107)**	**ADA 40 mg q.2.w. (N = 101)**	**PL (N = 106)**	**IXE 80 mg q.2.w. (N = 123)**	**IXE 80 mg q.4.w. (N = 122)**	**PL (N = 118)**
n	63	69	62	42	75	76	51
Baseline, mean (SD)	5.54 (2.05)	5.83 (1.80)	5.54 (2.02)	5.40 (1.96)	6.65 (1.37)	6.50 (1.37)	6.78 (1.35)
LS mean change (SE)	−2.91 (0.25)	−2.74 (0.23)	−2.42 (0.25)	−1.25 (0.27)	−3.6 (0.35)	−3.7 (0.36)	−2.1 (0.38)
LS mean difference (95% CI vs. PL)	−1.65 (−2.35 to −0.96)	−1.49 (−2.16 to −0.82)	−1.17 (−1.86 to −0.48)		−1.5 (−2.1 to −0.9)	−1.6 (−2.3 to −1.0)	
P value vs. PL	< 0.001	< 0.001	0.001		< 0.001	< 0.001	

ADA = adalimumab; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ITT = intention-to-treat population; IXE = ixekizumab; LS = least squares; MMRM = mixed-effects model for repeated measures; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation; SE = standard error; TNF = tumour necrosis factor; vs. = versus.

[a] LS mean, LS mean difference, SE, CI, and *P* value are from an MMRM with treatment, region, baseline conventional DMARD experience, visit, and treatment-by-visit interaction as fixed factors, and response value at baseline as a covariate.

[b] LS mean, SE, 95% CI, and *P* value are based on an MMRM model that includes treatment, visit, geographic region, TNF inhibitor experience (inadequate responder to 1 TNF inhibitor, inadequate responder to 2 TNF inhibitors, or intolerance to a TNF inhibitor), treatment-by-visit interaction, geographic region–by-visit interaction, and TNF inhibitor experience–by-visit interaction as well as the continuous, fixed covariates of baseline value and baseline value–by-visit interaction, with variance-covariance structure set to unstructured (for change from baseline).

Source: Clinical Study Reports for SPIRIT-P1[3] and SPIRIT-P2.[4]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- American College of Rheumatology (ACR) 20/50/70
- Psoriatic Arthritis Response Criteria (PsARC)
- minimum disease activity (MDA)
- Health Assessment Questionnaire–Disability Index (HAQ-DI)
- Work Productivity and Activity Impairment–Specific Health Problem (WPAI-SHP)
- patient's assessment of pain by visual analogue scale (pain-VAS)
- Fatigue Severity Numeric Rating Scale (FSNRS)
- Short Form (36) Health Survey (SF-36)
- EuroQol 5-Dimensions (EQ-5D)
- Leeds Enthesitis Index (LEI)
- Leeds Dactylitis Index–Basic (LDI-B)
- modified Total Sharp Score (mTSS)
- Psoriasis Area and Severity Index (PASI)
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Findings

Table 24: Characteristics of Outcome Measures in the Included Studies

Instrument	Type	Evidence of Validity	MCID	References
ACR20/50/70	Providing a composite measure of ≥ 20%, ≥ 50%, or ≥ 70% improvement in both swollen and tender joint counts and at least 3 of 5 additional disease criteria	Yes	ACR20	36-40
PsARC	Measuring signs and symptoms of PsA assessed by tender and/or swollen joint count, physician global assessment (0 to 5 Likert scale), and patient global assessment (0 to 5 Likert scale)	Unknown	Unknown	40-42
MDA	A composite outcome measure developed as a target of treatment for patients with PsA that encompasses the different aspects of disease domains	Yes	Unknown	43,44
HAQ-DI	Assessing physical disability and pain in rheumatoid arthritis or PsA	Yes	0.13 to 0.35	45-48
WPAI-SHP	Measuring the impact of disease on productivity using 6 questions to determine employment status and hours missed from work due to PsA	Unknown	Unknown	3

Instrument	Type	Evidence of Validity	MCID	References
Pain-VAS	Scored on a 0 mm to 100 mm horizontal line on which 0 represents "no pain" and the 100 mm mark represents "pain as severe as can be imagined"	Yes	10 mm	[49]
FSNRS	A validated, patient-administered, single-item 11-point scale, consisting of numerals from 0 to 10 on a horizontal line	Yes	[redacted]	[3,50,51]
SF-36	A general health status instrument	Yes	2.5 to 5 points	[52-56]
EQ-5D-5L	A general health status instrument	Yes	Index score: summarized mean 0.056 (SD 0.011), summarized median 0.056 (IQR 0.049 to 0.063)	van Reenen 2015[57] Health Quality Council of Alberta 2014[58] McClure 2017[59]
PASI	Numeric score ranging from 0 to 72 based on assessments of four body areas and severity of induration, erythema, and scaling	Yes	PASI 75	[26,60-63]
LEI	A new enthesitis index designed for use in PsA RCTs assessing lateral humeral epicondyles (elbows), medial femoral epicondyles (knees), and Achilles tendons (heels) bilaterally and scored as 0 (no pain) or 1 (painful)	Yes	Unknown	[64]
LDI-B	Evaluating for a ≥ 10% difference in the circumference of the digit compared with the opposite digit	Yes	Unknown	[65,66]
BASDAI	Self-administered disease-specific questionnaire, a composite index containing 6 questions related to 5 major symptoms of ankylosing spondylitis, scores ranging from 0 to 10	Yes	2 units	[67-72]
mTSS	For the assessment of two different aspects of joint damage: articular erosions and joint space narrowing	Yes	Unknown	Guillemin 2005[73] Van der Heijde 2005[74]

ACR20/50/70 = American College of Rheumatology 20%/50%/70% response; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; FSNRS = Fatigue Severity Numeric Rating Scale; HAQ-DI = Health Assessment Questionnaire–Disability Index; IQR = interquartile range; LDI-B = Leeds Dactylitis Index–Basic; LEI = Leeds Enthesitis Index; MCID = minimal clinically important difference; MDA = minimum disease activity; pain-VAS = patient's assessment of pain–visual analogue scale; mTSS = modified Total Sharp Score; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; RCT = randomized controlled trial; SD = standard deviation; SF-36 = Short Form (36) Health Survey; WPAI-SHP = Work Productivity and Activity Impairment–Specific Health Problem.

American College of Rheumatology 20/50/70

ACR criteria for assessing joint status was originally developed for rheumatoid arthritis patients. They provide a composite measure of ≥ 20%, ≥ 50%, or ≥ 70% improvement in both swollen and tender joint counts and at least three of five additional disease criteria including patient's global assessment of disease activity using a 10 cm VAS, physician's global assessment of disease activity using VAS, HAQ-DI, patient assessment of pain intensity, and acute-phase reactant value (levels of C-reactive protein [CRP] or erythrocyte sedimentation rate).[36] The ACR joint count assesses 68 joints for tenderness and 66 joints for swelling. Assessment of the proximal interphalangeal and distal interphalangeal joints of the hands and feet (i.e., 78 joints for tenderness and 76 for swelling) is not typically included for psoriatic arthritis (PsA) because of difficulty distinguishing proximal and distal

interphalangeal joint inflammation in the toes.[37] The ACR has been shown to have good inter-observer and intra-observer reliability in PsA[38,39] and was shown to be a valid outcome measure in randomized controlled trials.[40] The ACR20 is generally accepted as the minimally clinically important difference (MCID) indicating a response to treatment, while the ACR50 and ACR70 more likely reflect truly important change for the long-term management of arthropathy. The ACR is a general measure of clinical response of peripheral joint disease and does not include assessment of enthesitis, dactylitis, the spine, or the skin. Consequently, it represents only some of the clinical features of PsA; therefore, the use of additional assessment instruments to assess other clinical features is necessary.

Psoriatic Arthritis Response Criteria

PsARC[40] measures signs and symptoms of PsA as assessed by tender or swollen joint count (SJC), physician global assessment (0 to 5 Likert scale), and patient global assessment (0 to 5 Likert scale). To be a PsARC responder, a patient must have at least a 30% reduction in tender or SJC as well as a 1-point reduction on the 5-point patient or physician global assessment scales and no worsening on any score. PsARC has been shown to be a responsive and discriminate outcome instrument in PsA randomized controlled trials.[41] However, the PsARC tends to have a higher percentage response than the ACR20, which may be explained by the requirement that tender *or* swollen joint change is required, not both, and possibly due to the absence of the HAQ score and measurement of erythrocyte sedimentation rate or CRP.[42] As with the ACR, the PsARC does not account for psoriasis severity and is only a general assessment of clinical status.

Minimum Disease Activity

Minimum disease activity (MDA) is a composite outcome measure that was developed as a target of treatment for patients with PsA and encompasses the different aspects of disease domains.[75] Patients were considered as achieving MDA if they fulfilled the following five of seven outcome measures: ≤ 1 tender joint count, ≤ 1 SJC, PASI ≤ 1 or body surface area ≤ 3%, patient pain-VAS ≤ 15, patient global VAS ≤ 20, HAQ-DI ≤ 0.5, and tender entheseal points ≤ 1.[43] These criteria for MDA were validated in patients with active PsA using interventional trial data.[43] In an observational PsA cohort study, it was found that patients who achieved sustained MDA (sustained MDA was defined as achieving MDA on consecutive visits for a minimum duration of 12 months) had a reduction in joint damage progression, where 69% of patients who achieved sustained MDA showed no progression of joint damage, compared with 51% in the control group; in addition the mean change in damaged joint counts was 0.931 in the sustained MDA group and 2.245 in the controls ($P < 0.001$).[44]

Health Assessment Questionnaire–Disability Index

The HAQ-DI was developed to assess physical disability and pain in rheumatoid arthritis[45] and has been used extensively in randomized controlled trials in arthritis, including for PsA. Patients assess and score the difficulty in performing activities in eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities) using a self-assessed questionnaire. The performance scores range from 0 (without any difficulty) to 3 (unable to do) and are adjusted for use of aids, devices, or persons who help with the activity. The summed score is then divided by the number of answered questions and reported. Scores are evaluated based on change from baseline. The MCID for the HAQ-DI has been estimated from a phase III trial of etanercept in PsA[46] to be 0.3 (unlike 0.22 for rheumatoid arthritis), which was estimated using a distribution-based method based on standard error of measurement. Mease et al.[48] have determined that the MCID for the HAQ-

DI in PsA patients using anchor-based methods is 0.35, while the MCID has been estimated to be 0.13 in PsA patients using an anchor-based approach (equal bidirectional magnitudes for improvement and worsening) by Kwok and Pope.[47] Blackmore et al. have shown that the HAQ-DI adequately captures clinically important changes in functional status and pain in patients with PsA.[76] However, the HAQ-DI focuses on physical disability and may not adequately capture disability in patients with predominantly skin disease.[76] Modified versions of the HAQ to include spinal domains (HAQ-S) or skin disease assessment (HAQ-SK) have not proven to be significantly better in assessment of health status in PsA than the original HAQ-DI.[76,77]

Work Productivity and Activity Impairment–Specific Health Problem

WPAI-SHP is a self-administered instrument used to measure the impact of disease on productivity.[67] Change from baseline to each post-baseline visit was reported in the pivotal studies.[3] The WPAI-SHP consists of six questions to determine employment status, hours missed from work due to PsA, hours missed from work for other reasons, hours actually worked, the degree to which PsA affected work productivity while at work, and the degree to which PsA affected activities outside of work. Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), an overall work impairment score that combines absenteeism and presenteeism, and percentage of impairment in activities performed outside of work. Higher scores indicate greater impairment and poorer productivity.[67] This instrument is not validated in patients with PsA. The MCID of WPAI-SHP is currently unknown.

Patient's Assessment of Pain–Visual Analogue Scale

Pain-VAS was scored on a 0 mm to 100 mm horizontal line on which 0 represents "no pain" and the 100-mm mark represents "pain as severe as can be imagined."[49] Patients were asked to place a vertical line on the horizontal line to indicate the level of their arthritis pain on the day of the visit.[49] The MCID of patient's assessment of pain was defined as an improvement (reduction) in pain of 10 mm or more from baseline.[49] Patient's assessment of pain is part of the ACR core set of measures in arthritis.[78]

Fatigue Severity Numaric Rating Scale

FSNRS is a validated, patient-administered, single-item, 11-point scale, consisting of numerals from 0 to 10 on a horizontal line, with 0 representing "no fatigue" and 10 representing "fatigue as bad as you can imagine." Patients were asked to rate their fatigue (weariness, tiredness) during the past week on the scale, choosing a single number from 0 to 10.[3,50] A 1-point decrease from baseline was suggested as MCID for FSNRS.[51]

Short Form (36) Health Survey

The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[79] The SF-36 consists of eight health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. [52] For each of the eight domains, a subscale score can be calculated. The SF-36 also provides two component summaries — the physical component summary and the mental component summary — derived from aggregating the eight domains according to a scoring algorithm. The physical and mental component summary 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 physical and mental component summary scales are transformed to have a mean of 50 and a standard deviation (SD) of 10 in the

general US population. Therefore, all scores above or below 50 are considered above or below average for the general US population. Husted et al.[80] and Leung et al.[56] reported that the SF-36 is reliable and valid for the assessment of patients with PsA and could be used to distinguish PsA patients from patients without PsA. [56] The SF-36 is at least equally responsive as the HAQ instrument to short-term changes in perceived health status and inflammatory disease activity in patients with PsA.[81]

The MCID for either the physical or mental component summary of the SF-36 is typically between 2.5 and 5 points.[53-55] Leung et al. [82] reported MCIDs of 3.74 and 1.77 for the physical or mental component summary subsections, respectively, in PsA patients treated with anti-TNF alpha drugs using an anchor-based approach. The mental component summary was observed in a phase III trial [82] to be weaker in differentiating drug and placebo effects. However, the trial was limited by its small sample size (n = 17).[82]

EuroQol 5-Dimensions Questionnaire

EQ-5D is a generic quality of life instrument developed by the EuroQol Group. It may be applied to a wide range of health conditions and treatments.[57] As a generic measure of health-related quality of life that can capture the net effect of treatment benefits and harms, the EQ-5D provides valuable information from a patient perspective. In addition to this purpose, the EQ-5D is used in clinical trials to obtain utility weights for economic models.[58] The EQ-5D 5-Levels version (EQ-5D-5L) was introduced in 2005 based on an earlier version (EQ-5D-3L). It consists of an EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions — mobility, self-care, usual activities, pain/discomfort, and anxiety/depression — each with five levels: a level 1 response represents “no problems”; level 2, “slight problems”; level 3, “moderate problems”; level 4, “severe problems”; and level 5, “extreme problems” or “unable to perform,” which is the worst response in the dimension. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. In total there are 3,125 possible unique health states defined by the EQ-5D-5L, with 11111 and 55555 representing the best and worst health states. The numerical values assigned to the levels 1 to 5 for each dimension reflect rank order categories of function. In terms of measurement properties, these are ordinal data; they do not have interval properties and therefore should not be summed or averaged, for example, to produce an individual dimension score. Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm taking the local patient and population preferences into account. Therefore, the index score is a country-specific value and a major feature of the EQ-5D instrument.[58] The range of index scores will differ according to the scoring algorithm used; however, in all scoring algorithms of the EQ-5D-5L, a score of 0 represents the health state “dead” and 1.0 reflects “perfect health.” Negative scores are also possible for those health states that society (not the individual patient) considers to be “worse than dead.”

The EQ VAS records the respondent’s self-rated health on a vertical VAS where the end points are labelled 0 (“the worst health you can imagine”) and 100 (“the best health you can imagine”). The respondents are asked to mark an X to the point on the VAS that best represents their health on that day. The EQ-5D index and VAS scores can be summarized and analyzed as continuous data.[57,59]

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, 21143, etc.
2. a population preference-weighted health index score based on the descriptive system

3. a self-reported assessment of health status based on the EQ VAS.

EQ-5D-5L has been validated in a diverse patient population in six countries.[57] However, no studies specifically validating EQ-5D-5L in patients with PsA were identified. The MCID estimates for the index score in Canadian population have a summarized mean of 0.056 (SD 0.011), and a summarized median of 0.056 (interquartile range 0.049 to 0.063).[59]

Psoriasis Area and Severity Index

PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It produces a numeric score ranging from 0 to 72. In general, a PASI score of 5 to 10 is considered moderate disease and a score more than 10 is considered severe disease. A 75% reduction in the PASI score (PASI 75) is the current benchmark for most clinical trials in psoriasis and the criterion for efficacy of new psoriasis treatments approved by the FDA.[83] PASI 75 is a dichotomous (yes/no) scale indicating whether a patient achieved ≥ 75% improvement from baseline PASI score. In calculating the PASI, severity is determined by dividing the body into four regions — head, upper extremities, trunk, and lower extremities — that account for 10%, 20%, 30%, and 40% of the total body surface area, respectively.[62] Each of these areas is assessed separately for erythema, induration, and scaling on a scale of 0 (none) to 4 (very severe). The extent of psoriatic involvement is graded as follows: 0 = no involvement; 1 = 1% to 9%; 2 = 10% to 29%; 3 = 30% to 49%; 4 = 50% to 69%; 5 = 70% to 89%; and 6 = 90% to 100%. The following formula (where E = erythema, I = induration, S = scaling, A = area, h = head score, t = trunk score, u = upper extremities score, and l = lower extremities score) is used to calculate the PASI score:

$$PASI = 0.1 (Eh + Ih + Sh) Ah + 0.2 (Eu + Iu + Su) Au + 0.3 (Et + It + St) At + 0.4 (El + Il + Sl) Al$$[62]

A number of limitations of the PASI have been identified:

- The PASI has been criticized as not correlating the clinical extent of the disease with quality of life and the psychological stress caused by psoriasis. The patient's measure of quality of life is often worse than the physician-rated clinical severity.[84]
- There are significant inter-rater reliability issues regarding the measurement of body surface area.[60,61]
- The PASI often fails to predict severity as seen from the patient's perspective.[60,61]
- Improvements in PASI score are not linearly related to severity or improvements in psoriasis. [60,61] The extent of psoriatic involvement is measured using a scale of 1 to 6, and the areas corresponding to each score are nonlinear.
- Some severe disease (clinically) may be scored low. For example, scores as low as 3 (on palms and soles) may represent psoriasis that disables a patient from work and other life activities.
- Most patients fall into a narrow band of scores, thereby decreasing the usefulness of the full range of scores (e.g., scores above 40 are rare).[60] Validity of this scale may be overrated, in part because of the skew toward lower scores.[63]
- There is little research on the reliability of the assessments for erythema, desquamation, and induration together with overall PASI scores.[60]
- Criterion validity is restricted by the lack of a gold standard measure of psoriatic severity.[85]

- The PASI lacks sensitivity, as erythema, desquamation, and induration are scored with equal weight within each of the four body regions. Thus, a reduction in scaling with a concomitant increase in skin erythema could be recorded with the same PASI score.
- Improvement of the histological phenotype of psoriasis can be underestimated by the per cent improvement in PASI (e.g., reduction of T cells, loss of K16 expression, and reduction in epidermal thickness).[83]
- Little work has been done to determine the clinical relevance of derived PASI scores.[60]

Leeds Dactylitis Index–Basic

Dactylitis, the swelling of an entire digit related to articular and periarticular inflammation, is a characteristic of inflammatory spondyloarthropathies, including PsA. The LDI-B was developed to measure the severity of dactylitis. The LDI-B total score is based on the presence of dactylitis in one or more digits. For each digit that is dactylitic, as defined by a minimum increase of 10% in circumference of the dactylitic digit (A) over the contra-lateral digit (B), the ratio (A/B) of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot is measured. Presence of dactylitis is assessed using the LDI–Basic, which evaluates for a minimum increase of 10% difference in the circumference of the digit compared with the opposite digit.[65,66] The calculated ratio (A/B) is then subtracted by 1, multiplied by 100, and multiplied by a tenderness score (C) of 0 (not tender) or 1 (tender). The results of each digit are then added to produce the LDI-B total score: LDI-B total score = sum ((((A/B) − 1) × 100) × C).

No MCID for LDI-B was identified from the literature.

Leeds Enthesitis Index

Enthesitis, the inflammation at the bone insertion of a tendon or ligament, is common in PsA. The LEI is a new enthesitis index designed for use in PsA and recently adopted for use in randomized controlled studies involving patients with PsA.[64] Enthesitis was assessed by examining six sites — the lateral humeral epicondyles (elbows), medial femoral epicondyles (knees), and Achilles tendons (heels) bilaterally — and scored them as 0 (no pain) and 1 (painful).[3,64] No MCID for LEI was identified.

Modified Total Sharp Score

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

The most recent modification of the Sharp scoring system for rheumatoid arthritis was performed by van der Heijde.[86] Van der Heijde scores erosions are as follows:

Sharp/van der Heijde[73]	
Erosions	
0	Normal
1	Discrete erosions
2 to 3	Larger erosions according to surface area involved
4	Erosion extending over the middle of the bone
5	Complete collapse
Joint Space Narrowing	
0	Intact bony outlines and normal joint space
1	Erosion < 1 mm in diameter or JSN
2	One or several small erosions (diameter > 1 mm)
3	Marked erosions
4	Severe erosions (usually no joint space left and the original bony outlines are only partly preserved)
5	Mutilating changes (the original bony outlines have been destroyed)

The van der Heijde erosion score includes 16 joints from the hands and wrists (graded from 0 to 5) and six joints from the feet (graded from 0 to 10). The joint space narrowing score includes 15 areas from the hands and wrists (graded from 0 to 4) and six areas from the feet (also graded from 0 to 4). The maximum erosion score is 160 for hands and wrists and 120 for feet, while the maximum joint space narrowing score is 120 for hands and 48 for feet.[87] Maximum total scores for both erosion and joint space narrowing are as follows. The maximum possible total score for patients with rheumatoid arthritis is 448.

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

In the van der Heijde mTSS adapted for PsA, the maximum possible score for erosions is 200 for the hands and 120 for the feet; the maximum possible score for joint space narrowing is 160 for the hands and 48 for the feet. Therefore, the maximum possible scores are 320 for erosions, 208 for joint space narrowing, and 528 for the total score.[74]

The van der Heijde modification has become the most commonly used for a few reasons: it includes both hands and feet; it measures erosions and joint space narrowing; and it covers a broad spectrum of joints, providing sensitivity to change. [88]

In the early stages of rheumatoid arthritis, inflammation rather than actual damage to joints appears to be the main contributor to increased disability.[89,90] The relationship between radiological and functional changes has been studied. A reanalysis of published data performed by Welsing et al. found that patients must reach a certain amount of radiological damage before an increase in damage will impact disability. The authors also found that changes in Sharp scores had a greater impact on disability with advancing age. A study by Sabin et al. found that radiologic damage assessed by the van der Heijde method was highly correlated with HAQ scores in a population with mean disease duration of seven years. They also cited findings from another study, which found that Sharp scores became correlated with HAQ after six years' disease duration. At the other end of the spectrum, a study by Clarke et al. found that radiological scores assessed using the Genant method were positively correlated with HAQ in patients with 20 years' disease duration. [91] Therefore, radiological changes assessed by Sharp scores and functional changes

assessed by the HAQ do not correlate with each other early in rheumatoid arthritis, but do correlate after several years of disease.

Several limitations exist with using radiographs for assessing clinical status in rheumatoid arthritis. Radiographs tend to change slowly in rheumatoid arthritis, requiring at least six months to a year to detect changes in a single patient. Inter-rater and intra-rater reliability are also a concern due to the subtle nature of changes and subjective interpretation. The images themselves can also vary between samples, due to positioning and quality. Radiographs should be read in random order to reduce the potential bias of interpretation at different time points. [92] Given these limitations, beginning in the early 1990s, the use of magnetic resonance imaging was being examined as an alternative for assessing disease progression. [93] However, the use of magnetic resonance imaging for assessing clinical status of rheumatoid arthritis is limited due to cost and accessibility.

In a study by Bruynesteyn, authors determined an MCID of 4.6 units for the Sharp/van der Heijde method in patients with rheumatoid arthritis, using a panel of experts. [94] They defined the MCID as a progression in radiologic joint damage that makes a rheumatologist change therapy. An MCID for mTSS in patients with PsA was not identified.

Bath Ankylosing Spondylitis Disease Activity Index

The most common and widely used validated measure of inflammatory activity of ankylosing spondylitis is the BASDAI.[95] This instrument for disease activity is a self-administered patient questionnaire. The BASDAI is a composite index that records a patient's responses to major symptoms of ankylosing spondylitis. 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).[68,69] The patient's responses for each question are recorded on a 10 cm VAS. The final BASDAI score has a range from 0 to 10. The higher the score, the greater the degree of disease activity. A reduction in the BASDAI score is considered improvement. The definition of treatment response includes a change in the BASDAI value defined as two units (on a 0 to 10 scale) of the BASDAI.[70] The recall period for BASDAI is "past week." The MCID for the BASDAI has been determined as a change of −1.96 on the 10-point BASDAI scale.[67]

In previous research, the BASDAI has been shown to have good test-retest reliability, validity, and responsiveness in patients with ankylosing spondylitis. [69,71,72] Content and face validity were assessed through an appraisal of item content, while external construct validity required comparison of instrument scores with those for other measures of health, clinical, sociodemographic, and health service use variables.[71] In addition, the BASDAI was found to be quick and simple to complete, and it appeared to be sensitive to change in disease activity. [68]

Conclusion

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

Appendix 6: Summary of Findings of 52-Week Extension Period in Study SPIRIT-P1

Aim

To summarize the efficacy and safety results of the 52-week extension period from the study SPIRIT-P1.[96,97]

Findings

Study Design and Baseline Disease Characteristics

In SPIRIT-P1, eligible participants were randomized at a 1:1:1:1 ratio to one of four treatment groups: ixekizumab 80 mg every two weeks (with a starting dose of 160 mg at week 0), ixekizumab 80 mg every four weeks (with a starting dose of 160 mg at week 0), adalimumab 40 mg every two weeks, and placebo. Adalimumab 40 mg was compared with placebo in this study for the purpose of providing internal evidence of assay sensitivity. At week 16, inadequate responders receiving adalimumab or placebo were re-randomized to either ixekizumab 80 mg every two weeks or ixekizumab 80 mg every four weeks and received rescue therapy; inadequate responders who were already assigned to ixekizumab at baseline continued their ixekizumab and received rescue therapy after week 16. Rescue therapy referred to modifications made to the patient's background therapy, e.g., conventional DMARDs, NSAIDs, analgesics, or corticosteroids.

The overall study design is presented in Figure 2 in the main text. The baseline characteristics for patients who entered the extension period are summarized in Table 25. Briefly, SPIRIT-P1 was a phase III, randomized, double-blind (dose-blind for patients and investigators to week 52) superiority trial for ixekizumab in which patients were randomized at a 1:1:1:1 ratio to one of four treatment groups: ixekizumab 80 mg every two weeks (with a starting dose of 160 mg at week 0), ixekizumab 80 mg every four weeks (with a starting dose of 160 mg at week 0), adalimumab 40 mg every two weeks, and placebo. Patients were determined to be responders or inadequate responders (defined as patients who failed to meet defined criteria for improvement in tender and swollen joints at week 16). At week 24 (week 16 for inadequate responders from the placebo group, eight-week washout for patients in the adalimumab group before starting ixekizumab), patients were re-randomized to ixekizumab every two weeks or ixekizumab every four weeks (see Figure 2). Six groups were assessed in the extension period (weeks 24 to 52): those who started with ixekizumab every four weeks and continued with ixekizumab every four weeks, those who started with ixekizumab every two weeks and continued with ixekizumab every two weeks, those who started with adalimumab and were switched to ixekizumab every four weeks, those who started with adalimumab and were switched to ixekizumab every two weeks, those who started with placebo and were switched to ixekizumab every four weeks, and those who started with placebo and were switched to ixekizumab every two weeks. Patients initially assigned to placebo received a 160 mg starting ixekizumab dose at week 16 for inadequate responders or at week 24 for responders. Patients initially assigned to adalimumab entered an eight-week placebo washout before receiving their first ixekizumab dose (160 mg ixekizumab at week 24 for adalimumab inadequate responders or 80 mg at week 32 for adalimumab responders). During the extension phase, patients were discontinued if they failed to demonstrate ≥ 20% improvement from baseline in both tender and swollen joint counts at week 32 or a subsequent visit. The primary clinical outcome in the double-blind phase was the 20% American College of Rheumatology response

(ACR20, defined as an improvement of at least 20% in both swollen and tender joint counts and at least three of five additional disease criteria) at week 24. Outcomes assessed during the extension phase (24 to 52 weeks) included ACR20/50/70; 28 diarthrodial joint Disease Activity Score based on C-reactive protein (DAS28-CRP); Psoriatic Arthritis Response Criteria (PsARC); minimum disease activity (MDA)' Health Assessment Questionnaire–Disability Index (HAQ-DI); Work Productivity and Activity Impairment–Specific Health Problem (WPAI-SHP); symptoms reduction (pain and fatigue); Short Form (36) Health Survey (SF-36 physical and mental component summaries); Psoriasis Area and Severity Index (PASI) 75/90/100 response rates; Leeds Enthesitis Index (LEI) for patients with enthesitis; Leeds Dactylitis Index–Basic (LDI-B) for patients with dactylitis; modified Total Sharp Score (mTSS); and safety outcomes including all adverse events (AEs) and serious adverse events (SAEs) at week 52. AEs of special interest included injection site reactions and infections (including serious candida and tuberculosis infections). The extension-period population (EPP) included patients who received one or more doses of study medication during the extension period.

Table 25: Baseline Characteristics (Extension-Period Population, at Week 0)

	IXE q.4.w. / IXE q.4.w.	IXE q.2.w. / IXE q.2.w.	ADA / IXE q.4.w.	ADA / IXE q.2.w.	PL / IXE q.4.w.	PL / IXE q.2.w.
	n = 97	n = 96	n = 49	n = 48	n = 45	n = 46
Age, years	48.7 (10.2)	49.6 (12.8)	50.0 (12.6)	46.2 (12.1)	50.5 (13.2)	51.0 (11.3)
Male, n (%)	40 (41)	44 (46)	21 (43)	30 (63)	19 (42)	23 (50)
Weight, kg	86.1 (22.4)	81.3 (17.3)	89.0 (19.7)	90.1 (18.5)	85.3 (23.9)	84.5 (17.3)
Race, n (%)						
White	93 (96)	89 (93)	47 (96)	44 (92)	41 (91)	43 (93)
PsA diagnosis, years	6.2 (6.5)	7.3 (8.3)	7.5 (7.8)	5.9 (5.6)	7.9 (7.6)	5.5 (6.5)
cDMARD Experience, n (%)						
Naive	15 (15)	16 (17)	8 (16)	5 (10)	4 (9)	8 (17)
Past use	21 (22)	22 (23)	10 (20)	9 (19)	15 (33)	8 (17)
Current use	61 (63)	58 (60)	31 (63)	34 (71)	26 (58)	30 (65)
Patient With Specific Disease Characteristics, n (%)						
Current psoriasis	91 (94)	88 (92)	46 (94)	47 (98)	45 (100)	44 (96)
Current dactylitis[a]	48 (49)	35 (36)	11 (22)	11 (23)	16 (36)	19 (41)
Current enthesitis[a]	67 (69)	54 (56)	28 (57)	25 (52)	22 (49)	26 (57)
Tender joint count (68 joints)	20.8 (13.6)	21.3 (13.8)	18.8 (11.9)	18.8 (12.8)	18.5 (11.6)	19.2 (14.0)
Swollen joint count (66 joints)	11.0 (7.3)	12.2 (7.3)	10.1 (7.4)	9.6 (5.5)	9.6 (6.2)	10.7 (7.1)
Pain-VAS, 0 to 100	59.4 (19.8)	58.1 (21.5)	58.0 (21.0)	58.6 (19.8)	53.8 (22.3)	60.7 (23.3)
PGA, mm	57.4 (19.4)	57.4 (19.1)	51.6 (20.4)	58.6 (16.5)	52.3 (17.9)	58.4 (20.1)
PtGA, mm	62.3 (19.1)	62.3 (20.1)	55.6 (20.8)	62.1 (17.9)	59.6 (22.5)	62.2 (23.2)
CRP, mg/L	13.1 (17.0)	15.5 (26.7)	12.5 (12.7)	14.4 (24.7)	15.4 (29.5)	16.9 (20.4)
HAQ-DI	1.3 (0.6)	1.2 (0.5)	1.1 (0.6)	1.1 (0.6)	1.1 (0.6)	1.2 (0.6)
DAS28-CRP	5.0 (1.0)	5.0 (1.1)	4.9 (0.9)	4.8 (1.0)	4.8 (0.9)	4.9 (1.2)
LEI	2.7 (1.6)	3.0 (1.7)	3.0 (1.5)	2.9 (1.7)	2.6 (1.5)	3.2 (1.9)
LDI-B	61.5 (102.1)	46.0 (57.2)	99.6 (125.2)	96.7 (104.6)	47.7 (62.6)	46.2 (75.4)
BASDAI	5.9 (1.8)	5.5 (2.0)	5.4 (1.8)	5.6 (2.1)	5.3 (1.9)	5.4 (2.1)
mTSS	19.6 (33.3)	15.2 (29.1)	15.6 (24.3)	15.4 (30.2)	11.5 (15.5)	24.5 (37.3)

	IXE q.4.w. / IXE q.4.w.	IXE q.2.w. / IXE q.2.w.	ADA / IXE q.4.w.	ADA / IXE q.2.w.	PL / IXE q.4.w.	PL / IXE q.2.w.
	n = 97	n = 96	n = 49	n = 48	n = 45	n = 46
PASI total score	7.0 (6.5)	6.0 (7.0)	5.7 (5.9)	5.3 (7.1)	6.3 (8.6)	6.3 (7.0)

ADA = adalimumab; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BMI = body mass index; BSA = body surface area; cDMARD = conventional disease-modifying antirheumatic drug; CRP = C-reactive protein; DAS28-CRP = 28-joint Disease Activity Score using C-reactive protein; EPP = extension-period population; HAQ-DI = Health Assessment Questionnaire–Disability Index; IXE = ixekizumab; LDI-B = Leeds Dactylitis Index–Basic; LEI = Leeds Enthesitis Index; mTSS = modified Total Sharp Score; pain-VAS = patient's assessment of pain–visual analogue scale; PASI = Psoriasis Area and Severity Index; PGA = physician's global assessment; PL = placebo; PsA = psoriatic arthritis; PtGA = patient's global assessment; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation.
Note: Values are presented as mean (SD), unless otherwise specified.
[a] Patients with active disease at baseline (week 0).
Source: Clinical Study Report of SPIRIT-P1,[97] van der Heijde.[96]

Patient Disposition

Among a total of 417 patients randomized at baseline (week 0), 381 (91.4%) patients completed the double-blind period. All 381 patients enrolled in the extension period, including 36 inadequate responders (27 from the placebo group and nine from the adalimumab group). Most of the patients (n = 304, 80% EPP; 73% intention-to-treat) completed the extension period. Reasons for discontinuation were similar across the six treatment groups.[97]

Results: Efficacy and Harms

Efficacy

American College of Rheumatology Response

It was reported that in the ixekizumab every-four-weeks to ixekizumab every-four-weeks and ixekizumab every-two-weeks to ixekizumab every-two-weeks groups, ACR20, ACR50, and ACR70 response rates maintained stable from week 24 to week 52.[96,97] Patients re-randomized to ixekizumab (i.e., from placebo or adalimumab) also demonstrated relatively high ACR response rates at week 52 (see Table 26).[96,97] At week 52, the ACR20, ACR50, and ACR70 response rates in the EPP were 69%, 55%, and 39% in ixekizumab every four weeks to ixekizumab every four weeks as well as 69% 53%, and 40% in ixekizumab every two weeks to ixekizumab every two weeks, respectively (Table 26).

Psoriatic Arthritis Response Criteria

At week 52, the PsARC (EPP) was achieved 67%, 65%, 69%, 63%, 58%, and 74% in patients treated with ixekizumab every four weeks to ixekizumab every four weeks, ixekizumab every two weeks to ixekizumab every two weeks, adalimumab to ixekizumab every four weeks, adalimumab to ixekizumab every two weeks, placebo to ixekizumab every four weeks and placebo to ixekizumab every two weeks, respectively (Table 26).

Minimum Disease Activity

In the trial, MDA was assessed by both static physician global assessment of psoriasis ($MDA_{sPGA)}$) and Psoriasis Area and Severity Index (MDA_{PASI}). The MDA_{PASI} utilizes the PASI as the skin assessment component, whereas the MDA_{sPGA} utilizes the static physician global assessment as the skin assessment component. The percentage of patients who achieved MDA_{PASI} and MDA_{sPGA} was similar across all six groups (Table 26).

Health Assessment Questionnaire–Disability Index

Physical function improved at week 52, as demonstrated by reduction in HAQ-DI (mean change from baseline ± standard deviation [mean ± SD]) of −0.53 ± 0.56 in the ixekizumab every-four-weeks to ixekizumab every-four-weeks group and −0.55 ± 0.52 in the ixekizumab every-two-weeks to ixekizumab every-two-weeks group (Table 26). At week 52, 57.1% of patients in both the ixekizumab every-four-weeks to ixekizumab every-four-weeks group and the ixekizumab every-two-weeks to ixekizumab every-two-weeks group achieved the minimal clinically important difference (MCID) (≥ 0.35 improvement) in HAQ-DI (Table 26). HAQ-DI improved −0.47 ± 0.48, −0.42 ± 0.47, −0.38 ± 0.53, and −0.42 ± 0.60 in adalimumab to ixekizumab every four weeks, adalimumab to ixekizumab every two weeks, placebo to ixekizumab every four weeks, and placebo to ixekizumab every two weeks, respectively (Table 26). The MCID was achieved by 60.5%, 47.6%, 43.2%, and 40% of patients in the adalimumab to ixekizumab every-four-weeks, adalimumab to ixekizumab every-two-weeks, placebo to ixekizumab every-four-weeks, and placebo to ixekizumab every-two-weeks groups, respectively (Table 26).

Work Productivity and Activity Impairment–Specific Health Problem

Reported as exploratory outcomes, the WPAI-SHP observed numerical improvement compared with baseline in all six groups (Table 26).

Psoriatic Arthritis Symptoms (Pain and Fatigue)

The patient's assessment of pain by visual analogue scale (pain-VAS) was reported during the extension period. All treatment groups showed an improvement from baseline (week 0), based on the mean change from baseline (Table 26). The improvement in the pain-VAS at week 52 was similar in all six treatment groups (Table 26).

The patient-administered Fatigue Severity Numeric Rating Scale (FSNRS) was reported. At week 52, all six treatment groups showed an improvement in the score from baseline (week 0). The improvement from baseline in the FSNRS score at week 52 was similar in all six treatment groups (Table 26).

Short Form (36) Health Survey

At week 52, all six treatment groups showed an improvement in both the SF-36 physical component summary and the SF-36 mental component summary from baseline (week 0). The improvement from baseline in the SF-36 physical and mental component summaries were similar across all six treatment groups (Table 26).

Psoriasis Area and Severity Index

At week 52, PASI 75, PASI 90, and PASI 100 response rates were 79%, 67%, and 56% in the ixekizumab every-four-weeks to ixekizumab every-four-weeks group and 82%, 78%, and 67% in the ixekizumab every-two-weeks to ixekizumab every-two-weeks group, respectively. Patients re-randomized to ixekizumab (i.e., placebo to ixekizumab and adalimumab to ixekizumab) also achieved PASI 75 response rates from 61% to 67%, PASI 90 response rates from 50% to 62%, and PASI 100 response rates from 35% to 48%, respectively (Table 26).

Leeds Dactylitis Index–Basic and Leeds Enthesitis Index

At week 52, in patients with baseline LDI-B > 0, 86% of patients in the ixekizumab every-four-weeks to ixekizumab every-four-weeks group and 88% of patients in the ixekizumab every-two-weeks to ixekizumab every-two-weeks group achieved resolution of dactylitis. In patients with baseline LEI > 0, 55% of patients in the ixekizumab every-four-weeks to ixekizumab every-four-weeks group and 50% of patients in the ixekizumab every-two-weeks to ixekizumab every-two-weeks group achieved resolution of enthesitis at week 52. Patients re-randomized to ixekizumab every four weeks and every two weeks (i.e., placebo to ixekizumab and adalimumab to ixekizumab) also showed improvements in LED-B and LEI at week 52 (Table 26).

Bath Ankylosing Spondylitis Disease Activity Index

All treatment groups showed a similar improvement from baseline (week 0) at week 52 among patients with BASDAI > 4 at baseline (Table 26).

Modified Total Sharp Score

Over a 52-week period, minimal changes in mTSS were observed in all six groups of patients (Table 26; pre-specified linear extrapolation, EPP). A post hoc analysis of mTSS change from baseline to week 52 was similar to the pre-specified analysis, showing minimal radiographic progression over this period (Table 26). The percentages of patients without radiographic progression at week 52, defined as a change from baseline ≤ 1.32 (the smallest detectable change at week 52), ≤ 0.5, and ≤ 0, were similar between the ixekizumab every-four-weeks to ixekizumab every-four-weeks group and the ixekizumab every-two-weeks to ixekizumab every-two-weeks group (Table 26). For patients re-randomized to ixekizumab groups (i.e., placebo to ixekizumab and adalimumab to ixekizumab), the percentage without radiographic progression at week 52 ranged from 86% to 97% (Table 26).

Table 26: Efficacy Results at Week 52 (Extension-Period Population)

	IXE q.4.w. / IXE q.4.w.	IXE q.2.w. / IXE q.2.w.	ADA / IXE q.4.w.	ADA / IXE q.2.w.	PL / IXE q.4.w.	PL / IXE q.2.w.
	n = 97	n = 96	n = 49	n = 48	n = 45	n = 46
ACR[a]						
ACR20, n (%)	67 (69.1)	66 (68.8)	34 (69.4)	28 (58.3)	26 (57.8)	33 (71.7)
ACR50, n (%)	53 (54.6)	51 (53.1)	29 (59.2)	21 (43.8)	19 (42.2)	21 (45.7)
ACR70, n (%)	38 (39.2)	38 (39.6)	17 (34.7)	14 (29.2)	9 (20.0)	14 (30.4)
DAS28-CRP	−2.3 (1.3)	−2.4 (1.3)	−2.2 (1.3)	−2.1 (0.9)	−1.9 (1.2)	−2.1 (1.1)
PsARC, n (%)	65 (67.0)	62 (64.6)	34 (69.4)	30 (62.5)	26 (57.8)	34 (73.9)
MDA[a]						
MDA $_{PASI}$, n (%)	42 (43.3)	38 (39.6)	20 (40.8)	15 (31.3)	15 (33.3)	19 (41.3)
MDA $_{sPGA}$, n(%)	42 (43.3)	38 (39.6)	20 (40.8)	15 (31.3)	15 (33.3)	19 (41.3)
HAQ-DI	−0.53 (0.56)	−0.55 (0.52)	−0.47 (0.48)	−0.42 (0.47)	−0.38 (0.53)	−0.42 (0.60)
≥ 0.35 HAQ-DI improvement,[a] n/N (%)	52/91 (57.1)	48/84 (57.1)	26/43 (60.5)	20/42 (47.6)	16/37 (43.2)	16/40 (40.0)
WPAI-SHP						
Change from baseline	−28.8 (29.4)	−26.3 (23.8)	−24.0 (24.7)	−17.5 (23.1)	−24.3 (18.3)	−15.5 (24.2)
% improved (SD)	61.9 (67.2)	65.6 (42.7)	59.0 (46.7)	27.0 (119.6)	77.6 (26.1)	35.6 (73.2)
Pain-VAS	−33.4 (28.48)	−34.4 (27.43)	−34.2 (26.42)	−32.9 (24.38)	−29.8 (27.99)	−36.6 (23.86)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	IXE q.4.w. / IXE q.4.w.	IXE q.2.w. / IXE q.2.w.	ADA / IXE q.4.w.	ADA / IXE q.2.w.	PL / IXE q.4.w.	PL / IXE q.2.w.
SF-36						
PCS	9.5 (9.5)	9.2 (9.4)	7.3 (7.7)	9.0 (8.8)	7.3 (9.6)	8.1 (8.5)
MCS	4.7 (11.8)	3.4 (9.2)	4.4 (12.1)	3.8 (8.5)	5.3 (10.4)	4.4 (9.0)
PASI[a]						
PASI 75, n/N (%)	52/66 (78.8)	45/55 (81.8)	22/34 (64.7)	22/33 (66.7)	19/31 (61.3)	19/29 (65.5)
PASI 90, n/N (%)	44/66 (66.7)	43/55 (78.2)	17/34 (50.0)	17/33 (51.5)	16/31 (51.6)	18/29 (62.1)
PASI 100, n/N (%)	37/66 (56.1)	37/55 (67.3)	12/34 (35.3)	15/33 (45.5)	15/31 (48.4)	13/29 (44.8)
LEI						
Mean (SD)	−1.9 (1.7)	−1.8 (1.6)	−2.0 (1.9)	−1.1 (2.3)	−1.1 (2.2)	−1.7 (2.0)
LEI = 0,[a] n/N (%)	36/65 (55.4)	26/52 (50.0)	14/28 (50.0)	6/23 (26.1)	9/22 (40.9)	11/26 (42.3)
LDI-B						
Mean (SD)	−57.9 (103.9)	−43.4 (55.5)	−96.5 (125.5)	−93.1 (102.5)	−47.7 (62.6)	−21.3 (21.7)
LDI-B = 0,[a] n/N (%)	30/35 (85.7)	21/24 (87.5)	6/8 (75.0)	7/10 (70.0)	7/10 (70.0)	8/14 (57.1)
BASDAI (CFB)[b]	−3.1 (2.2)	−3.3 (2.1)	−2.8 (2.2)	−3.0 (1.9)	−2.8 (2.2)	−3.5 (2.1)
Pre-specified mTSS, linear extrapolation						
N of patients (%)	80 (82.5)	80 (83.3)	36 (73.5)	34 (70.8)	31 (68.9)	37 (80.4)
Mean (SD)	0.54 (2.12)	0.09 (0.95)	0.32 (1.02)	−0.03 (0.39)	0.27 (0.84)	0.41 (0.81)
Post hoc mTSS, linear extrapolation						
No of patient	97	96	47	45	44	45
Mean (SD)	0.47 (1.94)	0.09 (0.88)	0.24 (0.90)	0.06 (0.54)	0.25 (0.79)	0.51 (1.10)
Post hoc mTSS ≤ 0						
n/N (%)	68/81 (84.0)	70/83 (84.3)	35/40 (87.5)	29/35 (82.9)	29/34 (85.3)	22/35 (62.9)
Post hoc mTSS ≤ 0.5						
n/N (%)	72/81 (88.9)	75/83 (90.4)	35/40 (87.5)	32/35 (91.4)	32/34 (94.1)	23/35 (65.7)
Post hoc mTSS ≤ 1.32 (SDC)						
n/N (%)	75/81 (92.6)	77/83 (92.8)	36/40 (90.0)	34/35 (97.1)	33/34 (97.1)	30/35 (85.7)

ACR20/50/70 = American College of Rheumatology 20%/50%/70% response; ADA = adalimumab; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CFB = change from baseline; DAS28-CRP = 28-joint Disease Activity Score using C-reactive protein; EPP = extension-period population; HAQ-DI = Health Assessment Questionnaire–Disability Index; IXE = ixekizumab; LDI-B = Leeds Dactylitis Index–Basic; LEI = Leeds Enthesitis Index; MCS = mental component summary; MDA = minimum disease activity; mTSS = modified Total Sharp Score; PAIN-VAS = patient's assessment of pain–visual analogue scale; PASI = Psoriasis Area and Severity Index; PL = placebo; PCS = physical component summary; PsARC = Psoriatic Arthritis Response Criteria; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation; SDC = smallest detectable change; SF-36 = Short Form (36) Health Survey; sPGA = static physician global assessment; WPAI-SHP = Work Productivity and Activity Impairment–Specific Health Problem.

Note: Data presented as mean change from baseline (SD), unless otherwise specified.

[a] Nonresponder imputation.

[b] Change from baseline among patients with baseline BASDAI > 4.

Source: Clinical Study Report of SPIRIT-P1 (extension),[97] van der Heijde et al.[96]

Safety

During the extension period, treatment-emergent AE (TEAE) frequency ranged from 40.8% to 62.2% across the six treatment groups (Table 27). The most frequently reported TEAE (defined as more than or equal to 4% in any treatment group) were nasopharyngitis, injection site reaction, upper respiratory tract infection, back pain, injection site erythema, and pharyngitis. No death was reported. Four patients discontinued as a result of an AE. The frequencies of SAEs ranged from zero in the ixekizumab every-two-weeks to ixekizumab every-two-weeks group to 10.2% (5 of 49 patients) in the smaller adalimumab to ixekizumab every-four-weeks group (Table 27). There were no active tuberculosis and no invasive candida or other invasive or endemic fungal infections reported during the

extension period. No patients reported with inflammatory bowel disease. The safety profile over the 52-week extension period was similar to that in the double-blind phase (Table 27).

Table 27: Adverse Events Reported During the Extension Period (EPP, Weeks 24 to 52)

	IXE q.4.w. / IXE q.4.w.	IXE q.2.w. / IXE q.2.w.	ADA / IXE q.4.w.	ADA / IXE q.2.w.	PL / IXE q.4.w.	PL / IXE q.2.w.
	n = 97	n = 96	n = 49	n = 48	n = 45	n = 46
TEAE	54 (55.7)	54 (56.3)	20 (40.8)	21 (43.8)	28 (62.2)	27 (58.7)
Most Frequent TEAE (≥ 4% of Patients in Each Treatment Group)						
Nasopharyngitis	7 (7.2)	10 (10.4)	2 (4.1)	1 (2.1)	4 (8.9)	2 (4.3)
URTI	5 (5.2)	4 (4.2)	4 (8.2)	0	1 (2.2)	1 (2.2)
Psoriatic arthropathy	3 (3.1)	1 (1.0)	0	0	0	0
Urinary tract infection	2 (2.1)	2 (2.1)	1 (2.0)	1 (2.1)	1 (2.2)	0
SAE	4 (4.1)	0	5 (10.2)	1 (2.1)	1 (2.2)	1 (2.2)
Deaths	0	0	0	0	0	0
Discontinued due to AE	1 (1.0)	0	0	0	1 (2.2)	1 (2.2)
AE of Special Interest						
Infections[a]	31 (32.0)	32 (33.3)	8 (16.3)	12 (25.0)	14 (31.1)	9 (19.6)
Oral candidiasis	0	3 (3.1)	0	1 (2.1)	1 (2.2)	0
Esophageal candidiasis	0	0	0	0	0	0
Serious infections	1 (1.0)	0	0	0	0	0
Injection site reactions[b]	9 (9.3)	9 (9.4)	5 (10.2)	4 (8.3)	6 (13.3)	8 (17.4)
Inflammatory bowel disease	0	0	0	0	0	0
Hepatic event	1 (1.0)	4 (4.2)	0	1 (2.1)	1 (2.2)	2 (4.3)
Allergy/hypersensitivity	2 (2.1)	4 (4.2)	0	0	3 (6.7)	1 (2.2)
Neutropenia	12 (12.4)	12 (12.5)	1 (2.0)	2 (4.2)	4 (8.9)	11 (23.9)
Leukopenia	12 (12.4)	10 (10.4)	1 (2.0)	4 (8.3)	4 (8.9)	11 (23.9)
Thrombocytopenia	4 (4.1)	2 (2.1)	2 (4.1)	1 (2.1)	1 (2.2)	2 (4.3)

ADA = adalimumab; AE = adverse event; EPP = extension-period population; IXE = ixekizumab; PL = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection.
Note: Data presented as n (%).
[a] Candida infections were limited to mucocutaneous infections.
[b] Includes all terms for reactions at the injection site (e.g., erythema, pain, papule, bruising, pruritus, rash, and mass).
Source: Clinical Study Report of SPIRIT-P1 (extension),[97] van der Heijde et al.[96]

Limitation

The main limitation for the findings at week 52 is the lack of a control group. It is particularly problematic for the interpretation of patient-reported outcomes. Background therapy changes (rescue) during the extension period were not reported. In addition, the study (SPIRIT-P1) was designed as a three-year trial (Figure 2); however, long-term (from week 52 to week 156) efficacy or safety outcomes were not reported by the manufacturer. In addition, the dosing regimen of ixekizumab in the extension study (ixekizumab 80 mg every two weeks throughout the entire study period) was not consistent with the Health Canada–recommended dose (for patients receiving ixekizumab 80 mg every two week, the frequency of ixekizumab is changed to every four weeks after 12 weeks of treatment).

Summary

The improvements in clinical and patient-reported outcomes, which were observed over 24 weeks of the study SPIRIT-P1 in both ixekizumab every four weeks and ixekizumab every two weeks dosing regimens, were maintained throughout the 52-week extension period. Patients re-randomized to ixekizumab every four weeks or ixekizumab every two weeks from placebo or adalimumab also showed improvements in clinical and patient-reported outcomes at week 52 that were similar to the efficacy achieved by the ixekizumab to ixekizumab groups at week 52. The safety profile of ixekizumab over 52 weeks was consistent with that observed during 24 weeks, with no unexpected safety signals reported. Due to the nature of the single-arm study and the potential impact of background therapy (rescue), the efficacy findings reported at week 52 should be interpreted with caution.

Appendix 7: Summary of Indirect Comparisons

Introduction

Background

The treatment groups of studies included in this review included ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo. The SPIRIT-P1 study also included a group that received adalimumab 40 mg every two weeks, but this study was not designed to make statistical comparisons between ixekizumab and adalimumab. Due to the lack of direct evidence that compared ixekizumab to other biologic drugs in the context of psoriatic arthritis (PsA), the manufacturer performed a network meta-analysis to assess the relative efficacy and safety of ixekizumab in adult patients with active PsA. The objective of this section is to summarize and critically review this unpublished report and other available published indirect evidence that examines the relative efficacy and harms of ixekizumab compared with other treatments for PsA.

Methods

One network meta-analysis submitted by the manufacturer was reviewed in this section.[2] In addition, an information specialist performed a literature search for published indirect treatment comparisons, and one relevant publication was identified and reviewed in this section.[98]

Description of Indirect Treatment Comparisons Identified

The inclusion criteria for each of the network meta-analyses are summarized in Table 28. The manufacturer-submitted network meta-analysis applied a literature search cut-off of August 2016, but the authors indicated that some literature was identified after August 2016, without stating the time frame of the update to their literature search.

Table 28: PICOS Criteria for Study Inclusion

	Manufacturer-Submitted Network Meta-Analysis[2]	Wu et al.[98]
Population	• Adults with active PsA • Biologic-naive or biologic-experienced patients	• Adults with PsA
Interventions	• IXE 80 mg q.2.w. or q.4.w. • Adalimumab 40 mg q.2.w. • Apremilast 30 mg b.i.d. • Certolizumab pegol 200 mg q.2.w. or 400 mg q.4.w. • Etanercept 25 mg 2.q.w. or 50 mg q.w. • Golimumab 50 mg q.4.w. • Infliximab 5 mg/kg q.8.w. • Secukinumab 150 mg or 300 mg q.4.w. • Ustekinumab 45 mg or 90 mg q.12.w.	• IL-6, IL-12/23 and IL-17 inhibitors: • IXE 80 mg q.2.w. or q.4.w. • Ustekinumab 45 mg or 90 mg q.12.w. • Secukinumab 75 mg or 150 mg or 300 mg monthly • Clazakizumab 25 mg or 100 mg or 200 mg monthly
Comparisons	• Comparisons were made between the above-mentioned regimens and placebo	• Comparisons were made between the above-mentioned regimens and placebo
Outcomes	• ACR20/50/70: as conditional probabilities (credible interval), relative risk (95% CI), odds ratio (95% CI), risk difference (95% CI), NNT (95% CI) • ACR: combined ACR data using standard normal probit scale with placebo as reference, probability of being the best treatment, median rank, SUCRA	• ACR20/50; odds ratio (95% CI) SUCRA • AEs, SAEs, WDAEs • Overall rank using a composite of ACR20/50, AEs, and SAEs

	Manufacturer-Submitted Network Meta-Analysis[2]	Wu et al.[98]
	• PASI 50/75/90/100: as conditional probabilities (credible interval), odds ratio (95% CI), data using standard normal probit scale with placebo as reference, probability of being the best treatment, median rank, SUCRA • PsARC response: as conditional probabilities (credible interval), odds ratio (95%CI), probability of being the best treatment, median rank, SUCRA • HAQ-DI: change from baseline difference in means (95% CI), probability of being the best treatment, median rank, SUCRA • AEs, SAEs, WDAEs, study discontinuation	
Study Design	• RCTs	• RCTs
Other	• Base-case analyses included biologics approved in Europe. Base-case analyses used data from time points between 12 and 16 weeks. • Other analyses included only biologics approved by NICE and used data from time points between 12 and 24 weeks.	• Treatment effects were evaluated based on ACR20/50 at week 24 and safety at week 16 or 24.

2.q.w. = twice weekly; ACR20/50/70 = American College of Rheumatology 20%/50%/70% response; ADA = adalimumab; AE = adverse event; b.i.d. = twice daily; CI = confidence interval; HAQ-DI = Health Assessment Questionnaire–Disability Index; IL = interleukin; IXE = ixekizumab; NICE = National Institute for Health and Care Excellence; NNT = number needed to treat population; PASI = Psoriasis Area and Severity Index; PICOS = population, interventions, comparisons, outcomes, study design; PL = placebo; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; q.w. = once weekly; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; RCT = randomized controlled trial; SAE = serious adverse event; SUCRA = surface area under the cumulative ranking curve; WDAE = withdrawal due to adverse event.

Review and Appraisal of Indirect Treatment Comparisons

Review of Indirect Treatment Comparison Submitted by the Manufacturer

Objectives and Rationale for Indirect Treatment Comparison Submitted by the Manufacturer

The objective of the indirect treatment comparison was to conduct a network meta-analysis to assess the relative efficacy and safety of ixekizumab 80 mg every two weeks and every four weeks versus other approved biologic treatments and apremilast for the treatment of adult patients with active PsA. Comparators selected for this network meta-analysis were ixekizumab, adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab. Study populations included both biologic-naive patients and patients with prior exposure to biologics. The report was written by a third party for Eli Lilly to be used for international Health Technology Assessment submissions.

Network analyses for efficacy included two base-case analyses, five analyses restricted to drugs and doses used in the UK, and two sensitivity analyses. Five additional sensitivity analyses were planned but not performed. One analysis for safety was performed. The performed network meta-analyses are summarized in Table 29. The most relevant analyses for the purposes of this report were deemed to be the base case A and the base case B analyses, because they contained the largest networks that reflected treatment options available in Canada.

Table 29: Network Meta-Analyses Performed by the Manufacturer

Network	Population	Description
Base Case A	Biologic-naive	• Biologics approved in Europe at approved doses • Used data from 12 weeks if available (or up to week 16 if 12-week data unavailable) • If no data were available for in the biologic-naive population exclusively, data from full population were used
Base Case B	Biologic-experienced	• If no data were available for the biologic-experienced population exclusively, data from full population were used
UK1A	Biologic-naive	• NICE-approved biologics at approved dosages • Used data from 12 weeks if available (or up to week 16 if 12-week data unavailable)
UK2A	Biologic-naive	• NICE-approved biologics at approved dosages • Same as UK1A except IXE data at week 16 were used • NMA was not pre-planned
UK1B	Biologic-experienced	• NICE-approved biologics at approved dosages • Used data from 12 weeks if available (or up to week 16 if 12-week data unavailable)
UK2B	Biologic-experienced	• NICE-approved biologics at approved dosages • NMA was not pre-planned
UK3B	Biologic-experienced	• Same as UK1B but included secukinumab and certolizumab
Sensitivity Analysis 3A	Biologic-naive	• Used a 24 week time point
Sensitivity Analysis 3B	Biologic-experienced	• Used a 24 week time point
Safety	Full population (biologic-experienced or biologic-naive)	• Used for safety (harms) analyses

IXE = ixekizumab; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis.

Methods for Indirect Treatment Comparison Submitted by the Manufacturer

Study Eligibility and Selection Process

A systematic literature review was performed of literature published before August 2016. The authors stated that some literature was identified after August 2016, but the updated time point for the systematic literature search was not provided. The authors did not specify which databases were searched. The study selection process was not described.

The study inclusion and exclusion criteria were articulated implicitly in the results sections of the report, and it was evident that the authors included randomized controlled trials that were performed in adults with PsA. However, there were no explicit inclusion and exclusion criteria stated in the report and so it was not clear if criteria were established a priori.

Data Extraction

[redacted]

Table 30: Study Characteristics

Study	Year of Publication	Interventions (N)	Outcome Time Point	Used in Biologic-Naive NMA	Used in Biologic-Experienced NMA
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study	Year of Publication	Interventions (N)	Outcome Time Point	Used in Biologic-Naive NMA	Used in Biologic-Experienced NMA

Source: Manufacturer-provided network meta-analysis.[2]

Comparators

In the 19 included trials, there were nine different biologics used across 42 treatment arms. All trials shared placebo as a common comparator, and the SPIRIT-P1 trial was the only trial with an active comparator group (adalimumab). The regimens are described in Table 30 and, according to the clinical expert for this review, the doses used in the included trials are similar to the doses used in Canada to treat patients with PsA.

Abatacept is indicated for treatment of PsA in Canada, but it was not included in any of the networks in this report. According to the clinical expert for this review, the omission of abatacept would not be expected to have a large impact on generalizability of the results, because abatacept does not have widespread use for PsA in Canada.

Outcomes

Outcomes of interest were 20%, 50%, or 70% American College of Rheumatology response (ACR20/50/70, defined as an improvement of at least 20%, 50%, or 70%, respectively, in both swollen and tender joint counts and at least three of five additional disease criteria) (relative risk, odds ratio, risk difference, number needed to treat, and ranking), Psoriasis Area and Severity Index (PASI) 50/75/90/100 (conditional probabilities, odds ratio, ranking), Psoriatic Arthritis Response Criteria (PsARC) response (conditional probabilities, odds ratio, ranking), and Health Assessment Questionnaire–Disability Index (HAQ-DI) (mean change from baseline, ranking). Harms data were also extracted from the included studies and analyzed in the form of adverse events (AEs), serious adverse events (SAEs) and withdrawals due to adverse events (WDAEs). Overall study discontinuations were also analyzed where available.

A summary of the available outcomes by treatment is summarized in Table 31 for the two main analyses of the network meta-analysis.

Table 31: Available Outcome Data by Treatment

Table 31 contains confidential information and was redacted at the request of the manufacturer.

Source: Manufacturer-provided network meta-analysis.[2]

Quality Assessment of Included Studies

There was no quality assessment of the included studies reported. There was no discussion about how quality of the included trials was taken into consideration in the analyses.

Evidence Network

Figure 4: Evidence Network for ACR, Biologic-Naive Analysis (Base Case A)

Figure 4 contains confidential information and was redacted at the request of the manufacturer.

Source: Manufacturer-provided network meta-analysis.[2]

Figure 5: Evidence Network for ACR, Biologic-Experienced Analysis (Base Case B)

Figure 5 contains confidential information and was redacted at the request of the manufacturer.

Source: Manufacturer-provided network meta-analysis.[2]

Indirect Comparison Methods

Statistical Methods

The network meta-analyses were performed using Bayesian methods, and both random-effects and fixed-effects models were run for each network. Treatment group–specific data with an arm-based likelihood were used. For ordered categorical data (ACR, PASI), a multinomial model with a probit link was used. For binomial event data (PsARC response, safety and withdrawal data), a binomial model with a logit link was used. For continuous data (HAQ-DI), a normal model with the identity link was used.

Bayesian analyses used three chains and vague priors: N (0, 10,000) for treatment effects and trial baselines (and covariates in meta-regression), uniform [0,5] for binomial and multinomial standard deviations (SDs), uniform [0,5] for continuous SDs, uniform [0,5] for multinomial categories.

A burn-in of 30,000 and subsequent run of 30,000 and thinning parameter of 2 were used initially. These could be altered to improve convergence or reduce autocorrelation if necessary. Convergence was assessed by reviewing trace plots, density plots, Brooks-Gelman-Rubin plots, and autocorrelation plots for key parameters.

The deviance information criterion was used to assess whether the fixed-effects or random-effects model fit the data better. The model with lowest deviance information criterion is the best fit, taking into account the number of parameters in the model. If the difference in deviance information criterion between fixed effects and random effects was less than 5

points, the simpler fixed-effects model was preferred. If the fixed-effects model was a better fit, this indicated that there is no evidence of substantial between-study heterogeneity.

Bayesian network meta-regression was performed in the biologic-naive networks to investigate the impact of the following variables on outcomes: year of study, gender, PsA duration, and placebo response rate. There were insufficient studies to perform meta-regression in the biologic-experienced networks. Meta-regression for baseline risk was planned and performed for base case A (biologic-naive population) for the outcomes of ACR, PASI, PsARC, and HAQ-DI. Meta-regression for baseline risk was planned but not performed for base case B (biologic-experienced population).

For all network meta-analyses, results from fixed-effects models were presented, as the majority of edges in the networks only consisted of one study. For this reason, authors report that it was difficult to estimate between-study heterogeneity accurately in random-effects models, and in several cases the random-effects models had fairly poor convergence diagnostics and large uncertainty in the between-study heterogeneity parameter estimate. The fixed-effects model results were presented for all analyses, even if the deviance information criterion was more than 5 points higher than the random-effects model.

Results

[redacted]

Table 32: [redacted]

Table 32 contains confidential information and was redacted at the request of the manufacturer.

[redacted]

Source: Manufacturer-provided network meta-analysis.[2]

Table 33: [redacted]

Table 33 contains confidential information and was redacted at the request of the manufacturer.

[redacted]

Source: Manufacturer-provided network meta-analysis.[2]

[redacted]

Table 34: [redacted]

Table 34 contains confidential information and was redacted at the request of the manufacturer.

[redacted]

Source: Manufacturer-provided network meta-analysis.[2]

Table 35: [redacted]

Table 35 contains confidential information and was redacted at the request of the manufacturer.

[redacted]

Source: Manufacturer-provided network meta-analysis.[2]

Health Assessment Questionnaire–Disability Index: Biologic-Naive Population (Base Case A)

The biologic-naive population HAQ-DI network included 10 studies, seven treatments, and placebo.

For HAQ-DI (cross tabulation, Table 36), ixekizumab 80 mg every two weeks demonstrated a higher likelihood of improvement compared with apremilast. For HAQ-DI, both ixekizumab doses had a lower likelihood of improvement compared with infliximab.

Table 36: [redacted]

Table 36 contains confidential information and was redacted at the request of the manufacturer.

[redacted]

Source: Manufacturer-provided network meta-analysis.[2]

Psoriatic Arthritis Response Criteria: Biologic-Naive Population (Base Case A)

The biologic-naive population PsARC network included 12 studies, 10 treatments, and placebo.

For PsARC (cross tabulation, Table 37), ixekizumab 80 mg every two weeks demonstrated a higher likelihood of response compared with apremilast. For PsARC, both ixekizumab doses had a lower likelihood of response compared with infliximab, etanercept, and golimumab.

Table 37: [redacted]

Table 37 contains confidential information and was redacted at the request of the manufacturer.

[redacted]

Source: Manufacturer-provided network meta-analysis.[2]

[redacted]

Table 38:

Table 38 contains confidential information and was redacted at the request of the manufacturer.

Source: Manufacturer-provided network meta-analysis.[2]

Table 39:

Table 39 contains confidential information and was redacted at the request of the manufacturer.

Source: Manufacturer-provided network meta-analysis.[2]

Table 40:

Table 40 contains confidential information and was redacted at the request of the manufacturer.

Source: Manufacturer-provided network meta-analysis.[2]

Table 41:

Table 41 contains confidential information and was redacted at the request of the manufacturer.

Source: Manufacturer-provided network meta-analysis.[2]

Health Assessment Questionnaire–Disability Index: Biologic-Experienced Population (Base Case B)

The biologic-experienced population the HAQ-DI network included two studies, three treatments, and placebo.

For HAQ-DI (cross tabulation, Table 42), ixekizumab did not demonstrate a higher or lower likelihood of improvement relative to certolizumab, the single comparator in the model.

Table 42: [redacted]

Table 42 contains confidential information and was redacted at the request of the manufacturer.

[redacted]

Source: Manufacturer-provided network meta-analysis.[2]

Psoriatic Arthritis Response Criteria: Biologic-Experienced Population (Base Case B)

The biologic-experienced population PsARC network included three studies, five treatments, and placebo.

For PsARC (cross tabulation, Table 43), ixekizumab did not demonstrate a higher or lower likelihood of response relative to any comparator.

Table 43: [redacted]

Table 43 contains confidential information and was redacted at the request of the manufacturer.

[redacted]

Source: Manufacturer-provided network meta-analysis.[2]

Safety Analyses (Biologic-Naive and Biologic-Experienced Patients)

Treatment-Emergent Adverse Events

The network for treatment-emergent AEs included five studies, five treatments (ixekizumab at two doses, infliximab, adalimumab, certolizumab pooled doses), and placebo. Treatments that had a higher likelihood of treatment-emergent AEs relative to placebo were ixekizumab (both doses) and adalimumab. For occurrence of treatment-emergent AEs, ixekizumab did not demonstrate a higher or lower likelihood of occurrence relative to any comparator.

Serious Adverse Events

The network for SAEs included 15 studies, 12 treatments (ixekizumab at two doses, infliximab, adalimumab, certolizumab pooled doses, apremilast, etanercept, golimumab, secukinumab at two doses, ustekinumab at two doses), and placebo. No treatments had a higher likelihood of SAEs relative to placebo. For occurrence of SAEs, ixekizumab did not demonstrate a higher or lower likelihood of occurrence relative to any comparator.

Withdrawals Due to Adverse Events

The network for WDAEs included 14 studies, nine treatments (ixekizumab at two doses, infliximab, adalimumab, apremilast, golimumab, certolizumab pooled doses, ustekinumab at two doses), and placebo (Table 44). Both doses of ixekizumab did not have a higher or lower likelihood of WDAEs relative to placebo. Ixekizumab 80 mg every two weeks had a higher likelihood of WDAEs relative to both doses of ustekinumab. Ixekizumab 80 mg every four weeks did not have a higher or lower likelihood of WDAEs relative to either dose of ustekinumab. Ixekizumab did not have a higher or lower likelihood of WDAEs relative to other drugs (except ustekinumab).

Table 44: [redacted]

Table 44 contains confidential information and was redacted at the request of the manufacturer.

Source: Manufacturer-provided NMA.[2]

Critical Appraisal

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. The authors stated that random-effects models were sometimes difficult to fit, and so fixed-effects model results were used, but there may be heterogeneity in the network. The authors state that the treatment effects from the fixed-effects models are too precise. Given the higher deviance information criterion reported for the fixed-effects model compared with the random-effects model, it would appear that the random-effects model would be more appropriate.

Data from the full population instead of a pure biologic-naive or biologic-experienced population were used for several networks where data from biologic-naive or biologic-experienced subgroups were not available. Therefore these analyses are not representative of the treatment effect in a pure biologic-naive or biologic-experienced population.

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

The most recent date of the literature search was not clearly stated, so it is not known if there are important studies missing from the network meta-analyses.

All of the outcomes of interest in the network meta-analysis were also outcomes of interest in the protocol for this CDR report. The CDR report additionally specified health-related quality of life as an outcome of interest, but this was not reported in the network meta-analysis.

The analyses use relatively short time points (e.g., 12 weeks) and do not reflect the durability of relative response over the length of time that patients are likely to be using these biologics.

Review of Indirect Treatment Comparison by Wu et al.[98]

Objectives and Rationale for Wu et al.

The objective of the indirect treatment comparison was to investigate the comparative efficacy, safety, and tolerability of interleukin (IL)-6, IL-12/23, and IL-17 inhibitors for patients with PsA.

Methods for Wu et al.

A systematic literature search was performed to identify randomized controlled trials in patients with active PsA. Two reviewers independently screened the literature. Risk of bias assessment was performed using the Cochrane Collaboration risk of bias assessment tool. Traditional meta-analysis was performed using random-effects modelling. Bayesian network meta-analyses were used to assess indirect comparisons. Planned extraction of outcomes included ACR20/50/70, AEs (in particular, nasopharyngitis, headache, and upper respiratory tract infection), SAEs, and WDAEs. The authors report that no funding was received to perform the work described in their publication.

Results of Wu et al.

Six studies were included (N = 2,411 for efficacy analysis). All trials were judged as having low risk of bias. Treatment regimens included ustekinumab 45 mg or 90 mg every 12 weeks, secukinumab 75 mg or 150 mg or 300 mg monthly, clazakizumab 25 mg or 100 mg or 200 mg monthly, ixekizumab 80 mg every two weeks, and ixekizumab 80 mg every four weeks. Direct treatment effect analysis showed that all drugs improved ACR20 and ACR50 at week 24 compared with placebo.

There was no evidence from the network meta-analysis of ACR20 and ACR50 data showing that ixekizumab had greater or less likelihood of response compared with any other biologic. There was no strong evidence from the network meta-analysis of AEs, SAEs, or WDAEs to suggest that ixekizumab had a greater or lesser likelihood of these events relative to the other biologics. The authors attempted to combine ranked data from ACR20/50, AEs, SAEs, and WDAEs and concluded that secukinumab “may be the safest and most efficacious short-term treatment for peripheral PsA” among the included drugs.

Critical Appraisal of Indirect Treatment Comparison by Wu et al.

The main limitation of this network meta-analysis is that it restricted included studies to biologics affecting the IL pathways and so does not represent the alternative biologic treatment options available in Canada for PsA. Their analysis included clazakizumab, which is not currently available in Canada. In addition, the analysis did not include outcomes that assessed skin response, which is an important component to assess disease outcome in this condition. The methods for arriving at their overall ranking system were not clearly explained by the authors.

Discussion

[redacted]

[redacted]

Ixekizumab was more likely to show benefit compared with apremilast for PsARC and HAQ-DI, but less likely to show benefit relative to infliximab for HAQ-DI. Ixekizumab was less likely to show benefit compared with infliximab, etanercept, and golimumab for PsARC.

[redacted]

[redacted]

[redacted]

The network meta-analysis by Wu et al. was of good quality but has limited application because of the omission of important dermatologic outcomes for PsA and inclusion of a nonrelevant comparator (clazakizumab).

The network meta-analysis submitted by the manufacturer suggested that there were differences between ixekizumab and other drugs for some outcomes, whereas Wu et al. reported few differences in their cross tabulation analyses. One possible explanation for the difference in these two reports is that Wu et al. confined their comparisons to a smaller number of studies, and the overall analyses lacked statistical power to show differences between treatments. Another possible explanation is that Wu et al. did not perform separate analyses for biologic-naive and biologic-experienced populations.

Conclusion

In the absence of sufficient head-to-head trial data comparing ixekizumab to other biologic drugs to treat PsA, the manufacturer conducted an indirect treatment comparison analysis based on a systematic review of randomized controlled trials and compared the short-term efficacy and safety of ixekizumab with adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab. Efficacy and safety outcomes were evaluated, but no health-related quality of life data were assessed. Analyses in biologic-naive populations suggest that ixekizumab performs better over the short term for skin outcomes (PASI) but not as well in the ACR, PsARC, and HAQ-DI analyses relative to other biologics. Analyses in biologic-experienced populations showed no difference between ixekizumab and other biologic drugs for efficacy outcomes. There were no differences in likelihood of short-term AEs or SAEs between ixekizumab and other biologics in the mixed biologic-naive and biologic-experienced population. Ixekizumab may have a higher likelihood of WDAEs relative to ustekinumab.

There was insufficient information about the individual trials in the manufacturer-submitted meta-analysis, limiting the ability to assess clinical heterogeneity of the included studies, and thus the credibility of findings is uncertain.

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