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CADTH Reimbursement Review

Upadacitinib (Rinvoq)

Sponsor: AbbVie Corporation

Therapeutic area: Ankylosing spondylitis

Clinical Review
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Abbreviations

ACE	Arthritis Consumer Experts
AD	atopic dermatitis
AE	adverse event
AO	as observed
AO-MI	as observed with nonresponder imputation
AO-NRI	as observed with multiple imputation
AS	ankylosing spondylitis
ASAS	Assessment in SpondyloArthritis international Society
ASAS5/6	Assessment in SpondyloArthritis international Society 20% improvement in 5 of 6 domains
ASAS20	Assessment in SpondyloArthritis international Society 20% improvement
ASAS40	Assessment in SpondyloArthritis international Society 40% improvement
ASAS HI	Assessment of SpondyloArthritis international Society Health Index
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASDAI50	Bath Ankylosing Spondylitis Disease Activity Index 50% improvement
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BASMIlin	Linear Bath Ankylosing Spondylitis Metrology Index
bDMARD	biologic disease-modifying antirheumatic drug
bDMARD-IR	biologic disease-modifying antirheumatic drug–inadequate response
CAPA	Canadian Arthritis Patient Alliance
CDEC	CADTH Canadian Drug Expert Committee
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CI	confidence interval
CPK	creatine phosphokinase
CRA	Canadian Rheumatology Association
CRP	C-reactive protein
CSA	Canadian Spondylitis Association
DMARD	disease-modifying antirheumatic drug
DVU	discovertebral unit
EQ-5D-5L	5-Level EQ-5D
EQ VAS	EQ-5D Visual Analogue Scale

FACIT-F	Functional Assessment of Chronic Illness Therapy–Fatigue
FAS	full analysis set
HLA-B27	human leukocyte antigen B27
HRQoL	health-related quality of life
hsCRP	high-sensitivity C-reactive protein
IBD	inflammatory bowel disease
ID	inactive disease
IL-17	interleukin-17
IL-17i	interleukin-17 inhibitor
IRT	interactive response technology
ITC	indirect treatment comparison
ITT	intention-to-treat
JAK	Janus kinase
JAKi	Janus kinase inhibitor
LDA	low disease activity
MACE	major adverse cardiac event
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCID	minimal clinically important difference
MCP	mental component summary
MID	minimal important difference
MMRM	mixed-effect model for repeated measures
NMA	network meta-analysis
NRI	nonresponder imputation
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug
PCS	physical component summary
PR	partial remission
PsA	psoriatic arthritis
PtGA	Patient Global Assessment of Disease Activity
RA	rheumatoid arthritis
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SIJ	sacroiliac joint
SpA	spondyloarthritis

SPARCC	Spondyloarthritis Research Consortium of Canada
STIR	Short-T1 inversion recovery
TEAE	treatment-emergent adverse event
TNF	tumour necrosis factor
TNFi	tumour necrosis factor inhibitor
tsDMARD	targeted synthetic disease-modifying antirheumatic drug
VAS	visual analogue scale
WDAE	withdrawal due to adverse event
WPAI-SpA	Work Productivity Activity Impairment–Spondyloarthritis

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Upadacitinib (Rinvoq), 15 mg and 30 mg extended-release tablets, oral
Indication	For the treatment of adults with active ankylosing spondylitis who have had an inadequate response to a biologic disease-modifying antirheumatic drug or when use of those therapies is inadvisable; may be used as monotherapy or in combination with nonsteroidal anti-inflammatory drugs
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	July 14, 2022
Sponsor	AbbVie Corporation

NOC = Notice of Compliance.

Note: The sponsor indicated that 30 mg was not submitted for review.

Introduction

Ankylosing spondylitis (AS), also known as radiographic axial spondyloarthritis (SpA), is a chronic inflammatory disease primarily involving the spine and the sacroiliac joints (SIJs).[1,2] AS usually begins in young adults (aged < 45 years), with a peak age of onset between the ages of 20 to 30 years. AS is more common among men than among women.[1] Patients with AS exhibit radiographic abnormalities consistent with sacroiliitis. Patients experience back pain and progressive spinal stiffness and may also suffer from extra-articular manifestations such as uveitis, skin psoriasis, and inflammatory bowel disease (IBD). The symptoms of AS and the rate of progression fluctuate with time and can vary substantially between patients. AS negatively affects patients' health-related quality of life (HRQoL).[1-3] A diagnosis of AS can be made based on clinical features, biological testing, and imaging examinations of the disease.[2] The modified New York classification criteria for AS have often been applied as a diagnostic instrument.[4,5] A population-based study in Canada published by Haroon et al. showed that the prevalence of AS nearly tripled in Ontario from 1995 to 2010, the 2010 estimate being 0.2%.[6] In the same study, the annual incidence of AS remained relatively stable, with a rate of 15 per 100,000 individuals.[6] In 2019, AS was estimated to have affected 300,000 patients in Canada.[7]

The goals of treatment for patients with AS are to maximize long-term HRQoL, control symptoms and inflammation, maintain spinal flexibility and normal posture, reduce functional limitations, maintain work ability, decrease disease complications, and prevent progressive structural damage.[8,9] Several drug classes are used in the pharmacologic therapy of AS. Nonsteroidal anti-inflammatory drugs (NSAIDs), including nonselective and selective cyclooxygenase-2 inhibitors, are the first choice of treatment for adult patients with active AS. Should NSAIDs fail or if there are contraindications, the next line of treatment is a biologic

disease-modifying antirheumatic drug (bDMARD), a class that includes inhibitors of tumour necrosis factor (TNF), interleukin-17 (IL-17), and Janus kinase (JAK). Current practice is to start with a TNF inhibitor (TNFi) or IL-17 inhibitor (IL17i). TNFi drugs marketed in Canada for treatment of AS include adalimumab, certolizumab, etanercept, golimumab, and infliximab. IL-17i drugs marketed in Canada for the treatment of AS includes ixekizumab and secukinumab (Table 3). The treatment recommendations for AS and nonradiographic axial SpA are similar.[8]

Upadacitinib is an oral, selective Janus kinase inhibitor (JAKi).[10] JAK inhibitors are also classified as targeted synthetic biologic disease-modifying antirheumatic drugs (tsDMARDs). JAKs are intracellular enzymes that transduce signals from cell surface receptors for cytokines or growth factors involved in a broad range of cellular processes, including inflammatory responses, hematopoiesis, and immune surveillance.[10] Upadacitinib is available as a 15 mg or 30 mg extended-release tablet.[10] Health Canada previously approved indications for upadacitinib for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or are intolerant to methotrexate, adults with active psoriatic arthritis (PsA) who have had an inadequate response or are intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs), and adults and adolescents aged 12 years and older with refractory moderate-to-severe atopic dermatitis (AD) who are not adequately controlled with a systemic treatment (e.g., steroid or biologic) or when use of those therapies is inadvisable.[10] Upadacitinib was previously reviewed by CADTH for the indication of RA in February 2020,[11] PsA in August 2021,[12] and AD in June 2022.[13] The CADTH Canadian Drug Expert Committee (CDEC) has recommended that use of upadacitinib be reimbursed for the indications of RA, PsA, and AD if certain conditions are met.[11-13]

Currently, the Health Canada–approved upadacitinib indication of interest for this review is for the treatment of adults with active AS who have had an inadequate response to a bDMARD or when use of such a therapy is inadvisable. The recommended dose regimen is a 15 mg tablet administered orally once daily. Upadacitinib may be used as monotherapy or in combination with NSAIDs. (Table 3). The sponsor's reimbursement request is identical to the Health Canada–approved indication.[10]

The objective of this review is to review the beneficial and harmful effects of upadacitinib (extended-release tablets, 15 mg and 30 mg), 15 mg once daily, administered orally, for the treatment of adult patients with active AS who have had an inadequate response to a bDMARD or when use of those therapies is inadvisable. Upadacitinib may be used as monotherapy or in combination with NSAIDs.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

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

Two responses to CADTH's call for patient input for this review were received from Arthritis Consumer Experts (ACE) and through a joint submission from the Canadian Arthritis Patient Alliance (CAPA), Arthritis Society Canada, the Canadian Spondylitis Association (CSA), and Creaky Joints Canada. ACE, CAPA, Arthritis

Society Canada, CSA, and Creaky Joints Canada serve individuals living with arthritis, including AS, and their caregivers, health care providers, and community members.

Patient perspectives from the joint input were obtained from a survey shared via email, social media, and the 4 organizations' websites from October 12, 2022, to October 30, 2022. Patient perspectives from the ACE input were obtained from an ACE Survey Monkey platform.

Among the 264 joint survey participants living with AS, 9 had direct experience with upadacitinib and close to 90% indicated they live with back pain, while 72% have back pain, 86% have joint stiffness, and 51% experienced sore heels and feet. Patient respondents were also faced with other symptoms of AS, such as anxiety and depression (52% of respondents), bowel inflammation (49%), psoriasis (35%), migraine (32%), uveitis (31%), osteoporosis (23%), and heart problems (11%). Most survey participants rated their disease severity at 59 out of 100. In addition, patients reported having trouble managing symptoms, including fatigue, difficulty concentrating, stress, mobility issues, and loss of appetite. Similarly, respondents from the ACE patient input described experiencing fatigue, mobility issues, weight gain, and constant pain, and indicated that the disease affects their quality of life, daily activities, and mood. Caregivers of patient respondents from the ACE input also stated that the disease affected their quality of life as they must pay attention to time management.

The joint patient input stated that, during an AS flare, which is a period of worsening symptoms, patients may have difficulties performing day-to-day activities. Patient respondents with AS reported that the disease severely affects all aspects of their lives, from their physical and mental health to their family life, self-esteem, work, intimacy, and participation in social and leisure activities.

According to the joint patient input, many treatments are available to manage AS, including NSAIDs, corticosteroids, conventional synthetic DMARDs (csDMARDs), and bDMARDs. The joint patient input stated that the effectiveness and tolerance of these treatments varies significantly among patients, with more than 40% of patient respondents indicating that they had an inadequate response to currently available treatments. The joint patient input indicated that some patients had to change their medication after a short period of time; others did not respond adequately to currently available treatments. In addition, the joint patient input stated that side effects of current AS medications were another major concern for people living with AS. Fatigue, nausea and vomiting, increased risk of infections, liver toxicity, and weight gain can all affect patient adherence to medication and their daily activities.

According to the patient respondents from the ACE patient input, currently available treatments can manage their disease symptoms. However, concerns were raised regarding the cost of the medications, side effects, and the need to change medications due to decreased effectiveness within a short period of time.

The joint patient input highlighted that other treatment options, such as medical cannabis and/or nonpharmacological approaches to managing AS symptoms, are challenging to access because they are not reimbursed, not offered, or require lengthy waits. According to the joint patient input, health care providers need to consider many factors to determine the most effective treatment, such as side effects, mode of administration, time required for treatment, travel, patient preferences, and cost.

Nine respondents from the joint input reported having experience with upadacitinib. Positive aspects of treatment with upadacitinib reported by patient respondents included the simple route of administration, improved disease symptoms, mobility, and better quality of life with more energy. Few patient respondents experienced more frequent infections and headaches while being treated with upadacitinib.

Patient respondents from the joint patient input stated that management of AS can be improved by having access to affordable treatments that have a simple administration route (e.g., pills), fewer adverse effects and infection rates, and are able to reduce disease-related symptoms, enhance their quality of life, and allow them to pursue their daily activities. The ACE input noted that patient respondents value additional treatment options with fewer adverse events (AEs) and improved pain control and remission rates.

Clinician Input

This section was prepared by CADTH staff based on input from the clinical expert consulted by CADTH.

The clinical expert consulted by CADTH for this review indicated that not all patients respond to available treatments. The Assessment in SpondyloArthritis international Society 40% improvement (ASAS40) is a common primary end point in clinical trials, which corresponds to a 40% improvement in 3 out of 4 domains (patient global assessment, total back pain, Bath Ankylosing Spondylitis Functional Index [BASFI], and morning stiffness) with an absolute improvement of at least 2 domains and no worsening of the remaining domains. Roughly 40% of patients are able to achieve this response in clinical trials. Response rates to more stringent measures, such as Assessment of SpondyloArthritis international Society (ASAS) partial remission (PR) or Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (ID), are much lower. Roughly 10% of patients with AS also have IBD. While a TNFi can be effective in treating both, many patients with severe IBD do not respond to a TNFi even at a high dose (infliximab 10 mg/kg every 4 weeks) or initially respond but experience loss of efficacy or have to stop due to side effects (i.e., drug-induced psoriasis, lupus, or multiple sclerosis). IL-17i drugs would be contraindicated in these patients, leaving few options available to patients. Roughly half of patients experience a loss in efficacy with their first biologic within 3 to 5 years. When patients fail a biologic, clinicians often consider switching to a different mechanism of action. In the event of a secondary loss of effect, clinicians can consider switching within class. Additionally, some patients may have a contraindication to available therapies. With a TNFi, clinicians are cautious in patients with a personal or family history of multiple sclerosis, lupus, or drug-induced psoriasis. With an IL-17i, clinicians would try to avoid prescribing such a drug to patients with a history of IBD. Finally, no oral bDMARD options are available, and many patients are young, may enjoy travelling, or have an aversion to needles.

The clinical expert consulted by CADTH for this review indicated that treatment data from the upadacitinib trials in axial SpA show treatment response rates that appear to be comparable to those of other biologic drugs, such as TNFi or IL-17i options. Because JAKi options do not appear to work through a TNF or IL-17 pathway, an alternative mechanism of action would be ideal for these patients. Upadacitinib has been shown to reduce objective markers of inflammation such as C-reactive protein (CRP) and bone marrow edema in the SIJ and spine on MRI. Bone marrow edema has been shown to be a strong predictor of future syndesmophyte formation. If a patient requires escalation in therapy, clinicians will decide whether a TNFi, IL-17i, or JAKi would be most appropriate and initiate therapy. Currently the approved Health Canada

label calls for use of these drugs if a previous biologic has failed or if other biologics are unsuitable; most rheumatologists were disappointed with that decision and were hoping to use this drug as a first-line DMARD in the appropriate patients. As upadacitinib was recently shown to be effective for nonradiographic axial SpA in a study with a sufficient sample size, the expectation is that the sponsor will want to get Health Canada approval for use as a first-line drug under this indication. The drug under review would provide further options to treat patients due to contraindications to a TNFi or IL-17i, previous failures to these drugs, convenience to patients in the form of an oral option, and efficacy in patients with both IBD and axial SpA. Patients should first try 2 NSAIDs for 2 to 4 weeks unless there is a contraindication. If they still have high disease activity, DMARDs are expected to be a first-line option available to patients, along with a TNFi and IL-17i. With the current Health Canada indication of a second-line drug, patients who have previously failed a biologic or who have a contraindication would be able to use it. From a safety perspective, most rheumatologists are comfortable with using this drug as a first-line biologic as it has been approved to treat RA.

The clinical expert consulted by CADTH for this review indicated that any patient with active AS would likely benefit from treatment with upadacitinib. Patients who also have active IBD, prefer an oral option, or have failed or have a contraindication to a TNFi or IL-17i may also benefit. Patients with high disease activity are in most in need of an intervention. Elevated CRP and bone marrow edema on MRI may be predictive of a greater response, but many patients with neither of these will also respond very well. The diagnosis of AS involves characteristic clinical findings in conjunction with identifying sacroiliitis in a pelvic X-ray. There can be quite a lot of interreader reliability issues, especially with early disease. Many rheumatologists typically confirm a diagnosis with MRI of the SIJ before proceeding with a bDMARD. The probability of under or overdiagnosis is largely related to the experience of the clinician. Most cases are straightforward, and convincing imaging and clinical features — and possibly a positive test for human leukocyte antigen B27 (HLA-B27) — can help a rheumatologist make a definitive diagnosis. The experience of the radiologist reading the X-ray, CT, or MRI scan is also important. Predictors of treatment response would be early onset of symptoms, male gender, elevated CRP, and degree of bone marrow edema seen on MRI.

The clinical expert consulted by CADTH for this review indicated that clinicians typically follow up with a patient after 3 months of therapy. If there is absolutely no response, clinicians would consider switching to a different drug. If there is a partial response, clinicians may wait for up to 6 months to determine the benefit. In daily practice, treatment response is measured by improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or ASDAS. Typically, a BASDAI improvement of 2 points or a 50% reduction is a reasonable response. Clinicians would see patients every 3 to 6 months to ensure stability of their disease. In clinical trials, clinicians would want to see an ASAS40 and a statistically significant improvement in other measures, such as ASDAS inadequate response, CRP, MRI, Assessment of SpondyloArthritis international Society Health Index (ASAS HI), Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire, or Linear Bath Ankylosing Spondylitis Metrology Index (BASFI). The clinical expert consulted by CADTH for this review indicated that clinicians would discontinue the medication if patients were developing side effects such as infections. If a patient's symptoms were to recur, clinicians may consider switching the patient to another medication if clinicians were convinced that this was due to active disease. The clinical expert consulted by CADTH for this review indicated that a rheumatologist would be needed to confirm a diagnosis, treat, and

monitor patients with AS. If other manifestations are involved, they may be co-followed by ophthalmology, gastroenterology, and dermatology.

Clinician Group Input

The Canadian Rheumatology Association (CRA) provided clinical input. Two clinicians who are members of the Spondylarthritis Research Consortium of Canada (SPARCC) executive committee and were involved in the 2014 CRA/SPARCC treatment recommendations contributed to these submissions.

Clinician group input indicated that there is an unmet need for the treatment of patients with AS for the following reasons: not all patients respond to currently available treatments; medications become less effective more frequently, which requires a switch to another medication; various adverse effects of the current therapies; persistence of constant spinal pain; and active extra-articular manifestations are common. The lack of orally administrated options can also affect compliance and adherence to a treatment plan.

The views of the clinician group were consistent overall with those of the clinical expert consulted by CADTH. The clinician group indicated that the most essential treatment goals are reducing pain and improving function.

The group advocated for NSAIDs as first-line pharmacologic therapy for AS and a TNFi or IL-17i as a first-line biologic therapy when NSAIDs are insufficient. Other classes of biologic treatments, such as a JAKi or other tsDMARD, could be used if initial treatments fail.

Clinician input suggested that patients would benefit more from upadacitinib, a selective JAKi for axial SpA, given its unique mechanism of action and oral administration, which are considered ideal options for many patients, particularly those who have failed treatment with continuous NSAIDs and who continue to have high measures of disease activity. However, people with severe active infections, acute or chronic, and people with severe hepatic disorders may not be suitable for upadacitinib use.

Drug Program Input

The drug plans identified considerations for initiation of therapy as a jurisdictional implementation issue. The clinical expert consulted by CADTH provided responses to the drug program implementation questions (Table 4).

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

Two manufacturer-sponsored, 14-week, double-blind, randomized controlled trials (RCTs), Study 944 (N = 420) and Study 098 (N = 187), are included in this review. The 2 trials evaluated the efficacy and safety of upadacitinib 15 mg administered orally once daily compared to placebo in patients with active AS. Study 944 was conducted in patients with AS who responded inadequately or were intolerant to 1 or 2 bDMARDs. Study 098 was conducted in patients with AS who responded inadequately or were intolerant to 2 or more NSAIDs but were bDMARD-naive. The primary outcome in both trials was the proportion of patients meeting

the ASAS40 response criteria at week 14. The key secondary outcomes (multiplicity-controlled) included change from baseline in ASDAS; change from baseline in MRI SPARCC score (spine); Bath Ankylosing Spondylitis Disease Activity Index 50% improvement (BASDAI50) response; Assessment in SpondyloArthritis international Society 20% improvement (ASAS20) response; ID (ASDAS score < 1.3); change from baseline in patient assessment of total back pain; change from baseline in patient assessment of nocturnal back pain; low disease activity (LDA) (ASDAS score < 2.1); change from baseline in the BASFI); PR; change from baseline in ASQoL; change from baseline in ASAS HI; change from baseline in the Linear Bath Ankylosing Spondylitis Metrology Index (BASMIlin); and change from baseline in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).

Both Study 944 and Study 098 study included 4 periods: a screening period, a double-blinded treatment period (for 14 weeks), an extended treatment period (up to week 104), and a posttreatment follow-up period (30 days after last visit). Both Study 944 and Study 098 were conducted in multiple countries, including Canada, the US, Europe, Australia, New Zealand, and Asian countries. Study 944 also included Mexico and countries from South America. Results of the extension phase at week 52 of [redacted] Study 098) as well as week 104 for Study 098 are also presented in this report. Study 944 is ongoing. The long-term efficacy and safety outcome at week 104 in Study 944 was not available at the time of this review. Study 098 was complete.

Efficacy Results

Key efficacy and safety results at week 14 are summarized in Table 2.

Clinical response (e.g., ASAS40) at week 14: In Study 944, the proportions of patients achieving ASAS40 were 44.5% and 18.2% in the upadacitinib (15 mg, oral, once daily) and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was 26.4% (95% confidence interval [CI], 17.9% to 34.9%; P < 0.0001). In Study 098, the proportions of patients achieving ASAS40 were 51.6% and 25.5% in the upadacitinib (15 mg, oral, once daily) and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was 26.1% (95% CI, 12.6% to 39.5%; P < 0.001). According to the clinical expert CADTH consulted for this review, ASAS20 at week 12 has been considered an acceptable clinical response for bDMARD trials in patients with AS. Therefore, ASAS40 at week 14 represents a more substantial clinical improvement, and more recent trials have utilized this as the primary end point.

Measures of AS symptoms (e.g., total back pain) at week 14: In Study 944, the means of changes from baseline for total back pain were −3.00 (95% CI, −3.30 to −2.70) and −1.47 (95% CI, −1.77 to −1.16) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.53 (95% CI, −1.96 to −1.11; P < 0.0001). In Study 098, the means of changes from baseline for total back pain were −3.21 [redacted] and −1.68 [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was [redacted]. The improvement in total back pain may be considered clinical meaningful (or useful) [redacted].

Function and disability (i.e., BASFI) at week 14: In Study 944, the means of changes from baseline for BASFI were −2.26 (95% CI, −2.53 to −2.00) and −1.09 (95% CI, −1.35 to −0.83) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.17 (95% CI, −1.55 to −0.80; P < 0.0001). In Study 098, the means of changes from baseline for BASFI were −2.29 (95% CI, −2.73 to −1.85) and −1.30 (95% CI, −1.74 to −0.86) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.00 (95% CI, −1.60 to 0.39; P < 0.001). The improvement in the BASFI was considered clinical meaningful.

HRQoL (ASQoL) at week 14: In Study 944, the means of changes from baseline for ASQoL were −5.10 (95% CI, −5.69 to −4.52) and −2.03 (95% CI, −2.62 to −1.44) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −3.07 (95% CI, −3.90 to −2.24; P < 0.0001). In Study 098, the mean changes from baseline for ASQoL were −4.20 (95% CI, −5.12 to −3.29) and −2.67 (95% CI, −3.58 to −1.75) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.54 (95% CI, −2.78 to 0.30; P < 0.016). The improvement in ASQoL was considered clinical meaningful in Study 944, but not in Study 098.

Work productivity (i.e., Work Productivity Activity Impairment–Spondyloarthritis [WPAI-SpA] Overall Work Impairment) at week 14: In Study 944, the means of changes from baseline for WPAI Overall Work Impairment were [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was [redacted] In Study 098, the means of changes from baseline for WPAI Overall Work Impairment were −18.11 (95% CI, −24.73 to −11.50) and −12.60 (95% CI, −19.04 to −6.15) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −5.52 (95% CI, −13.82 to 2.78; P = 0.19 [not statistically significant]).

ASDAS (CRP): In Study 944, the means of changes from baseline for ASDAS (CRP) were −1.52 (95% CI, −1.64 to −1.39) and −0.49 (95% CI, −0.62 to −0.37) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.02 (95% CI, −1.20 to −0.85; P < 0.0001). In Study 098, the means of changes from baseline for ASDAS (CRP) were −1.45 (95% CI, −1.62 to −1.28) and −0.54 (95% CI, −0.71 to −0.37) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −0.91 (95% CI, −1.14 to −0.68; P < 0.001). A cut-off of 1.1 or higher is considered a clinically important improvement, which was seen in Study 944 but not in Study 098.

BASDAI50 at week 14: In Study 944, the proportions of patients achieving BASDAI50 were 43.1% and 16.7% in the upadacitinib and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was 26.4% (95% CI, 18.0% to 34.8%; P < 0.0001). In Study 098, the proportions of patients achieving BASDAI50 at week 14 were in 45.2% and 23.4% in the upadacitinib and placebo groups,

respectively. The mean between-groups difference (upadacitinib versus placebo) was 21.8% (95% CI, 8.5% to 35.0%; P = 0.002). A BASDI50 response was considered clinical meaningful in both studies.

MRI SPARCC Index (spine) at week 14: In Study 944, the means of changes from baseline for MRI SPARCC Index (spine) were −3.95 (95% CI, −5.06 to −2.83) and −0.04 (95% CI, −1.14 to 1.06) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −3.90 (95% CI, −5.47 to −2.33; P < 0.0001). In Study 098, the means of changes from baseline for MRI SPARCC Index (spine) were −6.93 (95% CI, −8.58 to −5.28) and −0.22 (95% CI, −2.01 to 1.57) in the upadacitinib 15 mg, oral, once-daily and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −6.71 (95% CI, −9.01 to −4.41; P < 0.001). The improvement of MRI SPARCC Index (spine) was considered clinical meaningful in Study 098 but not in Study 944.

MASES at week 14: In Study 944, the means of changes from baseline for MASES were −2.6 (95% CI, −3.0 to −2.2) and −1.1 (95% CI, −1.5 to −0.8) in the upadacitinib 15 mg, oral, once-daily and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.50 (95% CI, −2.00 to −0.90; P < 0.0001). However, whether the improvement in MASES in Study 944 is clinical meaningful remains unclear. In Study 098, at week 14, the means of changes from baseline for MASES were −2.25 (95% CI, −2.86 to −1.64) and −1.41 (95% CI, −2.02 to −0.80) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −0.84 (95% CI, −1.68 to 0.00; P < 0.049, which was considered not significant).

BASMI at week 14: In Study 944, the means of changes from baseline for the BASMI were −0.48 (95% CI, −0.58 to −0.38) and −0.16 (95% CI, −0.26 to −0.06) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −0.32 (95% CI, −0.46 to −0.18; P < 0.0001). However, whether the improvement in the BASMI shown in Study 944 is clinical meaningful remains unclear. In Study 098, the means of changes from baseline for BASMI were −0.37 (95% CI, −0.52 to −0.21) and −0.14 (95% CI, −0.29 to 0.01) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −0.22 (95% CI, −0.43 to −0.02; P < 0.03, which was considered not significant).

Efficacy reported in extension phase: The efficacy achieved at week 14 appeared to be maintained at 52 weeks [redacted] and week 104 (for Study 098).

Harms Results

The overall frequency of patients with treatment-emergent adverse events (TEAEs) in patients treated with upadacitinib appeared to be low, but higher compared to those in the placebo group in both Study 944 (40.8% verus 36.8%, respectively) and in Study 098 (62.4% versus 55.3%) by week 14. In Study 944, no TEAEs occurred in at least 5% of patients in either of the arms. In Study 098, the most common TEAEs (> 5% of patients in either of the treatment groups) had increased levels of blood creatine phosphokinase (CPK), diarrhea, nasopharyngitis, headache, and nausea. The overall frequency of patients with serious adverse events (SAEs) by week 14 seemed to be very low (< 3%) in both studies by week 14. It was noted that no

patients withdrew due to AEs in the upadacitinib group in Study 944. In Study 098, patient withdrawal due to adverse event (WDAE) was also very low (< 3%). No deaths were reported by week 14 in either of the studies. The incidence of notable harms identified in this review (including serious infection, anemia, neutropenia, lymphopenia, thrombocytopenia, malignancies, thrombosis including increased platelets, elevation of CPK, other gastrointestinal SAEs, hypersensitivity, acne, and folliculitis) was also low. No major adverse cardiac event (MACE), gastrointestinal perforation, hepatotoxicity, dyslipidemia, opportunistic infection excluding tuberculosis, herpes zoster, or active case of tuberculosis was reported in either of the studies. Based on the input from the clinical expert CADTH consulted for this review, the TEAEs reported in both Study 944 and Study 098 were commonly observed in other upadacitinib clinical trials for RA, PsA, and AD. Notable harms were unremarkable.

For the extension phase, the proportion of patients with a TEAE was not reported in either study. Instead, the number of TEAEs and the number of TEAE person-years were provided. The clinical expert CADTH consulted for the review indicated that the safety profiles of upadacitinib for AS over [redacted] and over week 104 were consistent with that observed by week 14, with no new safety signals reported. The overall observed AEs aligned with the known safety profile of upadacitinib. No new safety signals were identified between week 14 and week 104.

Table 2: Summary of Key Results From Pivotal and Protocol-Selected Studies (at Week 14)

Outcomes	Study 944		Study 098	
	UPA 15 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
Efficacy				
ASAS40, (NRI, MI, FAS)				
Response, n[a] (%)	94 (44.5)	38 (18.2)	48 (51.6)	24 (25.5)
Between-groups difference (upadacitinib vs. placebo),[b] % (95% CI)	26.4 (17.9 to 34.9)		26.1 (12.6 to 39.5)	
P value vs. PBO	< 0.0001		< 0.001	
ASAS20				
Response, n[a] (%)	[redacted] (65.4)	[redacted] (38.3)	[redacted] (64.5)	[redacted] (40.4)
Between-groups difference UPA-PBO), % (95% CI)	27.1 (17.9 to 36.3)		24.1 (10.2 to 38.0)	
P value	< 0.0001		0.001	
Total back pain				
Week 14, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean	7.45	7.41	[redacted]	[redacted]
Week 14, mean	[redacted]	[redacted]	[redacted]	[redacted]

Outcomes	Study 944		Study 098	
	UPA 15 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
Total back pain CFB, mean (95% CI)	−3.00 (−3.30 to −2.70)	−1.47 (−1.77 to −1.16)		
Between-groups difference of CFB (upadacitinib vs. placebo), mean (95% CI)	−1.53 (−1.96 to −1.11)			
P value	< 0.0001			
Nocturnal back pain				
Week 14, n (%)				
Baseline, mean	7.10	7.20		
Week 14, mean				
Nocturnal back pain CFB, mean (95% CI)	−3.21 (−3.52 to −2.89)	−1.52 (−1.84 to −1.20)		
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	−1.69 (−2.14 to −1.24)			
P value	< 0.0001			
BASFI				
Week 14, n (%)				
Baseline, mean	6.25	6.20		
Week 14, mean				
BASFI CFB, mean (95% CI)	−2.26 (−2.53 to −2.00)	−1.09 (−1.35 to −0.83)	−2.29 (−2.73 to −1.85)	−1.30 (−1.74 to −0.86)
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	−1.17 (−1.55 to −0.80)		−1.00 (−1.60 to −0.39)	
P value	< 0.0001		0.001	
ASQoL				
Week 14, n (%)				
Baseline, mean	11.63	11.48		
Week 14, mean				
ASQoL CFB (95% CI)	−5.10 (−5.69 to −4.52)	−2.03 (−2.62 to −1.44)	−4.20 (−5.12 to −3.29)	−2.67 (−3.58 to −1.75)
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	−3.07 (−3.90 to −2.24)		−1.54 (−2.78 to −0.30)	
P value	< 0.0001		0.016	
BASDAI50 response, n (%)	(43.1)	(16.7)	(45.2)	(23.4)

Outcomes	Study 944		Study 098	
	UPA 15 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
Between-groups difference (UPA-PBO), % (95% CI)	26.4 (18.0 to 34.8)		21.8 (8.5 to 35.0)	
P value	< 0.0001		0.002	
ASDAS (CRP) CFB				
Week 14, n (%)				
Baseline, mean	3.86	3.87		
Week 14, mean				
ASDAS (CRP) CFB, mean (95% CI)	−1.52 (−1.64 to −1.39)	−0.49 (−0.62 to −0.37)	−1.45 (−1.62 to −1.28)	−0.54 (−0.71 to −0.37)
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	−1.02 (−1.20 to −0.85)		−0.91 (−1.14 to −0.68)	
P value	< 0.0001		< 0.001	
ASDAS inactive disease response, n (%)	(12.8)	(1.9)		
Between-groups difference (upadacitinib vs. placebo), % (95% CI)	10.9 (6.0 to 15.8)			
P value	< 0.0001			
ASDAS low disease activity response, n (%)	(44.1)	(10.1)	46 (49.5)	10 (10.6)
Between-groups difference (UPA-PBO), % (95% CI)	34.0 (26.2 to 41.8%)		38.8 (26.9 to 50.7)	
P value	< 0.0001		nominal P < 0.001	
SPARCC MRI spine				
Week 14, n (%)				
Baseline, mean				
Week 14, mean				
SPARCC MRI Spine (CFB) (95% CI)	−3.95 (−5.06 to −2.83)	−0.04 (−1.14, 1.06)	−6.93 (−8.58 to −5.28)	−0.22 (−2.01 to 1.57)
Between-groups difference of CFB (UPA-PBO), % (95% CI)	−3.90 (−5.47 to −2.33)		−6.71 (−9.01 to −4.41)	
P value	< 0.0001		< 0.001	
Harms				
Any TEAE, n (%)			58 (62.4)	52 (55.3)
SAE, n (%)	6 (2.8)	1 (0.5)	1 (1.1)	1 (1.1)
WDAE (from treatment), n (%)				
All deaths, n(%)	0 (0.0)	0 (0.0)	0	0

Outcomes	Study 944		Study 098	
	UPA 15 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
Most common notable harms (> 5% of patient with AE in any arm in either of the 2 studies), n (%)				
Infection	31 (14.7)	27 (12.9)	19 (20.4)	26 (27.7)
Elevated CPK	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic disorder	6 (2.8)	2 (1.0)	5 (5.4)	2 (2.1)

AE = adverse event; ASAS20 = Assessment of SpondyloArthritis international Society 20% improvement; ASAS40 = Assessment of SpondyloArthritis international Society 40% improvement; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = ankylosing spondylitis quality of life; BASDAI50 = Bath Ankylosing Spondylitis Disease Activity Index 50% improvement; BASFI = Bath Ankylosing Spondylitis Functional Index; CFB = change from baseline; CI = confidence interval; CPK = creatine phosphokinase; CRP = C-reactive protein; FAS = full analysis set; MI = multiple imputation; NRI = nonresponder imputation; PBO = placebo; q.d. = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event; SPARCC = Spondyloarthritis Research Consortium of Canada; UPA = upadacitinib; vs. = versus; WDAE = withdrawal due to adverse event including death.

Notes: NRI-MI is nonresponder imputation incorporating multiple imputations to handle missing data due to COVID-19. Standard deviations of the mean for baseline and week 14 were not available from the sponsor.

[a]n is calculated by N and MI-aggregated response rate (%).

[b]Treatment difference, associated CI, and P value for the test of difference between the upadacitinib group and the placebo group is constructed based on the MI inference. Risk difference and standard error is estimated using Cochran-Mantel-Haenszel test and screening high-sensitivity CRP status as stratification factor within each imputed "complete" dataset, after which Rubin's rule is used to combine the results from 30 imputed "complete" datasets to produce an aggregated treatment difference, associated CI and P value.

Sources: Study 944, week 14 Clinical Study Report,[14] Study 098 week 14 Clinical Study Report,[15] and sponsor's submission.[16]

Critical Appraisal

Randomization appeared sufficient and blinding appeared to be maintained throughout the study. Missing data were minimal and unlikely to affect study results. A multiplicity adjustment was conducted for the primary and main secondary outcomes at week 14; however, in Study 944, no multiplicity adjustment was performed for other secondary or exploratory outcomes, such as Assessment in SpondyloArthritis international Society 20% improvement in 5 of 6 domains (ASAS5/6), 5-Level EQ-5D (EQ-5D-5L), Short Form (36) Health Survey (SF-36), Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), Work Productivity Activity Impairment–Spondyloarthritis (WPAI-SpA), and MRI SPARCC score (SIJ). In Study 098, no multiplicity adjustment was performed for symptom measurement scale (total back pain and nocturnal back pain), ID (ASDAS score < 1.3), LDA (ASDAS score < 2.1); HRQoL (EQ-5D-5L and SF-36), FACIT-F and MRI SPARCC score (SIJs). Given the large number of comparisons in the study, a statistically significant finding ($P < 0.05$) for the comparisons between upadacitinib and placebo for these outcomes without multiplicity adjustment may present a high risk of bias due to an inflated type I error rate. The statistical significance (P value) reported for those outcomes without a multiplicity adjustment therefore remains uncertain. One limitation was that both Study 944 and Study 098 were not designed to assess the comparative efficacy and safety between upadacitinib and the existing bDMARDs marketed in Canada (i.e., TNFi and IL-17i) for the treatment of AS. The direct comparative efficacy and safety of upadacitinib and other bDMARDs therefore remains unknown. In addition, extra-articular manifestations were not assessed as an efficacy in either of the studies, and the efficacy of upadacitinib on the extra-articular manifestations in the patients with AS remains to be investigated.

Regarding limitations for the long-term, the findings at week 52 for both studies and at 104 weeks for Study 098 in the extension phase were limited by the lack of any control group and the nature of the open-label study. Efficacy data beyond week 52 were not provided for the ongoing Study 944. The clinical expert CADTH consulted for this review indicated that, in clinical trials, the efficacy magnitude (particularly for those patient self-reported outcomes) is commonly overestimated due to the nature of the open-label protocol and the absence of a control group. Moreover, patients who enter into a long-term extension are generally responding to the medication, or are aware they will now receive the medication, and are relatively free of AEs, which further increases biases observed around efficacy and safety. The long-term outcome efficacy should therefore be interpreted with consideration of this limitation, although this would apply to all long-term extension studies. Finally, for the extension phase, the proportion of patients with TEAEs was not reported in either study. Instead, the numbers of TEAEs and TEAE person-years were provided.

The clinical expert CADTH consulted for this review indicated that exclusion of patients with total ankylosis of the spine and those who had inadequate response to 2 or more bDMARDs in the trials was a "clinical trial strategy" to exclude patients who were not likely to demonstrate changes in numerous outcome measures. However, this is consistent with previous AS clinical trials (e.g., secukinumab, ixekizumab, anti-TNFs). In real-world practice, it is possible that patients with total ankylosis who failed more than 2 bDMARDs may still demonstrate decreases in pain, stiffness, and fatigue and meaningful improvements in quality of life with the treatment. Overall, according to the clinical expert involved in the review, in both Study 944 and Study 098, the patients included in the trial were similar to those seen in Canadian clinical settings, except that those patients with total ankylosis of the spine who had failed more than 2 bDMARDs would also be considered eligible for therapy and be treated in a clinic. There is little concern about the generalizability in Canada of the findings from both Study 944 and Study 098.

Indirect Comparisons

Description of Studies

The sponsor submitted an indirect treatment comparison (ITC) of upadacitinib in adults with AS, and it is included in this review. [redacted]

A focused literature search identified 2 published ITCs, which are also included in the review.[18,19]

Efficacy Results

[redacted]

The published ITCs had similar findings. One used a frequentist approach and did not specify prior bDMARD exposure.[18] The number of included studies was larger than the sponsor-submitted ITC. Fewer efficacy outcomes were assessed, but it also included an assessment of SAEs. Upadacitinib was superior to placebo and did not differ from relevant comparators with respect to efficacy outcomes. The other published ITC used a Bayesian approach to estimate the comparative efficacy of JAKi drugs and secukinumab in patients with no prior exposure to bDMARDs.[19] Secukinumab was the only relevant comparator for the Canadian context included in this ITC. Upadacitinib was superior to placebo and similar to secukinumab for efficacy outcomes.

Harms Results

[redacted] Both published ITCs included comparative estimates for SAEs. In the ITC that used a frequentist approach, upadacitinib was no different than placebo or other relevant comparators for SAEs.[18] In the published ITC that used a Bayesian approach, upadacitinib was no different than placebo or secukinumab for SAEs.[19]

Critical Appraisal

A key limitation in the sponsor-submitted ITC is the evidence base for patients who had an inadequate response to a previous bDMARD, which appears to be the primary target population for this drug based on the Health Canada indication.[10] The ITC provides comparative efficacy for only ixekizumab and secukinumab in patients with an inadequate response to a prior bDMARD. Although comparative efficacy is available for all relevant comparators in a bDMARD-naive population, it is uncertain if the comparative efficacy results for bDMARD-naive patients can be generalized to patients who had an inadequate response to a bDMARD. The clinical expert consulted by CADTH noted that bDMARD patients with an inadequate response would be expected to have a lower response compared to bDMARD-naive patients.

Another a key limitation of the sponsor-submitted study is the presence of heterogeneity in baseline patient characteristics among studies. Additional aspects of study design may also contribute to heterogeneity. Many of the baseline characteristics with heterogeneity have been identified in the literature as treatment-effect modifiers in AS. [redacted] There is therefore increased uncertainty in the ITC findings.

One[18] of the 2 published ITCs had similar limitations related to heterogeneity of baseline patient characteristics among the included studies, while heterogeneity in the other study[19] could not be evaluated because no baseline patient characteristics were provided. One study had additional concerns about heterogeneity related to the time points used for efficacy assessment.[18] Both ITCs also have limitations related to reporting of methods and results, as well as details about included studies.

Other Relevant Evidence

No other relevant evidence was identified.

Conclusions

Two double-blind RCTs of patients with active AS were included in this review. Study 944 was conducted in patients with inadequate response to or intolerance of 1 or 2 bDMARDs, and Study 098 was conducted in patients with inadequate response to at least 2 NSAIDs, but who were bDMARD-naive. The observed evidence indicated that, at week 14, once-daily, oral upadacitinib 15 mg showed a **statistically significant** and **clinically meaningful (or useful) benefit** as demonstrated by clinical response (e.g., ASAS40), AS symptom reduction (e.g., total back pain in Study 944), function and disability improvement (i.e., BASFI), HRQoL (ASQoL in Study 944), AS disease activity reduction (e.g., BASDAI50, ASDAS) and MRI-detected axial inflammation (i.e., MRI spine SPARCC change in Study 098) compared with placebo. Treatment with upadacitinib also demonstrated a **statistically significantly greater** improvement (in Study 944) in terms of ASAS HI, MRI spine SPARCC change, enthesitis (MASES) and spinal mobility (BASMI) compared with placebo at week 14. Treatment with upadacitinib also appeared to be **favourable compared with placebo** in terms of WPAI-SpA (in Study 944) and patient global assessment. The magnitude of clinical response (ASAS40) to upadacitinib appeared similar in bDMARD-experienced patients compared with bDMARD-naive patients, even though most clinical trials assessing efficacy in patients with an inadequate response to a bDMARD have demonstrated reduced treatment response. The efficacy achieved at week 14 appeared to be maintained at 52 weeks [redacted]) and week 104 (for Study 098). The overall observed AEs aligned with the known safety profile of upadacitinib. No new safety signals were identified at week 14 and up to week 104. The evidence from 3 ITCs suggests that no treatment for AS is favoured over others for most efficacy outcomes in bDMARD-naive patients and patients who had an inadequate response to a bDMARD, although the evidence base is limited in the latter population. No treatment is favoured over others for the outcome of SAEs. The presence of heterogeneity in the included studies increases uncertainty in the findings.

Introduction

Disease Background

Ankylosing spondylitis, also referred to as radiographic axial SpA, is a chronic inflammatory disease primarily involving the spine and SIJs.[1,2] "Ankylosing" means fusing and "spondylitis" means inflammation of the spine. AS is considered an autoimmune disease[20] that usually begins in young adults (aged < 45 years), with a peak age of onset of between 20 and 30 years. AS is more common among men than among women.[1] Patients with AS exhibit radiographic abnormalities consistent with sacroiliitis. Patients experience back pain and progressive spinal stiffness and may also suffer from extra-articular manifestations such as uveitis, skin psoriasis, and IBD. AS symptoms and the rate of progression fluctuate with time and can vary substantially among patients. They result in functional impairment and subsequent potential socioeconomic consequences and disability; AS therefore negatively affects patients' HRQoL.[1-3] A diagnosis of AS can be made based on the clinical features, biological testing, and imaging examinations of the disease.[2] The modified New York classification criteria for AS have often been applied as a diagnostic instrument.[4,5] The exact prevalence of AS is unknown and varies widely across countries, with Africa having the lowest prevalence (0.07%) and the US having the highest prevalence (0.32%).[21] Studies have also suggested a

difference in AS prevalence within the same country, which may be partly due to socioeconomic status and genetic variation.[21] The worldwide prevalence of AS is reportedly 0.18%.[22] A population-based study published by Haroon et al. showed that the prevalence of AS nearly tripled in Ontario from 1995 to 2010, the 2010 estimate being 0.2%. In the same study, the annual incidence of AS remained relatively stable, with a rate of 15 per 100,000 individuals.[6] In 2019, AS was estimated to affect 300,000 patients in Canada.[7] Population data from Alberta indicates similar provincial rates; however, there is a higher prevalence in First Nations populations (0.6%).[23] The American College of Rheumatology/Spondylitis Association of America/ Spondyloarthritis Research and Treatment Network Recommendations (2019),[8] defines active AS as a disease causing symptoms at an unacceptably bothersome level to the patient and judged by the examining clinician to be due to inflammation. Stable AS was defined as asymptomatic or causing symptoms but at an acceptable level as reported by the patient. A minimum of 6 months was required to qualify as clinically stable.[8]

Standards of Therapy

According to the update of ASAS–European Alliance of Associations for Rheumatology *Recommendations on the management of axial spondyloarthritis* (2022)[9] and the practice guidelines developed by the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network in 2019,[8] the goals of treatment for patients with AS are to maximize long-term HRQoL, control symptoms and inflammation, maintain spinal flexibility and normal posture, reduce functional limitations, maintain work ability, decrease disease complications, and prevent progressive structural damage.[8,9] Treatment decisions are based on the degree of disease activity, functional disability, and HRQoL.[8] There are no internationally accepted remission criteria for AS. Remission has been defined as the persistent absence of clinical and radiologic signs of disease activity without treatment over a specific period of time. The only criterion that has been formally derived is the ASAS PR criteria, which evaluates symptomatic improvement and represents a state of low-level disease activity rather than remission. Patients who achieve PR are clinically equivalent to those with no symptoms or significant damage, consistent with a BASDAI score of 0 to 1, a BASFI score of 0 to 1, and an ASDAS of 0 to 1. However, this set of criteria is used primarily in clinical trials.[16,24] Although no treatment has currently proven to result in complete remission of AS, measuring remission is important as it should be the aim of therapy, where a treatment that results in remission represents the optimal therapeutic approach.[24]

Several drug classes are used in the pharmacologic therapy of AS. NSAIDs, including nonselective and selective cyclooxygenase-2 inhibitors, are the first choice of treatment for adult patients with active AS. Should NSAIDs fail or if there are contraindications, the next line of treatment is a bDMARD, including a TNFi, IL-17i, or a JAKi. Current practice is to start with a TNFi or IL-17i. TNFis marketed in Canada for the treatment of AS include adalimumab, certolizumab, etanercept, golimumab, and infliximab. IL-17is marketed in Canada for the treatment of AS include ixekizumab and secukinumab (Table 3). Clinical evidence has shown that these drugs are associated with significant improvements in disease activity and function, and a higher proportion of patients meeting the ASAS response criteria, compared to placebo. After failure of the first TNFi, switching to another bDMARD (TNFi or IL-17i) or a JAKi should be considered[1,8,9,25] In addition, csDMARDs such as sulfasalazine can be used in patients with AS and peripheral arthritis when they have

contraindications to or decline treatment with a TNFi.[8,25] In adults with active AS, systemic glucocorticoids are not recommended; however, locally administered parenteral glucocorticoids can be used in adults with AS with stable axial disease and active enthesitis or active peripheral arthritis.[8,25] The treatment recommendations for AS and nonradiographic axial SpA are similar.[8]

Drug

Upadacitinib is an oral, selective JAKi.[10] These inhibitors are also classified as tsDMARDs. JAKs are intracellular enzymes that transduce signals from cell surface receptors for cytokines or growth factors involved in a broad range of cellular processes, including inflammatory responses, hematopoiesis, and immune surveillance.[10] Upadacitinib has greater inhibitory potency for the JAK1 protein relative to the JAK2, JAK3, and TYK2 proteins. Upadacitinib is available as 15 mg or 30 mg extended-release tablets.[10] Indications previously approved by Health Canada for upadacitinib include the treatment of adults with moderately to severely active RA who have had an inadequate response or are intolerant to methotrexate; treatment of adults with active PsA who have had an inadequate response or are intolerant to methotrexate or other DMARDs; and treatment of adults and adolescents aged 12 years and older with refractory moderate-to-severe AD who are not adequately controlled with a systemic treatment (e.g., steroid or biologic) or when use of those therapies is inadvisable.[10] Upadacitinib was previously reviewed by CADTH in February 2020 for the indication of adults with moderately to severely active RA, and a final recommendation for reimbursement with conditions was issued.[11] It was also reviewed by CADTH in June 2021 for the indication of adult patients with active PsA who have had an inadequate response or are intolerant to methotrexate or other DMARDs, with a final recommendation of reimbursement if certain conditions are met.[12] Recently, it has been reviewed by CADTH (October 2022) for the treatment of adults and adolescents aged 12 years and older with refractory moderate-to-severe AD who are not adequately controlled with a systemic treatment (e.g., a steroid or biologic) or when use of those therapies is inadvisable. A final recommendation of reimbursement if certain conditions are met was issued.[13]

The Health Canada–approved indication of interest for this review is for the treatment of adults with active AS who have had an inadequate response to a biologic DMARD or when use of those therapies is inadvisable. The recommended dose regimen is 15 mg, administered orally, once daily. Upadacitinib may be used as monotherapy or in combination with NSAIDs (Table 3). The sponsor's reimbursement request is identical to the Health Canada–approved indication.

The characteristics of upadacitinib and its most common comparators for the purpose of this review are presented in Table 3.

Table 3: Key Characteristics of Upadacitinib, Ixekizumab, Secukinumab, Adalimumab, Certolizumab Pegol, Etanercept, Golimumab, and Infliximab

Characteristics	Upadacitinib	Ixekizumab	Secukinumab	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab
Mechanism of action	Janus kinase inhibitor	A humanized IgG4 monoclonal antibody that selectively binds and neutralizes the proinflammatory cytokine IL-17A Inhibits the release of proinflammatory cytokines and chemokines	A fully human IgG1k monoclonal antibody that selectively binds and neutralizes the proinflammatory cytokine IL-17A Inhibits the release of proinflammatory cytokines and chemokines	A recombinant human IgG1 monoclonal antibody that inhibits binding of TNF to TNF-alpha receptors; modulates biological responses that are induced or regulated by TNF	A recombinant, humanized antibody Fab' fragment inhibits binding of TNF to TNF-alpha receptors	A dimeric fusion protein consisting of the extra-cellular ligand-binding portion of the human 75 kilodalton (p75) TNF receptor linked to the Fc portion of human IgG1 Inhibits binding of TNF-alpha and -beta to TNF receptors	A human IgG1 monoclonal antibody that inhibits binding of TNF to TNF receptors	A chimeric IgG1 monoclonal antibody that inhibits binding of TNF to TNF receptors
Indication[a]	Treatment of adults with active AS who have had an inadequate response to a biologic DMARD or when use of those therapies is inadvisable May be used as monotherapy or in combination with NSAIDs	Treatment of adult patients with active AS who have responded inadequately or are intolerant to conventional therapy Other indications: PP, PsA	Reduce the signs and symptoms of active AS Other indications: PsA and PP	Reducing signs and symptoms in patients with active AS who have had an inadequate response to conventional therapy Other indications: RA, polyarticular JIA, PsA, CD, UC, HS, PP	Reducing signs and symptoms in adult patients with active AS who have had an inadequate response to conventional therapy Other indications: RA, PsA, nonradiographic axSpA	Reducing signs and symptoms of active AS Other indications: RA, polyarticular JIA, and PsA	Reducing signs and symptoms in adult patients with active AS who have had an inadequate response to conventional therapies Other indications: RA, PsA, UC, nonradiographic axial SpA	Reduction of signs and symptoms; improvement in physical function in patients with active AS who responded inadequately or are intolerant to conventional therapies

Characteristics	Upadacitinib	Ixekizumab	Secukinumab	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab
	Other indications: RA, PsA, and AD							Other indications: RA, CD, UC, PsA and PP
Route of administration	Oral	SC						IV
Recommended dose	Adults: 15 mg once daily	80 mg, SC, q.4.w. For patients with inadequate response or intolerant to at least 1 TNFi, 160 mg (80 mg × 2), SC, at week 0; followed by 80 mg q.4.w may be considered A conventional DMARD (e.g., sulfasalazine), corticosteroid, NSAID, and/or analgesics may be continued during treatment	Loading dose at weeks 0, 1, 2, and 3, followed by a monthly maintenance dose of 150 mg SC starting at week 4	40 mg administered every other week as an SC injection	Loading dose of 400 mg (given as 2 SC injections of 200 mg each) initially (week 0) and at weeks 2 and 4 followed by a maintenance dose of 200 mg every 2 weeks or 400 mg q.4.w.	50 mg per week in 1 SC injection or as two 25 mg SC injections on the same day once weekly or 3 or 4 days apart	50 mg SC monthly, on same date each month	5 mg/kg given as an IV infusion followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter
Serious side effects and safety issues	Tuberculosis, invasive fungal infections, bacterial, viral, including herpes zoster, and other opportunistic infections;	Infections (TB and serious infection in particular), hypersensitivity reactions and inflammatory bowel disease (exacerbations or new onset)		Serious infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic infections, malignancies, hypersensitivity reactions (allergic reactions and injection-site reactions) The clinical expert consulted by CADTH indicated these drugs induced psoriasis, lupus, and multiple sclerosis				

Characteristics	Upadacitinib	Ixekizumab	Secukinumab	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab
	malignancies, thrombosis, lymphopenia, neutropenia							

AS = ankylosing spondylitis; SpA = spondyloarthritis; CD = Crohn disease; DMARD = disease-modifying antirheumatic drug; HS = hidradenitis suppurativa; IgG4 = immunoglobin G4; IgG1 = immunoglobin G1; IgG1k = immunoglobin G1 kappa; IL-17A = interleukin-17A; JIA = juvenile idiopathic arthritis; NSAID = nonsteroidal anti-inflammatory drug; PP = plaque psoriasis; PsA = psoriatic arthritis; q.4.w. = every 4 weeks; RA = rheumatoid arthritis; SC = subcutaneous; TB = tuberculosis; TNF = tumour necrosis factor; TNFi = tumour necrosis factor inhibitor; UC = ulcerative colitis.

[a]Health Canada indication.

Sources: Health Canada product monographs for upadacitinib,[10] ixekizumab,[26] secukinumab,[27] adalimumab,[28] certolizumab pegol,[29] etanercept,[30] golimumab,[31] and infliximab.[32]

Stakeholder Perspectives

Patient Group Input

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

Two responses to CADTH's call for patient input for this review were received from ACE and through a joint submission from CAPA, Arthritis Society Canada, the CSA, and Creaky Joints Canada. ACE, CAPA, Arthritis Society Canada, the CSA, and Creaky Joints Canada serve individuals living with arthritis, including AS, and their caregivers, health care providers, and community members.

Patient perspectives from the joint input were obtained from a survey shared via email, social media, and the 4 organizations' websites from October 12, 2022, to October 30, 2022. Patient perspectives from the ACE input were obtained from an ACE Survey Monkey platform.

Among the 264 joint survey participants living with AS, 9 had direct experience with upadacitinib and close to 90% indicated they live with back pain, while 72% have back pain, 86% have joint stiffness, and 51% experienced sore heels and feet. Patient respondents were also faced with other symptoms of AS, such as anxiety and depression (52% of respondents), bowel inflammation (49%), psoriasis (35%), migraine (32%), uveitis (31%), osteoporosis (23%), and heart problems (11%). Most survey participants rated their disease severity as 59 out of 100. In addition, patients indicated having trouble managing symptoms, including fatigue, difficulty concentrating, stress, mobility issues, and loss of appetite. Similarly, patient respondents from the ACE patient input reported experiencing fatigue, mobility issues, weight gain, and constant pain, and indicated that the disease affects their quality of life, daily activities, and their mood. Caregivers of patient respondents from the ACE input also stated that the disease affected their quality of life as they must pay attention to their time management.

The joint patient input stated that, during an AS flare, which is a period of worsening symptoms, patients may have difficulties performing day-to-day activities. Patient respondents with AS reported that the disease severely affects all aspects of their lives, from their physical and mental health to their family life, self-esteem, work, intimacy, and participation in social and leisure activities.

According to the joint patient input, many treatments are available to manage AS, including NSAIDs, corticosteroids, csDMARDs, and bDMARDs. The joint patient input stated that the effectiveness and tolerance of these treatments vary significantly among patients, with more than 40% of respondents indicating that they had an inadequate response to currently available treatments. The joint patient input indicated that some patients had to change their medication after a short period of time; others did not respond adequately to the currently available treatments. In addition, the joint patient input stated that side effects of current AS medications were another major concern for people living with AS. Fatigue, nausea and vomiting, increased risk of infections, liver toxicity, and weight gain affect patient adherence to medication and daily activities.

According to the patient respondents from the ACE patient input, currently available treatments can effectively manage their disease symptoms. However, concerns were raised regarding the cost of the

medications, side effects, and the need to change medications due to decreased effectiveness within a short period of time.

The joint patient input highlighted that other treatment options, such as medical cannabis and/or nonpharmacological approaches to managing AS symptoms, are difficult to access because they are not reimbursed, not offered, or because these options require lengthy waits. According to the joint patient input, many factors, such as side effects, mode of administration, time required for treatment, travel, patient preferences, and cost, need to be considered by health care providers to determine the most effective treatment.

Nine respondents from the joint input reported having experience with upadacitinib. Positive aspects of treatment with upadacitinib reported by patient respondents included the simple route of administration, improved disease symptoms, mobility, and better quality of life with more energy. Few patient respondents experienced more frequent infections and headaches from treatment with upadacitinib.

Patient respondents from the joint patient input stated that managing AS can be improved by having access to affordable treatments that have a simple administration route (e.g., pills) and fewer adverse effects and infection rates, and are also able to reduce disease-related symptoms, improve their quality of life, and enable them to pursue their daily activities. The ACE patient input highlighted that patient respondents value additional treatment options with fewer AEs and improved pain control and remission rates.

Clinician Input

Input From Clinical Expert Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of AS.

Unmet Needs

The clinical expert indicated that not all patients respond to available treatments. ASAS40 is a common primary end point in clinical trials, which corresponds to a 40% improvement in 3 out of 4 domains (patient global assessment, total back pain, BASFI, and morning stiffness) with an absolute improvement of at least 2 and no worsening of the remaining domain. Roughly 40% of patients are able to achieve this response in clinical trials. Response rates to more stringent measures, such as ASAS PR and ID, are much lower.

The clinical expert indicated that roughly 10% of patients with AS also have IBD. While TNFis can effectively treat both, many patients with severe IBD do not respond to a TNFi even at high doses (e.g., ixekizumab 10 mg/kg every 4 weeks) or they initially respond but experience a loss of efficacy or have to stop due to side effects (drug-induced psoriasis). An IL-17i would be contraindicated in these patients, leaving few options available to patients.

The clinical expert indicated that the efficacy of the first biologic is lost within 3 to 5 years in roughly half of patients. When patients fail a biologic due to inadequate efficacy, clinicians often consider switching to a different mechanism of action. If they have a secondary loss of effect, the clinician can consider switching within class.

The clinical expert also indicated that some patients may have a contraindication to available therapies. With a TNFi, clinicians are cautious in patients with a personal or family history of multiple sclerosis, lupus, or drug-induced psoriasis. Clinicians would try to avoid prescribing IL-17is to patients with a history of IBD.

The clinical expert indicated that no oral bDMARD options are available, and many patients are young, may enjoy travelling, or have an aversion to needles.

Place in Therapy

The clinical expert indicated that treatment data from the upadacitinib trials in axial SpA show treatment response rates that appear to be comparable to those of other biologic drugs, such as TNF and IL-17 inhibitors. Because JAKi drugs do not appear to work through a TNF or IL-17 pathway, an alternative mechanism of action would be ideal for these patients.

The clinical expert indicated that upadacitinib has been shown to reduce objective markers of inflammation such as CRP and bone marrow edema in the SIJs and spine on MRI. Bone marrow edema has been shown to be a strong predictor of future syndesmophyte formation. Clinicians can also extrapolate from the PsA data, which indicate that upadacitinib can inhibit radiographic progression in peripheral joint disease.

The clinical expert indicated that if a patient requires an escalation in therapy, a clinician would decide whether a TNFi, IL-17i, or JAKi would be the most appropriate, and start the patient on that therapy in that situation. In rare circumstances, the clinician may have to combine biologics. For example, if a patient has severe Crohn disease and is not responsive to a TNFi, as well as in cases of axial disease, a clinician will often consider combining vedolizumab (Entyvio) with a TNFi. A drug such as upadacitinib would be an ideal candidate as it has been shown in a network meta-analysis (NMA) to be extremely effective for the treatment of IBD, as well as axial and peripheral disease.

The clinical expert indicated that the approved Health Canada label is to use these drugs if a previous biologic has failed or if other biologics are unsuitable. Most rheumatologists were disappointed with that decision and were hoping to use upadacitinib as a first-time DMARD in appropriate patients. In a recent study with a sufficient sample size, upadacitinib was shown to be effective for nonradiographic axial SpA, and the sponsor is expected to request Health Canada approval for use as a first-line drug under this indication.

The clinical expert indicated that the drug under review would provide further options to treat patients, either due to contraindications to TNFis and IL-17is, previous failures to these drugs, convenience to patients in the form of an oral option, and efficacy in patients with both IBD and axial SpA.

The clinical expert indicated that patients should first try 2 NSAIDs for 2 to 4 weeks unless there is a contraindication. If they still have high disease activity, this should be a first-line option available to patients, along with a TNF and IL-17 inhibitor. With the current Health Canada indication as a second-line drug, this

could be used if patients who have previously failed a biologic or who have a contraindication. From a safety perspective, most rheumatologists are comfortable with using this drug as a first-line biologic drug because it has been approved to treat RA.

Patient Population

The clinical expert indicated that any patient with active AS without a contraindication to a JAKi would likely benefit from treatment with upadacitinib. Patients who also have active IBD, prefer an oral option, or have failed or have a contraindication to a TNFi or IL-17i may also benefit.

The clinical expert indicated that patients with high disease activity are most in need of an intervention. Elevated CRP and bone marrow edema on MRI may be predictive of a higher response but many patients with neither of these symptoms will also respond very well. In these patients, the degree of structural damage should be comparable to that seen in the SIJ on MRI or CT.

The clinical expert indicated that patients with longstanding disease tend to have a reduced response to all therapies, but even patients with total fusion of the spine have been demonstrated a benefit versus placebo in RCTs.

The clinical expert indicated that patients would need to see a rheumatologist to confirm the diagnosis and determine the level of activity (ruling out other possible causes of symptoms).

The clinical expert indicated that the diagnosis of AS involves characteristic clinical findings in conjunction with identifying sacroiliitis in a pelvic X-ray. There can be considerable inter-reader reliability issues, particularly with early disease. Many rheumatologists typically confirm a diagnosis with an SIJ MRI before proceeding with a bDMARD. This is a major challenge in parts of the country where access to MRI is limited.

The clinical expert indicated that, in addition to a description of back pain, features such as uveitis, psoriasis, IBD, peripheral inflammatory arthritis, enthesitis, HLA-B27, CRP, and MRI are all helpful clues to make a diagnosis.

The clinical expert indicated that the probability of under or overdiagnosis is largely related to the experience of the clinician. Most cases are straightforward, and convincing imaging, clinical features, and possibly a positive HLA-B27 can help a rheumatologist make a definitive diagnosis. However, as with all diseases in rheumatology, these are clinical syndromes and there are often patients whose presentation is not as clear. The experience of the radiologist reading the X-ray, CT, or MRI is also important.

The clinical expert indicated that predictors of treatment response would be early onset of symptoms, male gender, CRP elevation, and degree of bone marrow edema seen on MRI.

Assessing Response to Treatment

The clinical expert indicated that clinicians typically follow up with a patient after 3 months of therapy. If there is absolutely no response, clinician would consider switching to a different drug. If there is partial remission, the clinician may give up to 6 months to determine benefit.

The clinical expert indicated that, in daily practice, treatment response is measured by improvement in the BASDAI or ASDAS. Typically, a BASDAI50 reduction is a reasonable response. Control of uveitis, psoriasis, and IBD as well as resolution of inflammatory arthritis and enthesitis are also taken into consideration. If the CRP was elevated at baseline, this may be followed; however, many individuals may have an elevated CRP for reasons other than AS. Additionally, most patients with active AS do not have an elevated CRP.

The clinical expert indicated that clinicians would see patients every 3 to 6 months to ensure stability of their disease.

The clinical expert indicated that, in clinical trials, clinicians would want to see an ASAS40 response and statistically significant improvement in other measures such as ASDAS, CRP, MRI, ASAS HI, ASQoL, and BASFI.

Discontinuing Treatment

The clinical expert indicated that a clinician would discontinue the medication if the patient was developing side effects such as infections. Given the possible association of JAK molecules increasing the risk of venous thrombosis, cardiovascular disease, and malignancy, clinicians may avoid this class in high-risk individuals. If these were to occur, a clinician would strongly consider discontinuing the medication.

The clinical expert indicated that, if a patient's symptoms were to recur, the clinician may consider switching to another medication if they were convinced that this was due to active disease.

The clinical expert indicated that, if the patient were to develop other manifestations such as severe uveitis, the clinician would either try to treat the uveitis alone with topical therapy or methotrexate or consider switching to a monoclonal TNFi.

The clinical expert indicated that some studies of TNFi drugs show that it may be possible to consider decreasing the dose in patients who are stable; however, complete discontinuation of medication almost always results in a flare (80% within 1 year).

Prescribing Conditions

The clinical expert indicated that a rheumatologist would be needed to confirm a diagnosis, treat, and monitor patients with AS. If other manifestations are involved, they may be co-followed by ophthalmology, gastroenterology, and dermatology. In some rural areas of Canada, patients may be followed by a general internist with a special interest in rheumatology.

Clinician Group Input

The CRA provided this input. Two clinicians who are members of the SPARCC executive committee and were involved in the 2014 CRA/SPARCC treatment recommendations contributed to these submissions.

Clinician group indicated that there is an unmet need for the treatment of patients with AS for the following reasons: not all patients respond to currently available treatments; medications become less effective more frequently, which requires a switch to another medication; various adverse effects of the current therapies;

persistence of constant spinal pain and active extra-articular manifestations. The lack of orally administrated options also affects compliance and adherence to treatment plans.

Overall, the views of the clinician group were consistent with those of the clinical expert consulted by CADTH. The clinician group indicated that the most essential treatment goals are reducing pain and improving function.

The group advocated for the use of NSAIDs as first-line pharmacologic therapy for AS and for biologic options (a TNFi- or IL-17i) as first-line biologic therapies when NSAIDs are insufficient. Other classes of biologic treatments, such as a tsDMARD (JAKi), could be used if initial treatments fail.

Clinician input suggested that patients would benefit more from upadacitinib, a selective JAKi for axial SpA, given its unique mechanism of action and oral administration, which are considered ideal options for many patients, particularly those who have failed treatment with continuous NSAIDs and continue to have high measures of disease activity. However, people with severe active infections, acute or chronic, and people with severe hepatic disorders might not be suitable for upadacitinib use.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may affect their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical expert consulted by CADTH are summarized in Table 4.

Table 4: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
The clinical trials were multicentre, randomized, double-blind, and placebo-controlled. Is placebo an appropriate comparator given the number of treatment options available? There are a variety of treatment options available, and if failure occurs on 1 bDMARD, patients would likely be able to trial an alternative mechanism of action.	It is important to demonstrate the drug works vs. placebo. It would have been helpful to have a comparator arm such as adalimumab. Nonetheless, the treatment response rates were what we would expect with either a TNFi or IL-17i.
The criteria for access to bDMARDs for treatment of AS varies greatly across jurisdictions. TNFi and IL-17i classes are the currently available bDMARDs for treatment of AS. Secukinumab (Cosentyx) was reviewed by CDEC for the indication of AS in 2016, and successfully completed pCPA negotiations, and therefore is a benefit in most jurisdictions. Taltz was reviewed by CDEC for the indication of AS in 2020, and given a positive recommendation with criteria/conditions, 1 condition being a reduction in price. pCPA negotiations for Taltz for AS concluded without an agreement.	For CDEC discussion

Drug program implementation questions	Clinical expert response
Considerations for initiation of therapy	
There is significant variation in criteria for coverage of Cosentyx and TNFi drugs across Canada. Current initiation of bDMARD therapies in most jurisdictions for AS require patients to have a score of ≥ 4 on the BASDAI. A number of other factors are also considered in different jurisdictions, such as: • visual analogue scale • HAQ, or ability to return to work HAQ • indicators of disease. Renewal of coverage of bDMARDs in most jurisdictions requires at least a 50% reduction in baseline BASDAI, or a reduction by ≥ 2 units to demonstrate response to therapy. Generally, it is noted that these improvements in scores must be maintained for continuation of coverage.	For CDEC discussion
The indication for Rinvoq for AS is for patients who have had inadequate response to bDMARDs, or for whom use of those therapies is inadvisable. Is it possible to define for which patients bDMARDs are inadvisable? Drug plans may receive requests for Rinvoq in situations where bDMARDs are inadvisable. If these patients have inadequate response or intolerance to Rinvoq, they may then want access bDMARDs.	Ultimately patients must be comfortable with therapy. The absolute serious infection risk is quite small with bDMARDs; however, a patient must be comfortable with that risk. Circumstances where 1 drug would be preferrable might include: Pregnancy/lactation: TNFi Active malignancy: IL-17i Active IBD: TNFi or JAKi Previous cardiovascular disease: TNFi or IL-17i Congestive heart failure: IL-17i Severe psoriasis: IL-17i Paradoxical psoriasis: IL-17i or JAKi Recurrent/severe uveitis: TNFi Preference for oral option: JAKi Personal and/or family history of multiple sclerosis: IL-17i and possibly JAKi
The indication places Rinvoq as either third- or fourth-line therapy, behind NSAIDs and/or DMARDs, and bDMARDs. Currently, to access bDMARDs for treatment of AS, patients must fail NSAIDs at maximally tolerated dosages. Many NSAIDs are available over the counter. Some jurisdictions also require trial of conventional DMARDs to meet criteria for bDMARDs. There is variability across jurisdictions.	For CDEC discussion Sponsor's comment: The ASAS/EULAR 2022 guidelines indicate that patients with purely axial disease should not be treated with a csDMARD; sulfasalazine may be considered in patients with peripheral arthritis. In some jurisdictions a conventional DMARD trial is required if the patient has peripheral arthritis.
Is there evidence to suggest Rinvoq is efficacious in patients who have failed a TNFi or IL-17i or both? What is the optimal sequencing of these products?	The SELECT-AXIS 2 trial showed impressive efficacy in patients who had failed either TNF or IL-17 inhibitors. The trial did not include patients who had failed both TNF and IL-17 inhibitors. If axial symptoms are the only issue, there is no optimal sequencing.

Drug program implementation questions	Clinical expert response
Are patients with axial disease treated similarly to those with peripheral disease?	Peripheral disease may respond to cortisone injections or csDMARDs such as methotrexate, sulfasalazine, or leflunomide. If these are ineffective (typically a 3-month trial of 2 csDMARDs is recommended), a biologic would be a reasonable option.
Is there a need to progress to more advance treatments sooner in patients with axial disease?	Some patients with axial SpA have severe and debilitating disease. In these patients, escalating sooner may help maintain their function. In the INFAST trial, about 30% of patients with AS and activity on MRI were able to achieve remission with naproxen alone. RCTs have shown no benefit with axial disease using csDMARDs such as methotrexate, sulfasalazine, and leflunomide.
Do patients with peripheral disease respond to treatment similarly to those with axial disease?	Patients with peripheral and axial disease tend to respond well to bDMARD treatment, although about 40% of patients were able to achieve roughly a 50% improvement in peripheral joint disease) in psoriatic arthritis trials. Psoriatic arthritis is considered to be within the spectrum of SpA.
Consistency with initiation criteria associated with other drugs reviewed by CADTH in the same therapeutic space	
The requested indication for this drug is after bDMARDs; therefore, it would not make sense to align the criteria with that for bDMARDs. How should failure of bDMARD be defined for the purpose of reimbursement? (Helpful if this was consistent with current listing criteria for bDMARDs, relating to BASDAI).	The clinician should be allowed to decide when a JAKi would be most appropriate. If treatment with a TNFi or IL-17i does not result in adequate efficacy within 3 months or if their use is not advisable, a JAKi should be an option. In patients already on a TNFi or IL-17i, some response would be expected within 3 months and definitely by 6 months.
Is a washout period required when stopping bDMARD and initiating Rinvoq?	There are little data regarding the need for a washout period. The clinical expert reported never using a washout period for a TNFi, IL-17i, or JAKi.
If a patient has had a partial response to a bDMARD, and moves on to Rinvoq, how should further response to Rinvoq be assessed? Clinical trials used ASOS40.	In clinical practice, it is common to measure the BASDAI. A standard expected treatment response would be an improvement by 2 or a 50% reduction from baseline BASDAI score. The ASDAS could be used; however, this requires a calculator and a point of care for CRP is often not available. Most trials use ASAS40 but this is not commonly used in clinical practice (similar to the way ACR50 is not measured regularly in rheumatoid arthritis patients, except in clinical trials).
If the patient had demonstrated partial response to bDMARD before Rinvoq, their disease activity scores may be lower on baseline than those who had not been treated with a bDMARD. How should response to therapy with Rinvoq be assessed in these patients, and what is an appropriate response for continued reimbursement?	This would depend on the reason for switching. If the patients had a side effect or another extra-musculoskeletal manifestation such as IBD, score stability would be required. If a change in treatment is due to lack of efficacy, an improvement in BASDAI by 2 or 50% improvement compared to baseline would be sufficient. Usually, a decision to switch would require a BASDAI score of at least 4.
What measure of response should be used with patients with peripheral disease?	Improvement in the swollen joint count, tenosynovitis, or enthesitis should be captured.
Considerations for continuation or renewal of therapy	
Current criteria for bDMARDs varies across jurisdictions with respect to assessment of response.	The ASAS20 and ASAS40 responses reflect a change (i.e., roughly 20% or 40% improvement, respectively) whereas the BASDAI is a state (i.e., a pain described as 4 out of 10). ASAS

Drug program implementation questions	Clinical expert response
Some measures that are used are: • BASDAI – reduction of 50% or 2 points (most consistent) • VAS • HAQ or ability to return to work • symptoms • Reductions in pain medications In SELECT-AXIS 1 and SELECT-AXIS 2 the primary end point was examined at **week 14** and week 52. The primary outcome measure was ASAS40. (TNFi drugs are assessed for initial response after 12 weeks, and IL-17s after 16 weeks). The clinical trials for Taltz looked at the ASAS40 response at 16 weeks. Clinical trials considered during the Cosentyx reimbursement review looked at the ASAS20 response at week 16 as the primary outcome. How does ASAS40 and ASAS20 relate to the BASDAI score?	scores are common primary or secondary end points in clinical trials but are not used in clinical practice in the same way we often use ACR20 or ACR50 as end points for rheumatoid arthritis but never calculated in clinical practice.
What is the appropriate outcome measure for response in AS?	The most common outcome measure would most likely be a 50% or 2-point absolute improvement in the BASDAI. Another option would be ASDAS improvement by 1.1. ASDAS is not as commonly used because an app is required to calculate it, as well as a same-day CRP test. CRA treatment recommendations are being drafted, and the BASDAI is the most common measure in use.
There is variation in renewal criteria across the country (refer to previous comments)	For CDEC discussion
Considerations for discontinuation of therapy	
How should loss of response be measured? Should initial treatment effect be maintained for continued reimbursement? Tracking patients over time becomes difficult when assessing coverage.	Most clinicians are used to serially reporting a BASDAI for reimbursement purposes. There can be a discordance between the BASDAI score and disease activity if patients have other causes of pain (e.g., disc herniation or fibromyalgia). In this situation, a clinician may write a short note explaining the discrepancy. A clinician would not be expected to have to repeat that note indefinitely. Many patients may describe gradual loss of efficacy but there may be reasons for not wanting to switch. For example, they may have a fear of needles and be satisfied with the current level of disease control. An extra-musculoskeletal manifestation may be difficult to control, and the ongoing axial symptoms may be tolerable, or they may have failed previous mediations and that may be the best option they have tried thus far. It should be left to the discretion of the clinician whether to continue the medication. Patients often achieve a new normal after treatment. Initially they may report a pain score of 9 out of 10 that later improves to 2 out of 10. Over years they may report their pain rises to 8, but if they stop their medication, it may become clear that the drug a helping considerably.
There is variation across renewal criteria across jurisdictions.	For CDEC discussion

Drug program implementation questions	Clinical expert response
Considerations for prescribing of therapy	
The dosage is 15 mg extended-release oral tablet, administered once daily, with or without food.	For CDEC discussion
Rinvoq will be the first oral, targeted DMARD treatment for the treatment of AS.	For CDEC discussion
Access to rheumatologists may be limited in some jurisdictions. Some jurisdictions allow internists to prescribe in their criteria. Time frames for assessment of response for the bDMARDs varies from 12 (TNFIs) to 16 weeks (Cosentyx)	For CDEC discussion
Can CDEC provide a comment on the potential for combination use of Rinvoq with: • bDMARDs? • conventional DMARDs?	A case series on the use of tofacitinib with either an IL-17 or IL-23 inhibitor for the treatment of severe refractory PsA has been published. These patients still have active disease despite having failed multiple biologics often at supertherapeutic doses. There are no data on the use of upadacitinib in combination with bDMARDs. Many clinicians may also consider combining upadacitinib with vedolizumab if there is severe bowel disease in conjunction with joint disease. A drug such as methotrexate may be added if there is ongoing peripheral arthritis, psoriasis, or uveitis. Considerable data are available on the safety of this combination from the RA trials as it is a common combination in that condition.
The indication places Rinvoq after bDMARDs; it may therefore be difficult to have alignment within the criteria.	For CDEC discussion
Generalizability	
Populations of interest matching the indication but with insufficient data Were patients with peripheral disease adequately represented in clinical trials?	Most clinical trials for AS do not have many patients with peripheral arthritis. It is typical to extrapolate from the psoriatic arthritis trials because it is believed there is a strong overlap of these 2 diseases and they likely represent manifestations of the spectrum of the same condition (or a highly similar condition). This is still a matter of debate in the spondyloarthritis community at large.[33] Sponsor's comment: Rinvoq's effectiveness in peripheral disease has been shown both in the PsA (SELECT- PsA 1 and PsA 2 previously reviewed by CADTH) and AS clinical trials. In Study 944, there was an improvement in the number of tender joints in favour of upadacitinib vs. placebo based on change from baseline in TJC68 at week 14 (−2.3 in the upadacitinib group and −1.2 in the placebo group) (nominal P = 0.0022) and an improvement in the number of swollen joints based on changes from baseline in SJC66 at week 14 (−0.9 in the upadacitinib group and −0.4 in the placebo group) (nominal P = 0.0026).
SELECT-AXIS 1 included a population of bDMARD-naive adults who had an inadequate response to NSAIDs. This population is not consistent with the reimbursement request but may be of interest to clinicians and patients.	For CDEC discussion

Drug program implementation questions	Clinical expert response
Rinvoq has also been studied in IBD, and there may be interest in Rinvoq in patients with concurrent IBD and AS, as there is frequent overlap in the 2 conditions. The CDEC review for Rinvoq for UC has been placed on hold pending an NOC for this indication. A positive recommendation and listing of Rinvoq for AS may mean patients with UC and AS may be able to access therapy with Rinvoq. Whereas patients with UC alone will not be able to access Rinvoq.	
Care provision issues	
On October 31, 2022, Health Canada issued a Professional Risk Communication regarding the risk of a MACE, thrombosis (including fatal events), and malignancy associated with JAK inhibitors (CIBINQO, INREBIC, JAKAVI, OLUMIANT, and RINVOQ).	For CDEC discussion Sponsor's comment: Health Canada initiated a safety review in light of the emerging safety findings of tofacitinib (in ORAL Surveillance) and baricitinib, specifically related to MACEs, venous thrombotic events, malignancies, and all-cause mortality. The safety review aimed to determine whether risks are associated with all JAK inhibitors authorized in Canada (upadacitinib, baricitinib, tofacitinib, abrocitinib, fedratinib, and ruxolitinib) and whether regulatory action is warranted. During this review, Health Canada did not find any new information on these identified risks specifically for upadacitinib, and this safety review was not based on any new safety data for upadacitinib. There were no changes to the approved indications of Rinvoq following this review. Ask: Please revise the sentence to provide further clarity: "On October 31, 2022, Health Canada issued a Professional Risk Communication regarding the risk of major adverse cardiovascular events, thrombosis (including fatal events) and malignancy associated with the emerging safety findings of tofacitinib and baricitinib. Health Canada did not find any new information on these identified risks specifically for upadacitinib, and this safety review was not based on any new safety data for upadacitinib. Health Canada has recommended product labelling updates for JAK inhibitors including upadacitinib as a precautionary approach (CIBINQO, INREBIC, JAKAVI, OLUMIANT, and RINVOQ)."
System and economic issues	
JAKi drugs such as Rinvoq have the potential for generics in the future.	For CDEC discussion Sponsor's comment: All patented pharmaceutical products will by definition have a loss of exclusivity, which could lead to the availability of generic options on the market, this is not exclusive to Rinvoq alone. Notably, Rinvoq remains the only JAKi approved by Health Canada for use in AS. Ask: Please remove this sentence as it does not pertain to RINVOQ specifically but to all drugs in general.
There are a number of biosimilar TNFis available for the treatment of AS. Cosentyx has successfully completed pCPA negotiations for AS. Biosimilars are on the horizon, but with no availability date at this time.	For CDEC discussion

Drug program implementation questions	Clinical expert response
Taltz for AS did not complete successful pCPA negotiations. Rinvoq has completed successful pCPA negotiations for PsA and RA. For Rinvoq for RA and psoriatic arthritis: CDEC recommended a price point that drug plan cost should not exceed for treatment with the least costly bDMARD or tsDMARD reimbursed for these conditions. Rinvoq is currently under consideration for negotiation at pCPA for atopic dermatitis.	
An oral therapy may provide greater access to treatment for patients with AS. A cost-utility analysis conducted by the sponsor noted that for patients who had not had adequate response to bDMARD therapy, upadacitinib dominated other treatments. For the bDMARD-inadvisable population the cost was $10,861 per QALY gained compared to conventional therapy.	For CDEC discussion

ACR20 = American College of Rheumatology 20% response; ACR50 = American College of Rheumatology 50% response; AS = ankylosing spondylitis; ASAS = Assessment of SpondyloArthritis international Society; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; bDMARD = biologic disease-modifying antirheumatic drug; CDEC = CADTH Canadian Drug Expert Committee; CRP = C-reactive protein; csDMARD = conventional synthetic disease-modifying antirheumatic drug; EULAR = European Alliance of Associations for Rheumatology; HAQ = Health Assessment Questionnaire; IBD = inflammatory bowel disease; IL-17 = interleukin-17; IL-17i = interleukin-17 inhibitor; IL-23 = interleukin-23; JAKi = Janus kinase inhibitor; NOC = Notice of compliance; NSAID = nonsteroidal anti-inflammatory drug; pCPA = pan-Canadian Pharmaceutical Alliance; QALY = quality-adjusted life-year; RA = rheumatoid arthritis; RCT = randomized controlled trial; tsDMARD = targeted synthetic disease-modifying antirheumatic drug; TNF = tumour necrosis factor; TNFi = tumour necrosis factor inhibitor; UC = ulcerative colitis; VAS = visual analogue scale; vs. = versus.

Clinical Evidence

The clinical evidence included in the review of upadacitinib is presented in 3 sections. The first section, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence from the sponsor and indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes additional relevant studies (If available) that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of upadacitinib (extended-release tablets,15 mg and 30 mg), 15 mg once daily, administered orally, for the treatment of adult patients with active AS who have had an inadequate response to a biologic DMARD or when use of those therapies is inadvisable. Upadacitinib may be used as monotherapy or in combination with NSAIDs.

Methods

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

Table 5. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 5: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Adult patients with active AS who have had an inadequate response to a biologic DMARD or when use of those therapies is inadvisable **Subgroups of interest:** • Baseline disease activity • Previous use of bDMARDs vs. no previous use of bDMARDs • Number of previous uses of bDMARDs • Patients who have responded inadequately to, or who were intolerant to bDMARDs • Upadacitinib monotherapy vs. upadacitinib combination with NSAIDs • AS with extra-articular manifestations vs. AS alone
Intervention	• Upadacitinib (extended-release tablets,15 mg and 30 mg), 15 mg once daily, orally • Upadacitinib may be used as monotherapy or in combination with NSAIDs
Comparators	**Currently approved bDMARDs for AS in Canada:** • Ixekizumab • Secukinumab • Certolizumab pegol • Infliximab • Golimumab • Adalimumab • Etanercept
Outcomes	**Efficacy outcomes:** • Clinical response (e.g., ASAS40) • Measures of AS symptoms (e.g., pain, fatigue)[a] • Measures of function and disability (e.g., BASFI)[a] • Health-related quality of life (generic and disease-specific, e.g., SF-36, EQ-5D-5L ASAS HI)[a] • Work productivity (e.g., WPAI-SpA)[a] • Disease activity(e.g., BASDAI, ASDAS)[a] • Radiographic changes (e.g., MRI Spine SPARCC) • Patient global assessment • MASES • BASMIlin **Harms outcomes:** • Mortality • SAEs[a] • AEs[a] • WDAEs • Notable harms (AEs of special interest): For example, serious infection (including herpes zoster, tuberculosis and fungal infection),[a] anemia, neutropenia, lymphopenia, thrombocytopenia, malignancies,

Criteria	Description
	thrombosis (including increased platelets), MACE, elevation of CPK, gastrointestinal perforations and other gastrointestinal SAEs,[a] hypersensitivity, hepatotoxicity, dyslipidemia, acne, folliculitis
Study design	Published and unpublished phase III and IV randomized controlled trials

AE = adverse event; AS = ankylosing spondylitis; ASAS40 = Assessment of SpondyloArthritis international Society 40% improvement; ASAS HI = ASAS Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMIlin = Linear Bath Ankylosing Spondylitis Metrology Index; bDMARD = biologic disease-modifying antirheumatic drug; CPK = creatine phosphokinase; EQ-5D-5L = 5-Level EQ-5D; MACE = major adverse cardiovascular event; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; NSAID = nonsteroidal anti-inflammatory drug; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; SPARCC = Spondyloarthritis Research Consortium of Canada; vs. = versus; WDAE = withdrawal due to adverse event; WPAI-SpA = Work Productivity Activity Impairment–Spondyloarthritis.

Note: The sponsor indicated that 30 mg was not submitted for review.

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

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[34]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Rinvoq (upadacitinib). Clinical trials registries searched included the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

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

The initial search was completed on November 11, 2022. Regular alerts updated the search until the meeting of CDEC on March 22, 2023.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist.[35] Included in this search were the websites of regulatory agencies (FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Appendix 1 provides more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH 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 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included, and differences were resolved through discussion.

Findings From the Literature

Two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 6. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

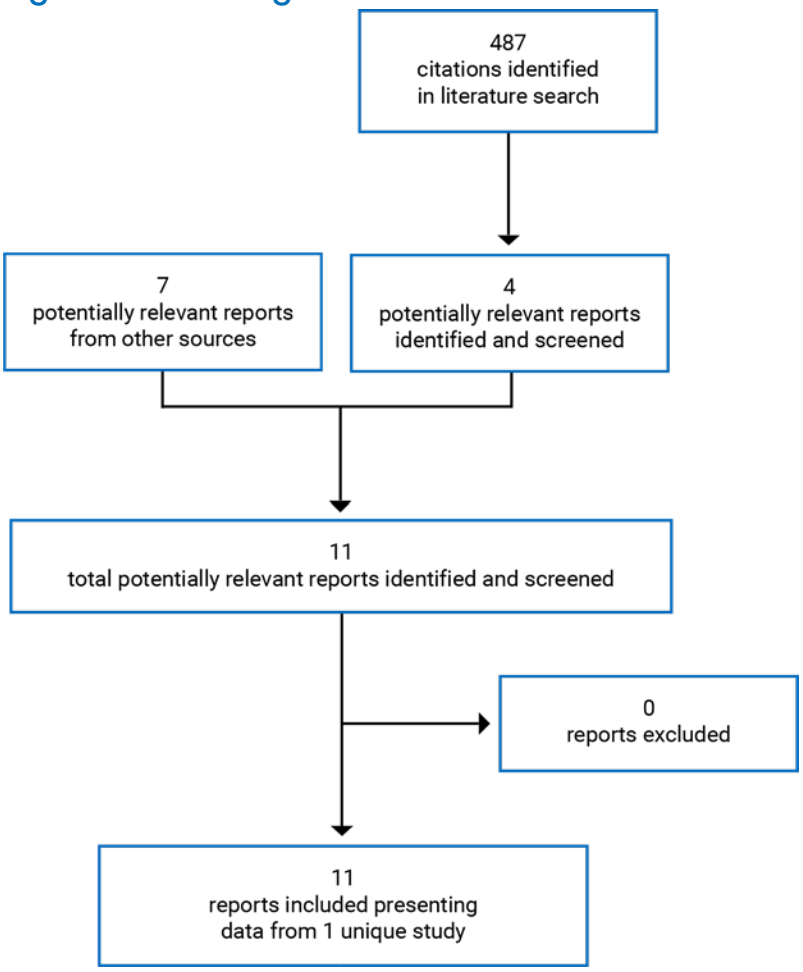


Table 6: Details of Included Studies

Detail	Study 944[14,36]	Study 098[15,37]
Designs and populations		
Study design	Multicentre, double-blind, placebo-controlled RCT, phase III	Multicentre, double-blind, placebo-controlled RCT, phase II and III
Locations	119 sites in 22 countries: Canada, the US, Mexico, Australia, New Zealand, and European, South American, and Asian countries	62 sites in 20 countries: Canada, the US, Australia, New Zealand, and European and Ascian countries

Detail	Study 944[14,36]	Study 098[15,37]
Patient enrolment dates	Date of first patient's first visit: November 26, 2019 Last patient's last visit for double-blind (period 1, week 14): August 26, 2021 Last patient's last visit for extension period (period 2: week 52): May 23, 2022. Expected end of the trial: July 2025	Date of first patient's first visit: October 24, 2017. Last patient's last visit for double-blind (Period 1, week 14): January 21, 2019. Last patient's last visit for extension period (period 2: week 52): January 31, 2020 Last patient's last visit for extension period (period 2: 2-year interim analysis): November 26, 2020 (This was the data cut-off date for week 104) reported in this report.) Final analysis (104 weeks): Clinical Study Report is under development (not available at the submission time)
Randomized (N)	420	187
Inclusion criteria	• Male or female ≥ 18 years of age at screening • A clinical diagnosis of AS and meeting the modified New York Criteria for AS • Inadequate response to at ≥ 2 NSAIDs over a ≥ 4-week period in total at maximum recommended or tolerated doses, or an intolerance to or contraindication for NSAIDs as defined by the Investigator • Prior exposure to 1 or 2 bDMARDs and discontinued due to lack of efficacy and/or intolerance; washout periods defined in protocol • Screening and baseline disease activity as defined by having a BASDAI score ≥ 4 and a patient assessment of total back pain score ≥ 4 based on a 0-to-10 NRS • If entering the study on specified concomitant csDMARDs, oral corticosteroids, or NSAIDs, participant must be on specified stable dose for specified time period	• Male or female ≥ 18 years of age • Patient with a clinical diagnosis of AS and meeting the modified New York criteria for AS • Patient must have baseline disease activity as defined by having a BASDAI score ≥ 4 and a patient assessment of total back pain score ≥ 4 based on a 0-to-10 NRS at the screening and baseline visits • Patient has had an inadequate response to at least 2 NSAIDs over a period of at least 4 weeks in total at maximum recommended or tolerated doses, or patient has an intolerance to or contraindication for NSAIDs as defined by the investigator • If entering the study on concomitant methotrexate, leflunomide, sulfasalazine, and/or hydroxychloroquine, patient must be on a stable dose of methotrexate (≤ 25 mg/week) and/or sulfasalazine (≤ 3 g/day) and/or hydroxychloroquine (≤ 400 mg/day) or leflunomide (≤ 20 mg/day) for at least 28 days before the baseline visit. A combination of up to 2 background csDMARDs is allowed except the combination of methotrexate and leflunomide • If entering the study on concomitant oral corticosteroids, patient must be on a stable dose of prednisone (≤ 10 mg/day), or oral corticosteroid equivalents, for at least 14 days before the baseline visit • If entering the study on concomitant NSAIDs, tramadol, a combination of acetaminophen and codeine or hydrocodone, and/or nonopioid analgesics, patient must be on stable dose(s) for at least 14 days before the baseline visit; patient is judged to be in good health as determined by the principal investigator based upon the results of medical history, laboratory profile, and physical examination performed at the screening visit

Detail	Study 944[14,36]	Study 098[15,37]
Exclusion criteria	• Total spinal ankylosis (patients who had total spinal ankylosis), which for the purpose of this study was defined as bridging syndesmophytes (fusion) in a total sum of ≥ 5 C2-to-T1 or T12-to-S1 spine segments, were excluded • Lack of efficacy to 2 bDMARDs • Prior exposure to any JAKi • Use of prohibited concomitant treatments within specified time frame before baseline visit • Receipt of live vaccine within 28 days of first dose of study drug or expectation of need for live vaccine during study or within 30 days after last study drug dose • Systemic use of strong CYP3A inhibitors or strong CYP3A inducers from screening through end of study drug administration • Treatment with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) • History of allergic reaction or sensitivity to constituents of study drug • Female that is pregnant, breastfeeding or considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug • History of clinically significant drug or alcohol abuse within the last 6 months • Current or past history of infections, as protocol-specified • Protocol-specified medical diseases or disorders, including recent cardiovascular events • Use of high-potency opiates • Patients with extra-articular manifestations that are not clinically stable for at least 30 days before study entry are excluded from the study	Patients were not eligible for study participation if they met any of the following criteria: • Prior exposure to any JAKi (including but not limited to tofacitinib, baricitinib, and filgotinib) • Prior exposure to any biologic therapy with a potential therapeutic impact on SpA • Patient has been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) before the first dose of study drug or is currently enrolled in another clinical study • Intra-articular joint injections, spinal/paraspinal injection (s), or parenteral administration of corticosteroids within 28 days before the baseline visit; inhaled or topical corticosteroids are allowed • Patient on any other DMARDs (other than those allowed), thalidomide, or apremilast within 28 days or 5 half-lives (whichever is longer) of the drug before baseline visit • Patient on opioid analgesics (except for combination acetaminophen/codeine or acetaminophen/hydrocodone which are allowed) or use of inhaled marijuana within 14 days before baseline visit • Patient has a history of inflammatory arthritis of different etiology other than axial SpA (including but not limited to RA and PsA) or any arthritis with onset before 17 years of age • Patient with extra-articular manifestations (e.g., psoriasis, uveitis, or IBD) that are not clinically stable for at least 30 days before study entry • Patient has total spinal ankylosis • Active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days before the first dose of study drug
Drugs		
Intervention	15 mg upadacitinib orally, once daily	15 mg upadacitinib orally, once daily
Comparator(s)	Placebo for upadacitinib, orally, once daily	Placebo for upadacitinib, orally, once daily
Duration		
Phase		
Screen period	Up to 35 days	Up to 35 days
Double-blind	14 weeks	14 weeks
Open-label extension	90 weeks	90 weeks

Detail	Study 944[14,36]	Study 098[15,37]
Remission withdrawal period	• Patients in remission at week 104 were eligible for the remission withdrawal period • Patients were followed without study drug treatment and assessed for disease flare through week 152 • Flare is defined as an ASDAS (CRP) ≥ 2.1 at 2 consecutive visits, which are at least 2 weeks apart, or an ASDAS (CRP) > 3.5 at 1 visit • Patients who experience a flare receive open-label upadacitinib 15 mg once daily from the time of flare for 24 weeks (re-treatment) or longer per local country requirements • Patients who do not flare are followed without upadacitinib treatment until week 152	NA
Follow-up	Patients who were not in remission at week 104 will complete the study after the 30 days follow-up visit, if applicable, will have the option to enter open-label treatment with upadacitinib until a predefined time period only per local country requirement	30 days
Outcomes		
Primary end point	ASAS40 response at week 14	ASAS40 response at week 14
Secondary and exploratory end points	**Multiplicity-controlled secondary end points at week 14** • Change from baseline in ASDAS • Change from baseline in MRI SPARCC score (spine) • BASDAI50 response • ASAS20 response • ASDAS inactive disease (score < 1.3) • Change from baseline in patient assessment of total back pain • Change from baseline in patient assessment of nocturnal back pain) • ASDAS LDA (score < 2.1) • Change from baseline in BASFI • ASAS PR (an absolute score of ≤ 2 units for each of the 4 domains identified in ASAS40) • Change from baseline in ASQoL • Change from baseline in ASAS HI • Change from baseline in BASMIlin • Change from baseline in MASES **Additional secondary end point at week 14 (not controlled for multiplicity)**	**Multiplicity-controlled secondary end points at week 14** • Change from baseline in ASDAS • Change from baseline in MRI SPARCC score (Spine) • Proportion of patients with BASDAI50 response (defined as 50% improvement in BASDAI) • Change from baseline in ASQoL • Proportion of patients with ASAS PR (defined as an absolute score of ≤ 2 units for each of the 4 domains identified in ASAS 40) • Change from baseline in BASFI • Change from baseline in BASMIlin • Change from baseline in MASES • Change from baseline in WPAI-SpA • Change from baseline in ASAS HI **Additional key secondary end points at week 14 (not controlled for multiplicity)** • ASAS 20 response at week 14 • Change from baseline in MRI SPARCC score (SIJ) at week 14 **Additional end point (exploratory outcomes) at week 14**

Detail	Study 944[14,36]	Study 098[15,37]
	• Change from baseline in MRI SPARCC score (SIJ) **Additional outcomes (exploratory outcomes)** • Patient global assessment of pain • PGA • PtGA • SF-36 • TJC and SJC • WPAI • FACIT-F • NSAID score	Additional end points are the following measurements assessed in patients treated with upadacitinib vs. placebo at scheduled time points other than those specified for the primary and key secondary variables: • ASAS 20 response • ASAS PR • ASAS5/6 (20% improvement from baseline in 5 out of the following 6 domains: BASFI, patient's assessment of total back pain, PtGA, inflammation [mean of items 5 and 6 of the BASDAI] lateral lumbar flexion from BASMIlin, and high-sensitivity CRP • ASDAS inactive disease (score < 1.3) • ASDAS major improvement (change from baseline at least 2.0) • ASDAS clinically important improvement (change from baseline of at least 1.1) • CRP • Dactylitis • FACIT-F • Insomnia Severity Index; • mSASSS • Patient assessment of total back pain • Patient assessment of nocturnal back pain • Patient global assessment of pain • PGA • PtGA • TJC and SJC
Publications	Van der Heijde et al. (2022)[38]	Van der Heijde et al. (2019)[39] Deodhar et al. (2022)[40] Van der Heijde et al. (2022)[41]

AS = ankylosing spondylitis; ASAS = Assessment in SpondyloArthritis international Society; ASAS5/6 = Assessment in SpondyloArthritis international Society 20% improvement in 5 of 6 domains; ASAS20 = Assessment of SpondyloArthritis international Society 20% improvement; ASAS40 = Assessment of SpondyloArthritis international Society 40% improvement; ASAS HI = Assessment of SpondyloArthritis international Society Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50 = Bath Ankylosing Spondylitis Disease Activity Index 50% improvement; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMIlin = Linear Bath Ankylosing Spondylitis Metrology Index; bDMARD = biologic disease-modifying antirheumatic drug; CRP = C-reactive protein; csDMARD = conventional synthetic disease-modifying antirheumatic drug; DMARD = disease-modifying antirheumatic drug; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; IBD = inflammatory bowel disease; JAKi = Janus kinase inhibitor; LDA = low disease activity; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; mSASSS = Modified Stoke Ankylosing Spondylitis Spine Score; NA = not applicable; NRS = numerical rating scale; NSAID = nonsteroidal anti-inflammatory drug; PGA = Physician's Global Assessment; PR = partial remission; PsA = psoriatic arthritis; PtGA = Patient's Global Assessment of Disease Activity; RA = rheumatoid arthritis; RCT = randomized controlled trial; SF-36 = Short Form (36) Health Survey; SIJ = sacroiliac joint; SJC = swollen joint count; SpA = spondyloarthritis; SPARCC = Spondyloarthritis Research Consortium of Canada; TJC = tender joint count; WPAI-SpA = Work Productivity Activity Impairment–Spondyloarthritis.

Notes: Study 944 included study 1 and study 2. In this review, Study 944 specifically indicates Study 944 – study 1. For this review, only study 1 (for bDMARD–inadequate response AS) in Study 944 was relevant. Study 2 in Study 944 (for nonradiological axial SpA) was not relevant and not included in this review.[16] The final Clinical Study Report for week 104 for Study 098 was not available at the time of the submission. The sponsor indicated that, regarding the availability of the final analysis (104 weeks, February 23, 2022), the Clinical Study Report for M16 to 098, the Clinical Study Report is expected to be finalized in the first quarter of 2023. No major impact on the efficacy and safety conclusions is expected. (November 10, 2022 in response to CADTH request).[16] Two additional report was included (2 Health Canada reviewer reports).[42,43]

Sources: Clinical Study Reports,[14,15,36,37] sponsor's submission,[16] and Health Canada reviewers' report.[42,43]

Description of Studies

Two trials (STUDY 944[15,36] and STUDY 098[14,37]) were included for this review. Study 944 (i.e., Study 1 of Study M19 to 944, SELECT -AXIS 2, N = 420) was a phase II multicentre, randomized, double-blind, placebo-controlled trial of the efficacy and safety of upadacitinib 15 mg administered orally once daily compared to placebo in patients with active AS who were intolerant or had an inadequate response to a bDMARD. Study 944 examined the efficacy and safety of upadacitinib 15 mg administered orally once daily against placebo. Study 944 included a 14-week double-blind period (period 1) and a 90-week, open-label, single-arm extension period (period 2) (Figure 2). The study consisted of 5 phases; the first was a screening period (lasting up to 35 days before period 1, determining patient eligibility); the second was period 1, a double-blinded treatment period from week 0 (baseline) to week 14 inclusive evaluating the efficacy and safety of upadacitinib compared to placebo in which patients who completed the double-blinded 14-week study were eligible to enter into the extension phase; the third was an extended treatment period after week 14 to week 104 inclusive assessing the long-term efficacy and safety of upadacitinib; the fourth was a remission withdrawal period, which will last up to 152 weeks; and the fifth was a follow-up phase lasting 30 days. For this review, results of the 52-week extension phase are included at the time of the submission. The results of the 104-week extension and the remission withdrawal period are not available. Study 944 was conducted in 119 sites in 22 countries including Canada, the US, Mexico, Australia, New Zealand, and European, South American, and Asian countries.

Study 098 (i.e., Study M16 to 098, SELECT-AXIS 1, N = 187) was a phase II and III, randomized, double-blind, placebo-controlled trial in adult patients with active AS who had an inadequate response or are intolerant to 2 or more NSAIDS, but bDMARD-naive. The objective of Study 098 was to examine the efficacy and safety of upadacitinib 15 mg administered orally once daily with placebo. Study 098 study included 4 phases (Figure 3); the first was a screening period (lasting up to 35 days before period 1, determining patient eligibility); the second was period 1, a double-blinded treatment period from week 0 (baseline) to week 14 inclusive, evaluating the efficacy and safety of upadacitinib compared to placebo, in which patients who completed the double-blinded 14-week study were eligible to enter the extension phase; the third was an extended treatment period after week 14 to week 104 inclusive, assessing the long-term efficacy and safety of upadacitinib; and the fourth was a follow-up phase lasting 30 days. Study 098 was conducted in 62 sites in 20 countries: Canada, the US, Australia, New Zealand, and European and Asian countries.

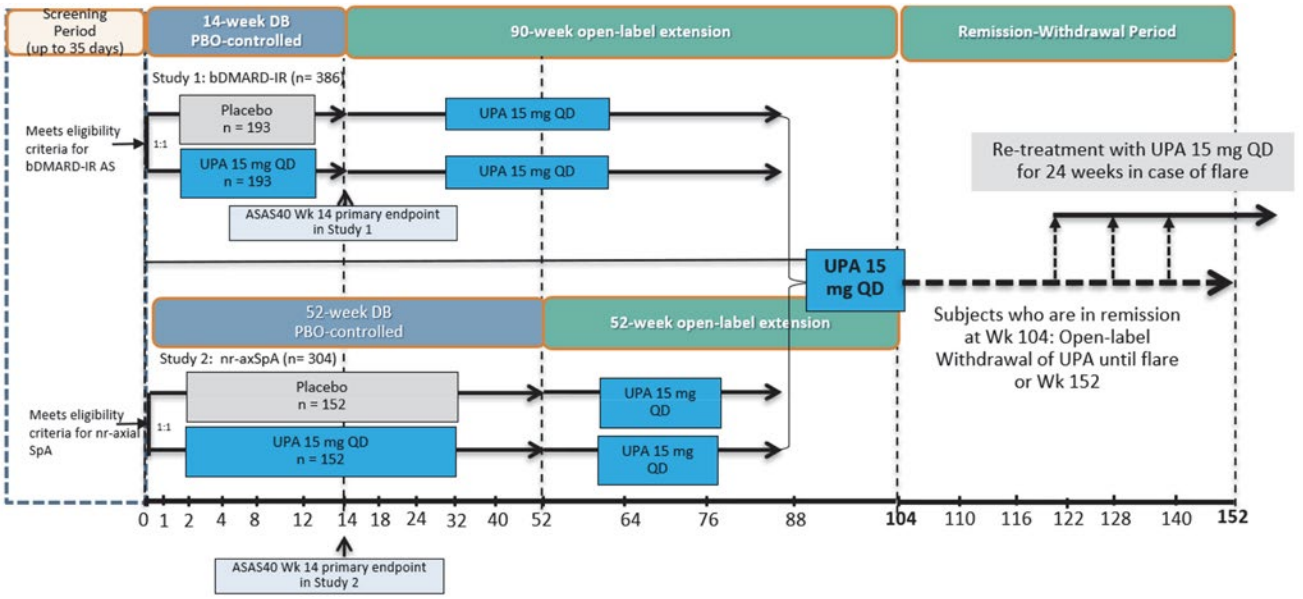
In Study 944, at least 1 protocol deviation was reported in [redacted] patients in the upadacitinib group and [redacted] patients in placebo group. Eligibility criteria violation was the most frequent deviation (upadacitinib versus placebo) [redacted] The totality of the protocol deviations incurred during the study did not affect the study outcomes, interpretation of study results, and/or conclusions. In Study 098, at least 1 protocol deviation was reported in [redacted] (Table 28).

Populations

Inclusion and Exclusion Criteria

In Study 944, the main selection criteria were adult patients (aged ≥ 18 years) who had an AS diagnosis (fulfillment of modified New York criteria based on a central reading of SIJ radiographs). Patients had active disease at screening and baseline defined as a BASDAI score and a patient assessment of total back pain score of 4 or higher on a 0-to-10 numerical rating scale (NRS), an inadequate response to 2 or more NSAIDs or intolerance to or contraindication for NSAIDs, and an inadequate response to bDMARD therapy. An inadequate response to bDMARD therapy was defined as discontinuing bDMARD therapy (TNFi or IL-17i) due to lack of efficacy (after ≥ 12 weeks of treatment at an adequate dose) based on the investigators' assessment of intolerance (irrespective of treatment duration). Prior exposure to 2 bDMARDs was allowed for no more than 30% of patients; among patients with prior exposure to 2 bDMARDs, a lack of efficacy to a single bDMARD and intolerance to another was permitted. Patients receiving concomitant oral corticosteroids or NSAIDs must have been on a stable dose for at least 14 days before baseline, while those receiving concomitant csDMARDs were required to be on a stable dose for at least 28 days before baseline. The key exclusion criteria were patients with total spinal ankylosis; lack of efficacy to 2 bDMARDs, previous exposure to any JAKi, and patients with extra-articular manifestations (i.e., psoriasis, uveitis, or IBD) who were not clinically stable for at least 30 days before study entry.

Figure 2: Study 944 — Study Schematic

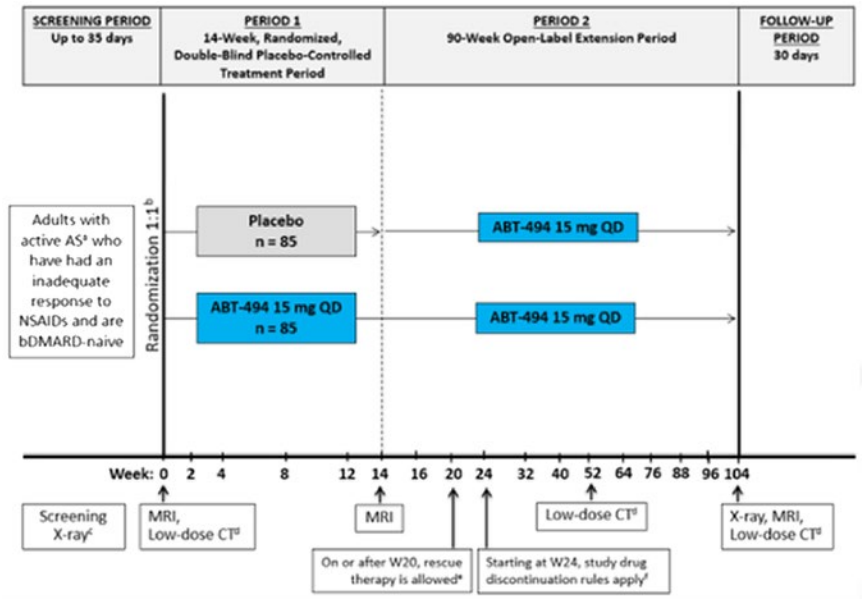


AS = ankylosing spondylitis; ASAS = Assessment of SpondyloArthritis international Society; DB = double-blind; bDMARD-IR = biologic disease-modifying antirheumatic drug–inadequate responder; nr-axSpA = nonradiographic axial spondyloarthritis; PBO = placebo; QD = once daily; SI = sacroiliac; UPA = upadacitinib; Wk = week.

Source: Clinical Study Report and Study 0944[15,36]

In Study 098, eligible adult patients (aged ≥ 18 years) met the modified New York criteria for AS based on a central reading of radiographs of the SIJs, had active disease at baseline defined as a score of 4 or more and a patient assessment of back pain score of 4 or higher (on an NRS of 0 to 10) at screening and baseline visits. The key characteristic differentiating the patients from those in Study 944 was an inadequate response to at least 2 NSAIDS or intolerance to or contraindication for NSAIDs, but without experience with bDMARDs. Patients receiving concomitant csDMARDs, i.e., methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine, at a stable dose for ≥ 28 days before baseline) or oral glucocorticoids, NSAIDs, and analgesics (a stable dose for ≥ 14 days before baseline) were eligible. The key exclusion criteria were patients with total spinal ankylosis, previous exposure to any JAKi, prior exposure to any biologic therapy with a potential therapeutic impact on SpA, and extra-articular manifestations (i.e., psoriasis, uveitis, or IBD) that were not clinically stable for at least 30 days before study entry.

Figure 3: Study 098 — Study Design Schematic



ABT-494 = upadacitinib; AS = ankylosing spondylitis; ASAS = Assessment of SpondyloArthritis international Society; ASAS20 = Assessment of SpondyloArthritis international Society 20% improvement; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; bDMARD = biologic disease-modifying antirheumatic drugs; hsCRP = high-sensitivity C-reactive protein; NRS = numerical rating scale; NSAID = nonsteroidal anti-inflammatory drug; QD = once daily; ULN = upper limit of normal; W = week.

[a] Clinical diagnosis of AS and meeting the modified New York criteria for AS. Patient must have baseline disease activity as defined by having BASDAI score of 4 or higher and a patient assessment of total back pain score of 4 or higher based on a 0-to-10 NRS at the screening and baseline visit.

[b] Stratified by geographic region (US and Canada, Japan, and rest of the world) and hsCRP (≤ ULN versus > ULN).

[c] The X-rays of the spine and pelvis will not be required during the screening period if the patient had a previous anteroposterior pelvis X-ray and lateral spine X-rays within 90 days of the screening period, provided that the X-rays are confirmed to be adequate for the required evaluations and are deemed acceptable by the central imaging vendor.

[d] For patients at select sites who consented to participation in the low-dose CT scan substudy.

[e] Starting at week 16, patients who do not achieve at least an ASAS20 response at 2 consecutive visits will have the option to add or modify doses of NSAIDs, acetaminophen and/or paracetamol, low-potency opioid medications (tramadol or a combination of acetaminophen and codeine or hydrocodone), and/or modify the dose of methotrexate or sulfasalazine at week 20 or thereafter.

[f] Starting at week 24, patients who still do not achieve at least ASAS20 at 2 consecutive visits were discontinued from study drug treatment.

Source: Study 098 Clinical Study Report.[14,37]

Baseline Characteristics

The demographics and baseline characteristics in the full analysis set (FAS) population (equivalent to the intention-to-treat [ITT] populations) for Study 944 and Study 098 are presented in Table 7, Table 8, and Table 9.

In Study 944, overall, the baseline characteristics were balanced between treatment groups. The mean age of patients ranged from 42.2 to 42.6 years between the treatment groups; the majority of patients were male (72.5% to 75.6%) and white (79.6% to 80.9%). The mean duration of AS symptoms was 12.6 to 12.9 years. The mean time since AS diagnosis was 7.5 to 7.9 years. The mean total BASDAI score was 6.8 in both treatment groups. The baseline ASDAS score was 3.9 in both treatment groups. The mean total back pain score was 7.4 to 7.5. The mean MRI of spine SPARCC score ranged from 8.8 to 10.7. The proportion of patients positive for HLA-B27 ranged from 81.2% to 85.3%. In addition, 73.0% patients in the upadacitinib group and 75.6% patients in the placebo group had a prior inadequate response to a TNFi and 13.5% patients in the upadacitinib group and 11.5% patients in the placebo group had a prior inadequate response to an IL-17i. A total of 21.3% patients in the upadacitinib group and 23.4% patients in the placebo group had prior intolerance to a TNFi or an IL-17 inhibitor.

In Study 098, overall, the baseline characteristics were balanced between treatment groups. The mean age of patients ranged from 43.7 to 47.0 years between the treatment groups; the majority of patients were male (68.0% to 73.0%) and white (81.0% to 85.0%). The mean duration of AS symptoms was 14.0 to 14.8 years. The mean time since AS diagnosis was 6.0 to 7.8 years. The mean total BASDAI score ranged from 6.3 to 6.5 between treatment groups. The baseline ASDAS score ranged from 3.5 to 3.7 between treatment groups. The mean total back pain score was 6.7 to 6.8. The mean MRI of spine SPARCC score ranged from 10.4 to 11.9. The proportion of patients positive for HLA-B27 ranged from 75.0% to 78.0%. [redacted].

Table 7: Summary of Baseline Characteristics

Characteristics	Study 944		Study 098	
	Upadacitinib 15 mg q.d. (N = 211)	Placebo (N = 209)	Upadacitinib 15 mg q.d. (N = 93)	Placebo (N = 94)
Male, n (%)	153 (72.5)	158 (75.6)	63 (68)	69 (73)
Race, n (%)				
White	168 (79.6)	169 (80.9)	79 (85)	76 (81)
Asian	42 (19.9)	37 (17.7)	13 (14)	16 (17)
Black or African American	1 (0.5)	3 (1.4)	1 (1%)	2 (2)
Age (years)				
Mean (SD)	42.6 (12.39)	42.2 (11.78)	47.0 (12.8)	43.7 (12.1)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg)				

Characteristics	Study 944		Study 098	
	Upadacitinib 15 mg q.d. (N = 211)	Placebo (N = 209)	Upadacitinib 15 mg q.d. (N = 93)	Placebo (N = 94)
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

q.d. = once daily; SD = standard deviation.

Notes: Percentages calculated on nonmissing values. A patient was counted in the category closest to user.

Sources: Study 0944 Clinical Study Reports[15,36] and Study 098 Clinical Study Reports.[14,37]

Table 8: Baseline Disease Characteristics — General

Characteristics	Study 944		Study 098	
	Upadacitinib 15 mg q.d. (N = 211)	Placebo (N = 209)	Upadacitinib15 mg q.d. (N = 93)	Placebo (N = 94)
Duration (years) since AS symptoms				
Mean (SD)	12.9 (9.08)	12.6 (9.29)	14.8 (11.6)	14.0 (9.9)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Duration (years) since AS diagnosis				
Mean (SD)	7.9 (7.54)	7.5 (7.51)	7.8 (10.6)	6.0 (6.8)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
HLA-B27, n (%)				
Positive	180 (85.3)	168 (81.2)	70 (75%)	73 (78%)
Negative	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of prior bDMARDs use, n (%)				
One TNFi	154 (73.0)	158 (75.6)	0	0
One IL-17i	29 (13.7)	24 (11.5)	0	0
Other (prior exposure to 2 bDMARDs)	28 (13.3)	26 (12.4)	0	0
Missing (no prior bDMARD use)	0	1 (0.5)[a]		
Discontinuation reason of prior bDMARDs, n (%)				
Intolerance (without lack of efficacy and regardless of other reasons)	[redacted]	[redacted]	0	0
Lack of efficacy (without intolerance and regardless of other reasons)	[redacted]	[redacted]	0	0
Lack of efficacy to TNFi therapy	[redacted]	[redacted]	0	0
Lack of efficacy to IL-17i therapy	[redacted]	[redacted]	0	0
Previous NSAID use, n (%)	[redacted]	[redacted]	92 (99)	94 (100)

AS = ankylosing spondylitis; bDMARD = biologic disease-modifying antirheumatic drug; HLA-B27 = human leukocyte antigen-B27; IL-17i = interleukin-17 inhibitor; NSAID = nonsteroidal anti-inflammatory drug; q.d. = once daily; SD = standard deviation; TNFi = tumour necrosis factor inhibitor.

Sources: Study 0944 Clinical Study Reports[15,36] and Study 098 Clinical Study Reports.[14,37]

Table 9: Baseline Disease Characteristics — Outcome-Related

Characteristics	Study 944		Study 098	
	Upadacitinib 15 mg q.d. (N = 211)	Placebo (N = 209)	Upadacitinib 15 mg q.d. (N = 93)	Placebo (N = 94)
Patient's assessment of total back pain (NRS of 0 to 10)				
N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	7.5 (1.48)	7.4 (1.43)	6.8 (1.77)	6.7 (1.78)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Patient assessment of nocturnal back pain (NRS of 0 to 10)				
n (%)	[redacted]	[redacted]	NR	NR
Mean (SD)	7.1 (1.77)	7.2 (1.50)	NR	NR
Median (range)	[redacted]	[redacted]	NR	NR
Patient global assessment of pain (NRS of 0 to 10)				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Patient Global Assessment of Disease Activity (NRS of 0 to 10)				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	7.4 (1.48)	7.2 (1.40)	6.6 (1.81)	6.8 (1.66)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI (0 to 10)				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	6.8 (1.34)	6.8 (1.26)	6.3 (1.8)	6.5 (1.6)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Inflammation (mean of items 5 and 6 of BASDAI NRS of 0 to 10)				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	6.9 (1.84)	6.8 (1.55)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
BASFI (0 to 10)				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	6.3 (2.03)	6.2 (1.87)	5.4 (2.4)	5.5 (2.2)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
ASDAS (CRP)				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	3.9 (0.79)	3.9 (0.77)	[redacted]	[redacted]

Characteristics	Study 944		Study 098	
	Upadacitinib 15 mg q.d. (N = 211)	Placebo (N = 209)	Upadacitinib 15 mg q.d. (N = 93)	Placebo (N = 94)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
ASDAS (CRP) categories, n (%)				
> 3.5	[redacted]	[redacted]	[redacted]	[redacted]
≤ 3.5	[redacted]	[redacted]	[redacted]	[redacted]
hsCRP at screening (mg/L)				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	15.8 (17.69)	14.5 (17.84)	9.6 (12.6)	11.7 (11.1)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Screening hsCRP levels, n (%)[b]				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
> ULN	165 (78.2)	163 (78.0)	67 (72%)	68 (72%)
≤ ULN	46 (21.8)	46 (22.0)	26 (28.0)	26 (27.7)
> 5 mg/L	[redacted]	[redacted]	NR	NR
≤ 5 mg/L	[redacted]	[redacted]	NR	NR
MRI SPARCC score (spine)				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	10.7 (15.43)	8.8 (12.52)	10.4 (14.4)	11.9 (14.5)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
MRI SPARCC score (sacroiliac joints)				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	5.0 (10.80)	5.6 (10.63)	7.9 (10.9)	5.4 (8.6)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
BASMI				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	3.9 (1.57)	3.9 (1.55)	3.7 (1.5)	3.5 (1.5)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
MASES for patients with baseline enthesitis (MASES > 0)[a]				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	4.9 (2.99)	4.2 (3.13)	3.9 (2.8)	3.7 (2.7)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
ASQoL				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	Study 944		Study 098	
	Upadacitinib 15 mg q.d. (N = 211)	Placebo (N = 209)	Upadacitinib 15 mg q.d. (N = 93)	Placebo (N = 94)
Mean (SD)	11.6 (4.38)	11.5 (4.44)	10.0 (5.3)	10.3 (4.7)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
ASAS HI				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
FACIT-F				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	NR	NR
SF-36				
Physical component summary				
n (%)	[redacted]	[redacted]	NR	NR
Mean (SD)	[redacted]	[redacted]	NR	NR
Median (range)	[redacted]	[redacted]	NR	NR
Mental component summary				
n (%)	[redacted]	[redacted]	NR	NR
Mean (SD)	[redacted]	[redacted]	NR	NR
Median (range)	[redacted]	[redacted]	NR	NR
Work Productivity Activity Impairment (overall)				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
mean (SD)	[redacted]	[redacted]	54.3 (28.1)	53.3 (24.6)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]

ASAS HI = Assessment of SpondyloArthritis international Society Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = ankylosing spondylitis quality of life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; CRP = C-reactive protein; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; hsCRP = high-sensitivity C-reactive protein; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; NR = not reported; NRS = numerical rating scale; q.d. = once daily; SD = standard deviation; SF-36 = Short Form (36) Health Survey; SPARCC = Spondyloarthritis Research Consortium of Canada.

[a]Based on MASES > 0 at baseline.

[b]Upper limit of normal = 2.87 mg/L.

Sources: Study 0944 Clinical Study Reports[15,36] and Study 098 Clinical Study Reports.[14,37]

Interventions

In both Study 944 and Study 098, patients were allocated to randomized and blinded treatment based on a unique identification number generated by interactive response technology (IRT) at the screening visit. For patients who re-screened, the number assigned by the IRT at the initial screening visit was used. The IRT

assigned a randomization number that would encode the patient's treatment-group assignment according to a randomization schedule set by the AbbVie statistics department. In the double-blind period, patients were randomized in a 1:1 ratio to the upadacitinib (15 mg oral, once-daily) or placebo group (placebos were presented as orally administered tablets that were identical in appearance). At week 14, patients entered an open-label extended treatment period (weeks 14 to 104). During the open-label period, all patients received 15 mg upadacitinib orally once daily.

In Study 944, randomization was stratified by screening high-sensitivity C-reactive protein (hsCRP ≤ or > an upper limit of normal of 2.87 mg/L), class of prior bDMARD use (a TNFi, an IL-17i, or 2 bDMARDs), and geographical region. The sponsor, investigators, study-site personnel, and the patients were blinded to the treatment assignments. In Study 098, randomization was stratified by screening hsCRP (≤ or > an upper limit of normal of 2.87 mg/L) and geographical region. The sponsor, investigators, study-site personnel, and the patients were blinded to the treatment assignments.

Use of Concomitant NSAIDs and csDMARDs

In Study 944, slightly more patients in the upadacitinib group received 1 or more concomitant csDMARDs than in the placebo group (upadacitinib versus placebo) [redacted] According to the clinical expert consulted for this review, this imbalance was unlikely to have affected the study results. [redacted]

In the double-blind period of Study 098, 76.3% of patients in the upadacitinib group and 86.2% of patients in the placebo group took 1 or more concomitant NSAIDs. Similar proportions in the 2 groups received concomitant csDMARD therapy (upadacitinib versus placebo: 14.0% versus 18.1%, respectively); [redacted]

Rescue Therapy

In Study 944, at week 24, patients who do not achieve an ASAS20 response at both week 18 and week 24 were allowed to add or modify any of the background axial SpA medications (such as NSAIDs, csDMARDs, or a corticosteroid). After week 24 (e.g., at week 32 through week 104 visits), addition or modification of the background axial SpA medications could be made according to the investigator's judgment regardless of the disease activity status. In Study 098, with rescue therapy starting at week 16, patients who do not achieve at least an ASAS20 response at 2 consecutive visits had the option to add or modify doses of NSAIDs, and/or modify the dose of methotrexate or sulfasalazine at week 20. Change in dose or addition of DMARDs other than methotrexate or sulfasalazine is not permitted for rescue. Starting at week 24, patients who did not achieve at least an ASAS20 response at 2 consecutive visits discontinued from study drug treatment.

No detailed information on rescue medication use was reported in either of the 2 studies.

Outcomes

A list of efficacy end points identified in the CADTH review protocol (Table 5) that were assessed in the clinical trials included in this review is provided in Table 10. These end points are further summarized in

the following section. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

Assessment of SpondyloArthritis international Society Criteria

ASAS40 and ASAS20

The primary efficacy outcome in Study 944 and Study 098 was the proportion of patients who met ASAS40 response criteria at week 14. An ASAS40 response is defined as an improvement of 40% or greater and an absolute improvement from baseline of 2 or more units (range = 0 to 10) in at least 3 of 4 main domains (i.e., patient global assessment, spinal pain, function, and inflammation), without any worsening in the remaining domain. ASAS20 was assessed as a main secondary outcome (i.e., it was analyzed with multiplicity adjustment) in both Study 944 and Study 098. ASAS20 response is defined as an improvement of 20% or greater and an absolute improvement from baseline of 1 or more units (range = 0 to 10) in at least 3 of 4 main domains, without any worsening of 20% or greater and 1 or more units (range = 0 to 10) in the remaining domain.

ASAS40 and ASAS20 are composite measures containing 4 main domains: Patient's Global Assessment of Disease Activity (PtGA) on an NRS, with a score ranging from 0 (not active) to 10 (very active); assessment of back pain intensity with an NRS from 0 (not active) to 10 (very active); function represented by the BASFI as measured by an NRS ranging from 0 (not active) to 10 (very active); and inflammation represented by mean duration and severity of morning stiffness (measured by the average scores from the last 2 questions on the BASDAI, using a scale of 0 to 10). Two additional domains were included: spinal mobility represented by the BASMI lateral spinal flexion assessment and CRP.

ASAS Partial Remission

ASAS PR was assessed as a main secondary outcome (i.e., it was analyzed with multiplicity adjustment) in both Study 944 and Study 098. An ASAS PR response is defined as a value not above 2 units (range = 0 to 10 on an NRS) in each of the following 4 main domains: patient global assessment, spinal pain, function, and inflammation.

Assessment in SpondyloArthritis international Society 20% Improvement in 5 of 6 Domains

The Assessment in SpondyloArthritis international Society 20% improvement in 5 of 6 domains (ASAS5/6) was as additional outcome (i.e., exploratory outcome, without multiplicity adjustment) in Study 098. The ASAS5/6 was not assessed in Study 944. The ASAS5/6 includes assessments of all 6 individual ASAS domains and represents improvement of 20% or greater in at least 5 domains.

Symptom Measurement

In both Study 944 and Study 098, The AS symptom measures included the total back pain, total nocturnal back pain, and fatigue (FACIT-F). Both the total back pain and total nocturnal back pain were assessed as main secondary outcomes in Study 944 but were exploratory outcomes in Study 098. Both the total back pain and total nocturnal back pain were assessed with an NRS (0 to 10). A higher score indicates more severe pain.

Functional Assessment of Chronic Illness Therapy–Fatigue

The FACIT-F is a patient self-completed questionnaire to assess the intensity of fatigue (and its impact on daily life) during usual daily activities over the past week. It consists of a 13-item questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue. The level of fatigue is measured on a 4-point Likert scale (4 = not at all fatigued; 0 = very much fatigued). The instrument scoring yields a range from 0 to 52, with higher scores representing better overall health status (i.e., less fatigue). A meaningful within-patient change for the FACIT-F total score is estimated to be 3.1 to 6.3 points in patients with AS.

Bath Ankylosing Spondylitis Functional Index

The BASFI is 1 of the 4 main components of ASAS criteria. The BASFI is a validated, patient self-administered, composite instrument widely used in AS to assess physical function. The BASFI consists of 8 specific questions regarding function in AS and 2 questions reflecting the patient's ability to cope with everyday life. Each question is answered on a 10 cm horizontal visual analogue scale (VAS) or an NRS (0 to 10), the mean of which gives the BASFI score (on a scale of 0 to 10). The higher the BASFI score, the greater the degree of functional impairment with reductions from baseline indicating improvement. The minimal clinically important difference (MCID) was 0.6 units on a 10-unit scale. In both studies, the BASFI was assessed as a main secondary outcome.

Health-Related Quality of Life

Ankylosing Spondylitis Quality of Life

Patient-reported impacts of AS on HRQoL included the impact of disease on sleep, mood, motivation, coping, activities of daily living, independence, relationships, and social life. ASQoL was assessed with a NRS of 0 to 10. A higher score indicates poorer quality of life. It was reported that increase of 1 point indicated "worsening" and a decrease of −2 indicated "improvement."[44] In both studies, ASQoL was assessed as a main secondary outcome.

Assessment of SpondyloArthritis international Society Health Index

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

A minimal important difference (MID) for the ASAS HI was not identified in the literature. In both Study 944 and Study 098, the ASAS HI was assessed as a main secondary outcome.

5-Level EQ-5D

The EQ-5D-5L scale is a generic quality-of-life instrument that may be applied to a wide range of health conditions and treatments. The first of 2 parts of the EQ-5L-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into 1 of 243 distinct health states. The descriptive system consists of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each

dimension has 5 possible levels of response (no problems, slight problems, moderate problems, severe problems, or extreme problems). Respondents are asked to choose the level that reflects their health state for each of the 5 dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights. The second part is a 20 cm VAS (EQ VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ VAS that best represents their health on that day. The EQ-5D index score is generated by applying a multiattribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all 5 attributes) varies depending on the utility function that is applied to the descriptive system (e.g., to −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores of less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1 are assigned to the health states "dead" and "perfect health," respectively. Reported MCIDs for this scale have ranged from 0.033 to 0.074. But an MID has not been specifically identified in AS patients. The EQ-5D was assessed as another secondary outcome in Study 944, but it was not assessed in Study 098.

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. The SF-36 consists of 8 health domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems. For each of the 8 categories, a subscale score can be calculated. The SF-36 also provides 2 component summaries, the physical component summary (PCS) and the mental component summary (MCS). PCS and MCS scores range from 0 to 100, with higher scores indicating a better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a standard deviation of 10 in the general US population. All scores above or below 50 are therefore considered above or below average, respectively, for the general US population. Changes of between 2.5 to 5.0 points in the PCS and MCS of the SF-36 are considered clinically relevant, as are changes of 5 to 10 points in the domain scores. However, an MID for the SF-36 has not been specifically measured in AS patients. In Study 944, the SF-36 was assessed as an exploratory outcome. However, the SF-36 was not assessed in Study 098.

Work Productivity Activity Impairment–Spondyloarthritis

The WPAI-SpA is a 6-item, patient-reported instrument designed to assess the impact of SpA on work productivity and activity impairment. Four scores are derived: percentage of absenteeism, percentage of presenteeism, an overall work impairment score that combines absenteeism and presenteeism, and percentage of impairment in activities performed outside of work. Greater scores indicate greater impairment. No MID was identified in the literature. WPAI-SpA was assessed as an exploratory outcome in Study 944 and as a main secondary outcome in Study 098.

Bath Ankylosing Spondylitis Disease Activity Index

The BASDAI is the most common and widely used validated measure of inflammatory activity of AS. The BASDAI is a self-administered patient questionnaire that generates a composite index of patient responses to major symptoms of AS. It includes 6 questions addressing 5 major symptoms: fatigue, axial (spinal) and peripheral joint pain, localized tenderness, and morning stiffness (both the degree of stiffness and the length of time for which stiffness persists). Patient responses are recorded on a 10-unit horizontal NRS or 10 cm VAS or a numeric response scale (1 to 10). The scores for questions 5 and 6 (severity and duration of morning stiffness) are averaged to produce a result that is then averaged with the scores from the remaining 4 questions. The final BASDAI score has a range of 0 to 10: the higher the score, the greater the measured degree of disease activity. A reduction in the BASDAI score is considered improvement. The definition of treatment response (i.e., MCID) includes a change in the BASDAI value defined as 2 units (on a 0-to-10 scale) of the BASDAI. BASDAI50, which reflects an improvement of 50%, was assessed as a main secondary outcome in both Study 944 and Study 098. But the change from baseline of the BASDAI was assessed as an exploratory outcome in both studies.

Ankylosing Spondylitis Disease Activity Score

The ASDAS is a composite index to assess disease activity in AS. The parameters used for the ASDAS (with CRP as an acute-phase reactant) are total back pain (BASDAI question 2); patient global assessment (individual ASAS domain); peripheral pain and/or swelling (BASDAI question 3); duration of morning stiffness (BASDAI question 6); and CRP (mg/L). The ASDAS CRP score is calculated with the following equation: 0.121 × total back pain + 0.110 × patient global + 0.073 × peripheral pain/swelling + 0.058 × duration of morning stiffness + 0.579 × ln (CRP + 1). Four disease activity states have been defined by ASAS consensus:

- an ASDAS less than 1.3 defines ID
- an ASDAS greater than or equal to 1.3 and less than 2.1 defines LDA
- an ASDAS greater than or equal to 2.1 and no more than 3.5 defines high disease activity
- an ASDAS greater than 3.5 defines very high disease activity.

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

Inactive AS (an ASDAS score of < 1.3) and ASDAS LDA (an ASDAS score of < 2.1) were assessed as a main secondary outcome in Study 944. But they were assessed as an exploratory outcome in Study 098. A clinically important improvement, defined as change of 1.1 or more units, was assessed as an exploratory outcomes in both studies.

Patient Global Assessment

The PtGA relates to a single specific ASAS domain based on an NRS. For this assessment, the patient was asked to respond to the following question: “How active was your spondylitis on average during the last

week?" The answer was recorded on an NRS and was rated between 0 (not active) and 10 (very active). Additionally, an international validation study on the ASAS HI assessed PtGA using cut-off values of less than 3 and greater than 6 on an NRS to distinguish between a "good" and a "poor" health status, respectively. While an MID for PtGA was not identified in the literature, the minimum change that should be considered detectable would be approximately 2 to 3 units on a scale of 0 to 10. The PtGA was assessed as an exploratory outcome in both studies.

MRI Spine SPARCC Index

The SPARCC MRI Index for the spine is an MRI-based scoring system that assesses the presence, 3-dimensional extent, and signal intensity of active inflammatory lesions represented by bone marrow edema, in the spine of affected patients. In the spine, the scoring system measures edema in the bone marrow of discovertebral units (DVUs), each unit representing the region between 2 imaginary lines drawn through the middle of adjacent vertebrae. All 23 DVUs of the spine (from C2 to S1) were scored for bone marrow edema. A single DVU has a scoring range of 0 to 18, bringing the maximum total score to 414, with higher scores reflecting worse disease. An MID of 5.0 units for the SPARCC MRI score for the spine has been identified. The MRI Spine SPARCC Index was assessed as a main secondary outcome (multiplicity was adjusted in the analysis) in both Study 944 and Study 098.

MRI SIJ SPARCC Index

The MRI SPARCC score for the SIJ is a scoring method based on the assessment of an increased signal denoting bone marrow edema on T2-weighted short-T1 inversion recovery (STIR) sequences. All signal changes within the iliac bone and sacrum up to the sacral foramina are scored on 6 consecutive slices through the SIJ. Each SIJ is divided into 4 quadrants: upper iliac, lower iliac, upper sacral, and lower sacral. The presence of an increased signal on STIR in each of these 4 quadrants was scored on a dichotomous basis, where 1 indicates an increased signal and 0 a normal signal. Total SIJ SPARCC scores can range from 0 to 72, with higher scores reflecting worse disease. An MID of 2.5 units for the SPARCC MRI score for SIJ has been identified. The MRI SIJ SPARCC Index was assessed as an exploratory outcome in both studies.

Linear Bath Ankylosing Spondylitis Metrology Index

The BASMIlin was assessed as a main secondary outcome in both studies. It was assessed with an NRS of 0 to 10. A higher score indicates poorer mobility. No MID information was identified.

Maastricht Ankylosing Spondylitis Enthesitis Score

The MASES was assessed as a main secondary outcome in both studies using an NRS of 0 to 10. A higher score indicates poorer mobility. No MID information was identified.

Safety Outcomes

In both trials, safety data are presented as AEs, SAEs, death, WDAEs, and notable AEs. All AE data presented in this review report are for TEAEs, defined as an AE with an onset date that was after the first dose of the study drug, and no more than 30 days after the last dose of the study drug.

Table 10: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure (week 14)	Study 944 (Study 1)	Study 098
	Primary, secondary, or exploratory	
ASAS40	Primary	Primary
ASDAS change from baseline	Main secondary	Main secondary
MRI SPARCC score (spine)	Main secondary	Main secondary
BASDAI50	Main secondary	Main secondary
ASAS20	Main secondary	Additional secondary
ASDAS inactive disease (ASDAS score < 1.3)	Main secondary	Additional (exploratory)
Patient assessment of total back pain	Main secondary	Additional (exploratory)
Patient assessment of nocturnal back pain	Main secondary	Additional (exploratory)
ASDAS LDA (score < 2.1)	Main secondary	Additional (exploratory)
BASFI	Main secondary	Main secondary
ASAS partial remission (absolute score of ≤ 2 units for each of the 4 domains identified in ASAS40)	Main secondary	Main secondary
ASQoL	Main secondary	Main secondary
ASAS HI	Main secondary	Main secondary
BASMIlin	Main secondary	Main secondary
MASES	Main secondary	Main secondary
WPAI-SpA	Additional (exploratory)	Main secondary
MRI SPARCC score (sacroiliac joint)	Additional secondary	Additional secondary
5-Level EQ-5D	Additional (exploratory)	NR
Functional Assessment of Chronic Illness Therapy–Fatigue	Additional (exploratory)	Additional (exploratory)
Patient Global Assessment of Disease Activity	Additional (exploratory)	Additional (exploratory)
Short Form (36) Health Survey	Additional (exploratory)	NR
ASDAS clinically important improvement (change from baseline of at least 1.1)	Additional (exploratory)	Additional (exploratory)
ASAS5/6	NR	Additional (exploratory)
BASDI change from baseline	Additional (exploratory)	Additional (exploratory)

ASAS5/6 = Assessment in SpondyloArthritis international Society 20% improvement in 5 of 6 domains; ASAS20 = Assessment of SpondyloArthritis international Society 20% improvement; ASAS40 = Assessment of SpondyloArthritis international Society 40% improvement; ASAS HI = Assessment of SpondyloArthritis international Society Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI50 = Bath Ankylosing Spondylitis Disease Activity Index 50% improvement; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMIlin = Linear Bath Ankylosing Spondylitis Metrology Index; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; NR = not reported; SPARCC = Spondyloarthritis Research Consortium of Canada; WPAI-SpA = Work Productivity Activity Impairment–Spondyloarthritis

Note: Main secondary means the multiplicity-controlled secondary end points at week 14.

Sources: Study 0944 Clinical Study Reports[15,36] and Study 098 Clinical Study Reports.[14,37]

Statistical Analysis

Primary Outcome of the Studies

Power Calculation

In Study 944, the planned total sample size of 386 patients for this study (with a 1:1 randomization ratio for placebo and upadacitinib 15 mg) provides at least 90% power for the primary end point of an ASAS40 response of upadacitinib 15 mg versus placebo using a 2-sided chi-square test at the 0.05 level. For ASAS40, the assumed response rates for upadacitinib and placebo are 24% and 6%, respectively. [redacted] These assumptions were based on a review of historical bDMARD clinical studies of AS patients.[45-47]

In Study 098, the planned sample size of 170 for this study (with a 1:1 randomization ratio) provides at least 90% power for a 26% difference in ASAS40 response rate (assuming a placebo ASAS40 response rate of 20%). Power and sample-size calculations are performed at a 2-sided significance level of 0.05 and accounting for a 10% dropout rate.[14]

In both Study 944 and Study 098, all efficacy analyses were conducted in the FAS. In addition, per-protocol analysis for the primary end point was performed. All tests were 2-sided at an alpha level of 0.05. "Baseline" refers to the last nonmissing observation before the first administration of the study drug or randomization if no study drug was given. Two sets of efficacy analysis were planned: for the double-blind period and the long-term (extension phase).

The primary analysis was performed after all patients had completed the double-blind period or discontinued the study in the double-blind period and the database had been locked. This was the only and final analysis for the primary and secondary efficacy end points as well as all other efficacy end points in the double-blind period. Analyses were performed for the protocol-defined primary time point by randomized treatment groups (upadacitinib 15 mg once daily and placebo). No protocol-defined treatment switching occurred in the double-blind period. Formal statistical inference was generated, and results from this set of analyses were used as the key efficacy findings of this study.

Statistical Test or Model

Unless otherwise specified, binary variables were analyzed using a Cochran-Mantel-Haenszel test, stratified by screening hsCRP level status (hsCRP > upper limit of normal, hsCRP ≤ upper limit of normal). Continuous variables were analyzed using a mixed-effect model for repeated measures (MMRM) or analysis of covariance method adjusting for screening hsCRP level status. Unless otherwise specified, any patient who was randomized based on an incorrect stratum was analyzed according to the actual stratum the patient belongs to. In both Study 944 and Study 098, the primary analyses for continuous efficacy outcomes were made using the MMRM. The primary analyses for MRI SPARCC scores was based on the observed case using analysis of covariance.

A long-term efficacy analysis was conducted at week 52 for both Study 944 and Study 098 or week 104 (Study 098 only). There was no statistical testing for long-term efficacy analysis up to week 52 or week 104; descriptive statistics were provided by randomized treatment-group sequences: placebo group upadacitinib 15 mg once-daily group; and upadacitinib 15 mg once daily group upadacitinib 15 mg once-daily group.

Analysis Populations

The following analysis populations were used for the analyses in both Study 944 and Study 098. The FAS includes all randomized patients who received at least 1 dose of the study drug. Patients were included in the analysis based on the treatment group as randomized. The FAS was used for all efficacy and baseline analyses. The per-protocol analysis set represents a subset of the FAS consisting of all FAS patients who did not have any major protocol violations that affected the primary efficacy analysis. The primary end point was also analyzed in the per-protocol analysis set. The final criteria and the exclusion of patients from the per-protocol analysis set was finalized before unblinding for the primary analysis. The safety analysis set consists of all patients who received at least 1 dose of the study drug. For the safety analysis set, patients were assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized. Unless otherwise specified, efficacy and health outcomes analyses were conducted on the FAS (equivalent to the ITT population).

Data Imputation Methods

For missing data, it was assumed that they were missing at random. The following methods for imputation of missing data were used for analyses for the double-blind phase:

- Nonresponder imputation (NRI): Analyses of categorical efficacy outcomes were assessed using an NRI method. Patients were considered nonresponders for the NRI analysis if they did not meet the clinical response criteria, without at least 1 postbaseline observation, had missing clinical response data at the week 14 or discontinued study drug at any time before week 14 for any reason.
- Multiplicity adjustment: a multiple testing procedure (i.e., the Hochberg procedure) was used to control the family-wise type I error rate at a 2-sided alpha level of 0.05. The multiplicity-controlled secondary end points (also known as key or main secondary outcomes) at week 14 are presented Table 28 for Study 944 and Table 29 in Study 098 in Appendix 3.

Subgroup Analyses

In Study 944, key subgroup analysis (subgroups of interest for this review) for the primary outcome (ASAS40) were based on patients' prior experience with bDMARDs (i.e., TNFi and IL-17i drugs).

Sensitivity Analyses

In both Study 944 and Study 098, sensitivity analysis (i.e., analysis as observed [AO], AO with nonresponder imputation [AO-NRI] and AO with multiple imputation [AO-MI]) for ASAS40 were conducted.

Table 11: Statistical Analysis of Efficacy End Points in Study 944 and Study 098

End point	Statistical model	Adjustment factors	Sensitivity analyses
ASAS40	Cochran-Mantel-Haenszel	hsCRP level (> ULN vs. ≤ ULN)	NRI NRI-MI MI AO AO-MI Per protocol
For multiplicity-controlled secondary continuous efficacy variables (Table 28 and Table 29 in Appendix 3)	MMRM ANCOVA	hsCRP level (> ULN vs. ≤ ULN) Continuous variables were also adjusted for baseline values No other adjustment for covariates	NRI NRI-MI MI AO AO-MI
Additional efficacy analyses (Table 6)	MMRM ANCOVA	hsCRP level (> ULN vs. ≤ ULN) Continuous variables were also adjusted for baseline values No other adjustment for covariates	AO

ANCOVA = analysis of covariance; AO = as observed; hsCRP = high-sensitivity C-reactive protein; MI = multiple imputation; MMRM = mixed-effect model for repeated measures; NRI = nonresponder imputation; ULN = upper limit of normal; vs. = versus.

Sources: Study Clinical Study Reports[15,36] and Study 098 Clinical Study Reports.[14,37]

Results

Patient Disposition

Patient disposition for Study 944 and Study 098 are presented in Table 12. In the Study 944, 1,352 patients were screened. A total of 420 were randomized. Of the 420 randomized patients, 211 received upadacitinib (i.e., 15 mg orally once daily) and 209 received placebo (i.e., FAS population); all patients received at least 1 dose of the treatment (i.e., the FAS population is equivalent to the ITT population). Of the FAS population, 97.6% of the patients in the upadacitinib group and 97.1% of patients in the placebo group completed the study. The proportions of patients who discontinued from the study were 2.4% in the upadacitinib group and 2.9% in the placebo group. Discontinuations were due to AEs (upadacitinib versus placebo: 0% versus 1.4%, respectively); withdrawal by patient (upadacitinib versus placebo: 0.9% versus 0.5%); lost to follow-up (upadacitinib versus placebo: 0.5% versus 0.5%); lack of efficacy (upadacitinib versus placebo: 0.5% versus 0.5%); COVID-19 logistical restrictions (upadacitinib versus placebo: 0.5% versus 0.0%), and other (upadacitinib versus placebo: 1.4% versus 0.5%).

In the Study 098, a total of 395 patients were screened and 187 were randomized. Of the 187 randomized patients, 93 received upadacitinib (i.e., 15 mg orally once daily) and 94 received placebo (i.e., the FAS population); All patients received at least 1 dose of the treatment. Of the FAS population, 95.7% of the patients in the upadacitinib group and 94.7% of the patients in the placebo group completed the study. The proportions of patients who discontinued from the study were 4.3% in the upadacitinib group and 5.3% in the placebo group. Discontinuations were due to AEs (upadacitinib versus placebo: 2.2% versus 3.2%,

respectively); withdrawal by patient (upadacitinib versus placebo: 2.2% versus 1.1%); lost to follow-up (upadacitinib versus placebo: 0.0% versus 1.1%), and other upadacitinib versus placebo: 1.1% versus 1.15%).

In Study 944, [redacted] In Study 098, 95.7% patients in the upadacitinib group and 94.7% of the placebo group entered the open-label extension phase. A total of 83.9% of the upadacitinib group and 87.2% of the placebo group completed the study drug at week 64 (no information was provided for week 52). In addition, 76.3% of patients in the upadacitinib group and 77.7% of patients in the placebo group completed the study drug at week 104 (Table 12).

Exposure to Study Treatments

At week 14, in Study 944, the mean treatment durations were [redacted] in the upadacitinib group and [redacted] in the placebo group. In Study 098, the mean treatment durations [redacted] in the upadacitinib group and [redacted] in the placebo group. In both studies, [redacted] (Table 13 and Table 14).

Table 12: Patient Disposition

Disposition	Study 944		Study 098	
	Upadacitinib 15 mg q.d. (N = 211)	Placebo (N = 209)	Upadacitinib 15 mg q.d. (N = 93)	Placebo (N = 94)
Screened, n	1,352		395	
Randomized, n	211	209	93	94
Treated, n	211	209	93	94
Completed study drug in week 14 double-blind period, n (%)	206 (97.6)	203 (97.1)	89 (95.7)	89 (94.7)
Discontinued study drug in double-blind period n (%)	5 (2.4)	6 (2.9)	4 (4.3)	5 (5.3)
All reasons,[a] n (%)	5 (2.4)	6 (2.9)	4 (4.3)	5 (5.3)
Adverse event	0	3 (1.4)	2 (2.2)	3 (3.2)
Withdrawal by patient	2 (0.9)	1 (0.5)	2 (2.2)	1 (1.1)
Lost to follow-up	1 (0.5)	1 (0.5)	0	1 (1.1)
Lack of efficacy	1 (0.5)	1 (0.5)	0	0
COVID-19 infection	0	0	0	0
COVID-19 logistical restrictions	1 (0.5)	0	0	0
Other	3 (1.4)	1 (0.5)	0	0
Completed study in double-blind period, n (%)	206 (97.6)	204 (97.6)	89 (95.7)	89 (95.7%)
Discontinued study in double-blind period 1, n (%)	5 (2.4)	5 (2.4)	4 (4.3)	4 (4.2)
Patients entering the open-label period 2, n (%)	206 (97.6)	204 (97.6)	89 (95.7)	90 (95.8)
Patients entering the open-label period on drug, n (%)	206 (97.6)	204 (97.6)	89 (95.7)	89 (94.7)

Disposition	Study 944		Study 098	
	Upadacitinib 15 mg q.d. (N = 211)	Placebo (N = 209)	Upadacitinib 15 mg q.d. (N = 93)	Placebo (N = 94)
Full analysis set, N (%)	211 (100)	209 (100)	93 (100)	94 (100)
Per-protocol set, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Safety set, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
For open-label periods week 52 to week 104				
Completed study drug in open-label period, n (%) (at week 52 for Study 944 and week 64 for Study 098)	[redacted]	[redacted]	78 (83.9)	82 (87.2)
Discontinued study drug in open-label period n (%) (at week 52 for Study 944 and week 64 for Study 098)	[redacted]	[redacted]	11 (16.1)	7 (12.8)
Completed study drug at week 104 open-label period, n (%)	[redacted]	[redacted]	71 (76.3)	73 (77.7)
Discontinued study drug at week 104 open-label period, n (%)	[redacted]	[redacted]	18 (23.7)	16 (22.3)

NR = not reported; q.d. = once daily.

[a]Patients who discontinued the study drug are counted under each reason given for discontinuation; the sum of the counts given for the reasons therefore may be greater than the overall number of discontinuations.

Sources: Study 0944 Clinical Study Reports[15,36] and Study 098 Clinical Study Reports.[14,37]

Table 13: Extent of Exposure (Safety Analysis Set)

Period Week 14 (DB period 1)	Study 944		Study 098	
	UPA 5 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
Duration (days)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Duration interval, n (%)				
≥ 2 weeks	[redacted]	[redacted]	[redacted]	[redacted]
≥ 1 month	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3 months	[redacted]	[redacted]	[redacted]	[redacted]

DB = double-blind; PBO = placebo; q.d. = once daily; SD = standard deviation; UPA = upadacitinib.

Sources: Study 0944 Clinical Study Reports[15,36] and Study 098 Clinical Study Reports.[14,37]

Table 14: Extent of Exposure (Long-term, period 2, Safety Analysis Set)

Long-term (period 2)	Any UPA 15 mg q.d. (N = 414) at week 52	UPA 15 mg q.d. (N = 182) week 52	UPA 15 mg q.d. (N = 182) week 104
Duration (days)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Duration interval, n (%)			
≥ 6 months	[redacted]	[redacted]	[redacted]
≥ 9 months	[redacted]	[redacted]	[redacted]
≥ 12 months	[redacted]	[redacted]	[redacted]
≥ 18 months	[redacted]	[redacted]	[redacted]
≥ 2 years	[redacted]	[redacted]	[redacted]

DB = double-blind; PBO = placebo; q.d. = once daily; SD = standard deviation; UPA = upadacitinib.
Sources: Study 0944 Clinical Study Reports[15,36] and Study 098 Clinical Study Reports.[14,37]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported here. Appendix 3 provides detailed efficacy data.

Clinical Response

Primary Analysis

The primary outcome in both Study 944 and Study 098 was ASAS40 at week 14. The results of ASAS40 are presented in Table 15, Figure 4, and Figure 5.

In Study 944, in the primary analysis (i.e., the FAS), the proportions of patients achieving ASAS40 were 44.5% and 18.2% in the upadacitinib (15 mg, oral, once daily) and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was 26.4% (95% CI, 17.9% to 34.9%; P < 0.0001). [redacted] The subgroup analysis showed that the proportion of patients achieving ASAS40 [redacted]. Other sensitivity analysis (i.e., AO, AO-NRI, and AO-MI) for ASAS40 were also reportedly [redacted] Table 15 and Figure 4).

In Study 098, in the primary analysis (i.e., the FAS), the proportions of patients achieving ASAS40 were 51.6% and 25.5% in the upadacitinib (15 mg, oral, once daily) and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was 26.1% (95% CI, 12.6% to 39.5%; P < 0.001). [redacted]

(Table 15). Other sensitivity analysis (i.e., AO, AO-NRI, and AO-MI for ASAS40 [redacted] (Table 15 and Figure 5).

Table 15: ASAS40 Response at Week 14

Analysis	Study 944		Study 098	
	UPA 15 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
Week 14				
Primary analysis				
ASAS40, (NRI, MI, FAS)				
Response, n[a] (%)	94 (44.5)	38 (18.2)	[redacted] (51.6)	[redacted] (25.5)
% difference (95% CI) vs. PBO[b]	26.4 (17.9 to 34.9)		26.1 (12.6 to 39.5)	
P value vs. PBO	< 0.0001		< 0.001	
Subgroup analysis				
1 TNF inhibitor	[redacted]	[redacted]	NR	NR
Response, n (%)	[redacted]	[redacted]	NR	NR
% difference (95% CI) vs. PBO	[redacted]		NR	NR
P value vs. PBO	[redacted]		NR	NR
1 IL-17 inhibitor	[redacted]	[redacted]	NR	NR
Response, n (%)	[redacted]	[redacted]	NR	NR
% difference (95% CI) vs. PBO	[redacted]		NR	NR
P value vs. PBO	[redacted]		NR	NR
Other	[redacted]	[redacted]	NR	NR
Response, n (%)	[redacted]	[redacted]	NR	NR
% difference (95% CI) vs. PBO	[redacted]		NR	NR
P value vs. PBO	[redacted]		NR	NR
Sensitivity analysis				
ASAS40, (NRI, FAS)	N = 211	N = 209	N = 93	N = 94
Response, n (%)	94 (44.5)	38 (18.2)	[redacted] (51.6)	[redacted] (25.5)
% difference (95% CI) vs. PBO	26.4 (17.9 to 34.9)		26.1 (12.6 to 39.5)	
P value vs. PBO	< 0.0001		< 0.001	
ASAS40, (NRI, per-protocol)	[redacted]	[redacted]	[redacted]	[redacted]
Response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
% difference (95% CI) vs. PBO	[redacted]		[redacted]	
P value vs. PBO	[redacted]		[redacted]	

Analysis	Study 944		Study 098	
	UPA 15 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
ASAS40, (AO)				
Response, n (%)				
% difference (95% CI) vs. PBO				
P value vs. PBO				
ASAS40, (AO with NRI, FAS)				
Response, n (%)				
% difference (95% CI) vs. PBO				
P value vs. PBO				
ASAS40, (AO-MI, FAS)				
Response, n (%)				
% difference (95% CI) vs. PBO				
P value vs. PBO				
Long-term (week 52 or week 104)				
ASAS40, (NRI, MI FAS) response, % at week 52			69.9	69.1
ASAS40, (NRI, MI) response, % at week 104			85.9	88.7

AO = as observed; ASAS40 = Assessment of SpondyloArthritis international Society 40% improvement; CI = confidence interval; FAS = full analysis set; IL-17 = interleukin-17; MI = multiple imputation; NA = not applicable; NR = not reported; NRI = nonresponder imputation; PBO = Placebo; q.d. = once daily; TNF = tumour necrosis factor; UPA = upadacitinib; vs. = versus.

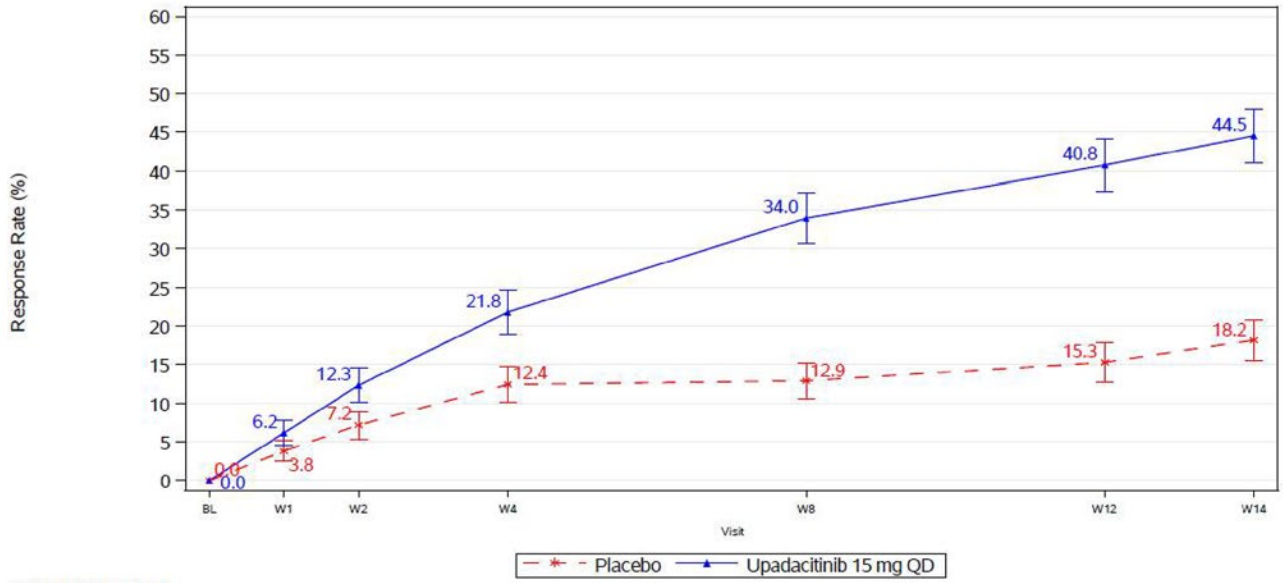
Note: NRI-MI is nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19.

[a]n is calculated by N and MI-aggregated response rate (%).

[b]Treatment difference, associated CI, and P values for tests of differences between the UPA and PBO groups were constructed based on the MI inference. Risk difference and standard error were estimated using a Cochran-Mantel-Haenszel test and screening high-sensitivity C-reactive protein status as a stratification factor within each imputed "complete" dataset, after which Rubin's rule was used to combine the results from 30 imputed "complete" datasets to produce an aggregated treatment difference, associated CI, and P value.

Sources: Study 944, week 14 Clinical Study Report[14,36] and Study 098 week 14 Clinical Study Report.[15,37]

Figure 4: ASAS40 Response at Week 14 — Study 944 (NRI-MI, Full Analysis Set)



Note: NRI-MI is non-responder imputation (NRI) incorporating multiple imputation (MI) to handle missing data due to COVID-19.
The error bar is +/- standard error.

ASAS40 = Assessment of SpondyloArthritis international Society 40% improvement; MI = multiple imputation; NRI = nonresponder imputation; QD = once daily.
Note: Nominal P ≤ 0.05 at weeks 4 to 12 and P < 0.0001 at week 14.
Sources: Study 944, week 14 Clinical Study Report.[14]

Figure 5: ASAS40 Response at Week 14 — Study 098 (NRI, Full Analysis Set) — Redacted

ASAS40 = Assessment of SpondyloArthritis international Society 40% improvement; NRI = nonresponder imputation.
Notes: Nominal P < 0.001 at each time point.
This figure has been removed at the request of the sponsor.
Source: Study 098 week 14 Clinical Study Report.[15]

ASAS40 Subgroup Analysis

In Study 944, the subgroup analysis showed that the proportions of patients achieving ASAS40 at week 14 [redacted] in the upadacitinib and placebo groups, respectively, among patients with experienced with 1 TNFi; and [redacted] in the upadacitinib and placebo groups, respectively, among patients with experienced with 1 IL-17i (refer to Table 15).

No subgroup analysis of the interest in this review was reported in Study 098.

Sensitivity Analysis

In both study 944 and Study 098, sensitivity analysis (i.e., AO, AO-NRI, and AO-MI) for ASAS40 [redacted] (Table 15).

Extension Period at Week 52

In Study 944, the proportions of patients who achieved ASAS40 were [redacted] to the upadacitinib group, respectively. In Study 098, the proportions of patients who achieved ASAS40 were 69.9% in the upadacitinib group and 69.1% in the placebo-to- upadacitinib group (refer to Table 15 and Table 30).

Extension Period at Week 104

In Study 098, the proportions of patients who achieved ASAS40 were 65.6% in upadacitinib group and 63.8% in the placebo-to- upadacitinib group (refer to Table 15 and Table 31).

Secondary Outcomes

ASAS20 at Week 14

ASAS20 response was reported as a main secondary outcome (i.e., it was multiplicity-controlled) in both Study 944 and Study 098. The results of ASAS40 at week 14 are presented in Table 16, Figure 6, and Figure 7.

In the FAS analysis of Study 944, the proportions of patients who achieved ASAS20 at week 14 were 65.4% and 38.3% in the upadacitinib (15 mg, oral, once daily) and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was 27.1% (95% CI, 17.9% to 36.3; P < 0.0001).

In the FAS analysis of Study 098, the proportions of patients who achieved ASAS20 at week 14 were 65.4% and 44.4% in the upadacitinib (15 mg, oral, once daily) and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was 24.1% (95% CI, 10.2% to 38.0%; P < 0.001).

The multiplicity-adjusted statistical significance results of the main secondary outcomes at week 14 are presented in Table 29 and Table 30 in Appendix 3 for Study 944 and Study 098, respectively.

ASAS 20 — Extension Period at Week 52

In Study 944, the proportion patients who achieved ASAS20 [redacted]

In Study 098, the proportions of patients who achieved ASAS20 were 76.3% in the upadacitinib group and 84.0% in the placebo-to-upadacitinib group (refer to Table 31).

Extension Period at Week 104

In Study 098, the proportions of patients who achieved ASAS20 were 67.1% in the upadacitinib group and 69.1% in the placebo-to-upadacitinib group (refer to Table 31).

Table 16: Primary and Multiplicity-Controlled Secondary Outcomes at Week 14 (FAS)

Outcomes	Study 944		Study 098	
	UPA 15 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
Primary outcomes				
ASAS40 response, n (%)	94 (44.5)	38 (18.2)	[redacted] (51.6)	[redacted] (25.5)
Between-groups difference (UPA-PBO), % (95% CI)	26.4 (17.9 to 34.9)		26.1 (12.6 to 39.5)	
P value	< 0.0001		< 0.001	
Secondary outcomes				
Clinical response				
ASAS20 response, n (%)	[redacted] (65.4)	[redacted] (38.3)	[redacted] (64.5)	[redacted] (40.4)
Between-groups difference (UPA-PBO), % (95% CI)	27.1 (17.9 to 36.3)		24.1 (10.2 to 38.0)	
P value	< 0.0001		0.001	
ASAS partial remission, response, n (%)	[redacted] (17.5)	[redacted] (4.3)	[redacted] (19.4)	[redacted] (1.1)
Between-groups difference (UPA-PBO), % (95% CI)	13.2 (7.4 to 19.0)		18.3 (10.0 to 26.6)	
P value	< 0.0001		< 0.001 (not significant)	
ASAS5/6, response, n (%)	NR	NR	[redacted]	[redacted]
Between-groups difference (UPA-PBO), % (95% CI)	NR		[redacted]	
P value	NR		[redacted]	
Measures of AS symptoms				
Total back pain				
Week 14, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean	7.45	7.41	[redacted]	[redacted]
Week 14, mean	[redacted]	[redacted]	[redacted]	[redacted]
Total back pain CFB, mean (95% CI)	−3.00 (−3.30 to −2.70)	−1.47 (−1.77 to −1.16)	[redacted]	[redacted]
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	−1.53 (−1.96 to −1.11)		[redacted]	
P value	< 0.0001		[redacted]	
Nocturnal back pain				
Week 14, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean	7.10	7.20	[redacted]	[redacted]

Outcomes	Study 944		Study 098	
	UPA 15 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
Week 14, mean				
Nocturnal back pain CFB, mean (95% CI)	−3.21 (−3.52 to −2.89)	−1.52 (−1.84 to −1.20)		
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	−1.69 (−2.14 to −1.24)			
P value	< 0.0001			
FACIT-F (AO)				
Week 14, n (%)				
Baseline, mean				
Week 14, mean				
FACIT-F (CFB), mean (95% CI)				
Between-groups difference of CFB (UPA-PBO), mean (95% CI)				
P value				
Measures of function and disability (BASFI)				
Week 14, n (%)				
Baseline, mean	6.25	6.20		
Week 14, mean				
BASFI CFB, mean (95% CI)	−2.26 (−2.53 to −2.00)	−1.09 (−1.35 to −0.83)	−2.29 (−2.73 to −1.85)	−1.30 (−1.74 to −0.86)
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	−1.17 (−1.55 to −0.80)		−1.00 (−1.60 to −0.39)	
P value	< 0.0001		0.001 (not significant)	
Health-related quality of life				
ASQoL				
Week 14, n (%)				
Baseline, mean	11.63	11.48		
Week 14, mean				
ASQoL, CFB (95% CI)	−5.10 (−5.69 to −4.52)	−2.03 (−2.62 to −1.44)	−4.20 (−5.12 to −3.29)	−2.67 (−3.58 to −1.75)
Between-groups difference of CFB (upadacitinib vs. placebo), mean (95% CI)	−3.07 (−3.90 to −2.24)		−1.54 (−2.78 to −0.30)	
P value	< 0.0001		0.016	

Outcomes	Study 944		Study 098	
	UPA 15 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
ASAS Health Index				
Week 14, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean	[redacted]	[redacted]	[redacted]	[redacted]
Week 14, mean	[redacted]	[redacted]	[redacted]	[redacted]
ASAS Health Index (CFB), mean (95% CI)	−2.93 [redacted]	−1.07 [redacted]	−2.75 (−3.48 to −2.02)	−1.38 (−2.11 to −0.65)
Between-groups difference of CFB (UPA-PBO), mean, (95% CI)	−1.85 (−2.47 to −1.24)		−1.37 (−2.37 to −0.37)	
P value	< 0.0001		0.007 (not significant)	
EQ-5D				
5-Level EQ-5D (AO)				
Week 14, n (%)	[redacted]	[redacted]	NR	NR
Baseline, mean	[redacted]	[redacted]	NR	NR
Week 14, mean	[redacted]	[redacted]	NR	NR
5-Level EQ-5D CFB, mean (95% CI)	[redacted]	[redacted]	NR	NR
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	[redacted]		NR	
P value	[redacted]		NR	
EQ-5D Visual Analogue Scale (AO)				
Week 14, n (%)	[redacted]	[redacted]	NR	NR
Baseline, mean	[redacted]	[redacted]	NR	NR
Week 14, mean	[redacted]	[redacted]	NR	NR
EQ-5D visual analogue scale CFB, mean (95% CI)	[redacted]	[redacted]	NR	NR
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	[redacted]		NR	
P value	[redacted]		NR	
SF-36				
SF-36 mental component summary (AO)				
Week 14, n (%)	[redacted]	[redacted]	NR	NR
Baseline, mean	[redacted]	[redacted]	NR	NR
Week 14, mean	[redacted]	[redacted]	NR	NR

Outcomes	Study 944		Study 098	
	UPA 15 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
Mental component summary CFB, mean (95% CI)	[redacted]	[redacted]	NR	NR
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	[redacted]		NR	
P value	[redacted]		NR	
SF-36 physical component summary (AO)				
Week 14, n (%)	[redacted]	[redacted]	NR	NR
Baseline, mean	[redacted]	[redacted]	NR	NR
Week 14, mean	[redacted]	[redacted]	NR	NR
SF-36 physical component summary CFB, mean (95% CI)	[redacted]	[redacted]	NR	NR
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	[redacted]		NR	
P value	[redacted]		NR	
Work productivity				
WPAI Overall Work Impairment (AO for Study 944)				
Week 14, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean	[redacted]	[redacted]	[redacted]	[redacted]
Week 14, mean	[redacted]	[redacted]	[redacted]	[redacted]
WPAI Overall Work Impairment CFB at week 14 (CFB), mean (95% CI) (not ranked for Study 944)	[redacted]	[redacted]	−18.11 (−24.73 to −11.50)	−12.60 (−19.04 to −6.15)
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	[redacted]		−5.52 (−13.82 to 2.78)	
P value	[redacted]		0.190 (not significant)	
Disease activity				
BASDAI50, response, n (%)	[redacted] (43.1)	[redacted] (16.7)	[redacted] (45.2)	[redacted] (23.4)
Between-groups difference (UPA-PBO), % (95% CI)	26.4 (18.0 to 34.8)		21.8 (8.5 to 35.0)	
P value	< 0.0001		0.002	
BASDAI CFB				
[redacted], n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean	[redacted]	[redacted]	[redacted]	[redacted]
Week 14, mean	[redacted]	[redacted]	[redacted]	[redacted]

Outcomes	Study 944		Study 098	
	UPA 15 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
BASDI CFB, mean (95% CI)				
Between-groups difference of CFB (UPA-PBO), mean (95% CI)				
P value				
ASDAS (CRP) CFB				
Week 14, n (%)				
Baseline, mean	3.86	3.87		
Week 14, mean				
ASDAS (CRP) CFB (95% CI)	−1.52 (−1.64 to −1.39)	−0.49 (−0.62 to −0.37)	−1.45 (−1.62 to −1.28)	−0.54 (−0.71 to −0.37)
Between-groups difference of CFB UPA-PBO), mean (95% CI)	−1.02 (−1.20 to −0.85)		−0.91 (−1.14 to −0.68)	
P value	< 0.0001		< 0.001	
ASDAS inactive disease response, n (%)	(12.8)	(1.9)		
Between-groups difference (UPA-PBO), % (95% CI)	10.9 (6.0 to 15.8)			
P value	< 0.0001			
ASDAS low disease activity response, n (%)	(44.1)	(10.1)	46 (49.5)	10 (10.6)
Between-groups difference (UPA-PBO), % (95% CI)	34.0 (26.2 to 41.8)		38.8 (26.9 to 50.7)	
P value	< 0.0001		nominal P < 0.001	
ASDAS clinical important response %				
Between-groups difference (UPA-PBO), % (95% CI)				
P value				
Radiographic changes				
SPARCC MRI Spine				
Week 14, n (%)				
Baseline, mean				
Week 14, mean				
SPARCC MRI Spine (CFB) (95% CI)	−3.95 (−5.06 to −2.83)	−0.04 (−1.14 to 1.06)	−6.93 (−8.58 to −5.28)	−0.22 (−2.01 to 1.57)
Between-groups difference of CFB (UPA-PBO), % (95% CI)	−3.90 (−5.47 to −2.33)		−6.71 (−9.01 to −4.41)	

Outcomes	Study 944		Study 098	
	UPA 15 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
P value	< 0.0001		< 0.001	
SPARCC SIJ (AO)				
Week 14, n (%)				
Baseline, mean				
Week 14, mean				
SPARCC SIJ (CFB), mean (95% CI)			−3.91 (−5.05 to −2.77)	−0.22 (−1.47, 1.04)
Between-groups difference of CFB (UPA-PBO), mean (95% CI)			−3.69 (−5.31 to −2.08)	
P value			< 0.001	
Patient's Global Assessment of Disease Activity (AO)				
Week 14, n (%)				
Baseline, mean	7.36	7.26		
Week 14, mean				
PtGA of disease activity CFB, mean (95% CI)				
Between-groups difference of CFB (UPA-PBO), mean (95% CI)				
P value				
MASES				
Week 14, n (%)				
Baseline, mean				
Week 14, mean				
MASES CFB (95% CI)	−2.6	−1.1	−2.25 (−2.86 to −1.64)	−1.41 (−2.02 to −0.80)
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	−1.5 (−2.0 to −0.9)		−0.84 (−1.68 to 0.00)	
P value	< 0.0001		0.049 (not significant)	
BASMI				
Week 14, n (%)				
Baseline, mean				
Week 14, mean				
BASMI (CFB) (95% CI)	−0.48	−0.16	−0.37 (−0.52 to −0.21)	−0.14 (−0.29 to 0.01)

Outcomes	Study 944		Study 098	
	UPA 15 mg q.d. (N = 211)	PBO (N = 209)	UPA 15 mg q.d. (N = 93)	PBO (N = 94)
Between-groups difference of CFB (UPA-PBO), mean (95% CI)	−0.32 (−0.46 to −0.18)		−0.22 (−0.43 to −0.02)	
P value	< 0.0001		0.030 (not significant)	

AO = as observed; AS = ankylosing spondylitis; ASAS = Assessment of SpondyloArthritis international Society; ASAS5/6 = Assessment in SpondyloArthritis international Society 20% improvement in 5 of 6 domains; ASAS20 = Assessment of SpondyloArthritis international Society 20% improvement; ASAS40 = Assessment of SpondyloArthritis international Society 40% improvement; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = ankylosing spondylitis quality of life; BASDAI50 = Bath Ankylosing Spondylitis Disease Activity Index 50% improvement; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; CFB = change from baseline; CI = confidence interval; CRP = C-reactive protein; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; FAS = full analysis set;; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score NR = not reported; PBO = placebo; q.d. = once daily; SF-36 = Short Form (36) Health Survey; SIJ = sacroiliac joint; SPARCC = Spondyloarthritis Research Consortium of Canada; UPA = upadacitinib; vs. = versus; WPAI = Work Productivity Activity Impairment.

Note: For Study 098, the ASAS Health Index between-groups difference was not statistically significant because the chain was broken before the ASAS Health Index, and therefore it was not evaluated. Data are percent or mean change from baseline unless noted otherwise. ASDAS low disease activity was defined as ASDAS (CRP) of less than 2.1 and ASDAS inactive disease as ASDAS (CRP) of less than 1.3. Standard deviations of the mean for baseline and week 14 were not available from the sponsor.

[a]For categorical end points, a Cochran-Mantel-Haenszel test was used with nonresponder imputation incorporating multiple imputations to handle missing data due to COVID-19. For continuous end points, a mixed model for repeated measures was used, and N is number of unique patients contributing to model estimates.

[b]P value is unadjusted.

[c]Results are obtained via the sequential multiple testing procedure controlling the overall type I error rate of all primary and multiplicity-controlled secondary end points at the significance level of 0.05 (2-sided).

Sources: Study 944, week 14 Clinical Study Report,[14] Study 098 week 14 Clinical Study Report,[15] and sponsor's submission.[16]

Figure 6: ASAS20 Response at Week 14 — Study 944 (NRI-MI, Full Analysis Set) — Redacted

ASAS20 = Assessment of SpondyloArthritis international Society 20% improvement; MI = multiple imputation; NRI = nonresponder imputation.

Notes: Nominal P ≤ 0.05 at weeks 1 through 12 and P < 0.0001 at week 14.

This figure has been removed at the request of the sponsor.

Source: Study 944, week 14 Clinical Study Report.[14]

Figure 7: ASAS20 Response at Week 14 — Study 098 (NRI, Full Analysis set) — Redacted

ASAS20 = Assessment of SpondyloArthritis international Society 20% improvement; NRI = nonresponder imputation.

Note: This figure has been removed at the request of the sponsor.

Source: Study 098 week 14 Clinical Study Report.[15]

ASAS PR Responses at Week 14

ASAS PR response was reported as a main secondary outcome (i.e., it was multiplicity-controlled) in both Study 944 and Study 098. The results of ASAS PR at week 14 are presented in Table 16.

In the FAS analysis of Study 944, the proportions of patients who achieved ASAS PR at week 14 were 17.5% and 4.3% in the 15 upadacitinib mg, oral, once-daily and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was 13.2% (95% CI, 7.4% to 19.0%; P < 0.0001).

In the FAS analysis of Study 098, the proportions of patients who achieved ASAS PR at week 14 were 19.4% and 1.1% in the upadacitinib 15 mg, oral, once-daily and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was 18.3% (95% CI, 10.0% to 26.6%, P < 0.001).

ASAS PR — Extension Period at Week 52

[redacted]

In Study 098, the proportions of patients achieving ASAS PR were 50.6% in the upadacitinib group and 45.2% in the placebo-to-upadacitinib group (refer to Table 30).

ASAS PR — Extension Period at Week 104

In Study 098, the proportions of patients who achieved ASAS PR were 51.4% in the upadacitinib group and 43.7% in the placebo-to-upadacitinib group (refer to Table 31).

ASAS5/6 at Week 14

ASAS5/6 response was not reported in Study 944.

In Study 098, ASAS5/6 was reported as an exploratory secondary outcome (i.e., it was not multiplicity-controlled). The results of ASAS5/6 at week 14 are presented in Table 16. [redacted]

ASAS5/6 — Extension Period at Week 52

In Study 944, the proportions of patients who achieved ASAS5/6 were not reported.

In Study 098, the proportions of patients who achieved ASAS5/[redacted] groups, respectively (refer to Table 30).

ASAS5/6 — Extension Period at Week 104

In Study 098, the proportions of patients who achieved ASAS5/6 were [redacted] to the upadacitinib group, respectively (refer to Table 31).

Measures of Ankylosing Spondylitis Symptoms

The results of the AS symptom measures at week 14 (i.e., total back pain, nocturnal back pan, and fatigue) are presented in Table 16.

Total Back Pain at Week 14

Total back pain is 1 of the 6 ASAS criteria components. It was assessed as a main secondary outcome in Study 944 and an exploratory outcome in Study 098.

In Study 944, at week 14, the means of changes from baseline for total back pain were −3.00 (95% CI, −3.30 to −2.70) and −1.47 (95% CI, −1.77 to −1.16) in the upadacitinib (15 mg, oral, once daily) and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.53 (95% CI, −1.96 to −1.11; P < 0.0001).

In Study 098, at week 14, the means of changes from baseline for total back pain were [redacted] and [redacted] in the upadacitinib (15 mg, oral, once daily) and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was [redacted]

Total Back Pain Change From Baseline — Extension Period at Week 52

[redacted]

In Study 098, the total back pain CFB means were −4.48 [redacted] in the upadacitinib group and −4.52 [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

Total Back Pain Change From Baseline — Extension Period at Week 104

In Study 098, the total back pain CFB means were −4.40 [redacted] in the upadacitinib group and −4.30 [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

Nocturnal Back Pain at Week 14

Nocturnal back pain was assessed as a main secondary outcome in Study 944 and an exploratory outcome in Study 098.

In Study 944, at week 14, the means of changes from baseline for nocturnal back pain were −3.21 (95% CI, −3.52 to −2.89) and −1.52 (95% CI, −1.84 to −1.20) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.69 (95% CI, −2.14 to −1.24; P < 0.0001).

In Study 098, at week 14, the means of changes from baseline for nocturnal back pain were [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was [redacted]

Nocturnal Back Pain Change From Baseline — Extension Period at Week 52

[redacted]

In Study 098, the nocturnal back pain change from baseline means (95% CI) were −4.47 [redacted] in the upadacitinib group and −4.64 [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

Nocturnal Back Pain Change From Baseline — Extension Period at Week 104

In Study 098, the total nocturnal Back Pain change from baseline means (95% CI) were −4.32 [redacted] in the upadacitinib group and −4.59 [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

Fatigue at Week 14

Fatigue was assessed with FACIT-F as an exploratory outcome in both Study 944 and Study 098.

In Study 944, at week 14, the means of changes from baseline for FACIT-F were [redacted]) in the upadacitinib 15 mg, oral, once-daily and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was [redacted]

In Study 098, at week 14, the means of changes from baseline for FACIT-F were [redacted] and [redacted] in the upadacitinib 15 mg, oral, once-daily and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) [redacted].

FACIT-F Change From Baseline — Extension Period at Week 52

[redacted]

In Study 098, the FACIT-F change from baseline means (95% CI) were [redacted] in the upadacitinib group and [redacted] in the placebo-to-UPA group (refer to Table 31).

FACIT-F Change From Baseline — Extension Period Week 104

In Study 098, the FACIT-F change from baseline means (95% CI) were [redacted] in the upadacitinib group and [redacted] in the placebo-to-UPA group (refer to Table 31).

Function and Disability (Bath Ankylosing Spondylitis Functional Index) at Week 14

The BASFI is 1 of the 6 ASAS criteria components. It was assessed as a main secondary outcome in Study 944 and an exploratory outcome in Study 098. The results of BASFI are presented in Table 16.

In Study 944, at week 14, the mean changes from baseline for BASFI were −2.26 (95% CI, −2.53 to −2.00) and −1.09 (95% CI, −1.35 to −0.83) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.17 (95% CI, −1.55 to −0.80; P < 0.0001).

In Study 098, at week 14, the means of changes from baseline for BASFI were −2.29 (95% CI, −2.73 to −1.85) and −1.30 (95% CI, −1.74 to −0.86) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.00 (95% CI, −1.60 to 0.39; P < 0.001) (Table 16).

BASFI Change From Baseline — Extension Period at Week 52

[redacted]

In Study 098, the BASFI CFB means were −3.49 [redacted] in the upadacitinib group and −3.40 [redacted]) in the placebo-to-upadacitinib group (refer to Table 31).

BASFI Change From Baseline — Extension Period at Week 104

In Study 098, the BASFI CFB means were the upadacitinib 3.50 [redacted] in the upadacitinib group and −3.26 [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

Health-Related Quality of Life

Ankylosing Spondylitis Quality of Life

The ASQoL was assessed as a main secondary outcome in both Study 944 and Study 098. The results of the ASQoL are presented in Table 16.

ASQoL at Week 14

In Study 944, at week 14, the means of changes from baseline for ASQoL were −5.10 (95% CI, −5.69 to −4.52) and −2.03 (95% CI, −2.62 to −1.44) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −3.07 (95% CI, −3.90 to −2.24; P < 0.0001).

In Study 098, at week 14, the means of changes from baseline for ASQoL were −4.20 (95% CI, −5.12 to −3.29) and −2.67 (95% CI, −3.58 to −1.75) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.54 (95% CI, −2.78 to 0.30. P < 0.016) (Table 16).

ASQoL Change From Baseline — Extension Period at Week 52

[redacted]

In Study 098, the ASQoL CFB means were −6.15 (95% CI, −7.06 to −5.25) in the upadacitinib group and −5.51 (95% CI, −6.40 to −4.62) in the placebo-to-upadacitinib group (refer to Table 31).

ASQoL Change From Baseline — Extension Period at Week 104

In Study 098, the ASQoL CFB means were −6.68 (95% CI, −7.47 to −5.89) in the upadacitinib group and −5.88 (95% CI, −6.67 to −5.09) in the placebo-to-upadacitinib group (refer to Table 31).

Assessment of SpondyloArthritis international Society Health Index

The ASAS HI was assessed as a main secondary outcome in both Study 944 and Study 098. The results of the ASAS HI are presented in Table 16.

ASAS HI at Week 14

In Study 944, at week 14, the means of changes from baseline for ASAS HI were −2.93 [redacted] and −1.07 (95% CI, −1.51 to −0.64) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −3.07 (95% CI, −2.47 to −1.24; P < 0.0001).

In Study 098, at week 14, the means of changes from baseline for ASAS HI were −2.75 (95% CI, −3.48 to −2.02) and −1.38 (95% CI, −2.11 to −0.65) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.37 (95% CI, −2.37 to 0.37; P < 0.007). The result was designated as not significant because the chain was broken before the ASAS HI, and therefore it was not evaluated (Table 16).

ASAS HI Change From Baseline — Extension Period at Week 52

[redacted]

In Study 098, the ASAS HI CFB means were [redacted] in the upadacitinib group and [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

ASAS HI Change From Baseline — Extension Period at Week 104

In Study 098, the ASAS HI CFB means were −4.48 (95% CI, −5.17 to −3.80) in the upadacitinib group and −4.04 (95% CI, −4.72 to −3.36) in the placebo-to-upadacitinib group (refer to Table 31).

EQ-5D at Week 14

The EQ-5D-5L was assessed as an exploratory outcome in Study 944 only. It was not assessed in Study 098 (Table 16).

In Study 944, at week 14, the means of changes from baseline for EQ-5D-5L were [redacted] and 0.07 [redacted] in the upadacitinib 15 mg, oral, once-daily and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) [redacted].

The EQ VAS was assessed as an exploratory outcome in Study 944 only. It was not assessed in Study 098 (Table 16).

In Study 944, at week 14, the means of changes from baseline for the EQ VAS were [redacted] in the and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was [redacted].

EQ-5D — Extension Period at Week 52

[redacted]

EQ-5D — Extension Period at Week 104

In Study 098, the EQ-5D-5L change from baseline was not reported.

Short Form (36) Health Survey

The SF-36 was assessed as an exploratory outcome in Study 944 only. It was not assessed in Study 098 (Table 16).

SF-36 at Week 14

Mental Component Summary

Study 944, at week 14, the means of changes from baseline for SF-36 MCS were [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was [redacted].

Physical Component Summary

Study 944, at week 14, the means of changes from baseline for the SF-36 PCS were [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was [redacted].

SF-36 Mental Component Summary Change From Baseline — Extension Period at Week 52

[redacted].

In Study 098, the SF-36 MCS change from baseline was not reported.

SF-36 Mental Component Summary Change From Baseline — Extension Period at Week 104

In Study 098, the SF-36 MCS change from baseline was not reported.

SF-36 Physical Component Summary Change From Baseline — Extension Period at Week 52

[redacted]

In Study 098, the SF-36 PCS change from baseline was not reported.

SF-36 Physical Component Summary Change From Baseline — Extension Period at Week 104

In Study 098, the SF-36 PCS change from baseline was not reported.

Work Productivity

Work productivity as measured by the WPAI-SpA was assessed as an exploratory outcome in Study 944, and as a main secondary outcome in Study 098 (Table 16).

WPAI Overall Work Impairment at Week 14

In Study 944, at week 14, the means of changes from baseline for WPAI Overall Work Impairment were [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) [redacted]

In Study 098, at week 14, the means of changes from baseline for WPAI Overall Work Impairment were −18.11 (95% CI, −24.73 to −11.50) and −12.60 (95% CI, −19.04 to −6.15) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −5.52 (95% CI, −13.82 to 2.78; P = 0.19).

WPAI Overall Work Impairment Change From Baseline — Extension Period at Week 52

[redacted]

In Study 098, the WPAI Overall Work Impairment change from baseline means were [redacted]) in the upadacitinib group and [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

WPAI Overall Work Impairment Change From Baseline — Extension Period at Week 104

In Study 098, the WPAI Overall Work Impairment change from baseline means were [redacted] in the upadacitinib group and [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

Disease Activity (Ankylosing Spondylitis Disease Activity Score)

ASDAS (C-Reactive Protein) at Week 14

The ASDAS (CRP) was assessed as a main outcome in both Study 944 and Study 098 (Table 16).

In Study 944, at week 14, the means of changes from baseline for ASDAS (CRP) were −1.52 (95% CI, −1.64 to −1.39) and −0.49 (95% CI, −0.62 to −0.37) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.02 (95% CI, −1.20 to −0.85; P < 0.0001).

In Study 098, at week 14, the means of changes from baseline for ASDAS (CRP) were −1.45 (95% CI, −1.62 to −1.28) and −0.54 (95% CI, −0.71 to −0.37) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −0.91 (95% CI, −1.14 to −0.68; P < 0.001).

ASDAS (CRP) Change From Baseline — Extension Period at Week 52

[redacted]

In Study 098, the ASDAS (CRP) change from baseline means were −1.97 (95% CI, −2.12 to −1.82) in the upadacitinib group and −2.00 (95% CI, −2.14 to −1.86) in the placebo-to-upadacitinib group (refer to Table 31).

ASDAS (CRP) Change From Baseline — Extension Period at Week 104

In Study 098, the ASDAS (CRP) change from baseline means were −1.98 (95% CI, −2.15 to −1.82) in the upadacitinib group and −1.93 (95% CI, −2.09 to −1.77) in the placebo-to-upadacitinib group (refer to Table 31).

Ankylosing Spondylitis Disease Activity Score (Inactive Disease)

The ASDAS ID was assessed as a main outcome in Study 944 and an exploratory outcome in Study 098 (Table 16).

ASDAS Score (Inactive Disease) at Week 14

In Study 944, in the FAS analysis, the proportions of patients who achieved ASDAS ID at week 14 were 12.8% and 1.9% in the upadacitinib 15 mg, oral, once-daily and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was 10.9% (95% CI, 6.0 to 15.8; P < 0.0001).

In the FAS of Study 098, the proportions of patients who achieved ASDAS ID at week 14 were 16.1% and 0.00% in the upadacitinib 15 mg, oral, once-daily and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was not reported (P < 0.001) (Table 16).

ASDAS Score (Inactive Disease) — Extension Period at Week 52

[redacted]

In Study 098, the proportions of patients who achieved ASDAS ID were [redacted] in the upadacitinib group and [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

ASDAS Score (Inactive Disease) — Extension Period at Week 104

In Study 098, the proportions of patients who achieved ASDAS ID were [redacted] in the upadacitinib group and [redacted] in the placebo-to-upadacitinib group respectively (refer to Table 31).

Ankylosing Spondylitis Disease Activity Score (Low Disease Activity)

The ASDAS LDA was assessed as a main outcome in study 944 and an exploratory outcome in Study 098 (Table 16).

ASDAS (Low Disease Activity) at Week 14

In the FAS of Study 944, the proportions of patients who achieved ASDAS LDA at week 14 were 44.1% and 10.1% in the upadacitinib and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was 34.0% (95% CI, 26.2% to 41.8%; P < 0.0001).

In the FAS of Study 098, the proportions of patients who achieved ASDAS LDA at week 14 were 49.5% and 10.6% in the upadacitinib and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was not reported (P < 0.001). (Table 16).

ASDAS (Low Disease Activity) — Extension Period at Week 52

[redacted]

In Study 098, the proportions of patients who achieved ASDAS LDA [redacted] respectively (refer to Table 31).

ASDAS (Low Disease Activity) — Extension Period at Week 104

In Study 098, the proportions of patients who achieved ASDAS LDA were [redacted] (refer to Table 31).

ASDAS Clinically Important Improvement

ASDAS clinically important improvement was assessed as an exploratory outcome in both Study 944 and Study 098 (Table 16).

ASDAS Clinically Important Improvement at Week 14

In the FAS of Study 944, the proportions of patients who achieved ASDAS clinically important improvement at week 14 were [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) [redacted].

In the FAS of Study 098, the proportions of patients who achieved ASDAS clinically important improvement at week 14 were reported in [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) [redacted] (Table 16).

ASDAS Clinically Important Improvement — Extension Period at Week 52

[redacted]

In Study 098, the proportions of patients who achieved ASDAS clinically important improvement were [redacted] groups, respectively (refer to Table 31).

ASDAS Clinically Important Improvement — Extension Period at Week 104

In Study 098, the proportions of patients who achieved ASDAS clinically important improvement were [redacted] (refer to Table 31).

Bath Ankylosing Spondylitis Disease Activity Index 50% Improvement at Week 14

BASDAI50 was assessed as a main outcome in both study 944 and Study 098 (Table 16).

In the FAS of Study 944, the proportions of patients who achieved BASDAI50 at week 14 were 43.1% and 16.7% in the upadacitinib and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was 26.4% (95% CI, 18.0% to 34.8%; P < 0.0001) (Table 16).

In the FAS of Study 098, the proportions of patients who achieved BASDAI50 at week 14 were 45.2% and 23.4% in the upadacitinib and placebo groups, respectively. The mean between-groups difference (upadacitinib versus placebo) was 21.8% (95% CI, 8.5% to 35.0%; P = 0.002) (Table 16).

BASDAI50 — Extension Period at Week 52

[redacted]

In Study 098, the proportions of patients who achieved BASDAI50 were 77.8% in the upadacitinib group and 76.2% in the placebo-to-upadacitinib group (refer to Table 31).

BASDAI50 — Extension Period at Week 104

In Study 098, the proportions of patients who achieved BASDAI50 were 88.7% in the upadacitinib group and 84.5% in the placebo-to-upadacitinib group (refer to Table 31).

BASDAI Change From Baseline at Week 14

The BASDAI change from baseline was assessed as an exploratory outcome in both Study 944 and Study 098. The results of BASDAI change from baseline are presented in Table 16.

In Study 944, at week 14, the means of changes from baseline for BASDAI were [redacted] and [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was [redacted].

In Study 098, at week 14, the means of changes from baseline for BASDAI were [redacted] and [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was [redacted]

BASDAI Change From Baseline — Extension Period at Week 52

[redacted]

In Study 098, the BASDAI change from baseline means were [redacted] in the upadacitinib group [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

BASDAI Change From Baseline — Extension Period at Week 104

In Study 098, the BASDAI change from baseline means were [redacted] in the upadacitinib group [redacted] placebo-to-upadacitinib group (refer to Table 31).

MRI SPARCC Index (Spine) at Week 14

The MRI SPARCC Index (Spine) was assessed as a main outcome in both Study 944 and Study 098. The results of the MRI SPARCC Index (Spine) change from baseline are presented in Table 16.

In Study 944, at week 14, the means of changes from baseline for the MRI SPARCC Index (Spine) were −3.95 (95% CI, −5.06 to −2.83) and −0.04 (95% CI, −1.14 to 1.06) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −3.90 (95% CI, −5.47 to −2.33; P < 0.0001).

In Study 098, at week 14, the means of changes from baseline for MRI SPARCC Index (Spine) were − 6.9 3 (95% CI, −8.58 to −5.28) and −0.22 (95% CI, −2.01 to 1.57) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −6.71 (95% CI, −9.01 to −4.41; P < 0.001).

MRI SPARCC Index (Spine) Change From Baseline — Extension Period at Week 52

[redacted]

MRI SPARCC Index (Spine) Change From Baseline — Extension Period at Week 104

In Study 098, the MRI SPARCC Index (Spine) change from baseline means were [redacted] in the upadacitinib group and [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

MRI SPARCC Index (Sacroiliac Joint) at Week 14

The MRI SPARCC Index (SIJ) was assessed as an exploratory outcome in both Study 944 and Study 098. The results of the MRI SPARCC Index (SIJ) change from baseline are presented in Table 16.

In Study 944, at week 14, the means of changes from baseline for MRI SPARCC Index (SIJ) were [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was [redacted]

In Study 098, at week 14, the means of changes from baseline for MRI SPARCC Index (SIJ) were −3.91 (95% CI, −5.05 to −2.77) and −0.22 (95% CI, −1.47 to 1.04) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −3.69 (95% CI, −5.31 to −2.08. P < 0.001).

MRI SPARCC Index (Sacroiliac Joints) Change From Baseline — Extension Period at Week 52

[redacted]

MRI SPARCC Index (Sacroiliac Joints) Change From Baseline — Extension Period at Week 104

In Study 098, the MRI SPARCC Index (SIJ) change from baseline means were [redacted] in the upadacitinib group and [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

Patient's Global Assessment of Disease Activity at Week 14

The PtGA was assessed as an exploratory outcome in both Study 944 and Study 098. The results of PtGA change from baseline are presented in Table 16.

In Study 944, at week 14, the means of changes from baseline for PtGA were [redacted]) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was [redacted].

In Study 098, at week 14, the means of changes from baseline for PtGA were [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was [redacted]

PtGA Change From Baseline — Extension Period at Week 52

[redacted]

In Study 098, the PtGA change from baseline means were [redacted] in the upadacitinib group and [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

PtGA Change From Baseline — Extension Period at Week 104

In Study 098, the PtGA change from baseline means were −4.37 [redacted] in the upadacitinib group and −4.24 [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

Maastricht Ankylosing Spondylitis Enthesitis Score at Week 14

The MASES was assessed as a main outcome in both Study 944 and Study 098. The results of the MASES change from baseline are presented in Table 16.

In Study 944, at week 14, the means of changes from baseline for the MASES were −2.6 [redacted] and −1.1 [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −1.50 (95% CI, −2.00 to −0.90; P < 0.0001).

In Study 098, at week 14, the means of changes from baseline for MASES were −2.25 (95% CI, −2.86 to −1.64) and −1.41 (95% CI, −2.02 to −0.80) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −0.84 (95% CI, −1.68 to 0.00; P < 0.049 [considered not significant]) (Table 16).

MASES Change From Baseline — Extension Period at Week 52

[redacted]

In Study 098, the MASES change from baseline means were [redacted] in the upadacitinib group and [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

MASES Change From Baseline — Extension Period at Week 104

In Study 098, the MASES change from baseline means were −[redacted] in the upadacitinib group and [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

Bath Ankylosing Spondylitis Metrology Index at Week 14

The BASMI was assessed as a main outcome in both Study 944 and Study 098. The results of the BASMI change from baseline are presented in Table 16.

In Study 944, at week 14, the means of changes from baseline for BASMI were −0.48 [redacted] and −0.16 [redacted] in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −0.32 (95% CI, −0.46 to −0.18; P < 0.0001).

In Study 098, at week 14, the means of changes from baseline for BASMI were −0.37 (95% CI, −0.52 to −0.21) and −0.14 (95% CI, −0.29 to 0.01) in the upadacitinib and placebo groups, respectively. The mean between-groups difference in change from baseline (upadacitinib versus placebo) was −0.22 (95% CI, −0.43 to −0.02; P < 0.03 [considered not significant]) (Table 16).

BASMI Change From Baseline — Extension Period at Week 52

[redacted]

In Study 098, the BASMI CFB means were −0.76 [redacted] in the upadacitinib group and −0.65 [redacted] in the placebo-to-upadacitinib group (refer to Table 31).

BASMI Change From Baseline — Extension Period at Week 104

In Study 098, the BASMI CFB means were −0.79 (95% CI, −0.97 to −0.60) in the upadacitinib group and −0.64 (95% CI, −0.82 to −0.46) in the placebo-to-upadacitinib group (refer to Table 31).

Harms

Only those harms identified in the review protocol are reported here.

Week 14

Adverse Events

In Study 944, overall TEAEs were reported by 40.8% and 36.8% of patients in upadacitinib (15 mg once daily) and placebo groups, respectively. The most common TEAEs (> 3% in either of the treatment groups) were headache (3.3% versus 1.4%), arthralgia (0.0% and 3.8%) and COVID-19 (3.3% versus 1.9%) in patients in the upadacitinib and placebo groups, respectively (Table 17).

In Study 098, overall TEAEs were reported by 62.4% and 55.3% of patients in the upadacitinib and placebo groups, respectively. The most common TEAEs (> 3% in either of the treatment groups) were increased blood CPK (8.6% versus 2.1%), diarrhea (5.4% versus 5.3%), nasopharyngitis (5.4% versus 4.3%), headache (5.4% versus 2.1%), alanine transaminase increased (4.3% versus 2.1%), dyspepsia (3.2% versus 1.1%), nausea (1.1% versus 5.3%), back pain (1.1% versus 4.3%), rhinitis (1.1% versus 4.3%), and upper respiratory tract infection (1.1% versus 3.2%) in patients in the upadacitinib and placebo groups, respectively (Table 17).

Table 17: Overview of Treatment-Emergent Adverse Events at Week 14 (Safety Analysis Set)

Adverse events	Study 944		Study 098	
	Upadacitinib 15 mg q.d. (N = 211)	Placebo N = 209)	Upadacitinib 15 mg q.d. (N = 93)	Placebo (N = 94)
Any treatment-emergent AE, n (%)	86 (40.8)	77 (36.8)	58 (62.4)	52 (55.3)
Most common TEAEs (≥ 3% of patients with TEAE in any arm in either of the 2 studies), n (%)				
Increased blood creatine phosphokinase	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	5 (2.4)	3 (1.4)	5 (5.4)	4 (4.3)
Headache	7 (3.3)	3 (1.4)	5 (5.4)	2 (2.1)
Increased alanine transaminase	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	1 (1.1)	5 (5.3)
Back pain	[redacted]	[redacted]	1 (1.1)	4 (4.3)
Rhinitis			[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	1 (1.1)	3 (3.2)
COVID-19	[redacted]	[redacted]	NR	NR
SAE, n (%)	6 (2.8)	1 (0.5)	1 (1.1)	1 (1.1)
WDAE (from treatment), n (%)	0 (0.0)	3 (1.4)	[redacted]	[redacted]
Any AE leading to death, (%)	0 (0.0)	0 (0.0)	0	0
All deaths, n (%)	0 (0.0)	0 (0.0)	0	0
Notable harms, n (%)				
Infection	[redacted]	[redacted]	[redacted]	[redacted]
Serious infection	5 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Malignancy	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Malignancy other than NMSC	0 (0.0)	1 (0.5)	[redacted]	[redacted]
Hepatic disorder	6 (2.8)	2 (1.0)	5 (5.4)	2 (2.1)
Anemia	3 (1.4)	1 (0.5)	0 (0.0)	0 (0.0)
Neutropenia	6 (2.8)	2 (1.0)	1 (1.1)	0 (0.0)
Lymphopenia	1 (0.5)	2 (1.0)	0 (0.0)	0 (0.0)
Herpes zoster	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated major adverse cardiac event	0 (0.0)	0 (0.0)	[redacted]	[redacted]

Adverse events	Study 944		Study 098	
	Upadacitinib 15 mg q.d. (N = 211)	Placebo N = 209)	Upadacitinib 15 mg q.d. (N = 93)	Placebo (N = 94)
Adjudicated gastrointestinal perforation	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Dyslipidemia,	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity,	[redacted]	[redacted]	[redacted]	[redacted]
Active tuberculosis	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated venous thromboembolic events	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Opportunistic infection excluding tuberculosis and herpes zoster	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Acne	[redacted]	[redacted]	[redacted]	[redacted]
Elevated creatine phosphokinase	[redacted]	[redacted]	[redacted]	[redacted]
folliculitis	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; CI = confidence interval; NMSC = nonmelanoma skin cancer; NR = not reported; q.d. = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

Sources: Study 944, week 14 Clinical Study Report[14] and Study 098 week 14 Clinical Study Report.[15]

Serious Adverse Events

In Study 944, SAEs occurred in 2.8% of patients in the upadacitinib group and 0.5% of the placebo group. The most common (> 1.0%) SAE, COVID-19 pneumonia, occurred in [redacted] of patients in the upadacitinib group, and [redacted] of patients in placebo group (Table 17).

In Study 098, SAEs occurred in 1.1% of patients in both the upadacitinib and placebo groups. The most common (> 1.0%) SAE, cardiovascular disorder, occurred in 0% of patients receiving upadacitinib, and 1.1% of the patients in the placebo group (Table 17).

Withdrawal Due to Adverse Events

In Study 944, WDAEs occurred in 0 patients in the upadacitinib group and 3 patients (1.4%) in placebo group.

In Study 098, WDAEs occurred in 2 patients [redacted] in the upadacitinib group and 3 patients [redacted] in the placebo group (Table 17).

Mortality

No deaths were reported at week 14 in either Study 944 or Study 098 (Table 17).

Notable Harms

Notable harms identified in this review are serious infection (including herpes zoster, tuberculosis, and fungal infection), anemia, neutropenia, lymphopenia, thrombocytopenia, malignancies, thrombosis (including increased platelets), MACE, gastrointestinal perforation and other gastrointestinal SAEs, hypersensitivity, hepatotoxicity, dyslipidemia, and acne (Table 5). Notable harms reported in Study 944 and Study 098 are presented in Table 17.

In Study 944, the most common (> 2% in either arm) notable harms were infection, hepatic disorder, and neutropenia. Infections occurred in [redacted] patients receiving upadacitinib group and [redacted] patients in the placebo group. Hepatic disorder occurred in 6 patients (2.8%) in the upadacitinib group and 2 patients (1.0%) in the placebo group. Neutropenia occurred in 6 patients (2.8%) in the upadacitinib group and 2 patients (1.0%) in the placebo group.

In Study 098, the most common (> 2% in either arm) notable harms were infection and hepatic disorder. Infections occurred in [redacted] patients in the upadacitinib group and [redacted] patients in the placebo group. Hepatic disorder occurred in 5 patients (5.4%) in the upadacitinib group and 2 patients (2.1%) in the placebo group.

Harms Reported in Open-Label Phase

The proportion of patients with AEs was not reported in either Clinical Study Report for the extension phase. Instead, the number of AEs events and the number of events per 100 person-years of exposure were reported. The results of the AEs during the extension phase were reported as in a whole group (i.e., the combination in all patients including patients who continued in the upadacitinib group and patients in the placebo group who were switched to the upadacitinib group) (refer to Table 32).

Safety at Week 52 (Study 944)

[redacted]

Safety at Week 104 (Study 098)

With regard to safety in the 182 patients (representing 308.6 person-years) receiving upadacitinib 15 mg once daily during periods 1 and/or 2, the rate of TEAEs was 242.7 per 100 person-years. The 3 most common AEs were nasopharyngitis (46 events; 14.9 per 100 person-years), increased blood CPK levels (35 events; 11.3 per 100 person-years), and upper respiratory tract infection (28 events; 9.1 per 100 person-years).

The rate of serious AEs was 6.2 per 100 person-years, and the rate of AEs leading to discontinuation was 5.5 per 100 person-years. No serious infections, active tuberculosis, adjudicated main adverse cardiovascular events, lymphoma, nonmelanoma skin cancer, renal dysfunction, or gastrointestinal perforations were observed. The exposure-adjusted incidence rate of uveitis was [redacted] among the total population and [redacted] among patients without a history of uveitis.

Critical Appraisal

Internal Validity

Both Study 944 and Study 098 were double-blind, randomized, placebo-controlled trials lasting 14 weeks. Both studies included a 90-week open-label and single-arm follow-up period (i.e., until week 104). Appropriate methods of randomization, blinding and allocation concealment were reported in both studies.

In both Study 944 and Study 098, multiplicity adjustment was used for the primary and main secondary outcomes to control the family-wise type I error. In general, important patient baseline demographic and disease characteristics were similar between treatment groups in both studies. Appropriate statistical methods were used in both trials. Although the 2 included studies were relatively well designed overall, several potential limitations of the 2 included pivotal studies are discussed in the following section.

Limitations for the Double-Blind Randomized Controlled Trial Period (Week 14)

In Study 944, at least 1 protocol deviation was reported in 12.8% of patients in the upadacitinib group and [redacted] patients in the placebo group. Eligibility criteria violation was the most frequent protocol deviation (upadacitinib versus placebo: [redacted]) (Table 28). In Study 098, patients with at least 1 protocol deviation were reported in [redacted] (Table 27). However, all protocol deviations in each study were carefully reviewed and assessed by the sponsor for their impact on analyses, data integrity, and/or patient safety. The totality of the protocol deviations did not affect the study outcomes, interpretation of study results, and/or conclusions. The clinical expert CADTH consulted for this review indicated that a protocol violation reported in the trial was unlikely to have had a major impact on the study findings, In addition, the results from the per-protocol analysis were consistent with those of the primary FAS.

Concomitant NSAIDs used during the trial were balanced across the treatment groups in each study. However, In Study 944, slightly more patients in the upadacitinib group received 1 or more concomitant therapy compared with the placebo group (upadacitinib versus placebo: [redacted]); also, slightly more patients in the upadacitinib group received 1 or more concomitant oral corticosteroids compared with the placebo group (upadacitinib versus placebo: 13.7% versus 10.5%, respectively). However, according to the clinical expert CADTH consulted for this review, this minor imbalance was unlikely to have affected the comparative efficacy results, particularly as csDMARDs and oral corticosteroids are ineffective for the treatment of axial symptoms.

An additional limitation was that neither Study 944 nor Study 098 were designed to assess the comparative efficacy and safety of upadacitinib and the existing bDMARDs marketed in Canada (i.e., TNF and IL-17 inhibitors) for the treatment of AS. The direct comparative efficacy and safety evidence for upadacitinib and other bDMARDs therefore remains unknown.

Furthermore, in both studies, patients with extra-articular manifestations (such as psoriasis, uveitis, or IBD) that are not clinically stable for at least 30 days before study entry were excluded from the study. The extra-articular manifestations were not assessed as an efficacy outcome in either of the studies. The efficacy of upadacitinib on the extra-articular manifestations in the patients with AS therefore requires further investigation.

In Study 944, no multiplicity adjustment was performed for other secondary outcomes, additional exploratory outcomes, such as ASAS5/6, HRQoL (EQ-5D-5L and SF-36), FACIT-F, WPAI-SpA, and MRI SPARCC score (SIJ). In Study 098, no multiplicity adjustment was performed for symptom measurement scale (total back pain and nocturnal back pain), ASDAS ID (score < 1.3), ASDAS LDA (score < 2.1); HRQoL (EQ-5D-5L and SF-36),

FACIT-F, and MRI SPARCC score (SIJ). Given the large number of comparisons in the study, a statistically significant finding (P < 0.05) for the comparisons between upadacitinib and placebo for these outcomes without multiplicity adjustment may have an inflated type I error rate. The statistical significance (P value) reported for those outcomes without multiplicity adjustment therefore remains uncertain and is at high risk of bias.

The number of patients missing data at 14 weeks was very low for most end points and unlikely to bias the results; moreover, numerous sensitivity analyses support the main findings. However, for some end points (e.g., HRQoL), the number of patients missing data was higher. Although the amount of missing data was similar between the groups, it is unclear how missing data for some end points may have affected the study results. The subgroups presented were not part of the randomization scheme; as a result, any observed differences could be biased due to differences in characteristics between the patients included in the subgroup analysis. However, overall, the results of subgroups were consistent with the overall observed effects.

Finally, radiographic progression is an important outcome in AS trials. In both studies, the MRI SPARCC (SIJ) was analyzed as an exploratory outcome. The primary analyses for MRI SPARCC SIJ scores were conducted using an analysis of covariance based on AO case analysis. However, because only a few patients were not included in the AO analysis, this approach was unlikely to have affected the results.

Limitations for the Long-Term Extension Period (From Week 14 to Week 104)

The findings at week 52 [redacted] and at 104 weeks for Study 098 in the extension phase were limited due to the lack of a control group and the nature of open-label studies. Efficacy data beyond week 52 was not provided for the ongoing Study 944 [redacted] The clinical expert CADTH consulted for this review indicated that, in clinical trials, the efficacy magnitude (particularly in patient self-reported outcomes) are often overestimated due to the nature of the open-label trial and the absence of a control group. The long-term outcome efficacy should therefore be interpreted with the consideration of this limitation. The clinical expert also pointed out that this is the case for all long-term extension studies using AO data.

Furthermore, in both studies, no detail information on concomitant medication (NSAIDs and csDMARDs) and rescue medication use were provided in the open-label period (i.e., week 52 [redacted] and week 104 for Study 098). The impact of the concomitant and rescue medications on the long-term efficacy assessment therefore remains unclear.

The long-term efficacy and safety outcomes at week 104 of Study 098 are based on an interim Clinical Study Report[37] because the final Clinical Study Report was not ready at the time of this review.[16] Nevertheless, the sponsor indicated that the final Clinical Study Report for week 104 is expected to be completed in the first quarter of 2023 and "No major impact on the efficacy and safety conclusions is expected."[16]

External Validity

Patients enrolled in Study 944 and Study 098 had very high disease (AS) activity based on the baseline ASDAS and BASDAI score. Exclusion of patients with total spinal ankylosis may limit the generalizability of results to those patients with total ankylosis in clinical practice. Given the very large number of screening failures (69% in Study 944 and 53% in Study 098), the patients were likely a highly selected group. The clinical expert CADTH consulted for this review indicated that exclusion of patients with total ankylosis of the spine in the trials was a "clinical trial strategy" to exclude patients who would likely demonstrate a lower degree of improvement in numerous outcome measures. However, this is consistent with previous clinical trials of AS drugs (e.g., secukinumab, ixekizumab, and anti-TNFs). In clinical practice, it is possible that patients with total ankylosis may demonstrate decreased pain, stiffness, and fatigue, and meaningful improvements in quality of life.

Both Study 944 and Study 098 included a patient population that was predominantly male (68% to 76% across the groups) and most patients were white (80% to 85% across the groups). According to the clinical expert CADTH consulted for this review, the data in male patients are applicable to female patients. It is also unlikely that the response will differ by race.

The patients included in Study 944 were limited to those who had an inadequate response to a bDMARD (i.e., a TNFi or IL-17i) or those who had an inadequate response to 1 bDMARD and were intolerant to another. Patients who had inadequate responses to 2 or more bDMARDs were excluded. Again, the clinical expert CADTH consulted for this review indicated that, exclusion of patients' inadequate responses to 2 or more bDMARDs was a "clinical trial strategy" to increase the probability of demonstrating a clinical response. However, this is consistent with previous clinical trials of AS drugs (e.g., secukinumab, ixekizumab, and anti-TNFs). It is possible that patients who have failed multiple biologics may have severe symptoms not related to SpA or may represent a more severe phenotype. Clinically, it is common practice for patients to try more than 2 bDMARDs until the patient finds an effective treatment. Differentiating active SpA from other causes of back pain can be challenging, and this is reflected in the most recent update to the European Alliance of Associations for Rheumatology (EULAR) guidelines, which suggest re-evaluating the diagnosis in patients who do not respond as expected to bDMARD therapy.

Overall, according to the clinical expert involved in the review, the patients included in both Study 944 and Study 098 are similar to those seen in Canadian clinical settings, except that those AS patients with total ankylosis of the spine would also be treated in a clinic. There is little concern about the generalizability of the findings from both Study 944 and Study 098 to a Canadian setting.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

This section aims to consider comparative efficacy of upadacitinib with relevant drug therapies identified in the protocol (Table 5). As no direct evidence is available, evidence from ITCs is summarized and critically appraised. A focused literature search for ITCs dealing with AS was run in MEDLINE All (1946–)

on November 11, 2022. No limits were applied to the search. The sponsor submitted an ITC and CADTH identified 2 published relevant ITCs in the focused literature search.

Description of the Sponsor-Submitted Indirect Comparison

The sponsor-submitted ITC described the NMAs that were performed. The objective was to determine the [redacted]

Study Selection Methods

A systematic search was performed to include evidence to May 2020 and was updated with evidence from May 2020 to March 2021,[16] following the National Institute for Health and Care Excellence *Guide to the Methods of Technology Appraisal 2013*[48] and the Centre for Reviews and Dissemination *Guidance for Undertaking Reviews in Health Care*.[49] Manual searches were conducted on trial registries, health technology assessment websites, relevant conference websites, and reference lists from identified systematic reviews and meta-analyses. Eligibility criteria and databases searched are summarized in Table 18.

Two researchers independently reviewed records for inclusion. Disagreements were discussed, and a third researcher was consulted if agreement could not be reached. Full-text publications were reviewed if there was insufficient information in an abstract to confirm the study met the inclusion criteria. Data were extracted by 1 researcher using a data extraction form in Microsoft Excel and independently audited by a second researcher. Discrepancies were discussed, and a third researcher was consulted if agreement could not be reached. Quality was assessed using the User Guide for Company Evidence Submission Template[50] recommended in the National Institute for Health and Care Excellence Single Technology Appraisal[51] by 2 researchers working independently and resolved by discussion or, if needed, a third researcher when there was disagreement. No action was taken as a result of the quality assessment.[16]

Table 18: Study Selection Criteria and Methods for the Sponsor-Submitted ITC

Criteria	Sponsor-submitted ITC
Population	[redacted]
Intervention	[redacted]
Comparator	• [redacted]
Outcome	• [redacted]

Criteria	Sponsor-submitted ITC
Study design	[redacted]
Publication characteristics	[redacted]
Exclusion criteria	[redacted]
Databases searched	[redacted]
Selection process	[redacted]
Data extraction process	[redacted]
Quality assessment	[redacted]

ITC = indirect treatment comparison.

[a]Defined as a BASDAI score equal to or greater than 4.

[redacted]

Sources: Sponsor-submitted ITC[17] and sponsor-submitted systematic literature review.[16]

Feasibility Assessment

[redacted]

Indirect Treatment Comparison Analysis Methods

[redacted]

Secondary and Subgroup Analysis

[redacted]

Results of the Sponsor-Submitted Indirect Treatment Comparison

Summary of Included Studies

[redacted]

Table 19: Indirect Treatment Comparison Analysis Methods

Method	ITC1
ITC methods	[redacted]
Priors	[redacted]
Assessment of model fit	[redacted]
Assessment of consistency	[redacted]
Assessment of convergence	[redacted]
Outcomes	[redacted]
Follow-up time points	[redacted]
Construction of nodes	[redacted]

Method	ITC1
Secondary analyses	[redacted]
Subgroup analysis	[redacted]
Methods for pairwise meta-analysis	[redacted]

[redacted]

ITC = indirect treatment comparison.

Source: Sponsor-submitted ITC.[17]

Table 20: Summary of Patient Characteristics

Study and treatment arm	Random-ized, N	Age, mean (SE)	Male, %	HLA-B27, %	CRP (mg/L), mean (SE)	bDMARD-experienced, %	Concomitant NSAID, %	Concomitant conventional DMARD, %	Concomitant glucocorticoid, %	Diagnosis duration, years (SE)	Symptom duration, years (SE)	BASDAI, 0 to 10 (SE)	BASFI, 0 to10 (SE)
[redacted]													
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Study and treatment arm	Random-ized, N	Age, mean (SE)	Male, %	HLA-B27, %	CRP (mg/L), mean (SE)	bDMARD-experienced, %	Concomitant NSAID, %	Concomitant conventional DMARD, %	Concomitant glucocorticoid, %	Diagnosis duration, years (SE)	Symptom duration, years (SE)	BASDAI, 0 to 10 (SE)	BASFI, 0 to10 (SE)
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Study and treatment arm	Random-ized, N	Age, mean (SE)	Male, %	HLA-B27, %	CRP (mg/L), mean (SE)	bDMARD-experienced, %	Concomitant NSAID, %	Concomitant conventional DMARD, %	Concomitant glucocorticoid, %	Diagnosis duration, years (SE)	Symptom duration, years (SE)	BASDAI, 0 to 10 (SE)	BASFI, 0 to10 (SE)
[redacted]													
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Study and treatment arm	Random-ized, N	Age, mean (SE)	Male, %	HLA-B27, %	CRP (mg/L), mean (SE)	bDMARD-experienced, %	Concomitant NSAID, %	Concomitant conventional DMARD, %	Concomitant glucocorticoid, %	Diagnosis duration, years (SE)	Symptom duration, years (SE)	BASDAI, 0 to 10 (SE)	BASFI, 0 to10 (SE)
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Study and treatment arm	Random-ized, N	Age, mean (SE)	Male, %	HLA-B27, %	CRP (mg/L), mean (SE)	bDMARD-experienced, %	Concomitant NSAID, %	Concomitant conventional DMARD, %	Concomitant glucocorticoid, %	Diagnosis duration, years (SE)	Symptom duration, years (SE)	BASDAI, 0 to 10 (SE)	BASFI, 0 to10 (SE)
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Study and treatment arm	Random-ized, N	Age, mean (SE)	Male, %	HLA-B27, %	CRP (mg/L), mean (SE)	bDMARD-experienced, %	Concomitant NSAID, %	Concomitant conventional DMARD, %	Concomitant glucocorticoid, %	Diagnosis duration, years (SE)	Symptom duration, years (SE)	BASDAI, 0 to 10 (SE)	BASFI, 0 to10 (SE)
[redacted]													
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ADA = adalimumab; AS = ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biologic disease-modifying antirheumatic drug; BIW = twice weekly; CrI = credible interval; CRP = C-reactive protein; CZP = certolizumab pegol; DMARD = disease-modifying antirheumatic drug; ETN = etanercept; GOL = golimumab; HLA-B27 = human leukocyte antigen B27; INF = infliximab; IR = inadequate response and/or intolerance; ITC = indirect treatment comparison; IXE = Ixekizumab; NMA = network meta-analysis; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; QD = once daily; QW = once weekly; RCT = randomized controlled trial; SAE = serious adverse event; SE = standard error; SEC = secukinumab; TOF = tofacitinib; UPA = upadacitinib.

Source: Sponsor-submitted ITC.[17]

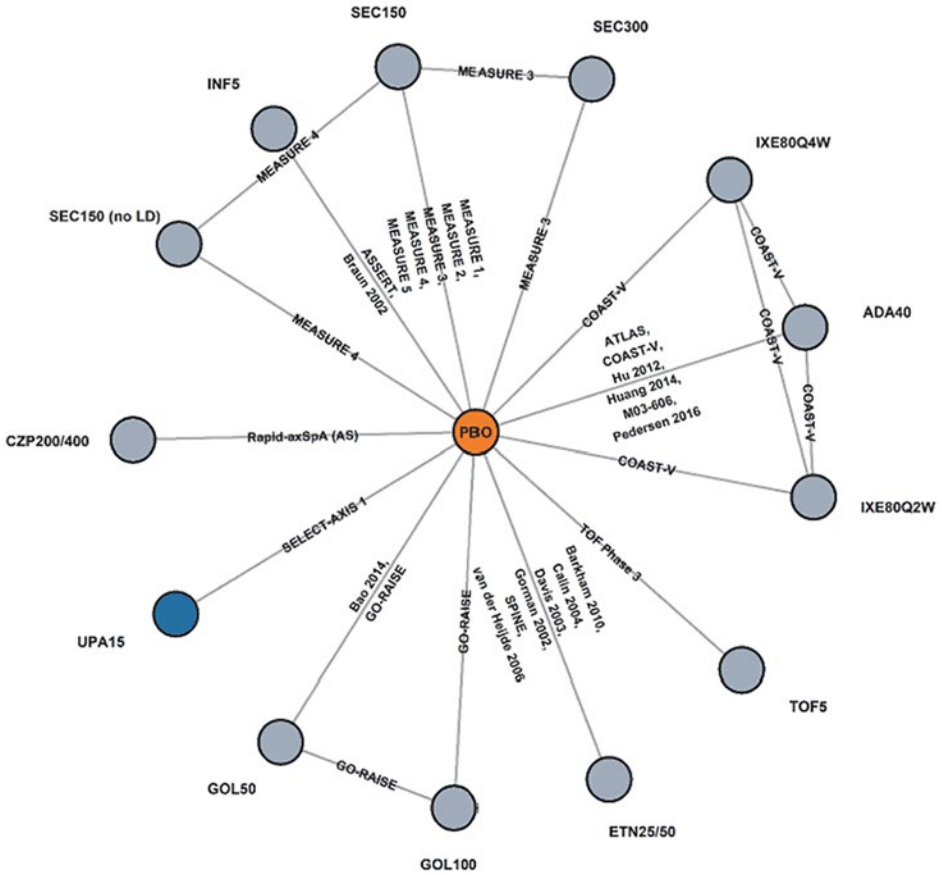
Evidence Networks

Primary evidence networks for patients who were bDMARD-naive and those who had an inadequate response to a bDMARD are illustrated in Figure 8 and Figure 9. The networks are star-shaped with few closed loops. All comparative evidence about upadacitinib originates from indirect comparisons. The number of studies and patients contributing to each outcome is reported along with the results in Table 23 and Table 24.

Study Quality

[redacted]

Figure 8: Network of Studies Included in the bDMARD-Naive Analysis



ADA = adalimumab; ETN = etanercept; GOL = golimumab; INF = infliximab; IXE = Ixekizumab; LD = low dose; Q2W = every 2 weeks; SEC = secukinumab; TOF = tofacitinib; UPA = upadacitinib.

Source: Sponsor-submitted indirect treatment comparison.[17]

[redacted]

Potential Sources of Heterogeneity

[redacted]

Figure 9: Network of Studies Included in the bDMARD-IR Analysis

IXE = Ixekizumab; LD = low dose; Q2W = every 2 weeks; SEC = secukinumab; UPA = upadacitinib.
Source: Sponsor-submitted indirect treatment comparison.[17]

[redacted]

Table 21: Placebo Response (Baseline Risk) Assessment — bDMARD-Naive Network

Response	Lower range		Upper range	
	Estimate	Study	Estimate	Study
ASAS20	[redacted]	[redacted]	[redacted]	[redacted]
ASAS40	[redacted]	[redacted]	[redacted]	[redacted]
ASAS PR	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI CFB	[redacted]	[redacted]	[redacted]	[redacted]
BASFI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Total back pain	[redacted]	[redacted]	[redacted]	[redacted]

ASAS = Assessment in SpondyloArthritis international Society; ASAS 20 = Assessment in SpondyloArthritis international Society 20% improvement; ASAS40 = Assessment in SpondyloArthritis international Society 40% improvement; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50 = Bath Ankylosing Spondylitis Disease Activity Index 50% improvement; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biologic disease-modifying antirheumatic drug; CFB = change from baseline; PR = partial response.

Source: Sponsor-submitted indirect treatment comparison.[17]

Table 22: Placebo Response (Baseline Risk) Assessment — bDMARD-IR Network

Response	Lower range		Upper range	
	Estimate	Study	Estimate	Study
ASAS20	[redacted]	[redacted]	[redacted]	[redacted]
ASAS40	[redacted]	[redacted]	[redacted]	[redacted]
ASAS PR	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI CFB	[redacted]	[redacted]	[redacted]	[redacted]
BASFI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Total back pain	[redacted]	[redacted]	[redacted]	[redacted]

ASAS = Assessment in SpondyloArthritis international Society; ASAS20 = Assessment in SpondyloArthritis international Society 20% improvement; ASAS40 = Assessment in SpondyloArthritis international Society 40% improvement; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50 = Bath Ankylosing Spondylitis Disease Activity Index 50% improvement; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD-IR = biologic disease-modifying antirheumatic drug–inadequate response; CFB = change from baseline; PR = partial response.

Source: Sponsor-submitted indirect treatment comparison.[17]

Model Selection and Network Meta-Analysis Results

[redacted]

Table 23: Network Meta-Analysis Results for bDMARD-Naive Patients

Upadacitinib vs.	Odds ratios (median [95% CrI]) for outcomes at 12 weeks				CFB differences (median [95% CrI]) for outcome at 12 weeks		
	ASAS20	ASAS40	ASAS PR	BASDAI50	BASDAI CFB	BASFI CFB	Total back pain CFB
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol 200 mg/400 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Upadacitinib vs.	Odds ratios (median [95% CrI]) for outcomes at 12 weeks				CFB differences (median [95% CrI]) for outcome at 12 weeks		
	ASAS20	ASAS40	ASAS PR	BASDAI50	BASDAI CFB	BASFI CFB	Total back pain CFB
Etanercept 25 mg/50 mg							
Golimumab 100 mg							
Golimumab 50 mg							
Infliximab 5 mg							
Ixekizumab 80 mg q.2.w							
Ixekizumab 80 mg q.4.w							
Secukinumab 150 mg, no loading dose							
Secukinumab 150 mg							
Secukinumab 300 mg							
Number of studies (patients)							
Preferred model							

[a]Indicates a superior result.

ASAS = Assessment in SpondyloArthritis international Society; ASAS20 = Assessment in SpondyloArthritis international Society 20% improvement; ASAS40 = Assessment in SpondyloArthritis international Society 40% improvement; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50 = Bath Ankylosing Spondylitis Disease Activity Index 50% improvement; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biologic disease-modifying antirheumatic drug; CFB = change from baseline; CrI = credible interval; PR = partial response; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks.

Source: Sponsor-submitted indirect treatment comparison.[17]

Table 24: Network Meta-Analysis Results for bDMARD-IR Patients

Upadacitinib vs.	Odds ratios (median [95% CrI]) for outcome at 12 weeks				CFB differences (median [95% CrI]) for outcome at 12 weeks		
	ASAS20	ASAS40	ASAS PR	BASDAI50	BASDAI CFB	BASFI CFB	Total back pain CFB
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q.2.w.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q.4.w.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg, no loading dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of studies (patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Preferred model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]Indicates a superior result.

ASAS = Assessment in SpondyloArthritis international Society; ASAS20 = Assessment in SpondyloArthritis international Society 20% improvement; ASAS40 = Assessment in SpondyloArthritis international Society 40% improvement; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50 = Bath Ankylosing Spondylitis Disease Activity Index 50% improvement; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biologic disease-modifying antirheumatic drug–inadequate response; CFB = change from baseline; CrI = credible interval; PR = partial response; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; vs. = versus.

Source: Sponsor-submitted indirect treatment comparison.[17]

Assessment of Consistency

[redacted].

Critical Appraisal of the Sponsor-Submitted Indirect Treatment Comparison

The ITC aimed to determine comparative efficacy of upadacitinib in adult patients with AS who were not adequately controlled with NSAIDs, and who had no prior exposure or had an inadequate response to bDMARDs. The patient population with an inadequate response to bDMARDs aligns with 1 of the populations in the Health Canada indication ("adults with active ankylosing spondylitis who have had an inadequate

response to a biologic DMARD or when use of those therapies is inadvisable").[10] It is less clear if the indication wording, "or when use of those therapies is inadvisable," aligns fully with the population without prior bDMARD exposure, as some patients may have prior DMARD exposure but, due to adverse effects or other factors, treatment is deemed inadvisable.

The sponsor-submitted ITC was based on a systematic literature review[16] of clinical and nonclinical evidence that was comprehensive. Appropriate predefined inclusion and exclusion criteria for the ITC were provided. All relevant comparators for the current Canadian context were included in the ITC. The literature search strategy was provided and was acceptable. Multiple databases were searched. Appropriate reasons for individual study exclusion were reported, although the specific studies excluded were not identified in the technical report[17] and not readily identifiable in the systematic literature review.[16] Data were extracted using appropriate methods. An established risk-of-bias tool and acceptable methods were used to assess individual studies, and results were reported; however, no action was taken related to this assessment (e.g., a sensitivity analysis to exclude studies with high risk of bias or uncertain risk of bias), despite evidence of some studies with a high risk of bias and many studies with uncertain risk of bias. Inclusion of studies that are at risk of bias increased the uncertainty in the ITC findings. No assessment of potential publication bias was reported, also increasing the uncertainty in the findings.

The evidence base for the ITC was large for the bDMARD-naive population, with 24 studies and 5,039 patients, while the evidence base for the biologic disease-modifying antirheumatic drug–inadequate response (bDMARD-IR) population was less robust, with 8 studies and 1,167 patients available for analysis. Importantly, upadacitinib lacks direct comparative data for any active treatment, and most comparative evidence in the ITC is indirect. The star-shaped geometry (Figure 8 and Figure 9) and lack of more than 1 study for many comparisons reduces confidence in effect estimates. Additionally, although the assessment of consistency did not show evidence of inconsistency, the statistical test is underpowered in this context. Evidence of comparative efficacy is available for all relevant comparators for the Canadian context in the bDMARD-naive population, but based on the Health Canada indication, upadacitinib may be less likely to be used in this setting. There is no comparative evidence for adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab in patients who had an inadequate response to a bDMARD; the sponsor-submitted ITC provides comparative efficacy with the relevant comparators of ixekizumab and secukinumab only. Therefore, no data are available to guide selection between upadacitinib and TNFi drugs in a population with inadequate response to a bDMARD. The clinical expert indicated that it may be reasonable to assume similar efficacy between upadacitinib and TNFi and IL-17i drugs in the bDMARD-IR population because: a) TNFi treatments were included as active comparators in some of the IL-17i trials, b) upadacitinib showed similar efficacy to IL-17i treatments in the ITC analysis of bDMARD–inadequate response patients, and c) upadacitinib showed similar efficacy to TNFi treatments in the ITC analysis of bDMARD-naive patients. The clinical expert also indicated that patients who are inadequate responders to TNFi treatments may respond better to a different mechanism of action, although no trials conducted to date confirm this.

The efficacy outcomes were assessed at 12 to 16 weeks, which may have resulted in biased estimates. Secondary analyses were performed for both the bDMARD-naive and bDMARD-IR networks using the sponsor's 14-week end points, and [redacted]. No information is available on longer-term outcomes

in the sponsor-submitted ITC, although a publication of 1-year results for upadacitinib is available,[40] and longer-term data are also available for other treatments. No HRQoL outcomes were reported in the ITC, despite their importance to patients; Additionally, the sponsor-submitted systematic literature review[16] identified studies with HRQoL outcomes. No safety outcomes were reported in the ITC, and this is an important gap in evidence.

Heterogeneity among studies was assessed using several approaches. The sponsor identified a priori patient characteristics that were potential effect modifiers and other study factors that could contribute to heterogeneity. It also examined placebo response rates as a proxy for all known and unknown study effects and provided this information graphically. Inspection of these variables revealed heterogeneity among studies. The clinical expert CADTH consulted for this review agreed that there was important heterogeneity among the studies. Models adjusted for heterogeneity were generated, but results were not presented unless selected as the preferred model based on model-fit statistics, and results from models adjusted for heterogeneity were presented in a minority of outcomes.

A large amount of data on patient characteristics that were potential treatment-effect modifiers was missing, which meant that heterogeneity could not be fully assessed; for example, just over half of the treatment arms did not report the time since diagnosis, and one-quarter did not report age or proportion of males. The ITC methods indicated that, if discernable heterogeneity was found, baseline risk (placebo response) would be used to adjust for it; however, the sponsor used model-fit statistics to decide whether to select an adjusted model as the preferred model for each outcome. This resulted in only 4 of 7 outcomes in the bDMARD-naive population and 1 of 7 outcomes in the bDMARD-IR population being adjusted for heterogeneity. Given the wide range of mean values of many patient characteristics that are potential treatment-effect modifiers, it is probable the principle of transitivity, which underpins NMAs, may have been violated, and effect estimates are likely biased, although the magnitude and direction of the bias are unclear.

The sponsor's approach to model selection based on model fit discounted the plausibility of model assumptions. The evidence base for the bDMARD-naive population is extensive. Assumptions for random-effects models are much more plausible than those for fixed-effects models; yet in 3 of 7 outcomes, a fixed-effect model was selected and may result in biased estimates of treatment effects.

The 95% credible intervals around many of the efficacy estimates are wide, reflecting a lack of precision. This may be related to the inclusion of a number of small studies, which typically have larger variance, in the ITC, or it could be related to heterogeneity in treatment-effect modifiers.

As noted by the sponsor, data imputation methods may have become more conservative over the 20-year evidence base. However, it is unclear whether the evidence shows more conservative data imputation methods only being used in recently approved drugs and whether any differences are biasing the ITC results toward larger effect estimates for older drugs in the bDMARD-naive network. Additionally, supportive care may have improved during this 20-year period. These time-dependent changes may increase certainty in the findings that upadacitinib is no different than other treatments for most outcomes assessed; however, without evidence from a head-to-head study using an active comparator, upadacitinib cannot be considered superior to any currently available therapies.

Description of Published Indirect Treatment Comparisons

Two published ITCs of adult patients with AS that included treatment with upadacitinib and relevant comparators were identified in a focused literature search by CADTH. The ITC by Cao and colleagues[18] included patients with AS, although little additional detail on the included population was provided. Studies of bDMARD-naive patients and those who had an inadequate response to bDMARDs were included in a frequentist NMA using random-effects models. The list of interventions included all 7 relevant comparators and many drugs that are not relevant to the Canadian context. Outcomes were assessed as change from baseline to the last follow-up date, meaning the NMA combined outcomes at different time points. The primary analysis performed the analyses at the drug class level and reported individual drugs in subgroup analyses. The number of included studies and patients was larger than the sponsor-submitted ITC. In addition to efficacy outcomes, the study also included SAEs as an outcome. The findings were similar to those of the sponsor-submitted ITC: upadacitinib was superior to placebo and no different than any of the relevant comparators for efficacy outcomes. For the safety outcome, upadacitinib was no different than placebo or relevant comparators. Additional details are reported in Table 25.

The second study by Lee[19] focused on JAK inhibitors and secukinumab for adult patients with AS who were bDMARD-naive. A Bayesian approach was used. Secukinumab was the only comparator of interest for the Canadian context, but the ITC included other treatments. This ITC included efficacy outcomes and an SAE outcome. The findings were similar to the sponsor's ITC and the other published ITC: upadacitinib was superior to placebo and no different than secukinumab for efficacy outcomes. There was no difference between upadacitinib and placebo or secukinumab for the SAE outcome. Additional details are reported in Table 25.

Key limitations to the ITC by Cao and colleagues[18] were the presence of heterogeneity in study populations and the timing of outcome assessment. The ITC by Lee[19] did not report the baseline characteristics of the included studies, or other details to allow for an assessment of heterogeneity among studies. The evidence base was small and the only relevant comparator for the Canadian context was secukinumab. No conclusions can be drawn from either study due to methodological limitations, the presence of heterogeneity (or no assessment of heterogeneity) and imprecision in effect estimates (a wide confidence or credible interval that included 1 for risk ratios and odds ratios).

Table 25: Summary of Published Indirect Treatment Comparisons

Characteristic	Cao (2022)	Lee (2022)
Population	Patients with AS	Patients with active AS, an inadequate response or intolerant to NSAIDs and who were TNFi-naive
Intervention and/or comparators	Adalimumab Bimekizumab Certolizumab pegol Etanercept Filgotinib Golimumab	Tofacitinib 5 mg Upadacitinib 15 mg Filgotinib 200 mg Secukinumab 150 mg Placebo Upadacitinib data came from the SELECT-AXIS

Characteristic	Cao (2022)	Lee (2022)
	Infliximab Ixekizumab Netakimab Risankizumab Secukinumab Tocilizumab Tofacitinib Upadacitinib Ustekinumab Placebo or sulfasalazine Upadacitinib data came from the SELECT-AXIS 1 trial, in biologic naive patients,[39] whereas the sponsor-submitted ITC also includes SELECT-AXIS 2 trial in biologic experienced patients[84]	1 trial, in biologic naive patients,[39] whereas the sponsor-submitted ITC also includes SELECT-AXIS 2 trial in biologic experienced patients[84]
Outcomes	• ASAS20[a] • ASAS40 • BASDAI or ASDAS[a] • BASFI[a] • SAEs Change from baseline to last follow-up value was used for ASAS20 and ASAS40, and time period was unstated for the other outcomes	• ASAS20 • ASAS40 • SAEs At 12 to 16 weeks
Study design	Parallel group RCTs; 43 studies included, with 8,995 patients	RCTs with JAKi or secukinumab vs. placebo; 6 studies included with 937 patients
ITC analysis methods	NMA was conducted using the frequentist approach; random-effects multivariate meta-regression models were used Primary analysis was by drug class; subgroup analysis reported ASAS40 and SAEs by individual drug. The analysis made no distinction between patients who were bDMARD-naive or bDMARD-IR. Risk ratios and 95% confidence intervals were estimated for efficacy and safety outcomes of individual drugs; inconsistency and node-splitting tests were used to assess consistency within each network; if inconsistency was identified, a sensitivity analysis was used to identify potential sources Quality of the identified studies was assessed using the Cochrane risk-of-bias tool and studies assessed as low quality were excluded from the analysis; studies published in non–Science Citation Index journals were also excluded to control quality of the included studies; publication bias was assessed by funnel plots and Egger's test	Bayesian NMA was conducted The primary analysis used fixed-effects models. A sensitivity analysis was done using random-effects models; the authors did not report number of chains, priors used, assessment of convergence or model fit. The authors stated that they used inconsistency models to test for consistency but no closed loops were present in the network figure Odds ratios and 95% CrIs were estimated for each outcome No assessment of quality of included studies was reported

Characteristic	Cao (2022)	Lee (2022)
Key limitations	Substantial clinical heterogeneity was noted; for example, mean age among studies varied from 15 to 47 years; percentage of male patients varied from 45% to 93% Additionally, the ITC included both bDMARD-naive and bDMARD-IR populations; no other baseline characteristics that could be potential effect modifiers were provided, increasing the uncertainty of the findings Timing of outcome assessment varied from 1.87 months to 48 months; insufficient reporting of methods was also evident	The only relevant comparator in the ITC was secukinumab The evidence base was small, with 6 studies included with 937 patients No baseline characteristics of patients in the included trials was provided so clinical heterogeneity could not be assessed; insufficient reporting of methods was also evident
Relevant findings	Upadacitinib was superior to placebo and no different than other relevant comparators (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab) as measured by ASAS40 The incidence of SAEs was no different between upadacitinib and placebo or other relevant comparators	Upadacitinib was superior to placebo and no different than secukinumab as measured by ASAS20 and ASAS40 The incidence of SAEs was no different between upadacitinib and placebo or secukinumab

AS = ankylosing spondylitis; ASAS20 = Assessment in SpondyloArthritis international Society 20% improvement; ASAS40 = Assessment in SpondyloArthritis international Society 40% improvement; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biologic disease-modifying antirheumatic drug; bDMARD-IR = biologic disease-modifying antirheumatic drug–inadequate response; CrI = credible interval; ITC = indirect treatment comparison; JAKi = Janus kinase inhibitor; NMA = network meta-analysis; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; SAE = serious adverse event; TNFi = tumour necrosis factor inhibitor.

[a]Not reported for individual drugs.

Sources: Cao et al.(2022)[18] and Lee (2022).[19]

Other Relevant Evidence

No other relevant evidence was identified.

Discussion

Summary of Available Evidence

Two manufacturer-sponsored double-blind RCTs (14 weeks), Study 944 (N = 420) and Study 098 (N = 187), are included in this review. The 2 trials evaluated the efficacy and safety of upadacitinib 15 mg administered orally once daily compared to placebo in patients with active AS. Study 944 was conducted in patients with AS who inadequately responded or were intolerant to 1 or 2 bDMARDS. Study 098 was conducted in patients with AS who inadequately responded or were intolerant to 2 or more NSAIDs but were bDMARD-naive. The primary outcome in both trials was the proportion of patients meeting the ASAS40 response criteria at week 14. The key secondary outcomes (multiplicity-controlled) included change from baseline in ASDAS; change from baseline in MRI SPARCC score (spine); BASDAI50 response; ASAS20 response; ASDAS ID response (score < 1.3); change from baseline in patient assessment of total back pain; change from baseline in patient assessment of nocturnal back pain; ASDAS LDA (score < 2.1); change from baseline in BASFI; ASAS PR;

change from baseline in ASQoL; change from baseline in ASAS HI; change from baseline in BASMIlin; and change from baseline in MASES).

Results of an extension phase at week 52 of Study 944 and Study 098 as well as week 104 for Study 098 are also presented in this report. Study 944 was ongoing at the time of this review. The long-term efficacy and safety outcome for Study 944 at week 104 is therefore not available.

Study 098 was conducted in patients with active AS who were bDMARD-naive. The CADTH review team noted that the [redacted] for the Health Canada–approved indication (i.e., the indication for this current CADTH review), "for the treatment of adults with active ankylosing spondylitis who have had an inadequate response to a biologic DMARD or when use of those therapies is inadvisable…" The [redacted]

Furthermore, the clinical expert CADTH consulted for this review indicated that Study 098 potentially supports the bDMARD-inadvisable patient population (such as patients who were contraindicated or hypersensitivity to bDMARDs, patients with needle phobia, and those who have a difficulty injecting themselves) who therefore would not have used a prior bDMARD, though Study 098 was conducted in a bDMARD-naive population, members of which were not purely or directly in the population for whom use of the bDMARDs were inadvisable. The clinical expert indicated that this represents approximately 20% to 30% of AS patients for whom use of the bDMARDs are inadvisable.

In addition, due to the lack of a head-to-head trial comparing upadacitinib to other active bDMARDs treatments for AS, a summary of the sponsor-submitted ITC analysis is presented that evaluated the comparative efficacy and safety of upadacitinib to other bDMARDs in the treatment of patients with active AS in both the population who were inadequately responded to or were intolerant of bDMARDs and the bDMARD-naive population.

Interpretation of Results

Efficacy

At 14 Weeks

Clinical Response (e.g., ASAS40 and ASAS20)

At week 14 of both Study 944 and Study 098, a statistically and clinically significant greater proportion of patients treated with upadacitinib 15 mg administered orally once daily achieved ASAS40 and ASAS20 compared with patients receiving placebo treatment. Twenty-six percent more patients in the upadacitinib group in both Study 944 and Study 098 achieved ASAS40 compared with those in the placebo group. The ASAS40 response based on a per-protocol analysis and various sensitivity analysis are all consistent with the primary analysis, which indicated the clinical response results are robust. In addition, according to the

clinical expert CADTH consulted for this review, ASAS20 at week 12 is considered an acceptable clinical response for a bDMARDs trial for AS, although ASAS40 at week 14 would be considered akin to a major clinical improvement. The response rates of ASAS40 and ASAS20 reported in both Study 944 and Study 098 are considered clinically meaningful.

Symptoms Reduction

In Study 944, patients treated with upadacitinib showed a statistically greater reduction in total back pain and nocturnal back pain compared with patients treated with placebo. No MCID was identified for these symptom measurement scales. However, the most important AS symptom, total back pain (i.e., spinal pain) is a main component of ASAS criteria. It is therefore reasonable to expect that the observed difference of total back pain and nocturnal back pain between upadacitinib treatment and placebo may be clinically meaningful. In Study 098, patients treated with upadacitinib showed a greater reduction in total back pain and nocturnal back pain compared with patients treated with placebo. However, as they were analyzed with no multiplicity adjustment in Study 098, the statistical significance (P value) remains uncertain, as it is at high risk of a type I error. In addition, patients treated with upadacitinib appeared to [redacted]

Function and Disability Improvement (i.e., BASFI)

In both studies, statistically and clinically significant greater improvement (in BASFI) was observed in patients receiving upadacitinib compared with patients receiving placebo based on the MID for BASFI (0.6 units on a 10-unit scale).

Quality-of-Life Improvement

In terms of quality of life measured by ASQoL, in Study 944, patients treated with upadacitinib showed a statistically and clinically significant greater improvement in ASQoL compared with patients treated with placebo based on an MID of −2.[16,44] However, in Study 098, patients treated with upadacitinib showed a statistically but not clinically significant greater improvement in ASQoL compared with patients treated with placebo. In terms of quality of life measured by ASAS HI, in Study 944, patients treated with upadacitinib showed a statistically significant greater improvement in ASAS HI compared with patients treated with placebo. Because no MID was identified for the ASAS HI, whether the between-groups difference of the ASAS HI is clinical meaningful remains unknown. In Study 098, no statistically significant between-groups difference in change from baseline was observed. The quality of life measured by the SF-36 (i.e., PCS and MCS) and EQ-5D (i.e., EQ-5D-5L and EQ VAS) were only assessed in Study 944, but not in Study 098. It was reported [redacted]

Work Productivity (i.e., WPAI-SpA Score)

In Study 944, patients treated with upadacitinib showed [redacted].

In Study 098, patients treated with upadacitinib showed nonstatistically greater improvement in WPAI-SpA scores compared with patients treated with placebo.

Disease Activity Reduction

A statistically and clinically significant greater proportion of patients achieved BASDAI50 in patients receiving upadacitinib compared with patients receiving placebo in both studies. In terms of BASDI change from baseline, it also showed [redacted] However, BASDI change from baseline was assessed as an exploratory outcome with no multiplicity adjustment. Therefore, [redacted]

In terms of ASDAS change from baseline, In Study 944, patients treated with upadacitinib showed a statistically and clinically significant greater improvement in ASDAS compared with patients treated with placebo (based on an MID reduction of ≥ 1.1 units). However, in Study 098, patients treated with upadacitinib showed a statistically, but not clinically, significantly greater improvement in ASDAS compared with patients treated with placebo.

In Study 944, patients treated with upadacitinib showed a statistically and clinically significant greater response rate in both ASDAS ID (< 1.3 units) and ASDAS LDA (1.3 ≤ ASDAS < 2.1) compared with the placebo group. In Study 098, a numerically greater response rate was observed in the upadacitinib group than in the placebo group. In addition, more patients in the upadacitinib group achieved the ASDAS clinically important improvement (i.e., ≥ 1.1 units reduction) than in the placebo group in both studies. However, this outcome was analyzed as exploratory only, with no multiplicity adjustment in both studies, and the statistical significance (P value) remains uncertain due to the high risk of a type I error.

MRI SPARCC Score

In terms of MRI Spine SPARCC scores, in Study 944, patients treated with upadacitinib showed a statistically significant greater improvement compared with patients treated with placebo, but the difference was not clinically meaningful (based on an MID of 5 units). However, in Study 098, patients treated with upadacitinib showed a statistically and clinically significant greater improvement in MRI Spine SPARCC scores compared with patients treated with placebo. In terms of MRI SPARCC Index (SIJ), patients treated with upadacitinib showed a greater improvement compared with patients treated with placebo [redacted] However, this outcome was analyzed as exploratory only, with no multiplicity adjustment in both studies, and the statistical significance (P value) remains uncertain due to the high risk of a type I error.

Patient Global Assessment

A notable treatment difference was also observed [redacted]. However, because PtGA was analyzed with no multiplicity adjustment, the statistical significance remains uncertain due to the high risk of a type I error. In addition, no MID was identified for PtGA. Because PtGA is a main component of the ASAS criteria, [redacted]

Maastricht Ankylosing Spondylitis Enthesitis Score

In Study 944, patients treated with upadacitinib showed a statistically significant greater improvement in MASES compared with patients treated with placebo. However, no MID was identified for MASES, and whether the between-groups difference of MASES scores for upadacitinib and placebo is clinical meaningful

remains unclear. In Study 098, no statistically significant between-groups difference in change from baseline was reported in MASES scores.

Bath Ankylosing Spondylitis Metrology Index

In Study 944, patients treated with upadacitinib showed a statistically significant greater improvement in the BASMI compared with patients treated with placebo. However, no MID was identified for BASMI, and whether the between-groups difference of MASES scores for upadacitinib and placebo is clinical meaningful remains unclear. In Study 098, no statistically significant between-groups difference in change from baseline was reported for the BASMI.

Overall, at week 14, the magnitude of clinical response to upadacitinib was largely similar in TNFi- or IL-17i–experienced patients in Study 944 compared with bDMARD-naive patients in Study 098. The clinicians would typically expect a lower response in patients who had an inadequate response to bDMARDs as they likely represent a more severe phenotype, and it was therefore impressive to find similar results between patients who are bDMARD-naive and those with an inadequate response to bDMARDs. It is possible that this finding was due to the fact that JAKis do not work along the TNF or IL-17 pathway, although it would be difficult to make this claim confidently without a head-to-head study.

At Long-Term Extension Period

The efficacy achieved at week 14 appeared to be maintained at 52 weeks [redacted] and week 104 (for Study 098).

The sponsor submitted a single ITC of upadacitinib and relevant comparators for 7 efficacy outcomes. Separate analyses for the bDMARD-naive and bDMARD-IR populations were conducted. The evidence base for the bDMARD-naive population included 24 studies and 5,039 patients, while the evidence base for patients with an inadequate response to bDMARDs included 8 studies and 1,167 patients. Two published ITCs of upadacitinib and other drugs for the treatment of AS were identified from the literature.[18,19] One did not specify prior bDMARD experience and included 43 studies and 8,995 patients.[18] The other ITC included upadacitinib, other JAK inhibitors and secukinumab in patients who were bDMARD-naive, and 6 studies with 937 patients.[19] Overall, [redacted]

Harms

The overall frequency of patients with TEAEs in patients treated with upadacitinib appeared to be low, but higher compared to that in placebo group in both Study 944 (40.8% versus 36.8%, respectively) and in Study 098 (62.4% versus 55.3%) by week 14. In Study 944, no TEAE occurred in 5% or greater of the patients in either of the arms. In Study 098, the most common TEAEs (> 5% patients in either of the treatment groups)

were [redacted], nasopharyngitis, headache and [redacted]. The overall frequency of patients with SAEs appeared to be low (< 3%) in both studies by week 14. No patients withdrew due to AEs in the upadacitinib group in Study 944. I study 098, WDAEs were also low (< 3%). No deaths were reported in either of the studies by week 14. Furthermore, the incidence of notable harms identified in this review (including serious infection, anemia, neutropenia, lymphopenia, thrombocytopenia, malignancies, thrombosis including increased platelets, elevation of CPK, other gastrointestinal SAEs, [redacted], and folliculitis) was low. No MACE, gastrointestinal perforation, hepatotoxicity, dyslipidemia, opportunistic infection excluding tuberculosis and herpes zoster, or case of active tuberculosis was reported in either of the studies.

Based on the clinical expert CADTH consulted for this review, the TEAE reported in both Study 944 and Study 098 were common TEAEs as observed in other upadacitinib clinical trials for RA, PsA, and AD. Notable harms involved nothing unexpected.

For the extension phase, the proportion of patients with a TEAE was not reported in either of the studies. Instead, the number of TEAE and TEAE person-years were provided. The clinical expert CADTH consulted for the review indicated that the safety profile of upadacitinib for AS [redacted] and over week 104 was consistent with that observed by week 14, with no new safety signals reported.

As indicated in the Health Canada reviewer report,[42] due to diagnosis of AS at a younger age, it is anticipated that AS patients will have longer disease and treatment durations compared with PsA and RA patients. Compared to the RA population, the AS population was younger and predominantly male; and patients generally have lower usage of corticosteroids and csDMARDs. The rate of serious infections tends to be lower in AS patient populations compared with RA populations. Furthermore, the long-term efficacy and safety at week 104 is based on Study 098 (involving a bDMARD-naive population) only, and whether these observed safety profiles can be generalized to patients with experience with a bDMARD remains unclear.

Conclusions

Two double-blind RCTs of patients with active AS were included in this review. One (i.e., Study 944) was conducted in patients with inadequate response or intolerance to 1 or 2 bDMARDs, and the other (i.e., Study 098) was conducted in patients with inadequate response to at least 2 NSAIDs, but who were bDMARD-naive. The observed evidence indicated that, at week 14, once-daily, oral, upadacitinib 15 mg showed a **statistically significant** and **clinically meaningful (or useful) benefit** as demonstrated by clinical response (i.e., ASAS40), AS symptom reduction (e.g., total back pain in Study 944), function and disability improvement (i.e., BASFI), HRQoL (ASQoL in Study 944), AS disease activity reduction (e.g., BASDAI50, ASDAS), and MRI-detected axial inflammation (i.e., MRI Spine SPARCC change in Study 098) compared with placebo. Treatment with upadacitinib also demonstrated a **statistically significant greater** improvement (in Study 944) in terms of ASAS HI, MRI Spine SPARCC change, enthesitis (MASES) and spinal mobility (BASMI) compared with placebo at week 14. Furthermore, treatment with upadacitinib also appeared **favourable compared with placebo** in terms of WPAI [redacted]) and PtGA. The magnitude of clinical response (ASAS40) to upadacitinib appeared similar in bDMARD-experienced populations compared with patients who were naive to bDMARDs

patients, even though most clinical trials assessing efficacy in bDMARD-IR populations have demonstrated reduced treatment response. The efficacy achieved at week 14 appeared to be maintained at 52 weeks (in both studies) and at week 104 (for Study 098). The overall observed AEs were aligned with the known safety profile of upadacitinib. No new safety signals were identified at weeks 14 and up to week 104. The evidence from 3 ITCs suggests [redacted] in patients who were bDMARD-naive and those who had an inadequate response to a bDMARD, although the evidence base is limited in the latter population. No treatment is favoured over others for the outcome of SAEs. The presence of heterogeneity in the included studies increases uncertainty in the findings.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946–)
- Embase (1974–)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: November 11, 2022

Alerts: Bi-weekly search updates until CADTH Canadian Drug Expert Committee (CDEC) meeting

Search filters applied: No filters were applied to limit the retrieval by study type.

Limits

- Publication date limit: none
- Language limit: none
- Conference abstracts: excluded

Table 26: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical 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
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.dq	Candidate term word (Embase)
.pt	Publication type

Syntax	Description
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

1. (rinvoq* or upadacitinib* or abt-494 or abt494 or 4RA0KN46E0 or NEW4DV02U5 or 7KCW9IQM02).ti,ab,kf,ot,hw,nm,rn.
2. 1 use medall
3. *upadacitinib/
4. (rinvoq* or upadacitinib* or abt-494 or abt494).ti,ab,kf,dq.
5. or/3-4
6. 5 use oemezd
7. 6 not (conference abstract or conference review).pt.
8. 2 or 7
9. remove duplicates from 8

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | rinvoq OR upadacitinib OR abt-494 OR abt494 | Spondylitis, Ankylosing OR Axial Spondyloarthritis]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms -- (rinvoq OR upadacitinib OR abt-494 OR abt494) AND (ankylosing spondylitis OR spondyloarthritis)]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- (rinvoq OR upadacitinib) AND (ankylosing spondylitis OR spondyloarthritis)]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- (rinvoq OR upadacitinib) AND (ankylosing spondylitis OR spondyloarthritis)]

Grey Literature

Search dates: November 02, 2022 – November 11, 2022

Keywords: [Rinvoq, upadacitinib, ankylosing spondylitis, axial spondyloarthritis, radiographic axial spondyloarthritis, AS, AxSpA, r-AxSpA, or rAxSpA]

Limits: Publication years: 2017-present for guidelines, no limits for other sections

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

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

Appendix 2: Excluded Studies

Note that this appendix has not been copy-edited.

Table 27: Excluded Studies

Reference	Reason for exclusion
None	None

Appendix 3: Detailed Outcome Data

Note that this appendix has not been copy-edited.

Table 28: Protocol Deviations (All Randomized Patients)

Category	Study 944		Study 098	
	UPA15 mg QD (N = 211)	PBO (N = 209)	UPA15 mg QD (N = 93)	PBO (N = 94)
Patients with at least one protocol deviation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients who entered the study even though they did not satisfy the eligibility criteria, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients who developed withdrawal criteria during the study but were not withdrawn, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received the wrong treatment or incorrect dose, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received an excluded concomitant treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

N = the # of patients with event; PBO = placebo; QD = once daily, UPA = upadacitinib.

Note: Includes important protocol deviation categories as suggested in the ICH E3 Guideline. Patients are counted only once in each category for which they had a deviation.

Source: Study 0944 Clinical Study Reports[15,36] Study 098 Clinical Study Reports[14,37]

Table 29: Primary and Multiplicity-Controlled Secondary End Points at Week 14 (Study 944)

Outcomes and ranks	Study 944				
	UPA 15 mg QD (N = 211)	PBO (N = 209)	Between-groups difference (upadacitinib vs. placebo) Mean or % (95% CI)	P value	Multiplicity-adjusted significance
Primary					
ASAS40, %	44.5	18.2	26.4 (17.9 to 34.9)	< 0.0001	Statistically significant
Secondary					
1. ASDAS (CRP) CFB, mean	−1.52	−0.49	−1.02 (−1.20 to −0.85)	< 0.0001	Statistically significant
2. SPARCC MRI Spine (CFB), mean	−3.95	−0.04	−3.90 (−5.47 to −2.33)	< 0.0001	Statistically significant
3. BASDAI50, %	43.1	16.7	26.4 (18.0 to 34.8)	< 0.0001	Statistically significant

Outcomes and ranks	Study 944				
	UPA 15 mg QD (N = 211)	PBO (N = 209)	Between-groups difference (upadacitinib vs. placebo) Mean or % (95% CI)	P value	Multiplicity-adjusted significance
4. ASAS20, %	65.4	38.3	27.1 (17.9 to 36.3)	< 0.0001	Statistically significant
5. ASDAS Inactive Disease, %	12.8	1.9	10.9 (6.0 to 15.8)	< 0.0001	Statistically significant
6. Total Back Pain (CFB), mean	−3.00	−1.47	−1.53 (−1.96 to −1.11)	< 0.0001	Statistically significant
7. Nocturnal Back Pain (CFB), mean	−3.21	−1.52	−1.69 (−2.14 to −1.24)	< 0.0001	Statistically significant
8. ASDAS Low Disease Activity, %	44.1	10.1	34.0 (26.2 to 41.8%)	< 0.0001	Statistically significant
9. BASFI (CFB), mean	−2.26	−1.09	−1.17 (−1.55 to −0.80)	< 0.0001	Statistically significant
10. ASAS Partial Remission, %	17.5	4.3	13.2 (7.4 to 19.0)	< 0.0001	Statistically significant
11. ASQoL, (CFB), mean	−5.10	−2.03	−3.07 (−3.90 to −2.24)	< 0.0001	Statistically significant
12. ASAS Health Index, (CFB), mean	−2.93	−1.07	−1.85 (−2.47 to −1.24)	< 0.0001	Statistically significant
13. BASMI (CFB), mean	−0.48	−0.16	−0.32 (−0.46 to −0.18)	< 0.0001	Statistically significant
14. MASES, (CFB), mean	−2.6	−1.1	−1.5 (−2.0 to −0.9)	< 0.0001	Statistically significant

ASAS40 = Assessment of SpondyloArthritis international Society 40% improvement; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASAS = Assessment of SpondyloArthritis international Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = AS quality of life; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMIlin = Linear Bath Ankylosing Spondylitis Metrology Index; CFB = Change from baseline; CI = confidence interval; diff = difference; FAS = Full Analysis Set; HI = Health Index; ID = Inactive Disease; LDA = Low Disease Activity; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MRI = MRI; n = # of patients with the event; N = number of patients in the analysis population; NRI = nonresponder imputation; n = number of patients in the specified category; PBO = placebo; PR = partial remission; QD = once daily; SPARCC = Spondyloarthritis Research Consortium of Canada; UPA = upadacitinib;

Note: For categorical end points, Cochran-Mantel-Haenszel (CMH) test was used with nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-MI). For continuous end points, MMRM is used, and N is number of unique patients contributing to MMRM model estimates.

Source: Study 944, week 14 Clinical Study Report,[14]

Table 30: Primary and Multiplicity-Controlled Secondary End Points at Week 14 (Study 098)

Outcomes	Study 098				
	UPA 15 mg QD (N = 93)	PBO (N = 94)	Btw group Difference (upadacitinib vs. placebo) %,(95% CI)	Nominal P value	Multiplicity-adjusted results
Primary					
ASAS40 (response, %)	51.6	25.5	26.1 (12.6 to 39.5)	< 0.001*	Statistically significant
Secondary					
1. ASDAS(CRP) CFB mean	−1.45	−0.54	−0.91 (−1.14 to −0.68)	< 0.001*	Statistically significant
2. SPARCC Score – Spine, CFB, mean	−6.93	−0.22	−6.71 (−9.01 to 4.41)	< 0.001*	Statistically significant
3. BASDAI 50 response (%)	45.2	23.4	21.8 (8.5 to 35.0)	0.002*	Statistically significant
4. ASQoL CFB, mean	−4.20	−2.67	−1.54 (−2.78 to −0.30)	0.016	Not Statistically significant
5. ASAS PR response, %	19.4	1.1	18.3 (10.0 to 26.6)	< 0.001*	Statistically significant
6. BASFI CFB, mean	−2.29	−1.30	−1.00 (−1.60 to −0.39)	0.001*	Statistically significant
7. BASMI CFB, mean	−0.37	−0.14	−0.22 (−0.43 to −0.02)	0.030*	Not Statistically significant
8. MASES CFB, mean	−2.25	−1.41	−0.84 (−1.68 to 0.00)	0.049*	Not Statistically significant
9. WPAI Overall Work Impairment CFB, mean	−18.11	−12.60	−5.52 (−13.82 to 2.78)	0.190	Not Statistically significant
10. ASAS HI CFB, mean	−2.75	−1.38	−1.37 (−2.37 to −0.37)	0.007*	Not Statistically significant [f]

ASAS40 = Assessment of SpondyloArthritis international Society 40% improvement; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASAS = Assessment of SpondyloArthritis international Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = AS quality of life; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMIlin = Linear Bath Ankylosing Spondylitis Metrology Index; CFB = Change from baseline; CI = confidence interval; diff = difference; FAS = Full Analysis Set; HI = Health Index; ID = Inactive Disease; LDA = Low Disease Activity; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MRI = MRI; n = # of patients with the event; N = number of patients in the analysis population; NRI = nonresponder imputation; n = number of patients in the specified category; PBO = placebo; PR = partial remission; QD = once daily; SPARCC = Spondyloarthritis Research Consortium of Canada; UPA = upadacitinib;

Note: For categorical end points, Cochran-Mantel-Haenszel (CMH) test was used with nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-MI). For continuous end points, MMRM is used, and N is number of unique patients contributing to MMRM model estimate.

Note: for study 098, ASAS HI between-group difference was designated as not statistically significant because the chain was broken before ASAS HI, and therefore it was not evaluated.

Source: Study 098 w14 Clinical Study Report,[15]

Table 31: Long-Term Efficacy Results From Open-Label Periods

Outcomes	Study 944		Study 098			
	UPA 15 mg QD (N = 211)	PBO to UPA 15 mg QD (N = 209)	UPA 15 mg QD (N = 93)	PBO to UPA 15 mg QD (N = 94)	UPA 15 mg QD (N = 93)	PBO to UPA 15 mg QD (N = 94)
	At Week 52		At Week 52		At Week 104	
Clinical response (%)						
ASAS40, (NRI, MI FAS)						
# of patients included in analysis, N (%),	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder, n (%),	[redacted]	[redacted]	65 (69.9)	65 (69.1)	61 (65.6)	60 (63.6)
ASAS20 (NRI, FAS)						
# of patients included in analysis, N (%),	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder, n (%),	[redacted]	[redacted]	71 (76.3)	79 (84.0)	63 (67.7)	65 (69.1)
ASAS PR (AO-GLMM)						
# of patients included in analysis, N (%),	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder, n (%),	[redacted]	[redacted]	41 (50.0)	38 (45.2)	37 (51.4)	31 (43.7)
ASAS 5/6 (AO/GLMM)						
# of patients included in analysis, N (%),	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder, n (%)	[redacted]	[redacted]	61 (75.3)	67 (79.8)	58 (81.7)	58 (82.9)
Measures of AS symptoms (Mean CFB)						
Total Back Pain CFB (AO-MMRM)						
# of patients included in analysis, N (%),	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Back Pain CFB (AO-MMRM), mean (95% CI)	[redacted]	[redacted]	- 4.48 [redacted]	- 4.52 [redacted]	- 4.40 [redacted]	- 4.30 [redacted]
Nocturnal Back Pain CFB,(AO-MMRM)						
# of patients included in analysis, N (%),	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	- 4.47 [redacted]	- 4.64 [redacted]	- 4.32 [redacted]	- 4.59 [redacted]
FACIT-F (AO-MMRM)						
# of patients included in analysis, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACIT-F (AO-MMRM) CFB, Mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Measures of function and disability BASFI (AO-MMRM)						
# of patients included in analysis, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Measures of function and disability BASFI (AO-MMRM) CFB mean (%95CI)	[redacted]	[redacted]	- 3.49 [redacted]	- 3.40 [redacted]	- 3.50 [redacted]	- 3.26 [redacted]

Outcomes	Study 944		Study 098			
	UPA 15 mg QD (N = 211)	PBO to UPA 15 mg QD (N = 209)	UPA 15 mg QD (N = 93)	PBO to UPA 15 mg QD (N = 94)	UPA 15 mg QD (N = 93)	PBO to UPA 15 mg QD (N = 94)
	At Week 52		At Week 52		At Week 104	
Health-related quality of life (mean CFB)						
ASQoL (AO-MMRM)						
# of patients included in analysis, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASQoL (AO-MMRM) CFB, mean (95% CI)	[redacted]	[redacted]	- 6.15 (−7.06 to − 5.25)	- 5.51 (- 6.40 to − 4.62)	- 6.68 (- 7.47 to − 5.89)	- 5.88 (−6.67 to −5.09)
ASAS Health Index (HI) (AO-MMRM)						
# of patients included in analysis, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASAS Health Index (HI) (AO-MMRM) CFB, mean (95% CI)	[redacted]	[redacted]	- 4.39 (−5.12 to − 3.65)	- 3.57 (−4.29 to − 2.84)	- 4.48 (−5.17 to − 3.80)	- 4.04 (−4.72 to −3.36)
EQ-5D-5L (AO-MMRM)						
# of patients included in analysis, N (%)	[redacted]	[redacted]	NR	NR	NR	NR
EQ-5D-5L (AO-MMRM) CFB, mean (95% CI)	[redacted]	[redacted]	NR	NR	NR	NR
EQ-5D- VAS (AO-MMRM)						
# of patients included in analysis, N (%)	[redacted]	[redacted]	NR	NR	NR	NR
EQ-5D- VAS (AO-MMRM) CFB, mean (95% CI)	[redacted]	[redacted]	NR	NR	NR	NR
SF-36 MCS (AO-MMRM)						
# of patients included in analysis, N (%)	[redacted]	[redacted]	NR	NR	NR	NR
SF-36 MCS (AO-MMRM) CFB, mean (95% CI)	[redacted]	[redacted]	NR	NR	NR	NR
SF-36 PCS (AO-MMRM)						
# of patients included in analysis, N (%)	[redacted]	[redacted]	NR	NR	NR	NR
SF-36 PCS (AO-MMRM) CFB, mean (95% CI)	[redacted]	[redacted]	NR	NR	NR	NR
WPAI Overall Work Impairment (AO-MMRM), Mean CFB						
# of patients included in analysis, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI Overall Work Impairment (AO-MMRM), CFB, mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Outcomes	Study 944		Study 098			
	UPA 15 mg QD (N = 211)	PBO to UPA 15 mg QD (N = 209)	UPA 15 mg QD (N = 93)	PBO to UPA 15 mg QD (N = 94)	UPA 15 mg QD (N = 93)	PBO to UPA 15 mg QD (N = 94)
	At Week 52		At Week 52		At Week 104	
Disease activity						
BASDAI50 (AO-GLMM)						
# of patients included in analysis: N (%)	[redacted]	[redacted]	81 (87.1)	84 (89.4)	71 (76.4)	71 (75.5)
Responder, n (%),	[redacted]	[redacted]	63 (77.8)	64 (76.2)	63 (88.7)	60(84.5)
BASDAI Mean CFB						
# of patients included in analysis, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI CFB, Mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASDAS (CRP) mean CFB (AO-MMRM)						
# of patients included in analysis, N (%)	[redacted]	[redacted]	91 (97.8)	93 (98.9)	91 (97.8)	93 (98.9)
ASDAS (CRP) mean CFB (AO-MMRM) CFB, mean (95% CI)	[redacted]	[redacted]	−1.97 (−2.12 to −1.82)	−2.00(−2.14 to −1.86)	- 1.98 (- 2.15 to − 1.82)	- 1.93 (- 2.09 to − 1.77)
ASDAS (CRP) ID (NRI, FAS)						
# of patients included in analysis: N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASDAS (CRP) LDA(NRI, FAS)						
# of patients included in analysis: N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder, n (%),	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASDAS (CRP) Clinically Important Improvement (NRI, FAS)						
# of patients included in analysis: N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radiographic changes (Mean CFB)						
MRI SPARCC Score of Spine (MMRM)						
# of patients included in analysis: N (%)	[redacted]	[redacted]	NR	NR	83 (89.2)	78 (83.0)
MRI SPARCC Score of Spine (MMRM) CFB, Mean (95% CI)	[redacted]	[redacted]	NR	NR	−7.61 (−9.67 to −5.56)	- 6.98 (−9.11 to −4.85)
MRI SPARCC Score of SIJ (MMRM)						
# of patients included in analysis: N (%)	[redacted]	[redacted]	NR	NR	70 (75.3)	66 (70.2)

Outcomes	Study 944		Study 098			
	UPA 15 mg QD (N = 211)	PBO to UPA 15 mg QD (N = 209)	UPA 15 mg QD (N = 93)	PBO to UPA 15 mg QD (N = 94)	UPA 15 mg QD (N = 93)	PBO to UPA 15 mg QD (N = 94)
	At Week 52		At Week 52		At Week 104	
MRI SPARCC Score of SIJ (MMRM) CFB, Mean (95% CI)	[redacted]	[redacted]	NR	NR	−4.55 (−5.59 to −3.52)	−5.61 (−6.67 to −4.55)
PtGA of Disease Activity (AO-MMRM)						
# of patients included in analysis: N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PtGA of Disease Activity (AO-MMRM) CFB, Mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MASES (Mean CFB)						
# of patients included in analysis: N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MASES mean CFB, (AO-MMRM),CFB, Mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASMI mean CFB (MMRM)						
# of patients included in analysis: N (%)	[redacted]	[redacted]	93 (100)	92 (97.9)	93 (100)	92 (97.9)
BASMI CFB (MMRM), mean (95% CI)	[redacted]	[redacted]	−0.76 [redacted]	−0.65 [redacted]	−0.79 (−0.97 to − 0.60)	−0.64 (−0.82 to − 0.46)

AO = as observed; ANCOVA = analysis of covariance; ASAS40 = Assessment of SpondyloArthritis international Society 40% improvement; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASAS = Assessment of SpondyloArthritis international Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = AS quality of life; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMIlin = Linear Bath Ankylosing Spondylitis Metrology Index; CFB = Change from baseline; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Diff = difference; CRP = C-reactive protein; diff = difference; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels Health State Instrument; FAS = Full Analysis Set; GLMM = generalized linear mixed model; HI = Health Index; ID = Inactive Disease; LDA = Low Disease Activity; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MMRM = mixed-effect model repeated measurements; MRI = MRI; n = # of patients with the event; N = number of patients in the analysis population; NRI = nonresponder imputation; n = number of patients in the specified category; PBO = placebo; PR = partial remission; PtGA = Patient's Global Assessment of Disease Activity; QD = once daily; SF-36 PCS = Medical Outcomes Study 36-Item Short Form Health Survey physical component summary; SPARCC = Spondyloarthritis Research Consortium of Canada; UPA = upadacitinib; VAS = visual analogue scale;

Source: Clinical Study Reports[36,37], Deodhar et al. (2022),[40] van der Heijde et al. 2022,[41]

Table 32: TEAEs in Extension Phase (Safety Analysis Set)

Exposure-adjusted event rate	Study 944	Study 098	
	UPA15 mg QD (N = 414) (PYs = 534.4) Events (E/100PYs)	UPA15 mg QD (N = 182) (PYs = 237.6) Events (E/100PYs)	UPA 15 mg QD (N = 182) (PYs = 308.6) Events (E/100PYs)
	At Week 52	At Week 52	At Week 104
Any treatment-emergent AE, n (%)	[redacted]	618 (260.1)	749 (242.7)
Most common TEAEs (Events with ≥ 10 TEAE), n (%)			

Exposure-adjusted event rate	Study 944	Study 098	
	UPA15 mg QD (N = 414) (PYs = 534.4) Events (E/100PYs)	UPA15 mg QD (N = 182) (PYs = 237.6) Events (E/100PYs)	UPA 15 mg QD (N = 182) (PYs = 308.6) Events (E/100PYs)
	At Week 52	At Week 52	At Week 104
Blood creatine phosphokinase increased	[redacted]	28 (11.8)	35 (11.3)
Leukopenia	[redacted]	1 (0.4)	[redacted]
COVID-19	[redacted]	NR	[redacted]
COVID-19 pneumonia	[redacted]	NR	[redacted]
Herpes zoster	[redacted]	5 (2.1)	5 (1.6)
Iridocyclitis	[redacted]	10 (4.2)	[redacted]
Asymptomatic COVID-19	[redacted]	NR	[redacted]
Neutropenia	[redacted]	6 (2.5)	[redacted]
Diarrhea	[redacted]	12 (5.1)	[redacted]
Nasopharyngitis	[redacted]	37 (15.6)	[redacted]
Aspartate aminotransferase increased	[redacted]	7 (2.9)	[redacted]
Ankylosing spondylitis	[redacted]	11 (4.6)	[redacted]
Headache	[redacted]	16 (6.7)	[redacted]
Alanine aminotransferase increased	[redacted]	12 (5.1)	[redacted]
Hyperuricemia	[redacted]	NR	[redacted]
Hypertension	[redacted]	9 (3.8)	[redacted]
Arthralgia	[redacted]	6 (2.5)	[redacted]
Back pain	[redacted]	6 (2.5)	[redacted]
Upper respiratory tract infection	[redacted]	26 (10.9)	[redacted]
SAE, n (%)	[redacted]	14 (5.9)	19 (6.2)
AE leading to withdrawal of study treatment, n (%)	[redacted]	15 (6.3)	17 (5.5)
Any AE leading to death, n (%)	[redacted]	0	0
All deaths, n (%)	[redacted]	0	0
Notable harms, n (%)			
Infection	[redacted]	205 (86.3)	246 (79.7)
Serious infection	[redacted]	0	0

	Study 944	Study 098	
	UPA15 mg QD (N = 414) (PYs = 534.4) Events (E/100PYs)	UPA15 mg QD (N = 182) (PYs = 237.6) Events (E/100PYs)	UPA 15 mg QD (N = 182) (PYs = 308.6) Events (E/100PYs)
Exposure-adjusted event rate	At Week 52	At Week 52	At Week 104
Malignancy	[redacted]	1 (0.4)	1 (0.3)
Malignancy other than NMSC	[redacted]	1 (0.4)	[redacted]
Hepatic disorder	[redacted]	24 (10.1)	32 (10.4)
Anemia	[redacted]	3 (1.3)	5 (1.6)
Neutropenia	[redacted]	7 (2.9)	9 (2.9)
Lymphopenia	[redacted]	2 (0.8)	3 (1.0)
Herpes zoster	[redacted]	5 (2.1)	5 (1.6)
Hypersensitivity	[redacted]	NR	[redacted]
Adjudicated MACE*	[redacted]	0	[redacted]
Adjudicated gastrointestinal perforation	[redacted]	0	[redacted]
Dyslipidemia	[redacted]	2 (0.8)	[redacted]
Hepatotoxicity	[redacted]	NR	[redacted]
Active tuberculosis	[redacted]	0	0
Adjudicated venous thromboembolic events**	[redacted]	0	1 (0.3)
Opportunistic infection excluding tuberculosis and herpes zoster	[redacted]	2 (0.8)	2 (0.6)
Acne	[redacted]	5 (2.1)	[redacted]
Elevated CPK	[redacted]	28 (11.8)	35 (11.3)
Folliculitis	[redacted]	5 (2.1)	6 (1.9)

AAT = Alanine aminotransferase; AE = adverse event; CI = confidence interval; COVID-19 = coronavirus disease of 2019; CPK = creatine phosphokinase; GI = gastrointestinal; MACE = major adverse cardiac event; n = number of patients with event; N = total number of patients included in the analysis; NMSC = non-melanoma skin cancer; NR = not reported; PY = patient year; QD = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = Withdrawal due to adverse events;

Source: Clinical Study Reports[36,37]

Appendix 4: Description and Appraisal of Outcome Measures

Note that this appendix has not been copy-edited.

Aim

To describe the following outcome measures (Table 33) and review their measurement properties (validity, reliability, responsiveness to change, and MID) (Table 34).

Table 33: Outcome Measures Included in Each Study

Outcome measure	Study 944	Study 098
ASAS response		
ASAS40	Primary	Primary
ASAS20	Key Secondary	Additional Secondary
ASAS Partial Remission	Key Secondary	Key Secondary
ASAS HI	Key Secondary	Key Secondary
ASAS5/6	NR	Exploratory
Patient Global Assessment of Disease Activity (ASAS individual component)	Exploratory	Exploratory
ASDAS	Key Secondary	Key Secondary
BASDAI	Key Secondary	Key Secondary
BASFI	Key Secondary	Key Secondary
ASQoL	Key Secondary	Key Secondary
MRI SPARCC (spine)	Key Secondary	Key Secondary
MRI SPARCC (SI joints)	Additional Secondary	Additional Secondary
SF-36	Exploratory	NR
EQ-5D-5L	Exploratory	NR
WPAI	Exploratory	Key Secondary
BASMI	Key Secondary	Key Secondary
MASES	Key Secondary	Key Secondary
FACIT-F	Exploratory	Exploratory

ASAS = Assessment of SpondyloArthritis international Society; ASAS HI = Assessment of SpondyloArthritis international Society - Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = Ankylosing Spondylitis quality of life questionnaire; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MRI = MRI; NR = not reported; SF-36 = Short From (36) Health Survey; SI = sacroiliac; SPARCC = Spondyloarthritis Research Consortium of Canada; WPAI = Work Productivity and Activity Impairment.

Findings

Table 34: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
ASAS response	A composite set of response criteria which are commonly used in AS trials, contains 6 domains.[85]	See ASAS variations below	None identified.
ASAS40	40% improvement and absolute improvement from baseline of ≥ 2 units (range 0 to 10) in ≥ 3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), without any worsening in the remaining domain.[85]	The ASAS40 has good discriminating capacity between treatment (with infliximab) and placebo.[86]	NA
ASAS20	≥ 20% improvement and an absolute improvement from baseline of ≥ 1 units (range 0 to 10) in ≥ 3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), without any worsening of ≥ 20% and ≥ 1 unit (range 0 to 10) in the remaining domain.[85]	The criteria for the ASAS20 were identified as the best performing criteria out of 20 different ASAS-based criteria, with strong discriminatory performance.[87]	NA
ASAS Partial Remission	A value not above 2 units (range 0 to 10; NRS) in each of the following 4 ASAS domains: Patient Global, Spinal Pain, Function, and Inflammation.[85]	None identified	NA
ASAS-HI	The ASAS HI is an axSpA-specific 17-item patient-reported instrument designed to assess functioning, disability, and health. Total scores range from 0 to 17, with lower scores indicating better health.[85]	The sum score of the 17 items correlated significantly with BASDAI and total back pain as well as with Bath AS Functional Index and Bath AS-patient Global Score.[88] In AS patients, construct validity showed a Spearman correlation coefficient ranging from moderate to high, internal consistency was high, and responsiveness was moderate to large.[89]	None identified.
ASAS5/6	The ASAS5/6 includes assessments of all 6 individual ASAS domains and represents improvement of ≥ 20% in at least 5 domains.[85]	Good discriminating capacity between treatment (with infliximab) and placebo.[86]	NA
Patient Global Assessment of Disease Activity (ASAS individual component)	The Patient Global Assessment of Disease Activity relates to a single specific ASAS domain based on an NRS. For this assessment, the patient was asked to respond to the following question: "How active was your spondylitis on average during the last week?" The answer was recorded on an NRS and was rated between "0" (not active) and "10" (very active).[85]	Moderately correlated with the ASAS HI.[89]	None identified.

Outcome measure	Type	Conclusions about measurement properties	MID
ASDAS	A composite index to assess disease activity in rad-axSpA that include the following parameters: Total back pain (BASDAI Question 2); Patient Global Assessment of Disease Activity (individual ASAS domain); Peripheral pain/swelling (BASDAI Question 3); Duration of morning stiffness (BASDAI Question 6); hsCRP.[85]	The ASDAS is correlated with other measures including the BASDAI,[79,90] ASAS-HI,[91] C-reactive protein,[92] MRI sacroiliac joints inflammation[92] and MRI total inflammation scores,[92] patient's global assessment,[93] and physician's global assessment.[93]	≥ 1.1 units in AS patients.[94]
BASDAI	Self-administered, disease-specific questionnaire, pertaining to the 5 major symptoms of AS: fatigue; spinal pain; peripheral joint pain/swelling; areas of localized tenderness; and morning stiffness. Scores ranging from 0 to 18, higher scores indicating greater disease activity.[85]	Test-retest results were significantly intercorrelated for BASDAI.[95] BASDAI appeared to be sensitive to change, reflecting a 16% (mean) improvement in inpatient scores after 3 weeks of intensive physiotherapy treatment.[96]	2 units in AS patients.[97]
BASFI	Self-administered 8-question instrument addressing physical function and patient's ability to cope with everyday life on 10 cm visual analogue scales.[85]	Test-retest results showed significant intercorrelation for BASFI.[95] BASFI is one of 3 AS assessment instruments with the most extensive evidence for validity through comparison with instruments that measure similar or related constructs, and/or with measures of mobility.[98]	7 mm on VAS or 17.5% of the baseline score[99] or 0.6 units on a 10-unit scale in AS patients.[100]
ASQoL	An 18-item AS specific QoL questionnaire including items related to the impact of disease on sleep, mood, motivation, coping, activities of daily living, independence, relationships, and social life. Total scores range from 0 to 18, with higher scores representing worse QoL.[85]	Evidence of excellent internal consistency, test-retest reliability and validity in AS patients.[101] High test-retest reliability and a good correlation with BASDAI.[102]	One unit of worsening (i.e., + 1) or 2 units improvement (i.e., to −2) in AS patients.[44]
MRI SPARCC (spine)	An MRI-based scoring system that assesses the presence, 3-dimensional extent, and signal intensity of active inflammatory lesions represented by bone marrow edema, in the spine of affected patients.[85]	When assessing the 6 most affects units, the overall intra-observer reproducibility was excellent for the 3 readers, and the mean percentage intra-observer concordance for the selection of affected discovertebral units was 78.8%, 87.9%, and 80.3% for the 3 readers.[103]	5.0 units in AS patients.[104]
MRI SPARCC (SI joints)	A MRI-based scoring method that assesses increased signal denoting bone marrow edema on T2-weighted STIR sequences.[85]	The intraobserver reproducibility of the total score based on 3 readers was excellent while the ICC for change (in MRI activity) scores was lower.[105] The SPARCC MRI score for SI joint has been shown to be correlated with the ASDAS.[106]	2.5 units in AS patents.[104]

Outcome measure	Type	Conclusions about measurement properties	MID
SF-36	A 36-items generic health state instrument. Contains 8 domains and 2 component summaries on physical and mental health. Domain scores and summary scores ranging from 0 to 100.[85]	The SF-36 had a strong correlation with the Mander Enthesitis Index and the BASDAI.[107] Evidence of construct validity and good internal consistency reliability in AS patients.[108]	2.5 to 5 points for the component scores in various arthritis patients.[109]
EQ-5D-5L	The EQ-5D-5L is a generic QOL instrument consisting of 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a VAS for rating health today. Weighted scoring produces an index score.[85]	When compared to the SF-6D and the well-being rating scale (RS) in AS patients, the ICCs indicated moderate agreement.[110] Instruments correlated equally with disease activity, functioning and quality of life. Compared with EQ-5D and RS, SF-6D showed smaller average differences in utility between patients with better and worse disease.[110]	0.033 to 0.074 for general population.[111] None identified for AS patients.
WPAI	A patient-reported measure of work productivity including presenteeism, absenteeism, overall work productivity loss, and daily activity impairment.[85]	Construct validity was demonstrated using median scores of other measures including the BASDAI and SF-36. Patients with AS of the worst severity (BASDAI > median) demonstrated significantly greater overall work impairment, presenteeism, and daily activity impairment, based on the WPAI.[112]	None identified
BASMI	Assesses spinal mobility in patients with AS. In the clinical trials the Linear BASMI (BASMIlin) composite score was calculated using the BASMI components: lateral lumbar flexion; tragus-to-wall distance, lumbar flexion, intermalleolar, and cervical rotation. Scores for each assessment range from 0 to 10, and the BASMIlin total score is the average of the 5 assessment scores. Higher scores indicate decreased spinal mobility.[85]	Accurate and reproducible for both intraobserver and interobserver variability.[113] Correlated positively with total radiology score.[114] The linear BASMI was more sensitive to changes in range of motion than the 10-step BASMI in AS patients.[115]	None identified
MASES	A validated enthesis index for AS with a score ranging from 0 to 13, correlating with the number of painful entheses out of the total of 13 assessed.[116]	Weak positive correlations between MASES and BASDAI, BASFI, and fatigue as measured by the BASDAI question 1.[117] MASES was not significantly correlated with BASRI, BASMI, or ASQoL.[117]	None identified
FACIT-F	A self-administered questionnaire that assesses both the physical and functional consequences of fatigue.[118] It is a 13-item questionnaire with each question scored from 0 “not at all” to 4 for a total score range of 0 to 52 with	Mean FACIT-F scores decreased (i.e., worse fatigue symptoms) for patients reporting greater clinical severities in the BASDAI fatigue item, BASDAI pain item, total back pain, and BASFI,	3.1 to 6.3 points for the FACIT-F total score for a meaningful within-patient change in AS patients.[118]

Outcome measure	Type	Conclusions about measurement properties	MID
	higher scores denoting lower levels of fatigue.[118]	supporting construct validity.[108] Good internal consistency reliability.[108]	

AS = ankylosing spondylitis; ASAS = Assessment of SpondyloArthritis international Society; ASAS HI = Assessment of SpondyloArthritis international Society - Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = Ankylosing Spondylitis quality of life questionnaire; axSpA = Axial spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; BASRI = Bath Ankylosing Spondylitis Radiology Index; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; hsCRP = high-sensitivity C-reactive protein; ICC = intraclass correlation coefficient; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MRI = MRI;; NR = not reported; NRS = numerical rating scale; QoL = quality of life; SF-36 = Sort Form (36) Health Survey; SF-6D = Short Form 6-dimensions; SI = sacroiliac; SPARCC = Spondyloarthritis Research Consortium of Canada; SRM = standardized response mean; STIR = short tau inversion recovery; WPAI = Work Productivity and Activity Impairment.

Assessment in Ankylosing Spondylitis Response

The ASAS Working Group developed a composite set of response criteria that is commonly used in AS clinical trials. The ASAS Working Group is an international group of rheumatologists, epidemiologists, patients with AS, and pharmaceutical industry representatives from more than 21 countries.[119,120]

The ASAS International working group has defined core domains that are important in assessing the ASAS20, ASAS40, and ASAS5/6. These domains include Patient Global Assessment of Disease Activity, spinal pain, function, inflammation (mean of BASDAI question 5 and 6), CRP, and spinal mobility (lateral spinal flexion).[121]

Patient Global Assessment of Disease Activity is described below. Spinal pain is assessed based on the ASAS Handbook through the following questions: “How much pain of your spine due to ankylosing spondylitis do you have?”, and “How much pain of your spine due to ankylosing spondylitis do you have at night?” The responses are assessed using an NRS from 0 (no pain) to 10 (most severe pain).[121] Function is assessed using the BASFI. Inflammation is assessed using the mean of BASDAI questions 5 and 6 which relate to intensity and duration of morning stiffness (described below). CRP, a measure of acute-phase reactant, is measured using high-sensitivity assay at the central laboratory. Spinal mobility is assessed using BASMI, a combined index of the following measurements: lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schrober), maximal intermalleolar distance, and cervical rotation.[121]

The ASAS response criteria were developed to establish a uniform minimum core set of variables for inclusion in all research projects that may help prevent dilemmas such as AS studies that may have employed inconsistent and excessive numbers of assessment methods. This approach is hoped to help prevent such dilemmas by ensuring change occurrences of statistically significant differences between groups are minimized; investigators do not introduce bias by selectively publishing only favourable variables; and comparisons can be made between studies including meta-analyses.[122]

ASAS40

The ASAS40 is derived from patient-reported assessments.[86] An ASAS40 response is defined as a ≥ 40% improvement and an absolute improvement from baseline of ≥ 2 units (range 0 to 10) in ≥ 3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), without any worsening in the remaining domain.[86]

Using data derived from 2 RCTs (n = 99) the criteria for the ASAS40 was identified out of 50 different ASAS criteria as 1 of 2 best performing criteria (the ASAS5/6 is the other best performing criteria, although neither of these 2 criteria is clearly superior on statistical grounds).[86] The ASAS40 was determined using Boolean type criteria. The power of different criteria was evaluated using chi-square values with 95% CIs calculated using bootstrap methods. Based on the data from an infliximab trial, the ASAS40 was determined to have a chi-square = 26.5 (95% CI = 13.3 to 41.1) and a low placebo response rate of 5.7%, this indicated good discriminating capacity between treatment (with infliximab) and placebo.[86]

ASAS20

The ASAS20 is derived from patient-reported assessments. An ASAS20 response is defined as a ≥ 20% improvement and an absolute improvement from baseline of ≥ 1 units (range 0 to 10) in ≥ 3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), without any worsening of ≥ 20% and ≥ 1 unit (range 0 to 10) in the remaining domain.[121]

Using a random subset of two-thirds of the data from 3 NSAIDs trials (n = 923) the criteria for the ASAS20 was identified as the best performing criteria out of 20 different ASAS-based criteria based on its chi-square value = 36.4% (P < 0.001), and a placebo response rate that did not exceed 25%.[87] This finding was validated using the remaining one-third of data from the 3 NSAID trials which found very similar results.[87]

ASAS Partial Remission

The ASAS partial remission is derived from patient-reported assessments. An ASAS PR response is defined as a value not above 2 units (range 0 to 10; NRS) in each of the following 4 domains: Patient Global, Spinal Pain, Function, and Inflammation.[121] Validity and reliability assessments were not identified in the literature.

ASAS HI

The ASAS HI is an axSpA-specific 17-item patient-reported instrument designed to assess functioning, disability, and health.[88] The ASAS HI has scores ranging from 0 (good health) to 17 (poor health). Each item consists of 1 question that the patient needed to respond to with either “I agree” (score of 1) or “I do not agree” (score of 0). A score of “1” was given where the item was affirmed, indicating adverse health. All item scores are summed to give a total score or index.[88]

The 17 items on the ASAS HI were selected from an item pool of 251 items that had been selected to cover all categories of the International Classification of Functioning, Disability and Health (ICF) core set. The final 17 items cover most of the ICF core set and showed the best representation of the health status of patients with AS.[88]

The 251-item pool was reduced to 17 items that showed the best reliability and fit to the Rasch model, no residual correlation, and absence of consistent differential item function and a Person Separation Index of 0.82.[88] The sum score of the 17 items correlated significantly with BASDAI and total back pain (r = 0.6) as well as with Bath AS Functional Index and Bath AS—patient Global Score (r = 0.7), (all P < 0.0001).[88]

The ASAS HI was assessed in an international validation study that included translations of the ASAS HI in 23 countries.[89] Construct validity showed a Spearman correlation coefficient ranging from moderate (WPAI absenteeism: 0.38) to high (BASFI: 0.71 or SF-36 PSC 0.73). Internal consistency was high (Cronbach alpha = 0.93). The reliability among 578 patients was good (ICC = 0.87; 95% CI = 0.84 to 0.89). Responsiveness among 246 patients was moderate to large (SRM = −0.44 for NSAIDs to −0.69 for csDMARDs, and −0.85 for TNFi drugs).[89]

An MID was not identified in the literature, the smallest detectable change was identified at 3.0 units.[89] The threshold of ASAS HI which differentiated patients with "good/very good" health from those with "moderate" health state, was identified as being 5.0. The most clinically relevant threshold of ASAS HI for "moderate" versus "poor/very poor" health was identified as a score of 12.0 or above.[89]

ASAS5/6

The ASAS5/6 includes assessments of all 6 individual ASAS domains and represents improvement of ≥ 20% in at least 5 domains.[86] The ASAS5/6 has been identified as advantageous as it includes the objective domains of spinal mobility and acute-phase reactants, but only requires 20% improvement.[86]

The ASAS5/6 was evaluated in the same study as the ASAS40 using methods described above.[86] The criteria for the ASAS5/6 was identified out of 50 different ASAS criteria as 1 of 2 best performing criteria (the ASAS40 is the other best performing criteria).[86] Based on the data from an infliximab trial, the ASAS5/6 was determined to have a chi-square = 31.9 (95% CI, 18.0 to 46.9) and a low placebo response rate of 2.9%, this indicated good discriminating capacity between treatment (with infliximab) and placebo.[86]

Patient Global Assessment of Disease Activity (Individual ASAS Domain)

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

The Patient Global Assessment of Disease Activity is moderately correlated with the ASAS HI (r = 0.57).[89] While a MID was not identified in the literature, a validation study determined that for individual domains on the ASAS (e.g., Patient Global Assessment of Disease Activity), the minimum change that should be considered detectable would be approximately 2 to 3 units on a scale of 0 to 10.[87] Additionally, an international validation study on the ASAS HI assessed Patient Global Assessment of Disease Activity using cut-off values of < 3 and > 6 on NRS to distinguish between "good" and "poor" health status.[89]

Ankylosing Spondylitis Disease Activity Score

The ASDAS is a composite index to assess disease activity in rad-axSpA that include the following parameters[123]:

- Total back pain (BASDAI Question 2)

- Patient Global Assessment of Disease Activity (individual ASAS domain)
- Peripheral pain/swelling (BASDAI Question 3)
- Duration of morning stiffness (BASDAI Question 6), and
- CRP in mg/L (acute-phase reactant)

The ASDAS CRP is calculated with the following equation: 0.121 × total back pain + 0.110 × patient global + 0.073 × peripheral pain/swelling + 0.058 × duration of morning stiffness + 0.579 × Ln (CRP + 1).[123,124]

Four disease activity states have been defined by ASAS consensus[94,125]:

- ASDAS < 1.3 defines inactive disease
- 1.3 ≤ ASDAS < 2.1 defines low disease activity
- 2.1 ≤ ASDAS ≤ 3.5 defines high disease activity, and
- ASDAS > 3.5 defines very high disease activity.

The ASDAS is correlated with other measures including the BASDAI (concordance coefficients = 0.81;[90] 0.76[92]), ASAA-HI (correlation coefficient = 0.56),[91] C-reactive protein (correlation coefficient = 0.79),[92] MRI sacroiliac joints inflammation (correlation coefficient = 0.46)[92] and MRI total inflammation scores (correlation coefficient = 0.34)[92] patient's global assessment (correlation coefficient = 0.71)[93] and physician's global assessment (correlation coefficient = 0.65)[93.]

Clinically important improvement based on the ASDAS is defined as change ≥ 1.1 units, and major improvement is defined as change ≥ 2.0 units or achieving the minimum ASDAS score of 0.6361 at postbaseline visit.[94] Conclusions by the ASAS consensus defined clinically important worsening as an increase in ASDAS of at least 0.9 points.[126]

Bath Ankylosing Spondylitis Disease Activity Index

The most common and widely used validated measure of inflammatory activity of AS is the BASDAI.[127] This instrument for disease activity is a self-administered patient questionnaire. The BASDAI is a composite index that records patients' responses to major symptoms of AS. It was designed by a multidisciplinary team (rheumatologists, physiotherapists, and research associates) with input from patients. It includes 6 questions addressing 5 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).[96] Patients' responses are recorded on a 10-unit horizontal NRS or 10 cm VAS or a numeric response scale (1 to 10). The scores for questions 5 and 6 (severity and duration of morning stiffness) are averaged; the result is then averaged with the remaining 4 question scores. The final BASDAI score has a range from zero to 10: the higher the score, the greater the measured degree of disease activity.[96]

BASDAI 20, 50, 70 and 90 reflect an improvement of ≥ 20%, 50%, 70% and 90%, respectively, over an initial assessment at a given point in time of treatment of an AS patient.[96]

The 2005 International ASAS consensus statement for the use of anti-TNF drugs in patients with AS recommends the BASDAI follow after initiation of treatment. The recognized MID/treatment response is a change in the BASDAI of 2 units (on a zero to 10 scale) of the BASDAI.[97]

Garrett and colleagues developed, as well, as evaluated this instrument through analysis of user friendliness, reliability (consistency), score distribution, sensitivity to change and comparisons to a previous Bath disease Activity Index and the Newcastle Enthesitis Index.[96] In this assessment, the BASDAI was completed by 154 patients receiving 3 weeks of intensive physiotherapy (inpatients and outpatients). It was found by patients to be relatively quick (mean 67 seconds, range 30 to 120 seconds) and simple to complete. BASDAI appeared to be sensitive to change, reflecting a 16% (mean) improvement in inpatient scores after 3 weeks of intensive physiotherapy treatment.[96]

Haywood et al., completed a structured review of the measurement properties for all disease-specific multi-item, patient assessed health instruments in patients with AS including BASDAI.[98] In this investigation, systematic literature searches were made to identify instruments, using predefined criteria relating to reliability (measurement stability over time), validity (instrument measures what is intended, content and face), responsiveness (ability of an instrument to measure clinically important change) and precision.[98] The investigators report 72 published instrument evaluations following completion by patients with AS (including 17 for reliability and 37 for validity). Their assessment of reliability, validity, and responsiveness for BASDAI is presented below:

Table 35: Haywood et al. Review — Summary of Measurement Properties for AS Instruments[98]

	Reliability		Validity		Responsiveness	
Instrument	Thoroughness	Results	Thoroughness	Results	Thoroughness	Results
BASDAI (Disease Activity)	+++	+++	+++	+++	+++	+++
BASFI (Function)	+++	+++	+++	+++	+++	+++
BAS-G (Global well-being)	++	++	++	+	++	++
ASQoL (HRQoL)	++	++	++	++	++	++

Notes: Thoroughness of evaluation: 0 = no published evidence; + = basic information only; ++ = several types of test, or several evaluations in different populations; +++ = all major forms of validity, reliability/ responsiveness reported, several good quality evaluations in different populations; Results of evaluation: 0 = no published numerical results; + = weak evidence only; ++ = moderate evidence; +++ = strong evidence

Maravic et al., also evaluated the psychometric properties of different translated versions of the BASDAI available (English, Turkish, French, Swedish, and Spanish) including assessing face validity, content validity, construct validity (factorial analysis, convergent and divergent validity), reliability (test-retest, Cronbach coefficient Alpha which indicates the degree of relatedness between items) and responsiveness.[128] Face validity was validated in all versions. The authors outline that no version initially defined the dimensions for

content validity and construct validity was partially studied and validated in English, French and Spanish. Reliability was validated in English, French and Turkish. Responsiveness was demonstrated in all versions except for French.

Calin et al., set out to answer the question of whether the composite index is an accurate reflection of the components parts or whether weighting would provide increased accuracy of assessment.[129] Four hundred and 70–three (473) patients with AS randomly received placebo or NSAID therapy for 6 weeks. Disease activity was assessed using BASDAI and the individual components of BASDAI relating to morning stiffness, pain, fatigue, and discomfort - analyzed separately. A principal component analysis was used to explore the best combination of variable and to assess whether a simple sum, as is currently used for the BASDAI index, or a weighted index would best define disease activity. The BASDAI as a simple sum of its components was found to have excellent content validity.[129]

Madsen et al., examined the reproducibility of BASDAI in anti-TNF-treated SpA patients already familiar with the use of the indice.[95] Testing was performed twice on 2 different days (median interval 7 days, range 4 to 10 days) under standardized conditions in 26 out-clinic patients (median age 39 years, range 22 to 56 years). Limits of agreement were calculated as the 95% likely range for the difference between paired scores. Test-retest results were significantly intercorrelated with r (s) = 0.90 for BASDAI. Internal consistency reliability and construct validity of BASDAI was deemed acceptable by the authors.[95]

Pavy et al., investigated the MCID of BASDAI and BASFI.[99] They administered both questionnaires to 125 patients with AS at baseline and 2 weeks after an intensive physiotherapy program. Along with the final assessment, a global validated 15-point rating scale was used to examine each domain. Receiver operating characteristic (ROC) curves were used to determine the score change that most accurately classified patients with respect to a clinically meaningful change. According to analyses of ROC curves, the MCID was 10 mm or 22.5% for BASDAI with sensitivity = 0.65 and specificity = 0.82. Regression analysis showed that MCID values were independent of the patients' baseline scores.[99] These results were similar to a study by Kviatkovsky et al. (2016) that identified the minimally clinically important improvement to be 1.1 units on a 10 unit scale.[100]

Cohen et al., conducted a survey of patients' perceptions about current disease control.[130] One thousand questionnaires were mailed to members of a spondyloarthropathic patient organization to estimate the best BASDAI cut-off for discriminating between poor and well-controlled groups, from a patient's perspective. A proportion of 55.3% perceived inadequate control of their disease. The mean BASDAI in the overall population was 43.5 +/− 22.9, 30.4 +/− 19.9 in the well-controlled group and 54 +/− 19.4 in the poorly controlled group (P < 0.001). From the ROC curve, the best BASDAI cut-off for discriminating between patients in the 2 groups was found to be 39 (sensitivity 74.6% and specificity 72.4%). According to sex, the best cut-off was 44 for women and 36 for men.[130]

Bath Ankylosing Spondylitis Functional Index

The BASFI is a validated, patient self-administered, composite instrument widely used in AS to assess physical function. The BASFI consists of 8 specific questions regarding function in AS and 2 questions reflecting the patient's ability to cope with everyday life.[131] Each question is answered on a 10 cm horizontal VAS or a numeric response scale (0 to 10), the mean of which gives the BASFI score (on a scale of zero to 10). The higher the BASFI score, the greater the degree of functional impairment with reductions from baseline indicating improvement.

Calin and colleagues (1994) developed the BASFI and evaluated it in comparison to the published Douglas Functional Index (DFI).[131] In this investigation, the questionnaire was completed 257 times in total; once by 116 outpatients and by 47 inpatients on 3 occasions over a 3-week intensive physiotherapy course. The BASFI was analyzed in terms of all validity criteria and compared with the DFI. Patient scores covered 95% of the BASFI range, producing a normal distribution of results. Sensitivity results of the BASDAI in comparison to DFI were reported.[131] Over the 3-week period of inpatient treatment, the BASFI revealed a significant improvement in function (20%, P = 0.004) while there was less change in the DFI (6%, P = 0.03).

Spoorenberg et al. (1999) conducted a comparative study of the usefulness of BASFI and the DFI in assessment of AS in 191 outpatients in Europe.[132] The external criterion for disease activity was both patient and physician assessment on a VAS and the BASDAI. The external criterion for damage was 2 radiological scores of the spine (BASRI-s Bath AS Radiology Index spine) and a modified Stoke AS Spine Score (mSASSS). Both BASFI and DFI appeared to correlate equally well with disease activity and damage. The average correlation with disease activity variables was 0.42 for BASFI and 0.41 for DFI. The correlation for both BASFI and DFI with BASRI-s was 0.42 and with mSASSS 0.36. Sensitivity for the BASFI and DFI was between 76 and 94% for distinguishing between patients with high and low disease activity, while specificity was between 66 and 87%.[132]

The study carried out by Madsen et al. (2010) also examined the reproducibility of BASFI in anti-TNF-treated SpA patients.[95] With the same study population and protocol that have been mentioned for BASDAI, test-retest results showed significant intercorrelation with r (s) = 0.92 for BASFI.[95] Limit of agreement for BASFI was +/−1.4. Internal consistency reliability and construct validity of BASFI was deemed acceptable by the authors, but they also mentioned that random measurement error of BASFI was not negligible.[95]

In a review of AS instruments, Haywood et al. (2005) reported on 70 published instrument evaluations for BASFI following completion by patients with AS.[98] The authors comment that BASFI is 1 of 3 AS assessment instruments with the most extensive evidence for validity through comparison with instruments that measure similar or related constructs, and/or with measures of mobility.[98]

As mentioned for BASDAI, Pavy et al. (2005) investigated the MCID of BASFI in 125 AS patients undergoing an intensive physiotherapy program.[99] Using that protocol and according to analyses of ROC curves, the MCID was 7 mm or 17.5% for BASFI with sensitivity = 0.60 and specificity = 0.85. As shown by regression analysis, MCID values were independent of the patients' baseline scores. These results were similar to a

study by Kviatkovsky et al. (2016) that identified the minimally clinically important improvement to be 0.6 units on a 10-unit scale.[100]

AS Quality of Life Questionnaire

The ASQoL is an 18-item validated disease-specific questionnaire for measuring quality of life in patients with AS.[101] Items assess the impact of disease on sleep, mood, motivation, coping, activities of daily living, independence, relationships and social life. The self-reported questionnaire is composed of yes/no questions; hence the ASQoL overall score ranges from 0 to 18 with higher score indicating worse HRQoL. The instrument showed evidence of excellent internal consistency (alpha = 0.89 to 0.91), test-retest reliability (r(s) = 0.91 to 0.92) and validity in AS patients.[101] Another publication reported high test-retest reliability (> 0.90) for ASQoL and its good correlation with BASDAI (0.79).[102] In a recent systematic review of 13 studies among patients with AS and non-radiographic axial spondyloarthritis, the ICC value of test-retest reliability was 0.85 (95% CI 0.80 to 0.89) and the Cronbach alpha was 0.89 (95% CI 0.86 to 0.92), indicating high test-retest reliability and internal consistency reliability, respectively.[133]

In patients with AS, 1 unit of worsening (i.e., + 1) or 2 units improvement (i.e., to −2) were considered clinical meaningful.[44]

The SpondyloArthritis Research Consortium of Canada MRI Index for Spine

The SPARCC MRI index for spine is an MRI-based scoring system that assesses the presence, 3-dimensional extent, and signal intensity of active inflammatory lesions represented by bone marrow edema, in the spine of affected patients.[104] In the spine, the scoring system measures bone marrow edema in the bone marrow of DVUs, each unit representing the region between 2 imaginary lines drawn through the middle of adjacent vertebrae.[104]

All 23 DVUs of the spine (from C2 to S1) were scored for bone marrow edema. A single DVU has a scoring range of 0 to 18, bringing the maximum total score to 414, with higher scores reflecting worse disease.[103]

When assessing the 6 most affected units, the overall intra-observer reproducibility was excellent (ICC 0.93 to 0.98) for the 3 readers, and the mean percentage intra-observer concordance for the selection of affected DVUs was 78.8%, 87.9%, and 80.3% for the 3 readers.[103] The average ICC for the interobserver reproducibility of change (in MRI activity) scores was 0.82.[103] A minimally important change (MIC) of 5.0 units for the SPARCC MRI score for the spine has been identified.[104]

The SPARCC MRI Score for Sacroiliac Joints

The SPARCC MRI score for SIJs is a scoring method based on the assessment of increased signal denoting bone marrow edema on T2-weighted STIR sequences. All signal changes within the iliac bone and sacrum up to the sacral foramina are scored on 6 consecutive slices through the SI joint. Each SI joint is divided into 4 quadrants: upper iliac, lower iliac, upper sacral, and lower sacral. The presence of increased signal on STIR in each of these 4 quadrants was scored on a dichotomous basis, where 1 = increased signal and 0 = normal signal. Total SIJ SPARCC scores can range from 0 to 72, with higher scores reflecting worse disease.[105]

The intraobserver reproducibility of the total score based on 3 readers was excellent (ICC = 0.90 to 0.98) while the ICC for change (in MRI activity) scores was lower (ICC 0.53).[105] In another study assessing inter-reader reliability, the SPARCC showed an ICC for the total status score of 0.55 and 0.52 for the change score.[106] The SPARCC MRI score for SI joints has been shown to be correlated with the ASDAS (pre-treatment, R2 = 0.2038).[106] A MIC of 2.5 units for the SPARCC MRI score for SI joints has been identified.[104]

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.[134] The SF-36 consists of 8 health domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems.[135] For each of the 8 categories, a subscale score can be calculated. The SF-36 also provides 2 component summaries, the PCS and MCS. The PCS and MCS scores range from zero to 100 with higher scores indicating better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a standard deviation of 10 in the general US population. Therefore, all scores above/below 50 are considered above/below average for the general US population. Changes between 2.5 to 5.0 points in the physical and mental component scores of the SF-36 are considered to be clinically relevant, as are changes of 5 to 10 points in the domain scores.[109]

Turan and colleagues[107] reported that the SF-36 had a strong correlation with the Mander Enthesitis Index, and the BASDAI in 46 AS patients in an study conducted to investigate which parameters of disease activity, functional condition and other clinical parameters had a greater effect on quality of life.[107] The internal consistency, construct validity and responsiveness to change of SF-36 has been assessed in 2 RCTs comparing adalimumab with placebo for the treatment of AS.[108] SF-36 had a good internal consistency (alpha = 0.74 to 0.92). At baseline, the SF-36 score correlated with ASQoL scores ($r = -0.36$ to -0.66; $P < 0.0001$). SF-36 scores varied by indicators of clinical severity, with greater impairment observed for more severe degrees of clinical activity (all $P < 0.0001$), supporting convergent validity.[108]

5-Level EQ-5D

The EQ-5D-5L is a HRQoL instrument that may be applied to a wide range of health conditions and treatments.[136,137] The first of 2 parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into 1 of 243 distinct health states. The descriptive system consists of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 possible levels of response (no problems, slight problems, moderate problems, severe problems, or extreme problems). Respondents are asked to choose the level that reflects their health state for each of the 5 dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[136,137] The second part is a 20 cm VAS (EQ VAS) that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state.” Respondents are asked to rate their health by drawing a line from an anchor box to

the point on the EQ VAS which best represents their health on that day. Hence, the EQ-5D produces 3 types of data for each respondent:

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

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all 5 attributes) varies depending on the utility function that is applied to the descriptive system (e.g., to −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported MCIDs for this scale have ranged from 0.033 to 0.074 in the general population.[111]

The validity of EQ-5D was compared with the Short Form 6-dimensions (SF-6D) and the well-being rating scale (RS) in 254 AS patients (134 patients from an observational cohort and 120 from a RCT).[110] The median score was 0.69 (range; −0.08 to 1.00) for the EQ-5D. Intraclass correlation coefficients were of moderate agreement (0.46 to 0.55). Instruments correlated equally with disease activity, functioning and quality of life. Compared with EQ-5D and RS, SF-6D showed smaller average differences in utility between patients with better and worse disease. The smallest detectable differences in the control group of RCT were 0.36, 0.17 and 0.33 for EQ-5D, SF-6D and RS, respectively. The ability to detect treatment effect in the intervention trial showed standardized effect sizes that were moderate for EQ-5D and SF-6D (0.63 and 0.64) and low for the RS (0.23).[110]

Work Productivity and Activity Impairment Questionnaire

The WPAI is a 6-item, patient-reported instrument designed work productivity including presenteeism, absenteeism, overall work productivity loss, and daily activity impairment. Greater scores indicate greater impairment.[112]

Construct validity was demonstrated using median scores of other measures including the BASDAI and SF-36. Patients with AS of the worst severity (BASDAI > median) demonstrated significantly greater overall work impairment (difference = −14.5, P < 0.001), presenteeism (difference = −20.3, P < 0.001) and daily activity impairment (difference = −19.5, P < 0.001) based on the WPAI-SpA[112] Similar results were found when patients with the worst health was defined by the median SF-36 PCS and MCS values.[112] No MID was identified in the literature for the indicated patient population.

Bath Ankylosing Spondylitis Metrology Index

Jenkinson et al. developed and evaluated the BASMI in 193 AS patients.[113] Metrology was performed on 327 occasions. The measurement tool was assessed for reliability, speed and both inter and intraobserver

variability. The investigators reported that the instrument was quick to complete (7 minutes) and was reproducible and sensitive to change across the disease spectrum of AS. When tested on a new group of 40 patients the measures were demonstrated to be accurate and reproducible for both intraobserver variability ($r = 0.99$, $P < 0.001$) and interobserver variability ($r = 0.97$, $P < 0.001$).[113] One study compared the BASMI with radiology as a measure of disease outcome in 53 patients.[114] Patients were blindly and independently assessed using BASMI and a radiology score of 4 main spinal areas affected by AS. BASMI correlated positively with the total radiology score ($r = 0.74$).[114]

In the sponsor-submitted trials, the Linear BASMI (BASMIlin) composite score was calculated using the BASMI components: lateral lumbar flexion; tragus-to-wall distance, lumbar flexion, intermalleolar, and cervical rotation. Scores for each assessment range from 0 to 10, and the BASMIlin total score is the average of the 5 assessment scores. Higher scores indicate decreased spinal mobility.[85] In the GO-RAISE study among 277 patients with active AS, Guyatt's effect size (mean change divided by the standard deviation of the placebo group) was greater for the BASMIlin than the BASMI10 at both week 14 (0.58 versus 0.53) and week 24 (0.76 versus 0.69), indicating that the BASMIlin method was more sensitive to changes than the BASMI10 in range of motion exhibited by patients with AS.[115]

Maastricht Ankylosing Spondylitis Enthesitis Score

The MASES is a validated enthesis index for AS developed as a more concise and feasible index to the Mander enthesis index.[116] The score for MASES index ranges from 0 to 13, correlating with the number of painful entheses out of the total of 13 assessed.[116] In the sponsor-submitted clinical trials the following left and right locations were graded for presence (1) or absence (0) of enthesitis: first costochondral joint, seventh costochondral joint, posterior superior iliac spine, anterior superior iliac spine, iliac crest, proximal insertion of Achilles tendon; the fifth lumbar spinous process was also graded for enthesitis.[85]

In a study of 421 patients with AS there were weak positive correlations between MASES and BASDAI ($r = 0.228$), BASFI ($r = 0.195$) and fatigue as measured by the BASDAI question 1 ($r = 0.226$).[117] MASES was not significantly correlated with BASRI, BASMI, OR ASQoL.[117] Similarly, a study of 100 patients with AS examining the MASES (as assessed by a physician) found a moderate correlation with the BASFI ($r = 0.464$), a weak correlation with the BASDAI ($r = 0.342$), and no significant correlation with the BASMI ($r = 0.121$).[138] A lack of correlation with the BASMI may be due to the fact that disease activity and range of motion are different constructs which require a separate evaluation.[117] No MID was identified in the literature for the indicated patient population.

Functional Assessment of Chronic Illness Therapy–Fatigue

The FACIT-F scale is a self-administered questionnaire that assesses both the physical and functional consequences of fatigue.[118] It is a 13-item questionnaire with each question scored from 0 "not at all" to 4 for a total score range of 0 to 52 with higher scores denoting lower levels of fatigue.[118] A study examining data from 2 trials of adalimumab among patients with active AS (n = 397) found that mean FACIT-F scores decreased (i.e., worse fatigue symptoms) as clinical severity increased as measured by the BASDAI fatigue, BASDAI pain, total back pain, and BASFI, supporting known-groups validity.[108] For instance, mean FACIT-F

scores were the lowest for patients with a BASDAI fatigue score ≥ 7 compared with patients with a BASDAI fatigue score < 4. Construct validity was evident by correlations between the FACIT-F scores and the BASDAI fatigue item (r = −0.69), the BASDAI (r = −0.60), and the BASFI (r = −0.56). The internal consistency reliability for the FACIT-F was high with Cronbach alpha = 0.82 and 0.86 at baseline and week 12, respectively.[108]
A study by Cella et al. examined data from 2 trials of tofacitinib in patients with active AS (n = 476) and found that correlation coefficients between FACIT-F and other patient-reported outcomes such at the SF-36, the BASFI, BASDAI, and ASQoL were all ≥ 0.40, supporting convergent validity.[118] Known-groups validity was supported by large differences in FACIT-F domain/total scores between 'no disease activity' (Patient Global Assessment of Disease Activity = 0) and 'very active disease' (Patient Global Assessment of Disease Activity = 10) patient groups, and effect sizes of all differences were large ≥ 1.17. Evidence of responsiveness was demonstrated by an approximately linear relationship between changes in Patient Global Assessment of Disease Activity scores and FACIT-F domain/total scores. Meaningful within-patient change was estimated as 3.1 to 6.3 points for the FACIT-F total score.[118]

Pharmacoeconomic Review

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Abbreviations

AE	adverse event
AS	ankylosing spondylitis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASDAI50	Bath Ankylosing Spondylitis Disease Activity Index 50% improvement
BASFI	Bath Ankylosing Spondylitis Functional Index
bDMARD	biologic disease-modifying antirheumatic drug
bDMARD-IR	biologic disease-modifying antirheumatic drug–inadequate response
BIA	budget impact analysis
CFB	change from baseline
DMARD	disease-modifying antirheumatic drug
ICER	incremental cost-effectiveness ratio
ITC	indirect treatment comparison
mSASSS	modified Stoke Ankylosing Spondylitis Spinal Score
NMA	network meta-analysis
NSAID	nonsteroidal anti-inflammatory drug
QALY	quality-adjusted life-year
TB	tuberculosis

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Upadacitinib (Rinvoq), 15 mg extended-release oral tablets
Submitted price	Upadacitinib, $49.22 per tablet
Indication	For the treatment of adults with active ankylosing spondylitis who have had an inadequate response to a biologic DMARD or when use of those therapies is inadvisable; may be used as monotherapy or in combination with NSAIDs
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	July 14, 2022
Reimbursement request	As per indication
Sponsor	AbbVie Corporation
Submission history	Previously reviewed: Yes **Atopic Dermatitis** Indicated for the treatment of adults and adolescents aged 12 years and older with refractory moderate-to-severe atopic dermatitis who are not adequately controlled with a systemic treatment or when the use of those therapies is inadvisable Recommendation date: June 8, 2022 Recommendation: Reimburse with clinical criteria and/or conditions **Psoriatic Arthritis** Indicated for the treatment of adults with active psoriatic arthritis who have had an inadequate response to methotrexate or other DMARDs Recommendation date: August 20, 2021 Recommendation: Reimburse with clinical criteria and/or conditions. **Rheumatoid Arthritis** Indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate Recommendation date: February 4, 2020 Recommendation: Reimburse with clinical criteria and/or conditions

NOC = Notice of Compliance; DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal anti-inflammatory drug.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree combined with a Markov model

Component	Description
Target populations	Adults with AS diagnosed with BASDAI activity and total back pain scores ≥ 4 2 subpopulations were considered: • bDMARD-inadvisable: patients who are biologic-naive and failed NSAID treatment (due to inadequate response or intolerance) and for whom treatment with a biologic (tumour necrosis factor or interleukin-17 inhibitors) is inadvisable • bDMARD–inadequate response: patients who failed NSAID treatment (due to inadequate response or intolerance) as well as at least 1 biologic therapy
Treatment	Upadacitinib
Comparators	• Adalimumab • Etanercept • Golimumab • Infliximab • Secukinumab • Conventional therapy (corticosteroids, NSAIDs, or csDMARDs such as sulfasalazine, methotrexate, or leflunomide)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (60 years, to a maximum age of 100)
Key data sources	SELECT-AXIS 1, SELECT-AXIS, sponsor-submitted NMA
Submitted results	• bDMARD-inadvisable subpopulation: upadacitinib was dominated by secukinumab and etanercept (i.e., patients receiving secukinumab or etanercept gained more QALYs, at a lower cost) • bDMARD–inadequate response subpopulation: upadacitinib dominated both secukinumab and conventional therapy (i.e., upadacitinib was less expensive [saving $8,224 vs. secukinumab and $11,799 vs. conventional therapy] and provided more QALYs [gaining 0.097 QALYs vs. secukinumab and 2.849 QALYs vs. conventional therapy])
Key limitations	• The comparative effect of upadacitinib on key clinical outcomes is uncertain due to a lack of direct comparative evidence for relevant comparators and the high degree of uncertainty in the sponsor's NMA. The CADTH Clinical Review concluded there were no differences in efficacy between therapies used to treat AS considered in the sponsor's NMA for both the bDMARD-inadvisable and bDMARD–inadequate response subpopulations. No comparative safety or discontinuation information was available. • The timing for the initial treatment effect for BASDAI and BASFI, as well as the baseline scores to which the treatment effects were applied, were incorrectly implemented. This affected the total QALYs estimated for all treatments included in the analyses. • The sponsor assumed that conventional therapy would have no effect on treatment response status or disease progression. This was inconsistent with the submitted NMA and clinical expectations. • While evidence was available for the 150 mg and 300 mg doses of secukinumab, only data for the 150 mg dose were used in the sponsor's analysis. However, a [redacted]% to [redacted]% dose split was assumed, overestimating the costs associated with the 150 mg dose and omitting efficacy information specific to the 300 mg dose. • While certolizumab pegol satisfied the criterion for relevant comparators, the absence of subpopulation specific trial data led to its exclusion from the sponsor's base case. Further,

Component	Description
	several relevant comparators (i.e., infliximab, golimumab, etanercept, adalimumab) were omitted from the bDMARD–inadequate response subpopulation due to a lack of evidence.
CADTH reanalysis results	• CADTH conducted a reanalysis incorporating changes to the sponsor's economic submission to address key limitations. These changes included: more appropriate assumptions regarding the calculation and timing of treatment effects, use of overall instead of response-stratified baseline BASDAI and BASFI, use of consistent dosing for secukinumab to calculate costs, assumption of a treatment effect with conventional therapy and the inclusion of relevant comparators as permitted by the evidence available for each subpopulation. ◦ In the biologic-inadvisable subpopulation: upadacitinib was dominated by secukinumab and etanercept (i.e., patients receiving secukinumab or etanercept gain more QALYs, at a lower cost). ◦ In the biologic–inadequate response subpopulation (which did not consider all relevant TNF inhibitors): upadacitinib dominated secukinumab. The ICER for upadacitinib relative to conventional therapy was $52,442 per QALY gained. • The results of these analyses are dependent on estimates of treatment effect from the sponsor's NMA, which is associated with uncertainty and assumes that these differences in treatment effect translate into clinically meaningful improvements in disease status for patients.

AS = ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biologic disease-modifying antirheumatic drug; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; NSAID = nonsteroidal antirheumatic drug; QALY = quality-adjusted life-year; TNF = tumour necrosis factor; vs. = versus.

Conclusions

Based on an appraisal of the SELECT-AXIS 1 and SELECT-AXIS 2 trials, CADTH clinical reviewers found that the efficacy of upadacitinib was superior to that of placebo for treatment response, disease activity, and physical functioning in adult patients with active ankylosing spondylitis (AS). In the absence of direct evidence comparing upadacitinib with the biologics used to treat active AS, estimates of comparative efficacy were established through Bayesian network meta-analyses (NMAs). The CADTH Clinical Review concluded from the NMAs that there are no differences in efficacy for upadacitinib in comparison with existing biologic treatments indicated for this population. This was consistent across treatment response (Bath Ankylosing Spondylitis Disease Activity Index 50% improvement [BASDAI50]), disease activity (Bath Ankylosing Spondylitis Disease Activity Index [BASDA]), and physical functioning (Bath Ankylosing Spondylitis Functional Index [BASFI]). However, the presence of heterogeneity in the included studies increases uncertainty in these findings, and several relevant comparators were not assessed in the subpopulation with an inadequate response to biologic disease-modifying antirheumatic drugs (bDMARDs).

CADTH conducted a reanalysis incorporating changes to the sponsor's economic submission to address key limitations. These changes included: more appropriate assumptions regarding the calculation and timing of treatment effects, use of overall instead of response-stratified baseline BASDAI and BASFI values, use of consistent dosing for secukinumab to calculate costs, assumption of a treatment effect with conventional therapy, and the inclusion of relevant comparators as permitted by the evidence available for each subpopulation. CADTH was unable to address issues associated with missing comparators and with the NMA used to inform the comparative efficacy parameters of the model.

In the bDMARD-inadvisable subpopulation, upadacitinib was associated with fewer quality-adjusted life-years (QALYs) and increased costs to the health system (i.e., it was dominated) when compared to and etanercept. In the biologic disease-modifying antirheumatic drug–inadequate response (bDMARD-IR) subpopulation, relative to conventional therapy, upadacitinib had an incremental cost-effectiveness ratio (ICER) of $52,442 per QALY gained. Relative to secukinumab, the only other biologic included by the sponsor in this analysis, upadacitinib generated more QALYs at a lower cost. However, results from these analyses rely on uncertain differences in treatment effects estimated from the sponsor-submitted NMA, which may not correspond to clinically meaningful differences.

Given the limitations outlined by the CADTH Clinical Review regarding evidence from the NMA, limited conclusions can be drawn about the differences between upadacitinib and other biologics used to treat AS. If treatment with upadacitinib is expected to produce health outcomes similar to those of other biologics, the price of upadacitinib should be no more than that of the lowest-cost biologic approved to treat AS to ensure cost-effectiveness.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

Patient input for this review was obtained from Arthritis Consumer Experts and a joint submission from Arthritis Society Canada, the Canadian Arthritis Patient Alliance, the Canadian Spondylitis Association, and Creaky Joints Canada. Both submissions contained information collected from electronic surveys of patients living with AS. All survey participants were Canadian and 9 out of the 264 respondents to the Arthritis Society Canada survey had experience taking upadacitinib. Most patients had been treated with a conventional synthetic disease-modifying antirheumatic drug (DMARD) or a bDMARD. Respondents noted that treatments worked well until they experienced a flare or failure, and a new treatment option had to be considered. Neither submission identified a specific gap that upadacitinib was expected to address. However, patients who had received this treatment found it to be effective and well tolerated.

Registered clinical input was received from the Canadian Rheumatology Association. The current pathway of care is to reduce pain and improve function. In the Canadian context, nonpharmacologic therapies such as exercise, occupational therapy, diet, and weight loss are recommended for all patients. However, only a significant minority of patients will benefit from this strategy alone. Patients with ongoing spinal disease activity are typically prescribed 2 nonsteroidal anti-inflammatory drugs (NSAIDs) for 2 weeks each. In the event of nonresponse, a biologic (tumour necrosis factor inhibitor or interleukin-17 inhibitor) or targeted synthetic DMARD will be considered. While multiple treatment options available, the clinician input noted a significant unmet need, given that every patient will not respond to the current treatments. Those who do respond often experience a secondary loss of effect, resulting in dose escalations or the need to switch medications. Treatment options may also be limited by the side effects expected from specific medications. In addition, current treatments have undesirable attributes, such as the need for cold storage

or subcutaneous injection. The submission noted that upadacitinib would offer another effective treatment option to treat adults with AS. Upadacitinib may have a higher ranking for some clinicians as it is orally administered, does not require cold storage, and has shown to be effective at treating some comorbidities associated with AS (e.g., inflammatory bowel disease).

Drug plans noted that upadacitinib will be the first targeted DMARD for the present indication that is orally administered. Concerns were raised regarding the treatment's place in therapy, and the impact of prior biologic therapy on treatment efficacy.

Two of these concerns were addressed in the sponsor's model:

- The sponsor's model incorporated the risk of serious infection-related adverse events (AEs) and the impact of treatment on quality of life.
- The specification of subpopulations on the basis of prior biologic experience allowed the model to incorporate evidence of effectiveness for patients who failed at least 1 prior biologic.

CADTH was unable to address the concern raised in stakeholder input that treatment-switching between biologics was not considered in the model. As a result, the impact of the treatment in the context of its place in therapy is limited.

Economic Review

The current review is for upadacitinib (Rinvoq) for the treatment of adults with AS who have had an inadequate response to a bDMARD or when use of those therapies is inadvisable.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted an economic evaluation comparing upadacitinib against relevant bDMARDs and conventional therapy for the treatment of adults with AS.[1] To align with the population indicated within the Health Canada Notice of Compliance and the sponsor's reimbursement request, 2 subpopulations were considered in the submission. The bDMARD-inadvisable subpopulation was defined to include biologic-naive patients who failed treatment with an NSAID and for whom treatment with a biologic targeting tumour necrosis factor–alpha) or interleukin-17 receptor inhibition was inadvisable. The second subpopulation (bDMARD–inadequate response [bDMARD-IR]) referred to patients who failed NSAID treatment and at least 1 biologic therapy. In both subpopulations failure was attributed to inadequate response or intolerance to treatment.[1] Standard measures of disease severity (BASDAI) and functional capacity (total back pain score) were used to define AS diagnosis (scores > 4) and track disease progression.

Upadacitinib is available as 15 mg or 30 mg tablets and should be administered orally. For the treatment of AS, the recommended dose of upadacitinib is 15 mg once daily.[2] It may be used as monotherapy or in combination with NSAIDs. The submitted price was $49.22 per tablet, resulting in an annual cost of $17,978.

Alternatives to upadacitinib considered in the submission were restricted to licensed treatments indicated for adult AS that were eligible for public coverage. Those considered in the sponsor's submission included: adalimumab, etanercept, golimumab, infliximab, secukinumab, and conventional therapy.[1] Also known as best-supportive care or natural history, conventional therapy was defined as treatment via corticosteroids, NSAIDs, and conventional synthetic DMARDs.[1] An overview of drug costs is presented in Table 8. Comparators in the economic evaluation were conceptualized as treatment sequences comprising 1 biologic followed by conventional therapy. Additionally, conventional therapy was considered as an independent comparator without a preceding biologic. To accommodate differences in data availability, the specific treatment sequences considered in the economic evaluation differed for each subpopulation:[1]

- bDMARD-inadvisable: upadacitinib plus conventional therapy, etanercept plus conventional therapy, adalimumab plus conventional therapy, secukinumab plus conventional therapy, golimumab plus conventional therapy, infliximab plus conventional therapy, and conventional therapy alone
- bDMARD-IR: upadacitinib plus conventional therapy, secukinumab plus conventional therapy, and conventional therapy alone.

The economic evaluation adopted a Canadian public health care payer perspective to evaluate costs and outcomes, expressed as QALYs over a time horizon of 60 years. A cycle length of 3 months (12 weeks) was assumed, and a 1.5% annual discount rate was applied to both costs and QALYs.[1]

Model Structure

Consistent with prior economic evaluations of adult AS, the model structure was designed to track the amount of time patients spent on each treatment.[1,3,4] As presented in Figure 1, the model was described as a decision tree combined with a Markov structure with 3 states: biologic treatment, conventional therapy, and death.[1] This approach is analogous to a Markov structure with time-dependent transition probabilities with respect to time in the model and time in each state (treatment).

Patients initiated 1 of the eligible biologic treatments at model entry. Transitions from a biologic to conventional therapy were dependent on the amount of time the patient had been under treatment. After the first 3 months (1 cycle) on a biologic, patients could continue treatment if they achieved a treatment response. In the base case, this was defined as a 50% reduction in the Bath Ankylosing Spondylitis Disease Activity Index from baseline (BASDAI50).[1] An alternate scenario was also considered where treatment response was defined as a 40% improvement in the Assessment of SpondyloArthritis international Society.[1] Both definitions of treatment response have been used as end points in AS clinical trials.[5-9] However, the use of BASDAI50 in the base case maintained consistency with prior economic evaluations of biologic treatment for adult AS.[3,4] Patients who failed to achieve a treatment response transitioned to conventional therapy. Meanwhile, responders to the biologic remained on treatment and were subject to an ongoing risk of treatment withdrawal. It was assumed treatment withdrawal was attributable to a loss of treatment response or intolerance to the treatment. Once patients began conventional therapy, it was assumed they would remain in that state until death. Throughout the specified time horizon, patients were subject to an all-cause mortality risk that increased with age.[1]

In addition to tracking the time spent on each treatment, the model also tracked disease activity (measured by the BASDAI) and physical functioning (measured by the BASFI). These estimates of symptom severity were used to estimate the health utilities and the direct medical costs associated with each treatment. It was assumed that patients entered the model with baseline BASDAI and BASFI scores specific to each subpopulation. The BASDAI and BASFI scores following the first cycle of treatment were calculated as the difference between the response-stratified baseline values and the estimated change in baseline, conditional on treatment response status. In the remaining cycles on treatment, different approaches were used to estimate each component of disease progression. For BASDAI, the model assumed that any gains from treatment (i.e., reductions in baseline score) were maintained until discontinuation. Following the achievement of a treatment response, the BASFI score was estimated as the sum of the score from the preceding cycle and a constant progression rate. Upon withdrawal, it was assumed that both BASDAI and BASFI scores would rebound (increase) to their baseline values. This base-case assumption is known as rebound equal to gain and is considered a best-case scenario. A worst-case scenario, called rebound equal to natural history, was considered for the BASFI. In this circumstance, it was assumed that, upon withdrawal, BASFI would rebound (increase) to the point and rate that would have been observed had treatment never been initiated.[1] Additional details regarding the BASDAI and BASFI scoring procedures are presented in Appendix 3.

Model Inputs

Costs and effects were estimated using a homogeneous baseline population for each subpopulation. Multiple parameters for the economic evaluation were obtained from the sponsor's submitted systematic review of biologic treatment for adults with AS.[10-12] The data compiled from the identified trials informed patient demographics, baseline disease severity (BASDAI and BASFI scores), and the estimation of relative treatment effects estimated via a Bayesian NMA.

All data summarizing patient demographics or baseline disposition for this model were obtained from the SELECT-AXIS 1 and SELECT-AXIS 2 trials.[5,6] Characteristics of interest included baseline age and weight, as well as the proportion of patients who were male. Meanwhile, overall and BASDAI50 response-stratified BASDAI and BASFI scores were used to characterize baseline disposition for each subpopulation.

Estimates of relative efficacy were established from NMA short-term trial data on treatment response and change from baseline in disease severity. In each NMA, treatments with more than 1 relevant dose (secukinumab, etanercept, and golimumab) were treated as separate comparators. The treatment-response NMA included trials that reported the proportion of patients in each subpopulation achieving a BASDAI50 or a 40% improvement in the Assessment of SpondyloArthritis international Society.[5-9] Meanwhile, the change from baseline (BASDAI and BASFI scores) NMAs included data from trials that reported the mean change in the BASDAI or BASFI from baseline for each subpopulation. Both outcomes were assessed at the end of the randomized period in each study, which ranged from 12 to 16 weeks. Last, each NMA considered a fixed-effects and a random-effects model for both subpopulations. However, in the base case it was assumed that the fixed-effects models would apply to the bDMARD-IR patients and the random-effects models would apply to the bDMARD-inadvisable subpopulation. Another key difference in the NMAs for each subpopulation

involved the availability of data for each comparator. The absence of evidence specific to the biologic-IR subpopulation resulted in the exclusion of several potentially relevant comparators in the economic model.

To track the amount of time spent on each treatment, the model required 3 distinct transition probabilities: treatment response, treatment withdrawal, and mortality risk. The probability of achieving a treatment response was obtained directly from the absolute estimates of the BASDAI50 NMA. While conventional therapy was included as a comparator in the NMA, the sponsor assumed a 0% probability of achieving a BASDAI50 response from the intervention. The probability of treatment withdrawal differed by the type of bDMARD. For tumour necrosis factor–alpha inhibitors (adalimumab, etanercept, golimumab, and infliximab), a constant annual withdrawal rate of 11% was assumed. This input was obtained from the 2016 York model of adult AS.[3] It was estimated using a parametric survival curve, under an exponential distribution, of BASDAI50 responders from open-label extension studies of AS patients.[3] For the remaining treatments (secukinumab and upadacitinib), different withdrawal rates were assumed for the first and all subsequent years on treatment. The corresponding annual withdrawal rates were estimated from data reported in the SELECT-AXIS and MEASURE series of trials.[1,5,6,13-17] The same rate was assumed for both subpopulations, in the event data for 1 was unavailable. Given that estimates represented annual withdrawal rates, adjustments were applied to reflect the 3-month cycle length.[1]

The procedure to track disease progression (via the BASDAI and BASFI) required treatment-specific estimates of change from baseline conditional on treatment response (BASDAI50) status. However, the NMA only estimated the absolute change from baseline for each treatment, outcome, and subpopulation. A separate calculation was required to estimate the conditional change from baseline based on formulas. Three inputs were required for these formulas: the overall change from baseline (CFB), the probability of a BASDAI50 response, and the ratio of responders to nonresponders. This ratio was calculated from trials with available data for each treatment and subpopulation.[1] Treatments without trial data were assumed to follow the average across the respective subpopulations.[1]

$$CFB_{NonResponse} = \frac{CFB_{Overall}}{(Ratio \times BASDAI50) + (1 - BASDAI50)}$$

$$CFB_{Response} = \frac{CFB_{Overall}}{BASDAI50 + \frac{1 - BASDAI50}{Ratio}}$$

The approach used to capture the rate of progression in the BASFI while on treatment was consistent with previous economic evaluations of biologic treatments for adult AS.[1,3] It assumed the BASFI was a function of the annual rate of change in the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) and the expected change in the BASFI for each 1 unit change in mSASSS. The former was assumed to apply to the conventional therapy arm and was obtained from a study exploring long-term impacts of AS on radiographic damage.[1,18] For every other treatment, the assumption of a slower rate of progression was implemented using a relative rate of mSASSS change with treatment (mean = 0.420, standard error = 0.122).[3,19] The base case assumed an immediate treatment effect; however, in a separate scenario, the treatment effect on progression was delayed until year 4.[1]

All-cause mortality was incorporated by applying a risk of death during each model cycle. This risk was estimated as the common excess risk of death from AS relative to the general population and represented the weighted average for each sex. AS-related standardized mortality rates were identified from Bakland et al., and the general population mortality risk was obtained from Statistics Canada life tables published in January 2022.[20,21]

AEs considered within the economic model were restricted to serious infections. This was consistent with previous economic evaluations and involved the occurrence of reactivated tuberculosis (TB) or other serious infections.[1,3,4] The latter included sepsis, bronchopneumonia, kidney or urinary tract infections, unspecified lower respiratory infections, and chronic obstructive pulmonary disease or bronchitis. It was assumed that 5% of serious infections were TB.[22] The risk of serious infections was estimated as the average absolute risk across all observations from randomized controlled trials for each treatment.

The model estimated EQ-5D utilities as a function of the BASDAI and BASFI, sex, and age. Consistent with previous economic evaluations in adult AS, this approach assumed that the BASFI and BASDAI, sex, and age capture all relevant quality-of-life information.[1,3,4] The mapping algorithm used by the sponsor was generated from a linear mixed model that treated the EQ-5D questionnaire as an outcome and the remaining factors as covariates. However, the model was fitted using data specific to secukinumab from the MEASURE 1 and MEASURE 2 trials.[1,13,16] This was consistent with prior economic evaluations of adult AS.[4] The impact of alternate approaches to utility estimation were explored in a scenario analyses:[1]

$$\text{Utility}_{EQ5D} = 0.9610 - 0.0442 \times \text{BASDAI} - 0.0330 \times \text{BASFI} - 0.0111 \times \text{Sex} - 0.0005 \times \text{Age}$$

Costs were calculated as the total costs for drug acquisition, administration, monitoring, and direct medical and AEs. In estimating drug acquisition costs, the price of upadacitinib was obtained from the sponsor. All remaining treatment prices reflected wholesale prices recorded in the IQVIA DeltaPA database.[23] The base case assumed biosimilar products (adalimumab, etanercept, and infliximab) would be used where available and a separate scenario analysis restricted the comparators to their biologic-originator products. Dosing schedules were implemented following the indications specified within each product monograph. For secukinumab, the sponsor assumed a [redacted] weighted split between the 150 mg and 300 mg doses. Treatment administration costs were restricted to products administered via subcutaneous injection or IV infusion. The cost of subcutaneous administration from a registered nurse was assumed to be the time-adjusted hourly wage including benefits. The cost of IV administration incorporated time-adjusted wages (including benefits) for nursing, and pharmacist time. Hourly wages for nurses and pharmacists were obtained from Statistics Canada.[24,25] Treatment monitoring costs included physician follow-ups and tests and procedures on treatment initiation and over the course of follow-ups. Resource use estimates were obtained from a survey of 5 specialists across Canada. Prices for this exercise were obtained from the Ontario Schedule of Benefits for Professional Services, Laboratory Services, as well as the Ontario Case Costing Initiative for hospitalizations.[26-28]

Consistent with prior economic evaluations in adult AS, direct medical costs were incorporated as a function of BASFI progression. This algorithm was obtained from an exponential regression model, with adjustments made to convert coefficients to Canadian dollars and a 2022 price year.[1] Costs of AEs were determined as a

function of the frequency of either type of infection. For non-TB events, this reflected the relative frequency of each type of infection. Costs associated with treating each type of AE were obtained from a proprietary report, which was not included in the submission.[1]

$$\text{Direct medical cost} = 2357.52 \times exp(0.213 \times \text{BASFI})$$

Summary of Sponsor's Economic Evaluation Results

The costs and QALYs of each alternative were generated using a Monte Carlo simulation. While results from the base case were generated from a simulation of 5,000 iterations, those for each scenario were limited to 1,000 iterations. Deterministic and probabilistic results were aligned for the bDMARD-IR subpopulation, but not for the bDMARD-inadvisable subpopulation. This was expected given the difference in the number of comparators and the nonlinear model structure. Results from the probabilistic base case are summarized in the following section.

Base-Case Results

The submitted analysis was based on the publicly available prices of the comparator treatments. Results from the base case of the submitted economic evaluation are presented in Table 3.

In the bDMARD-inadvisable subpopulation, the expected costs and QALYs for the treatment sequence beginning with upadacitinib were $287,796 and 13.034, respectively. However, other sequences (secukinumab and etanercept) that offered more QALYs at a lower cost were identified. Given that upadacitinib was dominated by these alternatives, it was not expected to be cost-effective. Based on the sponsor's analysis, only the etanercept and secukinumab treatments had the potential to be cost-effective. At a willingness-to-pay threshold of $50,000 per QALY, upadacitinib had a 3.6% chance of being the most cost-effective treatment compared with probabilities of approximately 30% and 50% for etanercept and secukinumab.

In the bDMARD-IR subpopulation, the expected costs and QALYs for the treatment sequence beginning with upadacitinib were $325,721 and 12.697. Upadacitinib was expected to be cost-effective in this subpopulation, given that it dominated both secukinumab and conventional therapy. Upadacitinib therefore offered more QALYs at a lower cost than did either secukinumab or conventional therapy.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Total QALYs	Sequential ICER ($ per QALY)
Subpopulation: bDMARD-inadvisable			
Etanercept	251,925	13.165	Reference
Secukinumab	259,607	13.536	20,683
Adalimumab	258,752	12.921	Dominated by secukinumab and etanercept
Conventional therapy	261,351	10.599	Dominated by secukinumab and etanercept
Upadacitinib	287,796	13.034	Dominated by secukinumab and etanercept
Golimumab	299,935	12.918	Dominated by secukinumab and etanercept

Drug	Total costs ($)	Total QALYs	Sequential ICER ($ per QALY)
Infliximab	320,074	12.782	Dominated by secukinumab and etanercept
Subpopulation: bDMARD–inadequate response			
Upadacitinib	325,721	12.697	Reference
Secukinumab	333,945	12.600	Dominated by upadacitinib
Conventional therapy	337,520	9.848	Dominated by upadacitinib

bDMARD = biologic disease-modifying antirheumatic drug; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
Source: Sponsor's pharmacoeconomic submission.[1]

Additional information summarizing the sponsor's submitted economic evaluation and base-case results are reported in Appendix 3.

Sensitivity and Scenario Analysis Results

In addition to the base case, several scenario analyses were considered. The sponsor examined the impact of alternative discount rates (undiscounted and 3%), following CADTH guidelines. In addition, scenarios explored shorter time horizons (10 and 20 years) and a broader societal perspective on costs. These efforts also explored the impact of alternative assumptions relating to the definition of treatment response, the approach to estimating utility values, and the range of values used to predict direct medical costs.[1]

The extent to which each scenario affected the assessment of cost-effectiveness for upadacitinib was unclear in the bDMARD-inadvisable subpopulation, as the sponsor reported the incremental results in comparison with each intervention separately, and not the total costs and QALYs, which would have permitted the calculation of an incremental analysis. In the bDMARD-IR subpopulation, upadacitinib was dominated in every scenario except the 2 that considered shorter time horizons.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **Uncertain effectiveness and safety of upadacitinib compared to relevant comparators:** The relative effectiveness and safety of upadacitinib is uncertain for several reasons. First, there have been no head-to-head trials of upadacitinib and key comparators of interest (i.e., bDMARDs). In the absence of comparative evidence from clinical trials, the sponsor undertook an indirect treatment comparison (ITC) to inform key effectiveness parameters in its pharmacoeconomic model. As noted in the CADTH Clinical Review, important methodological limitations affect the validity and interpretation of the sponsor's ITC results with regard to key efficacy outcomes, such as treatment response and CFB scores for the BASDAI and BASFI. As a result of these limitations, the CADTH Clinical Review noted a lack of precision with the estimates from the ITC, with the magnitude and direction of bias unknown. When considering the pharmacoeconomic model results using inputs derived from the sponsor's ITC, differences in effectiveness were observed; however, this is not aligned with the findings from the CADTH Clinical Review. The Clinical Review noted that the ITCs considered in the CADTH appraisal suggest no treatment for AS is favoured over others for most efficacy outcomes,

including response, physical function, and disease activity. Second, the sponsor incorporated AEs and treatment discontinuation in the pharmacoeconomic model based on naive comparisons between trials. Because of the direct use of clinical trial data, it is not possible to determine if any observed differences in AEs or treatment discontinuation between therapies are due to treatment or, rather, due to bias or confounding (e.g., differences in study populations, definitions of outcomes, or study designs). This introduces additional uncertainty into the analysis.

Furthermore, the sponsor's ITC was unable to synthesize estimates of the comparative effectiveness of several key comparators (i.e., adalimumab, etanercept, golimumab, infliximab, and certolizumab pegol) in the bDMARD-IR subgroup. This resulted in their exclusion from the economic analysis for this subgroup; however, these are relevant comparators to upadacitinib and should be considered when determining the value of upadacitinib in the bDMARD-IR subpopulation.

  - CADTH could not address these limitations in its reanalysis.

- **Incorrect timing of treatment effects:** Consistent with similar economic evaluations, the sponsor incorporated treatment effects as the difference between the baseline BASDAI and BASFI and the expected CFB conditional on treatment response (BASDAI50) status. However, it was assumed that the treatment effect will be experienced in the first cycle on a biologic. This resulted in the misspecification of utilities and direct medical costs in 2 distinct ways. First, it incorporated the treatment effect for responders at a point in time when the response status is unknown. Consistent with clinical practice, the model assumed that the decision to continue a biologic will be made after the first 3 months on a specific treatment. As a result, the treatment effects should not have been recorded until the second cycle on that treatment. Second, it failed to consider the impact of treatment before the assessment of a treatment response. This is inconsistent with the methods of the original York AS model on which the present submission was based.[3] Clinical expert feedback obtained by CADTH confirmed it would be unlikely for a patient to receive no benefit during the first 3 months of treatment. As a result, the original York AS model assumed that the treatment effect before response assessment would be the difference between the baseline value and the expected CFB conditional on treatment nonresponse. This meant that patients would experience some improvement in BASDAI and/or BASFI, but not as much as would be expected for responders.
  - CADTH incorporated 2 modifications to the economic evaluation. In the first cycle on a treatment, it was assumed that the treatment effect would correspond to the CFB conditional on treatment nonresponse. In the second cycle on a treatment (when treatment response status is known), the treatment effect for those who continue would correspond to the CFB conditional on achieving a treatment response.
- **Use of response-stratified baseline values:** To track disease progression over time, baseline values specific to each subpopulation were used to calculate the treatment effect and implement specific rebound assumptions. At model entry, it was assumed that the baseline BASDAI and BASFI scores would represent the overall values for each subpopulation. However, treatment effects and rebound assumptions were calculated using baseline BASDAI and BASFI scores stratified by treatment-response status. The sponsor acknowledged that this was an attempt to be consistent with the

original York AS model.[1,3] The use of response-stratified baseline values was originally implemented as an attempt to consider factors other than treatment that may affect treatment response. However, its use is problematic for 3 reasons. First, it conflicts with the broader model assumption of a homogeneous cohort for each subpopulation at the time of model entry. Second, the stratification weakened fidelity to both rebound assumptions following discontinuation of a biologic. For rebound equal to gain, the predicted BASDAI and BASFI scores increased (worsened) to points that are greater (indicating a nonresponse) or less (indicating a response) than gain. Meanwhile, the rate of BASFI progression was inconsistent with the trajectory expected for the rebound equal to natural history assumption. Third, the stratification was performed using information that cannot be known at baseline.

    - In a CADTH reanalysis, the use of response-stratified baseline values was removed. This allowed the calculation of the treatment effect to be made from the overall baseline values for the BASDAI and BASFI. In addition, it enabled the rebound scenarios to follow their intended trajectories.

- **Treatment effects from conventional therapy:** The sponsor's model was designed to track the amount of time spent on a given treatment and the associated disease progression over the specified time horizon. To achieve this, treatment-specific estimates of BASDAI50 response and the CFB for the BASDAI and BASFI were estimated using a Bayesian NMA. While conventional therapy was included in each NMA, the sponsor assumed that this intervention would have no treatment effect in the economic model. In other words, the probability of a BASDAI50 response and the CFB estimates for conventional therapy were set to 0. However, the inconsistency between this assumption and the sponsor's own assessment of the evidence was not explicitly justified. Furthermore, the assumption that conventional therapy would have no effect was inconsistent with the methods of the York model for adult AS, on which the present submission was based. In the referenced model, conventional therapy was observed to have the smallest treatment effect of all available options. Clinical expert feedback obtained by CADTH confirmed that it would be unlikely for conventional therapy to be associated with no treatment effect. Given that conventional therapy was included as an independent comparator and as the intervention following discontinuation of a biologic, this resulted in underestimation of the BASDAI and BASFI. Direct medical costs and utilities were therefore underestimated in every arm of the economic model.
    - CADTH partially addressed this limitation. The treatment effect for conventional therapy was assumed to follow that of placebo as estimated from the sponsor's submitted NMA for BASDAI50 response and the CFB in the BASDAI and BASFI in the CADTH reanalysis. While this change affected the BASDAI and BASFI scoring procedures associated with the first treatment state, programming constraints prevented these changes from being reflected in the conventional therapy states following discontinuation of a biologic.
- **Inconsistent dosing for secukinumab:** The total costs and effects for secukinumab were estimated using inconsistent dosing assumptions. Unlike other biologics, evidence used to inform treatment response (BASDAI50) and disease progression (BASDAI and BASFI) was available for multiple doses of secukinumab (150 mg and 300 mg). In the sponsor's base case, it was assumed that only the

estimates of 150 mg would be relevant when tracking the amount of time spent on treatment and predicting disease progression. However, when estimating costs, it was assumed that there would be a [redacted]% to [redacted]% split between the 150 mg and 300 mg doses. This was problematic for 3 reasons. First, it assumed dose equivalence in terms of treatment response (BASDAI50), disease activity (BASDAI), and physical functioning (BASFI). This was inconsistent with the sponsor's submitted evidence from the NMA that there was distinct evidence available to inform the 150 mg and 300 mg doses. Second, this approach meant that the model failed to track secukinumab treatment in a manner consistent with the licensed indication. According to the product monograph, patients who do not respond to the 150 mg dose are eligible to receive 300 mg of secukinumab. Third, it resulted in the exclusion of a potentially relevant comparator: 300 mg of secukinumab.

The assumptions associated with secukinumab treatment affected the cost-effectiveness results in 2 distinct ways. First, it led to the misspecification of costs and effects relating to the use of 150 mg of secukinumab. The assumed [redacted] dose split resulted in an overestimate of treatment acquisition costs for this intervention. Second, exclusion of the 300 mg dose as a separate comparator resulted in a failure to consider all the available evidence for the decision problem. Either factor could have affected the identification of alternatives subject to any form of dominance and by extension the pairwise comparisons used to calculate ICERs.

  - CADTH removed the assumption of a [redacted] to [redacted] split between 150 mg and 300 mg of secukinumab. This allowed the model to be consistent with the assumption of a 150 mg dose for secukinumab for the relevant efficacy data (BASDAI50, as well as CFB in the BASDAI and BASFI). However, programming constraints prevented CADTH from considering the 300 mg dose of secukinumab following the failure of the 150 mg dose or as an independent comparator.

- **Exclusion of relevant comparator (certolizumab pegol):** The sponsor reported that alternative to upadacitinib considered in the submission were restricted to biologics with a licensed indication permitting use in adult AS. While certolizumab pegol satisfied this inclusion criteria, it was excluded from the economic evaluation because the relevant trials did not report results specific to each subgroup. It is unclear why this choice was made given that certolizumab pegol was included in the NMAs and budget impact model. Justification was not provided in the submitted pharmacoeconomic report. Clinical expert feedback obtained by CADTH confirmed that certolizumab pegol would be a relevant comparator treatment for the economic evaluation. Excluding any relevant comparator can have a significant impact on the determination of cost-effectiveness, particularly when multiple alternatives are available. It is important to include all relevant comparators to correctly identify alternatives subject to any form of dominance, thereby enabling the calculation of ICERs for the correct pairwise comparisons.
  - Certolizumab pegol was included as an independent comparator in the bDMARD-inadvisable subpopulation. Data were obtained from the sponsor's NMA, which assumed that the mixed population were all biologic-naive. Inclusion in the bDMARD-IR subpopulation was not possible due to a lack of data in this subgroup to inform the ITC.

- **Treatment of conditional CFB as an uncertain parameter:** To track disease progression, the model required the estimation of the CFB, conditional on treatment response status for both the BASDAI and BASFI. This parameter was estimated from 3 inputs: the overall CFB, the probability of a treatment response, and the ratio of responders to nonresponders on each treatment. Given that 2 of these inputs represented uncertain parameters, the conditional CFB should have been calculated after taking a random draw of each NMA result (BASDAI50, BASDAI, and BASFI). Instead, it was estimated using the mean values from the required NMAs (BASDAI50 and BASDAI; BASDAI50 and BASFI) and was assumed to follow a normal distribution. By treating the conditional CFB as an independent uncertain parameter, the sponsor may have generated results that were not reflective of the underlying evidence. This mischaracterization of parameter uncertainty will affect the estimated utilities and direct medical costs, and by extension the expected costs and QALYs of every alternative considered for each subpopulation.
  - CADTH could not address this limitation in its reanalysis.

Additionally, key assumptions made by the sponsor were appraised by CADTH (Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation

Sponsor's key assumption	CADTH comment
Patients in the bDMARD-inadvisable subpopulation will only receive a single bDMARD in their lifetime. Patients in the bDMARD-IR subpopulation will only receive 1 additional bDMARD in their lifetime.	While consistent with past economic evaluations, this does not reflect current clinical practice and patient experience. Recent economic evaluations of biologic treatments for other indications have incorporated treatment-switching.
Adverse events from treatment were restricted to serious infections.	Other adverse events are associated with advanced therapies. Unless these events occur at the same rate for each treatment, they may have some impact on resource utilization and health-related quality of life. The impact from their exclusion is unknown.

bDMARD = biologic disease-modifying antirheumatic drug; bDMARD-IR = biologic disease-modifying antirheumatic drug–inadequate response.

CADTH Reanalyses of the Economic Evaluation

Reanalysis Results

CADTH conducted a reanalysis maintaining the sponsor's estimates of treatment effect, AEs, and treatment discontinuation, while addressing other key limitations identified with the submitted model. This analysis was derived by making changes to the assumptions and parameter values of the submitted model, in consultation with clinical experts. Changes applied to the submitted economic evaluation are summarized in Table 5. For both subpopulations, costs and effects for each intervention were generated using Monte Carlo simulations of 5,000 iterations.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Changes to derive the CADTH reanalysis		
1. Incorrect timing of treatment effects	Treatment effect for BASDAI and BASFI response will occur in the first cycle on a biologic	First cycle on a biologic: treatment effect not yet known; patients experience some improvement, but not as much as would be expected for responders Second cycle on biologic: treatment effect known, and improvement matches that expected for responders to the treatment
2. Use of response-stratified baseline values	Baseline values, stratified by treatment response status, used to calculate treatment response.	Overall (unstratified) baseline BASDAI and BASFI values were used to calculate treatment response.
3. Treatment effects from conventional therapy	No treatment response, and no change from baseline were assumed from conventional therapy for BASDAI and BASFI	CT treatment effects follow estimates from relevant NMAs for placebo treatment arms
4. Secukinumab dosing	Secukinumab costs assumed a [redacted] split between the 150 mg and 300 mg doses; however, effectiveness data assumed 150 mg of secukinumab only	Dose split removed; assumed secukinumab restricted to 150 mg; model structure prevented consideration of 300 mg dose
5. Exclusion of relevant comparator	Certolizumab pegol was excluded as a relevant comparator in the economic evaluation, despite being available in the NMA	Certolizumab pegol included as a relevant comparator in the biologic-inadvisable subpopulation
CADTH combined reanalysis	—	Reanalysis 1 + 2 + 3 + 4 + 5

BADAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; NMA = network meta-analysis.

Results from the CADTH reanalysis are presented in Table 6 and Table 7. As with the sponsor's base case, this analysis was based on publicly available prices of the comparator treatments. Results from the Monte Carlo simulation are summarized in the following section.

In the bDMARD-inadvisable subpopulation, the expected costs and QALYs for the treatment sequence beginning with upadacitinib were $291,186 and 12.725, respectively. However, upadacitinib was dominated by secukinumab and as a result was not expected to be cost-effective. This means that secukinumab offered more QALYs at a lower cost. At a willingness-to-pay threshold of $50,000 per QALY gained, the probability that upadacitinib would be cost-effective was estimated to be 0.58%.

In the bDMARD-IR subpopulation, the expected costs and QALYs in the sequence beginning with upadacitinib were $317,910 and 12.792, respectively. Upadacitinib dominated secukinumab and was expected to be more expensive and more effective than conventional therapy. The ICER for upadacitinib relative to conventional therapy was estimated to be $52,442. At the $50,000 per QALY gained threshold, the probability of cost-effectiveness was estimated to be 44.6% for UPA, 36.2% for conventional therapy, and 19.2% for secukinumab.

Additional details summarizing the CADTH reanalysis results are included in Appendix 4. The key factors influencing results were the amount of time spent on a biologic and the magnitude of improvement in the BASDAI and BASFI from that treatment. The predicted BASDAI and BASFI values are important because they are used to estimate the utilities and direct medical costs associated with each treatment. This relationship means higher direct medical costs and utilities will be predicted as patients spend more time on a biologic.

Table 6: Summary of CADTH Reanalysis Results (bDMARD-Inadvisable Subpopulation)

Drug	Total costs	Total QALYs	ICER ($ per QALY)
Conventional therapy	$236,171	12.310	Reference
Secukinumab	$250,818	13.257	15,465
Etanercept	$256,160	12.843	Dominated by secukinumab
Adalimumab	$261,631	12.648	Dominated by etanercept and secukinumab
Upadacitinib	$291,186	12.725	Dominated by etanercept and secukinumab
Certolizumab pegol	$295,962	12.486	Dominated by etanercept and secukinumab
Golimumab	$300,756	12.729	Dominated by etanercept and secukinumab
Infliximab	$317,557	12.736	Dominated by etanercept and secukinumab

bDMARD = biologic disease-modifying antirheumatic drug; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Table 7: Summary of CADTH Reanalysis Results (bDMARD–Inadequate Response Subpopulation)

Drug	Total costs	Total QALYs	ICER ($ per QALY)
Conventional therapy	$279,109	12.027	Reference
Upadacitinib	$317,910	12.792	52,442
Secukinumab	$319,822	12.590	Dominated by upadacitinib

bDMARD = biologic disease-modifying antirheumatic drug; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

CADTH notes that this reanalysis remains highly uncertain. The estimates of relative effect obtained from the sponsor's NMAs for effectiveness parameters, as well as naive comparisons to inform AEs and discontinuation rates informing the model represent the largest source of uncertainty in the decision model. The outputs of the CADTH reanalysis suggest differences in treatment benefits between advanced therapies for the treatment of adult AS. These results will only be realized should the numerical differences observed in the NMA for treatment effects, as well as the naive comparisons for AEs and treatment discontinuation, be realized and lead to meaningful improvements for patients.

Issues for Consideration

- Upadacitinib may be self-administered and is the only other oral, small-molecule biologic drug in the current therapeutic space. This ease of administration was noted as an important outcome for patients and clinicians in their respective inputs.

- While ixekizumab received a positive listing recommendation from CADTH for AS, it was excluded from the sponsor's submission given that negotiations with the pan-Canadian Pharmaceutical Alliance concluded without agreement. As such, the cost-effectiveness of upadacitinib in comparison to ixekizumab was not assessed.
- The modelled price of biologic therapies is based on publicly accessible list prices and does not reflect existing confidential pricing that has been negotiated by public plans.

Overall Conclusions

Based on the appraisal of the SELECT-AXIS 1 and SELECT-AXIS 2 trials, CADTH clinical reviewers found that the efficacy of upadacitinib was superior to that of placebo for treatment response, disease activity, and physical functioning in adult patients with active AS. In the absence of direct evidence comparing upadacitinib with the biologics used to treat active AS, estimates of comparative efficacy were established through a Bayesian NMA. The CADTH Clinical Review concluded from the NMAs that there are no differences in efficacy for upadacitinib in comparison with existing biologic treatments indicated for this population. This was consistent across treatment response (BASDAI50), disease activity (BASDAI), and physical functioning (BASFI). The presence of heterogeneity in the included studies increases the uncertainty in these findings, and several relevant comparators were not assessed in the bDMARD-IR subpopulation.

CADTH conducted a reanalysis incorporating changes to the sponsor's economic submission to address key limitations. These changes included: more appropriate assumptions regarding the calculation and timing of treatment effects, use of overall instead of response-stratified baseline BASDAI and BASFI values, use of consistent dosing for secukinumab to calculate costs, an assumption of a treatment effect with conventional therapy, and the inclusion of relevant comparators as permitted by the evidence available for each subpopulation. CADTH was unable to address issues associated with missing comparators and with the NMA used to inform the comparative efficacy parameters of the model.

In the bDMARD-inadvisable subpopulation, upadacitinib was associated with fewer QALYs and increased costs to the health system (it was dominated) when compared to secukinumab and etanercept. In the bDMARD-IR subpopulation, relative to conventional therapy, upadacitinib had an ICER of $52,442 per QALY gained. Relative to secukinumab, the only other biologic included by the sponsor in this analysis, upadacitinib generated more QALYs at a lower cost. However, results from these analyses rely on uncertain differences in treatment effects estimated from the sponsor-submitted NMA that may not correspond to clinically meaningful differences.

Given the limitations outlined by the Clinical Review regarding evidence from the NMA, limited conclusions can be drawn on the differences between upadacitinib and other biologics used to treat AS. If treatment with upadacitinib is expected to have similar health outcomes relative to other biologics, the price of upadacitinib should be no more than that of the lowest-cost biologic approved to treat AS to ensure cost-effectiveness.

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Appendix 1: Cost-Comparison Table

Note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s) and drug plans. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost-Comparison Table for Ankylosing Spondylitis

Treatment	Strength	Form	Price	Recommended dosage	Daily cost	Annual cost
Upadacitinib (Rinvoq)	15 mg	Tablet	$49.2200[a]	15 mg once daily	$49.22	$17,965
IL-17 inhibitors						
Ixekizumab (Taltz)	80 mg/mL	Prefilled pen or syringe	$1670.4400	80 mg every 4 weeks	$59.45	$21,723
Secukinumab (Cosentyx)	150 mg/mL	Prefilled pen or syringe	$840.0000	150 mg at weeks 0 to 4, upon response use 150 mg every 4 weeks thereafter	Year 1 $36.80	Year 1 $13,440
					Year 2+ $29.90	Year 2+ $10,920
				150 mg at weeks 0 to 4, upon non-response use 300 mg every 4 weeks	Year 1 $62.90	Year 1 $22,680
					Year 2+ $59.79	Year 2+ $21,840
TNF-alpha inhibitors						
Biologic-originator products						
Adalimumab (Humira)	40 mg/0.8mL	Prefilled pen or syringe	$794.1000	40 mg every 2 weeks	$56.53	$20,647
Certolizumab pegol (Cimzia)	200 mg/mL	Prefilled pen or syringe	$664.5100[b]	400 mg at weeks 0, 2, 4, then 200 mg every 2 weeks or 400 mg every 4 weeks	Year 1 $52.76	Year 1 $19,271
					Year 2+ $47.30	Year 2+ $17,278
Etanercept (Enbrel)	25 mg	Vial	$202.9300	50 mg per week	$57.78	$21,105
	50 mg/mL	Prefilled syringe	$405.9850		$57.80	$21,112
Golimumab (Simponi)	50 mg/0.5mL	Prefilled pen or syringe	$1555.1700	50 mg every 4 weeks	$55.35	$20,218

Treatment	Strength	Form	Price	Recommended dosage	Daily cost	Annual cost
Infliximab (Remicade)	100 mg	Vial	$977.0000[b]	5mg/kg at weeks 0, 2, 6, then every 6 weeks	Year 1 $107.00	Year 1 $39,080
					Year 2+ $96.30	Year 2+ $35,172
				5mg/kg at weeks 0, 2, 6, then every 8 weeks	Year 1 $85.60	Year 1 $31,264
					Year 2+ $74.90	Year 2+ $27,356
Biosimilar products						
Adalimumab[c]	40 mg/0.4 mL	Prefilled pen or syringe	$471.2700	40 mg every 2 weeks	$33.55	$12,254
	20 mg/0.4 mL	Prefilled syringe	$235.6400			
	40 mg/0.8 mL	Prefilled pen or syringe	$471.2700			
Etanercept[d]	25mg/0.5 mL	Prefilled pen or syringe	$120.5000	50 mg per week	$34.31	$12,532
	50 mg/mL	Prefilled pen or syringe	$241.0000		$34.31	$12,532
Infliximab (Inflectra)	100 mg	Vial	$525.0000	5mg/kg at weeks 0, 2, 6 then every 6 weeks	Year 1 $57.49	Year 1 $21,000
					Year 2+ $51.75	Year 2+ $18,900
				5mg/kg at weeks 0, 2, 6 then every 8 weeks	Year 1 $46.00	Year 1 $16,800
					Year 2+ $40.25	Year 2+ $14,700
Infliximab (Renflexis, Avsola)	100 mg	Vial	$493.0000	5mg/kg at weeks 0, 2, 6 then every 6 weeks	Year 1 $53.99	Year 1 $19,720
					Year 2+ $48.59	Year 2+ $17,748
				5mg/kg at weeks 0, 2, 6 then every 8 weeks	Year 1 $43.19	Year 1 $15,776
					Year 2+ $37.79	Year 2+ $13,804
Conventional synthetic DMARDs						
Methotrexate (generic)	2.5mg	Tablet	$0.5027	7.5 mg to 25 mg per week until dose response	$0.21 to $0.72	$79 to $262

Treatment	Strength	Form	Price	Recommended dosage	Daily cost	Annual cost
	20 mg/2 mL	Prefilled syringe	$12.5000	10 mg to 25 mg per week until dose response	$0.64 to $0.89	$233 to $326
	50 mg/2 mL		$8.9200			
Leflunomide (generic)	10 mg	Tablet	$2.6463	100 mg daily on days 1 to 3, then 20 mg daily	Year 1 $0.93	Year 1 $340
	20 mg				Year 2+ $0.75	Year 2+ $276
Sulfasalazine (generic)	500 mg	Tablet	$0.2533	Days 1 to 7: 500 mg/day Day 8 to 14: 1,000 mg/day, Day 15 to 21: 1,500 mg/day then 2000 mg/day	Year 1 0.12	Year 1 $43
					Year 2+ $0.14	Year 2+ $53

DMARD = disease-modifying antirheumatic drug; IL-17 = interleukin-17.

Note: All prices were obtained from the Ontario Drug Benefit Formulary (accessed November 2022) unless otherwise indicated, and do not include dispensing fees.[29] For infliximab, costs assume a weight of 75 kg and include wastage of unused medication in vials. Daily costs assume 365.25 days per year.

[a]Sponsor's submitted price.

[b]Infliximab (Remicade) price obtained from Saskatchewan Online Formulary Database (accessed November 2022).[30]

[c]Adalimumab biosimilars: Yuflyma, Simlandi, Amgevita, Hulia, Hyrimoz, Hadlima, Abrilada, Idacio.

[d]Etanercept biosimilars: Brenzys, Erelzi.

Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

Table 9: Submission Quality

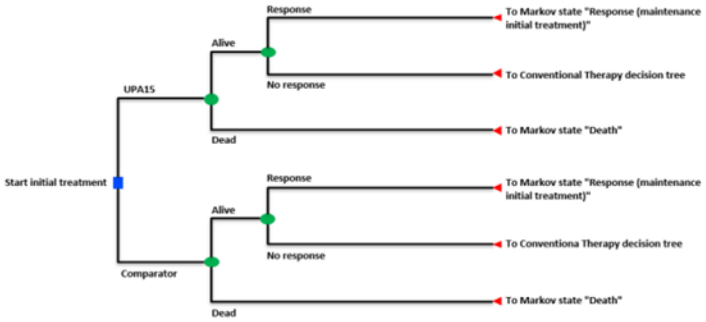
Description	Yes/No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	No	Exclusion of relevant comparators; see key limitation for more details
Model has been adequately programmed and has sufficient face validity	No	See limitations: incorrect timing of treatment effects, response stratification of baseline severity.
Model structure is adequate for decision problem	Yes	No comment
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	No	Uncertainty associated with parameter "Change from Baseline" conditional on treatment response is poorly characterized; see limitations for more details
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	No	Exclusion of relevant comparators and the inappropriate characterization of the conditional change from baseline are expected to have an impact on the estimates of costs and effects for every comparator' see limitations for more details
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	Yes	No comment

Appendix 3: Additional Information on the Submitted Economic Evaluation

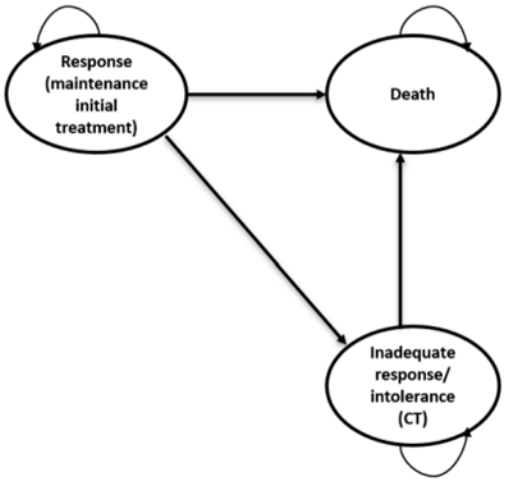
Note that this appendix has not been copy-edited.

Figure 1: Sponsor's Model Structure

First 3 months on treatment



Subsequent treatment cycles



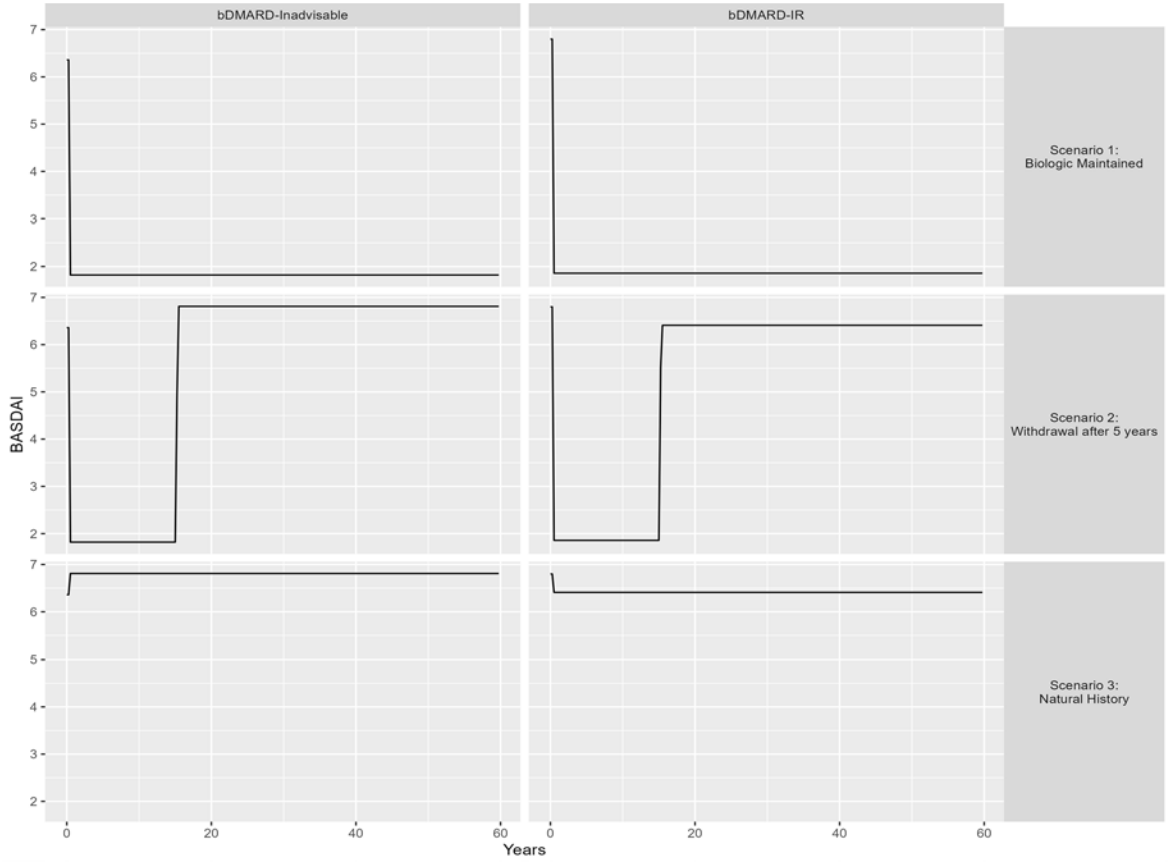
UPA: Upadacitinib; CT: conventional therapy.

Source: Sponsor's pharmacoeconomic submission.[1]

Figure 2 and Figure 3 present a graphical summary illustrating how disease progression was tracked by the model. This is important to understanding the model results given that disease activity (measured by BASDAI) and physical functioning (measured by BASFI) were used to estimate the utilities and direct medical costs associated with each treatment. To illustrate the procedure described in the report, figures were generated to describe the experience of a *single patient* in 3 distinct scenarios: i) successful maintenance on a biologic; ii) withdrawal 5 years after initial response; and iii) natural history (no biologic treatment).

For both subpopulations, data were generated assuming a treatment sequence of upadacitinib followed by conventional therapy. Each plot is organized into a grid where columns represent each subpopulation and rows represent 1 of the 3 specified scenarios.

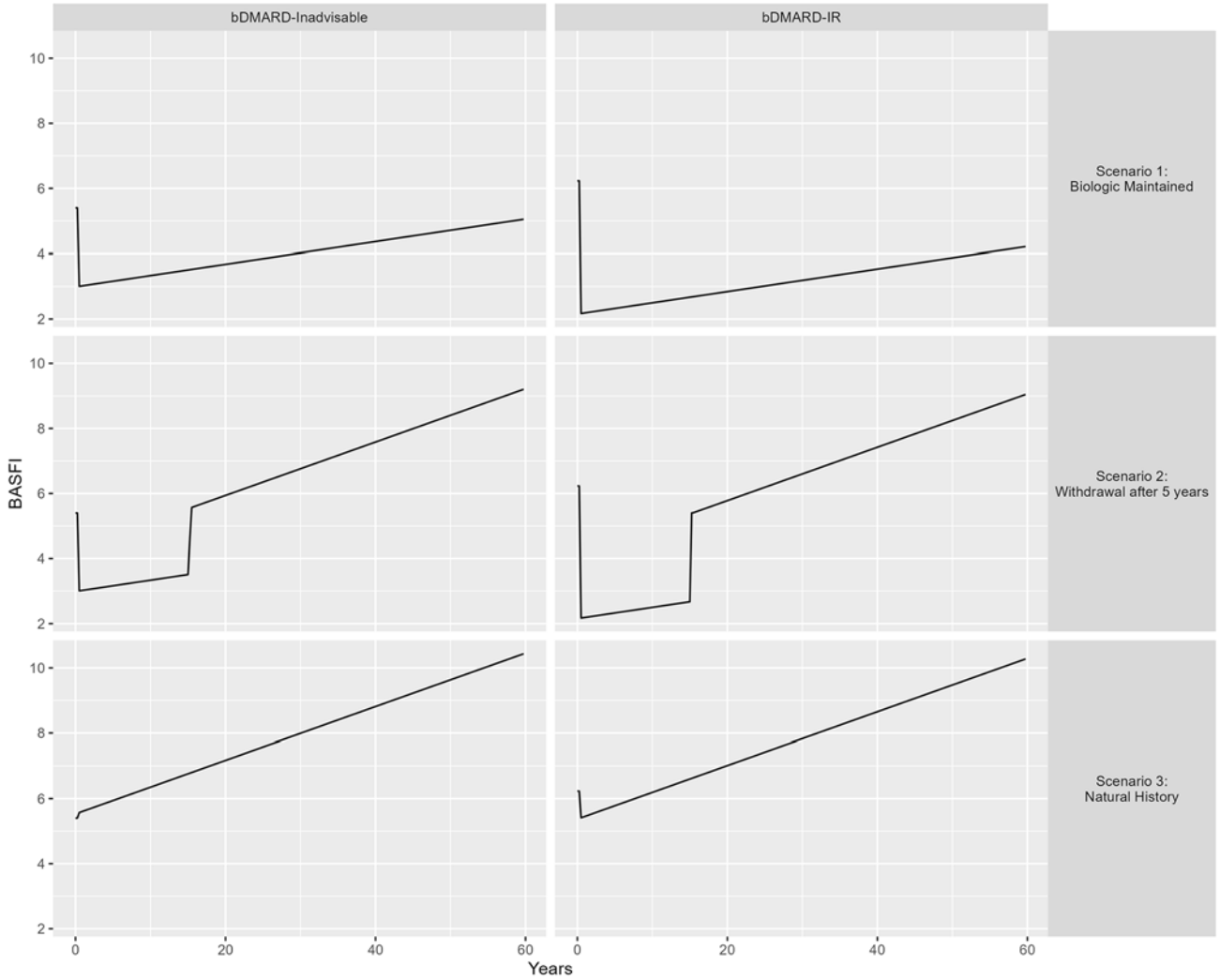
Figure 2: Demonstration of Sponsor Modelling of BASDAI



BASDAI = Bath Ankylosing Spondylitis Disease Activity Index 50% improvement; bDMARD = biologic disease-modifying antirheumatic drug; bDMARD-IR = biologic disease-modifying antirheumatic drug–inadequate response.

Note: Data generated for a single patient.

Figure 3: Demonstration of Sponsor Modelling for BASFI



BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biologic disease-modifying antirheumatic drug; bDMARD-IR = biologic disease-modifying antirheumatic drug–inadequate response.

Detailed Results of the Sponsor's Base Case

Table 10: Disaggregated Summary of Sponsor's Economic Evaluation Results (bDMARD-Inadvisable Subpopulation)

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)
Discounted LYs				
ETN	Total	25.526	NA	NA
ADA	Total	25.526	0	NA
SEC	Total	25.526	0	0
CT	Total	25.526	0	0
UPA	Total	25.526	0	0
GOL	Total	25.526	0	0
INF	Total	25.526	0	0
Discounted QALYs				
ETN	Cycle 1: bDMARD	0.118	NA	NA
	Continue: bDMARD	2.083	NA	NA
	Cycle 1: CT	8.395	NA	NA
	Continue: CT	2.569	NA	NA
	Total	13.165	NA	NA
ADA	Cycle 1: bDMARD	0.118	0.000	NA
	Continue: bDMARD	2.311	0.228	NA
	Cycle 1: CT	7.560	−0.835	NA
	Continue: CT	2.933	0.364	NA
	Total	12.921	−0.243	NA
SEC	Cycle 1: bDMARD	0.118	0.000	0.000
	Continue: bDMARD	2.782	0.699	0.471
	Cycle 1: CT	8.096	−0.299	0.536
	Continue: CT	2.540	−0.028	−0.393
	Total	13.536	0.371	0.615
CT	Cycle 1: bDMARD	0.118	0.000	0.000
	Continue: bDMARD	0.000	−2.083	−2.782
	Cycle 1: CT	10.482	2.086	2.385
	Continue: CT	0.000	−2.569	−2.540
	Total	10.599	−2.566	−2.937
GOL	Cycle 1: bDMARD	0.118	0.000	0.000
	Continue: bDMARD	2.905	0.821	2.905

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)
	Cycle 1: CT	6.132	−2.263	−4.349
	Continue: CT	3.763	1.195	3.763
	Total	12.918	−0.247	2.319
INF	Cycle 1: bDMARD	0.118	0.000	0.000
	Continue: bDMARD	3.646	1.563	0.742
	Cycle 1: CT	4.219	−4.176	−1.913
	Continue: CT	4.799	2.231	1.036
	Total	12.782	−0.383	−0.136
UPA	Cycle 1: bDMARD	0.118	0.000	0.000
	Continue: bDMARD	2.475	0.392	−1.171
	Cycle 1: CT	7.977	−0.418	3.758
	Continue: CT	2.464	−0.105	−2.335
	Total	13.034	−0.131	0.252
Discounted costs ($)				
ETN	Acquisition	36,477.86	NA	NA
	Administration	1,573.84	NA	NA
	Monitoring	1,955.09	NA	NA
	AEs	940.93	NA	NA
	Direct Medical	210,976.91	NA	NA
	Total	251,924.63	NA	NA
ADA	Acquisition	40,212.34	3,734.48	NA
	Administration	886.01	−687.83	NA
	Monitoring	2,142.01	186.92	NA
	AEs	501.98	−438.95	NA
	Direct Medical	215,009.40	4,032.48	NA
	Total	258,751.74	6,827.11	NA
SEC	Acquisition	54,163.58	17,685.72	40,212.34
	Administration	527.08	−1,046.76	886.01
	Monitoring	2,489.87	534.78	2,142.01
	AEs	446.69	−494.24	501.98
	Direct Medical	201,980.10	−8,996.81	215,009.40
	Total	259,607.32	7,682.69	855.58
CT	Acquisition	0.00	−36,477.86	54,163.58
	Administration	0.00	−1,573.84	527.08

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)
	Monitoring	0.00	−1,955.09	2,489.87
	AEs	0.00	−940.93	446.69
	Direct Medical	261,351.03	50,374.12	201,980.10
	Total	261,351.03	9,426.40	1,743.71
GOL	Acquisition	77,283.11	40,805.25	0.00
	Administration	515.82	−1,058.02	0.00
	Monitoring	2,583.71	628.62	0.00
	AEs	532.81	−408.12	0.00
	Direct Medical	219,019.78	8,042.87	261,351.03
	Total	299,935.23	48,010.60	38,584.20
INF	Acquisition	86,504.54	50,026.68	77,283.11
	Administration	8,761.15	7,187.31	515.82
	Monitoring	3,124.07	11,68.98	2,583.71
	AEs	1,210.28	269.34	532.81
	Direct Medical	220,473.87	9,496.96	219,019.78
	Total	320,073.91	68,149.28	20,138.68
UPA	Acquisition	65,080.99	28,603.13	86,504.54
	Administration	0.00	−1,573.84	8,761.15
	Monitoring	2,606.65	651.56	3,124.07
	AEs	0.00	−940.93	1,210.28
	Direct Medical	220,108.77	9,131.86	220,473.87
	Total	287,796.41	35,871.78	−32,277.50

Treatment	ICER vs. reference ($)	Sequential ICER ($)
ETN (least expensive option)	Reference	Reference
ADA	Dominated by reference	
SEC	$20,683	$20,683 vs. reference
CT	Dominated by SEC	
UPA	Dominated by SEC and ETN	
GOL	Dominated by UPA and SEC and ETN	
INF	Dominated by GOL and UPA and SEC and ETN	

AE = adverse event; ADA = adalimumab; CT = conventional therapy; ETN = etanercept; GOL = golimumab; ICER = incremental cost-effectiveness ratio; INF = infliximab; NA = not available; SEC = secukinumab; UPA = upadacitinib.

Source: Sponsor's pharmacoeconomic submission.[1]

Table 11: Disaggregated Summary of Sponsor's Economic Evaluation Results (bDMARD–Inadequate Response Subpopulation)

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)
Discounted LYs				
SEC	Total	27.031	NA	NA
CT	Total	27.031	0.000	NA
UPA	Total	27.031	0.000	0.000
Discounted QALYs				
SEC	Cycle 1: bDMARD	0.106	NA	NA
	Continue: bDMARD	3.079	NA	NA
	Cycle 1: CT	6.375	NA	NA
	Continue: CT	3.039	NA	NA
	Total	12.600	NA	NA
CT	Cycle 1: bDMARD	0.106	0.000	NA
	Continue: bDMARD	0.000	−3.079	NA
	Cycle 1: CT	9.742	3.367	NA
	Continue: CT	0.000	−3.039	NA
	Total	9.848	−2.752	NA
UPA	Cycle 1: bDMARD	0.106	0.000	0.000
	Continue: bDMARD	2.041	−1.039	2.041
	Cycle 1: CT	8.559	2.184	−1.183
	Continue: CT	1.992	−1.048	1.992
	Total	12.697	0.097	2.849
Discounted costs ($)				
SEC	Acquisition	62,407.17	NA	NA
	Administration	605.50	NA	NA
	Physician visits	2,812.60	NA	NA
	AEs	515.76	NA	NA
	Direct Medical	267,604.08	NA	NA
	Total	333,945.11	NA	NA
CT	Acquisition	0.00	−62,407.17	NA
	Administration	0.00	−605.50	NA
	Physician visits	0.00	−2,812.60	NA
	AEs	0.00	−515.76	NA
	Direct Medical	337,520.42	69,916.33	NA

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)
	Total	337,520.42	3,575.31	NA
UPA	Acquisition	52,639.01	−9,768.16	0.00
	Administration	0.00	−605.50	0.00
	Physician visits	2,222.04	−590.56	0.00
	AEs	2,622.32	2,106.57	0.00
	Direct Medical	268,237.77	633.69	337,520.42
	Total	325,721.14	−8,223.97	−11,799.28

Treatment	ICER vs. reference ($)	Sequential ICER ($)
UPA	Ref	Ref
SEC	Dominated by UPA	
CT	Dominated by SEC	

CT = conventional therapy; ICER = Incremental cost-effectiveness ratio; NA = not available; SEC = secukinumab; UPA = upadacitinib.
Source: Sponsor's pharmacoeconomic submission.[1]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has not been copy-edited.

Detailed Results of CADTH Reanalyses

To address some of the key limitations from the sponsor's submission, a series of changes were implemented to derive the CADTH reanalysis. Each revision listed in Table 5 was implemented independently and the results obtained from each revision are presented in Table 12, below. All estimates within Table 12 were obtained via deterministic simulation. Given the nonlinear model structure, they may not always be consistent with those obtained from Monte Carlo simulation. Therefore, the results presented from the stepped reanalysis should only be used for the independent verification of the changes to derive the CADTH reanalysis.

Table 12: Summary of the Stepped Analysis of the CADTH Reanalysis Results (bDMARD-Inadvisable Subpopulation)

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/ per QALY)
Sponsor base case	etanercept	249,714	13.162	Reference
	adalimumab	256,701	12.911	Dominated
	secukinumab	258,119	13.542	22,104
	CT	260,363	10.612	Dominated
	upadacitinib	285,031	13.038	Dominated
	golimumab	297,544	12.896	Dominated
	infliximab	309,496	12.764	Dominated
CADTH reanalysis 1	etanercept	249,707	13.152	Reference
	adalimumab	256,664	12.901	Dominated
	secukinumab	258,088	13.533	22,005
	CT	260,363	10.612	Dominated
	upadacitinib	285,006	13.030	Dominated
	golimumab	297,531	12.884	Dominated
	infliximab	309,453	12.749	Dominated
CADTH reanalysis 2	etanercept	254,553	12.854	Reference
	CT	257,173	10.696	Dominated
	adalimumab	260,350	12.648	Dominated
	secukinumab	261,817	13.275	17,258
	upadacitinib	290,176	12.749	Dominated

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/ per QALY)
	golimumab	298,618	12.735	Dominated
	infliximab	306,877	12.730	Dominated
CADTH reanalysis 3	CT	239,256	12.152	Reference
	etanercept	249,714	13.162	10,355
	adalimumab	256,701	12.911	Dominated
	secukinumab	258,119	13.542	22,104
	upadacitinib	285,031	13.038	Dominated
	golimumab	297,544	12.896	Dominated
	infliximab	309,496	12.764	Dominated
CADTH reanalysis 4	secukinumab	246,566	13.542	Reference
	etanercept	249,714	13.162	Dominated
	adalimumab	256,701	12.911	Dominated
	CT	260,363	10.612	Dominated
	upadacitinib	285,031	13.038	Dominated
	golimumab	297,544	12.896	Dominated
	infliximab	309,496	12.764	Dominated
CADTH reanalysis 5	etanercept	249,714	13.162	Reference
	adalimumab	256,701	12.911	Dominated
	secukinumab	258,119	13.542	22,104
	CT	260,363	10.612	Dominated
	upadacitinib	285,031	13.038	Dominated
	certolizumab pegol	291,905	12.672	Dominated
	golimumab	297,544	12.896	Dominated
	infliximab	309,496	12.764	Dominated
CADTH combined reanalysis (1 to 5)	CT	235,618	12.322	Reference
	secukinumab	250,234	13.266	15,483
	etanercept	254,546	12.845	Dominated
	adalimumab	260,315	12.638	Dominated
	upadacitinib	290,152	12.741	Dominated
	certolizumab pegol	293,719	12.471	Dominated
	golimumab	298,606	12.723	Dominated
	infliximab	306,836	12.715	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: Results were generated from deterministic simulations and should not be used to make conclusions regarding cost-effectiveness. Total costs estimated using biosimilar prices, where available.

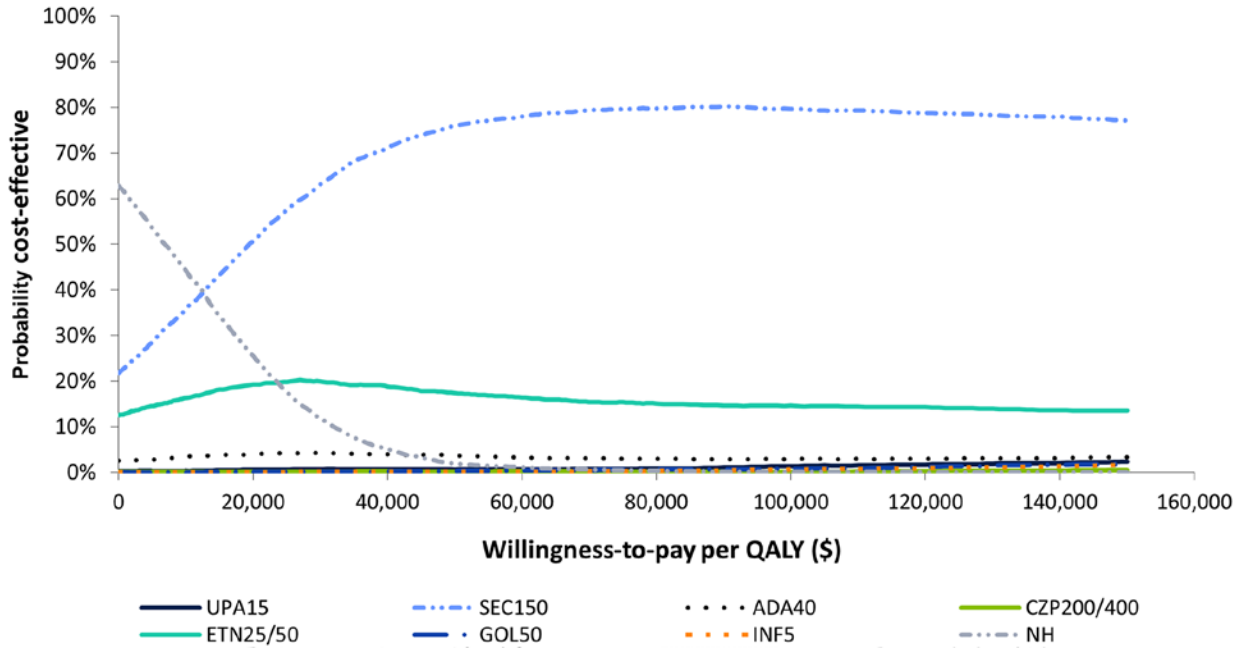
Table 13: Summary of the Stepped Analysis of the CADTH Reanalysis Results (bDMARD–Inadequate Response Subpopulation)

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($ per QALY)
Sponsor's base case	upadacitinib	324,039	12.709	Reference
	secukinumab	332,981	12.620	Dominated
	CT	337,540	9.865	Dominated
CADTH reanalysis 1	upadacitinib	324,011	12.702	Reference
	secukinumab	332,922	12.611	Dominated
	CT	337,540	9.865	Dominated
CADTH reanalysis 2	upadacitinib	317,611	12.821	Reference
	secukinumab	331,723	10.020	Dominated
	CT	332,275	12.625	Dominated
CADTH reanalysis 3	CT	280,011	12.030	Reference
	upadacitinib	324,039	12.709	64,914
	secukinumab	332,981	12.620	Dominated
CADTH reanalysis 4	secukinumab	319,576	12.620	Reference
	upadacitinib	324,039	12.709	50,395
	CT	337,540	9.865	Dominated
CADTH reanalysis 5	upadacitinib	324,039	12.709	Reference
	secukinumab	332,981	12.620	Dominated
	CT	337,540	9.865	Dominated
CADTH combined reanalysis (1 to 5)	CT	278,580	12.053	Reference
	upadacitinib	317,582	12.814	51,270
	secukinumab	318,807	12.616	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: Results were generated from deterministic simulations and should not be used to make conclusions regarding cost-effectiveness. All costs estimated using biologic originator prices reported by the sponsor.

Figure 4: Cost-Effectiveness Acceptability Curve (bDMARD-Inadvisable Subpopulation)



bDMARD = biologic disease-modifying antirheumatic drug; IR: Inadequate Response; UPA = upadacitinib; SEC = secukinumab; ADA = adalimumab; CZP = certolizumab pegol; ETN = etanercept; GOL = golimumab; INF = infliximab; NH = natural history (conventional therapy).

Table 14: Disaggregated Summary of CADTH's Economic Evaluation Reanalysis Results (bDMARD-Inadvisable Subpopulation)

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)
Discounted LYs				
CT	Total	25.529	NA	NA
SEC	Total	25.529	0	NA
ETN	Total	25.529	0	0
ADA	Total	25.529	0	0
UPA	Total	25.529	0	0
CZP	Total	25.529	0	0
GOL	Total	25.529	0	0
INF	Total	25.529	0	0
Discounted QALYs				
CT	Cycle 1: bDMARD	0.118	NA	NA
	Continue: bDMARD	2.432	NA	NA
	Cycle 1: CT	9.760	NA	NA

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)
	Continue: CT	0.000	NA	NA
	Total	12.310	NA	NA
SEC	Cycle 1: bDMARD	0.118	0.000	NA
	Continue: bDMARD	2.825	0.393	NA
	Cycle 1: CT	7.727	−2.033	NA
	Continue: CT	2.587	2.587	NA
	Total	13.257	0.947	NA
ETN	Cycle 1: bDMARD	0.118	0.000	0.000
	Continue: bDMARD	2.104	−0.328	0.393
	Cycle 1: CT	7.991	−1.769	−2.033
	Continue: CT	2.631	2.631	2.587
	Total	12.843	0.533	0.947
ADA	Cycle 1: bDMARD	0.118	0.000	0.000
	Continue: bDMARD	2.346	−0.086	−0.722
	Cycle 1: CT	7.206	−2.554	0.264
	Continue: CT	2.978	2.978	0.044
	Total	12.648	0.338	−0.414
UPA	Cycle 1: bDMARD	0.118	0.000	0.000
	Continue: bDMARD	2.476	0.044	0.242
	Cycle 1: CT	7.666	−2.094	−0.786
	Continue: CT	2.465	2.465	0.348
	Total	12.725	0.415	−0.195
CZP	Cycle 1: bDMARD	0.118	0.000	0.000
	Continue: bDMARD	2.654	0.222	0.130
	Cycle 1: CT	6.123	−3.637	0.461
	Continue: CT	3.592	3.592	−0.513
	Total	12.486	0.177	0.077
GOL	Cycle 1: bDMARD	0.118	0.000	0.000
	Continue: bDMARD	2.949	0.517	0.178
	Cycle 1: CT	5.799	−3.961	−1.543
	Continue: CT	3.864	3.864	1.127
	Total	12.729	0.420	−0.238
INF	Cycle 1: bDMARD	0.118	0.000	0.000
	Continue: bDMARD	3.747	1.315	0.295

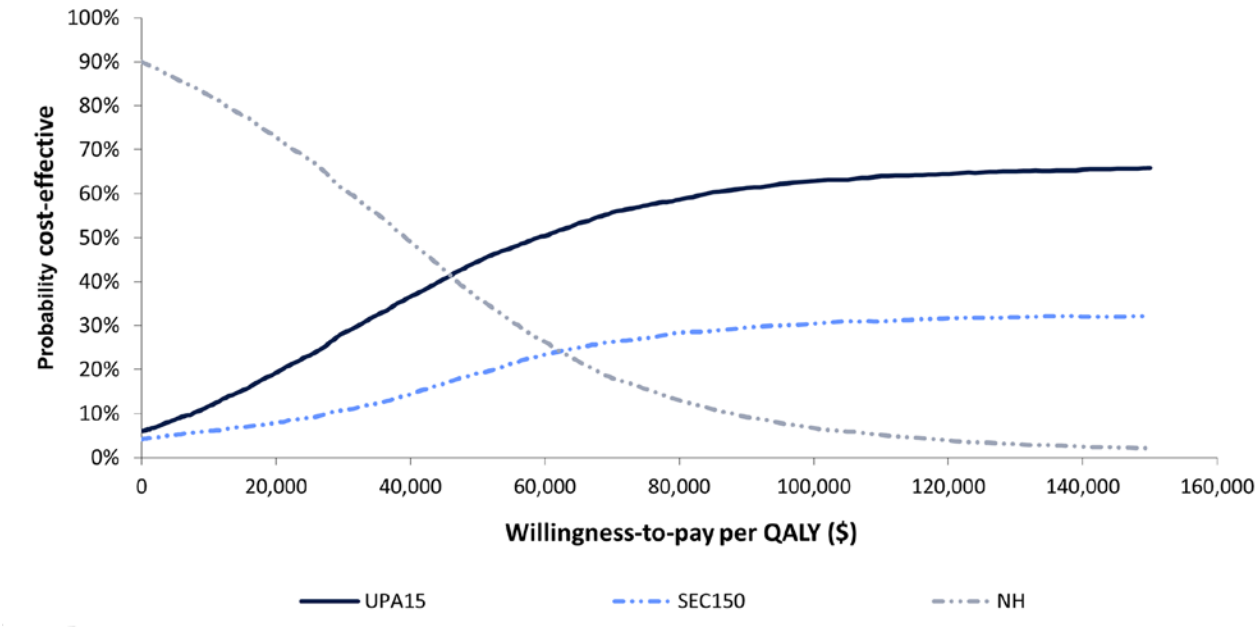
Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)
	Cycle 1: CT	3.926	−5.834	−0.324
	Continue: CT	4.946	4.946	0.272
	Total	12.736	0.426	0.243
Discounted costs ($)				
CT	Acquisition	0	NA	NA
	Administration	0	NA	NA
	Monitoring	0	NA	NA
	AEs	0	NA	NA
	Direct Medical	236,171	NA	NA
	Total	236,171	NA	NA
SEC	Acquisition	42,640	42,640	NA
	Administration	528	528	NA
	Monitoring	2,488	2,488	NA
	AEs	445	445	NA
	Direct Medical	204,718	204,718	NA
	Total	250,818	250,818	NA
ETN	Acquisition	36,472	36,472	−6,168
	Administration	1,576	1,576	1,048
	Monitoring	1,953	1,953	−535
	AEs	944	944	499
	Direct Medical	215,215	215,215	10,497
	Total	256,160	256,160	5,342
ADA	Acquisition	40,246	40,246	3,774
	Administration	889	889	−686
	Monitoring	2,141	2,141	188
	AEs	501	501	−443
	Direct Medical	217,853	217,853	2,638
	Total	261,631	261,631	5,470
UPA	Acquisition	63,988	63,988	23,742
	Administration	0	0	−889
	Monitoring	2,569	2,569	428
	AEs	0	0	−501
	Direct Medical	224,628	224,628	6,776
	Total	291,186	291,186	29,555

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)
CZP	Acquisition	69,596	69,596	5,608
	Administration	1,090	1,090	1,090
	Monitoring	2,459	2,459	−110
	AEs	982	982	982
	Direct Medical	221,836	221,836	−2,793
	Total	295,962	295,962	4,776
GOL	Acquisition	77,466	77,466	7,870
	Administration	519	519	−571
	Monitoring	2,588	2,588	129
	AEs	534	534	−449
	Direct Medical	219,650	219,650	−2,185
	Total	300,756	300,756	4,794
INF	Acquisition	87,317	87,317	9,852
	Administration	8,833	8,833	8,315
	Monitoring	3,150	3,150	562
	AEs	1,226	1,226	692
	Direct Medical	217,030	217,030	−2,620
	Total	317,557	317,557	16,801

Treatment	ICER vs. reference ($)	Sequential ICER ($)
CT	Reference	Reference
SEC	$15,465	$15,465
ETN	Dominated by SEC	
ADA	Dominated by ETN and SEC	
UPA	Dominated by ETN and SEC	
CZP	Dominated by ETN, ADA, UPA, and SEC	
GOL	Dominated by ETN and SEC	
INF	Dominated by ETN, UPA, GOL, and SEC	

ICER = incremental cost-effectiveness ratio; LY = life-year; NA = not applicable; QALY = quality-adjusted life-year; Reference = reference; vs. = versus; CT = conventional therapy; SEC = secukinumab; ETN = etanercept; ADA = adalimumab; UPA = upadacitinib; CZP = certolizumab pegol; GOL = golimumab; INF = infliximab.

Figure 5: Cost-Effectiveness Acceptability Curve (bDMARD–Inadequate Response Subpopulation)



bDMARD = biologic disease-modifying antirheumatic drug; QALY = quality-adjusted life-year; UPA = upadacitinib; SEC = secukinumab; NH = natural history (conventional therapy).

Table 15: Disaggregated Summary of CADTH's Economic Evaluation Reanalysis Results (bDMARD–Inadequate Response Subpopulation)

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)
Discounted LYs				
CT	Total	27.042	NA	NA
UPA	Total	27.042	0.000	NA
SEC	Total	27.042	0.000	0.000
Discounted QALYs				
CT	Cycle 1: bDMARD	0.106	NA	NA
	Continue: bDMARD	1.532	NA	NA
	Cycle 1: CT	10.389	NA	NA
	Continue: CT	0.000	NA	NA
	Total	12.027	NA	NA
UPA	Cycle 1: bDMARD	0.106	0.000	NA
	Continue: bDMARD	1.937	0.404	NA
	Cycle 1: CT	8.856	−1.532	NA

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)
	Continue: CT	1.893	1.893	NA
	Total	12.792	0.764	NA
SEC	Cycle 1: bDMARD	0.106	0.000	0.000
	Continue: bDMARD	2.998	1.465	1.465
	Cycle 1: CT	6.547	−3.842	−3.842
	Continue: CT	2.938	2.938	2.938
	Total	12.590	0.562	0.562
Discounted costs ($)				
CT	Acquisition	0	NA	NA
	Administration	0	NA	NA
	Physician visits	0	NA	NA
	AEs	0	NA	NA
	Direct Medical	279,109	NA	NA
	Total	279,109	NA	NA
UPA	Acquisition	51,329	51,329	NA
	Administration	0	0	NA
	Physician visits	2,171	2,171	NA
	AEs	2,554	2,554	NA
	Direct Medical	261,857	−17,252	NA
	Total	317,910	38,801	NA
SEC	Acquisition	48,835	48,835	−2,494
	Administration	604	604	604
	Physician visits	2,804	2,804	633
	AEs	514	514	−2,039
	Direct Medical	267,064	−12,044	5,208
	Total	319,822	40,713	1,912

Treatment	ICER vs. reference ($)	Sequential ICER ($)
CT	Ref	Ref
UPA	$50,775	$50,775
SEC	Dominated by UPA	

ICER = incremental cost-effectiveness ratio; LY = life-year; NA = not applicable; QALY = quality-adjusted life-year; CT = conventional therapy; UPA = upadacitinib; SEC = secukinumab.

A series of scenario analyses were conducted to explore the price reductions required to obtain an ICER for upadacitinib below the $50,000 per QALY threshold based on the CADTH reanalysis. All estimates were obtained from the incremental analysis of costs and QALYs generated by deterministic simulation.

Findings from this analysis are presented in Table 16 and Table 17. Based on public list prices, findings using the CADTH reanalysis inputs and assumption suggested that price reductions of at least 95%% and 3% would be needed for the inadvisable and inadequate response subpopulations, respectively. These results should be interpreted with caution given the limitations with the available clinical evidence and the missing comparators in the biologic inadequate response sub- population.

Table 16: CADTH Price-Reduction Analyses (bDMARD-Inadvisable Subpopulation)

Analysis	Upadacitinib's position on cost-effectiveness frontier	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	Dominated by ETN and SEC	Dominated by ETN and SEC
10%	Dominated by ETN and SEC	Dominated by ETN and SEC
20%	Dominated by ETN and SEC	Dominated by ETN and SEC
30%	Dominated by ETN and SEC	Dominated by ETN and SEC
40%	Dominated by ETN and SEC	Dominated by ETN and SEC
50%	Dominated by ETN	Dominated by ETN and SEC
60%	WTP ≤ $ 22,988 then upadacitinib is optimal WTP > $22,998 then secukinumab is optimal	Dominated by SEC
70%	WTP ≤ $35,729 then upadacitinib is optimal WTP > $35,729 then secukinumab is optimal	Extendedly dominated by CT and SEC
80%	WTP ≤ $48,470 then upadacitinib is optimal WTP > $48,470 then secukinumab is optimal	WTP < $7,697 then CT is optimal $7,697 ≤ WTP < $21,679 then upadacitinib is optimal WTP > $21,679 then secukinumab is optimal
90%	WTP ≤ $61,211 then upadacitinib is optimal WTP > $61,211 then secukinumab is optimal	WTP ≤ $33,881 then upadacitinib is optimal WTP > $33,881 then secukinumab is optimal

CT = conventional therapy; ETN = etanercept; ICER = incremental cost-effectiveness ratio; SEC = secukinumab; WTP = willingness-to-pay threshold.

Notes: Price-Reduction analyses performed using costs and QALYs obtained via deterministic simulation. WTP has been used to denote that if a value is above, below, or between the values stated, then the treatment is the most cost-effective options at that WTP value or range.

Table 17: CADTH Price-Reduction Analyses (bDMARD–Inadequate Response Subpopulation)

Analysis	ICERs for upadacitinib	
Price reduction	**Sponsor base case**	**CADTH reanalysis[a]**
No price reduction	UPA Dominates	$51,270
10%	UPA Dominates	$44,456
20%	UPA Dominates	$34,869

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; UPA = upadacitinib.

Note: Price-reduction analyses performed using costs and QALYs obtained via deterministic simulation.

[a]Comparison: upadacitinib vs. conventional therapy (reference). Secukinumab is dominated by upadacitinib.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 18: Summary of Key Take-Aways

Key take-aways of the budget impact analysis
• CADTH identified 2 key limitations in the sponsor's base case: i) market size was estimated using a claims-based approach, which relies on aggregated data summarizing total prescriptions or claims. It was not clear what steps were taken to identify individual patients within these data; ii) market size estimates also relied on 2 simplifying assumptions, which could not be verified. These related to the size of the AS population, and the proportion of AS patients with prior biologic experience. While both limitations affected the size of the target population, the impact on the estimated budget impact was unknown. • In the absence of more reliable input values, the sponsor's base case was maintained. • The net budget impact of upadacitinib was estimated to be $445,516 in Year 2, $2,282,075 in Year 2, and $3,632,308 in Year 3. The net budget impact over the 3-year time horizon was $6,359,james

Summary of Sponsor's Budget Impact Analysis

The submitted budget impact analysis (BIA) evaluated the introduction of upadacitinib for the treatment of adults with active Ankylosing Spondylitis. This population was defined as patients who had an inadequate response to a biologic DMARD (bDMARD-IR) or for whom treatment with a biologic is inadvisable. Unlike the economic evaluation, these groups were not treated as distinct subpopulations in the BIA.

A claims-based approach was used to estimate the eligible population size for the analysis. Estimates were generated from the perspective of CADTH-participating drug plans (all but Quebec) and the results were aggregated into pan-Canadian totals over a 3-year time horizon. The total number of AS patients receiving biologic treatment was determined from 4 distinct inputs. First, the IQVIA GPM database was queried to identify the total number of patients with spondylarthritis (SpA) treated with a biologic between August 2020 and July 2022. Second, the sponsor relied on internal market research to determine the proportion of SpA patients with AS (50%). While SpA indications can include AS and psoriatic arthritis (PsA), the queried data did not include this distinction. Third, the IQVIA Pharmastat database was used to identify the proportion of patients in each province eligible for public coverage. This input was estimated as the proportion of claims for secukinumab from 2015 to 2022. Fourth, it was assumed that 75% of patients eligible for public coverage would meet the eligibility criteria for upadacitinib. Key inputs to the BIA are reported in Table 19.

In the reference scenario, it was assumed that patients would be eligible for 1 of the currently available treatments for AS. Treatments currently approved and reimbursed in Canada included: etanercept, infliximab, certolizumab pegol, secukinumab, adalimumab, and golimumab. In the new drug scenario, it was assumed that upadacitinib would be included among the available treatments for adult AS in Canada.

Key assumptions:

- Both biologic-originator and biosimilar DMARDs were considered, where available. Treatments available in both forms included: etanercept, infliximab, and adalimumab.
- Two key inputs were assumed to follow sponsor's internal estimates: i) 50% of patients with SpA indications were assumed to have AS; ii) 75% of AS patients eligible for public coverage had an inadequate response to a preceding biologic or would be biologic-inadvisable.
- The claims for secukinumab from each drug plan were assumed to represent the proportion of patients eligible for public coverage. This was justified by 2 factors. First, treatment with secukinumab would not be affected by policies encouraging the use of biosimilars. Second, the sponsor expected that secukinumab and upadacitinib would be offered at the same point in therapy.
- 80% of market share for upadacitinib would come from IL-17 inhibitors like secukinumab. Justification was that the treatment of interest would be offered at the same point in therapy. It was assumed that upadacitinib would obtain market share of 2.55%, 7.03%, and 9.49% in Years 1 to 3. Scenario analyses included adjustments of ± 25% to the assumed market share.

Table 19: Summary of Key Model Parameters

Parameter	Sponsor's estimate		
Target Population			
Number of SpA patients on biologic treatment in Canada	29,243		
Distribution of AS among SpA indications	50%		
AS patients eligible for public coverage	40.52% (ON), 86.55% (BC), 51.01% (AB), 88.82% (SK), 77.34% (MB), 22.64% (NB), 28.58% (NS and PEI), 42.07 (NL), 100% (NIHB)		
AS patients eligible for upadacitinib	75%		
Patient Identification	**Year 1**	**Year 2**	**Year 3**
Number of patients eligible for drug under review	7,425	8,202	9,084
Market Uptake (3 Years)	**Year 1**	**Year 2**	**Year 3**
Uptake (Reference Scenario)			
Etanercept (Enbrel)	1.87%	0.00%	0.00%
Etanercept (Biosimilar)	12.03%	12.85%	12.12%
Infliximab (Remicade)	1.78%	0.00%	0.00%
Infliximab (Biosimilar)	6.68%	7.84%	7.48%
Certolizumab Pegol (Cimzia)	4.34%	4.41%	4.42%
Secukinumab (Cosentyx)	12.78%	13.02%	13.08%
Adalimumab (Humira)	5.13%	0.00%	0.00%
Adalimumab (Biosimilar)	28.57%	35.21%	36.56%
Golimumab (Simponi)	26.82%	26.67%	26.34%
Uptake (New Drug Scenario)			
Upadacitinib (Rinvoq)	2.55%	7.03%	9.49%

Parameter	Sponsor's estimate		
Etanercept (Enbrel)	1.86%	0.00%	0.00%
Etanercept (Biosimilar)	11.96%	12.64%	11.85%
Infliximab (Remicade)	1.77%	0.00%	0.00%
Infliximab (Biosimilar)	6.64%	7.71%	7.31%
Certolizumab Pegol (Cimzia)	4.31%	4.34%	4.33%
Secukinumab (Cosentyx)	10.74%	7.40%	5.49%
Adalimumab (Humira)	5.10%	0.00%	0.00%
Adalimumab (Biosimilar)	28.40%	34.64%	35.76%
Golimumab (Simponi)	26.66%	26.23%	25.76%
Cost of Treatment (per patient)			
Cost of treatment over 1 year	Loading Dose	Maintenance Only	–
Upadacitinib (Rinvoq)	$17,977.61	$17,977.61	–
Etanercept (Enbrel)	$21,183.72	$21,183.72	–
Etanercept (Biosimilar)	$12,575.04	$12,575.04	–
Infliximab (Remicade)	$31,601.92	$25,764.74	–
Infliximab (Biosimilar)	$15,776.00	$12,862.02	–
Certolizumab Pegol (Cimzia)	$19,270.79	$17,336.59	–
Secukinumab (Cosentyx)	$16,212.00	$13,104.00	–
Adalimumab (Humira)	$20,717.50	$20,717.50	–
Adalimumab (Biosimilar)	$12,295.10	$12,295.10	–
Golimumab (Simponi)	$18,662.04	$18,662.04	–

AS = Ankylosing Spondylitis; ON = Ontario, BC = British Columbia; AB = Alberta; SK = Saskatchewan; MB = Manitoba; NB = New Brunswick; NS = Nova Scotia; PEI = Prince Edward Island; NL = Newfoundland and Labrador; NIHB = Non-Insured Health Benefits; SpA = Spondylarthritis.

Summary of the Sponsor's Budget Impact Analysis Results

In the sponsor's base case, the net budget impact of upadacitinib was $445,516 in Year 1, $2,282,075 in Year 2, and $3,632,308 in Year 3. The 3-year net budget impact of upadacitinib was $6,359,899.

CADTH Appraisal of the Sponsor's Budget Impact Analysis

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Use of a claims-based approach to estimate market size:** The sponsor relied on public claims data to estimate the market size for each of the relevant comparators. Such data were used to estimate the number of patients with SpA using a biologic treatment and those covered by a provincial drug plan. The former relied on data obtained from the IQVIA GPM database, which included the total number of prescriptions and units dispensed. Meanwhile, it was assumed that claims for secukinumab included

within the IQVIA PharmaStat database would be representative of the latter. A key challenge with the claims-based approach is its reliance on aggregated data, making it difficult to distinguish individual patients. Given that multiple dispensations of a biologic are expected over time, it may not always be appropriate to assume that each claim or prescription represented a unique patient. As a result, there is a risk that the over-representation of individual patients in the underlying data yielded market share inputs which were incorrect. The extent to which this limitation will affect the net budget impact of upadacitinib is unknown.

    - CADTH was unable to address the limitations of a claims-based approach to estimate budget impact.

- **Assumptions used to estimate market size:** Two simplifying assumptions had to be made to facilitate the claims-based approach to estimate market size. First, it was assumed that 50% of patients with SpA will have AS. Second, it was assumed that 75% of AS patients had an inadequate response to a preceding biologic. Both assumptions are difficult to verify given that both were derived from data held by the sponsor. As a result, it may be appropriate to view the results of the BIA as uncertain. Importantly, the effect of each assumption on the results was explored through the sponsor's submitted sensitivity analyses.

    - CADTH was unable to identify superior inputs to those used by the sponsor and notes the uncertainty with the sponsor's estimated budget impact.

CADTH Reanalyses of the Budget Impact Analysis

In the absence of more reliable estimates to inform the key parameters of the BIA, the sponsor's submitted base case was maintained. CADTH expects that the budget impact of upadacitinib will be sensitive to more reliable inputs which may affect the market size calculation.

Table 20: Detailed Breakdown of the Budget Impact Analysis

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
Submitted base case	Reference	$126,191,614	$121,920,729	$127,475,183	$140,476,709	$389,872,621
	New drug	$126,191,614	$122,366,246	$129,757,258	$144,109,017	$396,232,520
	Budget impact	$0	$445,516	$2,282,075	$3,632,308	$6,359,899

Stakeholder Input

List of Tables

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Patient Input

Arthritis Consumer Experts

About Arthritis Consumer Experts

Canada's largest, longest running national arthritis patient organization headquartered in Vancouver, BC, Arthritis Consumer Experts (ACE) provides free, science-based information and education programs in both official languages to people with arthritis. ACE serves people living with all forms of arthritis by helping them take control of their disease and improve their quality of life through education and (em)powerment. Founded and led by people with arthritis, ACE also advocates on arthritis health policy and provides research-based education through ACE's JointHealth™ family of programs and the Arthritis Broadcast Network, directly to consumers/patients, media, and government. ACE operates as a non-profit in a fully transparent manner and is guided by a strict set of guiding principles, set out by an advisory board comprised of leading scientists, medical professionals, and informed arthritis consumers. Ultimately, we are guided by the needs of our members, who are people living with arthritis, and their caregivers.

Link to website: www.jointhealth.org

Information Gathering

The information was gathered from anonymous data collected from people living with ankylosing spondylitis who have previously submitted input for CADTH in 2019.The information was gathered in Canada on the ACE Survey Monkey platform; there are no updates to their disease journeys or perspectives.

Disease Experience

How does the disease impact the patients' day-to-day life and quality of life?

Ankylosing spondylitis (AS) has a significant effect on the lives of people living with it and they constantly consider the state of their disease and decide what they can, or more likely, cannot, cope with or achieve, how they can go about their daily lives, and how much help they may need along the way.

- **Patient A:** Living with AS for 30 years and also has Crohn's Colitis, psoriatic arthritis, and psoriasis. RA for approximately 30 years. They have limited mobility due to their AS.
- **Patient B:** Living with AS for 23 years. "I am aware that at any time, my back inflammation can flare up and severely limit my activity for a few days. So, I pace myself and pay attention to my posture."
- **Patient C:** Living with AS for 20 years. "Fatigue, pain, and subsequent deconditioning have led to other MSK issues (e.g., knee pain). The constant pain has also made me anxious and affects my mood when I am not able to go out to do things I would like to do, or sometimes even my daily activities."
- **Patient D:** Living with AS for 4 years and experiences unpredictable and disabling pain and fatigue.

How does the disease impact the caregivers' day-to-day life and quality of life?

Caregivers of people living with ankylosing spondylitis have indicated that time management is very important to them. When patients are in pain, caregivers have to help with house chores and many other aspects of life at home. Patient D did not provide an answer to this section.

- **Patient A:** "My caregiver has to help me dress, grocery shop, and help me with house chores."
- **Patient B:** Answered "Not applicable" to this question.
- **Patient C:** "It's hard for caregivers to understand what it is like when someone has inflammatory arthritis. They often don't know how best to provide emotional or physical support and can be frustrating for them. I'm fairly high functioning, but for others who need more care, it would be draining on a caregiver in terms of both time and energy and stress."

Are there any aspects of the illness that are more important to control than others?

- **Patient A:** "Movement."
- **Patient B:** "Back spasms."
- **Patient C:** "Pain and inflammation primarily – these are the source of the fatigue and low mood and deconditioning from moving/exercising less."
- **Patient D:** "Fatigue and weight gain."

Experiences With Currently Available Treatments

How well are patients managing their disease/condition with currently available treatments?

- **Patient A:** Takes Cimzia and methotrexate. In response to "How effective is current therapy in controlling the common aspects of AS?", the patient answered "average". They do not experience side effects from the therapy but finds the medication costly.
- **Patient B:** Taking anti-inflammatories and Tylenol as needed. At night, they take an anti-depressant to help with their sleep. They also include exercise in their treatment plan. Their treatment therapy is "good right now" at controlling the common aspects of AS. "My liver and kidney blood tests become "out of range" if I take too many anti-inflammatories or Tylenol."
- **Patient C:** Taking Humira. "It was previously very effective; however, it's effectiveness drastically decreased as of 3 months ago. I am still currently in a flare and awaiting to switch to Simponi." They do not experience side effects and have tolerated the biologic very well." Their extended medical insurance from work covers the cost of their biologics. They do not have a fear of needles so manage the mode of taking the medication fairly well.
- **Patient D:** Taking Humira and anti-inflammatories. The medication is good at controlling fatigue. Depending on the day, they still feel pain.

In general, the thousands of AS patients that ACE has interacted with over the past 19 years, have told us that having medication options is important to them, like it is for patients with cancer, HIV and other serious chronic diseases and illnesses. As stated in every patient input, we have submitted on our members' and the public's behalf, patient input respondents consider the "best treatment" is one that causes the fewest adverse effects and puts patients into remission.

Improved Outcomes

- **Patient A, B, and D:** Did not provide an answer to this section.
- **Patient C:** The following are unmet needs: "Better additional pain control when flaring (even if while on the biologic). NSAIDs have given me an ulcer and I am opioid sensitive, so I don't have many options for pain management."

Experience with Drug Under Review

None of the patients interviewed have experience with taking upadacitinib for ankylosing spondylitis.

Companion Diagnostic Test

Not applicable to this submission.

Anything Else?

Based on a large body of peer-reviewed evidence, ACE recommends a well-rounded treatment plan for AS that includes education (both disease and self-management), appropriate immunosuppressive medication(s), therapeutic and recreational exercise, appropriate amounts of rest during flares, physical therapy, healthy diet, and an overall healthy lifestyle. Paramount among these is the timely initiation of the most suitable medication(s), chosen by the patient in consultation with their rheumatologist. Biologics and targeted small molecule medications are proved to effectively address disease signs and symptoms – like swelling, pain, and fatigue – but also improve mortality and reduce heart disease and other complications of inflammatory arthritis.

Conflict of Interest Declaration — Arthritis Consumer Experts

Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

This submission was summarized and written solely by the staff of Arthritis Consumer Experts, free from consultation, advice, influence, or financial support from any outside individual, group, or company.

Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures for Arthritis Consumer Experts

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie Inc.	–	–	–	–

Arthritis Society Canada, Canadian Arthritis Patient Alliance, Canadian Spondylitis Association and Creaky Joints Canada

About Arthritis Society Canada, Canadian Arthritis Patient Alliance, Canadian Spondylitis Association, and Creaky Joints Canada

Arthritis Society Canada has been dedicated to extinguishing the fire of arthritis since 1948. Committed to a vision of living in a world where people are free from the devastating effects that arthritis has on the lives of Canadians. Arthritis Society Canada is the country's principal health charity providing education, programs, and support to the 6 million Canadians living with arthritis. Since its founding in 1948, Arthritis Society Canada has been the largest non-government funder of arthritis research in Canada, investing more than $200 million in projects that have led to breakthroughs in the diagnosis, treatment, and care of people with arthritis. Arthritis Society Canada is accredited under Imagine Canada's Standards Program. The website www.arthritis.ca provides more detailed information.

The Canadian Arthritis Patient Alliance (CAPA) is a grassroots, patient-driven and managed, independent, national education and advocacy organization with members and supporters across Canada. CAPA creates links between Canadians with arthritis, assists them to become more effective advocates and seeks to improve the quality of life of all people living with the disease.

CAPA believes the first expert on arthritis is the individual who has the disease, as theirs is a unique perspective. We assist members to become advocates not only for themselves but all people with arthritis. CAPA welcomes all Canadians with arthritis and those who support CAPA's goals to become members. Our website is updated regularly and can be viewed at: www.arthritispatient.ca.

The Canadian Spondylitis Association (CSA) plays an essential role in helping Spondyloarthritis (SpA) patients achieve their full health potential and live a better life. CSA is the only patient-led, not-for-profit organization focused solely on Canadians living with SpA, a group of chronic inflammatory arthritic conditions including Ankylosing Spondylitis (AS), Axial Spondyloarthritis (axSpA), Psoriatic Arthritis (PsA), Enteropathic Arthritis, Juvenile Idiopathic Arthritis, and related conditions. We provide credible and relevant resources for patients and healthcare providers. We offer support, information, awareness, and advocacy to inform and empower the patient community and the thousands at risk of being diagnosed. Visit www.spondylitis.ca for more information.

For more than two decades, CreakyJoints has served as a digital community for millions of arthritis patients and caregivers worldwide who seek education, support, advocacy, and patient-centered research. All of our programming and services are always provided free of charge. CreakyJoints is part of the non-profit Global Healthy Living Foundation, whose mission is to improve the quality of life for people living with chronic illnesses. In keeping with our work at CreakyJoints USA, CreakyJoints Canada inspires, empowers, and supports arthritis patients – and patients living with other chronic conditions – and their caregivers to put themselves at the center of their care by providing evidence-based education and tools that help people make informed decisions about the daily and long-term management of arthritis and other chronic conditions. At the heart of CreakyJoints Canada is collaboration. We continue to strengthen our work

with Canadian arthritis organizations and patient advocates that you know, love, and respect. We are all stronger together.

Information Gathering

We developed a survey to hear directly from people living with Ankylosing Spondylitis (AS) about their experiences with AS and experiences taking upadacitinib (Rinvoq). The survey was collaboratively developed by the Canadian Arthritis Patient Alliance (CAPA), Arthritis Society Canada, Canadian Spondylitis Association (CSA), and Creaky Joints Canada. The design was informed by the lived experiences of the organizations' members, many of whom live with various forms of arthritis. The survey was shared via e-mail, social media, and organization websites from all four organizations, through our respective Canadian networks and communities. The survey was open from October 12, 2022, to October 30, 2022.

There were 264 people that completed the survey with most participants living in Ontario (40%) followed by Quebec (24%), British Columbia (13%), Alberta (11%), Nova Scotia (4%), Manitoba (3%), Saskatchewan (2%), Newfoundland and Labrador (2%), New Brunswick (1%), and other provinces and territories like Prince Edward Island, Yukon, Nunavut, and Northwest Territories. The average age of survey participants is 52 years, with a range from 17 to 81 years of age. Nine survey participants have experience taking upadacitinib (Rinvoq).

Over 10% of participants identified as living with a disability and 3% are from the LGBTQ2s+ community. Over 4% of survey participants are from racialized communities with 35% self- identifying as white. One in three survey participants have a household income of under $75,000 per year, while a third earned from $75,000 to $150,000 annually. In terms of housing, around 2% of survey participants do not sleep in the same place/ housing each night and 30% rent housing while the majority (70%) own current housing.

Disease Experience

Ankylosing spondylitis (AS) is a form of Spondyloarthritis (SpA), a family of inflammatory rheumatic diseases. AS is a type of inflammatory arthritis that affects the spine and the sacroiliac joints that attach the pelvis to the base of the spine. With AS inflammation, the immune system attacks the ligaments and tendons attached to bone in the joints of the spine. The bone erodes at these sites and the body tries to repair itself by forming new bone. The bones of the spine begin to fuse, or grow together, causing the spine to become stiff, inflexible, and painful. Even though new bone forms, the original bone in the spine can become thin, increasing the risk of spinal fractures. In addition to the spine, AS can cause pain and stiffness in peripheral joints such as the hips and shoulders. As many as 1% of the Canadian adult population lives with AS.

One of the major issues facing people with AS is the inordinate amount of time it takes to be diagnosed. In fact, it can take up to 7-10 years for Canadians to be properly diagnosed from the time of onset of symptoms, during which time patients experience a significantly impacted quality of life and frustration. Delayed diagnosis and treatment can lead to irreversible damage as well. Factors that contribute to the delay to diagnosis include the fact that back pain is a common symptom for many other conditions, differing diagnostic criteria and a lack of understanding and awareness of the disease.

To better understand what it is like to live with AS, you can watch this short video of Marianne as she explains her diagnosis with AS, finding personalized treatment options, the impact of AS on her life and her experiences taking Upadacitinib (Rinvoq).

> "My biggest problem was being told that there was nothing wrong with me that would kill me and (to) stop complaining. By the time 13 years (went by), (the) best time to treat was over." — Person living with AS

Symptoms of AS include musculoskeletal pain, stiffness, fatigue, and limited range of motion in the joints. Close to 90% of people that completed our survey indicated that they live with back pain while 72% have back pain, 86% have joint stiffness and 51% have sore heels and feet. AS is also a systemic disease meaning that other parts of the body in addition to joints can be affected, including the eyes and heart, gastrointestinal system, and related musculoskeletal diseases like osteoarthritis. People with AS that completed our survey indicated they live with other related conditions like anxiety and depression (52%), bowel inflammation (49%), psoriasis (35%), migraine (32%), uveitis (31%), osteoporosis (23%) and heart problems (11%).

Figure 1: Woman Living With Ankylosing Spondylitis

> "It hurts to go on my daily walk, it hurts to try to get to sleep and it hurts to have pain all the time." — Person living with AS

AS can vary in severity from mild to very severe. Most survey participants rated their disease severity as a 59 out of 100. A person may experience active periods of disease (commonly known as flares or flare-ups) and times where there is decreased activity or even inactivity (remission). While people who have AS live with several symptoms, how they experience those symptoms, and the severity of AS can be different from person to person. There is currently no cure for AS. Survey participants indicated a range of symptoms that

are difficult to manage like fatigue (81%), difficulties concentrating (47%), stress (42%), issues with stability/ walking/falling (32%) and loss of appetite (11%).

> "I was an active athletic 55-year-old. Now after all the drugs I have tried unsuccessfully I count myself to be a disheartened disabled 59-year-old who has no future of being able to work or hold my grandchildren" — Person living with AS

Periods of very active disease are called a 'flare' and for some people, flares can be incapacitating. Flares are not predictable in terms of how severe they will be or how long they will last. They may last for a few hours, days, weeks or even months. Because of their unpredictability and dynamic nature of disability, flares must be dealt with reactively by people. The unpredictable nature of AS also often makes it feel like a person is not in control of their disease and can impact their ability to carry out day to day activities and life roles, such as contributing to the work.

> "It's difficult to work when symptoms aren't well managed. I have lost friends because I am unreliable. And daily pain is really messing with my emotional and mental well-being. My daughter has high anxiety worrying about my health." — Person living with AS

The disease impacts all aspects of a person's life including a variety of activities that people without AS take for granted such as walking, sleeping, standing, and taking care of everyday tasks, such as shopping, running errands, and cooking. Given the limitations in activities of daily living, AS impacts all aspects of a person's life including workplace participation and productivity, carrying out parenting and other social roles, and relationships with spouses, friends, and family members. When asked about the most significant impacts of AS on their daily quality of life, survey participants expressed that AS had a negative impact on exercise and physical activity (90%), work (62%), mental health (58%), self-esteem (57%), family life (51%), intimacy (50%), friendships (40%) and participation in school (10%).

> "L'habillement est difficile les marche ou même la marche en soi est difficile, la routine n'est pas toujours facile et me limite beaucoup dans toutes les activités qu'elle soit routinière ou physique. Je ne pratique plus de sport et l'entrainement est dur et le ménage n'est aussi pas évidente. Donc elle touche toutes les sphère de ma vie." — Person living with AS

People indicated difficulties in contributing and participating at school or work due to the fatigue, pain, and other symptoms of the AS. People with AS indicated that they missed work due to their disease, including 31% missing 1-3 workdays per month, 9% missing 4-6 days per month, and 30% indicating they do not work due to AS. AS impacts lives in many ways: daily tasks that many well individuals take for granted may become too difficult or exhausting to complete; participating in leisure activities or hobbies can be challenging; while caring for or spending time with family members, including children, spouses/partners, and other loved ones, also becomes difficult.

> "My parents are stressed out and worry about me constantly. They try to help but they cannot take away the pain." — Person living with AS

The impacts of AS extends to others within a person's support circle, including caregivers such as spouses/ partners and children who provide valuable emotional and direct support in complete activities of daily living. Often, these people take on additional chores or tasks such as cooking, cleaning, shopping, etc. to support the person with AS, and family roles change as spouses / partners take on more tasks, such as supporting their spouses / partners in getting to and from medical appointments. They may provide emotional support to help the person living with AS in navigating the health care system and the anxiety and stress of living with the condition.

> "There are challenges keeping up with others and my kids. I'm only in my late 30s, so it can be a struggle at times to feel "less than" due to limitations that present as the disease progresses. I have not had side effects of treatment and do not find dosage frequency or process to be an issue or interference." — Person living with AS

Experiences With Currently Available Treatments

Clinical practice guidelines emphasize early aggressive treatment of AS, which provides the best long-term outcomes for people living with the disease. A number of treatment approaches are used to manage AS including non-steroidal anti-inflammatory drugs (NSAIDS), corticosteroids and conventional synthetic Disease Modifying Anti-Rheumatic drugs (csDMARDs) such as Methotrexate, as well as biologic Disease-Modifying Anti-Rheumatic Drugs (bDMARDs), such as Etanercept and Infliximab. Effective treatments mean that people with AS do not need to live with the permanent damage, high medical costs (e.g., surgery, mobility aids, accessible housing) and disability. Early intervention is critical to allow people with AS the opportunity to fully participate in all aspects of life.

> "As of now, the only treatment that has provided any relief for my AS has been steroid injections in the SI joint, however, they are very painful, are not covered by insurance, and don't last very long." — Person living with AS

Notwithstanding the fact that numerous medication options exist, patients' responses to medication can vary significantly. Some medications are effective for some people with inflammatory arthritis while not effective for others. Survey participants indicated that they had experience with many medications, such as TNF blockers (55%), steroids (41%), Methotrexate (31%), Sulfasalazine (21%) and IL-17 inhibitors (21%).

> "Je ne me souviens plus sous quel traitement, je crois Cosentyx, j'ai perdu des ongles et mes cheveux…Puis sous Enbrel, plusieurs bronchitis." — Person living with AS

Some treatments will only manage the disease for a short period of time before the patient's immune system adapts to a drug's presence (i.e., becomes non-responsive to it) and they will have to switch to another medication. In some cases, patients with AS may not adequately respond to any of the DMARD's (conventional and biological) currently available. Over 40% of survey participants noted that they had an inadequate response to currently available treatments. As a result, patients need a number of medication options in order to effectively manage their disease throughout their lives. There are also no specific tests that identify which medication will be effective for a person living with AS.

> "I had stomach problems with the NSAIDS. Have to take anti-ulcer drugs. Nothing has adequately controlled my pain. I haven't had a pain free day since I was 24 & I'm now 73." — Person living with AS

This means that a person with the disease will need to go on one or more medications on a trial-and-error basis in order to find a medication that is effective.

Often, the treating physician will work with patients to determine which medication is most appropriate based on a number of factors such as patient preferences, mode of administration, anticipated side effects, etc. It is also an anxious and stressful experience if medications are not effective and may cost thousands of dollars out of pocket. Oftentimes, people with AS need to make difficult financial choices in order to pay for their medications.

Conventional synthetic DMARDs (csDMARDs) are difficult to take for people living with AS. Nausea, vomiting and a general malaise can persist for days after treatment with csDMARDs. Due to these experiences, many patients may not wish to take the medicine in question because the medication(s) is too difficult to take. This impacts adherence to treatment, increases health care costs (e.g., more visits to the doctor) and makes it difficult for people living with AS to work, carry out social roles and participate in other activities of daily living. Toxicity issues (e.g., liver) can also be of concern for people taking csDMARDs, such as Methotrexate, Imuran, and Leflunomide.

> « A 39 ans et avoir un style de vie de 70 ans c'est difficile surtout avec un enfant qui lui adore le sport je ne suis pas capable des journées de me lever et de fonctionner » — Person living with AS

Patients may also pursue medical cannabis and/or non-pharmacological approaches to manage AS symptoms, such as physiotherapy, occupational therapy, massage therapy, counselling, or acupuncture. These approaches can often help to address the symptoms of the disease, such as pain and fatigue. However, there are significant unmet patient needs in terms of accessing non-pharmacological treatments, often because they are not reimbursed through provincial health care systems, the treatment options are simply not offered, or there are lengthy waits.

> "(I) stopped taking Plaquenil by suggestion of ophthalmologist after eye evaluation." —Person living with AS

Patients identified many challenges in accessing treatment options. Expense, travel, and time required for treatment were all cited as being prohibitive. Some patients identified a difficulty in access to treatment relating to lack of access to specialists and general practitioner, and/or the COVID-19 pandemic restrictions. This means sometimes they need to seek care in the Emergency Departments that are dealing with the surge in COVID-19 and related illnesses and often requires lengthy waits. Around 10% of survey participants indicated they do not have any prescription drug coverage, 35% are covered by provincial/territorial drug plans, through disability support programs (4%) and 69% have private insurance through an employer or other plan.

> "There is a lack of more effective treatments of any kind for severe chronic pain and debilitating fatigue is extremely discouraging. Often the only option is going to ER during flares as primary physicians are overbooked. ER will treat chronic pain patients as drug-seekers. There truly is a lack of knowledge and empathy with AS patients. Skin conditions are often left untreated and disregarded. Social isolation due to pain and low energy can lead to anxiety and despair." — Person living with AS

Improved Outcomes

AS patients have identified several outcomes that are important to them and that should be considered when evaluating new therapies, including:

- route of drug administration (pills vs infusion vs self-injections)
- a reduction in pain and fatigue
- increased mobility
- ability to work and be productive at work
- ability to carry out activities of daily living
- ability to effectively carry out parenting tasks and other important social roles
- reduced infection rates
- less side effects
- affordability of the medication
- increased quality of life
- improved sleep
- increased energy / less fatigue

Current medications for the treatment of AS also have a number of negative side effects, such as fatigue which often persists beyond 24 hours (Methotrexate), nausea (Methotrexate, Arava, Imuran), increased infection risk (most DMARDs), liver toxicity and weight gain (Prednisone).

> "Amélioration au niveau de la douleur et de la qualité de vie ce serait déjà beaucoup." — Person living with AS
>
> "I would love the convenience of a daily pill. As with any treatment there are potential serious side effects. I would hope to achieve similar symptom improvement to what I have with a biologic. I don't think it is reasonable to expect to feel great all the time, but I would hope for fewer 'bad' days." Person living with AS
>
> "Consistency is the key. If any medication control pain n inflammation in consistency n build that rapport with patient/consumer that would be of immense help in all spheres of life." — Person living with AS

Experience with Drug Under Review

From those surveyed, nine people identified having experience with taking upadacitinib (Rinvoq). The survey participants shared both positive and negative effects of taking upadacitinib (Rinvoq):

> « J'ai eu des effets secondaires très nuisibles soit infection de gorge à répétition, gros maux de tête et des douleurs dans une jambe. »
>
> "I have my life back. I can participate on all normal functions in life."
>
> "No negative, all positive."

When comparing upadacitinib to other therapies and treatments, survey participants shared the following observations:

> "Diminution des raideurs"
>
> "No medications other than Rinvoq relieved my symptoms. Rinvoq relieves the inflammation in my SI joints."

Some patients experienced side effects with upadacitinib while others did not:

> « Les maux de tête sont acceptables puisqu'ils diminuent, mais les infections de gorge à répétition nuisent au quotidien. »
>
> "To date I haven't had any side effects."

Some patients shared that taking the medication in pill form was beneficial and made it easier to take. Long-term expectations of the medication include a decrease in joint damage and a happier life. Some patients reported that they had more energy and a better outlook because of increased activity. One individual noted that the side effects increased antibiotic use keeping them home more. About half of survey participants indicated that taking the medication had a positive impact on caregivers and others providing support.

To better understand what it is like to live with AS, you can watch this short video of Marianne as she explains her diagnosis with AS, finding personalized treatment options, the impact of AS on her life and her experiences taking Upadacitinib (Rinvoq).

Companion Diagnostic Test

Not applicable.

Anything Else?

Not applicable.

Conflict of Interest Declaration — Arthritis Society Canada, Canadian Arthritis Patient Alliance, Canadian Spondylitis Association and Creaky Joints Canada

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission?

No, we did receive any outside help.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

No, we did receive any outside help.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 2: Financial Disclosures for Canadian Arthritis Patient Alliance

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie Corporation	—	—	X	—
ACE Planning and Consulting	X	—	—	—
Canadian Rheumatology Association	X	—	—	—
CAPDM	X	—	—	—
FingerPost Consulting Ltd.	X	—	—	—
GlaxoSmithKline	X	—	—	—
Government of Canada	X	—	—	—
Innovative Medicines Canada	X	—	—	—
Janssen Inc.	X	—	—	—
Queens University	X	—	—	—
Arthritis Society Canada	X	—	—	—
The Brooks Group	X	—	—	—
UCB Canada Inc.	—	—	X	—
University of British Columbia	X	—	—	—
University of Calgary	X	—	—	—
University of Toronto	X	—	—	—
University of Waterloo	X	—	—	—
University of Western	X	—	—	—
Sparkplug coffee	X	—	—	—

Table 3: Financial Disclosures for Arthritis Society Canada

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie	—	—	X	—
Amgen*	—	—	—	X
Boehringer Ingelheim	—	—	X	—
BMS	—	—	X	—
Eli Lilly	X	—	—	—
Innovative Medicines Canada	X	—	—	—
J+J Shared Services	—	—	X	—
Janssen	—	X	—	—
Merck	—	—	X	—
Novartis	X	—	—	—
Pfizer	—	—	—	X
Valeo*	—	X	—	—

*Committed, not yet received

Table 4: Financial Disclosures for Creaky Joints Canada

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie	—	—	X	—

Table 5: Financial Disclosures for Canadian Spondylitis Association

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie	—	—	—	X
Organon	—	—	—	X
Pfizer	—	—	—	X
Novartis	—	—	—	X
UCB	—	—	X	—
Amgen	—	—	X	—
Janssen	—	—	X	—

Clinician Input

Canadian Rheumatology Association

About the Canadian Rheumatology Association

The Canadian Rheumatology Association (CRA) is the national professional association for Canadian rheumatologists. The **mission** of the Canadian Rheumatology Association is to represent Canadian rheumatologists and promote the pursuit of excellence in arthritis and rheumatic disease care, education, and research. https://rheum.ca/about-us/. The CRA Therapeutics Committee Identify and address all therapeutic issues that are relevant to the CRA membership as well as develop position statements and respond to drug shortages/withdrawals as required.

Dr. Jonathan Chan is a rheumatologist and assistant clinical professor at the University of British Columbia (https://rheumatology.med.ubc.ca/about/people/). His private office is also located in Vancouver (https://artushealth.com/). He is a member of the Spondyloarthritis Research Consortium of Canada (http://sparcc.ca) and has a research and clinical interest in axial spondyloarthritis.

Dr. Sherry Rohekar is a rheumatologist and associate professor of medicine at the University of Western Ontario (https://www.schulich.uwo.ca/rheumatology/docs/RohekarS.html). She is also a member of the Spondyloarthritis Research Consortium of Canada executive committee. She has a research and clinical interest in axial spondyloarthritis.

Both physicians were involved in the 2014 CRA/SPARCC treatment recommendations and are currently working on an update of these guidelines. Dr. Rohekar will be the lead author of the updated treatment recommendations.

Information Gathering

We searched within the collection of our guidelines and position papers; we added a complementary search on TRIPDatabase for further guidelines and relevant synthesis and primary evidence.

Current Treatments and Treatment Goals

Axial spondyloarthritis (axSpA) is an autoimmune disease-causing inflammation, pain, and stiffness. It usually manifests as low back/buttock/hip pain that begins in young adults (<45 years old) but often affects peripheral articulations as well as extra-articular manifestations such as uveitis, psoriasis, and inflammatory bowel disease.

The goal of therapy is to reduce pain and improve function. A survey of 542 Canadian spondyloarthritis patients reported 81% had work related issues due to their disease, including absenteeism in 43% reported and disability in 24% (https://asif.info/imas/). Over decades, untreated disease can result in irreversible fusion of the spine and increased cardiovascular risk (Ann Intern Med. 2015;163:409-416). There are no RCTs demonstrating disease modifying effects as RCTs typically run no longer than 2 years; however, well-designed observational studies have demonstrated a 50% reduction in spinal fusion over 10 years seen with biologics (Arthritis Rheum. 2013 Oct;65(10):2645-54). In place of placebo controlled RCTs

(which are logistically difficult and may be unethical) with outcomes of spinal fusion or other indicators of damage MRI is a sensitive tool that can detect active inflammation (bone marrow edema) which correlates with highest risk of developing more permanent bone abnormalities. Biologics and JAK inhibitors have been shown to substantially decrease bone marrow edema following treatment as well as blood levels of inflammation (CRP).

In the Canadian context, non-pharmacologic therapies (exercise, occupational therapy, diet, weight loss, and smoking cessation) are recommended for all patients though almost no patients can be adequately controlled in this manner alone. It is recommended that patients with ongoing spinal disease activity be trialled on two NSAIDs for two weeks each. If this is insufficient, a biologic (TNF- or IL-17- inhibitor) or targeted synthetic DMARD (JAK inhibitor) should be considered if their disease activity (measured by the BASDAI) is greater than 4 (on a scale of 0=no impact to 10=severe impact).

If there is predominant peripheral joint involvement, local corticosteroid injections or conventional synthetic DMARD such as methotrexate, sulfasalazine, or leflunomide may be considered although there is limited RCT data on their efficacy. A conventional synthetic DMARD may be tried for persistent enthesitis although only one trial has suggested possible benefit and did not have a placebo-controlled arm. Finally, a biologic / targeted synthetic DMARD may be initiated if patients with peripheral inflammatory arthritis or periarticular features are unresponsive to these measures.

The usual first line biologic therapies would include either TNF inhibitors (etanercept, infliximab, adalimumab, golimumab, or certolizumab) or an IL-17 inhibitor (secukinumab or ixekizumab). All classes of biologic agents can be used after failure of an initial biologic therapy. If there is a primary failure to a certain mechanism of action, strong consideration is given to using an alternate mechanism of action.

All approved biologic and small molecule treatments have been demonstrated to improve symptoms, function, and health related quality of life in patients. These treatments are summarized in the EULAR and ACR treatment recommendations (ARD 2017; 76:978-991; Arthritis Rheumatol. 2019 Oct;71(10):1599-1613).

Treatment Gaps (Unmet Needs)

Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

There is still a large unmet need in the management of axial spondyloarthritis. Limitations include:

- Not all patients respond to currently available treatment. Current biologics only result in approximately 60% of patients achieving a good response (achieving ASAS20)
- ASDAS partial remission is achieved in approximately 25% of patients with currently available biologic therapy.
- Frequent secondary loss of effect with biologics results in either dose escalations and/or the need to switch medications.
- Even with improvement in MSK symptoms with currently available biologics, persistence of active extra-articular manifestations is common.

- Side effects such as drug induced lupus, psoriasis, or multiple sclerosis (with TNFi) and inflammatory bowel disease (IL-17i) limit the use of the two approved biologics used to treat spondyloarthritis
- Ongoing severe spinal pain is common, despite treatment with currently available biologics.
- There are no oral options for spondylarthritis patients requiring advanced therapy, many of whom are young and may want to travel without the need to arrange for cold storage of medications or who may prefer to avoid injection medications.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

Upadacitinib would be used as a unique mechanism of action for the treatment of axSpA, and not as a complementary or additional treatment with other advanced therapeutics. Its mechanism of action, targeting the JAK-STAT pathway, both directly and indirectly inhibits the pathogenic immune response in spondyloarthritis (SpA). As such, upadacitinib has a modulating effect on multiple SpA clinical domains, above and beyond the musculoskeletal manifestations of the disease. There is also promising data with upadacitinib in inflammatory bowel disease, a frequent extra musculoskeletal manifestation/comorbid condition in patients with SpA. This is particularly important because IL-17 agents, one of the other main mechanisms of action available for the treatment of axSpA do not treat inflammatory bowel disease, and there are some concerns of worsening of inflammatory bowel disease with IL-17i treatment.

Further support that upadacitinib treats the underlying disease process may be found in evidence that it reduces MRI inflammatory spinal changes in axSpA. Imaging changes are objective and do not rely on patient reports. In SELECT AXIS-1 (van der Heijde D. et al., 2022), biologic disease modifying anti-rheumatic drug (bDMARD) naïve patients with axSpA were treated with upadacitinib 15 mg daily for 104 weeks (with a 14-week placebo-control arm that was later switched to active treatment). In this study, MRI spine and SI joint scores decreased from baseline to week 14 and 104 in the upadacitinib groups. These findings were mirrored in SELECT AXIS-2, which had a similar design, but included patients that were bDMARD inadequate responders (van der Heijde D. et al., 2022). One would anticipate that this group of patients would be more difficult to treat, given their previous drug failures. However, SELECT AXIS-2 again showed improvements in MRI SPARCC spine and SI joint scores at week 14 compared with placebo. As such, an argument may be made that upadacitinib addresses the underlying disease process in axSpA rather than merely providing symptomatic treatment.

Currently, upadacitinib is approved for use in axSpA in Canada after the failure of another bDMARD; so as second-line therapy. This decision was based on a small sample size in the SELECT AXIS-1 study even though upadacitinib was found to be statistically significantly superior to placebo in the trial. The opinion of these authors is that this decision is disappointing and that we were looking forward to having a JAKi as a first-line therapy for axSpA as its unique mechanism of action and oral administration are ideal for many of our patients. Nonetheless, the decision to approve this medication for bDMARD IR patients has already been made. As such, we will be using upadacitinib in patients who have failed, are intolerant, or who have contraindications to other bDMARDs for axSpA.

Many axSpA patients are young and prefer an oral mode of administration which is easier to take with them when travelling and working. We are also seeing an increasing prevalence of inflammatory bowel disease in our axSpA patients, and the promise of upadacitinib for treatment of this comorbidity means that it may hold a higher ranking in our list of therapeutic options (note upadacitinib has already been approved for the treatment of ulcerative colitis by the FDA).

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

There is no data that supports which patients are most likely to respond to upadacitinib. However, we can extrapolate from data from TNFi, and assume that reduction of inflammation will behave similarly. Data from Rudwaleit M. et. al. (2008) demonstrated that patients with a lower disease duration and a higher C-reactive protein were more likely to respond to treatment. Non-smokers may also be more likely to respond to treatment (Poddubnyy D. et. al., 2012). We suspect the same findings will hold for any mechanism of action that reduces inflammation in axSpA.

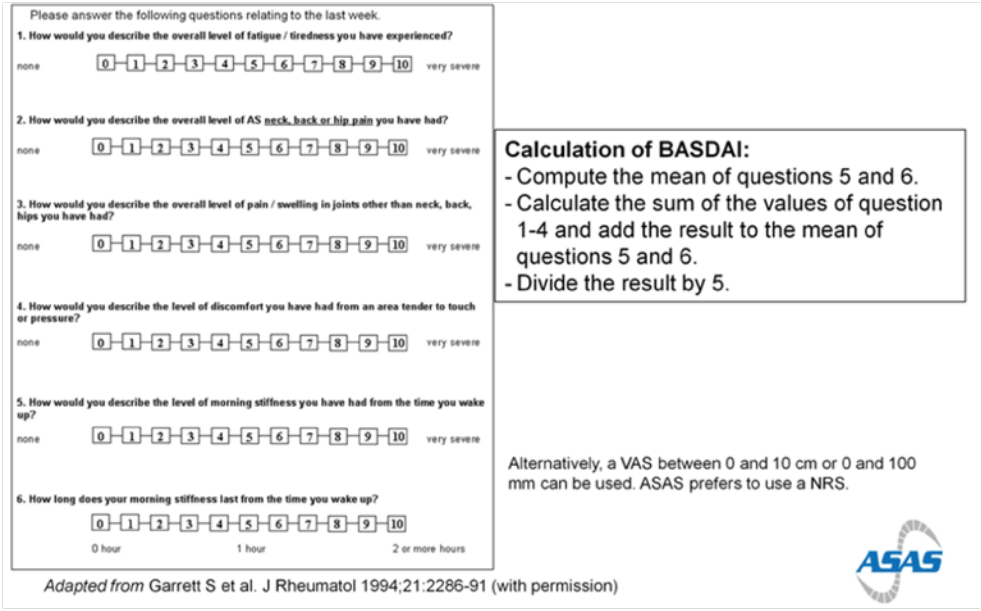
Patients most in need of intervention would be those who have failed treatment with continuous non-steroidal anti-inflammatories and continue to have high measures of disease activity. The most frequently used outcome measure for disease activity in axSpA in Canada is the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). This is also commonly used for insurance and reimbursement purposes.

There is not much data on axSpA population on which patients are less suitable for treatment. Extrapolating from other conditions and JAK inhibitors, people with severe active infections, acute or chronic, including latent TB and opportunistic infections might not be suitable, as well as people with severe hepatic disease. There are limited data available on pregnancy and childbirth, so contraception is advised for both female and male patients in the absence of adequate data.

In patients with a history of thromboembolic events initiation of a JAKi should be carefully evaluated based on the increased rates of VTEs in patients at risk for these events Patients with recurrent thromboembolic events will usually receive anticoagulation treatment likely counteracting the risk.

JAKi have not been studied and, therefore, are not recommended in combination with bDMARDs or potent immunosuppressive agents such as cyclosporine or tacrolimus because of the possibility of increased immunosuppression and increased risk of infection or lymphoma.

Figure 2: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) on an NRS



As demonstrated above, this questionnaire assesses several domains of the patient's experience with axSpA, including pain, fatigue, and morning stiffness. A score of 4 or higher is considered to be high disease activity and would be considered candidates for therapy with upadacitinib. (Image courtesy of the open-access slide deck of the Assessment of SpondyloArthritis International Society, https://www.asas-group.org/education/asas-slide-library/).

AxSpa does unfortunately suffer a high diagnostic delay of 5-10 years (Rudwaleit M. et. al., 2012; Ozgocmen S. et. al, 2012), as the complaint of back pain is common, and access to rheumatologists is limited. This makes prompt access to advanced therapeutics essential for treatment of disease. An MRI is often needed to help make the diagnosis of axSpA, adding to diagnostic delay in areas where access to MRI is limited by poor resources.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Clinically, rheumatologists in Canada consider an improvement in the BASDAI score of 2 points or 50% reduction from baseline to be a meaningful improvement. This is also what payers (insurance companies and provincial payers) consider to be a meaningful response to treatment.

Clinical trials often use an ASDAS response as an outcome measure instead of a BASADAI score.

Figure 3: Quick ASDAS-CRP Calculation Form

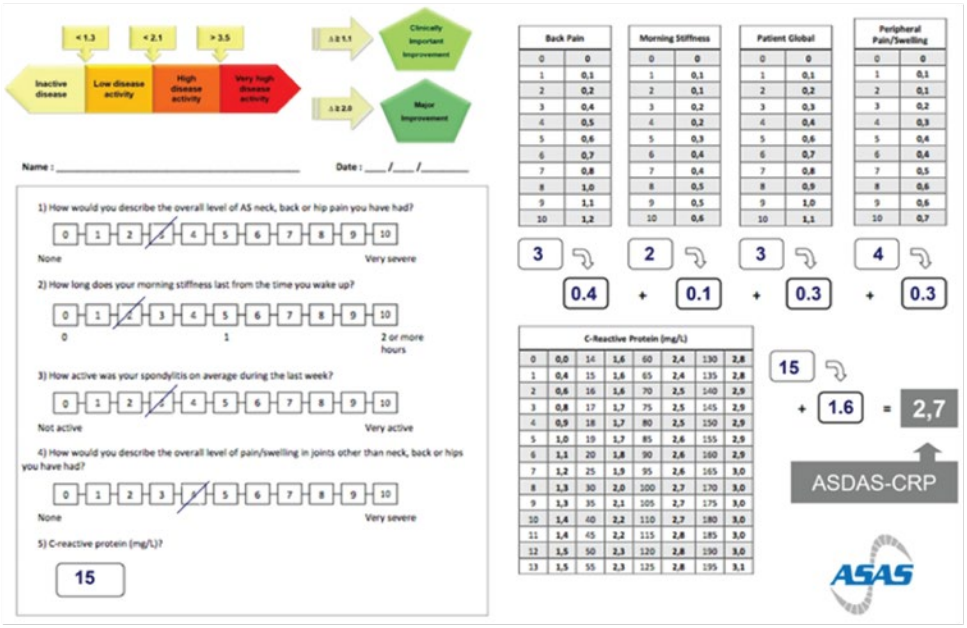


Image courtesy of the open-access slide deck of the Assessment of SpondyloArthritis International Society, https://www.asas-group.org/education/asas-slide-library/.

However, as seen above, this is extremely cumbersome for any typical practicing rheumatologist to calculate in their day-to-day practice, so it is often not used in “real life” outside of clinical trials.

Since the BASDAI is driven by patient-reported outcomes, it should not vary from physician to physician.

What factors should be considered when deciding to discontinue treatment with the drug under review?

- Lack of response to therapy.
- Adverse events (in particular, serious infection, multi-dermatomal or recurrent herpes zoster, venous thromboembolism, cardiovascular events).
- Patient preference, as part of the shared decision-making process, for example, if they have difficulty remembering to take the pills and would prefer an infusion.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Since upadacitinib is an orally administered advanced therapeutic, it would be a reasonable treatment option for any of our axSpA patients. It will be particularly useful for our large rural and remote population, who have difficulty coming to an infusion center or getting deliveries of injectable biologic medications from specialty pharmacies. Oral administration is also great for those who travel frequently and do not want to carry ice packs and the other paraphernalia needed with injectable biologics. Many patients also have phobias of needles, even in an auto-injector format, so oral administration is very helpful for this population.

A specialist (rheumatologist) will be required to prescribe upadacitinib and to monitor for adverse events. Regular bloodwork will need to be monitored by the rheumatologist to look for any adverse events.

Additional Information

Since axSpA currently only has two classes of advanced therapeutics, the addition of a third advanced mechanism of action is exciting for both clinicians and patients.

Conflict of Interest Declarations — Canadian Rheumatology Association

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission?

This document was completed by [redacted] without outside help for this submission.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission?

No outside help was received.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. Please note that this is required for *each clinician* who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.

Declaration for Clinician 1

Name: Sherry Rohekar

Position: Associate Professor

Date: 02-10-2022

Table 6: COI Declaration for Canadian Rheumatology Association — Clinician 1

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
AbbVie	—	—	X	—
Amgen	—	X	—	—
Eli-Lilly	—	—	X	—
Fresenius-Kabi	—	X	—	—
Janssen	—	X	—	—
Merck	—	X	—	—
Novartis	—	—	X	—

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Pfizer	–	X	–	–
Roche	–	X	–	–
Sandoz	–	X	–	–
UCB	–	–	X	–

Declaration for Clinician 2
Name: Jonathan Chan

Position: Assistant Professor

Date: 07-10-2022

Table 7: COI Declaration for Canadian Rheumatology Association — Clinician 2

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
AbbVie	–	–	X	–
Viatris	–	X	–	–
Eli-Lilly	–	–	X	–
Fresenius-Kabi	–	X	–	–
Janssen	–	–	X	–
Merck	–	X	–	–
Novartis	–	–	X	–
Pfizer	X	–	–	–
Roche	X	–	–	–
Sandoz	–	X	–	–
UCB	–	X	–	–

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