NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532

Contents:

The **final scope** **and** **final stakeholder list** following documents are made available to consultees and commentators:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ixekizumab for the treatment of people with axial spondyloarthritis for whom nonsteroidal anti-inflammatory drugs, or TNF-alpha inhibitors have been inadequately effective or not tolerated [ID1532]

Document B

Company evidence submission

May 2020

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1532_Ixekizumab in AxSpA_Document B_Updated_May 2020 [REDACTED]	Final	Yes	19/05/2020

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Abbreviations

Abbreviation	Definition
ADA	Adalimumab
AE	Adverse event
AESI	Adverse event of special interest
AG	Assessment Group
ANCOVA	Analysis of covariance
ASAS	Assessment of Ankylosing Spondylitis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AWMSG	All Wales Medicines Strategy Group
axSpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BHPR	British Health Professionals in Rheumatology
BIW	Bi-weekly
BNF	British National Formulary
BOCF	Baseline observation carried forward
BSR	British Society of Rheumatology
CEM	Cost-effectiveness model
CERTO	Certolizumab
cfb	Change from baseline
CHEM	Chemotherapy
CHMP	The Committee for Medicinal Products for Human Use
CI	Confidence interval
CiC	Commercial in confidence
CRD	University of York Centre for Reviews and Dissemination
CrI	Credible interval
CRP	C- reactive protein
CSR	Clinical study report
CUA	Cost-utility analysis
CZP	Certolizumab
DISCAE	Discontinuation due to adverse events
DMARD	Disease modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
DSA	Deterministic sensitivity analysis
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQol Five Dimensions
ESR	Erythrocyte sedimentation rate
ETA	Etanercept
ETN	Etanercept
EULAR	European League Against Rheumatism
FBC	Full blood count

FCE	Finished case episode
GOL	Golimumab
GP	General practitioner
HCHS	Hospital & Community Health Services
HLA	Human leukocyte antigen
HRG	Health resource group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IFX	Infliximab
IL	Interleukin
INF	Infliximab
INX	Infliximab
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
IXE	Ixekizumab
LD	Loading dose
LFT	Liver function test
LSM	Least-squares mean
LV	Last visit
LYG	Life years gained
mBOCF	Modified baseline observation carried forward
MCS	Mental component score
MedDRA	Medical Dictionary for Regulatory Activities
MIMS	Monthly Index of Medical Specialities
MMRM	Mixed effect model repeat measurement
mNY	Modified New York
MRI	Magnetic resonance imaging
mSASSS	Modified Stroke Ankylosing Spondylitis Spine Score
MTA	Multiple technology appraisal
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analyses
NR	Not reported
nr-axSpA	Non-radiographic axial spondyloarthritis
NRI	Non-responder imputation
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
OMERACT	Outcome Measures in Rheumatology
PAS	Patient access scheme
PBO	Placebo
PbR	Payment by results
PCS	Physical component summary

PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
Q2W	Every two weeks
Q4W	Every four weeks
QALY	Quality-adjusted life year
QW	Once a week
rad-axSpA	Radiographic axial spondyloarthritis
RCT	Randomised controlled trial
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEC	Secukinumab
SF	Short form
SIJ	Sacroiliac joint
SJC	Swollen joint count
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMR	Standardised mortality ratio
SPARCC	Spondyloarthritis Research Consortium of Canada
STA	Single technology appraisal
SW	South-west
TA	Technology appraisal
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
THT	Tuberculosis Heaf test
TNF	Tumour necrosis factor
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

The objective of this appraisal is to determine the clinical and cost-effectiveness of ixekizumab for the treatment of patients with axial spondyloarthritis (axSpA), including both radiographic axSpA (rad-axSpA; also known as ankylosing spondylitis [AS] in the literature) and non-radiographic axial spondyloarthritis (nr-axSpA), in accordance with the full marketing authorisation for ixekizumab in axSpA.

The decision problem addressed within this submission is consistent with the NICE final scope for this appraisal, as outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with axial spondyloarthritis for whom: • Nonsteroidal anti-inflammatory drugs or TNF-alpha inhibitors have been inadequately effective or not tolerated • TNF-alpha inhibitors are contraindicated	People with axial spondyloarthritis (radiographic [rad]-axSpA and non-radiographic [nr]-axSpA) for whom: • Nonsteroidal anti-inflammatory drugs or TNF-alpha inhibitors have been inadequately effective or not tolerated • TNF-alpha inhibitors are contraindicated	Clinical trials of ixekizumab are presented in this submission to demonstrate the clinical efficacy and safety of ixekizumab in patients with rad-axSpA (who have responded inadequately to conventional therapy and are naïve to biologic therapy (COAST V),[1, 2] or have responded inadequately to TNF-alpha inhibitors (COAST W),[3, 4] and non-radiographic axSpA who have responded inadequately to conventional therapy and are naïve to biologic therapy (COAST X).[5, 6] A clinical trial was not conducted in biologic-experienced nr-axSpA patients. However, given the disease is considered a continuum across a spectrum of nr- to rad-axSpA, the equivalent unmet need exists for novel therapies for the treatment of biologic-experienced nr-axSpA patients as it does for the patient populations evaluated in COAST-V, -W and -X. The cost-effectiveness of ixekizumab in this population was evaluated in a scenario analysis (see Section B.3.8.3). Similarly, no trials were conducted in patients who are contra-indicated to TNF-alpha inhibitors. However, cost-effectiveness analyses are presented versus the relevant comparators in this population [redacted] best supportive care) with data taken from the COAST trials, as the company deemed that ixekizumab should be considered by NICE for appraisal so as not to discriminate against patients who have this intolerance.
Intervention	Ixekizumab	• Biologic-naïve patients: Ixekizumab 80 mg by SC injection (one injection) at Week 0, followed by 80 mg every 4 weeks • Biologic-experienced patients: Ixekizumab 80 mg or 160 mg	In line with final NICE scope

		by SC injection (one or two injections – at clinician discretion) at Week 0, followed by 80 mg (one injection) every 4 weeks •	
Comparator(s)	Rad-axSpA: • TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) • IL-17A inhibitors (secukinumab) • Established clinical management without biological treatments Nr-axSpA: • TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab) • Established clinical management without biological treatments	Rad-axSpA: • TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) • IL-17A inhibitors (secukinumab)[a] • Established clinical management without biological treatments[a] Nr-axSpA: • TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab) • Established clinical management without biological treatments[a]	In line with final NICE scope
Outcomes	• Disease activity • Functional capacity • Disease progression • Pain • Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • Symptoms of extra-articular manifestations (including uveitis, inflammatory bowel	• Composite outcome (ASAS40) • Disease activity (ASDAS<2.1, BASDAI50, BASDAI cfb) • Functional capacity (BASFI) • Inflammation (SPARCC MRI spine and sacroiliac joint scores) • Pain (spinal pain NRS from BASDAI question 2) • Adverse effects of treatment	Given the amount of clinical data to be presented for the three COAST trials, priority was given to outcomes presented in the economic model and presented for axSpA in prior NICE submissions. As such peripheral symptoms and extra-articular manifestations are not presented in the submission. The impact of ixekizumab on dactylitis, enthesitis and peripheral arthritis has previously been documented in the NICE appraisal of ixekizumab in psoriatic arthritis (TA537).[7] Similarly, the impact of ixekizumab on psoriasis has been documented in TA442.[8] Disease progression is additionally

	disease and psoriasis) • HRQoL • Adverse effects of treatment	• HRQoL (SF-36 PCS)	assessed in the economic analysis through modelling the link between BASFI and the modified Stroke Ankylosing Spondylitis Spine Score [mSASSS].
Economic analysis	• The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and PSS perspective • The availability of any PASs for the intervention or comparator technologies will be taken into account	• A cost-effectiveness analysis has been conducted for ixekizumab versus relevant comparators • As per the NICE reference case, cost-effectiveness is expressed in terms of incremental cost per QALY • Costs are considered from the perspective of the NHS and PSS • A lifetime horizon is used to capture all costs and benefits associated with ixekizumab and its comparators • The cost of biosimilar adalimumab, biosimilar etanercept and biosimilar infliximab will be taken into consideration in the base case analysis	• PASs are in place in the NHS for certolizumab pegol, golimumab and secukinumab. The PAS for secukinumab is confidential and cannot be considered in this submission, however, the PASs for certolizumab pegol and golimumab are publicly available, and are considered in the submission • It is assumed that national tendering processes have taken place for comparators with biosimilar medicines available (adalimumab, etanercept and infliximab). However, a publicly available reference price could only be identified was for adalimumab, which has been included in the submission. Biosimilar prices sourced from MIMs were included for etanercept and infliximab.
Subgroups to be considered	• If the evidence allows, the subgroups of people who have had or not had TNF-alpha inhibitors will be considered	Please see 'population row'.	As described in the 'population row', patients with rad-axSpA were analysed by biologic experience in two separate clinical trials (COAST-V and -W), whilst biologic-naïve nr-axSpA patients were analysed in COAST-X.

			Biologic-experienced nr-axSpA patients are evaluated in a scenario analysis in the economic evaluation.
Special considerations including issues related to equity or equality	• The availability and cost of biosimilar products should be taken into account	Costs of biosimilars are taken into account, please see 'economic analysis' row.	In line with final NICE scope

[a]Comparators also relevant for the TNF-alpha inhibitor contraindicated population.
Abbreviations: ASAS: Assessment of SpondyloArthritis International Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; HRQoL: health-related quality of life; IL-17: interleukin-17; mSASSS: modified Stroke Ankylosing Spondylitis Spine Score; MRI: magnetic resonance imaging; MTA: multiple technology appraisal; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; nr-axSpA: non-radiographic axial spondyloarthritis; NRS: numeric rating score; NSAIDs: non-steroidal anti-inflammatory drugs; PAS: patient access scheme; PCS: physical component summary; PSS: Personal Social Services; QALY: quality-adjusted life year; rad-axSpA: radiographic axial spondyloarthritis; SC: subcutaneous; SF-36: Short Form-36; SJC: swollen joint count; SPARCC: Spondyloarthritis Research Consortium of Canada; TNF: tumour necrosis factor.
Source: NICE. Ixekizumab in AxSpA Final Scope. 2019[9]

B.1.2 *Description of the technology being appraised*

A description of ixekizumab for the treatment of axSpA is presented in Table 2, together with a summary of the mechanism of action, marketing authorisation status, costs and administration requirements.

The draft summary of product characteristics (SmPC) for ixekizumab is provided in the reference pack and more information is presented in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Ixekizumab (Taltz®)
Mechanism of action	• The pathogenesis of axSpA involves aberrant immune cell activation and release of inflammatory cytokines[10, 11] • Inflammatory signalling pathways such as those involving IL-17 and TNF-alpha lead to the proliferation of cells that break down bone (osteoclasts), which leads to damage and inflammation at the sacroiliac joint[10, 11] • Following this damage by osteoclasts, there is proliferation of osteoblasts (cells responsible for new bone formation) leading to aberrant bone remodelling, syndesmophyte formation and ankylosis of the sacroiliac joints and spine[10, 11] • **Ixekizumab is a humanised monoclonal antibody that selectively binds with IL-17A and inhibits its interaction with the IL-17 receptor, thereby reducing inflammatory signalling in the IL-17 pathway**[12]
Marketing authorisation/CE mark status	• CHMP opinion is expected [redacted] • Marketing authorisation is expected [redacted]

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	• Ixekizumab is anticipated to be licensed for the treatment of adult patients with active axSpA, comprising:
	  ○ Rad-axSpA: Adult patients with active rad-axSpA
	  ○ Nr-axSpA: Adult patients with active nr-axSpA with objective signs of inflammation defined as elevated (CRP) and /or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs
	• Ixekizumab already holds a marketing authorisation in plaque psoriasis and psoriatic arthritis (either alone or in combination with methotrexate), which have previously been appraised by NICE (TA537 and TA442)
	• Contraindications:
	  ○ Serious hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC
	  ○ Clinically important active infections such as active tuberculosis

Method of administration and dosage	• Biologic naïve patients: Ixekizumab 80 mg by SC injection (one injection) at Week 0, followed by 80 mg every 4 weeks • Biologic-experienced patients: Ixekizumab 80 mg or 160 mg by SC injection (one or two injections – at clinician discretion) at Week 0, followed by 80 mg (one injection) every 4 weeks •
Additional tests or investigations	No new tests or investigations in addition to those already performed for rad- and nr-axSpA in UK clinical practice are required for treatment with ixekizumab

List price and average cost of a course of treatment	• List price:
	  ○ 80 mg/ml solution for injection pre-filled pen: £1,125.00[13]
	• 80 mg/ml solution for injection pre-filled syringe: £1,125.00[13]
	• Per annum cost for patients receiving 80 mg LD (Biologic-naïve and -experienced)
	  ○ First year: 14 injections - £15,750
	  ○ Second year: 13 injections - £14,625
	• Per annum cost for patients receiving 160 mg LD (biologic-experienced)
	  ○ First year: 15 injections - £16,875
	  ○ Second year: 13 injections - £14,625

Patient access scheme (if applicable)	• PAS price:
	  ○ 80 mg/ml solution for injection pre-filled pen: £[redacted]
	  ○ 80 mg/ml solution for injection pre-filled syringe: £[redacted]
	• Per annum cost for patients receiving 80 mg LD (biologic-naive and -experienced)
	  ○ First year: 14 injections - £[redacted]
	  ○ Second year: 13 injections - £[redacted]
	• Per annum cost for patients receiving 160 mg LD (biologic-experienced)
	  ○ First year: 15 injections - £[redacted]
	  ○ Second year: 13 injections - £[redacted]

Abbreviations: axSpA: axial spondyloarthritis; CHMP: The Committee for Medicinal Products for Human Use; CRP: C-reactive protein; IL-17: interleukin-17; LD: loading dose; nr-axSpA: non-radiographic axial spondyloarthritis; PAS: patient access scheme; SC: subcutaneous; SmPC: Summary of Product Characteristics; TNF: tumour necrosis factor

B.1.3 *Health condition and position of the technology in the treatment pathway*

Summary box

Disease overview

- AxSpA is a continuous disease spectrum of two inflammatory rheumatic conditions involving inflammation at the sacroiliac joint and spine
- Rad-axSpA and nr-axSpA are differentiated by the ability (or not) to detect inflammatory changes of the sacroiliac joints via X-ray, respectively.[14] Both conditions are characterised by chronic back pain, stiffness, fatigue, and extra-articular symptoms, including inflammatory bowel disease, uveitis and psoriasis[15]
- Diagnosis of axSpA can be complex and there is an average diagnostic delay of 8.5 years in the UK[16]
- Prevalence estimates for axSpA vary. It has been estimated that there are 62,650 and 3,640 nr-axSpA patients and 100,815 and 5,836 rad-axSpA patients in England and Wales, respectively[17, 18]

Burden on patients, carers and society

- AxSpA has a high clinical, economic and productivity burden on patients due to symptoms including back pain, extra-articular symptoms and comorbidities, which impact on patients' ability to carry-out essential daily tasks, reduce life expectancy and impact on patient mental health[15]
- Despite the lack of radiographic changes, nr-axSpA patients experience a substantial disease burden, with functional impairments and self-reported disease activity comparable to patients with rad-axSpA.[19]
- The estimated direct medical costs of rad-axSpA to the NHS are £2,300–£3,300 per patient per year[20]

- The majority of axSpA patients are diagnosed in early adulthood, meaning patients are burdened by symptoms during their most productive time of life, and chronically[21]
- In the UK, around 40% of axSpA patients of working age are unemployed[20, 22]

Clinical pathway of care

- Following diagnosis, NICE recommends that patients with axSpA are offered conventional treatment, which comprises non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapies[23]
- Patients with rad- or nr-axSpA whose disease has responded inadequately to, or who cannot tolerate NSAIDs, have the option of receiving treatment with a tumour necrosis factor (TNF)-alpha inhibitor (adalimumab, certolizumab pegol, etanercept or golimumab).[23] Patients with rad-axSpA have the additional option of receiving an additional TNF-alpha inhibitor, infliximab, or the interleukin (IL)-17A inhibitor secukinumab[23]
- Response to treatment is monitored through the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score and spinal pain visual analogue scale (VAS). Biological treatment should be stopped if after 12 weeks (16 weeks for secukinumab in rad-axSpA) if patients have not demonstrated a response[24, 25]
- Patients with axSpA who cannot tolerate, or whose disease has not responded to, treatment with a first TNF-alpha inhibitor, are recommended to receive treatment with another TNF-alpha inhibitor or IL-17A inhibitor secukinumab (rad-axSpA only)[24, 26] In line with a recent licence extension, depending on their clinical response, patients treated with a 150 mg dose of secukinumab may have their dose up titrated to 300 mg per month[27]

Unmet need

- Only one-third of axSpA patients achieve partial remission with NSAIDs alone,[28] and approximately 20% of patients receiving their first biological therapy have an inadequate response to treatment, or experience adverse events (AEs)[25, 29]
- In phase 3 clinical trials in rad-axSpA patients, at Weeks 12–24 of treatment with TNF-alpha inhibitors, up to 60% of patients fail to achieve an ASAS40 response[30, 31]
- There is an unmet need for alternative therapy options for rad- and nr-axSpA with an alternative mechanism of action to TNF-alpha inhibition

Ixekizumab

- Ixekizumab is a monoclonal antibody which selectively binds to IL-17A, preventing its binding to the IL-17 receptor and thereby reducing the inflammatory signalling that leads to the symptoms of axSpA[12]
- Ixekizumab has been shown to be efficacious and safe in psoriatic arthritis and plaque psoriasis, and has a licence for use in these indications in the European Union[32]
- The efficacy and safety of ixekizumab in axSpA has been assessed in three pivotal trials COAST-V, COAST-W, COAST-X.[1, 2 3-6] In these trials, ixekizumab was shown to be superior to placebo in reducing disease activity and improving functional capacity and patient-reported health-related quality of life (HRQoL) at 16 and 52 weeks[1-6]

B.1.3.1 Axial spondyloarthritis

Disease overview

Spondyloarthritis (SpA) encompasses a group of related inflammatory rheumatic conditions that can affect either the axial or peripheral joints.[15] AxSpA occurs when the inflammation primarily affects the sacroiliac joints (the joints between the sacrum and the ilium bones of the pelvis) and the spine, while peripheral SpA includes conditions such as reactive arthritis, psoriatic arthritis, enteropathic SpA and undifferentiated SpA.[15] AxSpA is considered to be a progressive disease spectrum of two chronic conditions: rad-axSpA (also referred to as in the literature) and nr-axSpA.[33] The two conditions are differentiated by the ability (or not) to detect inflammatory changes of the sacroiliac joints via X-ray, respectively.[14] A proportion of nr-axSpA patients progress to rad-axSpA over the course of their disease, and this has been estimated at a rate of approximately 12% over two years.[34] Despite the lack of radiographic changes, nr-axSpA patients experience a substantial disease burden, with functional impairments and self-reported disease activity comparable to patients with rad-axSpA.[19] Clinical experts consider axSpA to be "one disease, two subtypes.[35]

For a patient to be diagnosed with rad-axSpA, they must meet the modified New York (mNY) classification criteria, which requires radiographic detection of sacroiliitis (inflammation at the sacroiliac joint) combined with one other clinical criterion.[36] Nr-axSpA is more challenging to diagnose, as patients experience axSpA symptoms without structural changes or inflammation that can be detected radiographically.[33, 37] The Assessment of SpondyloArthritis International Society (ASAS) criteria were developed to address this,[37] and specify that a patient must have either active inflammation at the sacroiliac joint visible by magnetic resonance imaging (MRI) (but *not* radiographically) with at least one other axSpA feature, or be positive for HLA-B27 or have elevated C-reactive protein (CRP), and display two or more additional axSpA features.[37] AxSpA is often misdiagnosed as mechanical lower back pain in non-specialist settings, leading to delays in diagnosis and treatment. In the UK, there is an average delay of 8.5 years between symptom onset and diagnosis, with only approximately 15% of cases receiving a diagnosis within three months of initial presentation.[16, 38]

The physical symptoms of both rad-axSpA and nr-axSpA comprise chronic back pain, stiffness, arthritis, enthesitis (inflammation of sites where bone joins a tendon) and dactylitis (swelling of the fingers).[15, 33] Around 40% of patients are also affected by extra-articular symptoms, which include inflammatory bowel disease, uveitis (inflammation of the eye) and psoriasis. AxSpA is also associated with co-morbidities such as cardiovascular disease, diabetes and osteoporosis, which further negatively impact patients' wellbeing.[33] At advanced stages of rad-axSpA, patients may experience bone fusion and sclerosis of the sacroiliac joints and spine, causing postural and skeletal changes.[33]

Dysregulation of the normal immune system underlies the pathogenesis of axSpA, which causes cascades of inflammatory signalling that result in inflammation at the axial joints.[10, 11] Treatments targeting the TNF-alpha and IL-17 cytokine families have been shown to reduce symptoms of the condition, indicating that the signalling pathways involving these cytokines may play a key role in the pathogenesis of the condition.[11] In axSpA, dysregulation of inflammatory signalling processes may be triggered by a number of factors, including stress on the entheses, or genes which increase the likelihood of developing the condition (e.g. HLA-B27).[11] The dysregulation of these pathways results in the recruitment of inflammatory cells to the sacroiliac joint, causing inflammation.[10, 11] Downstream consequences of this include the uncontrolled proliferation of cells that break down bone (osteoclasts), leading to damage of the axial joints.[10, 11] The body subsequently responds to this damage with the over-production of cells that produce new bone (osteoblasts), which leads to new, abnormal bone formation. Eventually, excessive osteoblast activity leads to ankylosis (fusing) of the sacroiliac joints and spine.[11]

Due to the difficulties associated with the diagnosis of axSpA, and the different classification criteria used clinically, prevalence rates of axSpA are uncertain, and estimates for prevalence in Europe vary, having been reported to range from 0.3–1.2% of the population.[15, 39] In 2016, the NICE resource impact reports for TA383 (TNF-alpha inhibitors for AS and nr-axSpA) and TA407 (secukinumab for AS after treatment with NSAIDs or TNF-alpha inhibitors) estimated the prevalence of nr-axSpA as 62,650 patients in England and 3,640 in Wales (prevalence rate of 0.15%),[17] whilst the estimated prevalence of rad-axSpA was greater, at 100,815 patients in England and 5,836 in Wales (prevalence rate of 0.24%).[18]

Burden on patients, carers and society

AxSpA incurs a substantial burden on patients.[21] The symptoms of axSpA, notably back pain and stiffness, interfere with patients' ability to perform daily activities, including dressing, walking, bathing and eating.[40, 41] These physical symptoms also result in reduced sleep quality, and approximately two-thirds of patients with axSpA experience fatigue.[41] For patients in the advanced stages of rad-axSpA who experience ankylosis of the spine, postural and skeletal changes that take place are likely to affect patients' mobility, in turn reducing their activity levels and increasing their risk of developing comorbidities such as diabetes and cardiovascular disease.[41] Accordingly, mortality in patients with rad-axSpA is approximately 1.5 times greater than the general population, predominantly caused by comorbidities and complications of axSpA including an increased risk of cardiovascular events and fractures due to osteoporosis.[42-44] A recent study comparing cohorts of rad- and nr-axSpA patients found nr-axSpA patients to have a similar comorbidity burden as those with rad-axSpA, with the most common comorbidities observed in both groups being anxiety (11%), heart disease (11%), cancer (11%), high blood pressure (9%), depression (8%) and diabetes (7%).[45]

In addition to the significant symptom burden described above, spinal deformation as a result of axSpA can result in significant body image disturbances, which are correlated with increased rates of anxiety and depression.[41] In line with these findings, 59% of patients with rad-axSpA report suffering from mental health problems; this compares to 25% in patients with musculoskeletal conditions overall.[21] The rates of diagnosed depression are 80% higher in women and 50% higher in men than in the general population.[41, 46]

Accordingly, axSpA has a significant impact on patient HRQoL.[41, 47] Patients with rad-axSpA have reported significantly poorer physical, general health and mental/emotional quality of life (QoL) scores, in comparison to matched population norms, as measured using the Short Form (SF)-36 scale.[47] Whilst the majority of literature on HRQoL in axSpA focuses on rad-axSpA, studies have also found a substantial burden of illness associated with nr-axSpA, with self-reported disease activity and functional impairments comparable to rad-axSpA.[19, 46, 48] A cross-sectional European study found that nr-axSpA was associated with a significant HRQoL and societal burden, as measured by EuroQol-Five Dimensions (EQ-5D).[49] Notably, HRQoL was significantly reduced in patients who did not respond to treatment in comparison with responders, highlighting the importance of further treatment options for non-responders.[49] As axSpA is a life-long, progressive condition, with an average age of onset of 24, this burden may be carried by patients for a large proportion of their lives.[21]

In addition to the clinical impact on patients, axSpA poses a significant economic burden to patients, carers and the NHS. A study examining the cost of rad-axSpA in the UK estimated a total cost to the NHS of between £2,300–£3,300 per patient per year, based on patient-reported questionnaires and medical records, which comprised of general practitioner (GP), hospital, prescription and investigation costs.[20] Patients with higher disease activity and higher functional impairment incurred significantly higher costs to the NHS than patients with less severe disease, highlighting the substantial economic burden of impaired disease control.[20] In addition to costs to the NHS, patients also incur out-of-pocket

costs of around £700 per person per year, whilst earning losses of unpaid carers was estimated at approximately £3,000 per patient per year.[20]

Given that 95% of axSpA cases are diagnosed under the age of 45, the disease can have a significant impact on patients in the most productive years of their life.[21] Approximately 40% of rad-axSpA patients of working age in the UK are unemployed or have retired early, with over 70% of these patients citing their disease as the cause.[20] For patients that are employed, axSpA can cause both absenteeism and presenteeism at work, at an estimated rate of 3.5% and 21.6% in the UK, respectively, with these rates increasing significantly in patients with higher disease activity and higher functional impairment.[20] Additionally, 78% of patients in the UK said that their condition had a negative impact on their working life.[38] As a result of this, lost work due to axSpA represents a substantial economic burden, with the costs of early retirement, absenteeism and presenteeism due to rad-axSpA estimated at £8,100, £411 and £3,425 per patient per year, respectively.[20]

Ixekizumab

Ixekizumab is a monoclonal antibody which selectively binds to IL-17A, preventing its binding to the IL-17 receptor and thereby reducing the inflammatory signalling that leads to the symptoms of axSpA.[12] Ixekizumab has been shown to be efficacious and safe in psoriatic arthritis and plaque psoriasis, and has a licence for use in these indications in the European Union.[32]

The efficacy and safety of ixekizumab in axSpA has been assessed in three pivotal trials which are presented in this submission. The patient populations included in each of these trials are:

- Rad-axSpA patients who have responded inadequately to, or are intolerant of, two or more NSAIDs (COAST-V)[1, 2]
- Rad-axSpA patients who have responded inadequately to one or two TNF-alpha inhibitors following inadequate response or intolerance to NSAIDs (COAST-W)[3, 4]
- Nr-axSpA patients who have responded inadequately to, or are intolerant of, two or more NSAIDs (COAST-X)[5, 6]

In these trials, ixekizumab was shown to be superior to placebo in reducing disease activity and short term progression of disease and improving functional capacity and patient reported HRQoL, after 16 weeks of double-blinded treatment.[1-5] Ixekizumab treatment was also continued from 16 weeks to 52 weeks in a double-blinded extended treatment period, showing maintained efficacy and safety over this time-period.[1-5]

B.1.3.2 Clinical pathway of care

Treatment guidelines

The treatment of axSpA in the UK has been assessed by NICE, both through published treatment guidelines and through previously considered technology appraisals. The treatment guidelines that are considered relevant to UK clinical practice are listed below:

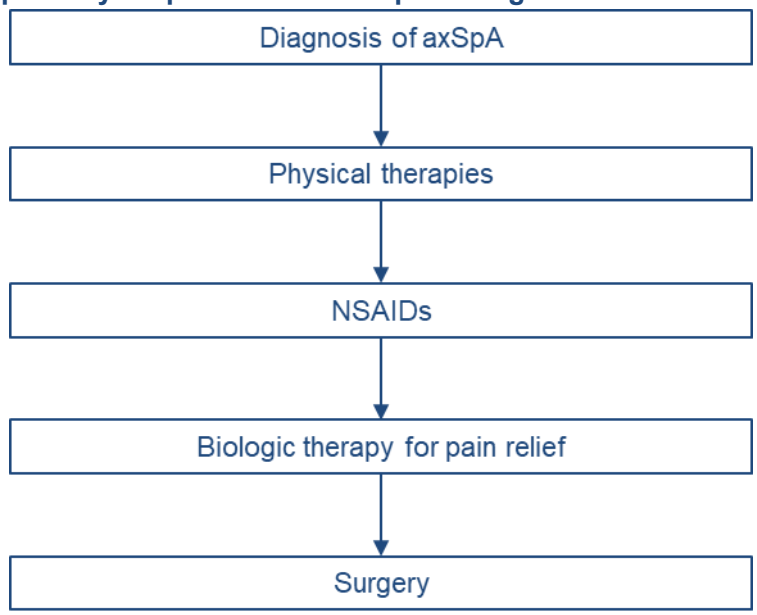
- NICE Clinical Guideline 65: Spondyloarthritis in over 16s: diagnosis and management (2017)[23]
- NICE TA383: TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (2015)[24]
- NICE TA407: Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors (2016)[25]

- NICE TA497: Golimumab for treating non-radiographic axial spondyloarthritis (2017)[50]
- British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines (2017)[51]
- Joint guidelines from Assessment of AS (ASAS) and the European League Against Rheumatism (EULAR) (2016 update)[33]

NICE-recommended treatment pathway

The treatment pathway for patients who have been diagnosed with axSpA in the UK, as per guidelines and technology appraisals published by NICE, is summarised in Figure 1, and described in more detail in the following section. The guidance provided by the BSR/BHPR and ASAS/EULAR is broadly concurrent with the treatment recommendations provided by NICE.

Figure 1: Treatment pathway for patients with axSpA in England and Wales

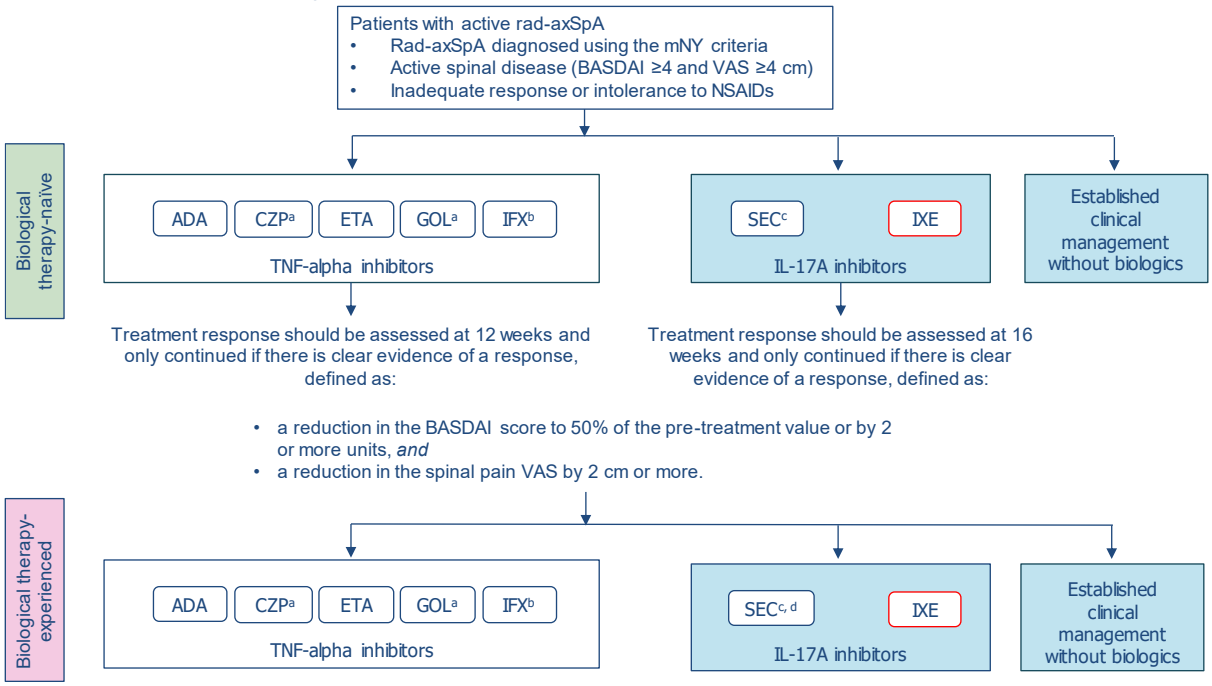


Abbreviations: axSpA: axial spondyloarthritis; NSAIDs: non-steroidal anti-inflammatory drugs
Source: NICE Pathways. Spondyloarthritis Overview. 2019[26]

Following diagnosis, patients with axSpA will be initially offered conventional treatment, which comprises NSAIDs and physical therapies.[26] NICE recommends that patients with axSpA associated with pain should be offered NSAIDs at the lowest effective dose, considering appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment.[23] If an NSAID, taken at the maximum tolerated dose for two to four weeks, does not provide adequate pain relief then patients can consider switching to another NSAID.[23, 26]

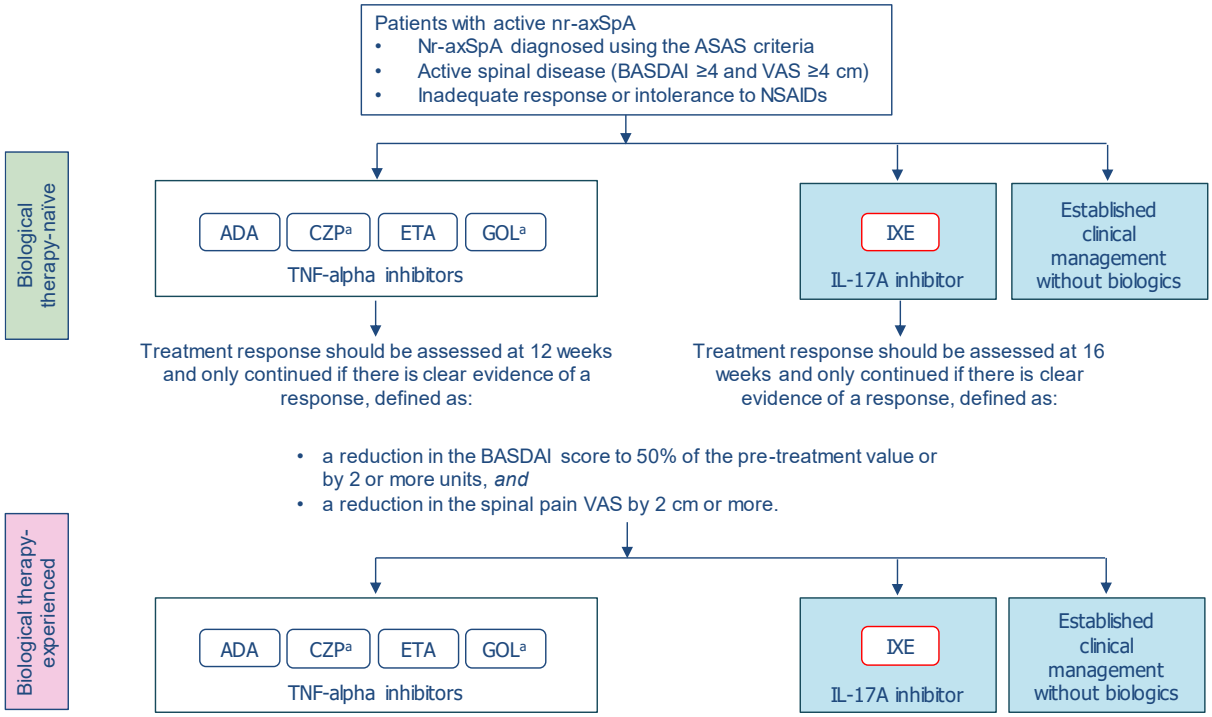
Patients with axSpA who have responded inadequately to, or cannot tolerate, NSAIDs can then be considered for biologic therapy (TNF-alpha inhibitors or IL-17A inhibitors). The treatment pathways for patients with rad-axSpA and nr-axSpA who have responded inadequately to, or cannot tolerate, conventional therapy are summarised in Figure 2 and Figure 3 respectively, and described in detail below.

Figure 2: NICE-recommended treatment pathway for patients with rad-axSpA who have responded inadequately to, or cannot tolerate, NSAIDs or TNF-alpha inhibitors



Boxes coloured **blue** indicate treatments that are **also** options for patients who are **contraindicated to TNF-alpha inhibitors** (in addition to being options for patients who do not have any contraindications); Red squares indicate anticipated position of ixekizumab in the treatment pathway. [a]Manufacturer submitted with a patient access scheme in TA383; [b]Recommended only if treatment is started with the least expensive infliximab product; [c]Manufacturer submitted with a patient access scheme in TA407 for SEC 150 mg. [d]A recent licence extension for SEC permits up-titration to a dose of 300 mg based on clinical response to the 150 mg dose (this dose has not been appraised by NICE in rad-axSpA).[27]
Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CZP: certolizumab pegol; ETA: etanercept; GOL: golimumab; IFX: infliximab; IXE: ixekizumab; IL-17A: interleukin 17A; mNY: modified New York; NSAID: non-steroidal anti-inflammatory drug; rad-axSpA: radiographic axSpA; SEC: secukinumab; TNF: tumour necrosis factor; VAS: visual analogue scale
Source: Adapted from NICE Pathways. Spondyloarthritis Overview. 2019[26]

Figure 3: NICE-recommended treatment pathway for patients with nr-axSpA who have responded inadequately to, or cannot tolerate, NSAIDs or TNF-alpha inhibitors



Boxes coloured **blue** indicate treatments that are **also** options for patients who are **contraindicated to TNF-alpha inhibitors** (in addition to being options for patients who do not have any contraindications). Red squares indicate anticipated position of ixekizumab in the treatment pathway. [a]Manufacturer submitted with a patient access scheme in TA383.
Abbreviations: ADA: adalimumab; ASAS: Assessment of SpondyloArthritis International Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CZP: certolizumab pegol; ETA: etanercept; GOL: golimumab; IXE: ixekizumab; IL-17A: interleukin 17A; mNY: Modified New York; NSAID: non-steroidal anti-inflammatory drug; rad-axSpA: radiographic axSpA; TNF: tumour necrosis factor; VAS: visual analogue scale
Source: Adapted from NICE Pathways. Spondyloarthritis Overview. 2019.[26]

Patients with severe active rad-axSpA whose disease has responded inadequately to, or who cannot tolerate, NSAIDs have the option of receiving adalimumab, certolizumab pegol, etanercept, golimumab and infliximab (Figure 2)). Infliximab is recommended only if treatment is started with the least expensive infliximab product, and people currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their NHS clinician consider it appropriate to stop.[23, 50]

Patients with severe nr-axSpA whose disease has responded inadequately to, or who cannot tolerate, NSAIDs have the option of receiving adalimumab, certolizumab pegol, etanercept or golimumab (Figure 3).[23]

For patients with nr-axSpA and rad-axSpA, the choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include considering associated conditions such as extra-articular manifestations. If more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes [PASs]) should be chosen.[23]

In patients with nr-axSpA and rad-axSpA, the response to adalimumab, certolizumab pegol, etanercept, golimumab or infliximab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as:

- A reduction in the BASDAI score to 50% of the pre-treatment value or by two or more units, *and*
- A reduction in the spinal pain VAS by 2 cm or more[24]

According to NICE guidelines, patients with axSpA who cannot tolerate, or whose disease has not responded to, treatment with a first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response, are recommended to receive treatment with another TNF-alpha inhibitor.[24] Patients with active rad-axSpA whose disease has responded inadequately to NSAIDs or TNF-alpha inhibitors also have the option of being treated with secukinumab.[26] The response to secukinumab should be assessed after 16 weeks of treatment and only continued if there is clear evidence of response, using the same definition as outlined in the Multiple Technology Assessment (MTA) for TNF-alpha inhibitors for treating rad-axSpA and nr-axSpA, described above.[25] A recent extension has been made to the licence for secukinumab, which indicates that based on clinical response, patients treated with a dose of 150 mg may have their dose up-titrated to 300 mg.[27] However, this licence extension has not been evaluated by NICE, and there are currently no recommendations regarding its use. A prospective real-world dose utilisation study was conducted by Lilly into the use of secukinumab in UK clinical practice between [redacted].[52] Of the sample studied ([redacted]), it was identified that [redacted].[52] [redacted]

Patients with axSpA should only be referred to a complex spinal surgery service to be assessed for spinal deformity correction if the spinal deformity is significantly affecting their QoL and is severe or progressing despite optimal non-surgical management, including physiotherapy (Figure 1).[26]

Unmet need

Whilst NSAIDs can provide pain relief for patients with axSpA, there is no clear evidence that long-term use of NSAIDs alters the structural progression of the disease, and only one-third of patients achieve partial remission with NSAIDs alone, even among those with early, active axSpA.[28, 42] Additionally,

NSAIDs are associated with significant side effects, including renal and gastrointestinal toxicity, especially when administered chronically.[33, 42]

Whilst patients who do not achieve remission with NSAIDs can then be treated with biological therapies, not all patients respond. It is estimated that more than 20% of patients receiving their first therapy may have an inadequate response to treatment or experience AEs, and this figure could be as high as 40%.[25, 29] This leaves a significant proportion of patients with inadequate disease management. Patients who have not responded to initial TNF-alpha inhibitor therapy in the UK will commonly be treated with another TNF-alpha inhibitor, however, there is a lack of robust clinical data to support the use of TNF-alpha inhibitors in patients who are biological therapy experienced.[24] Additionally, some patients are contraindicated or intolerant of TNF-alpha inhibitors and therefore require other treatment options.

Currently, only one other treatment with an alternative mechanism of action (secukinumab) is available for rad-axSpA patients who do not respond to TNF-alpha inhibitors. Compared to other rheumatic diseases, such as rheumatoid arthritis and psoriatic arthritis, treatment options for axSpA remain limited, meaning patients with axSpA who experience inadequate disease control from current treatments may benefit from additional new treatment options. Furthermore, market research commissioned by Lilly indicated that there is a need in clinical practice for another treatment option with an alternative mechanism of action to TNF inhibition.[53] Currently, patients with nr-axSpA have no licensed biologic treatment options with an alternative mechanism of action to TNF inhibition. Patient experts consulted during NICE TA383 further highlighted the importance of the availability of having options at different lines of therapy (e.g. once initial biologic therapy has failed) to patients' mental wellbeing.[24]

In line with its marketing authorisation, ixekizumab would be available for use in biological therapy-naïve and biological therapy-experienced rad- and nr-axSpA patients whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. Ixekizumab is a treatment option for patients who are contraindicated to TNF-alpha inhibitors.

B.1.4 *Equality considerations*

It is not anticipated that there will be any equality considerations related to the use of ixekizumab in axSpA.

B.2 Clinical effectiveness

Summary of clinical effectiveness of ixekizumab

- The efficacy of ixekizumab in axSpA has been demonstrated for up to 52 weeks in three Phase III, multicentre, double-blind, randomised controlled trials:
  - **COAST-V**: Rad-axSpA patients who have responded inadequately to ≥2 NSAIDs or have shown intolerance of NSAIDs (**biologic-naïve patients**)[1, 2, 54]
  - **COAST-W**: Rad-axSpA patients who have responded inadequately to or were intolerant to one to two TNF-alpha inhibitors, following inadequate response to ≥2 NSAIDs, or intolerance of NSAIDs (**biologic-experienced patients**)[3, 4, 55]
  - **COAST-X:** Nr-axSpA patients who have responded inadequately to ≥2 NSAIDs or are intolerant of NSAIDs (**biologic-naïve patients**)[5, 6]
- The primary endpoint of the COAST trials was the proportion of patients achieving an ASAS40 response at Week 16, and was met in all three trials for ixekizumab 80 mg every 4 weeks (Q4W):
  - In **COAST-V**, a statistically significantly greater proportion of patients met the primary endpoint (48.1%; p<0.0001) compared to placebo (18.4%). In the adalimumab reference arm, a numerically lower proportion of patients (35.6%; p=0.0053 versus placebo) of patients met the primary endpoint compared to ixekizumab Q4W
  - In **COAST-W**, a statistically significantly greater proportion of patients met the primary endpoint (25.4%; p=0.017) compared to placebo (12.5%)
  - In **COAST-X**, a statistically significantly greater proportion of patients met the primary endpoint (35%; p=0.0094) compared to placebo (19%)
  - In all three clinical trials, there was no significant difference in the primary endpoint at Week 16 between the 160 mg and 80 mg loading doses (LDs) for ixekizumab
  - Achievement of an ASAS40 response is a clinically meaningful outcome that has been shown to be associated with improvements in spinal pain at night, fatigue, sleep quality and SF-36 physical component summary (PCS)[56]
- Ixekizumab 80 mg Q4W also demonstrated significant improvements in patients' disease activity levels (BASDAI) and functional ability (Bath Ankylosing Spondylitis Functional Index [BASFI]) at Week 16 across all three COAST trials:
  - In **COAST-V:**
    - A statistically significantly greater proportion of patients achieved a BASDAI50 response (42.0%; p=0.0003) compared to placebo (17.2%)
    - BASDAI change from baseline (cfb) was also [redacted] compared to placebo ([redacted])
    - BASFI cfb was also [redacted] compared to placebo [redacted]
  - In **COAST-W:**
    - A [redacted] of patients achieved a BASDAI50 response ([redacted]) versus placebo ([redacted]
    - BASDAI cfb was also [redacted] compared to placebo [redacted])
    - BASFI cfb was also [redacted] versus placebo ([redacted])
  - In **COAST-X:**
    - A [redacted] of patients achieved a BASDAI50 response ([redacted]) compared to placebo ([redacted]

- BASDAI cfb was also significantly greater (−2.18; p=0.0306) compared to placebo (−1.51)
- BASFI cfb was also significantly improved (−2.01; p=0.0401) compared to placebo (−1.34)

- A number of other secondary endpoints were also met in all three trials at Week 16:
  - Ixekizumab demonstrated statistical superiority to placebo in the proportion of patients achieving low disease activity as measured by Ankylosing Spondylitis Disease Activity Score (ASDAS)<2.1
  - Spinal pain (BASDAI question 2) numeric rating scale (NRS) cfb was [redacted] compared to placebo
  - HRQoL (SF-36 PCS) cfb and inflammation (Spondyloarthritis Research Consortium of Canada [SPARCC]) were also improved compared to placebo at Week 16 in the COAST trials
- In outcomes that were measured over the 52-week period of the trial, which include ASAS40, BASDAI50, BASDAI and BASFI cfb, responses were maintained, demonstrating that ixekizumab is efficacious for up to 52 weeks in all three patient populations[5, 6, 54, 55]
- The results of COAST-V, -W and -X demonstrate that treatment with ixekizumab results in rapid, clinically significant and sustained improvements in the signs and symptoms of axSpA, including disease activity, functional ability, pain, inflammation and HRQoL in both rad- and nr-axSpA patients at different positions within the UK treatment pathway

Summary of the indirect treatment comparison[57]

- A network meta-analyses (NMA) was performed to assess the clinical effectiveness of ixekizumab versus relevant comparators in the three axSpA populations aligned to the COAST trials, where suitable comparator data were available. The efficacy data for ixekizumab inputted into the NMA were sourced from patients assigned to the loading and maintenance doses that are anticipated to be licensed
- Results are presented for ASAS40, BASDAI50, BASDAI and BASFI cfb at Weeks 12–18 in Section B.2.9, and statistically significant results are summarised here. For all other comparisons versus ixekizumab, there was no statistically significant difference, or required data for the comparison were not identified in the clinical SLR:
  - In the biologic-naïve rad-axSpA population at Week 12–18:
    - Ixekizumab Q4W (80 mg LD) was [redacted] for both ASAS40 response and BASDAI cfb
    - Ixekizumab Q4W (80 mg LD) was also [redacted] for BASDAI50 response and BASFI cfb
  - In the biologic-experienced rad-axSpA population at Week 12–18:
    - For ASAS40 response, ixekizumab Q4W (160 mg LD) was [redacted]
    - [redacted], whilst [redacted] to ixekizumab Q4W for both 80 mg and 160 mg LDs
    - For both BASDAI50 response and BASDAI cfb, ixekizumab was [redacted]
    - [redacted] to placebo, whilst [redacted] to ixekizumab.
    - Ixekizumab was [redacted] to [redacted] for BASFI cfb
  - In the biologic-naïve nr-axSpA population at Week 12–18:
    - For ASAS40 response, ixekizumab Q4W (80 mg LD) was [redacted]
    - For BASDAI50 response, ixekizumab Q4W (80 mg LD) was also [redacted]
    - For BASDAI cfb, ixekizumab Q4W (80 mg LD) was also [redacted]
    - For BASFI cfb, ixekizumab Q4W (80 mg LD) was also [redacted]

Summary of the safety results for ixekizumab

- Ixekizumab demonstrated a manageable safety profile in all three patient populations at Week 16
- In the pooled analysis of rad-axSpA patients from **COAST-V** and **COAST-W** at Week 16:[58]
  - Treatment-emergent adverse events (TEAEs) were reported by [redacted]) patients treated with ixekizumab and [redacted]) placebo-treated patients
  - Serious adverse events (SAEs) occurred in [redacted]) ixekizumab-treated patients and [redacted]) placebo-treated patients
  - [redacted]
  - The most commonly reported AEs of special interest (AESIs) [redacted]
- In **COAST-X** at Week 16:[5]
  - TEAEs were reported by [redacted]) patients treated with ixekizumab and [redacted]) placebo-treated patients
  - SAEs occurred in [redacted]) of ixekizumab-treated patients and [redacted]) placebo-treated patients
  - The most commonly reported AESIs were [redacted]
- The safety profile for ixekizumab was similar at Week 52. The data presented below are from the Safety Population of patients who were initially randomised to ixekizumab at Week 0:
  - **COAST-V:**[1]
    - TEAEs occurred in [redacted] of all patients; severe TEAEs were reported for [redacted] of all patients receiving ixekizumab
    - The most commonly reported AESIs were [redacted]
  - **COAST-W:**[4]
    - TEAEs occurred in [redacted] of all patients; severe TEAEs were reported for [redacted] of all patients receiving ixekizumab
    - The most commonly reported AESIs were [redacted]
  - **COAST-X:**[5, 6]
    - TEAEs occurred in [redacted] of all patients (ixekizumab Q2W: 77%; ixekizumab Q4W: 66%; placebo: 57%); severe TEAEs were reported for [redacted] of all ixekizumab patients
    - The percentages of patients with TEAEs judged by the investigator as possibly related to study drug were [redacted]
    - There was no difference in the percentage of patients with SAEs among the treatment groups
    - The most commonly reported AESIs were infections and injection-site reactions [redacted]; these were reported more frequently in each of the ixekizumab treatment groups than in the placebo group.
- Ixekizumab was well-tolerated in the COAST trials and the observed safety profile was consistent with the safety experience for ixekizumab in patients with moderate-to-severe plaque psoriasis and psoriatic arthritis[58]

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify relevant clinical evidence on the efficacy and safety of ixekizumab versus current disease-modifying anti-rheumatic treatments for nr- and rad-axSpA. The SLR included patients who had shown an inadequate response or intolerance to NSAIDS or prior biologic therapies. Full details of the SLR strategy, study selection processes and results can be found in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

Three clinical trials were identified in the SLR that provide clinical evidence for the efficacy and safety of ixekizumab for the treatment of axSpA: COAST-V (RHBV; NCT02696785), COAST-W (RHBW; NCT02696785) and COAST-X (RHBX; NCT02757352).[2, 3, 5, 6]

All three trials were multicentre, Phase III, double-blind, randomised controlled trials:

- COAST-V aimed to determine the efficacy and safety of ixekizumab in rad-axSpA patients who have responded inadequately to ≥2 NSAIDs or have shown intolerance of NSAIDs (biologic-naïve patients). Data from COAST-V have been published by van der Heijde *et al.* (2018) and further information is available from the COAST-V Clinical Study Reports (CSRs).[1, 2, 54]
- COAST-W aimed to determine the efficacy and safety of ixekizumab in rad-axSpA patients who have responded inadequately to or were intolerant to one to two TNF-alpha inhibitors, following inadequate response to ≥2 NSAIDs, or intolerance of NSAIDs (biologic-experienced patients). Data from COAST-W have been published by Deodhar *et al.* (2019) and further information is available from the COAST-W CSRs.[3, 4, 55]
- COAST-X aimed to determine the efficacy and safety of ixekizumab in nr-axSpA patients who have responded inadequately to ≥2 NSAIDs or are intolerant of NSAIDs (biologic-naïve patients). Data from COAST-X have been published by Deodhar *et al*. (2019) and further information is available from the COAST-X CSR.[5, 6]

An overview of these three trials is provided in Table 3.

Table 3: Clinical effectiveness evidence from COAST-V, COAST-W and COAST-X

Study	COAST-V[2]	COAST-W[3]	COAST-X[5, 6]
Study design	Multicentre, Phase III, double-blind, randomised, controlled trial	Multicentre, Phase III, double-blind, randomised, controlled trial	Multicentre, Phase III, double-blind, randomised, controlled trial
Population	Rad-axSpA patients who have responded inadequately to ≥2 NSAIDs or have shown intolerance of NSAIDs (biologic-naïve patients)	Rad-axSpA patients who have responded inadequately to or were intolerant to 1–2 TNF-alpha inhibitors, following inadequate response to ≥2 NSAIDs, or intolerance of NSAIDs (biologic-experienced patients).	Nr-axSpA patients who have responded inadequately to ≥2 NSAIDs or are intolerant of NSAIDs (biologic-naïve patients).
Intervention(s)	• IXE 80 mg or 160 mg subcutaneously at baseline followed by 80 mg Q2W (n=83) ○ LD: 80 mg (n=45) or 160 mg (n=38) • IXE 80 mg or 160 mg subcutaneously at baseline followed by 80 mg Q4W (n=81) ○ LD: 80 mg (n=42) or 160 mg (n=39)	• IXE 80 mg or 160 mg subcutaneously at baseline followed by 80 mg Q2W (n=98) ○ LD: 80 mg (n=48) or 160 mg (n=50) • IXE 80 mg or 160 mg subcutaneously at baseline followed by 80 mg Q4W (n=114) ○ LD: 80 mg (n=60) or 160 mg (n=54)	• IXE 80 mg or 160 mg subcutaneously at baseline followed by 80 mg Q2W (n=102) ○ LD: 80 mg (n=50) or 160 mg (n=52) • IXE 80 mg or 160 mg subcutaneously at baseline followed by 80 mg Q4W (n=96) ○ LD: 80 mg (n=47) or 160 mg (n=49)
Comparator(s)	• ADA subcutaneously 40 mg Q2W (n=90) ○ Reference arm only; trial was not powered to test equivalence or non-inferiority of the active treatment arms • Placebo subcutaneously Q2W (n=87)	• Placebo subcutaneously Q2W (n=104)	• Placebo subcutaneously Q2W (n=105)
Indicate if trial supports application for marketing authorisation	Yes	Yes	Yes
Indicate if trial used in the	Yes	Yes	Yes

economic model			
Rationale for use/non-use in the model	COAST-V is one of three pivotal Phase III clinical trials for IXE in axSpA. This trial informed the marketing authorisation application and considers a population directly relevant to the decision problem addressed in this submission	COAST-W is one of three pivotal Phase III clinical trials for IXE in axSpA. This trial informed the marketing authorisation application and considers a population directly relevant to the decision problem addressed in this submission	COAST-X is one of three pivotal Phase III clinical trials for IXE in axSpA. This trial informed the marketing authorisation application and considers a population directly relevant to the decision problem addressed in this submission
Reported outcomes specified in the decision problem	• Composite outcome (ASAS40) • Disease activity (ASDAS<2.1, BASDAI50, BASDAI cfb) • Functional capacity (BASFI) • Inflammation (SPARCC MRI spine and sacroiliac joint scores) • Pain (spinal pain NRS from BASDAI question 2) • Adverse effects of treatment • HRQoL (SF-36 PCS)	• Composite outcome (ASAS40) • Disease activity (ASDAS<2.1, BASDAI50, BASDAI cfb) • Functional capacity (BASFI) • Inflammation (SPARCC MRI spine scores)[a] • Pain (spinal pain NRS from BASDAI question 2) • Adverse effects of treatment • HRQoL (SF-36 PCS)	• Composite outcome (ASAS40) • Disease activity (ASDAS<2.1, BASDAI50, BASDAI cfb) • Functional capacity (BASFI) • Inflammation (SPARCC MRI sacroiliac joint scores) • Pain (spinal pain NRS from BASDAI question 2) • Adverse effects of treatment • HRQoL (SF-36 PCS)
All other reported outcomes	None	None	None

[a]In COAST-W spinal SPARCC MRI scores were only measured in patients who were included in the MRI addendum and who had results available at screening and at Week 16 (N=140)

Abbreviations: ADA: adalimumab; ASAS: Assessment of SpondyloArthritis international Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloarthritis; BASDAI: Bath AS Disease Activity Index; BASFI: the Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; HRQoL: health-related quality of life; IXE: ixekizumab; LD: loading dose; MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axial spondyloarthritis; NSAIDs: nonsteroidal anti-inflammatory drugs; NRS: numeric rating scale; PCS: physical component summary; Q2W: every 2 weeks; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis; SF-36: Short Form-36; SPARCC: Spondyloarthritis Research Consortium of Canada; TNF: tumour necrosis factor

Source: Deodhar *et al*. 2019;[3] van der Heijde *et al.* 2009;[59] van der Heijde *et al.* 2018;[2] COAST-X CSR: Week 16 and Week 52 report;[5] Deodhar *et al*. 2019.[6]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Trial design

COAST-V[2, 54]

COAST-V was a Phase III, multicentre, randomised, double-blind, active-controlled and placebo-controlled trial with a 1-year duration. Patients that completed COAST-V were eligible to enrol into a long-term study (COAST-Y) for up to two additional years. COAST-V aimed to determine the efficacy and safety of ixekizumab in rad-axSpA patients who have responded inadequately to two or more NSAIDs or have shown intolerance of NSAIDs (biologic-naïve patients). This study compared the efficacy of ixekizumab against placebo, and it also included an adalimumab treatment group, which was used during the masked treatment period as an active reference for comparison with the placebo group.

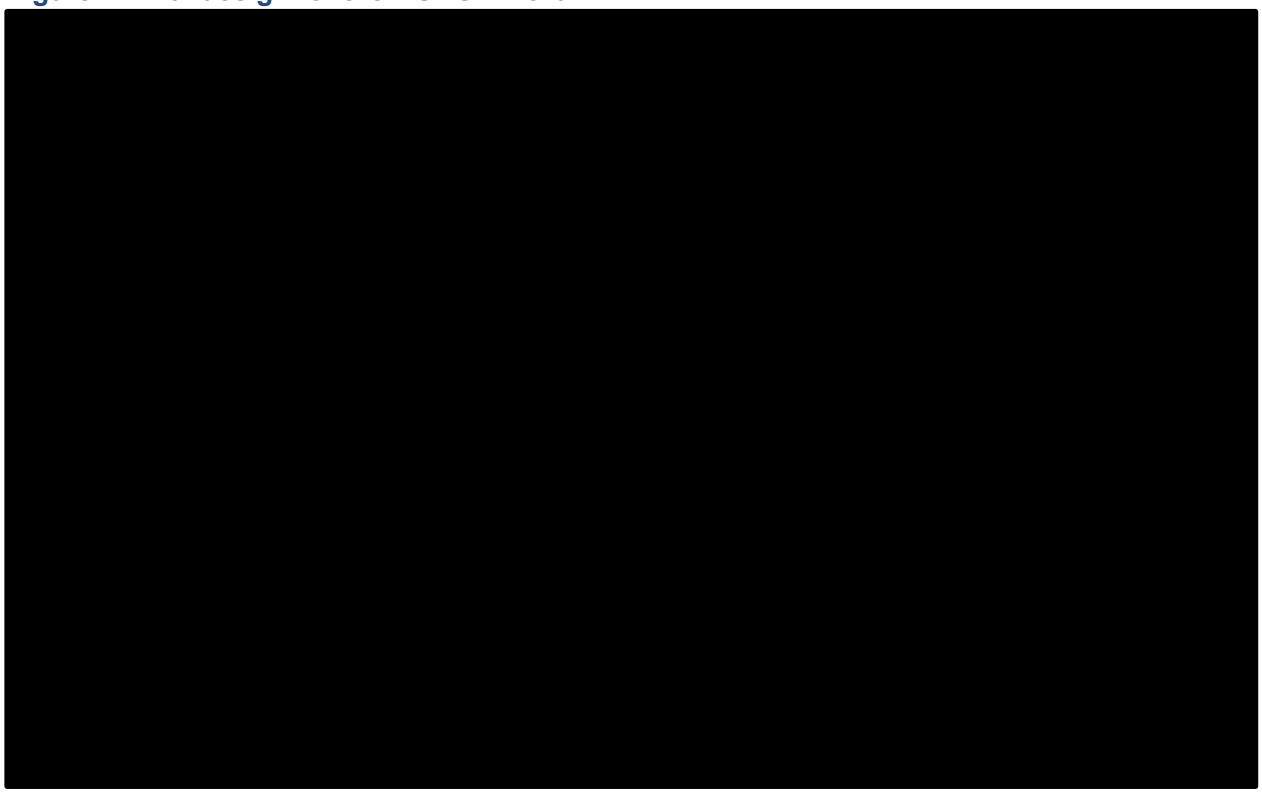
Patients with rad-axSpA were screened for eligibility based on the inclusion criteria outlined in Table 4, Section B.2.3.2. A total of 341 patients were randomly allocated in a 1:1:1:1 ratio to one of four treatment arms using a computer-generated random sequence with stratification by country and results of a CRP screen (≤5 mg/L or >5 mg/L). The first 16 weeks of the trial were double-blind. The four treatment arms are as follows: ixekizumab 80 mg Q2W (n=83), ixekizumab 80 mg Q4W (n=81), adalimumab 40 mg Q2W (n=90), or the matched placebo Q2W (n=87). In addition, patients assigned to ixekizumab treatment regimens were randomly assigned in a 1:1 ratio to receive a LD of either 80 mg ixekizumab (n=45 and n=42 for the Q2W and Q4W regimens, respectively) or 160 mg ixekizumab (n=38 and n=39 for the Q2W and Q4W regimens, respectively), as two 80 mg injections, for the first dose at Week 0.

At Week 16 of the trial, patients entered a blinded 36-week extended treatment period until Week 52; during this time, patients in the ixekizumab treatment regimens continued with their assigned regimens whilst patients in the placebo or adalimumab were randomly assigned to receive one of the two ixekizumab dosing regimens: ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W, with LDs of 160 mg. The patients in the adalimumab arm received their last adalimumab dose at Week 14; this was followed by a 6-week washout period before their first ixekizumab dose at Week 20. Masking of treatment allocation was maintained until Week 52. Upon completion of the 1-year trial period, patients who were eligible could transition to an optional 2-year extension study (COAST-Y).[60]

The primary endpoint of COAST-V was the proportion of patients achieving a 40% reduction in the ASAS criteria, known as the ASAS40 response, at Week 16. More information about the outcomes assessed in COAST-V can be found in Table 7, Section B.2.3.2.

A diagram of the trial design for COAST-V is presented in Figure 4.

Figure 4: Trial design for the COAST-V trial



Abbreviations: LV: last visit; LY: ixekizumab; Q2W: every 2 weeks; Q4W: every 4 weeks; SC: subcutaneous; V: visit; W: week.
Source: COAST-V: CSR: Week 16 Report[54]

COAST-W[3, 55]

COAST-W was a Phase III, multicentre, randomised, double-blind, placebo-controlled trial with a 1-year duration. Patients that completed COAST-V were eligible to enrol into a long-term study (COAST-Y) for up to 2 additional years. COAST-W aimed to determine the efficacy and safety of ixekizumab in rad-axSpA patients who have responded inadequately to or were intolerant to one to two TNF-alpha inhibitors, following inadequate response to two or more NSAIDs, or intolerance of NSAIDs (biologic-experienced patients).

Patients with rad-axSpA were screened for eligibility based on the inclusion criteria outlined in Table 5, Section B.2.3.2. A total of 316 patients were randomly allocated in a 1:1:1 ratio to one of three treatment arms using a computer-generated random sequence with stratification by country and results of a CRP screen (≤5 mg/L or >5 mg/L) and the number of prior TNF-alpha inhibitors taken (one or two). The first 16 weeks of the trial were double-blind. The three treatment arms were as follows: 80 mg ixekizumab Q2W (n=98), 80 mg ixekizumab Q4W (n=114), or the matched placebo Q2W from Week 0. Patients assigned to ixekizumab treatment regimens were randomly assigned in a 1:1 ratio to receive a LD of either 80 mg ixekizumab (n=48 and n=60 for the Q2W and Q4W regimens, respectively) or 160 mg ixekizumab (n=50 and n=54 for the Q2W and Q4W regimens, respectively) for the first dose at Week 0.

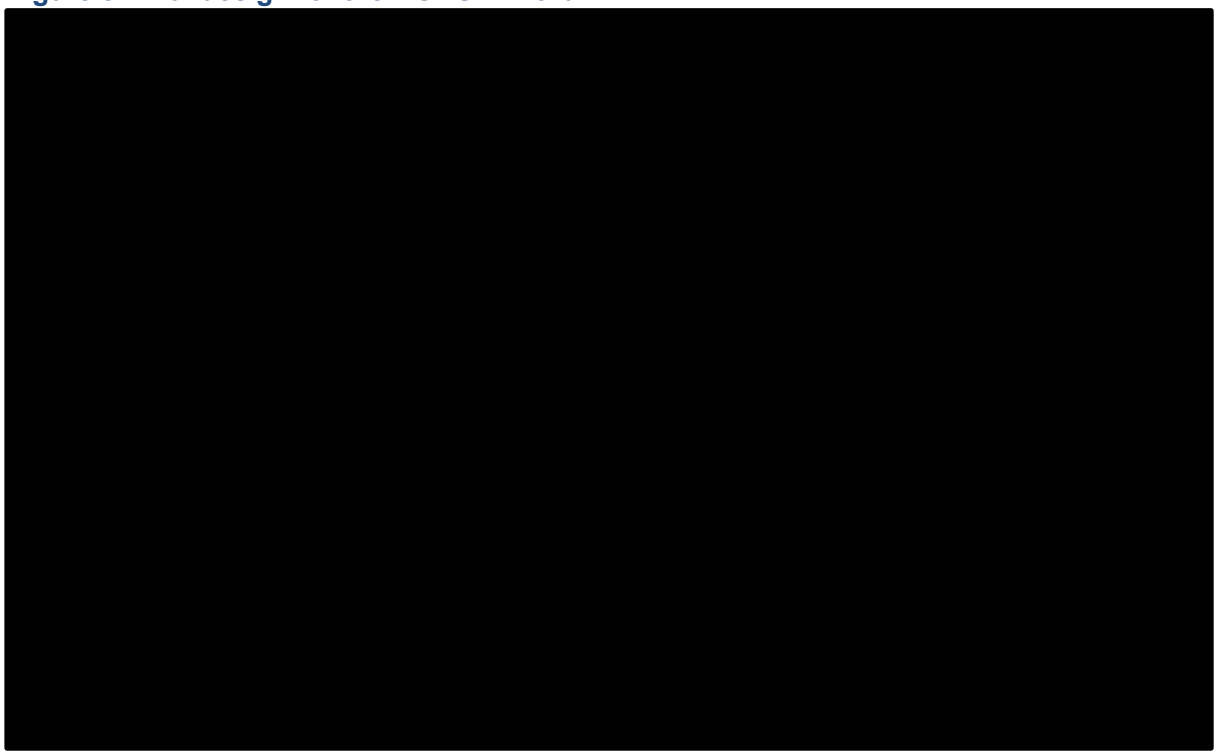
From Week 16 to Week 52, patients entered a blinded 36-week extended treatment period; during this time, patients in the placebo treatment arm were randomly assigned to receive one of the two ixekizumab dosing regimens: ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W, with LDs of 160 mg, whilst patients in the ixekizumab treatment regimens continued with their

assigned regimens. Masking of treatment allocation was maintained until Week 52. Upon completion of the 1-year trial period, patients who were eligible could transition to an optional 2-year extension study (COAST-Y).[60]

The primary endpoint of COAST-W was ASAS40 response at Week 16. More information about the outcomes assessed in COAST-W can be found in Table 7, section B.2.3.2.

A diagram of the trial design for COAST-W is presented in Figure 5.

Figure 5: Trial design for the COAST-W trial



Abbreviations: LV: last visit; LY: ixekizumab; Q2W: every 2 weeks; Q4W: every 4 weeks; SC: subcutaneous; V: visit; W: week.
Source: COAST-W CSR: Week 16 Report[55]

COAST-X[5, 6]

COAST-X was a Phase III, multicentre, randomised, double-blind, placebo-controlled trial with a 1-year duration. COAST-X aimed to determine the efficacy and safety of ixekizumab in nr-axSpA patients following inadequate response to NSAIDs, or intolerance to NSAIDs and who have not been treated with alpha-TNF inhibitors or immunomodulatory agents.

Patients with nr-axSpA patients were screened for eligibility based on the inclusion criteria outlined in Table 6, Section B.2.3.2. A total of 303 patients were randomly allocated in a 1:1:1 ratio to one of three treatment arms using a computer-generated random sequence with stratification by country and results of an MRI/CRP screen (i. positive MRI and elevated CRP, ii. positive MRI and non-elevated CRP; iii. negative MRI and elevated CRP [elevated CRP was defined as >5 mg/L]). The three treatment arms are as follows: 80 mg ixekizumab Q2W (n=102), 80 mg ixekizumab Q4W (n=96), or the matched placebo Q2W (n=105) from Week 0. Patients assigned to ixekizumab treatment regimens were randomly assigned in a 1:1 ratio to receive a LD of either 80 mg ixekizumab (n=50 and n=47 for the Q2W and Q4W regimens, respectively) or

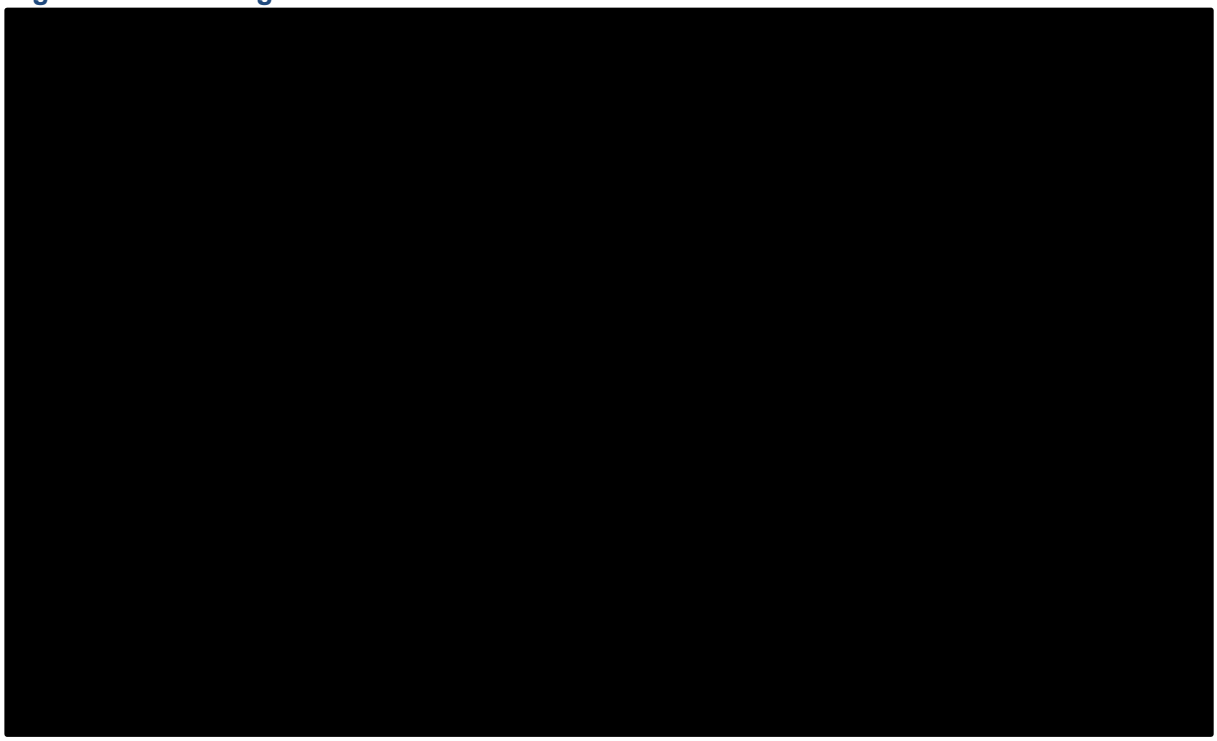
160 mg ixekizumab (n=52 and n=49 for the Q2W and Q4W regimens, respectively) for the first dose at Week 0.

From Week 16 to Week 44, any patient could be identified as an inadequate responder by an investigator based on clinical judgement, and a rescue treatment could be administered. During this time, changes in background therapy could be made at the investigator's discretion. Furthermore, investigators could decide to use a biologic rescue of ixekizumab 80 mg Q2W with an 80 mg LD; investigators remained blinded to the original randomisation and therefore patients in any treatment arm could be allocated to receive rescue with ixekizumab 80 mg Q2W. If patients did not require a rescue dose, they remained in their original treatment group until Week 52. Patients who did receive rescue therapy were regarded as non-responders and were not included in analysis. If in the opinion of the investigator, the patient did not show any clinical improvement after at least 8 weeks of the ixekizumab 80 mg Q2W rescue treatment, then the investigator could consider discontinuation of the patient from ixekizumab treatment.

The primary endpoint of COAST-X was the proportion of patients achieving an ASAS40 response at Week 16. This primary endpoint was required by the European Medicines Agency and is therefore considered to be the primary endpoint in this submission. ASAS40 response was also assessed as a primary endpoint at Week 52, as required by the Food and Drug Administration.

A diagram of the trial design for COAST-X is presented in Table 6.

Figure 6: Trial design for the COAST-X trial



Abbreviations: LV: last visit; LY: ixekizumab; Q2W: every 2 weeks; Q4W: every 4 weeks; SC: subcutaneous; V: study visit; W: study week.
Source: COAST-X CSR: Week 16 and Week 52 Report[5]

B.2.3.2 Trial methodology

Eligibility criteria

A summary of the eligibility criteria for COAST-V, COAST-W and COAST-X is presented in Table 4, Table 5 and Table 6, respectively.

Table 4: Eligibility criteria for COAST-V

Inclusion criteria	Exclusion criteria
• At least 18 years old • An established diagnosis of rad-axSpA and fulfilling ASAS criteria (sacroiliitis on radiograph by mNY criteria and at least one SpA feature) ○ Reading of the sacroiliac joint radiograph was done centrally by two readers, with adjudication if necessary • BASDAI of ≥4 and back pain of ≥4 on an NRS at screening and baseline • History of back pain of ≥3 months and <45 years old at onset • Have received ≥12 weeks therapy for axSpA • Inadequate response or intolerance to ≥2 NSAIDs • No prior treatment with TNF-alpha inhibitors, biologics or immunomodulatory agents	• Total ankylosis of the spine (local reading) • Current or previous history of lymphoproliferative or malignant disease within 5 years of baseline • Other medical conditions, treatments, or procedures that could pose an unacceptable risk to patients or that could confound interpretation of study results

Abbreviations: ASAS: Assessment of SpondyloArthritis international Society; axSpA: axial spondyloathritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; mNY: modified New York; NRS: numeric rating scale; NSAID: nonsteroidal anti-inflammatory drug; rad-axSpA: radiographic axial spondyloarthritis; SpA: spondyloarthritis; TNF: tumour necrosis factor
Source: van der Heijde *et al.* 2018[2]

Table 5: Eligibility criteria for COAST-W

Inclusion criteria	Exclusion criteria
• At least 18 years old • An established diagnosis of rad-axSpA and fulfilling ASAS criteria (sacroiliitis on radiograph by mNY criteria and at least one SpA feature) • Of <45 years age at onset • BASDAI of ≥4 back pain of ≥4 on an NRS at screening and baseline • History of back pain for ≥3 months with age of onset <45 years • Have received ≥12 weeks therapy for axSpA • Have had prior treatment with 1–2 TNF-alpha inhibitors • Have discontinued 1–2 TNF-alpha inhibitors	• Total ankylosis of the spine (local reading) • Current or previous history of lymphoproliferative or malignant disease within 5 years of baseline • Other medical conditions, treatments, or procedures that could pose an unacceptable risk to patients or that could confound interpretation of study results

either due to intolerance or due to inadequate response • Inadequate response or intolerance to ≥2 NSAIDs • If taking NSAID inhibitors, dose must be stable for ≥2 weeks prior to baseline randomisation	

Abbreviations: ASAS: Assessment of SpondyloArthritis international Society; axSpA: axial spondyloathritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; mNY: modified New York; NRS: numeric rating scale; NSAID: nonsteroidal anti-inflammatory drug; rad-axSpA: radiographic axial spondyloarthritis; SpA: spondyloarthritis; TNF: tumour necrosis factor
Source: COAST-W CSR: Week 16 Report;[55] Deodhar *et al*. 2019[3]

Table 6: Eligibility criteria for COAST-X

Inclusion criteria	Exclusion criteria
• Adult (≥18 years of age) nr-axSpA patients with sacroiliitis (present on MRI according to ASAS/OMERACT criteria and based on a central reading) and ≥1 SpA feature or positive for HLA-B27 with ≥2 SpA features • BASDAI of ≥4 and back pain ≥4 on an NRS • History of back pain for ≥3 months with age of onset of >45 years • Objective signs of inflammation, by sacroiliitis on MRI or elevated CRP • Have received ≥12 weeks therapy for axSpA • Have no prior treatment with TNF-alpha inhibitors, biologics or immunomodulatory agents • Have shown inadequate response or lack of tolerance to ≥2 NSAIDs	• An established diagnosis of rad-axSpA and fulfilling ASAS criteria (sacroiliitis on radiograph by mNY criteria and at least one SpA feature) • A history of other systemic inflammatory diseases or chronic pain conditions • Active Crohn's disease or active ulcerative colitis • Active anterior uveitis (an acute episode) within 4 weeks prior to baseline

Abbreviations: ASAS: Assessment of SpondyloArthritis international Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C Reactive Protein; HLA: Human Leukocyte antigen; mNY: modified New York; MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axial spondyloarthritis; NRS: numeric rating scale; NSAID: nonsteroidal anti-inflammatory drug; OMERACT: Outcome Measures in Rheumatology; rad-axSpA: radiographic axial spondyloarthritis; SpA: spondyloarthritis; TNF: tumour necrosis factor
Source: COAST-X CSR: Week 16 and Week 52 Report[5]; Deodar *et al.* 2019.[6]

Settings and locations where the data were collected

All three trials were conducted in a secondary care setting and data were collected at multiple sites in multiple countries, which were further grouped as European or non-European for statistical analysis.

COAST-V was carried out at 84 sites across 12 countries worldwide, comprising the Czech Republic, Germany, [redacted], the Netherlands, [redacted], [redacted], [redacted], Japan, South Korea, [redacted], Taiwan, and the USA.[54] In COAST-W, patient enrolment and data collection occurred at 106 sites in 15 countries comprising Argentina, Brazil, Canada, Finland, France, Germany, Israel, Italy, Republic of Korea, Mexico, Netherlands, Poland, Spain, United Kingdom and the United States. COAST-X was conducted at 107 sites in 15 countries worldwide comprising Argentina, Austria, Brazil, Canada, Czech Republic, Finland, Germany, Japan, Republic of Korea, Mexico, Netherlands, Poland, Romania, Russian Federation and the United States.[6]

Description of outcomes reported

A description of the primary and key secondary outcomes for which results are reported in Section 0 is presented in Table 7. The order of gated key secondary endpoints in each trial differed, as displayed in Appendix L.

Table 7: Outcome descriptions in COAST-V, COAST-W and COAST-X

Outcome	Description
Primary outcome	
ASAS40	ASAS40 is a composite measure of the following four domains: physical function (BASFI), back pain assessment, Patient's Global Assessment of disease activity, and inflammation, each with a range 0–10.[61] An ASAS40 response is defined as an improvement of 40% or more and at least two units compared to baseline in three or more of the four domains, with no worsening at all in the remaining domain. In all three trials, ASAS40 was measured at each post-baseline visit and assessment at Week 16 was defined as the primary endpoint.
Secondary outcomes	
BASDAI and BASDAI50	The BASDAI comprises six questions (each with a range of 0–10) that relate to five major symptoms of rad-axSpA: fatigue, spinal pain, joint point/swelling, areas of localised tenderness and morning stiffness (which is assigned two questions). To give each symptom equal weighting, the mean of the two scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0–10 BASDAI score.[62] BASDAI50 represents an improvement of ≥50% of the BASDAI score from baseline, and the proportion of patients achieving this was a secondary outcome in addition to the least squares mean change in BASDAI score from baseline in all three trials. In all three trials, BASDAI was measured at each post-baseline visit.
ASDAS<2.1	ASDAS is a composite outcome including five parameters: total back pain (BASDAI question 2), patient global assessment, peripheral pain/swelling, duration of morning stiffness, and CRP mg/L (or ESR values). Responses are each assessed on a 0–10 NRS and are weighted and combined to give a final ASDAS score.[63] An ASDAS of at least 2.1 indicates high disease activity, an ASDAS of <2.1 indicates low disease activity, and is endorsed as a treat to target endpoint in axSpA.[64]
BASFI	The BASFI consists of ten questions that relate to patients' daily life activities (each with a range of 0–10). The rating contains two questions pertaining to the patients' ability to cope with daily life, along with eight questions pertaining to tasks the patients' face in everyday life that depend on functional anatomy. The patients' final BASFI score is the mean of the 10-item scores completed on an NRS.[65] In all three trials, cfb in BASFI was measured at each post-baseline visit and assessment at Week 16 was defined as a secondary endpoint.
Spinal pain NRS score	Spinal pain was recorded on an NRS scale of (0–10) as part of question 2 of the BASDAI "How would you describe your overall level of neck, back or hip pain resulting from AS?" questionnaire. In all three trials, spinal pain (BASDAI Q2) was measured at each post-baseline visit.
SPARCC sacroiliac and spine scores	MRI images are collected of both the left and right sacroiliac joints, these MRIs are used to score the sacroiliac joints for bone marrow oedema. SPARCC scores can range from 0 to 72, with higher scores

	reflecting worse disease.[66] The SPARCC score was used to measure the cfb in MRI of the sacroiliac and/or spine in all three trials. In COAST-V, MRI of the spine and sacroiliac joints took place at Weeks 16 and 52; in COAST-W, MRI of the spine took place at Week 16 for a subset of patients (MRI addendum); in COAST-X, MRI of the sacroiliac joints took place at Week 16 and 52.
SF-36 PCS	The SF-36 is a 36-item patient-reported instrument used to measure HRQoL. The SF-36 measures 8 scales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. The PCS component is measured using the first four domains.[67] The summary scores range from 0 to 100; higher scores indicate better levels of function and/or better health. Items are answered on Likert scales of varying length. The SF-36 version 2 was used in these three trials, which uses a 1-week recall period.[68]

Abbreviations: ASAS: Assessment of SpondyloArthritis international Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloarthritis; BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HRQoL: health-related quality of life; NRS: numeric rating scale; MRI: magnetic resonance imaging; PCS: physical component summary; rad-axSpA: radiographic axial spondyloarthritis; SF-36: Short Form-36; SPARCC: Spondyloarthritis Research Consortium of Canada.
Source: Calin *et al.* 1994;[65] Deodhar *et al.* 2019;[3] Garrett *et al.* 1994;[62] van der Heijde *et al*. 2018;[2] Lins and Carvalho, 2016;[67] Maksymowych *et al.* 2005;[66] Siebenga *et al.* 2008;[69] Sieper *et al.* 2009;[61] Ware Jr, 2000;[68] COAST-V: CSR: Week 16 Report;[54] COAST-W CSR: Week 16 Report;[55] COAST-X CSR: Week 16 and Week 52 Report[5]

B.2.3.3 Baseline characteristics

Baseline demographics and disease characteristics of the patients included in the intention-to-treat (ITT) population of trials COAST-V, COAST-W and COAST-X are presented in Table 8, Table 9 and Table 10, respectively. The demographics of patients included in the trials may be considered generalisable to axSpA patients in the UK; the majority of patients in each trial were of white ethnicity[2, 3, 5] and the average age of onset was <45 years, which aligns with UK axSpA statistics.[70]

The baseline demographic characteristics were well-balanced between the treatment arms for all three trials.

Table 8: Baseline characteristics ITT population COAST-V

Characteristic	Ixekizumab Q2W (n=83)	Ixekizumab Q4W (n=81)	Adalimumab (n=90)	Placebo* (n=87)
Demographics				
Age, years (SD)	41.3 (11.2)	41.0 (12.1)	41.8 (11.4)	42.7 (12.0)
Sex Men, n (%) Women, n (%)	 64 (77) 19 (23)	 68 (84) 13 (16)	 73 (81) 17 (19)	 71 (83) 15 (17)
Mean weight, kg (SD) <70 (%) ⩾70 (%)	 76.6 (13.8) 29 (35) 54 (65)	 77.6 (14.7) 24 (30) 57 (70)	 78.2 (17.2) 29 (32) 61 (68)	 79.9 (17.1) 25 (29) 61 (71)
Race White, n (%)	 52 (63)	 52 (64)	 57 (63)	 52 (60)

Asian, n (%) Other, n (%)	25 (30) 6 (7)	25 (31) 4 (5)	29 (32) 4 (4)	28 (33) 6 (7)
Disease characteristics				
Mean age of onset of axSpA, years (SD)	25.8 (8.2)	25.4 (7.7)	26.5 (8.6)	26.4 (8.4)
Mean duration of symptoms since axSpA onset, years (SD)	15.8 (10.6)	15.8 (11.2)	15.6 (9.3)	16.6 (10.1)
Mean duration of disease since axSpA diagnosis, years (SD)	8.2 (9.0)	8.3 (9.6)	7.5 (7.5)	6.8 (7.6)
Use of NSAIDs at baseline, n (%)	79 (95)	72 (89)	83 (92)	78 (91)
Mean baseline CRP, mg/L (SD)	13.4 (15.3)	12.2 (13.3)	12.5 (17.6)	16.0 (21.0)
Number of patients with CRP concentration >5 mg/L (%)	55 (66)	52 (64)	52 (58)	60 (70)
ASDAS score, mean (SD)	3.8 (0.8)	3.7 (0.7)	3.7 (0.8)	3.9 (0.7)
BASDAI score, mean (SD)	6.7 (1.6)	6.8 (1.3)	6.7 (1.5)	6.8 (1.2)
BASFI score, mean (SD)	6.3 (2.1)	6.1 (1.8)	6.1 (2.1)	6.4 (1.9)
SF-36 PCS	34.1 (7.6)	34.0 (7.5)	33.5 (8.3)	32.0 (8.3)
SPARCC MRI spine score, mean (SD)	16.6 (23.8)	14.5 (20.6)	20.0 (28.4)	15.8 (21.2)
SPARCC MRI sacroiliac score, mean (SD)	6.4 (10.9)	4.5 (9.1)	4.7 (11.2)	5.0 (9.6)
Spinal pain (BASDAI question 2), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

*The placebo population excludes one patient who was excluded during screening and accidentally assigned to the placebo group. This patient discontinued before receiving study drug.
Abbreviations: ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloarthritis; BASDAI: the Bath AS Disease Activity Index; BASFI: BAS Functional Index; CRP: C reactive protein; ITT: intention-to-treat; MRI: magnetic resonance imaging; NSAID: nonsteroidal anti-inflammatory drug; PCS: physical component summary; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation; SF-36: Short Form-36; SPARCC: Spondyloarthritis Research Consortium of Canada.
Source: van der Heijde *et al.* 2018;[2] COAST-V CSR: Week 16 Report (Table RHBV.14.6)[54]

Table 9: Baseline characteristics ITT population COAST-W

Characteristic	Ixekizumab Q2W (n=98)	Ixekizumab Q4W (n=114)	Placebo (n=104)
Demographics			
Age, years (SD)	44.2 (10.8)	47.4 (13.4)	46.6 (12.7)
Sex			
Men, n (%)	75 (76.5)	91 (79.8)	87 (83.7)
Women, n (%)	23 (23.5)	23 (20.2)	17 (16.3)
Mean weight, kg (SD)	79.3 (17.3)	85.5 (20.2)	84.3 (17.9)
<70 (%)	25 (25.5)	24 (21.1)	21 (20.2)
≥70 (%)	73 (74.5)	90 (78.9)	83 (79.8)
Race			
White, n (%)	78 (79.6)	91 (79.8)	85 (81.7)
Asian, n (%)	13 (13.3)	14 (12.4)	13 (12.5)
Other, n (%)	7 (7.1)	9 (7.9)	6 (5.8)
Disease characteristics			
Mean age of onset of axSpA, years (SD)	28.1 (10)	28.9 (9.6)	27.1 (8.8)
Mean duration of symptoms since axSpA onset, years (SD)	16.5 (9.6)	18.8 (11.6)	19.9 (11.6)
Mean duration of disease since axSpA diagnosis, years (SD)	11.7 (8.8)	10.1 (7.8)	13.0 (10.5)
Use of NSAIDs at baseline, n (%)	71 (72.4)	86 (75.4)	84 (80.8)
Mean baseline CRP, mg/L (SD)	16.9 (19.8)	20.2 (34.3)	16.0 (22.3)
Number of patients with CRP concentration >5 mg/L, n (%)	72 (73.5)	70 (61.4)	65 (62.6)
ASDAS score, mean (SD)	4.2 (0.8)	4.2 (0.9)	4.1 (0.8)
BASDAI score, mean (SD)	7.5 (1.3)	7.5 (1.3)	7.3 (1.3)
BASFI score, mean (SD)	7.4 (1.4)	7.4 (1.8)	7.0 (1.7)
SF-36 PCS, mean (SD)	27.9 (7.3)	27.5 (8.3)	30.6 (7.8)

SPARCC MRI spine score, mean (SD)[a]	11.1 (20.3)	8.3 (16)	6.4 (10.2)
Prior TNF-alpha inhibitor use, n (%)[b]			
1 prior TNF-alpha inhibitors	66 (68.0)	70 (61.4)	62 (59.6)
2 prior TNF-alpha inhibitors	31 (32.0)	44 (38.6)	42 (40.4)
Reason for failing prior TNF-alpha inhibitor, n (%)[c]			
Inadequate response to 1 TNF-alpha inhibitor	66 (68.0)	75 (65.8)	64 (61.5)
Inadequate response to 2 TNF-alpha inhibitors	20 (20.6)	26 (22.8)	32 (30.8)
Intolerance of TNF-inhibitor	11 (11.3)	13 (11.4)	8 (7.7)
TNF-alpha inhibitor washout period, median (min-max) days[d]	143.0 (32.0–3,851.0)	153.5 (29.0–4,639.0)	123.5 (31.0–4,053.0)
Spinal pain (BASDAI question 2), mean (SD)	[redacted]	[redacted]	[redacted]

[a]Data were available for the MRI addendum population only (n=51 for the placebo group, n=58 for the IXE Q2W group, and n=53 for the IXE Q4W group).
[b]Patients were included regardless of whether they were inadequate responders to or intolerant of TNF-alpha inhibitors.
[c]If a patient had both an inadequate response to 1 TNF-alpha inhibitor and an intolerance of another TNF-alpha inhibitor, that patient was classified as having had an inadequate response to 1 TNF-alpha inhibitor. Patients in the intolerance category discontinued prior TNF-alpha inhibitor (1 or 2) due to intolerance only.
[d]Washout period for the last TNF-alpha inhibitor taken. Data were available for all but 1 IXE Q2W patient.
Abbreviations: ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloarthritis; BASDAI: the Bath AS Disease Activity Index; BASFI: BAS Functional Index; CRP: C-reactive protein; ITT: intention-to-treat; MRI: magnetic resonance imaging; NSAID: nonsteroidal anti-inflammatory drug; PCS: physical component summary; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation; SF-36: Short Form-36; SPARCC: Spondyloarthritis Research Consortium of Canada; TNF: tumour necrosis factor
Source: Deodhar *et al.* 2019;[3] COAST-W CSR: Week 16 Report (Table RHBW.14.6)[55]

Table 10: Baseline characteristics ITT population COAST-X

Characteristic	Ixekizumab Q2W (N=102)	Ixekizumab Q4W (N=96)	Placebo (N=105)
Demographics			
Age, years (SD)	40.0 (12.0)	40.9 (14.5)	39.9 (12.4)
Sex			
Men, n (%)	49 (48)	50 (52)	44 (42)
Women, n (%)	53 (52)	46 (48)	61 (58)
Mean weight, kg (SD)	77.3 (16.6)	79.5 (16.5)	75.8 (18.4)
<70 (%)	[redacted]	[redacted]	[redacted]
≥70 (%)	[redacted]	[redacted]	[redacted]
Race			

White, n (%) Asian, n (%) Other, n (%)	83 (81) 11 (11) 8 (8)	80 (83) 13 (14) 3 (3)	76 (73) 17 (16) 12 (11)
Disease characteristics			
Mean age of onset of axSpA, years (SD)	29.8 (9.5)	30.1 (9.7)	30.1 (9.8)
Mean duration of symptoms since axSpA onset, years (SD)	10.6 (10.1)	11.3 (10.7)	10.1 (8.3)
Mean duration of disease since axSpA diagnosis, years (SD)	[redacted]	[redacted]	[redacted]
Use of NSAIDs at baseline, n (%)	95 (93)	81 (84)	96 (91)
Mean baseline CRP, mg/L (SD)	12.1 (17.8)	12.4 (18.0)	14.3 (24.4)
Number of patients with CRP concentration >5 mg/L, n (%)	57 (56)	55 (57)	57 (54)
ASDAS, mean (SD)	3.88 (0.79)	3.78 (0.83)	3.83 (0.92)
BASDAI score, mean (SD)	7.27 (1.28)	7.02 (1.52)	7.18 (1.52)
BASFI score, mean (SD)	6.5 (1.8)	6.4 (2.1)	6.7 (2.0)
SF-36 PCS, mean (SD)	[redacted]	[redacted]	[redacted]
SPARCC MRI sacroiliac score, mean (SD)[a]	7.5 (10.8)	5.3 (8.3)	6.2 (9.1)
Spinal pain (BASDAI question 2), mean (SD)	[redacted]	[redacted]	[redacted]

[a]Data were available for n=100 for the placebo group, n=100 for the IXE Q2W group, and n=95 for the IXE Q4W group.
Abbreviations: ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloathritis; BASDAI: the Bath AS Disease Activity Index; BASFI: BAS Functional Index; CRP: C-reactive protein; ITT: intention-to-treat; MRI: magnetic resonance imaging; NSAID: nonsteroidal anti-inflammatory drug; PCS: physical component summary; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation; SF-36: Short Form-36; SPARCC: Spondyloarthritis Research Consortium of Canada
Source: COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.14.10)[5]; Deodhar *et al.* 2019.[6]

Summary of trial methodology

A summary of the trial methodology for COAST-V -W and -X is presented Table 11.

Table 11: Summary of methodology of ixekizumab studies

Trial	**COAST-V**[2, 54] (NCT02696785)	**COAST-W**[3, 55] (NCT02696798)	**COAST-X**[5, 6] (NCT02757352)
Location	International	International	International
Trial design	Phase III, multicentre, randomised, double-blind, active-controlled and placebo-controlled trial with a 1-year duration, followed by optional 2-year extension study	Phase III, multicentre, randomised, double-blind and placebo-controlled trial with a 1-year duration, followed by an optional 2-year extension study	Phase III, multicentre, randomised, double-blind and placebo-controlled trial with a 1-year duration, followed by an optional 2-year extension study
Eligibility criteria for participants	**Key inclusion criteria** ≥18 years old with rad-axSpA and fulfilling ASAS criteria. No prior treatment with TNF-alpha inhibitors, an inadequate response to or intolerance to NSAIDs and have received ≥12 weeks therapy for axSpA	**Key inclusion criteria** ≥18 years old with rad-axSpA and fulfilling ASAS criteria. Inadequate response to or intolerance to TNF-alpha inhibitors and NSAIDs and have received ≥12 weeks therapy for axSpA	**Key inclusion criteria** ≥18 years old with nr-axSpA fulfilling the ASAS 2009 criteria who show sacroiliitis on MRI or elevated CRP. No prior treatment with TNF-alpha inhibitors, inadequate response to or intolerance to NSAIDs and have received ≥12 weeks therapy for axSpA
Settings and locations where the data were collected	The study was conducted in a secondary care setting at 84 sites across 12 countries worldwide, comprising the Czech Republic, Germany, [redacted], the Netherlands, [redacted], Japan, South Korea, [redacted], Taiwan, and the USA	The study was conducted in a secondary care setting and patient enrolment and data collection occurred at 106 sites in 15 countries comprising Argentina, Brazil, Canada, Finland, France, Germany, Israel, Italy, Republic of Korea, Mexico, Netherlands, Poland, Spain, United Kingdom and the United States	The study was conducted in a secondary care setting and patient enrolment and data collection occurred at 107 sites in 15 countries worldwide comprising Argentina, Austria, Brazil, Canada, Czech Republic, Finland, Germany, Japan, Republic of Korea, Mexico, Netherlands, Poland, Romania, Russian Federation and the United States
Trial drugs *(the interventions for each group with sufficient details to allow replication,*	• A total of 341 patients were randomised in a 1:1:1:1 ratio to receive one of four treatment arms from Week 0	• A total of 316 patients were randomised in a 1:1:1 ratio to receive one of three treatment arms from Week 0	• A total of 303 patients were randomised in a 1:1:1 ratio to receive one of three treatment arms from Week 0

including how/when they were administered)	subcutaneously: ○ IXE 80 mg Q2W (n=83) ○ IXE 80 mg Q4W (n=81) ○ ADA 40 mg Q2W (n=90) ○ Matched placebo Q2W (n=87) • Patients assigned to IXE treatment regimens were randomly assigned in a 1:1 ratio to receive a LD, subcutaneously, of either: ○ 80 mg IXE (n=45 and n=42 for the Q2W and Q4W regimens, respectively) ○ 160 mg IXE (n=38 and n=39 for the Q2W and Q4W regimens, respectively), as two 80 mg injections • Between Week 16 and Week 52, patients in the placebo or adalimumab were randomly assigned to receive IXE 80 mg either Q2W or Q4W, subcutaneously, with a LD of 160 mg	subcutaneously: ○ 80 mg IXE Q2W (n=98) ○ 80 mg IXE Q4W (n=114) ○ Matched placebo Q2W (n=104) • Patients assigned to IXE treatment regimens were randomly assigned in a 1:1 ratio to receive a LD, subcutaneously, of either: ○ 80 mg IXE (n=48 and n=60 for the Q2W and Q4W regimens, respectively) ○ 160 mg IXE (n=50 and n=54 for the Q2W and Q4W regimens, respectively) • Between Week 16 and Week 52, patients in the placebo treatment arm were randomly assigned to receive one of the two IXE dosing regimens, subcutaneously, with a 160 mg LD	subcutaneously: ○ 80 mg IXE Q2W (n=102) ○ 80 mg IXE Q4W (n=96) ○ Matched placebo Q2W (n=105) • Patients assigned to IXE treatment regimens were randomly assigned in a 1:1 ratio to receive a LD, subcutaneously, of either: ○ 80 mg IXE (n=50 and n=47 for the Q2W and Q4W regimens, respectively) ○ 160 mg IXE (n=52 and n=49 for the Q2W and Q4W regimens, respectively) • Between Week 16 and Week 44, patients may be identified by the investigator as in inadequate responder and be administered a rescue treatment, this could result in them receiving IXE 80 mg Q2W with an 80 mg LD. If they did not require a rescue dose, they remained in their original treatment group until Week 52
Primary outcomes *(including scoring methods and timings of assessments)*	The proportion of patients achieving an ASAS40 response at Week 16	The proportion of patients achieving an ASAS40 response at Week 16	The proportion of patients achieving an ASAS40 response at Week 16
Other outcomes used in the economic model/specified in the scope	The proportion of patients at Week 16 and Week 52 who achieved: • ASAS40 • BASDAI50 Cfb at Week 16 and Week 52 in:	The proportion of patients at Week 16 and Week 52 who achieved: • ASAS40 • BASDAI50 Cfb at Week 16 and Week 52 in:	The proportion of patients at Week 16 and Week 52 who achieved: • ASAS40 • BASDAI50 Cfb at Week 16 and Week 52 in:

	• BASDAI • BASFI • Spinal pain NRS • SF-36 PCS • SPARCC MRI scores of the sacroiliac joint and spine	• BASDAI • BASFI • Spinal pain NRS • SF-36 PCS Cfb at Week 16 in a subset of patients: • SPARCC MRI score of the spine	• BASDAI • BASFI • Spinal pain NRS • SF-36 PCS • SPARCC MRI score of the sacroiliac joint
Pre-planned subgroups	• ASAS40 ○ Patient demographics ○ Geographic region ○ Baseline disease severity ○ Other patient characteristics • ASAS20 ○ Patient demographics ○ Geographic region ○ Baseline disease severity ○ Other patient characteristics	• ASAS40 ○ Patient demographics ○ Geographic region ○ Baseline disease severity ○ Other patient characteristics • ASAS20 ○ Patient demographics ○ Geographic region ○ Baseline disease severity ○ Other patient characteristics	• ASAS40 ○ Patient demographics ○ Geographic region ○ Baseline disease severity ○ Other patient characteristics • ASDAS <2.1 ○ Patient demographics ○ Geographic region ○ Baseline disease severity ○ Other patient characteristics

Abbreviations: ADA: Adalimumab; ASAS: Assessment of SpondyloArthritis international Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloarthritis; BASDAI: Bath AS Disease Activity Index; BASFI: the Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CRP: C-reactive protein; IXE: ixekizumab; LD: loading dose; MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axial spondyloarthritis; NRS: numeric rating scale; NSAID: nonsteroidal anti-inflammatory drug; PCS: physical component summary; Q2W: every 2 weeks; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis; SF-36: Short Form-36; SpA: spondyloarthritis; SPARCC: Spondyloarthritis Research Consortium of Canada; TNF: tumour necrosis factor.
Source: Deodhar *et al*. 2019;[3] Deodhar *et al.* 2019;[6] van der Heijde *et al*. 2019;[2] COAST-V: CSR: Week 16 Report;[54] COAST-W CSR: Week 16 Report;[55] COAST-X CSR: Week 16 and Week 52 Report;[5]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

The definitions of all study populations analysed from COAST-V, -W and -X are presented in Table 12 below.[1-6, 54, 55]

Table 12: Trial populations used for the analysis of outcomes COAST-V, -W and -X

Analysis set	Definition		
	COAST-V	COAST-W	COAST-X
Blinded treatment dosing period (Period 2; Week 0 to Week 16)			
ITT population	• [redacted] • [redacted] • [redacted] ○ IXE 80 mg Q4W/80 mg LD ○ IXE 80 mg Q4W/160 mg LD ○ IXE 80 mg Q2W/80 mg LD ○ IXE 80 mg Q2W/160 mg LD ○ Total IXE/80 mg LD ○ Total IXE/160 mg LD		• [redacted] • [redacted] • For patients who were deemed as inadequate responders by their investigators and were treated with biologic rescue of IXE 80 mg Q2W, only data up to the time of initiation of biologic rescue of IXE 80 mg Q2W has been included in the primary analyses • [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted]

Per protocol set	• Defined as all randomised patients who are compliant with therapy (compliance with therapy was defined as missing no more than 20% of expected doses, not missing two consecutive doses, and not having any occurrence of taking more injections at the same time point than specified in the protocol) during Period 2, who do not have a subset of important protocol deviations that impact the primary efficacy endpoint • [redacted] • [redacted] • [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted]	
Safety population	• Defined as all randomised patients who received at least one dose of study treatment • [redacted] • [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted]	• Defined as all randomised patients who received at least one dose of study treatment • [redacted] • For patients who were deemed as inadequate responders by their investigators and were treated with biologic rescue of IXE 80 mg Q2W, only data up to the time of initiation of biologic rescue of IXE 80 mg Q2W has been included in the primary analyses
Combined blinded treatment dosing period and extended treatment period (Combined Periods 2 and 3; Week 0 to Week 52)		
ITT population who were initially	• [redacted] • [redacted]	N/A

randomised to IXE	[redacted]	
Safety population who were initially randomised to IXE	[redacted]	N/A

Abbreviations: ADA: adalimumab; ITT: intention-to-treat; IXE: ixekizumab; LD: loading dose; N/A: not applicable; PBO: placebo; Q2W: every two weeks; Q4W: every four weeks.
Source: van der Heijde *et al.* (2018);[2] Deodhar *et al.* (2019);[3] Deodhar *et al.* 2019;[6] COAST-V: CSR: Week 16 Report (Table RHBV.9.4);[54] COAST-V CSR: Week 52 Report (Table RHBV.9.4);[1] COAST-W CSR: Week 16 Report (Table RHBW.9.4);[55] COAST-W CSR: Week 52 Report (Table RHBW.9.4);[4] COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.9.4)[5]

In all three trials the primary analysis for categorical variables at Week 16 was logistic regression analysis, with Fisher's exact test used as a secondary analysis method. The primary analysis for continuous variables at Week 16 was using an MMRM model, with the exception of MRI endpoints for which an ANCOVA was used. The secondary analysis for continuous variables was ANCOVA. For week 52 data, missing variables were imputed using the mBOCF method and for categorical outcomes missing data were imputed using non-responder imputation analysis. The detailed statistical analyses used to calculate the primary endpoint and other endpoints at Week 16 and Week 52 in all three COAST trials, alongside sample size calculations and methods for handling missing data, are presented in detail in Appendix L.

B.2.4.1 Participant flow in relevant randomised controlled trials

Full details of the participant flow and CONSORT diagrams for the three COAST trials are reported in Appendix D.

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

Table 13: Overview of risk of bias assessment for the trials included in the submission

Trial name	COAST-V	COAST-W	COAST-X
Was randomisation carried out appropriately?	Yes – low risk	Yes – low risk	Yes – low risk
Was the concealment of treatment allocation adequate?	Yes – low risk	Yes – low risk	Yes – low risk
Were the groups similar at the outset of the study in terms of prognostic factors	Yes – low risk	Yes – low risk	Yes – low risk
Were the care providers, participants and outcome assessors blind to treatment allocation?	Not clear – low risk (double-blind study)	Not clear – low risk (double-blind study)	Not clear – low risk (double-blind study)
Were there any unexpected imbalances in drop-outs between groups?	No – low risk	No – low risk	No – low risk
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – low risk	No – low risk	No – low risk
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes – low risk	Yes – low risk	Yes – low risk

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)

B.2.6 *Clinical effectiveness results overview*

Summary of ixekizumab clinical effectiveness results

COAST-V[1, 2, 54]

- In the biologic-naïve rad-axSpA population, ixekizumab 80 mg Q4W met the primary endpoint (ASAS40 response) and demonstrated significant improvements in patients' disease activity levels, functional ability, spinal pain, inflammation and HRQoL compared to placebo at Week 16:
  - A statistically significantly greater proportion of patients (48.1%; p<0.0001) achieved an ASAS40 response, compared to placebo (18.4%) The ASAS40 response rate was also numerically greater compared to adalimumab (35.6%; p=0.0053)
    - There were [redacted] between the [redacted]) LDs
  - A reduction in disease activity, as measured by BASDAI50 response, was statistically significantly greater (42.0%; p=0.0003) compared to placebo at (17.2%)
  - BASDAI cfb was also [redacted]) compared to placebo [redacted])
  - Functional ability, as measured by BASFI cfb was also significantly improved (−2.39; p<0.0001) compared to placebo (−1.16)
  - Ixekizumab also demonstrated superiority to placebo in the proportion of patients achieving an ASDAS score ≤2.1 (low disease activity), and significant improvements from baseline compared to placebo in spinal pain (NRS), HRQoL (SF-36 PCS) and inflammation at the spine and sacroiliac joint (SPARCC MRI spine and SIJ score)
- [redacted]

COAST-W[3, 4, 55]

- In the biologic-experienced rad-axSpA population, ixekizumab 80 mg Q4W met the primary endpoint and demonstrated significant improvements in patients' disease activity levels, functional ability, spinal pain, inflammation and HRQoL compared to placebo at Week 16:
  - A statistically significantly greater proportion of patients achieved an ASAS40 response (25.4%; p=0.017) compared to placebo (12.5%)
    - There were [redacted] between the [redacted]), however, the 160 mg loading dose resulted in a faster onset and a numerically greater response rate
  - BASDAI50 response was statistically [redacted] ([redacted]) versus placebo ([redacted]
  - BASDAI cfb was also [redacted]) compared to placebo ([redacted])
  - BASFI cfb was [redacted]) versus placebo ([redacted])
  - Ixekizumab also demonstrated superiority to placebo at Week 16 in the proportion of patients achieving low disease activity, as by measured by an ASDAS score ≤2.1, and demonstrated significant improvements from baseline compared to placebo in spinal pain (NRS), HRQoL (SF-36 PCS) and inflammation at the spine in a subset of patients (SPARCC MRI spine score)

[redacted]

COAST-X[5, 6]

- In the biologic-naïve nr-axSpA population, ixekizumab 80 mg Q4W met the primary endpoint and demonstrated significant improvements in patients' disease activity levels, functional ability, [redacted], inflammation and HRQoL compared to placebo at Week 16:
  - A statistically significantly greater proportion of patients achieved an ASAS40 response (35%; p=0.0094) compared to placebo (19%)
    - There were [redacted] between the [redacted] LDs
  - [redacted] proportion of patients achieved a BASDAI50 response [redacted] as compared to placebo [redacted]
  - BASDAI cfb was also significantly greater (−2.18; p=0.0306) compared to placebo (−1.51)
  - BASFI cfb at Week 16 was significantly greater (−2.01; p=0.0401) compared to placebo (−1.34)
- In COAST-X, outcomes were assessed for statistical significance compared to placebo up to Week 52:
  - At Week 52, a statistically significantly greater proportion of patients achieved an ASAS40 response in the ixekizumab Q4W arm (30%; p=0.0045) compared to placebo (13%)
  - [redacted] of patients achieved a BASDAI50 response in the ixekizumab Q4W arm [redacted] compared to placebo [redacted]
  - BASDAI cfb was significantly improved in the ixekizumab Q4W arm (−2.18; p=0.0306) compared to placebo (−1.51)
  - BASFI cfb was significantly improved in the ixekizumab Q4W arm (−2.01; p=0.0401) compared to placebo (−1.34)
- Ixekizumab demonstrated superiority to placebo at Week 16 and Week 52 in the proportion of patients achieving low disease activity by ASDAS; cfb was significantly greater compared to placebo for HRQoL (SF-36 PCS) and inflammation at the sacroiliac joints (SPARCC MRI SIJ score). Spinal Pain (NRS) cfb [redacted]

The clinical effectiveness of ixekizumab was demonstrated in three trials, COAST-V, COAST-W and COAST-X. The clinical effectiveness results from each trial is discussed in depth in the following sections:

- Section B.2.6.1 (COAST-V)
- Section B.2.6.2 (COAST-W)
- Section B.2.6.3 (COAST-X)

B.2.6.1 COAST-V

Primary endpoint: ASAS40 at Week 16

The primary endpoint in COAST-V was the ASAS40 response at Week 16. As discussed in Section B.2.3.2, ASAS40 is a stringent composite measure of disease activity, functional impairment, spinal pain and inflammation in axSpA.[1, 2]

The primary endpoint of COAST-V was met; in the ITT population, a statistically significantly greater proportion of patients achieved an ASAS40 response at Week 16 in both the ixekizumab Q4W (48.1%; p<0.0001) and Q2W (51.8%; p<0.0001) treatment groups compared to placebo (18.4%), as shown in Table 14.[2] A statistically significantly higher proportion of patients also achieved an ASAS40 response in the adalimumab group (35.6%; p=0.0053) compared to

placebo at Week 16.[2] The trial was not powered to assess non-inferiority between ixekizumab and adalimumab, however, the difference in the proportion of patients achieving an ASAS40 response with adalimumab was numerically lower compared to both ixekizumab doses.[54]

The proportion of patients achieving an ASAS40 response was [redacted] placebo from as early as [redacted] in the ixekizumab Q4W arm ([redacted]), ixekizumab Q2W arm ([redacted]) and adalimumab arm ([redacted]). ASAS40 responses from Week 0 to Week 16 are presented in Figure 7.[54]

There was no statistically significant difference between the two LDs within each ixekizumab arm ([redacted]), as displayed in Table 14.[54]

COAST-V is the first successful Phase III clinical study in rad-axSpA to include and meet ASAS40 as the primary endpoint; earlier trials typically used ASAS20 (a 20% improvement in ASAS criteria) as the primary efficacy endpoint, representing a lower level of response. This greater level of improvement may be more clinically relevant to patients and clinicians, as it has been shown that patients who achieve an ASAS40 response also report greater improvements in a number of patient reported outcomes compared to those who achieve only an ASAS20 response (see Section B.2.13).[2]

Table 14: ASAS40 response by dose for the ITT population with non-responder imputation, COAST-V, Week 16

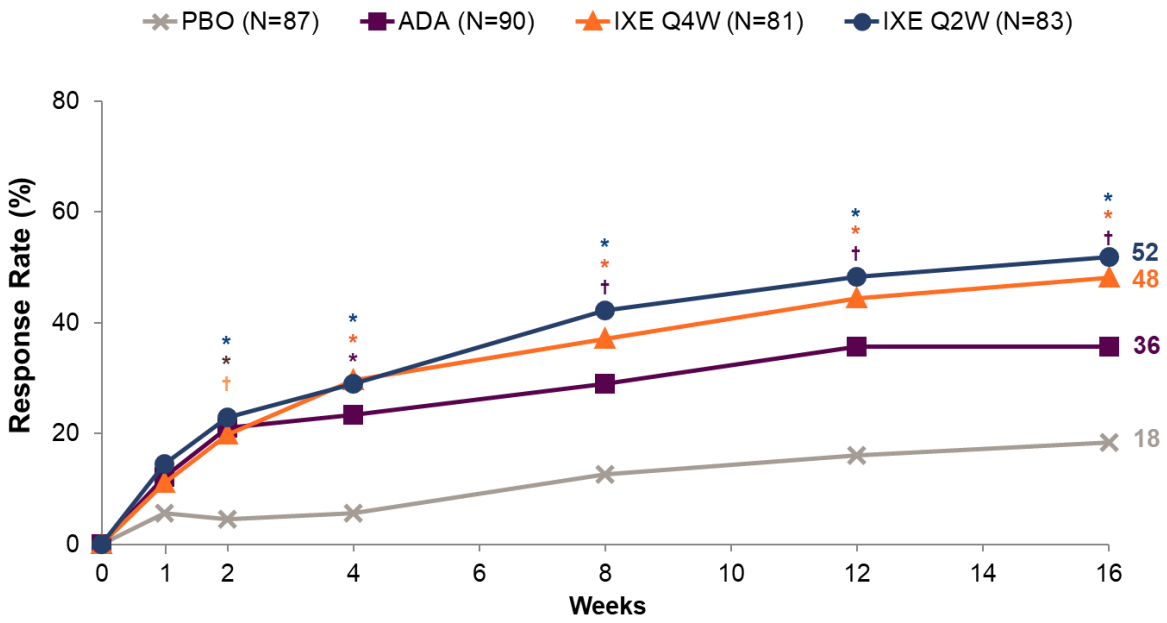
Dosing schedule	Response, n (%)	Difference versus PBO or 80 mg LD, % (95% CI)	p-value
PBO (N=87)	**16 (18.4)**	**-**	**-**
IXE Q4W (N=81)	**39 (48.1)**	**29.8 (16.2; 43.3)**	**<0.0001[a]**
IXE Q4W 80 mg LD ([redacted])	[redacted]	-	-
IXE Q4W 160 mg LD ([redacted])	[redacted]	[redacted]	[redacted]
IXE Q2W (N=83)	**43 (51.8)**	**33.4 (19.9; 46.9)**	**<0.0001[a]**
IXE Q2W 80 mg LD ([redacted])	[redacted]	-	-
IXE Q2W 160 mg LD ([redacted])	[redacted]	[redacted]	[redacted]
ADA Q2W (N=90)	**32 (35.6)**	**17.2 (4.4; 30.0)**	**0.0053[a]**

Notes: Emboldened text represents pooled loading doses. [redacted].

[a] p-value comparing to PBO using logistic regression analysis. [redacted]

Abbreviations: ADA: adalimumab; ASAS: Assessment of SpondyloArthritis International Society; CI: confidence interval; ITT: intention-to-treat; IXE: ixekizumab; LD: loading dose; N: number of patients in the analysis population; n: number of patients in the specified category; PBO: placebo; Q2W: every two weeks; Q4W: every four weeks.
Source: van der Heijde *et al.* 2018[2]; COAST-V CSR: Week 16 Report.[54]

Figure 7: ASAS40 response for the ITT population with non-responder imputation, COAST-V, up to Week 16



Notes: *p-value≤0.001 versus PBO; †p-value<0.01 versus PBO.
Abbreviations: ADA: adalimumab; ASAS: Assessment of SpondyloArthritis International Society; ITT: intention-to-treat; IXE: ixekizumab; N: number of patients in the analysis population; PBO: placebo; Q2W: every two weeks; Q4W: every four weeks.
Source: COAST-V CSR: Week 16 Report (Figure RHBV.14.2)[54]

ASAS40: Week 52

To assess the long-term efficacy of ixekizumab, ASAS40 response was monitored for up to 52 weeks in COAST-V. In patients from the ITT population who received ixekizumab 80 mg Q4W [redacted] or Q2W ([redacted] in the blinded treatment period, response rates [redacted], as displayed in Table 15.[1] These results demonstrate that ixekizumab is clinically effective and beneficial to biologic-naïve rad-axSpA patients on a long-term treatment basis.[1]

Table 15: ASAS40 response in the ITT Population who were initially randomised to ixekizumab, with non-responder imputation, COAST-V, Week 52

Treatment arm	Response, n (%)	95% CI[a]
IXE Q4W ([redacted])	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]

Notes: [redacted]
Abbreviations: ASAS: Assessment of SpondyloArthritis International Society; CI: confidence interval; ITT: intention-to-treat; IXE: ixekizumab; N: number of patients in the analysis population; PBO: placebo; Q2W: every two weeks; Q4W: every four weeks.
Source: COAST-V CSR: Week 52 Report (Table RHBV.14.12)[1]

Secondary endpoints

In addition to the primary efficacy endpoint, a number of secondary endpoints were assessed as part of the COAST-V trial, including measures of disease activity, functional capacity, structural progression, pain and HRQoL.[2]

Disease activity (BASDAI)

In the ITT population, BASDAI50 response rates were statistically significantly greater in both the ixekizumab Q4W (42.0%; p=0.0003) and Q2W (43.4%; p=0.0002) treatment arms compared to placebo (17.2%) at Week 16, as shown in Table 16.[2] The proportion of patients achieving a BASDAI50 response was also significantly higher in the adalimumab arm (32.2%; p=0.0119) compared to placebo, however, the response rate was numerically lower than both ixekizumab arms (Table 16).[2] There were [redacted] in BASDAI50 response at Week 16 between the 80 mg and 160 mg loading doses in the ixekizumab Q4W ([redacted]) and Q2W ([redacted]) arms, as shown in Appendix L.[53]

The significant difference in BASDAI50 response versus placebo was observed from as early as [redacted] in the ixekizumab Q4W arm (p=[redacted]) and [redacted] in the Q2W arm (p=[redacted]). BASDAI50 response rates from Week 0 to Week 16 are shown in Figure 8.[54]

In addition, a [redacted] cfb in overall BASDAI score was observed in the ixekizumab Q4W arm ([redacted]), ixekizumab Q2W arm ([redacted]) and adalimumab arm ([redacted]) versus placebo ([redacted]) at Week 16, as shown in Table 17.[54] There was [redacted] in BASDAI cfb between the 160 mg and 80 mg LD groups in the ixekizumab Q4W ([redacted]) and Q2W ([redacted]) arms at Week 16, as shown in Appendix L.[53]

In the ITT population, the cfb in BASDAI was significantly greater than placebo by [redacted] in the ixekizumab Q4W ([redacted]), ixekizumab Q2W ([redacted]) and adalimumab arms ([redacted]).[54]

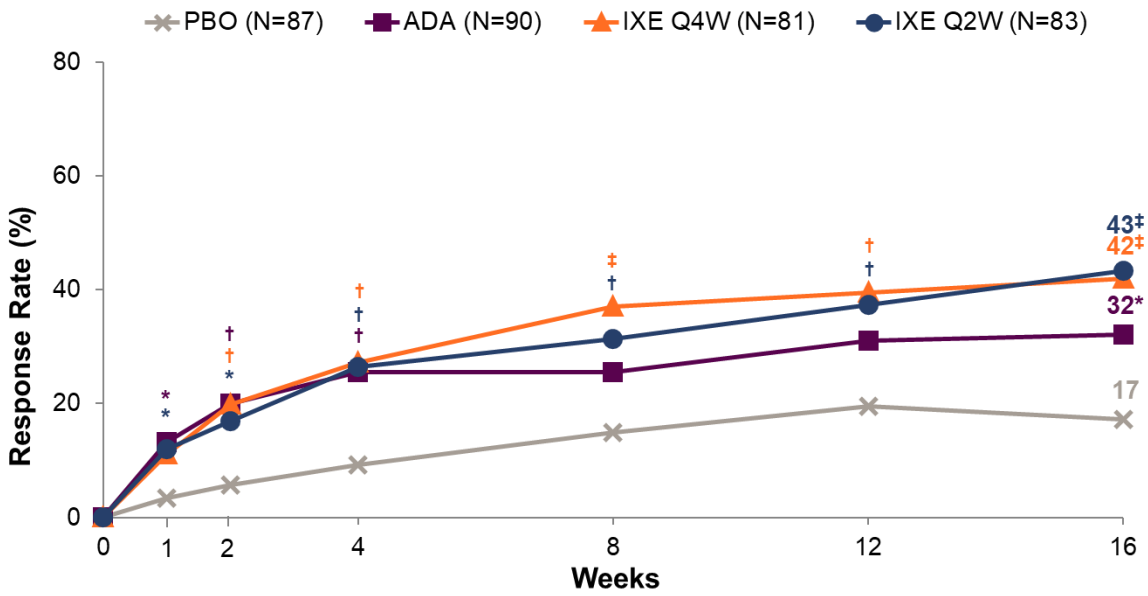
Overall, with ixekizumab Q4W, 42% of patients reported a ≥50% improvement across five major symptoms of axSpA, as measured by their BASDAI score, at Week 16. The mean reduction in the BASDAI score at Week 16 was [redacted] in this arm, representing a reduction in symptomatic burden for patients.[54]

Table 16: BASDAI50 response in the ITT population, with non-responder imputation, COAST-V, Week 16

Treatment arm	Response, n (%)	Difference versus PBO, % (95% CI)	p-value
PBO (N=87)	15 (17)	-	-
IXE Q4W (N=81)	34 (42)	24.7 (11.4; 38.1)	0.0003
IXE Q2W (N=83)	36 (43)	26.1 (12.8; 39.4)	0.0002
ADA Q2W (N=90)	29 (32)	15.0 (2.5; 27.5)	0.0119

Notes: Analysis by logistic regression with non-responder imputation for missing values, with treatment, geographic region and baseline CRP status as factors
Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; ITT: intention-to-treat; IXE: ixekizumab; N: number of patients in the analysis population; n: number of patients in the specified category; PBO: placebo; Q2W: every two weeks; Q4W: every four weeks.
Source: van der Heijde et al 2018[2]

Figure 8: BASDAI50 response rates at each post-baseline visit in the ITT population, with non-responder imputation, COAST-V, up to Week 16



Notes: *p-value≤0.001 versus PBO; †p-value<0.01 versus PBO.
Abbreviations: ADA: adalimumab; ASAS: Assessment of SpondyloArthritis International Society; ITT: intention-to-treat; IXE: ixekizumab; N: number of patients in the analysis population; PBO: placebo; Q2W: every two weeks; Q4W: every four weeks.
Source: COAST-V CSR: Week 16 Report (Figure RHBV.14.2).[54]

Table 17: BASDAI least squares mean change from baseline in the ITT population, MMRM, COAST-V, Week 16

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p−value
PBO (N=87)	[redacted]	–	–
IXE Q4W (N=81)	[redacted]	[redacted]	[redacted]
IXE Q2W (N=83)	[redacted]	[redacted]	[redacted]
ADA Q2W (N=90)	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CI: confidence interval; ITT: intention-to-treat; IXE: ixekizumab; LSM: least squares mean; MMRM: mixed models repeated measure analysis; N: number of patients in the analysis population; n: number of patients in the specified category; PBO: placebo; Q2W: every two weeks; Q4W: every four weeks; SE: standard error.
Source: COAST-V CSR: Week 16 Report (Table RHBV.14.32)[54]

The BASDAI50 response rate and cfb in BASDAI were monitored for up to 52 weeks in COAST-V. In the ITT population who were originally randomised to receive ixekizumab, BASDAI50 response rates were [redacted] in the ixekizumab Q4W [redacted] and Q2W [redacted] arms, as displayed in Table 18.[1]

The cfb in BASDAI was also [redacted] between [redacted] and [redacted] in the ITT population who were originally randomised to receive ixekizumab Q4W [redacted]) or Q2W [redacted], as shown in Table 19.[1] Therefore, ixekizumab treatment led to [redacted] in disease activity in biologic-naïve rad-axSpA patients over 52 weeks.

Table 18: BASDAI50 response in the ITT Population who were originally randomised to ixekizumab, with non-responder imputation, COAST-V, Week 52

Treatment arm	Response, n (%)	95% CI
IXE Q4W ([redacted])	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]

[redacted]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; ITT: intention-to-treat; IXE: ixekizumab; N: number of patients in the analysis population; n: number of patients in the specified category; Q2W: every two weeks; Q4W: every four weeks.
Source: COAST-V CSR: Week 52 Report (Table RHBV.14.16)[1]

Table 19: BASDAI mean change from baseline, in the ITT Population who were originally randomised to receive ixekizumab, mBOCF, COAST-V, Week 16 and Week 52

Treatment arm	Week 16	Week 52
	Cfb, mean (SD)	
IXE Q4W ([redacted])	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]

[redacted]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; ITT: intention-to-treat; IXE: ixekizumab; mBOCF: modified baseline observation carried forward; N: number of patients in the analysis population; Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation.
Source: COAST-V CSR: Week 52 Report (Table RHBV.14.15)[1]

Disease activity (ASDAS <2.1)

ASDAS is a composite index used to assess disease activity in axSpA (see Section B.2.3.2). In the ITT population, the number of patients who were defined as having low disease activity based on the clinically relevant definition of ASDAS <2.1 was significantly higher in the ixekizumab Q4W arm (43.2%, p<0.0001), Q2W arm (42.2%; p<0.0001) and adalimumab arm (37.8%; p=0.0002), compared to the placebo (12.6%) at Week 16, as displayed in Table 20.

The proportion of patients achieving ASDAS <2.1 was numerically improved at Week 52 in both the ixekizumab Q4W ([redacted]) and Q2W ([redacted]) arms, as shown in Table 21.[1]

Table 20: Proportion of patients achieving ASDAS <2.1 in the ITT population, with non-responder imputation, COAST-V, Week 16

Treatment arm	Response, n (%)	Difference versus PBO, % (95% CI)	p-value
PBO (N=87)	11 (12.6)	-	-
IXE Q4W (N=81)	35 (43.2)	30.6 (17.7; 43.4)	<0.0001
IXE Q2W (N=83)	35 (42.2)	29.5 (16.8; 42.2)	<0.0001
ADA Q2W (N=90)	34 (37.8)	25.1 (12.9; 37.3)	0.0002

Notes: Analysis by logistic regression with non-responder imputation for missing values, with treatment, geographic region and baseline CRP status as factors
Abbreviations: ADA: adalimumab; ASDAS: Ankylosing Spondylitis Disease Activity Score; CI: confidence interval; ITT: intention-to-treat; IXE: ixekizumab; N: number of patients in the analysis population; n: number of patients in the analysis population; PBO: placebo; Q2W: every two weeks; Q4W: every four weeks.
Source: van der Heijde et al 2018; COAST-V CSR: Week 16 Report (Table RHBV.14.41)[2, 54]

Table 21: Proportion of patients achieving ASDAS <2.1 in the ITT population who were initially randomised to ixekizumab, with non-responder imputation, COAST-V, Week 52

Treatment arm	Response, n (%)	95% CI
IXE Q4W ([redacted])	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]

Notes: [redacted]
Abbreviations: ASDAS: Ankylosing Spondylitis Disease Activity Score; CI: confidence interval; ITT: intention-to-treat; IXE: ixekizumab; N: number of patients in the analysis population; n: number of patients in the analysis population; Q2W: every two weeks; Q4W: every four weeks.
Source: COAST-V CSR: Week 52 Report (Table RHBV.14.19)[1]

Functional capacity (BASFI)

At Week 16, in the ITT population, improvements from baseline in BASFI were statistically significantly greater in the ixekizumab Q4W (−2.39; p<0.0001), ixekizumab Q2W (−2.43; p<0.0001), and adalimumab (−2.14; p=0.0012) treatment arms compared to placebo (−1.16). There were no significant differences between the ixekizumab LDs in either the ixekizumab Q4W (p=[redacted]) or Q2W (p=[redacted]) arms at Week 16.[54] BASFI least squares mean cfb at Week 16 is shown in Table 22.

The cfb in BASFI score was significantly higher compared to placebo from [redacted] in the ixekizumab Q4W ([redacted]), ixekizumab Q2W ([redacted]) and adalimumab ([redacted]) treatment arms.[54] The change in BASFI scores from Week 0 to 16 is summarised in Figure 9. There were no significant differences in BASFI cfb between the 80 mg and 160 mg LDs in the ixekizumab Q4W ([redacted]) and Q2W ([redacted]) arms, as shown in Appendix L.[53]

Treatment with ixekizumab, therefore, resulted in a significantly improved functional ability for patients from as early as [redacted], which was maintained for 16 weeks.[2, 54]

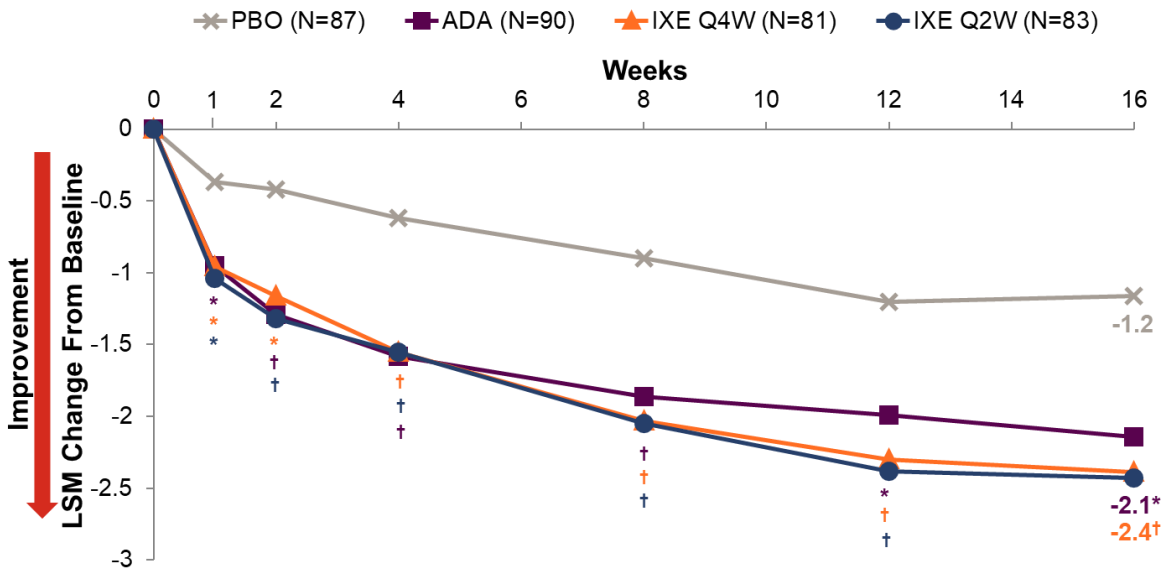
Table 22: BASFI least squares mean change from baseline in the ITT population, MMRM, COAST-V, Week 16

Treatment arm	Cfb, LSM (SE)	Difference versus PBO or 80 mg LD, (95% CI)	p-value
PBO (N=87)	−1.16 (0.22)	-	-

IXE Q4W (N=81)	−2.39 (0.22)	−1.22 (−1.83; −0.62)	0.0001
IXE Q2W (N=83)	−2.43 (0.22)	−1.27 (−1.86; −0.67)	0.0001
ADA Q2W (N=90)	−2.14 (0.21)	−0.97 (−1.56; −0.39)	0.0012

Notes: [redacted]
Logistic regression analysis with treatment, geographic region, and baseline CRP status in the model.
Abbreviations: ADA: adalimumab; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CI: confidence interval; ITT: intent-to-treat; IXE: ixekizumab; LSM: least squares mean; MMRM: mixed models repeated measure analysis; N: number of patients in the analysis population; PBO: placebo; Q2W: every two weeks; Q4W: every four weeks; SE: standard error.
Source: van der Heijde *et al.* 2018;[2] COAST-V CSR: Week 16 Report (Table RHBV.14.28)[2, 54]

Figure 9: BASFI score least squares mean change from baseline in the ITT population, MMRM analysis, COAST-V, up to Week 16



Notes: *p-value<0.01 versus PBO; †p-value<0.001 versus PBO.
Abbreviations: ADA: adalimumab; BASFI: Bath Ankylosing Spondylitis Functional Index; CI: confidence interval; ITT: intent-to-treat; IXE: ixekizumab; LD: loading dose; LSM: least squares mean; MMRM: mixed models repeated measure analysis; N: number of patients in the analysis population; PBO: placebo; Q2W: every two weeks; Q4W: every four weeks; SE: standard error.
Source: COAST-V CSR: Week 16 Report (Figure RHBV.14.3).[54]

BASFI scores were measured up to Week 52 in COAST-V. In the ITT population who were initially randomised to receive ixekizumab, BASFI mean cfb was [redacted] at Week 52 compared to Week 16 in the ixekizumab Q4W [redacted] and Q2W arms [redacted], as displayed in Table 23.[1]

Table 23: BASFI scores mean change from baseline, in the ITT Population who were originally randomised to ixekizumab, mBOCF, COAST-V, Week 16 and Week 52

Treatment arm	Week 16	Week 52
	Cfb, mean (SD)	
IXE Q4W ([redacted])	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]

[redacted].

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; ITT: intent-to-treat; IXE: ixekizumab; mBOCF: modified baseline observation carried forward; N: number of patients in the analysis population; Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation.
Source: COAST-V CSR: Week 52 Report (Table RHBV.14.13)[1]

Inflammation at the spine and sacroiliac joint

Inflammation at the spine and sacroiliac joint, as measured using the SPARCC MRI score, was recorded at baseline, Week 16 and Week 52 in the COAST-V. The cfb in SPARCC score of the spine in the ITT population was significantly higher in the ixekizumab Q4W arm (−11.02; p<0.0001), ixekizumab Q2W arm (−9.58; p<0.0001) and adalimumab arm (−11.57; p<0.0001) compared to placebo (−1.51), as shown in Table 24.[2]

The least squares mean change from baseline in SPARCC score of the sacroiliac joint was also significantly higher in the ixekizumab Q4W arm (−3.97; p<0.0001), ixekizumab Q2W arm (−4.25; p<0.0001) and adalimumab arm (−4.21; p<0.0001) compared to placebo, for which the score increased from baseline (0.92), as shown in Table 24.[2]

The mean reductions from baseline in SPARCC MRI scores of the spine using modified baseline observation carried forward (mBOCF) analysis in patients in the ITT population who were initially randomised to receive ixekizumab were [redacted], as displayed in Table 25.[1]

Active treatment, including both ixekizumab arms, therefore resulted in a reduction in inflammation at the sacroiliac joint and spine in biologic naïve rad-axSpA patients at Week 16 and Week 52, as summarised in Table 24 and Table 25.[1, 2]

Table 24: SPARCC MRI scores for the spine and sacroiliac joint, observed case analysis (ANCOVA), ITT population, COAST-V, Week 16

Treatment arm	SPARCC spine score			SPARCC sacroiliac joint score		
	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p-value	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p-value
PBO (n=87)	−1.51 (1.15)	-	-	0.92 (0.58)	-	-
IXE Q4W (n=81)	−11.02 (1.16)	−9.51 (−12.6; 6.4)	<0.0001	−3.97 (0.59)	−4.89 (−6.5; −3.3)	<0.0001
IXE Q2W (n=83)	−9.58 (1.17)	−8.08 (−11.2; 4.9)	<0.0001	−4.25 (0.59)	−5.17 (−6.8; −3.6)	<0.0001
ADA Q2W (n=90)	−11.57 (1.11)	−10.07 (−13.2; 6.9)	<0.0001	−4.21 (0.57)	−5.13 (−6.7; −3.5)	<0.0001

Notes: Analysis using ANCOVA on the basis of observed cases
Abbreviations: ADA Q2W: adalimumab every 2 weeks; cfb: change from baseline; CI: confidence interval; IXEQ2W: ixekizumab every 2 weeks; IXEQ4W: ixekizumab every 4 weeks; LSM: least squares mean; N: number of patients in the analysis population; PBO: placebo; SE: standard error; SPARCC: Spondyloarthritis Research Consortium of Canada.
Source: van der Heijde *et al.* 2018[2]

Table 25: SPARCC MRI scores for the spine and sacroiliac joint mean change from baseline, in the ITT Population who were originally randomised to ixekizumab, mBOCF, COAST-V, Week 16 and Week 52

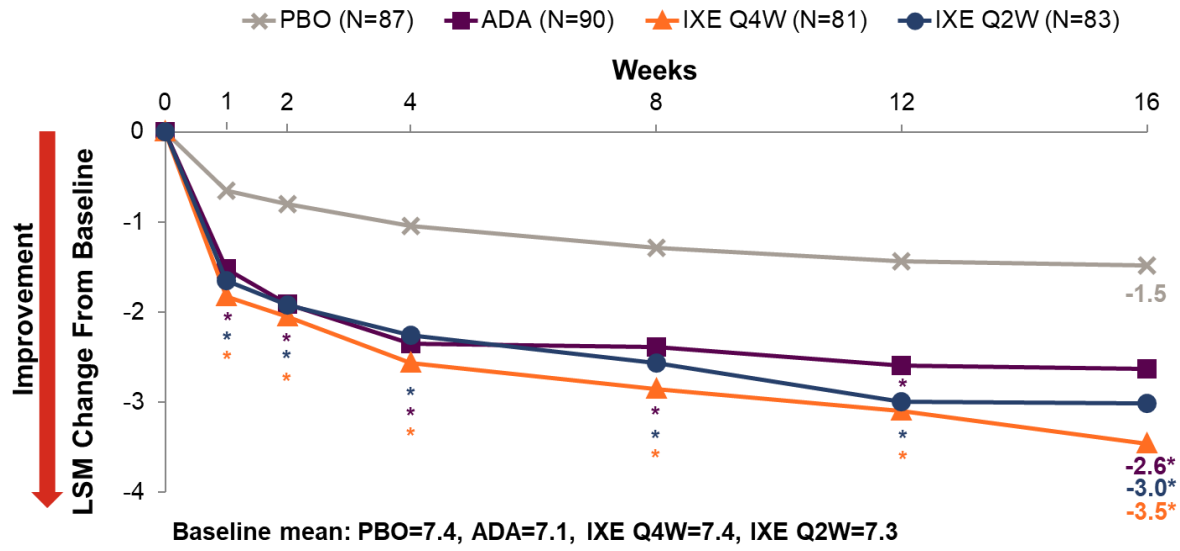
Treatment arm	SPARCC spine score		SPARCC sacroiliac joint score	
	Week 16	Week 52	Week 16	Week 52
	Cfb, mean (SD)			
IXE Q4W ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

Abbreviations: cfb: change from baseline; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; N: number of patients in the analysis population; mBOCF: modified baseline observation carried forward; PBO: placebo; SD: standard deviation; SPARCC: Spondyloarthritis Research Consortium of Canada.
Source: COAST-V CSR: Week 52 Report (Table RHBV.14.20).[1]

Spinal pain (NRS)

The mean reduction in spinal pain from baseline was [redacted] at Week 16 in patients treated with ixekizumab Q4W ([redacted]), ixekizumab Q2W [redacted]) and adalimumab [redacted] compared to placebo [redacted]) in the ITT population, as shown in Figure 10.[54] A reduction in spinal pain score of ≥2 is considered clinically relevant, and forms part of the criteria for continuation of biological therapies in NICE guidance.[71] In the ITT population who were initially randomised to receive ixekizumab, spinal pain (BASDAI Q2) mean cfb was numerically greater at Week 52 compared to Week 16 in the ixekizumab Q4W [redacted] and Q2W arms [redacted].[53]

Figure 10: Least squares mean spinal pain (BASDAI Question 2) change from baseline, ITT population, MMRM, COAST-V, Week 16



[redacted]

Abbreviations: ADA: adalimumab; cfb: change from baseline; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; MMRM: mixed models repeated measure analysis; PBO: placebo.
Source: Eli Lilly and Company. Data on file (2019).[53]

Health-related quality of life (SF-36 PCS)

Changes in SF-36 PCS scores from baseline to Week 16 were significantly greater in the ixekizumab Q4W (7.7; p=0.0002), ixekizumab Q2W (7.97; p<0.0001) and adalimumab arms (6.9; p=0.002) compared to placebo (3.64) in the ITT population, as shown in Table 26.[2]

Table 26: Change from baseline in SF-36 PCS scores, ITT population, MMRM, COAST-V, Week 16

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p-value
PBO (N=87)	3.64 (0.75)	-	-
IXE Q4W (N=81)	7.70 (0.78)	4.05 (1.94; 6.16)	0.0002
IXE Q2W (N=83)	7.97 (0.77)	4.33(2.23; 6.42)	<0.0001
ADA Q2W (N=90)	6.90 (0.73)	3.26 (1.20; 5.31)	0.0020

[redacted]

Abbreviations: ADA Q2W: adalimumab every 2 weeks; cfb: change from baseline; CI: confidence interval; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; N: number of patients in the analysis population; MMRM: mixed models repeated measure analysis; PBO: placebo; PCS: physical component summary; SF-36: short form-36.
Source: van der Heijde *et al.* 2018[2]

Improvements from baseline in SF-36 PCS scores, were [redacted] at [redacted] compared to [redacted] in the ITT population who were initially randomised to receive ixekizumab Q4W [redacted] and Q2W [redacted] demonstrating that HRQoL improvements, as measured by the SF-36 PCS, were [redacted] in biologic-naïve rad-axSpA patients treated with ixekizumab (Table 27).[1]

Table 27: SF-36 scores mean change from baseline, in the ITT Population who were originally randomised to ixekizumab, mBOCF, COAST-V, Week 52

Treatment arm	Week 16	Week 52
	Cfb, mean (SD)	
IXE Q4W ([redacted])	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]

[redacted]

Abbreviations: cfb: change from baseline; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; N: number of patients in the analysis population; mBOCF: modified baseline observation carried forward; PBO: placebo; PCS: physical component summary; SF-36: short form-36
Source: COAST-V CSR: Week 52 Report (Table RHBV.14.22).[1]

B.2.6.2 COAST-W

Primary endpoint: ASAS40 at Week 16

The primary efficacy endpoint in COAST-W was the proportion of patients achieving an ASAS40 response at Week 16.[3] The primary endpoint of COAST-W was met; in the ITT population, a statistically significantly greater proportion of patients achieved an ASAS40 response at Week 16 in both the ixekizumab Q4W (25.4%; p=0.017) and Q2W arms (30.6%; p=0.003) compared to placebo (12.5%), as shown in Table 28.[3, 55] There was no significant difference between the two LDs of ixekizumab in either the Q4W ([redacted]) or Q2W ([redacted]) treatment arms, as presented in Table 28, however, the 160 mg loading dose resulted in a faster onset and a numerically greater response rate.[55]

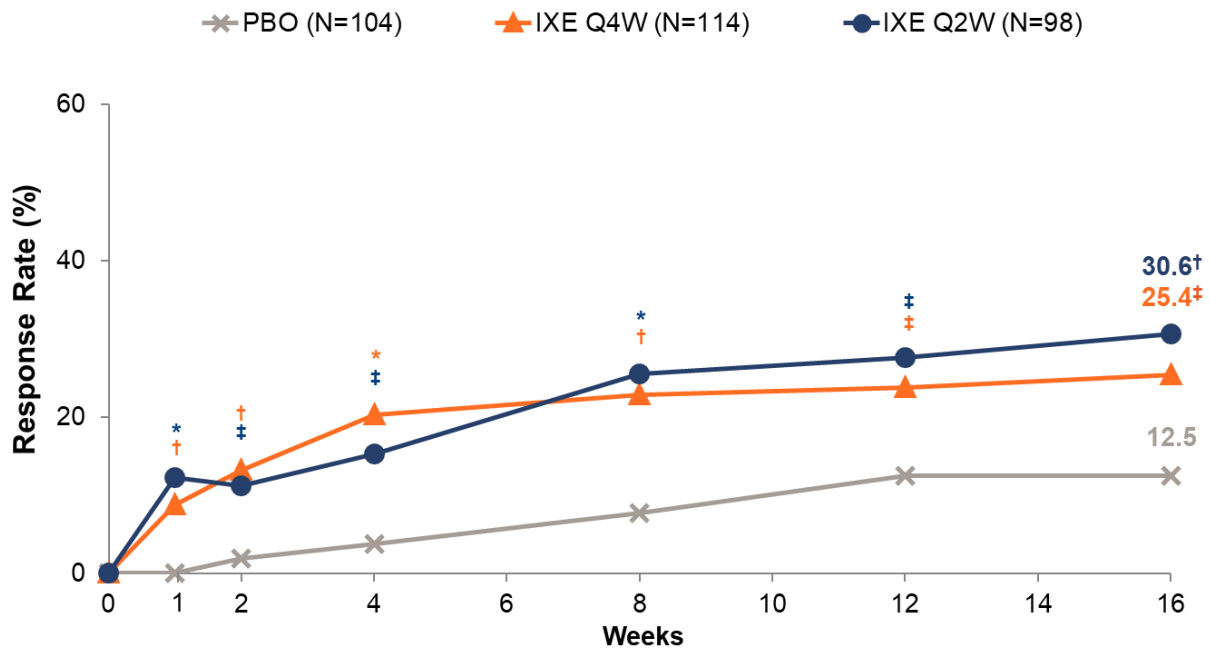
In the ITT population, a significantly higher proportion of patients achieved an ASAS40 response from as early as [redacted] in the ixekizumab Q4W arm (p=[redacted]) and ixekizumab Q2W arm (p≤[redacted]) compared to placebo [redacted].[3, 55] The proportion of patients achieving an ASAS40 response from Week 1 to Week 16 in the ITT population is summarised in Figure 10.[55] ASAS40 is a stringent measure of disease severity and it has been shown that patients who achieve an ASAS40 response report greater improvements in a number of patient reported outcomes compared to those who achieve only an ASAS20 response.[56]

Table 28: ASAS40 response by dose for the ITT population with non-responder imputation, COAST-W, Week 16

Dosing schedule	Response, n (%)	Difference versus PBO or 80 mg LD (95% CI)	p-value
PBO (N=104)	**13 (12.5)**	-	-
IXE Q4W (N=114)	**29 (25.4)**	**12.9 (2.7; 23.2)**	**0.017[a]**
IXE Q4W 80 mg LD ([redacted])	[redacted]	-	
IXE Q4W 160 mg LD ([redacted])	[redacted]	[redacted]	[redacted][b]
IXE Q2W (N=98)	**30 (30.6)**	**18.1 (7.0; 29.2)**	**0.003[a]**
IXE Q2W 80 mg LD ([redacted])	[redacted]	-	
IXE Q2W 160 mg LD ([redacted])	[redacted]	[redacted]	[redacted][b]

Notes: Emboldened text represents pooled LDs.
[a]p-value comparing to placebo. [redacted]
[b]p-value comparing 160 mg and 80 mg LD. [redacted]
Abbreviations: CI: confidence interval; IXE Q4W; ixekizumab every 4 weeks; IXE Q2W: ixekizumab every 2 weeks; LD: loading dose; N: number of patients in the analysis population; n: number of patients in the specified category; PBO: placebo.
Source: Deodhar *et al.* 2019; COAST-W CSR: Week 16 Report (Table RHBW.14.66).[3 55]

Figure 11: ASAS40 response for the ITT population with non-responder imputation, COAST-W, up to Week 16



Notes: *p-value ≤0.001 versus PBO; †p-value <0.01 versus PBO; ‡p-value <0.05 versus PBO.
Abbreviations: IXE Q2W: ixekizumab every two weeks; IXE Q4W: ixekizumab every four weeks; N: number of patients in the analysis population; PBO: placebo
Source: COAST-W CSR: Week 16 Report (Figure RHBW.14.2).[55]

ASAS40: Week 52

To assess the long-term efficacy of ixekizumab, ASAS40 response was monitored for up to 52 weeks in COAST-W. Response rates were [redacted] at Week 52 in the ITT population who were initially randomised to receive ixekizumab Q4W [redacted] or Q2W [redacted], as displayed in Table 29. These results demonstrate that ixekizumab is clinically effective and beneficial to biologic-experienced rad-axSpA patients on a long-term treatment basis.[4]

Table 29: ASAS40 response in the ITT Population who were initially randomised to ixekizumab, with non-responder imputation, COAST-V, Week 52

Treatment arm	Response, n (%)	95% CI[a]
IXE Q4W ([redacted])	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]

Notes: [redacted]

Abbreviations: ASAS: Assessment of SpondyloArthritis International Society; CI: confidence interval; ITT: intent-to-treat; IXE Q4W; ixekizumab every 4 weeks; IXE Q2W: ixekizumab every 2 weeks; N: number of patients in the analysis population; n: number of patients in the specified category.
Source: COAST-W CSR: Week 52 Report (Table RHBW.14.12).[4]

Secondary endpoints

In addition to the primary efficacy endpoint, a number of secondary endpoints were assessed as part of the COAST-W trial.

Disease activity (BASDAI)

In the ITT population, the proportion of patients achieving a BASDAI50 response at Week 16 was [redacted] in the ixekizumab Q4W ([redacted]) and Q2W arms ([redacted]) compared to placebo ([redacted], as presented in Table 30. BASDAI50 response was [redacted] in the ixekizumab Q4W arm from [redacted], and from [redacted] in the ixekizumab Q2W arm [redacted]).[55] There was no significant difference in BASDAI50 response rate between the 160 mg and 80 mg LD groups in the ixekizumab Q4W ([redacted]) and Q2W ([redacted]) arms, as displayed in Appendix L.[53]

BASDAI least squares mean cfb at Week 16 was also statistically significantly greater in the ixekizumab Q4W [redacted]) and Q2W arms [redacted]), compared to placebo ([redacted]), as shown in Table 31. BASDAI cfb was significantly improved compared to placebo from [redacted].[55] There was no significant difference in BASDAI cfb between the 160 mg and 80 mg LD groups in the ixekizumab Q4W ([redacted]) and Q2W ([redacted]) arms, as displayed in Appendix L.[53]

BASDAI cfb for the ITT population from Week 0 to Week 16 is summarised in Figure 12.[55]

Table 30: BASDAI50 response in the ITT population, with non-responder imputation, COAST-W, Week 16

Treatment arm	Response, n (%)	Difference versus PBO (95% CI)	p-value
PBO (N=104)	[redacted]	[redacted]	[redacted]
IXE Q4W (N=114)	[redacted]	[redacted]	[redacted]
IXE Q2W (N=98)	[redacted]	[redacted]	[redacted]

Notes: [redacted]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; N: number of patients in the analysis population; n: number of patients in the specified category; PBO: placebo.
Source: COAST-W CSR: Week 16 Report (Table RHBW.14.34).[55]

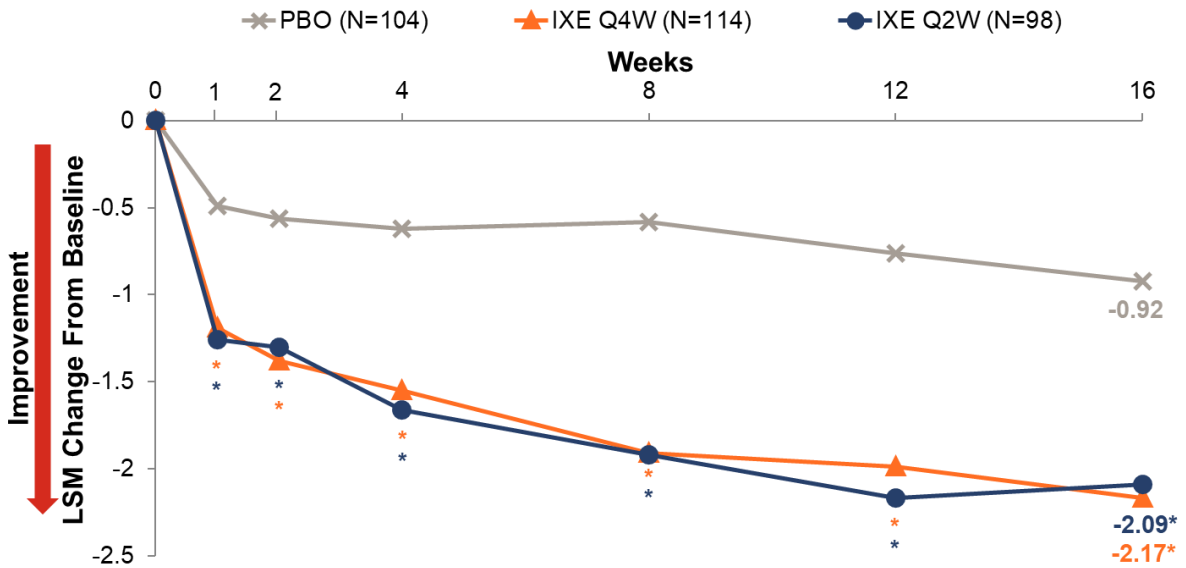
Table 31: BASDAI least squares mean change from baseline in the ITT population, MMRM, COAST-W, Week 16

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p-value
PBO (N=104)	[redacted]	-	-
IXE Q4W (N=114)	[redacted]	[redacted]	[redacted]
IXE Q2W (N=98)	[redacted]	[redacted]	[redacted]

Notes: [redacted]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; MMRM: mixed models repeated measure analysis; N: number of patients in the analysis population; PBO: placebo; SE: standard error.
Source: COAST-W CSR: Week 16 Report (Table RHBW.14.32).[55]

Figure 12: BASDAI score least squares mean change from baseline in the ITT population, MMRM analysis, COAST-W, up to Week 16



Notes: *p-value<0.01 versus PBO.
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ITT: intent-to-treat; IXE Q2W: ixekizumab every two weeks; IXE Q4W: ixekizumab every four weeks; LSM: least squares mean; MMRM: mixed models repeated measure analysis; N: number of patients in the analysis population; PBO: placebo
Source: COAST-W CSR: Week 16 Report (Figure RHBW.14.4).[55]

In the ITT population who were originally randomised to receive ixekizumab, BASDAI50 response rates were [redacted] at Week 52 in the ixekizumab Q4W [redacted] and Q2W [redacted] arms compared to Week 16, as displayed in Table 32.

The cfb in BASDAI was also [redacted] at Week 52 compared to Week 16, in the ITT population who were originally randomised to receive ixekizumab Q4W [redacted] and Q2W [redacted]), as shown in Table 33. Therefore, ixekizumab treatment led to maintained improvements in disease activity in biologic-experienced rad-axSpA patients over 52 weeks.

Table 32: BASDAI50 response in the ITT population who were originally randomised to ixekizumab, with non-responder imputation, COAST-W, Week 52

Treatment arm	Response, n (%)	95% CI[a]
IXE Q4W ([redacted])	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]

Notes: [redacted].
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; IXE Q4W; ixekizumab every 4 weeks; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; N: number of patients in the analysis population; n: number of patients in the specified category.
Source: COAST-W CSR: Week 52 Report (Table RHBW.14.16).[4]

Table 33: BASDAI score mean change from baseline in the ITT population who were originally randomised to ixekizumab, mBOCF, COAST-W, Week 16 and Week 52

Treatment arm	Week 16	Week 52
	Cfb, mean (SD)	
IXE Q4W ([redacted])	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]

[redacted]
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; ITT: intent-to-treat; IXE Q4W; ixekizumab every 4 weeks; IXE Q2W: ixekizumab every 2 weeks; mBOCF: modified baseline observation carried forward; N: number of patients in the analysis population; SD: standard deviation.
Source: COAST-W CSR: Week 52 Report (Table RHBW.14.15).[4]

Disease activity (ASDAS <2.1)

In the ITT population, at Week 16, the number of patients who were defined as having low disease activity based on the clinically relevant definition of ASDAS <2.1 was significantly higher in the ixekizumab Q4W ([redacted]) and Q2W arms ([redacted]) compared to placebo ([redacted]), as displayed in Table 34.

Table 34: Proportion of patients achieving ASDAS <2.1 in the ITT population, with non-responder imputation, COAST-W, Week 16

Treatment arm	Response, n (%)	Difference versus PBO (95% CI)	p-value
PBO (N=104)	[redacted]	-	-
IXE Q4W (N=114)	[redacted]	12.7 (4.6; 20.8)	[redacted]
IXE Q2W (N=98)	[redacted]	11.5 (3.1; 19.9)	[redacted]

Notes: Analysis by logistic regression with non-responder imputation for missing values, analysis with treatment, geographic region, baseline CRP status, and number of prior TNF-alpha inhibitors as factors.
Abbreviations: ASDAS: Ankylosing Spondylitis Disease Activity Score; IXE Q4W; ixekizumab every 4 weeks; IXE Q2W: ixekizumab every 2 weeks; N: number of patients in the analysis population; n: number of patients in the specified category; SD: standard deviation.
Source: Deodhar *et al.* 2019; COAST-W CSR: Week 16 Report (Table RHBW.14.41).[55]

In the ITT population who were initially randomised to receive ixekizumab, at Week 52, the percentage of patients with ASDAS scores <2.1 was [redacted] compared to Week 16 values in the ITT population in the ixekizumab Q4W ([redacted]) and Q2W arms ([redacted]), as presented in Table 35. These results demonstrate that treatment with ixekizumab resulted in low disease activity for [redacted] of biologic-experienced rad-axSpA patients at Week 52 of treatment.[4]

Table 35: Proportion of patients achieving ASDAS <2.1 in the ITT population who were initially randomised to ixekizumab, with non-responder imputation, COAST-W, Week 52

Treatment arm	Response, n (%)	95% CI[a]
IXE Q4W ([redacted])	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]

Notes: [redacted]
Abbreviations: ASDAS: Ankylosing Spondylitis Disease Activity Score; ITT: intent-to-treat; IXE Q4W; ixekizumab every 4 weeks; IXE Q2W: ixekizumab every 2 weeks; N: number of patients in the analysis population; n: number of patients in the specified category; SD: standard deviation.
Source: COAST-W CSR: Week 52 Report (Table RHBW.14.19).[4]

Functional capacity (BASFI)

In the ITT population at Week 16, BASFI score least squares mean cfb was [redacted] in the ixekizumab Q4W ([redacted]) and Q2W arms ([redacted]) compared to placebo ([redacted]), as shown in Table 36.[55] [redacted] was seen from [redacted] in the ixekizumab Q4W (p[redacted]) and Q2W arms (p[redacted]). There was no significant difference in BASFI cfb between the 160 mg and

80 mg LD groups in the ixekizumab Q4W ([redacted]) and Q2W ([redacted]) arms (Appendix L).[53,55] The cfb in BASFI score from Week 0 to 16 is summarised in Figure 13.

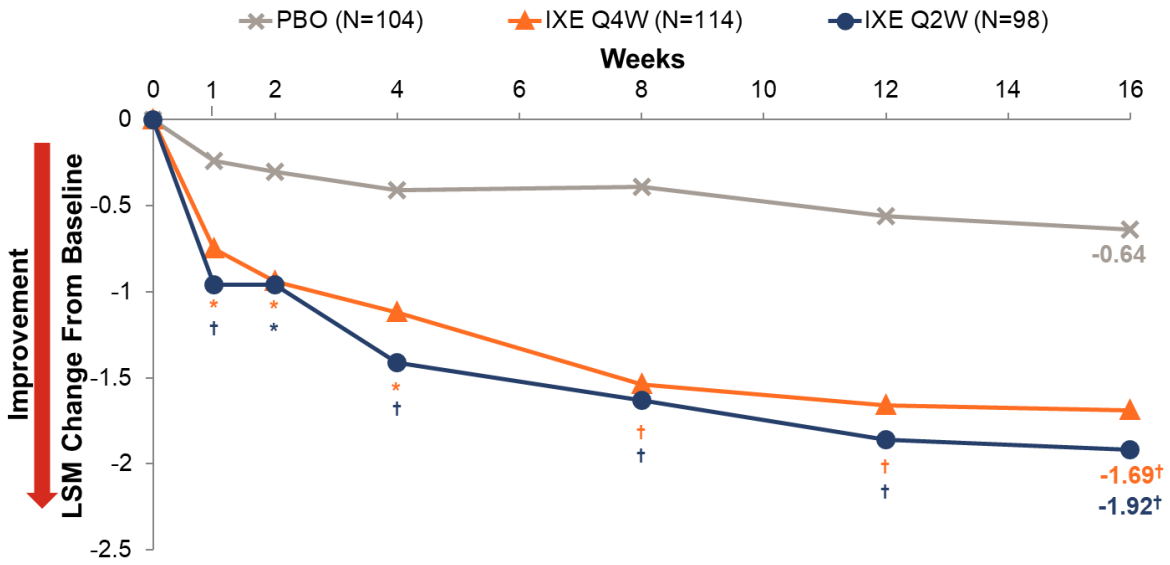
Table 36: BASFI least squares mean change from baseline in the ITT population, MMRM, COAST-W, Week 16

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p−value
PBO (N=104)	[redacted]	-	-
IXE Q4W (N=114)	[redacted]	[redacted]	[redacted]
IXE Q2W (N=98)	[redacted]	[redacted]	[redacted]

Notes: [redacted]

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; MMRM: mixed models repeated measure analysis; N: number of patients in the analysis population; PBO: placebo; SE: standard error.
Source: COAST-W CSR: Week 16 Report (Table RHBW.14.28).[55]

Figure 13: BASFI score least squares mean change from baseline in the ITT population, MMRM analysis, COAST-W, up to Week 16



Notes: *p-value <0.01 versus PBO; †p-value<0.001 versus PBO.
Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; IXE Q2W: Ixekizumab 80 mg every two weeks; IXE Q4W: Ixekizumab 80 mg every four weeks; LSM: least squares mean; PBO: placebo.
Source: COAST-W CSR: Week 16 Report (Figure RHBW.14.3). [55]

At Week 52, in the ITT population who were initially randomised to receive ixekizumab, mean BASFI cfb was [redacted] compared to Week 16 in the ixekizumab Q4W ([redacted]) and Q2W arms ([redacted]), as displayed in Table 37.[4]

Table 37: BASFI scores mean change from baseline, in the ITT Population who were originally randomised to ixekizumab, mBOCF, COAST-W, Week 16 and Week 52

Treatment arm	Week 16	Week 52
	Cfb, mean (SD)	
IXE Q4W ([redacted])	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]

[redacted]

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; ITT: intent-to-treat; IXE Q4W; ixekizumab every 4 weeks; IXE Q2W: ixekizumab every 2 weeks; mBOCF: modified baseline observation carried forward; N: number of patients in the analysis population; SD: standard deviation.
Source: COAST-W CSR: Week 52 Report (Table RHBW.14.13).[4]

Inflammation at the spine

Inflammation at the spine was measured using cfb in SPARCC MRI score for the spine. [redacted]. At Week 16, the least squares mean cfb in SPARCC score was significantly higher in the ixekizumab Q4W ([redacted]) and Q2W arms ([redacted]) compared to placebo ([redacted]), as shown in Table 38[55] Therefore, ixekizumab resulted in improvements in spinal inflammation over 16 weeks of treatment in biologic-experienced rad-axSpA patients.[55]

Table 38: SPARCC MRI scores for the spine least squares mean change from baseline, observed case analysis (ANCOVA), ITT population, COAST-W, Week 16

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p-value
PBO ([redacted])[a]	[redacted]	[redacted]	[redacted]
IXE Q4W ([redacted])[b]	[redacted]	[redacted]	[redacted]
IXE Q2W ([redacted])[c]	[redacted]	[redacted]	[redacted]

Notes: [redacted]

Abbreviations: ANCOVA: analysis of covariance; cfb: change from baseline; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; N: number of patients in the analysis population; PBO: placebo; SE: standard error.
Source: COAST-W CSR: Week 16 Report (Table RHBW.14.46).[55]

SPARCC MRI was not performed at Week 52 in COAST-W and therefore Week 52 data are not presented within the submission.

Spinal pain (NRS)

The least squares mean cfb in spinal pain (BASDAI question 2), was [redacted] in the ixekizumab Q4W ([redacted]) and Q2W arms ([redacted]) compared to placebo [redacted] at Week 16, as shown in Table 39[55] NICE deem a spinal pain change of ≥2 to represent a clinically relevant improvement.[71]

Table 39: Spinal pain measured by BASDAI question 2, least squares mean change from baseline in the ITT population, MMRM, COAST-W, Week 16

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p-value
PBO (N=104)	[redacted]	[redacted]	[redacted]
IXE Q4W (N=114)	[redacted]	[redacted]	[redacted]
IXE Q2W (N=98)	[redacted]	[redacted]	[redacted]
[redacted]			

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; MMRM: mixed models repeated measure analysis; N: number of patients in the analysis population; PBO: placebo; SE: standard error.
Source: COAST-W CSR: Week 16 Report (Table RHBW.14.32).[55]

Improvements in spinal pain cfb (BASDAI question 2) were maintained to Week 52 in the ITT population who were initially randomised to receive ixekizumab in the Q4W [redacted]) and Q2W arms ([redacted]), as displayed in Table 40.[4]

Treatment with ixekizumab therefore resulted in clinically relevant improvements in spinal pain through to [redacted] for biologic-experienced rad-axSpA patients.

Table 40: Spinal pain measured by BASDAI question 2, mean change from baseline in the ITT population who were originally randomised to receive ixekizumab, mBOCF, COAST-W, Week 52

Treatment arm	Week 16	Week 52
	Cfb, mean (SD)	
IXE Q4W ([redacted])	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]

Notes: Baseline is defined as the last non-missing assessment recorded on or prior to the date of first study drug injection at Week 0
Abbreviations: cfb: change from baseline; ITT: intent-to-treat; IXE Q4W; ixekizumab every 4 weeks; IXE Q2W: ixekizumab every 2 weeks; mBOCF: modified baseline observation carried forward; N: number of patients in the analysis population; SD: standard deviation.
Source: COAST-W CSR: Week 52 Report (Table RHBW.14.15).[4]

Health-related quality of life (SF-36 PCS)

In the ITT population at Week 16, least squares mean cfb in SF-36 PCS score was [redacted] in the ixekizumab Q4W ([redacted]) and Q2W arms ([redacted]) compared to placebo ([redacted]), as shown in Table 41.[55]

Table 41: Change from baseline in SF-36 PCS scores, ITT population, MMRM, COAST-W, Week 16

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p-value
PBO (N=104)	[redacted]	[redacted]	[redacted]
IXE Q4W (N=114)	[redacted]	[redacted]	[redacted]
IXE Q2W (N=98)	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: cfb: change from baseline; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; N: number of patients in the analysis population; MMRM: mixed models repeated measure analysis; PBO: placebo; PCS: physical component summary; SF-36: short form-36.
Source: COAST-W CSR: Week 16 Report (Table RHBW.14.55).[55]

Improvements in mean SF-36 PCS from baseline were [redacted] at Week 52 compared to Week 16 in the ITT population who were initially randomised to receive ixekizumab Q4W ([redacted]) or Q2W ([redacted]. as displayed in Table 42.[4]

Treatment with ixekizumab therefore led to improved HRQoL (as measured by the SF-36 PCS) for biologic-experienced rad-axSpA patients, which was maintained to Week 52.

Table 42: Change from baseline in SF-36 PCS scores, ITT population who were initially randomised to ixekizumab, mBOCF, COAST-W, Week 16 and Week 52

Treatment arm	Week 16	Week 52
	Cfb, mean (SD)	
IXE Q4W (N=114)	[redacted]	[redacted]
IXE Q2W (N=98)	[redacted]	[redacted]

[redacted]

Abbreviations: cfb: change from baseline; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; N: number of patients in the analysis population; mBOCF: modified baseline observation carried forward; PBO: placebo; PCS: physical component summary; SD: standard deviation; SF-36: short form-36
Source: COAST-W CSR: Week 52 Report (Table RHBW.14.20).[4]

B.2.6.3 COAST-X

ASAS40 at Week 16 and Week 52

The primary endpoint in COAST-X was the proportion of patients achieving an ASAS40 response at Week 16. At Week 16, in the ITT population, a statistically significantly greater proportion of patients achieved an ASAS40 response in both the ixekizumab Q4W (35.4%; p=0.009) and Q2W arms (40.2%; p=0.002) compared to placebo (19.0%).[6] At Week 52, in the ITT population, a statistically significantly greater proportion of patients achieved an ASAS40 response in the ixekizumab Q4W (30.2%; p=0.004) and Q2W arms (31.4%; p=0.004) compared to placebo (13.3%).[6] ASAS40 response rates for Week 16 and Week 52 are shown in Table 43.[5]

There were [redacted] between the 80 mg and 160 mg LDs in the ixekizumab Q4W ([redacted]) and Q2W ([redacted]) arms at Week 16, as shown in Table 44.[5]

The ASAS40 response rate was significantly greater than placebo from as early as Week 1 in the ixekizumab Q4W (p=0.008) and Q2W arms (p=0.012).[5, 6] The proportion of patients achieving an ASAS40 response in the ITT population from Week 0 to Week 52 is summarised in Figure 14.[5, 6]

Table 43: ASAS40 response for the ITT population with non-responder imputation, COAST-X, Week 16 and Week 52

Dosing schedule	Response rate, n (%)	Percentage difference versus PBO (95% CI)	p-value
Week 16			
PBO (N=105)	20 (19.0)	[redacted]	-
IXE Q4W (N=96)	34 (35.4)	[redacted]	0.0094
IXE Q2W (N=102)	41 (40.2)	[redacted]	0.0016
Week 52			
PBO (N=105)	14 (13.3)	[redacted]	-
IXE Q4W (N=96)	29 (30.2)	[redacted]	0.0045
IXE Q2W (N=102)	32 (31.4)	[redacted]	0.0037

Notes:
[redacted]. Logistic regression analysis with treatment, geographic region, and screening MRI/CRP status as factors.
Observed data after initiation of biologic rescue of ixekizumab 80 mg Q2W for inadequate responders is excluded.
Abbreviations: ASAS: Assessment of Ankylosing Spondylitis International Society; CI: confidence interval; ITT: intent-to-treat; IXE Q4W; ixekizumab every 4 weeks; IXE Q2W: ixekizumab every 2 weeks; N: number of patients in the analysis population; n: number of patients in the specified category; PBO: placebo.
Source: COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.14.24)[5]

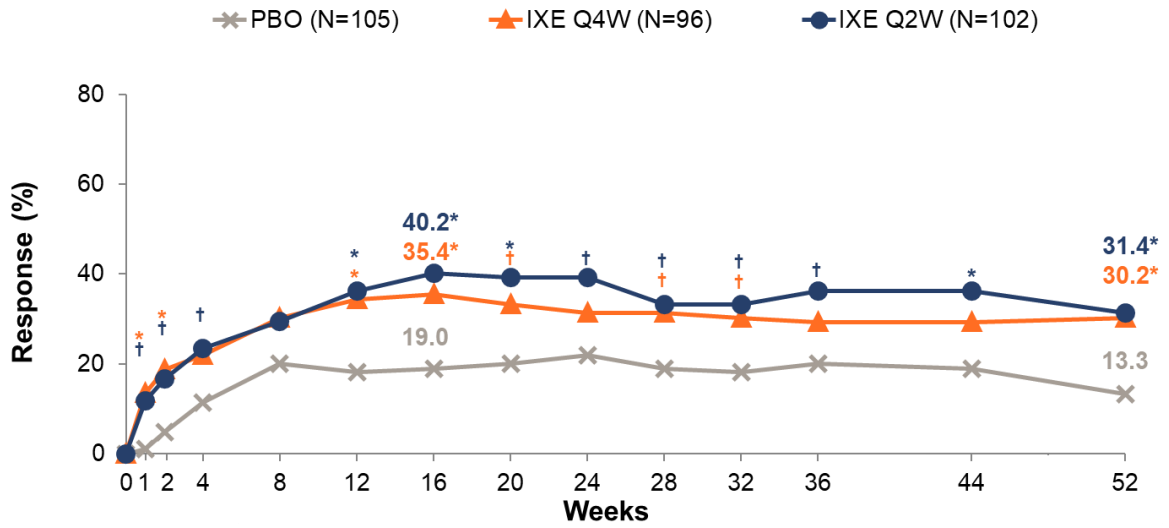
Table 44: ASAS40 response by loading dose for the ITT population with non-responder imputation, COAST-X, Week 16 and Week 52

Dosing schedule	Response rate, n (%)	Difference versus 80 mg LD, % (95% CI)[a]	p-value
Week 16			
IXE Q4W 80 mg LD ([redacted])	[redacted]	-	-
IXE Q4W 160 mg LD ([redacted])	[redacted]	[redacted]	[redacted]
IXE Q2W 80 mg LD ([redacted])	[redacted]	-	-
IXE Q2W 160 mg LD ([redacted])	[redacted]	[redacted]	[redacted]

Notes: [redacted]

Abbreviations: ASAS: Assessment of Ankylosing Spondylitis International Society; CI: confidence interval; ITT: intent-to-treat; IXE Q4W; ixekizumab every 4 weeks; IXE Q2W: ixekizumab every 2 weeks; LD: loading dose; N: number of patients in the analysis population; n: number of patients in the specified category; SD: standard deviation.
Source: COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.14.103)[5]

Figure 14: ASAS40 response for the ITT population with non-responder imputation, COAST-X, up to Week 52



Notes: *p-value<0.01 versus PBO; †p-value<0.05 versus PBO.
Observed data after initiation of biologic rescue of ixekizumab 80 mg Q2W for inadequate responders is excluded
Abbreviations: ASAS: Assessment of Ankylosing Spondylitis International Society; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; N: number of patients in the analysis population; PBO: placebo.
Source: COAST-X CSR: Week 16 and Week 52 Report (Figure RHBX.14.2).[5]

As described in Section B.2.3.1, in COAST-X, from Week 16 to Week 52, any patient who was deemed to be an inadequate responder by investigators could be rescued with ixekizumab 80 mg Q2W. In total, [redacted] patients initially treated with ixekizumab Q4W were rescued with ixekizumab Q2W. Observed ASAS40 response rates for the patient population who remained on ixekizumab Q4W throughout the study ([redacted] at Week 52) and for those who received rescue therapy with ixekizumab Q2W ([redacted] at Week 52) are displayed in Appendix L.[53] Despite being classed as inadequate responders, [redacted] of patients initially treated with ixekizumab Q4W achieved an ASAS40 response at Week 52. .[53]

Secondary endpoints

In addition to the primary efficacy endpoint, a number of secondary endpoints were assessed as part of the COAST-X trial.

Disease activity (BASDAI)

In the ITT population, the proportion of patients achieving a BASDAI50 response was [redacted] at Week 16 in the ixekizumab Q4W ([redacted]) and Q2W arms ([redacted]) compared to placebo ([redacted]).[5] At Week 52, the BASDAI50 response rate [redacted] in the ixekizumab Q4W ([redacted]) and Q2W arms ([redacted]) compared to placebo ([redacted]%). The BASDAI50 response rates at Week 16 and Week 52 are presented in Table 45. The proportion of patients achieving BASDAI50 [redacted] compared to placebo from as early as [redacted] in the ixekizumab Q4W ([redacted]) and Q2W arms ([redacted]).[5] There was no significant difference in BASDAI50 response between the 80 mg and 160 mg LD groups for either the ixekizumab Q4W or Q2W arms at Week 16, as displayed in Appendix L.

Table 45: BASDAI50 response in the ITT population, with non-responder imputation, COAST-X, Week 16 and Week 52

Treatment arm	Response, n (%)	Difference versus PBO, % (95% CI)[a]	p-value
Week 16			
PBO (N=105)	[redacted]	[redacted]	[redacted]
IXE Q4W (N=96)	[redacted]	[redacted]	[redacted]
IXE Q2W (N=102)	[redacted]	[redacted]	[redacted]
Week 52			
PBO (N=105)	[redacted]	[redacted]	[redacted]
IXE Q4W (N=96)	[redacted]	[redacted]	[redacted]
IXE Q2W (N=102)	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; N: number of patients in the analysis population; n: number of patients in the specified category; PBO: placebo.
Source: COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.14.53) [5]

In the ITT population, the least squares mean cfb in BASDAI score was significantly greater in the ixekizumab Q4W (−2.18; p=0.0306) and Q2W arms (−2.52; p=0.0011) compared to placebo (−1.51) at Week 16.[6] Using mBOCF analysis to impute data for non-responders, at Week 52 the least squares mean cfb in BASDAI score was significantly greater in both the ixekizumab Q4W [redacted] and Q2W arms [redacted] compared to placebo [redacted] (Table 46).[5] The least squares mean cfb in BASDAI score was also [redacted] from as early as [redacted] in the ixekizumab Q4W ([redacted]) and Q2W arms ([redacted]) compared to placebo.[5] There was [redacted] in BASDAI cfb between the 80 mg and 160 mg LD groups for either the ixekizumab Q4W or Q2W arms at Week 16, as displayed in Appendix L.

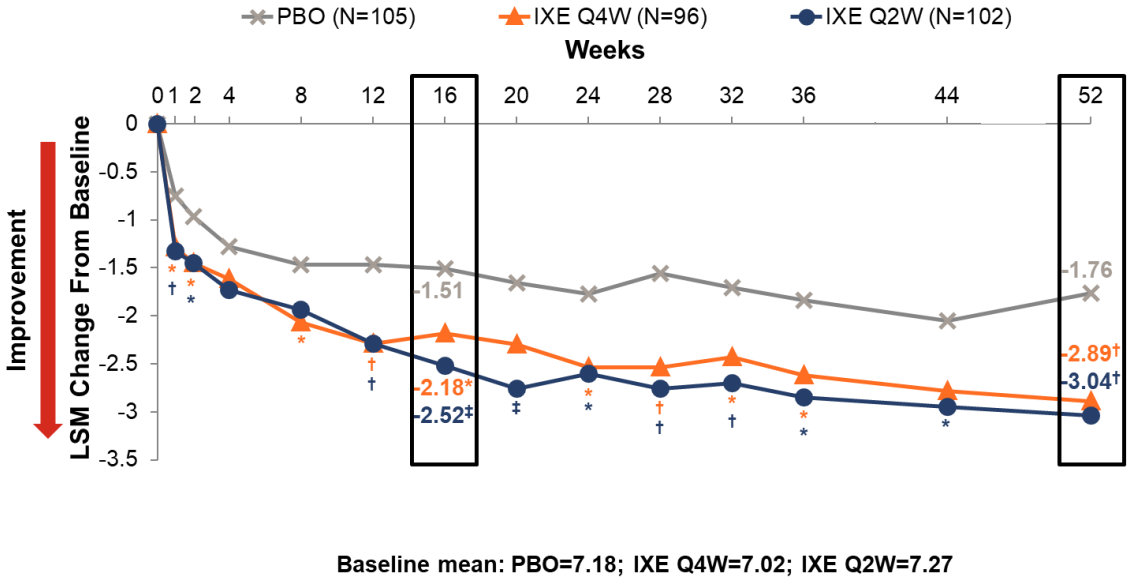
This represents a substantial reduction in disease burden for biologic-naïve nr-axSpA patients treated with ixekizumab for 52 weeks. BASDAI least squares mean cfb from Week 0 to Week 52, analysed using MMRM, is shown in Figure 15.

Table 46: BASDAI least squares mean change from baseline in the ITT population, COAST-X, Week 16 (MMRM) and Week 52 (mBOCF, ANCOVA)

Treatment arm	Cfb, LSM (SE)	Difference versus PBO, (95% CI)	p-value
Week 16, MMRM			
PBO (N=105)	−1.51 (0.22)	-	-
IXE Q4W (N=96)	−2.18 (0.22)	−0.67 (−1.28; −0.06)	0.031
IXE Q2W (N=102)	−2.52 (0.22)	−1.01 (1.61; −0.41)	0.001
Week 52, mBOCF			
PBO (N=105)	[redacted]	[redacted]	[redacted]
IXE Q4W (N=96)	[redacted]	[redacted]	[redacted]
IXE Q2W (N=102)	[redacted]	[redacted]	[redacted]

[redacted]The MMRM model includes treatment, geographic region, screening MRI/CRP status, baseline value, visit, baseline value-by-visit, treatment-by-visit interaction as fixed factors, [redacted]The ANCOVA model includes treatment, geographic region, screening MRI/CRP status and baseline value.
Observed data after initiation of biologic rescue of ixekizumab 80 mg Q2W for inadequate responders is excluded.
Abbreviations: ANCOVA: Analysis of covariance; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; mBOCF: modified baseline observation carried forward; MMRM: mixed models repeated measure analysis; N: number of patients in the analysis population; PBO: placebo; SE: standard error.
Source: Deodhar *et al.* (2019),[6] COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.14.38 and Table RHBX.39)[5]

Figure 15: BASDAI least squares mean change from baseline in the ITT population, COAST-X, Week 16 and Week 52 (MMRM)



Notes: *p≤0.05 versus PBO; †p≤0.01 versus PBO; ‡p=0.001 versus PBO.
Baseline is defined as the last non-missing assessment recorded on or prior to the date of first study drug injection at Week 0 (Visit 2)
The MMRM model includes treatment, geographic region, screening MRI/CRP status, baseline value, visit, baseline value-by-visit, treatment-by-visit interaction as fixed factors, with variance-covariance structure set to unstructured for BASDAI Change from Baseline.

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ITT: Intent-to-Treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; MMRM: mixed-model repeated measures; PBO: placebo.
Source: Eli Lilly and Company. Data on File.[53]

Disease activity (ASDAS <2.1)

In the ITT population, at Week 16, the number of patients who were defined as having low disease activity (ASDAS score <2.1) was significantly greater in the ixekizumab Q4W arm (28%; p=0.0080) and Q2W arm (32%; p=0.0009) compared to placebo (12%).[6] Response was maintained until Week 52 and was significantly greater in the ixekizumab Q4W (30%; p=0.0003) and Q2W (27%; p=0.0009) arms compared to placebo (9%), as shown in Table 47.[6]

Table 47: Proportion of patients achieving ASDAS <2.1 in the ITT population, with non-responder imputation, COAST-X, Week 16 and Week 52

Treatment arm	Response, n (%)	Difference versus PBO, % (95% CI)[a]	p-value
Week 16			
PBO (N=105)	13 (12.4)	[redacted]	-
IXE Q4W (N=96)	26 (27.7)	[redacted]	0.008
IXE Q2W (N=102)	33 (32.4)	[redacted]	<0.001
Week 52			
PBO (N=105)	9 (8.6)	[redacted]	-
IXE Q4W (N=96)	28 (29.8)	[redacted]	<0.001
IXE Q2W (N=102)	28 (27.5)	[redacted]	<0.001

Notes: [redacted]
Logistic regression analysis with treatment, geographic region and the screening MRI/CRP status as factors. Observed data after initiation of biologic rescue of ixekizumab 80 mg Q2W for inadequate responders is excluded
Abbreviations: ASDAS: Ankylosing Spondylitis Disease Activity Score; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; N: number of patients in the analysis population; n: number of patients in the specified category; PBO: placebo.
Source: Deodhar *et al.* (2019),[6] COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.14.36) [5]

Functional capacity (BASFI)

In the ITT population, the least squares mean cfb in BASFI score at Week 16 was statistically significantly greater in the ixekizumab Q4W (−2.01; p=0.04) and Q2W arms (−2.28; p=0.004) compared to placebo (−1.34).[6] Using mBOCF analysis to impute data for non-responders, at Week 52, the least squares mean cfb in BASFI was also significantly greater in both the ixekizumab Q4W arm [redacted]) and Q2W arm [redacted]) versus placebo [redacted], as shown in Table 48.[5]

The least squares mean cfb in BASFI score was significantly greater compared to placebo from [redacted] in the ixekizumab Q4W [redacted] and Q2W arms [redacted][5] The change in BASFI scores from baseline from Week 0 to 52, analysed using MMRM, is summarised in **Figure 16**.[5]

There was no significant difference in BASFI cfb between the 80 mg and 160 mg LD groups for either the ixekizumab Q4W ([redacted]) or Q2W ([redacted]) arms at Week 16, as displayed in Appendix L.[53]

Treatment with ixekizumab therefore resulted in significant improvements in biologic-naïve nr-axSpA patients' functional ability over the 52 weeks of the trial.

Table 48: BASFI least squares mean change from baseline in the ITT population, COAST-X, Week 16 (MMRM) and Week 52 (mBOCF ANCOVA)

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p−value
Week 16, MMRM			
PBO (N=105)	−1.34 (0.23)	-	-
IXE Q4W (N=96)	−2.01 (0.23)	−0.67 (−1.31; 0.03)	0.040
IXE Q2W (N=102)	−2.28 (0.23)	−0.94 (−1.57; 0.31)	0.004
Week 52, mBOCF			
PBO ([redacted])	[redacted]	[redacted]	[redacted]
IXE Q4W ([redacted])	[redacted]	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]	[redacted]

[redacted]The MMRM model includes treatment, geographic region, screening MRI/CRP status, baseline value, visit, baseline value-by-visit, treatment-by-visit interaction as fixed factors,[redacted]The ANCOVA model includes treatment, geographic region, screening MRI/CRP status and baseline value.
Observed data after initiation of biologic rescue of ixekizumab 80 mg Q2W for inadequate responders is excluded.
Abbreviations: ANCOVA: Analysis of covariance; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; mBOCF: modified baseline observation carried forward; MMRM: mixed models repeated measure analysis; N: number of patients in the analysis population; PBO: placebo; SE: standard error.[redacted]
Source: Deodhar *et al.* (2019),[6] COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.14.48 and Table RHBX.14.49)[5]

Figure 16: BASFI score least squares mean change from baseline in the ITT population, MMRM analysis, COAST-X, up to Week 52

[redacted]

Notes: [redacted]

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; IXE80Q2W: ixekizumab 80 mg every 2 weeks; IXE80Q4W: ixekizumab 80 mg every 4 weeks; LS: least squares; n: number of patients with non-missing values; PBO: placebo; SE: standard error.
Source: COAST-X CSR: Week 16 and Week 52 Report (Figure RHBX.14.3)[5]

Inflammation at the sacroiliac joint (SPARCC)

Inflammation at the sacroiliac joints was measured over the course of the trial using the cfb in the SPARCC sacroiliac joint score. In the ITT population, at Week 16, the least squares mean cfb in SPARCC score of the sacroiliac joint was statistically significantly improved in the ixekizumab Q4W (−3.38; p<0.001) and Q2W arms (−4.52; p<0.001) compared to placebo (0.31), as presented in Table 49.[5, 6] In the placebo arm, SPARCC MRI scores worsened. Using mBOCF analysis to impute data for non-responders, at Week 52, in the ITT population, the mean improvement from baseline in SPARCC score was [redacted] in the ixekizumab Q4W [redacted] and Q2W arms [redacted]) compared to placebo [redacted], as displayed in Table 49. This demonstrates that ixekizumab was effective in reducing inflammation at the sacroiliac joint in biologic-naïve nr-axSpA patients for up to 52 weeks.[5]

Table 49: SPARCC MRI scores for the sacroiliac joint, observed case analysis, ITT population, COAST-X, Week 16 (ANCOVA) and Week 52 (mBOCF ANCOVA)

Treatment arm	Change from baseline, LSM (SE)	Difference versus PBO (95% CI)	p−value
Week 16, ANCOVA			
PBO (N=105)	−0.31 (0.54)	[redacted]	-
IXE Q4W (N=96)	−3.38 (0.55)	[redacted]	<0.001
IXE Q2W (N=102)	−4.52 (0.53)	[redacted]	<0.001
Week 52, mBOCF			
PBO (N=105)	[redacted]	[redacted]	[redacted]
IXE Q4W (N=96)	[redacted]	[redacted]	[redacted]
IXE Q2W (N=102)	[redacted]	[redacted]	[redacted]

[redacted]

The ANCOVA model includes treatment, geographic region, screening MRI/CRP status and baseline value. Observed data after initiation of biologic rescue of ixekizumab 80 mg Q2W for inadequate responders is excluded
Abbreviations: ANCOVA: analysis of covariance; cfb: change from baseline; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; mBOCF: modified baseline observation carried forward; N: number of patients in the analysis population; PBO: placebo; SE: standard error.
Source: Deodhar *et al.* (2019),[6] COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.14.40 and Table RHBX.14.41).[5]

Spinal pain (NRS)

The least squares mean cfb in spinal pain (BASDAI question 2) at Week 16 in the ITT population was [redacted] in the ixekizumab Q4W [redacted]) and Q2W arms [redacted]) compared to placebo [redacted]). Using mBOCF analysis to impute data for non-responders, at Week 52, in the ITT population, the least squares mean cfb was [redacted] in the ixekizumab Q4W [redacted]) and Q2W arms [redacted]) versus placebo ([redacted]), as presented in Table 50.[5] As discussed previously, a reduction of ≥2 in spinal pain is required by NICE for continuation of therapy, and this endpoint was met by ixekizumab for biologic-naïve nr-axSpA patients for up to 52 weeks.[71]

Table 50: Spinal pain (BASDAI question 2), least squares mean change from baseline in the ITT population, COAST-X, Week 16 (MMRM) and Week 52 (mBOCF ANCOVA)

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p−value
Week 16, MMRM			
PBO ([redacted])	[redacted]	[redacted]	[redacted]
IXE Q4W ([redacted])	[redacted]	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]	[redacted]
Week 52, mBOCF			
PBO ([redacted])	[redacted]		
IXE Q4W ([redacted])	[redacted]	[redacted]	[redacted]
IXE Q2W ([redacted])	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: ANCOVA: Analysis of covariance; cfb: change from baseline; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; mBOCF: modified baseline observation carried forward; MMRM: mixed models repeated measure analysis; N: number of patients in the analysis population; PBO: placebo; SE: standard error.
Source: COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.14.38 and Table RHBX.14.39).[5]

Health related quality of life (SF-36 PCS)

The least squares mean cfb in SF-36 PCS score was significantly greater in both the ixekizumab Q4W (8.06; p=0.013) and Q2W arms (7.96; p=0.015) compared to placebo (5.21), at Week 16.[6] Using mBOCF analysis to impute data for non-responders, at Week 52, in the ITT population, the mean improvement in SF-36 PCS scores from baseline was [redacted] in both the ixekizumab Q4W ([redacted]) and Q2W arms ([redacted]) versus placebo ([redacted]), demonstrating that HRQoL improvements were maintained for up to 52 weeks in biologic-naïve nr-axSpA patients treated with ixekizumab.[5]

Table 51: Least squares mean change from baseline in SF-36 PCS scores, ITT population, COAST-X, Week 16 (MMRM) and Week 52 (mBOCF ANCOVA)

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p-value
Week 16, MMRM			
PBO (N=105)	5.21 (0.80)	[redacted]	-
IXE Q4W (N=96)	8.06 (0.81)	[redacted]	0.013
IXE Q2W (N=102)	7.96 (0.80)	[redacted]	0.015
Week 52, mBOCF			
PBO (N=105)	[redacted]	[redacted]	[redacted]
IXE Q4W (N=96)	[redacted]	[redacted]	[redacted]
IXE Q2W (N=102)	[redacted]	[redacted]	[redacted]

[redacted]

The MMRM model includes treatment, geographic region, screening MRI/CRP status, baseline value, visit, baseline value-by-visit, treatment-by-visit interaction as fixed factors, [redacted]

The ANCOVA model includes treatment, geographic region, screening MRI/CRP status and baseline value. Observed data after initiation of biologic rescue of ixekizumab 80 mg Q2W for inadequate responders is excluded.
Abbreviations: ANCOVA: Analysis of covariance; cfb: change from baseline; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; mBOCF: modified baseline observation carried forward; MMRM: mixed models repeated measure analysis; N: number of patients in the analysis population; PBO: placebo; SE: standard error.
Source: Deodhar *et al.* (2019),[6] COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.14.42 and Table RHBX.14.43).[5]

B.2.7 *Subgroup analysis*

In all three trials, the robustness and consistency of the primary analysis was confirmed by a series of pre-specified subgroup analyses.[5, 54, 55]

[redacted]

[redacted]

[redacted]

[redacted]

Table 52: Significant (p<0.10) treatment-by-subgroup interactions at Week 16 for the primary endpoint (ASAS40) in COAST-V, -W and -X

Outcome	COAST-V	COAST-W	COAST-X
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASAS: Assessment of SpondyloArthritis international Society; CRP: C-reactive protein; CSR: clinical study report; TNFi: tumour necrosis factor inhibitor.
Source: COAST-V: CSR: Week 16 Report (Table RHBV.14.71),[54] COAST-W CSR: Week 16 Report (Table RHBW.14.68),[55] COAST-X CSR: Week 16 and Week 52 Report (Figure RHBX.14.9).[5]

B.2.8 *Meta-analysis*

As the three clinical trials for ixekizumab were undertaken in three different patient populations in axSpA, a meta-analysis was not performed.

B.2.9 *Indirect and mixed treatment comparisons*

Summary of indirect comparison[57]

- An NMA was performed to assess the clinical effectiveness of ixekizumab versus relevant comparators in the three axSpA populations aligned to the COAST trials, where suitable comparator data were available. The efficacy data for ixekizumab inputted into the NMA was sourced from patients assigned to the loading and maintenance doses that are anticipated to be licensed
- Results are presented for ASAS40, BASDAI50, BASDAI and BASFI cfb at Weeks 12–18 in Section B.2.9.1 to, B.2.9.3 and statistically significant results are summarised below. For all other comparisons versus ixekizumab, there was no statistically significant difference, or required data were not identified in the clinical SLR.
  - In the biologic-naïve rad-axSpA population:
    - For ASAS40 response, ixekizumab Q4W [redacted] LD) [redacted]
    - For BASDAI50 response, ixekizumab Q4W [redacted] LD) was also [redacted]

- For BASDAI cfb, ixekizumab Q4W ( ) was also [redacted]
- For BASFI cfb, ixekizumab Q4W (LD) was also [redacted]

- In the biologic-experienced rad-axSpA population:
  - For ASAS40 response, ixekizumab Q4W LD) was [redacted] whilst [redacted] to ixekizumab Q4W (LD) ([redacted]
  - For BASDAI50 response, ixekizumab (LD) was [redacted] to placebo [redacted], whilst [redacted] to ixekizumab (LD) ([redacted]
  - BASDAI cfb was [redacted] for ixekizumab (compared to placebo ([redacted]). was [redacted] compared [redacted] (LD) ([redacted]
  - Ixekizumab ([redacted] to placebo for BASFI cfb ([redacted]
- In the biologic-naïve nr-axSpA population:
  - For ASAS40 response, ixekizumab Q4W LD) [redacted]
  - For BASDAI50 response, ixekizumab Q4W (LD) was also [redacted]
  - For BASDAI cfb, ixekizumab Q4W (LD) was also [redacted]
  - For BASFI cfb, ixekizumab Q4W (LD) was also [redacted]

- In summary, across all three populations, no statistically significant difference was observed versus comparators of interest for the majority of outcomes assessed. Exceptions to this include statistical superiority of ixekizumab to secukinumab for ASAS40 and BASDAI cfb in the biologic-naïve rad-axSpA population, and inferiority to infliximab for all reported outcomes, with the exception of BASFI cfb, in the biologic-experienced rad-axSpA population

An NMA has been performed to assess the comparative effectiveness of ixekizumab versus comparators relevant to the decision problem of this submission. The full methodology of the NMA is provided in Appendix D.

It was possible to conduct NMAs for the biologic-naïve and -experienced rad-axSpA populations, and the biologic-naïve nr-axSpA populations, in line with the COAST-V, COAST-W and COAST-X trials, respectively. As described in Appendix D, both base case and sensitivity NMAs were performed. The base case analysis included studies in which the patient population could clearly be classified into one of the three patient populations of interest, whilst the sensitivity analysis also incorporated studies in which populations were either mixed or are unclear. Due to the inclusion of a greater number of comparators relevant to the decision problem and use of these results in the economic analysis, results from the NMA sensitivity analysis are presented in Document B. Results of the NMA base case analysis are presented in Appendix D.

The ixekizumab data informing the NMAs is specific to the loading and maintenance doses of ixekizumab that are anticipated to be licensed, as follows:

- Biologic-naïve rad-axSpA patients: 80 mg Q4W (LD: 80 mg)
- Biologic-experienced rad-axSpA patients: 80 mg Q4W (LD: 160 mg)
- Biologic-naïve nr-axSpA patients: 80 mg Q4W (LD: 80 mg)

Results for the outcomes of ASAS40, BASDAI50, cfb in BASDAI score and cfb in BASFI score are presented in Document B, as these outcomes were deemed to provide the most informative results for relative efficacy between treatments, with the latter three outcomes also informing the cost-effectiveness model.

The results of the NMA are presented in the following sections:

- Section B.2.9.1: Biologic-naïve rad-axSpA results
- Section B.2.9.2: Biologic-experienced rad-axSpA results
- Section B.2.9.3: Biologic-naïve nr-axSpA results

As described in Section B.1, the licence for secukinumab has recently been updated to recommend that the dose can be increased from 150 mg to 300 mg based on clinical response, however, suitable data for this dose were not available to inform the NMA, and therefore results for the 150 mg dose are reported below.[27]

B.2.9.1 Results of the network meta-analysis: biologic-naïve rad-axSpA

For the biologic-naïve rad-axSpA population, all analyses were carried out for the ixekizumab 80 mg Q4W, with an 80 mg LD. The most suitable model for all outcomes was deemed to be the fixed-effects model. A summary of the studies providing data for each endpoint in the base case analysis and sensitivity analysis of the biologic-naïve rad-axSpA NMA is provided in Table 53. Please note that all studies included in the base case analysis are also included in the sensitivity analysis.

Table 53: Overview of studies included for each endpoint in the biologic-naive rad-axSpA NMA

Comparison vs IXE Q4W (FeFe)	ASAS20	ASAS40	ASDAS CRP	ASDAS 1.1	ASDAS 2.0	BASDAI	BASDAI 50	BASFI	BASMI	SF-36 MCS	AE	DISCAE	SAE
	Median OR (95% CrI)	Median OR (95% CrI)	Mean difference (95% CrI)	Median OR (95% CrI)	Median OR (95% CrI)	Mean difference (95% CrI)	Median OR (95% CrI)	Mean difference (95% CrI)	Mean difference (95% CrI)	Mean difference (95% CrI)	Median OR (95% CrI)	Mean difference based on normal model	Mean difference based on normal model
Base case													
ADA 40 mg	COAST-V ATLAS Huang 2014	COAST-V ATLAS Huang 2014	COAST-V Huang 2014	COAST-V Huang 2014	COAST-V Huang 2014	COAST-V ATLAS Huang 2014	COAST-V ATLAS Huang 2014	COAST-V Huang 2014	COAST-V ATLAS Huang 2014	COAST-V ATLAS Huang 2014	COAST-V Huang 2014	COAST-V *Lambert 2007*	COAST-V Huang 2014
ETN pooled	Calin 2004 Davis 2003 SPINE Van der Heijde 2006 *Gorman 2002*	Davis 2003 SPINE Van der Heijde 2006	SPINE	SPINE	SPINE	HEEL SPINE	SPINE Van der Heijde 2006 *Barkham 2010* *Brandt 2003*	SPINE	SPINE		HEEL SPINE *Barkham 2010*	Calin 2004 HEEL SPINE Van der Heijde 2006 *Barkham 2010* *Gorman 2002*	Calin 2004 HEEL SPINE *Gorman 2002*
GOL 50 mg	Bao 2014 GO-RAISE	Bao 2014 GO-RAISE	GO-RAISE		Bao 2014 GO-RAISE		Bao 2014 GO-RAISE	Bao 2014	Bao 2014	Bao 2014 GO-RAISE	Bao 2014 GO-RAISE		GO-RAISE
SEC 150 mg	MEASURE-2 MEASURE-4	MEASURE-2 MEASURE-4				MEASURE-2 MEASURE-4					MEASURE-2 MEASURE-4	MEASURE-2 MEASURE-4	MEASURE-2 MEASURE-4
Sensitivity analysis													
CZP pooled	*RAPID-axSpA*	*RAPID-axSpA*	*RAPID-axSpA*		*RAPID-axSpA*	*RAPID-axSpA*	*RAPID-axSpA*	*RAPID-axSpA*	*RAPID-axSpA*				
IFX 5 mg/kg	*ASSERT* *Braun 2002*	*ASSERT* *Braun 2002*				*ASSERT* *Braun 2002*	*Braun 2002*	*ASSERT* *Braun 2002*	*Braun 2002*			*Braun 2002*	*Braun 2002*

Abbreviations: AE: adverse event; ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CrI: credible interval; CZP: certolizumab pegol; DISCAE: discontinuation due to adverse events; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: ixekizumab; NMA: network meta-analysis; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SAE: serious adverse event; SEC: secukinumab; SF-36 MCS: short-form 36 mental component score.

ASAS40

The ASAS40 network diagram for the biologic-naïve rad-axSpA population is shown in Appendix D.[57]

The mean posterior rates for ASAS40 response in the biologic-naïve rad-axSpA population are displayed in Table 54. Ixekizumab was associated with the [redacted] mean posterior rate for ASAS40 response among all comparators ([redacted]), after [redacted]).

Table 54: Mean posterior rates (with 95% CrI); ASAS40 response at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Mean posterior rate	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
INX 5 mg/kg	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]
ETN pooled	[redacted]	[redacted]	[redacted]
SEC 150 mg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: ixekizumab; NMA: network meta-analysis; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.
Source: NMA report, rad-axSpA.[57]

The pairwise results for this analysis are presented in Table 55.The forest plot for all treatments compared with ixekizumab is provided in Figure 17. Ixekizumab was [redacted] ([redacted]) and [redacted] ([redacted]) for the achievement of ASAS40 response. [redacted].

Table 55: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (with 95% CrI); ASAS40 response at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	OR (95% CrI) vs IXE 80 mg Q4W
Placebo	[redacted]
INX 5 mg/kg	[redacted]
ADA 40 mg	[redacted]
GOL 50 mg	[redacted]
ETN pooled	[redacted]
SEC 150 mg	[redacted]
CZP pooled	[redacted]

Notes: [redacted])

Abbreviations: ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: ixekizumab; NMA: network meta-analysis; OR: odds ratio; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.
Source: NMA report, rad-axSpA.[57]

Figure 17: Forest plot of ORs of ixekizumab 80 mg Q4W relative to placebo and active comparators; ASAS40 response at 12–18 weeks, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Abbreviations: ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: Ixekizumab; INX: infliximab; NMA: network meta-analysis; OR: odds ratio; Q4W; every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.
Source: NMA report, rad-axSpA[57]

BASDAI50

The BASDAI50 network diagram for the biologic-naïve rad-axSpA population is shown in Appendix D.[57] The mean posterior rates for BASDAI50 response in the biologic-naïve rad-axSpA population are presented in Table 56. Ixekizumab was associated with a mean posterior rate for BASDAI50 response of [redacted], the [redacted] among all comparators, after [redacted]), [redacted]) and [redacted]).

Table 56: Mean posterior rates (with 95% CrI); BASDAI50 response at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Mean posterior rate	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]
ETN pooled	[redacted]	[redacted]	[redacted]
INX 5 mg/kg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: Ixekizumab; NMA: network meta-analysis; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA report, rad-axSpA.[57]

The pairwise results for this analysis are presented in Table 57. The forest plot for all treatments compared with ixekizumab Q4W is provided in Figure 18. Ixekizumab was [redacted] in achieving a BASDAI50 response compared to [redacted].

Table 57: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (with 95% CrI); BASDAI50 response at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Column vs. Row	OR (95% CrI) vs IXE 80 mg Q4W
Placebo	[redacted]
ADA 40 mg	[redacted]
GOL 50 mg	[redacted]
ETN pooled	[redacted]
INX 5 mg/kg	[redacted]
CZP pooled	[redacted]

Notes: [redacted]
Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: Ixekizumab; NMA: network meta-analysis; OR: odds ratio; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA report, rad-axSpA.[57]

Figure 18: Forest plot of ORs of ixekizumab 80 mg Q4W relative to placebo and active comparators; BASDAI50 at 12–18 weeks, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

[redacted]

Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: Ixekizumab; OR: odds ratio; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.

Source: NMA report, rad-axSpA.[57]

BASDAI change from baseline

The BASDAI cfb network diagram is shown in Appendix D.

The mean posterior outcomes for cfb in BASDAI score in the biologic-naïve population are presented in Table 58Ixekizumab was associated with the [redacted] mean posterior outcome of BASDAI cfb ([redacted]), after infliximab ([redacted]).

Table 58: Mean posterior outcomes (with 95% CrI); BASDAI change from baseline at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Mean posterior outcome	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
INX 5 mg/kg	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]
ETN pooled	[redacted]	[redacted]	[redacted]
SEC 150 mg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimu mab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; INX: infliximab; IXE: Ixekizumab; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.
Source: NMA report, rad-axSpA.[57]

The pairwise results for this analysis are presented in Table 59. The forest plot for all treatments compared with ixekizumab is provided in Figure 19Ixekizumab was [redacted] and [redacted] in cfb in BASDAI score. [redacted].

Table 59: Relative treatment effect of pairwise comparisons (with 95% CrI); BASDAI change from baseline at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Posterior median treatment difference (95% CrI) IXE 80 mg Q4W vs comparator
Placebo	[redacted]
INX 5 mg/kg	[redacted]
ADA 40 mg	[redacted]
ETN pooled	[redacted]
SEC 150 mg	[redacted]
CZP pooled	[redacted]

Notes: [redacted]
Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CrI: credible interval; CZP: Certolizumab Pegol; ETN: etanercept; INX: infliximab; IXE: Ixekizumab; OR: odds ratio; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.
Source: NMA report, rad-axSpA.[57]

Figure 19: Forest plot of posterior median treatment effect of ixekizumab 80 mg Q4W relative to placebo and active comparators; biologic-naïve rad-axSpA population, BASDAI change from baseline at Week 12–18, fixed-effects model, (sensitivity analysis)

Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CZP: Certolizumab Pegol; ETN: etanercept; INX: infliximab; IXE: ixekizumab; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.
Source: NMA report, rad-axSpA.[57]

BASFI

The BASFI network diagram for the biologic-naïve rad-axSpA population is shown in Appendix D. The mean posterior outcomes for BASFI response in the biologic-naïve rad-axSpA population are presented in Table 60Ixekizumab was associated with the [redacted] mean posterior rate of BASDAI cfb ([redacted]), after infliximab ([redacted]).

Table 60: Mean posterior outcomes (with 95% CrI); BASFI change from baseline at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Mean posterior outcomes	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
INX 5 mg/kg	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]
ETN pooled	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; BASFI: Bath Ankylosing Spondylitis Functional Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: ixekizumab; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA report, rad-axSpA.[57]

The pairwise results for the fixed-effects model for this analysis are presented in Table 61. The forest plot for all treatments compared with ixekizumab is provided in Figure 20. Ixekizumab was [redacted] for BASFI cfb. There were [redacted]

Table 61: Relative treatment effect of pairwise comparisons (with 95% CrI); BASFI change from baseline at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Posterior median treatment difference (95% CrI) IXE 80 mg Q4W vs comparator
Placebo	[redacted]
INX 5 mg/kg	[redacted]
GOL 50 mg	[redacted]
ADA 40 mg	[redacted]
CZP pooled	[redacted]
ETN pooled	[redacted]

Notes: [redacted]
Abbreviations: ADA: adalimumab; BASFI: Bath Ankylosing Spondylitis Functional Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; OR: odds ratio; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA report, rad-axSpA.[57]

Figure 20: Forest plot of posterior median relative treatment effect of ixekizumab 80 mg Q4W relative to placebo and active comparators; biologic-naïve rad-axSpA population, BASFI change from baseline at 12–18 weeks, fixed-effects model (sensitivity analysis)

Abbreviations: ADA: adalimumab; BASFI: Bath Ankylosing Spondylitis Functional Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: ixekizumab; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA report, rad-axSpA.[57]

B.2.9.2 Results of the network meta-analysis: biologic-experienced rad-axSpA

For the biologic-experienced rad-axSpA population, all analyses were carried out for the ixekizumab 80 mg Q4W for both the 80 mg and 160 mg LDs. The most suitable model for all outcomes was deemed to be the fixed-effects model. Below results for the 160 mg LD are presented, all results for the 80 mg loading dose are presented in Appendix D, Section D.1.11. A summary of the studies providing data for each endpoint in the base case analysis and sensitivity analysis of the biologic-experienced rad-axSpA NMA is provided in Table 62. Please note that all studies included in the base case analysis are also included in the sensitivity analysis.

Table 62: Overview of studies included for each endpoint in the biologic-experienced rad-axSpA NMA

Comparison vs IXE Q4W (FeFe)	ASAS20	ASAS40	ASDAS CRP	ASDAS 1.1	ASDAS 2.0	BASDAI	BASDAI 50	BASFI	BASMI	SF-36 MCS	AE	DISCAE	SAE
	Median OR (95% CrI)	Median OR (95% CrI)	Mean difference (95% CrI)	Median OR (95% CrI)	Median OR (95% CrI)	Mean difference (95% CrI)	Median OR (95% CrI)	Mean difference (95% CrI)	Mean difference (95% CrI)	Mean difference (95% CrI)	Median OR (95% CrI)	Mean difference based on normal model	Mean difference based on normal model
Base case													
SEC 150 mg	MEASURE-2 MEASURE-4	MEASURE-2 MEASURE-4				MEASURE-2 MEASURE-4					MEASURE-2 MEASURE-4	MEASURE-2 MEASURE-4	MEASURE-2 MEASURE-4
Sensitivity analysis													
CZP pooled	*RAPID-axSpA*	*RAPID-axSpA*	*RAPID-axSpA*		*RAPID-axSpA*	*RAPID-axSpA*	*RAPID-axSpA*	*RAPID-axSpA*	*RAPID-axSpA*				
IFX 5 mg/kg	*ASSERT* *Braun 2002*	*ASSERT* *Braun 2002*				*ASSERT* *Braun 2002*	*Braun 2002*	*ASSERT* *Braun 2002*	*Braun 2002*			*Braun 2002*	*Braun 2002*
ETN 25 mg	*Gorman 2002*						*Barkham 2010* *Brandt 2003*				*Barkham 2010*	*Barkham 2010* *Gorman 2002*	*Gorman 2002*
ADA 40 mg												*Lambert 2007*	

Abbreviations: AE: adverse event; ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CrI: credible interval; CZP: certolizumab pegol; DISCAE: discontinuation due to adverse event; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: ixekizumab; NMA: network meta-analysis; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SAE: serious adverse event; SEC: secukinumab; SF-36 MCS: short-form 36 mental component score.

ASAS40

The ASAS40 network diagram for the biologic-experienced rad-axSpA population is shown in Appendix D. The mean posterior rates for ASAS40 response in the biologic-experienced population are presented in Table 63 (ixekizumab 160 mg LD).
[redacted].

Table 63: Mean posterior rates (with 95% CrI); ASAS40 response at Week 12–18, biologic-experienced rad-axSpA population (160 mg LD), fixed-effects model (sensitivity analysis)

Intervention	Mean posterior rates	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
INX 5 mg/kg	[redacted]	[redacted]	[redacted]
SEC 150 mg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; INX: infliximab; IXE: Ixekizumab; LD: loading dose; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.
Source: NMA report, rad-axSpA.[57]

The pairwise results for the fixed-effects model for this analysis are presented in Table 64 (160 mg LD). The forest plot for all treatments compared with ixekizumab 80 mg Q4W 160 mg LD for the fixed-effects model is provided in Figure 21.

Ixekizumab (160 mg LD) was [redacted] ([redacted]) in achieving an ASAS40 response. [redacted] was statistically superior in achieving an ASAS40 response compared to ixekizumab ([redacted]).

Table 64: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (with 95% CrI); ASAS40 response at Week 12–18, biologic-experienced rad-axSpA population (160 mg LD), fixed-effects model (sensitivity analysis)

Intervention	OR (95% CrI) vs IXE 80 mg Q4W
Placebo	[redacted]
INX 5 mg/kg	[redacted]
SEC 150 mg	[redacted]
CZP pooled	[redacted]

Notes: [redacted]
Abbreviations: ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; INX: infliximab; IXE: Ixekizumab; LD: loading dose; OR: odds ratio; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.
Source: NMA report, rad-axSpA.[57]

Figure 21: Forest plot of median treatment difference of ixekizumab 160 mg LD; ASAS40 response at Week 12–18, biologic-experienced rad-axSpA population, fixed-effects model (sensitivity analysis)

Abbreviations: ASAS: Assessment of Spondyloarthritis International Society; CZP: certolizumab pegol; INX: infliximab; IXE: Ixekizumab; LD: loading dose; OR: odds ratio; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.
Source: NMA report, rad-axSpA.[57]

BASDAI50

The biologic-experienced rad-axSpA BASDAI50 network diagram is shown in Appendix D. The mean posterior rates for BASDAI50 response in biologic-experienced rad-axSpA patients are presented in in Table 65 (160 mg LD).

[redacted].

Table 65: Mean posterior rates (with 95% CrI); BASDAI50 response at Week 12–18, biologic-experienced rad-axSpA population (160 mg LD), fixed-effects model (sensitivity analysis)

Intervention	Mean posterior rates	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
ETN 25 mg BIW	[redacted]	[redacted]	[redacted]
INX 5 mg/kg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index: BIW: bi-weekly; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; INX: infliximab; IXE: ixekizumab; LD: loading dose; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA report, rad-axSpA.[57]

The pairwise results for the fixed-effects model for this analysis are presented in Table 66 (160 mg LD). The forest plot for all treatments compared with ixekizumab 80mg Q4W (160 mg LD) for the fixed-effect model is provided in Figure 22.

Ixekizumab was [redacted] in achieving a BASDAI50 response ([redacted] (160 mg LD). [redacted] was [redacted] in achieving a BASDAI50 response compared to [redacted] ([redacted]

Table 66: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (with 95% CrI); BASDAI50 response at Week 12–18, biologic-experienced rad-axSpA population (160 mg LD), fixed-effects model (sensitivity analysis)

Intervention	OR (95% CrI) vs IXE 80 mg Q4W
Placebo	[redacted]
ETN 25 mg BIW	[redacted]
INX 5 mg/kg	[redacted]
CZP pooled	[redacted]

Notes:
[redacted]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index: BIW: bi-weekly; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; INX: infliximab; IXE: ixekizumab; LD: loading dose; OR: odds ratio; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA report, rad-axSpA.[57]

Figure 22: Forest plot of median treatment difference of ixekizumab 80 mg Q4W, (160 mg LD) relative to placebo; BASDAI50 response at Week 12–18, biologic-experienced rad-axSpA population, fixed-effects model (sensitivity analysis)

[redacted]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index: BIW: bi-weekly; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; INX: infliximab; IXE: ixekizumab; LD: loading dose; radiographic axial spondyloarthritis.
Source: NMA report, rad-axSpA.[57]

BASDAI change from baseline

The biologic-experienced rad-axSpA cfb in BASDAI score network diagram is shown in Appendix D.[57] The mean posterior outcomes for BASDAI cfb in the biologic experienced rad-axSpA patient population are displayed Table 67 (160 mg LD). [redacted].

Table 67: Mean posterior outcomes (with 95% CrI); BASDAI change from baseline at Week 12–18, biologic-experienced rad-axSpA population (160 mg LD), fixed-effects model (sensitivity analysis)

Intervention	Mean posterior outcomes	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
INX 5 mg/kg	[redacted]	[redacted]	[redacted]
SEC 150 mg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; CZP: certolizumab pegol; INX: infliximab; IXE: ixekizumab; LD: loading dose; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.
Source: NMA report, rad-axSpA.[57]

The pairwise results for this analysis are presented in Table 68 (160 mg LD). The forest plot for all treatments compared with ixekizumab 80 mg Q4W (160 mg LD) is provided in Figure 23.

Ixekizumab was [redacted] for BASDAI cfb in the biologic-experienced rad-axSpA population [redacted]. [redacted] was [redacted] for BASDAI cfb compared [redacted] ([redacted]. [redacted].

Table 68: Relative treatment effect of pairwise comparisons (with 95% CrI); BASDAI change from baseline at Week 12−18, biologic-experienced rad-axSpA population (160 mg LD), fixed-effects model

Intervention	Posterior median treatment difference (95% CrI) IXE 80 mg Q4W vs comparator
Placebo	[redacted]
INX 5 mg/kg	[redacted]
SEC 150 mg	[redacted]
CZP pooled	[redacted]

Notes: [redacted]
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; CZP: certolizumab pegol; INX: infliximab; IXE: ixekizumab; LD: loading dose; OR: odds ratio; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.
Source: NMA report, rad-axSpA.[57]

Figure 23: Forest plot of median treatment effect of ixekizumab 80 mg Q4W, (160 mg LD) relative to placebo and active comparators; BASDAI change from baseline at Week 12–18, biologic-experienced rad-axSpA population, fixed-effects model (sensitivity analysis)

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; CZP: certolizumab pegol; INX: infliximab; IXE: ixekizumab; LD: loading dose; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab;.
Source: NMA report, rad-axSpA.[57]

BASFI

The BASFI cfb network diagram for the biologic-experienced rad-axSpA population is shown in Appendix D[57] The mean posterior outcomes for BASFI cfb in the biologic-experienced rad-axSpA population are presented in Table 69 (160 mg LD)..

Table 69: Mean posterior outcomes (with 95% CrI); BASFI cfb at Week 12–18, biologic-experienced rad-axSpA population (160 mg LD), fixed-effects model (sensitivity analysis)

Intervention	Mean posterior outcomes	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
INX 5 mg/kg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; CZP: certolizumab pegol; INX: infliximab; IXE: ixekizumab; LD: loading dose; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA report, rad-axSpA.[57]

The pairwise results for this analysis are presented in Table 70. The forest plot for all treatments compared with ixekizumab 80 mg Q4W (160 mg LD) is provided in Figure 24.

Ixekizumab was [redacted] for BASFI cfb ([redacted]).

Table 70: Relative treatment effect of pairwise comparisons (with 95% CrI); BASFI cfb at Week 12−18, biologic-experienced rad-axSpA population (160 mg LD), fixed-effects model (sensitivity analysis)

Intervention	Posterior median treatment difference (95% CrI) IXE 80 mg Q4W vs comparator
Placebo	[redacted]
INX 5 mg/kg	[redacted]
CZP pooled	[redacted]

Notes: [redacted]
Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; CZP: certolizumab pegol; INX: infliximab; IXE: ixekizumab; LD: loading dose; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA report, rad-axSpA.[57]

Figure 24: Forest plot of posterior median treatment effect of ixekizumab 80 mg Q4W (160 mg LD)relative to placebo and active comparators; BASFI cfb at Week 12–18, biologic-experienced rad-axSpA population, fixed-effects model (sensitivity analysis)

[redacted]

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; CZP: certolizumab pegol; INX: infliximab; IXE: ixekizumab; LD: loading dose; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA report, rad-axSpA[57]

B.2.9.3 Results of the network meta-analysis: biologic-naïve nr-axSpA population

For the biologic-naïve nr-axSpA population, all analyses were carried out for the ixekizumab 80 mg Q4W arm, with an 80 mg LD. The most suitable model for all outcomes was deemed to be the fixed-effects model. A summary of the studies providing data for each endpoint in the base case analysis and sensitivity analysis of the biologic-naïve nr-axSpA NMA is provided in Table 71. Please note that all studies included in the base case analysis are also included in the sensitivity analysis.

Table 71: Overview of studies included for each endpoint in the biologic-naïve NMA

Comparison vs IXE Q4W (FeFe)	ASAS20	ASAS40	ASDAS CRP	ASDAS 1.1	ASDAS 2.0	BASDAI	BASDAI 50	BASFI	BASMI	SF-36 MCS	AE	DISCAE	SAE
	Median OR (95% CrI)	Median OR (95% CrI)	Mean difference (95% CrI)	Median OR (95% CrI)	Median OR (95% CrI)	Mean difference (95% CrI)	Median OR (95% CrI)	Mean difference (95% CrI)	Mean difference (95% CrI)	Mean difference (95% CrI)	Median OR (95% CrI)	Mean difference based on normal model	Mean difference based on normal model
Base case													
ADA 40 mg	ABILITY-1 *Haibel 2008*	ABILITY-1 *Haibel 2008*		ABILITY-1	ABILITY-1		ABILITY-1				ABILITY-1 *Haibel 2008*	ABILITY-1 *Haibel 2008*	ABILITY-1 *Haibel 2008*
ETN 50 mg QW	EMBARK	EMBARK	EMBARK			EMBARK	EMBARK	EMBARK	EMBARK	EMBARK	EMBARK	EMBARK	EMBARK
GOL 50 mg	GO-AHEAD	GO-AHEAD					GO-AHEAD				GO-AHEAD	GO-AHEAD	GO-AHEAD
Sensitivity analysis													
CZP pooled	*RAPID-axSpA*	*RAPID-axSpA C-axSpAnd*	*RAPID-axSpA*		*RAPID-axSpA C-axSpAnd*	*RAPID-axSpA*	*RAPID-axSpA*	*RAPID-axSpA C-axSpAnd*	*RAPID-axSpA*				

Abbreviations: AE: adverse event; ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CrI: credible interval; CZP: certolizumab pegol; DISCAE: discontinuation due to adverse event; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; NMA: network meta-analysis; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SAE: serious adverse event; SF-36 MCS: short-form 36 mental component score.

ASAS40

The ASAS40 network diagram for the biologic-naïve nr-axSpA population is shown in Appendix D.

The mean posterior rates for ASAS40 response in the biologic-naïve nr-axSpA population are displayed in Table 72. Ixekizumab was associated with a [redacted] mean posterior rate for ASAS40 response ([redacted]), compared to [redacted]).

Table 72: Mean posterior rates (with 95% CrI); ASAS40 response at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Event rate	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]
ETN 50 mg QW	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.
Source: NMA report, nr-axSpA.[72]

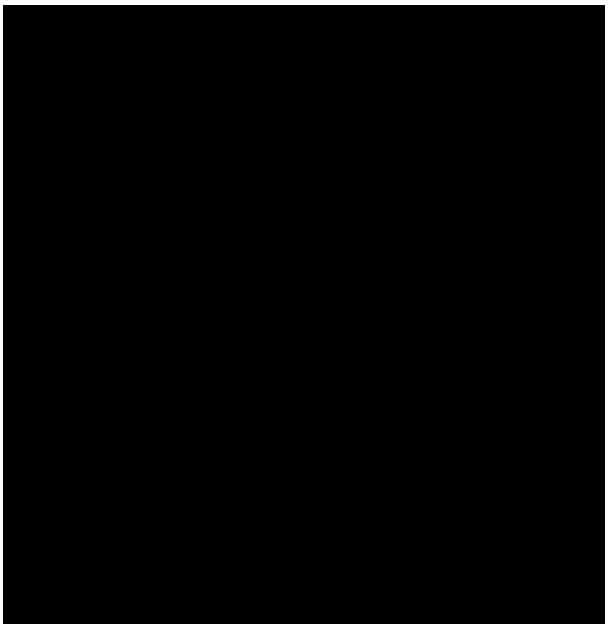
The pairwise results for this analysis are presented in Table 73. The forest plot for all treatments compared with ixekizumab is provided in Figure 25. Ixekizumab was [redacted] ([redacted]) for the achievement of ASAS40 response. [redacted].

Table 73: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (with 95% CrI); ASAS40 response at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	OR (95% CrI) vs IXE 80 mg Q4W
Placebo	[redacted]
ADA 40 mg	[redacted]
CZP pooled	[redacted]
ETN 50 mg QW	[redacted]
GOL 50 mg	[redacted]

Notes: [redacted])
Abbreviations: ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; OR: odds ratio; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.
Source: NMA report, nr-axSpA.[72]

Figure 25: Forest plot of ORs of ixekizumab 80 mg Q4W relative to placebo and active comparators; ASAS40 at 12–18 weeks, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)



Abbreviations: ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: Ixekizumab; OR: odds ratio; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly.
Source: NMA report, nr-axSpA.[72]

BASDAI50

The BASDAI50 network diagram for the biologic-naïve nr-axSpA population is shown in Appendix D.

The mean posterior rates for BASDAI50 response in the biologic-naïve nr-axSpA population are presented in Table 74. Ixekizumab was associated with a mean posterior rate for BASDAI50 response of [redacted], the [redacted] among all comparators, after [redacted]).

Table 74: Posterior rates (with 95% CrI); BASDAI50 response at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Event rate	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]
ETN 50 mg	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: Ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; Q4W: every four weeks.
Source: NMA report, nr-axSpA.[72]

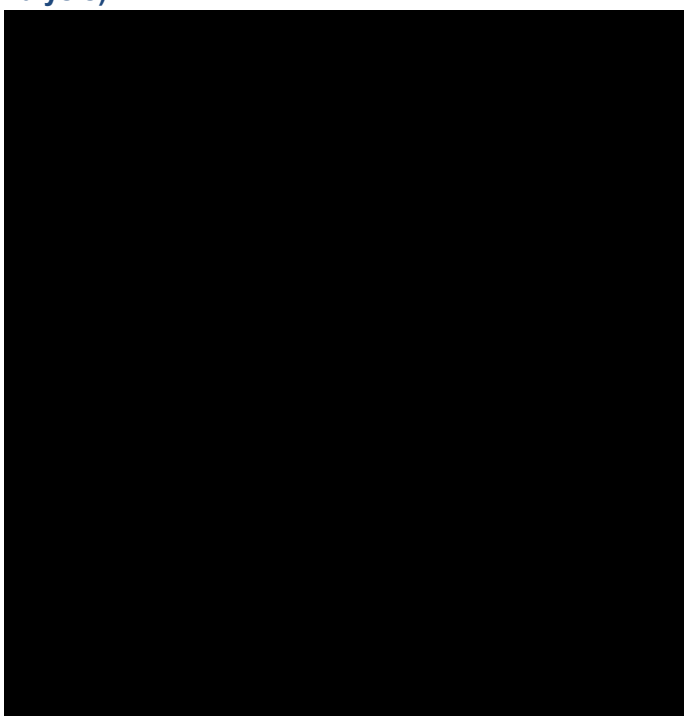
The pairwise results for this analysis are presented in Table 75. The forest plot for all treatments compared with ixekizumab Q4W is provided in Figure 26. Ixekizumab was [redacted] in achieving a BASDAI50 response compared to [redacted]. [redacted].

Table 75: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (with 95% CrI); BASDAI50 response at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	OR (95% CrI) vs IXE 80 mg Q4W
Placebo	[redacted]
ADA 40 mg	[redacted]
ETN 50 mg QW	[redacted]
GOL 50 mg	[redacted]
CZP pooled	[redacted]

Notes: [redacted]
Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: Ixekizumab; OR: odds ratio; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.
Source: NMA report, nr-axSpA.[72]

Figure 26: Forest plot of ORs of ixekizumab 80 mg Q4W relative to placebo and active comparators; BASDAI50 at 12–18 weeks, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)



Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: Ixekizumab; OR: odds ratio; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.
Source: NMA report, nr-axSpA.[72]

BASDAI change from baseline

The BASDAI cfb network diagram is shown in Appendix D.

The mean posterior outcomes for cfb in BASDAI score in the biologic-naïve population are presented in Table 76. Ixekizumab was associated with the [redacted] treatment effect with respect to BASDAI cfb ([redacted]), after [redacted]).

Table 76: Posterior outcomes (with 95% CrI); BASDAI cfb at Week 12–18; biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Treatment effect	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
ETN 50 mg QW	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; IXE: Ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; Q4W: every four weeks.
Source: NMA report, nr-axSpA.[72]

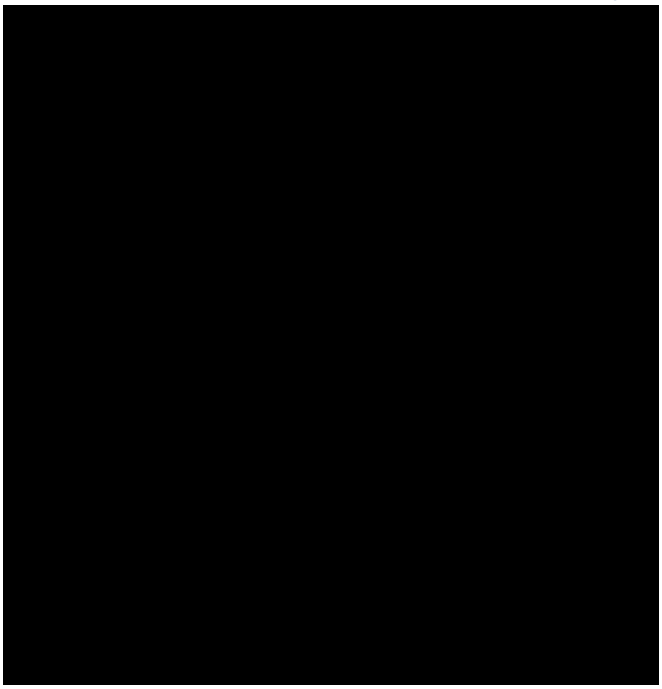
The pairwise results for this analysis are presented in Table 77. The forest plot for all treatments compared with ixekizumab is provided in Figure 27. Ixekizumab was [redacted]) for BASDAI cfb treatment effect. [redacted].

Table 77: Posterior median relative treatment effect (with 95% CrI); BASDAI cfb at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Posterior median treatment difference (95% CrI) IXE 80 mg Q4W vs comparator
Placebo	[redacted]
ETN 50 mg QW	[redacted]
CZP pooled	[redacted]

Notes: [redacted]
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CrI: credible interval; CZP: Certolizumab Pegol; ETN: etanercept; IXE: Ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.
Source: NMA report, nr-axSpA.[72]

Figure 27: Forest plot of posterior median treatment effect of ixekizumab 80 mg Q4W relative to placebo and active comparators; BASDAI change from baseline at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)



Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CZP: Certolizumab Pegol; ETN: etanercept; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.
Source: NMA report, nr-axSpA.[72]

BASFI

The BASFI network diagram for the biologic-naïve nr-axSpA population is shown in Appendix D.

The mean posterior outcomes for BASFI cfb in the biologic-naïve nr-axSpA population are presented in Table 78. Ixekizumab was associated with the [redacted] treatment effect for BASDAI cfb ([redacted]), after [redacted]

Table 78: Posterior outcomes (with 95% CrI); BASFI cfb at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Treatment effect	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]
ETN 50 mg QW	[redacted]	[redacted]	[redacted]

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.
Source: NMA report, nr-axSpA.[72]

The pairwise results for the fixed-effects model for this analysis are presented in Table 79. The forest plot for all treatments compared with ixekizumab is provided in Figure 28. Ixekizumab was [redacted] for

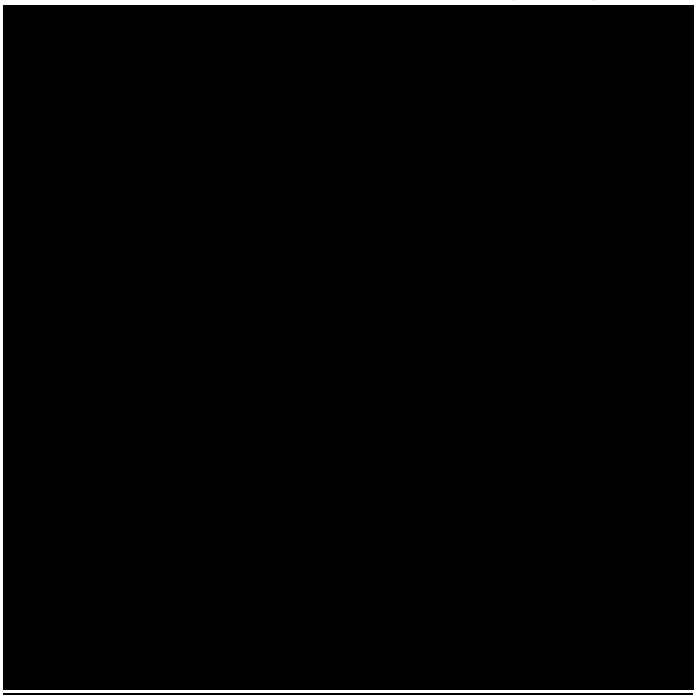
BASFI cfb. There were [redacted]

Table 79: Posterior median relative treatment effect of pairwise comparisons (with 95% CrI); BASFI cfb at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Posterior median treatment difference (95% CrI) IXE 80 mg Q4W vs comparator
Placebo	[redacted]
CZP pooled	[redacted]
ETN 50 mg QW	[redacted]

Notes: [redacted]
Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.
Source: NMA report, nr-axSpA.[72]

Figure 28: Forest plot of posterior median relative treatment effect of ixekizumab 80 mg Q4W relative to placebo and active comparators; BASFI cfb at 12–18 weeks, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)



Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.
Source: NMA report, nr-axSpA.[72]

B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons

As described earlier in the section, as identified by the SLR, insufficient data were available to develop full networks containing all comparators of interest to the decision problem for the base case NMA analyses. Therefore, in order to provide an analysis as informative to the decision problem as possible, which generated a greater number of efficacy inputs required for the economic model, a sensitivity analysis was performed to provide comparative efficacy estimates

between ixekizumab and a greater number of comparators. In addition to studies that exclusively provided data aligned to the three patient populations assessed in the COAST trials, the sensitivity analysis also included studies with either mixed or unclear patient populations with regards to biologic experience. To explore the impact of the increased population heterogeneity associated with the sensitivity analysis, the base case NMA results (presented in Appendix D) were compared to the sensitivity analysis results. Across the analyses for all three populations across ASAS40, BASDAI50, cfb in BASDAI and cfb in BASFI, no statistically significant differences between ixekizumab and any comparators were identified in the base case analyses that were not identified in the sensitivity analysis. The sensitivity analyses identified additional statistically significant differences between ixekizumab and infliximab (in favour of infliximab) for ASAS40, BASDAI50 and cfb in BASDAI score in the biologic-experienced rad-axSpA population (infliximab was not included in the equivalent base case analyses), as previously described in Section B.2.9.2. Accordingly, given the alignment in conclusions in comparative efficacy between the sensitivity analysis and base case analyses, it was deemed appropriate to present the larger data set in Document B and to include this within the economic analyses.

B.2.10 *Adverse reactions*

Summary of adverse reactions

- The safety and tolerability of ixekizumab compared with placebo in biologic-naïve rad-axSpA patients, biologic-experienced rad-axSpA patients and biologic-naïve nr-axSpA patients was assessed in COAST-V, COAST-W and COAST-X, respectively, through evaluations of TEAEs, SAEs, AESIs, rates and reasons for discontinuation, laboratory measurements, vital signs and immunogenicity markers[58]
- At Week 16 and Week 52, in all treatment arms, most TEAEs reported in COAST-V, -W and -X were mild-to-moderate in severity and SAEs occurred infrequently[1, 4, 5, 58]
- At Week 16 and 52, the most commonly reported AESIs in patients who were initially randomised to ixekizumab in the safety population, were infections and injection-site reactions, the majority of which were mild in severity[58]
- The observed safety profile was consistent with the known safety experience for ixekizumab in patients with moderate-to-severe plaque psoriasis and psoriatic arthritis[58]
- In conclusion, the safety results of the COAST trials demonstrate that ixekizumab is well-tolerated in patients with axSpA[58]

B.2.10.1 Treatment duration, dose interruptions and dose modifications

[redacted]

[redacted]

[redacted]

[redacted]

B.2.10.2 Safety analysis

The safety and tolerability of ixekizumab in axSpA at Week 16 (end of Blinded Treatment Period) and Week 52 (end of Extended Treatment Period) was evaluated in COAST-V, -W and X. Selected assessment for safety analyses at Week 16 were conducted on patients who were initially randomised to ixekizumab in the safety population. As described previously (Section B.2.4), the safety population was defined as all randomised patients who received at least one dose of the study treatment.[54, 55] [redacted]

During the studies, AEs were collected at every visit, regardless of relationship to study drug. These events were captured as actual terms and coded to Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 terms by blinded Lilly clinical personnel. Fisher's exact test was used to analyse all safety. The results of these safety analyses are detailed below.

COAST-V

Safety analysis at Week 16

A summary of the safety results reported in COAST-V at Week 16 is reported in Table 80.

TEAEs occurred in 43.5% of all patients (ixekizumab Q2W, 43.4%; ixekizumab Q4W, 42.0%; adalimumab, 48.9%; placebo, 39.5%). Most TEAEs reported at Week 16 in COAST-V were mild-to-moderate in severity; severe TEAEs were reported for 1.2% of all patients receiving ixekizumab. The percentages of patients with TEAEs judged by the investigator as possibly related to study drug were similar across treatment groups.[2, 54]

SAEs occurred infrequently and there was no clinically meaningful difference in the number of patients with SAEs among treatment groups. Overall, 1.2% of all patients receiving ixekizumab had at least one SAE through Week 16 (ixekizumab Q2W, 1.2%; ixekizumab Q4W, 1.2%; adalimumab, 3.3%; placebo, 0%). There were no deaths in the study.[2, 54]

There was no difference in the percentage of patients who discontinued from the study drug due to an AE among the treatment groups. Overall, 1.8% of all ixekizumab patients had AEs that led to study drug discontinuation through Week 16.[2, 54]

The most commonly reported AESIs were infections, which were reported similarly across treatment groups, and injection site reactions, which were both reported more frequently in the ixekizumab Q2W and the adalimumab Q2W groups than in the ixekizumab Q4W and placebo groups. The majority of infections were mild-to-moderate in severity and the majority of injection site reactions were mild in severity.[2, 54] A summary of the AESIs reported in COAST-V at Week 16 is reported in Table 81.

Table 80: Summary of safety analysis in COAST-V (safety population; Week 16)

AE, n (%)	Ixekizumab Q2W (N=83)	Ixekizumab Q4W (N=81)	Ixekizumab total (N=164)	Adalimumab Q2W (N=90)	Placebo (N=104)
TEAEs	36 (43.4)	38 (42.0)	70 (42.7)	44 (48.9)	34 (39.5)
Mild	28 (33.7)	22 (27.2)	50 (30.5)	28 (31.1)	22 (25.6)
Moderate	6 (7.2)	12 (14.8)	6 (7.2)	14 (15.6)	11 (12.8)
Severe	2 (2.4)	0	2 (1.2)	2 (2.2)	1 (1.2)
Patients with ≥1 SAE	1 (1.2)	1 (1.2)	2 (1.2)	3 (3.3)	0
[redacted]					
Discontinuation due to AE	3 (3.6)	0	3 (1.8)	1 (1.1)	0
[redacted]					

[a]Denominator adjusted gender-specific event for females: N=15 (PBO), N=17 (ADA40Q2W), N=13 (IXE80Q4W), N=19 (IXE80Q2W)
Abbreviations: AE: adverse event; Q2W: every 2 weeks; Q4W: every 4 weeks; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: COAST-V CSR: Week 16 Report (Table RHBV.14.75, Table RHBV.14.82 and Table RHBV.14.83)[54] and van der Heijde *et al*. (2018)[2]

Table 81: Summary of AESIs in COAST-V (safety population; Week 16)

AE, n (%)	Ixekizumab Q2W (N=83)	Ixekizumab Q4W (N=81)	Ixekizumab total (N=164)	Adalimumab Q2W (N=90)	Placebo (N=104)
[redacted]					
Hepatic	1 (1.3)	1 (1.2)	2 (1.2)	2 (2.2)	1 (1.2)
Infections	17 (20.5)	16 (9.8)	33 (20.1)	19 (21.1)	13 (15.1)
Injection site reactions	11 (13.3)	3 (3.7)	14 (8.5)	7 (7.8)	4 (4.7)

Allergic reactions and hypersensitivities	3 (3.6)	3 (3.7)	6 (3.7)	4 (4.4)	1 (1.2)
Potential anaphylaxis	0	0	0	0	0
Non-anaphylaxis	3 (3.6)	3 (3.7)	6 (3.7)	4 (4.4)	1 (1.2)
Confirmed cerebrocardiovascular events	0	1 (1.2)	1 (0.6)	0	0
Malignancies	0	0	0	0	0
Depression	0	0	0	1 (1.1)	0
Interstitial lung disease	0	0	0	0	0
Inflammatory bowel disease	1 (1.2)	0	1 (0.6)	0	0

[a]Cytopenias include neutropenia, leukopenia, and monocyte count decreased.
Abbreviations: AE: adverse event; AESI: adverse event of special interest; Q2W: every 2 weeks; Q4W: every 4 weeks.
Source: COAST-V CSR: Week 16 Report (Table RHBV.14.75)[54] and van der Heijde *et al*. (2018)[2]

Safety analysis at Week 52

A summary of the safety results reported in COAST-V at Week 52 is reported in Table 82.

[redacted][1]

[redacted][1]

[redacted][1]

[redacted][1] A summary of the AESIs reported in COAST-V at Week 52 is reported in Table 83.

Table 82: Summary of safety analysis in COAST-V (safety population who were initially randomised to ixekizumab; Week 52)

AE, n (%)	Ixekizumab Q2W (N=83)	Ixekizumab Q4W (N=81)	Ixekizumab total (N=164)
TEAEs	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Patients with ≥1 SAE	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
TEAE possibly related to study drug	[redacted]	[redacted]	[redacted]
Discontinuation due to AE	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; Q2W: every 2 weeks; Q4W: every 4 weeks; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: COAST-V CSR: Week 52 Report (Table RHBV.14.56, Table RHBV.14.65 and Table RHBV.14.67)[1]

Table 83: Summary of AESIs in COAST-V (safety population who were initially randomised to ixekizumab; Week 52)

AE, n (%)	Ixekizumab Q2W (N=83)	Ixekizumab Q4W (N=81)	Ixekizumab total (N=164)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[a]Cytopenias include neutropenia, leukopenia, and monocyte count decreased.
Abbreviations: AE: adverse event; AESI: adverse event of special interest; Q2W: every 2 weeks; Q4W: every 4 weeks.

Source: COAST-V CSR: Week 52 Report (Table RHBV.14.56)[1]

COAST-W

Safety analysis at Week 16

A summary of the safety results reported in COAST-W at Week 16 is reported in Table 84.

[redacted][55]

[redacted][55]

[redacted][55]

[redacted][55] A summary of the AESIs reported in COAST-W at Week 16 is reported in Table 85.

Table 84: Summary of safety analysis in COAST-W (safety population; Week 16)

AE, n (%)	Ixekizumab Q2W (N=98)	Ixekizumab Q4W (N=114)	Ixekizumab total (N=212)	Placebo (N=104)
TEAEs	59 (60.2)	73 (64.0)	132 (62.3)	51 (49.0)
Mild	23 (23.5)	34 (29.8)	57 (26.9)	18 (17.3)
Moderate	32 (32.7)	35 (30.7)	67 (31.6)	26 (25.0)
Severe	4 (4.1)	4 (3.5)	8 (3.8)	7 (6.7)
Patients with ≥1 SAE	3 (3.1)	4 (3.5)	7 (3.3)	5 (4.8)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Death	1 (1.0)	0	1 (0.5)	0
[redacted]				
Discontinuation due to AE (including death)	3 (3.1)	10 (8.8)	13 (6.1)	2 (1.9)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
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[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Abbreviations: AE: adverse event; Q2W: every 2 weeks; Q4W: every 4 weeks; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: COAST-W CSR: Week 16 Report (Table RHBW.14.75, Table RHBW.14.84)[55] and Deodhar *et al*. (2019)[3]

Table 85: Summary of AESIs in COAST-W (safety population; Week 16)

AE, n (%)	Ixekizumab Q2W (N=98)	Ixekizumab Q4W (N=114)	Ixekizumab total (N=212)	Placebo (N=104)
Cytopenia[a]	2 (2.0)	0	2 (0.9)	0
Hepatic	1 (1.0)	5 (4.4)	6 (2.8)	2 (1.9)
Infections	23 (23.5)	34 (29.8)	57 (26.9)	10 (9.6)
Injection site reactions	16 (16.3)	9 (7.9)	25 (11.8)	6 (5.8)
Allergic reactions and hypersensitivities	6 (6.1)	3 (2.6)	9 (4.2)	1 (1.0)
Potential anaphylaxis	0	0	0	0
Non-anaphylaxis	6 (6.1)	3 (2.6)	9 (4.2)	1 (1.0)

Confirmed cerebrocardiovascular events	1 (1.0)	0	1 (0.5)	1 (1.0)
Malignancies	0	1 (0.9)	1 (0.5)	0
Depression	2 (2.0)	0	2 (0.9)	5 (4.8)
Interstitial lung disease	0	0	0	0
Inflammatory bowel disease	0	3 (2.6)	3 (1.4)	1 (1.0)

[a]Cytopenias include neutropenia, leukopenia, and monocyte count decreased.
Abbreviations: AE: adverse event; AESI: adverse event of special interest; Q2W: every 2 weeks; Q4W: every 4 weeks.
Source: COAST-W CSR: Week 16 Report (Table RHBW.14.75)[55] and Deodhar *et al*. (2019)[3]

Safety analysis at Week 52

A summary of the safety results reported in COAST-W at Week 52 is reported in Table 86.

[redacted][4]

[redacted][4]

[redacted][4]

[redacted][4] A summary of the AESIs reported in COAST-V at Week 52 is reported in Table 87.

Table 86: Summary of safety analysis in COAST-W (safety population who were initially randomised to ixekizumab; Week 52)

AE, n (%)	Ixekizumab Q2W (N=98)	Ixekizumab Q4W (N=114)	Ixekizumab total (N=212)
TEAEs	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Patients with ≥1 SAE	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
TEAE possibly related to study drug	[redacted]	[redacted]	[redacted]
Discontinuation due to AE	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; Q2W: every 2 weeks; Q4W: every 4 weeks; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: COAST-W CSR: Week 52 Report (Table RHBW.14.55, Table RHBW.14.63 and Table RHBW.14.65)[4]

Table 87: Summary of AESIs in COAST-W (safety population who were initially randomised to ixekizumab; Week 52)

AE, n (%)	Ixekizumab Q2W (N=98)	Ixekizumab Q4W (N=114)	Ixekizumab total (N=212)
Cytopenia[a]	[redacted]	[redacted]	[redacted]

Hepatic	[redacted]	[redacted]	[redacted]
Infections	[redacted]	[redacted]	[redacted]
Injection site reactions	[redacted]	[redacted]	[redacted]
Allergic reactions and hypersensitivities	[redacted]	[redacted]	[redacted]
Potential anaphylaxis	[redacted]	[redacted]	[redacted]
Non-anaphylaxis	[redacted]	[redacted]	[redacted]
Confirmed cerebrocardiovascular events	[redacted]	[redacted]	[redacted]
Malignancies	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]	[redacted]
Inflammatory bowel disease	[redacted]	[redacted]	[redacted]

[a]Cytopenias include neutropenia, leukopenia, and monocyte count decreased.
Abbreviations: AE: adverse event; AESI: adverse event of special interest; Q2W: every 2 weeks; Q4W: every 4 weeks.
Source: COAST-W CSR: Week 52 Report (Table RHBW.14.55)[4]

COAST-X

Safety analysis at Week 16

A summary of the safety results reported in COAST-X at Week 16 is reported in Table 88.

[redacted]

[redacted]

[redacted]

[redacted] A summary of the AESIs reported in COAST-X at Week 16 is reported in Table 89.

Table 88: Summary of safety analysis in COAST-X (safety population; Week 16)

AE, n (%)	Ixekizumab Q2W (N=102)	Ixekizumab Q4W (N=96)	Ixekizumab total (N=198)	Placebo (N=104)
TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 SAE	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
TEAE possibly related to study drug	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation due to AE	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; Q2W: every 2 weeks; Q4W: every 4 weeks; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.12.1 and Table RHBX.12.5)[5]

Table 89: Summary of AESIs in COAST-X (safety population; Week 16)

AE, n (%)	Ixekizumab Q2W (N=102)	Ixekizumab Q4W (N=96)	Ixekizumab total (N=198)	Placebo (N=104)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Cytopenias include neutropenia, leukopenia, and monocyte count decreased.
Abbreviations: AE: adverse event; AESI: adverse event of special interest; Q2W: every 2 weeks; Q4W: every 4 weeks.
Source: COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.14.118)[5]

Safety analysis at Week 52

A summary of the safety results reported in COAST-X at Week 52 is reported in Table 90

TEAEs occurred in [redacted] of all patients (ixekizumab Q2W, 77.5%; ixekizumab Q4W, 65.6%; placebo, 57.7%).[6] [redacted] severe TEAEs were reported for [redacted], with the highest number in the ixekizumab 80 mg Q2W group. [redacted]

There was no difference in the percentage of patients with SAEs among the treatment groups. No SAEs were reported for more than 1 patient.[6] [redacted] There were no deaths in the study.[5, 6]

There was no difference in the percentage of patients who discontinued from the study drug due to an AE among the treatment groups. Overall, 1.0% of all ixekizumab patients had AEs that led to study drug discontinuation through Week 52.[5, 6]

The most commonly reported AESIs were infections and injection site reactions which were both reported more frequently in each of the ixekizumab treatment groups than in the placebo group. Infections and injection site reactions were mainly mild-to-moderate in severity.[5, 6] A summary of the AESIs reported in COAST-X at Week 16 is reported in Table 89.

Table 90: Summary of safety analysis in COAST-X (safety population; Week 52; prior to biologic rescue of ixekizumab Q2W)

AE[a], n (%)	Ixekizumab Q2W (N=102)	Ixekizumab Q4W (N=96)	Ixekizumab total (N=198)	Placebo (N=104)
TEAEs	79 (77.5)*	63 (65.6)	142 (71.7)	60 (57.7)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	7 (6.9)	1 (1.0)	8 (4.0)	4 (3.8)
Patients with ≥1 SAE	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaphylactoid reaction	0	0	0	1 (1.0)
Death	0	0	0	0
TEAE possibly related to study drug				
Discontinuation due to AE	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaphylactoid reaction	0	0	0	1 (1.0)

*p<0.05 versus placebo

Abbreviations: AE: adverse event; Q2W: every 2 weeks; Q4W: every 4 weeks; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: Deodhar *et al.* (2019),[6] COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.12.2, Table RHBX.12.6 and Table RHBX.12.9)[5]

Table 91: Summary of AESIs in COAST-X (safety population; Week 52)

AE, n (%)	Ixekizumab Q2W (N=102)	Ixekizumab Q4W (N=96)	Ixekizumab total (N=198)	Placebo (N=104)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic	5 (4.9)	3 (3.1)	8 (4.0)	6 (5.8)
Infections	43 (42.2)	38 (39.6)	81 (40.9)	30 (28.8)
Injection site reactions	25 (24.5)	18 (18.8)	43 (21.7)	7 (6.7)
Allergic reactions and hypersensitivities	3 (2.9)	4 (4.2)	7 (3.5)	4 (3.8)
Potential anaphylaxis	0	0	0	1 (1.0)
Non-anaphylaxis	3 (2.9)	4 (4.2)	7 (3.5)	3 (2.9)
Confirmed cerebrocardiovascular events	1 (1.0)	0	1 (0.5)	0
Malignancies	0	0	0	0
Depression	4 (3.9)	0	4 (2.0)	0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inflammatory bowel disease	0	0	0	1 (1.0)

[a]Cytopenias include neutropenia, leukopenia, and monocyte count decreased.
Abbreviations: AE: adverse event; AESI: adverse event of special interest; Q2W: every 2 weeks; Q4W: every 4 weeks.
Source: Deodhar *et al.* (2019),[6] COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.14.119)[5]

Pooled results

Safety analysis at Week 16

A summary of the pooled safety analysis of COAST-V and COAST-W at Week 16 is presented in Table 92.

[redacted]

Table 92: Summary of safety analysis in COAST-V and -W (safety population; Week 16)

AE, n (%)	Ixekizumab Q2W (N=181)	Ixekizumab Q4W (N=195)	Ixekizumab total (N=376)	Placebo (N=190)
TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Mild[a]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate[a]	[redacted]	[redacted]	[redacted]	[redacted]

Severe[a]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 SAE[b]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
TEAE possibly related to study drug	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation due to AE	[redacted]	[redacted]	[redacted]	[redacted]

[a]Patients with multiple occurrences of the same event are counted under the highest severity.
[b]The data collection for the clinical trial database does not contain specification on when events became serious, the numbers may represent more events considered serious than what was actually serious during the treatment period.
Abbreviations: AE: adverse event; Q2W: every 2 weeks; Q4W: every 4 weeks; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: COAST-V and COAST-W Pooled Analysis (Table 3.39 and Table 3.40)[58]

Table 93: Summary of AESIs in COAST-V and COAST-W (safety population; Week 16)

AE, n (%)	Ixekizumab Q2W (N=181)	Ixekizumab Q4W (N=195)	Ixekizumab total (N=376)	Placebo (N=190)
TEAE of special interest	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE, n (%)	Ixekizumab Q2W (N=181)	Ixekizumab Q4W (N=195)	Ixekizumab total (N=376)	Placebo (N=190)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]Cytopenias include neutropenia (COAST-V and COAST-W) and leukopenia (COAST-W).
Abbreviations: AE: adverse event; AESI: adverse event of special interest; Q2W: every 2 weeks; Q4W: every 4 weeks; TEAE: treatment-emergent adverse event.
Source: COAST-V and COAST-W Pooled Analysis (Table 3.39)[58]

B.2.11 *Ongoing studies*

Additional evidence to support the use of ixekizumab in patients with axSpA is expected following completion of the COAST-Y trial. COAST-Y is a multi-centre, long-term 104-week extension study, including a double-blind, placebo-controlled, 40-week extension period, to evaluate the maintenance of treatment effect of ixekizumab in patients with axSpA. Patients are eligible for inclusion in COAST-Y if they have completed the final study visit for COAST-V, COAST-W, or COAST-X.[60] Results for COAST-Y are expected in March 2020.

B.2.12 *Innovation*

Ixekizumab is a humanised monoclonal antibody that selectively binds to IL-17A. As described in B.1.2, there is compelling scientific evidence to demonstrate an important role of the IL-17/IL-23 pathway in the pathogenesis of axSpA.[10, 11] As such, inhibition of this pathway is likely to result in a reduction in the symptoms and progression of axSpA.

For over a decade, the treatment of axSpA has been predominantly through use of NSAIDs and TNF-alpha inhibitors. However, only one-third of patients obtain partial remission with NSAIDs alone, and between 20–40% of patients receiving their first TNF-alpha inhibitor therapy may have an inadequate response to treatment or experience AEs.[25, 28, 29, 42] As a result of this, there is a significant proportion of patients with axSpA who have inadequate disease management. In the UK, non-responders to first-line TNF-alpha inhibitor therapy will commonly be treated with another TNF-alpha inhibitor, however there is a lack of robust clinical data to support the effectiveness of this.[24] Patient experts consulted during NICE TA383 further highlighted the importance of the availability of having options at different lines of therapy (e.g. once initial biologic therapy has failed) to patients' mental wellbeing.[24]

Through the innovative targeting of IL-17 pathways, ixekizumab offers an alternative agent in instances of treatment failure where few alternative therapies currently exist. For patients with rad-axSpA whose disease has not responded to treatment with TNF-alpha inhibitors, there is currently only one other treatment with an alternative mechanism of action (secukinumab) and for patients with nr-axSpA, there are no biologic treatment options available in the UK with alternative mechanisms of action to TNF-alpha inhibitors. There is a need in clinical practice for another treatment option for axSpA which does not act through TNF-alpha inhibition. This is particularly important for patients who are contraindicated to TNF-alpha inhibitors.

Additionally, whilst ixekizumab and secukinumab both act through IL-17 inhibition, they differ with regards to some molecular and pharmacokinetic characteristics, which could result in differences in efficacy or safety profiles. For example, the *in vitro* binding affinity to IL-17A for ixekizumab is 1.8 pmol/L compared with 100–200 pmol/L for secukinumab.[2, 74] In the results of the indirect treatment comparison presented in this submission, ixekizumab was shown to be superior to secukinumab for both ASAS40 response and BASDAI cfb in the biologic-naïve rad-axSpA population at 12–18 weeks.[74]

The results of COAST-V, -W and -X demonstrate that treatment with ixekizumab results in rapid, clinically significant and sustained improvements in the signs and symptoms of axSpA, including disease activity, functional ability, pain, structural damage and HRQoL.[1-5, 54, 55, 60] Additionally, the primary endpoint in COAST-V, -W and -X was ASAS40, whilst historically clinical trials in axSpA have used ASAS20 as the primary endpoint. ASAS40 is a more challenging endpoint to achieve than ASAS20 and requires a high level of improvement in the patient's illness, defined as a relative improvement of ≥40% and an absolute improvement of ≥2 (range 0–10) in three of the four domains. The domains (overall disease, pain, inflammation/stiffness, and function) focus on the patient's perception of the disease and their ability to function, making ASAS40 a clinically meaningful and relevant treatment goal.[56] In an analysis assessing the association between ASAS response and patient reported outcomes in patients included in the COAST-V and -W trials, it was identified that compared to ASAS20 non-responders, patients achieving an ASAS40 response reported significantly greater mean changes in spinal pain at night, fatigue, sleep quality and SF-36 PCS ($p<0.0001$).[56]

In addition, COAST-W was the first trial to be specifically designed for rad-axSpA patients who had shown intolerance or inadequate response to TNF-alpha inhibitors and to show a statistically significant benefit in these patients.[3, 75] The patients enrolled onto COAST-W were highly refractory. A high proportion 89.6% had a previous inadequate response to TNF-alpha inhibitors, and a high proportion of patients had active signs of inflammation ([redacted] MRI SPARCC scores greater than two) and elevated baseline CRP ([redacted]).[55]

B.2.13 *Interpretation of clinical effectiveness and safety*

B.2.13.1 Principal findings from clinical evidence base

The clinical effectiveness of ixekizumab in axSpA has been demonstrated in three multi-centre, international, Phase III RCTs (COAST-V, COAST-W and COAST-X), in biologic-naïve rad-axSpA, biologic-experienced rad-axSpA and biologic-naïve nr-axSpA patients, respectively.

The primary endpoint of COAST-V, -W and -X was ASAS40 response at Week 16. ASAS40 is a stringent composite measure of disease activity, functional impairment, spinal pain and inflammation in axSpA, derived from patient-reported assessments, and is recommended by the EMA for use in clinical trials assessing treatments for axSpA.[76] Key secondary endpoints spanned the numerous elements of axSpA, including disease activity, functional capacity, pain, and health-related QoL. COAST-W was also the first trial to include SPARCC MRI evaluation in a subset of patients at Week 16 in TNF-alpha inhibitor experienced patients.[3]

The primary endpoint was met in all three clinical trials. In COAST-V (biologic-naïve rad-axSpA patients) in the ITT population at Week 16, a statistically significantly greater proportion of

patients achieved an ASAS40 response in both the ixekizumab Q4W (48.1%; p<0.0001) and Q2W (51.8%; p<0.0001) treatment groups compared to placebo (18.4%).[2] Similarly, in COAST-W (biologic-experienced rad-axSpA patients), in the ITT population at Week 16, response rates were higher in both the ixekizumab Q4W (25.4%; p=0.017) and Q2W groups (30.6%; p=0.003), compared to the treatment group receiving the placebo (12.5%).[3] Finally, in COAST-X (biologic-naïve nr-axSpA patients), in the ITT population at Week 16, response rates were again higher in both the ixekizumab Q4W (35.4%; p=0.009) and Q2W groups (40.2%; p=0.002), compared to the treatment group receiving the placebo (19.0%).[5, 6]

Additionally, in all three clinical trials, a statistically significantly greater proportion of patients achieved a clinically meaningful reduction in disease activity (as measure by BASDAI50 response rate) in both ixekizumab arms in comparison to placebo at Week 16. In COAST-V, BASDAI50 response rates were statistically significantly higher in both the ixekizumab Q4W (42.0%; p=0.0003) and Q2W (43.4%; p=0.0002) treatment arms compared to placebo (17.4%) at Week 16.[2] In COAST-W, at Week 16 BASDAI50 response rates were also statistically significantly greater in the ixekizumab Q4W ([redacted]%; p=[redacted]) and Q2W ([redacted]; p=[redacted]) treatment arms compared to placebo ([redacted]).[55]. Similarly, in COAST-X, BASDAI50 response rates were again statistically significantly greater in the ixekizumab Q4W ([redacted]) and Q2W ([redacted]) treatment arms compared to placebo ([redacted]) at Week 16.[5]

Ixekizumab also demonstrated significant improvements versus placebo for a number of secondary outcome measures in all three COAST trials, including cfb in BASDAI score, the proportion of patients achieving low disease activity by ASDAS <2.1, cfb in BASFI score, SPARCC MRI spinal and/or sacroiliac joint score, spinal pain, and SF-36 PCS scores. These results represent a substantial improvement in symptoms for patients, translating to less pain, increased ability to carry out daily activities, and improved health-related QoL. Additionally, COAST-V and -X demonstrate that ixekizumab is clinically effective throughout the treatment pathway in rad-axSpA, with both biologic-naïve and -experienced patients demonstrating statistically significant responses.[2, 3, 6]

[redacted] Demonstrating that ixekizumab has long-term efficacy in treating patients with axSpA.

Results of the ITC showed that ixekizumab was [redacted] for [redacted] and [redacted] in biologic-naïve rad-axSpA patients.[57]
[redacted].[57]
[redacted]; [redacted]
[redacted][57] In the biologic-naïve nr-axSpA population, ixekizumab was [redacted] to placebo for ASAS40 and BASDAI50 response and BASDAI and

BASFI cfb.

[redacted][57]

Ixekizumab was well-tolerated in patients with axSpA and the safety profile of ixekizumab in the COAST trials is consistent with published results of ixekizumab in other indications, such as psoriatic arthritis and psoriasis. Most TEAEs reported in the trials across all treatment arms were mild-to-moderate in severity and SAEs occurred infrequently. The most commonly reported AESIs in patients who were initially randomised to ixekizumab in the safety population, were infections and injection-site reactions, the majority of which were mild in severity.[1, 4, 5, 54, 55, 58]

B.2.13.2 Strengths and limitations of the clinical evidence base

Strengths

COAST-V, -W and -X are multi-centre, international, randomised, double-blind controlled trials, and are the first Phase III trials to investigate ixekizumab for the treatment of biologic-naïve rad-axSpA, biologic-experienced rad-axSpA and biologic-naïve nr-axSpA, respectively.[2, 3, 5] All three trials have high internal validity and are of high quality, as has been validated by a full quality assessment using the CRD criteria (see Section B.2.5).

Individual trials were carried out in the three populations of interest, each of which had a large sample size, increasing the power of the studies to assess the efficacy of ixekizumab in the relevant treatment populations. [2, 3, 5] Additionally, COAST-V is the first study in axSpA to include an active reference group (adalimumab), which provides additional context to the observed efficacy of ixekizumab.[2]

The primary endpoint used in the COAST trials was ASAS40, which is a more rigorous measure than the more commonly used ASAS20, and therefore may be more clinically relevant to patients and clinicians.[2, 3, 5, 56] Furthermore, the ASAS40 response criteria is recommended by the EMA as the preferred primary endpoint when assessing the efficacy of treatments for axSpA.[76] The COAST trials also investigated a large number of secondary endpoints which included assessment of disease activity, physical function, spinal MRI, radiographic progression and quality of life.[2, 3, 5]

The COAST trial programme also provides long-term assessment of the efficacy and safety of ixekizumab. Blinded treatment assessment was carried out until Week 16, following which each trial assessed the efficacy and safety of ixekizumab up to one year, and there is also an optional two-year extension study (COAST-Y) currently in progress, with data expected in March 2020.[1, 4, 5, 60]

Limitations

One of the limitations of the trials regarding external validity in the context of this submission is that,

[redacted] Additionally, the majority of patients in each trial were of white ethnicity,[2, 3, 5, 6] and

the average age of onset was <45 years, which aligns with UK axSpA statistics.[70] Therefore, the results from the trials are expected to be generalisable to UK clinical practice.

Another limitation of the trials is that no direct comparisons were conducted between ixekizumab and the comparators described in the NICE scope, necessitating an NMA to be conducted. COAST-W and COAST-X assessed ixekizumab Q2W and Q4W in comparison with placebo only, and whilst COAST-V also included an adalimumab 40 mg Q2W arm, this was an active reference group, and the study was not designed to test non-inferiority of ixekizumab compared with adalimumab.[2, 3, 5, 6] With regards to the NMA, as described in Section B.2.9.4, a limitation was that it was necessary to perform a sensitivity analysis in which the patient population criteria were expanded with regards to biologic experience, in order to generate comparative efficacy estimates between ixekizumab and more comparators relevant to the decision problem. However, in a comparison between the base case and sensitivity analysis results, no differences in comparative efficacy conclusions were identified for comparisons common to both sets of analyses.

A further limitation of the evidence base available in this indication is the lack of RCT data to support the use of ixekizumab in biologic-experienced nr-axSpA patients. A lack of data available in biologic-experienced patients in axSpA is a common limitation to this disease area, not just to ixekizumab, that has also been observed in previous NICE appraisals in this indication.[24, 25] However, previous RCTs of ixekizumab have demonstrated that efficacy is maintained across biologic-naïve and -experienced patients in similar indications, for example rad-axSpA and psoriatic arthritis.[2, 3, 77, 78] In line with this, clinical experts consulted during TA383 stated that they would consider the relative efficacy of a second TNF-alpha inhibitor (i.e. alternative biologic treatments) to be comparable in nr-axSpA and rad-axSpA.

Subgroup analyses were also not performed in the COAST trials for patients contraindicated to TNF-alpha inhibitors. However, given patients are classified as contraindicated due to safety reasons, there is no reason to believe that the efficacy of ixekizumab would differ in contraindicated patients compared to patients who are not contraindicated to TNF-alpha inhibitors. As such, data from the ITT populations of the COAST trial may be considered generalisable to this patient population.

B.3 Cost effectiveness

Summary of cost-effectiveness

- No published cost-effectiveness analyses were identified for ixekizumab in rad- or nr-axSpA in an SLR of economic evaluations, therefore a *de novo* model was developed to assess the cost-effectiveness of ixekizumab in the following populations:
  - **Biologic-naïve patients:** Rad-axSpA patients who have responded inadequately to two or more NSAIDs, or have shown intolerance of NSAIDs; in line with patients included in COAST-V
  - **Biologic-experienced patients:** Rad-axSpA patients who have responded inadequately to or were intolerant to one to two TNF-alpha inhibitors, following inadequate response to two or more NSAIDs, or intolerance of NSAIDs; in line with patients included in COAST-W
  - **Biologic-naïve patients**: Nr-axSpA patients who have responded inadequately to two or more NSAIDs, or are intolerant of NSAIDs; in line with patients included in COAST-X
  - Patients contraindicated to TNF-alpha inhibitors were included within these three populations
  - The cost-effectiveness of biologic-experienced nr-axSpA patients was considered in a scenario analysis
- The comparators to ixekizumab for each patient population are presented in Section B.3.2.3
- A cohort Markov model was developed with a 'trial period', represented by a set of tunnel states, followed by 'maintenance treatment', 'conventional care' and 'death', which were represented by traditional Markov health states
- Patients entered the model at the relevant treatment line (biologic-naïve or -experienced)
- The model employs a lifetime time horizon, a cycle length of month and costs and benefits were discounted at 3.5%, as per the NICE reference case
- Patients' disease status in the model was characterised by their BASDAI and BASFI scores:
  - Achievement of a BASDAI50 response after the trial period determined treatment continuation, following which patients experienced an improvement in their BASDAI and BASFI scores
  - Patients' BASFI score subsequently defined their disease progression over time
- In the base case, BASDAI50 response and cfb in BASDAI and BASFI data for each intervention were taken from the NMA sensitivity analysis (detailed in Section B.2.9). Where data were missing for comparators, a separate analysis was conducted to generate missing data and assessed in a scenario analysis, as described in Section B.3.3.3
- Long-term BASFI progression was modelled as a function of bony progression, as defined by mSASSS, with parameters for the change in mSASSS over time derived from the literature for rad- and nr-axSpA.[79-81] A treatment effect was applied which delayed BASFI progression for patients receiving a biologic therapy
- Upon treatment discontinuation, patients were assumed to 'rebound by their initial gain' in the base case, i.e. their BASFI scores deteriorated by the amount equal to the improvement achieved during response to biologic therapy, in addition to the amount of deterioration that occurred during maintenance treatment
- In each of the patient populations, an algorithm was applied which mapped patients' BASFI and BASDAI scores to EQ-5D-3L values adjusted to the UK value set
- The following costs were included in the model: drug acquisition and administration costs, treatment initiation and monitoring costs, disease related costs and AEs. A simple PAS, already established within the NHS for ixekizumab for two indications, was applied in the cost-effectiveness analysis

- In the base case for the biologic-naïve rad-axSpA population, ixekizumab was either cost-effective or dominant in pairwise comparisons against all biologic treatments recommended by NICE in this population, with the exception of adalimumab.
- In the base case for the biologic-experienced rad-axSpA population, pairwise ICERs for ixekizumab versus four biologic comparators fell into the cost-effective region of south-west quadrant of the cost-effectiveness plane.
- In the base case for the biologic-naïve nr-axSpA population, ixekizumab was found to be cost-effective versus two biologic treatments recommended by NICE in this population, as well as conventional care, indicating ixekizumab would also be a suitable option for patients contraindicated to TNF-alpha inhibitors.
- In all three populations, the probabilistic base case was aligned with the deterministic base case, and the results of the DSAs and scenario analyses similarly found the results to be robust.
- The results of the scenario analysis in biologic-experienced nr-axSpA patients demonstrated that ixekizumab may comprise a cost-effective treatment option, with cost-effective or dominant ICERs versus two biologic treatments recommended by NICE.
- [redacted]
- Overall, the results of the cost-effectiveness analysis demonstrate that ixekizumab offers physicians an additional cost-effective option in their armamentarium of biologic therapies to treat patients either biologic-naïve or experienced rad- or nr-axSpA, including patients contraindicated to TNF-alpha inhibitors.

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted from January to March 2017 and updated in 22nd October 2019 to identify studies evaluating the cost-effectiveness of ixekizumab and other relevant interventions for the treatment of rad-axSpA and nr-axSpA. This SLR was also used to identify HRQoL inputs and UK-relevant cost and resource use model inputs. The original and update searches identified 13,934 and 9,253 records from electronic databases and conference proceedings, respectively. Following duplicate removal, 11,272 and 4,593 records were left for title and abstract review, respectively. A total of 638 records (including 15 records identified through a hand search) were selected for full-text review against the study eligibility criteria. Subsequently, 121 records were included (98 articles in the original SLR and 23 articles in the update) and selected for data extraction. Of those included in the original and updated review, 26 were categorised as CEMs.

A summary of the UK cost-effectiveness studies identified in the SLR is presented in Table 94 and a summary of the reports of manufacturers' submissions for UK HTAs is presented in Table 95. Full details of the SLR methodology can be found in Appendix G.

Table 94: Summary list of published cost-effectiveness studies in rad-axSpA and nr-axSpA

Study	Summary of model	Intervention	Comparator(s)	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Rad-axSpA							
Ara *et al.* (2007)[82]	Individual patient model	ETA + NSAIDs	NSAIDs	NR	1,000 patients over 4 time periods: ETA: - 2 years: 1,185 - 5 years: 2,646 - 15 years: 5,739 - 25 years: 7,285 NSAIDs: - 2 years: 817 - 5 years: 1,831 - 15 years: 4,286 - 25 years: 5,700	1,000 patients over 4 time periods: ETA: - 2 years: £13,041,740 - 5 years: £26,389,802 - 15 years: £51,415,277 - 25 years: £62,516,684 NSAIDs: - 2 years: £2,889,706 - 5 years: £7,109,054 - 15 years: £18,596,422 - 25 years: £26,538,439	ETA + NSAIDs vs NSAIDs from a cohort of 1,000 patients over 4 time periods: - 2 years: £27,594 - 5 years: £23,649 - 15 years: £22,580 - 25 years: £22,704
Botteman *et al.* (2007)[83]	Microsimulation model	ADA	Conventional therapy	42 years	ADA: - 48 weeks: 0.5529 - 5 years: 2.6653 - 30 years: 9.2220 Conventional therapy:	ADA: - 48 weeks: £9,857 - 5 years: £36,802 - 30 years: £115,937 Conventional therapy: - 48 weeks: £4,832	ADA vs conventional therapy: - 48 weeks: £47,083 - 5 years: £26,332 - 30 years: £23,097

					- 48 weeks: 0.4461 - 5 years: 2.1613 - 30 years: 8.1891	- 5 years: £23,529 - 30 years: £92,080	
Kobelt *et al.* (2004)[84]	Decision tree + Markov model	IFX	Standard care	40.1 years	IFX vs standard care: The total gain in QALYs over 2 years was estimated at 0.175 (discounted by 1.5%), equivalent to more than 2 months at full health. When a discount rate of 3% is used for both costs and effects, the incremental cost is £6,624 for a QALY gain of 0.174.	IFX vs standard care: In the base case, total 2-year costs in the treatment arm are estimated at £17,240 (excluding the cost of IFX) compared with £25,126 in the placebo group. Cost offsets amount to £4,731 and £3,155 for direct and indirect costs, respectively. Treatment costs amount to £14,100, leading to an incremental cost of £6,214 (discounted by 6%). When the calculation is limited to 54 weeks, thus excluding any potential carry-over benefit of the treatment, the total incremental cost amounts to £7,341.	IFX vs standard care: £35,400/QALY gained (societal perspective) and £73,300/QALY gained (only health-care costs)

Kobelt *et al.* (2007)[85]	Decision tree + Markov model	IFX	Standard care	40 years	NR	NR	IFX vs standard care: £15,045 and £11,937 for the Braun and ASSERT trials, respectively (incremental costs: £12,156 and £10,540 for the Braun and ASSERT trials, respectively; incremental QALY gain: 0.81 and 0.88 for the Braun and ASSERT trials, respectively.)
Armstrong *et al.* (2013)[86]	Decision tree + Markov model	GOL	Conventional therapy ADA ETA	NR	Conventional treatment: 7.8762 GOL: 8.0296 ADA: 8.3683 ETA: 8.3712	Conventional treatment: £95,227 GOL: £99,361 ADA: £108,295 ETA: £108,347	Conventional treatment: - GOL: NA (Extendedly dominated) ADA: NA (Extendedly dominated) ETA: £26,505 (vs conventional treatment)
Corbett *et al.* (2016)[87]	Decision tree + Markov model	TNF-alpha inhibitors	Conventional care	40 years	*Strategy: Results for rebound equal to gain/Results for rebound to CC* CC: £ 110,821/109,933	*Strategy: Results for rebound equal to gain/Results for rebound to CC* CC: NA/NA CZP with PAS:	*Strategy: Results for rebound equal to gain/Results for rebound to CC* CC: NA/NA CZP with PAS:

					CC: 7.245/7.265 CZP with PAS: 8.163/7.867 GOL: 8.163/7.867 ADA: 8.163/7.867 ETA: 8.163/7.867 CZP: 8.163/7.867 IFX: 8.163/7.867	CZP with PAS: £128,485/130,277 GOL: £130,173/131,960 ADA: £130,257/132,045 ETA: £130,630/132,423 CZP: £132,059/133,851 IFX: £148,073/150,022	£19,240/£33,762 GOL: £21,079/£36,554 ADA: £21,170/£36,695 ETA: £21,577/£37,322 CZP: £23,133/£39,693 IFX: £40,576/£66,529
McLeod *et al.* (2007)[88]	Spreadsheet calculations with Markov assumptions for extension	ADA ETA IFX	Conventional care	40 years	*12 months* Conventional treatment: 521.7 per cohort of 1,000 patients ADA: 620.3 per cohort of 1,000 patients ETA: 620.3 per cohort of 1,000 patients IFX: 620.3 per cohort of 1,000 patients *2–20 years* Total QALYs (0-2y/0-3y/0-5y/0-10y/0-20y) Conventional treatment per	*12 months* Conventional treatment: £213 ADA: £5,860 ETA: £5,860 IFX: £12,059 *2–20 years* Total costs (0-2y/0-3y/0-5y/0-10y/0-20y) Conventional treatment: £425 / £632 / £1,033 / £1,962 / £3,546 ADA/ETA: £9,425 / £12,411 / £17,212 / £25,675 / £36,705 IFX: £22,779 / £30,969 / £44,573 / £62,213	*12 months* (Cost per QALY gained vs Conventional treatment) ADA: £57,258 ETA: £57,261 IFX: £120,109 *2–20 years* Incremental cost per QALY gained vs CC (0-2y/0-3y/0-5y/0-10y/0-20y) ADA/ETA: £52,534 / £52,932 / £56,976 / £71,454 / £98,910 IFX: £103,721 / £99,516 / £105,423 /

					1,000 patients: 1015.6 / 1489.2 / 2378.6 / 4292.3 / 7009.0 ADA/ETA per 1,000 patients: 1186.9 / 1711.7 / 2662.5 / 4624.2 / 7344.2 IFX per 1,000 patients: 1186.9 / 1711.7 / 2662.5 / 4624.2 / 7344.2		£128,399 / £175,000
Borse *et al.* (2017)[89]	Decision-analytic model was used: an initial short-term decision tree for the induction phase and long-term Markov model (with initial decision tree) for the maintenance phase	GOL	Conventional care and other TNF-alpha inhibitors (ETA, CZP, IFX, ADA)	39.3 years	TNF-alpha inhibitors vs CC and between different TNF-alpha inhibitors: - CC (reference) 10.553 -GOL: 11.633 -ADA: 11.630 -CZP: 11.696 -ETA: 11.586 -IFX: 11.682	TNF-alpha inhibitors vs CC -CC (reference) £160,837 -GOL: £181,427 -ADA: £181,589 -CZP: £183,017 -ETA: £183,540 -IFX: £208,856 Between different TNF-alpha inhibitors -CC (reference): £160,837 -GOL: £181,427 -ADA: £181,589 -CZP: £183,017 -ETA: £183,540 -IFX: £208,856	TNF-alpha inhibitors (vs CC): £19,070–42,532 per QALY gained TNF-alpha inhibitors vs CC -CC (reference) -GOL: 19,070 -ADA: 19,275 -CZP: 19,401 -ETA: 21,972 -IFX: 42,532 Between different TNF-alpha inhibitors -CC (reference) -GOL: 19,070 -ADA: Dominated by GOL -CZP: 25,000 -ETA: Dominated by both GOL and

							CZP -IFX: Dominated by CZP
Emery *et al*. (2018)[90]	3-month decision tree leading into a Markov model	SEC	Licensed TNF-inhibitors (including available biosimilars)	43.30 years	Biologic-naïve: SEC (at list price): 8.833 ADA: 8.680 CZP (at list price): 8.741 ETN (originator): 8.414 ETN (biosimilar): 8.414 GOL (at list price): 8.836 INF (originator): 8.859 INF (biosimilar): 8.859 Biologic-experienced: CC: 7.264 SEC (at list price): 8.282	Biologic-naïve: SEC (at list price): £124,064 ADA: £127,962 CZP (at list price): £125,995 ETN (originator): £122,927 ETN (biosimilar): £120,911 GOL (at list price): £129,941 INF (originator): £145,170 INF (biosimilar): £141,019 Biologic-experienced: CC: £122,858 SEC (at list price): £127,872	Biologic-naïve, ICER (£ per QALY): -SEC (at list price): £7524 (fully incremental analysis) -ADA: Dominated (fully incremental analysis); SEC dominates (pairwise) -CZP (at list price): Dominated (fully incremental analysis); SEC dominates (pairwise) -ETN (originator): Dominated (fully incremental analysis); £2712 (pairwise) -ETN (biosimilar): NR (fully incremental analysis); £7524 (pairwise) -GOL (at list price): Extendedly dominated (fully incremental

							analysis); £1,594,503^b (pairwise) -INF (originator): Dominated (fully incremental analysis); £818,873^b (pairwise) -INF (biosimilar): £657,820 (fully incremental analysis); £657,820^b (pairwise) Biologic-experienced, ICER (£ per QALY): £4927 Note: The fully incremental analysis finds all interventions other than SEC, ETN (biosimilar) and INF (biosimilar) to be dominated or extendedly dominated. The ICER for SEC vs. ETN (biosimilar) was £7524, and the ICER for INF (biosimilar) vs.

							SEC was £657,820 b ICERs for SEC vs. the comparators that are marked with an asterisk represent ICERs in the south-west quadrant of the cost-effectiveness plane (negative incremental costs and negative incremental QALYs with SEC). Therefore, the ICER is a positive value and should be interpreted as the cost savings per QALY foregone with SEC vs. the comparator
Harvard *et al.* (2017)[91]	NR	TNF-alpha inhibitors	Conventional care	33 ± 7.6 years	TNF-alpha inhibitor non-user: 0.61±0.01 TNF-alpha inhibitor user: 0.63±0.02	TNF-alpha inhibitor non-user: 756€ ± 644€ TNF-alpha inhibitor user: 16,952€ ± 1160€	TNF-alpha inhibitor user vs TNF-alpha inhibitor non-user: 766,217 €/QALY gained (264,164, Dominated)
Svedbom *et al.* (2019)[92]	-Markov cohort model -The York cost-effectiveness model, commissioned	Subcutaneous TNF-alpha inhibitors	Conventional care - may comprise as NSAIDs, conventional	40 years	Both Health care & societal perspectives - 10.2 (25% drop-out rate)	Health care perspective -£137,558 (25% drop-out rate) -£139,379 (20% drop-out rate)	ICER versus baseline (£/ QALY), Health care perspective -£17,227 (20% drop-out rate)

	and funded by the UK Health Technology Assessment (HTA) program on behalf of NICE, was reconstructed and customised		DMARDs and physiotherapy		- 10.3 (20% drop-out rate) - 10.4 (15% drop-out rate) - 10.7 (10% drop-out rate) - 11.2 (5% drop-out rate)	-£142,178 (15% drop-out rate) -£146,954 (10% drop-out rate) -£156,490 (5% drop-out rate) Societal perspective -£325,885 (25% drop-out rate) -£325,270 (20% drop-out rate) -£324,428 (15% drop-out rate) -£323,346 (10% drop-out rate) -£322,661 (5% drop-out rate)	-£17,472 (15% drop-out rate) -£17,771 (10% drop-out rate) -£18,161 (5% drop-out rate) ICER versus baseline (£/QALY), Societal perspective -cost-saving (20% drop-out rate) -cost-saving (15% drop-out rate) -cost-saving (10% drop-out rate) -cost-saving (5% drop-out rate)
Nr-axSpA							
Corbett *et al.* (2016)[87]	Decision tree + Markov model	TNF-alpha inhibitors	Conventional care	40 years	*Strategy: Results for rebound equal to gain/Results for rebound to CC* CC: 9.956/9.963 CZP with PAS: 11.351/11.200 ADA: 11.351/11.200 ETA: 11.351/11.200	*Strategy: Results for rebound equal to gain/Results for rebound to CC* CC: £89,493/90,219 CZP with PAS: £128,911/131,714 ADA: £130,316/133,109 ETA: £131,057/133,859 CZP: £132,484/135,286	*Strategy: Results for rebound equal to gain/Results for rebound to CC* CC: NA/NA CZP with PAS: £28,247/£33,555 ADA: £29,253/£34,684 ETA: £29,784/£35,290 CZP: £30,807/£36,444

					CZP: 11.351/11.200		
Borse *et al*. (2018)[93]	Short-term decision tree and a long-term Markov model	GOL	Conventional therapy, ADA, CZP and ETA	31.2 years	Conventional therapy (reference): 6.93 GOL: 9.00 ADA: 9.02 CZP: 9.45 ETA: 8.72	Conventional therapy (reference): £107,138 GOL: £146,908 ADA: £148,247 CZP: £154,233 ETA: £142,933	Conventional therapy (reference) GOL: £19,280 per QALY gained ADA: £19,737 per QALY gained CZP pegol: £18,710 per QALY gained ETA: £20,089 per QALY gained

Abbreviations: ADA: adalimumab; CC: conventional care; CZP: certolizumab pegol; GOL: golimumab; ETA: etanercept; ICER: incremental cost-effectiveness ratio; IFX: infliximab; NA: not applicable; NR: not reported; nr-axSpA: non-radiographic axial spondyloarthritis; NSAIDs: non-steroidal anti-inflammatory drugs; PAS: patient access scheme; QALYs: quality-adjusted life years; rad-axSpA: radiographic axial spondyloarthritis.

Table 95: Summary list of UK HTAs in rad-axSpA and nr-axSpA

Study	Intervention	Comparator(s)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Rad-axSpA and nr-axSpA					
SMC 960/14, advice following a submission (2014)[94]	CZP	ETA ADA GOL Conventional care	NR (SMC has agreed not to publish the estimated QALY gain)	NR	NR
Rad-axSpA					
NICE TA407, manufacturer's submission (2016)[25]	SEC	CC ADA ETA GOL IFX CZP	**Biologic-naïve:** SEC: 9.328 ETA: 8.566 CZP: 9.111 ADA: 9.153 GOL: 9.369	**Biologic-naïve:** SEC: £114,847 ETA: £115,779 CZP: £124,557 ADA: £127,919 GOL: £131,157	**Biologic-naïve:** ICERs vs SEC: ETA: Dominated CZP: Dominated ADA: Dominated GOL: £397,064

			IFX biosimilar: 9.420 IFX: 9.420 **Biologic-experienced:** CC: 8.105 SEC: 8.883	IFX biosimilar: £136,095 IFX: £139,598 **Biologic-experienced:** CC: £107,417 SEC: £109,164	IFX biosimilar: £230,769 IFX: £268,811 **Biologic-experienced:** SEC vs CC: £2,245
AWMSG 1211, Assessment report (2014)[95]	CZP	ETA ADA GOL Standard of care	CiC	CiC	Rad-axSpA base case CUA using 24-week data ICER vs standard of care/CZP vs comparator: CZP: £17,430 / NA ADA: £19,722 / Dominant ETA: £19,403 / Dominant GOL: £18,520 / £6,900
Nr-axSpA					
SMC 1124/16, advice following a submission (2016)[96]	GOL (also investigates other TNF-alpha inhibitors vs conventional therapy in additional analyses)	Conventional therapy	NR	NR	£19,280 (Δ costs = £39,770, ΔQALYs = 2.06)
SMC 858/13, advice following a submission (2013)[97]	ADA	Conventional therapy	NR	NR	ICER: £16,154 based on incremental costs of £8,349 and incremental QALYs 0.52
AWMSG 1211, Assessment report (2014)[95]	CZP	ADA Standard of care	CiC	CiC	nr-axSpA base case CUA using 12-week data ICER vs standard of care / CZP vs comparator: CZP: £16,033 / NA ADA: £31,528 / Dominant

AWMSG 1381, Assessment report (2014)[95]	ADA	Conventional therapy	ADA: 9.58 Conventional therapy: 9.06	ADA: £119,224 Conventional therapy: £110,875	£16,154 per QALY gained

Notes: The model developed for NICE TA383, which assessed TNF-alpha inhibitors in rad-axSpA and nr-axSpA, has been published by Corbett *et al.* (2016)[87] and is described in Table 94.

Abbreviations: ADA: adalimumab; AWMSG: All Wales Medicines Strategy Group; CiC; commercial in confidence; CC: conventional care; CUA: cost-utility analysis; CZP: certolizumab pegol; GOL: golimumab; ETA: etanercept; HTA: health technology assessment; ICER: incremental cost-effectiveness ratio; IFX: infliximab; NA: not applicable; NICE: National Institute for Health and Care Excellence; NR: not reported; nr-axSpA: non-radiographic axial spondyloarthritis; QALYs: quality-adjusted life years; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab; SMC: Scottish Medicines Consortium; TA: technology appraisal; TNF: tumour necrosis factor.

B.3.2 *Economic analysis*

The SLR did not identify any studies evaluating the cost-effectiveness of ixekizumab in rad-axSpA or nr-axSpA. A *de novo* cost-effectiveness analysis of ixekizumab versus comparators relevant to the decision problem for this submission was therefore performed for both indications.

B.3.2.1 Patient population

In line with the final NICE scope for this appraisal, and in accordance with the three randomised controlled trials for ixekizumab in rad-axSpA and nr-axSpA, the cost-effectiveness analysis presented here considers the following populations:

Rad-axSpA

- Rad-axSpA patients who have responded inadequately to two or more NSAIDs, or have shown intolerance of NSAIDs (biologic-naïve patients); in line with patients included in COAST-V
- Rad-axSpA patients who have responded inadequately to or were intolerant to one to two TNF-alpha inhibitors, following inadequate response to two or more NSAIDs, or intolerance of NSAIDs (biologic-experienced patients); in line with patients included in COAST-W

Nr-axSpA

- Nr-axSpA patients who have responded inadequately to two or more NSAIDs, or are intolerant of NSAIDs (biologic-naïve patients); in line with patients included in COAST-X

The three populations mirror the NICE-recommended treatment pathway for rad-axSpA and nr-axSpA presented in Section B.1 and include patients for whom TNF-alpha inhibitors are contraindicated. As described in Section B.1.1, a scenario analysis has been performed to understand the cost-effectiveness of ixekizumab in the biologic-experienced nr-axSpA population, details of which are presented in Section B.3.8.3.

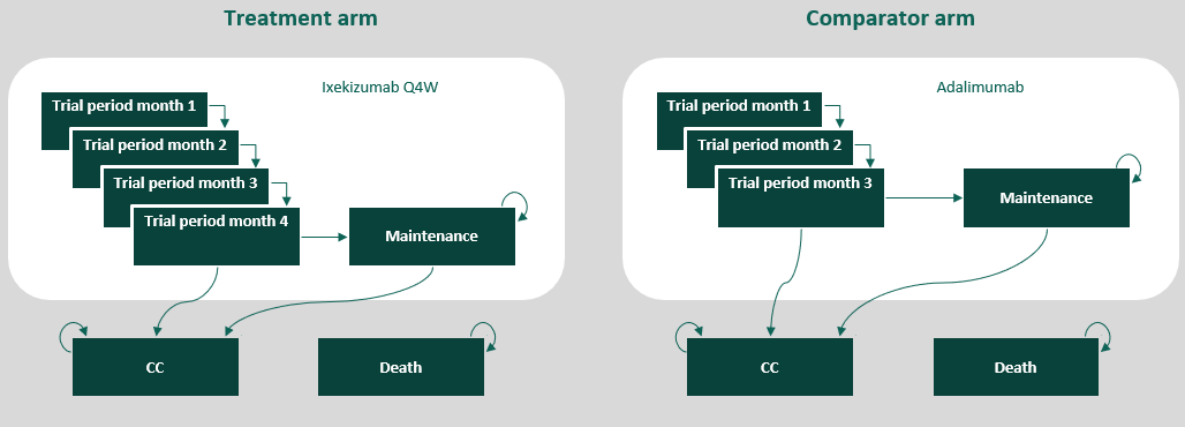
Two cost-effectiveness models have been developed for this appraisal, one in the relevant populations in rad-axSpA and one in the relevant populations in nr-axSpA. It should be assumed that the methodology applies to both models (and thus all three populations) unless otherwise stated.

B.3.2.2 Model structure

The model developed for this submission aligns closely with the 'York model', which was developed by the Assessment Group for use in the MTA TA383 for the evaluation of the cost-effectiveness of TNF-alpha inhibitors compared with conventional care in rad-axSpA and nr-axSpA.[24] The model developed for this submission also takes into account comments made by the NICE Committee in that appraisal.[24]

A cohort Markov model was developed to assess the cost-effectiveness of ixekizumab versus relevant comparators in rad-axSpA and nr-axSpA, as presented in Figure 29. The model health states comprise a 'trial period', which is represented by a set of tunnel states, followed by 'maintenance treatment', 'conventional care' and 'death', which are represented by traditional Markov health states. The ixekizumab model is able to model both biologic-naïve and -experienced populations in rad-axSpA and nr-axSpA, with the corresponding efficacy data for the relevant line of treatment for each intervention applied accordingly (see Section 0).

Figure 29: Cohort Markov model structure



Notes: Adalimumab has been included as an example comparator arm for illustrative purposes.
Abbreviations: CC: conventional care; Q4W: every 4 weeks.

Upon entering the model at the relevant treatment line, patients are allocated to ixekizumab or a comparator treatment and enter the 'trial period' for that treatment. The length of the trial period corresponds to the stopping rule specified by NICE in the Technology Assessment (TA) guidance for that intervention (see Section B.3.2.3), and is achieved through using the corresponding number of tunnel states, with a cycle length of four weeks. A tunnel state is a type of temporary health state which can only be visited once in a fixed sequence.[98]

At the end of the trial period the patient's response to treatment is assessed. Response in the model is defined using the BASDAI50 response, in line with previous NICE cost-effectiveness evaluations in axSpA.[86-88] Patients who respond to treatment transition to the 'maintenance treatment' health state, whilst patients who do not respond transition to conventional care.

Patients who enter the maintenance treatment state are modelled to receive continuous treatment, during which they are at risk of discontinuation as a consequence of severe AEs or loss of response. The drop-out rate is assumed to be constant over time and across treatment groups, as described in Section B.3.3.7. When patients discontinue treatment, they transition to conventional care.

Upon entering the conventional care health state patients remain there until death or the end of the simulation. In the model, death represents the absorbing state, accumulating patient flows from all health states. It is assumed that the probability of transition from any of the other health states to death is equal within each cycle (i.e. there is no assumption for treatment effect on mortality). The model included normal UK population mortality, with an increased risk of death observed in patients with axSpA compared to the normal population (see Section B.3.3.8).

Patients' disease status in the model is characterised by their level of two disease measures, BASDAI and BASFI. BASDAI is a measure of disease activity and BASFI is a measure of functional impairment due to axSpA. In the model, BASDAI is the measure upon which response to treatment (BASDAI50) and treatment continuation are determined, whilst BASFI is used to model disease progression over time. Improvements in both measures are applied to patients after the trial period.

Together, BASDAI and BASFI are used in an algorithm to estimate health state utility values (see Section B.3.4.5), whilst BASFI is used in an algorithm to estimate disease related costs (Section

B.3.5.2). Determination of patients' BASDAI and BASFI scores in the model is described further in Section B.3.3.

Justification for model structure

The model structure is aligned closely with previous models in nr-axSpA and rad-axSpA, particularly with the York model, built by the Assessment Group in TA383, and the model included in the manufacturer's submission for TA407.[24, 25]

The model aimed to reflect the UK clinical pathway of care for people with rad- or nr-axSpA for whom NSAIDs or TNF-alpha inhibitors have been inadequately effective or not tolerated, or for whom TNF-alpha inhibitors are contraindicated. As described in Section B.1, the pathway of care for these patients comprises treatment with a biologic therapy for an induction period, followed by assessment of response to determine whether the biologic therapy should be continued. In line with clinical guidelines and previous NICE TAs in this indication, the model structure enables assessment of response to treatment at the end of an induction (trial) period of 12 or 16 weeks.[24, 25, 42, 50]

The response criteria used in the model is BASDAI50 response at the end of the trial period (12 or 16 weeks). This is based on the BSR guidelines on prescribing TNF-alpha inhibitors in adults with rad-axSpA, which recommend that response to treatment should be defined as achievement of a BASDAI50 response or fall in BASDAI of two or more units, in addition to a reduction in the spinal pain VAS of two or more units.[42] The latter response option is not included in the model as there is insufficient data available to consider a two or more unit BASDAI change or a reduction in the spinal pain VAS of two or more units in the economic modelling.[24, 25] Additionally, clinical expert opinion elicited for TA407 judged that spinal pain VAS is used inconsistently in clinical practice to determine response. The York model and the model built for TA407 therefore also used BASDAI50 as a measure of response.[24, 25]

Disease state was modelled via short-term changes in BASDAI (which captures disease activity) and BASFI (which captures physical function), and long-term changes in BASFI, as described in Section B.3.3.3 and Section B.3.3.4. These two measures were also used to determine HRQoL associated with disease progression in axSpA, as described in Section B.3.4.5. Whilst there are limitations of modelling axSpA through BASDAI and BASFI scores, as noted by the Assessment Group of TA383,[24] these measures provide the only currently available method of linking disease progression to costs and quality-adjusted life years (QALYs). Therefore, the York model and the model built for TA407 also measure disease progression through BASDAI and BASFI scores.[24, 25]

The AEs included in the model were tuberculosis reactivation and severe infections, as described in Section B.3.3.6, which is in alignment with the York model and TA407.[24, 25] These AEs were included based on a Cochrane review of AEs in adults receiving TNF-alpha inhibitors.[99] Use of the same approach as the York model and TA407 is supported by the results of COAST-V, in which the safety profile of ixekizumab was found to be comparable to adalimumab.[2]

In alignment with the York model, AEs in the model were not associated with any loss of utility due to lack of data in the literature.[24]

Model characteristics

The economic analysis was conducted in accordance with the NICE reference case,[100] employing a patient lifetime horizon and the perspective of the NHS and Personal Social Services (PSS). A lifetime time horizon was selected as axSpA is a chronic, progressive and lifelong condition with no cure. The use of a lifetime time horizon is also consistent with previous models of axSpA, including TA383 and TA407.[24, 25] A cycle length of one month was used, which enables trial periods of varying durations and is sufficiently granular to reflect regular patient movement between health states. No half cycle correction was included in the model as the cycle length is considered to be sufficiently short in the context of a patient's lifetime. Costs and benefits were discounted at 3.5% per annum, in line with the NICE reference case.[100]

The features of the cost-effectiveness analysis are presented in Table 96, alongside a comparison of the approach taken in previous NICE appraisals.[24, 25]

Table 96: Features of the economic analysis

Factor	Previous appraisals		Current appraisal	
	York model TA383 (MTA)[24]	TA407[25]	Chosen values	Justification
Time horizon	Lifetime (60 years)	Lifetime (58 years)	Lifetime	In line with NICE reference case[100] Sufficient to capture all meaningful differences in costs and QALYs between technologies compared
Discount for utilities and costs	3.5% discounting per annum applied for both costs and benefits	3.5% discounting per annum applied for both costs and benefits	3.5% discounting per annum applied for both costs and benefits	In line with NICE reference case[100]
Cycle length	0.25 years	3 months	1 month	Sufficiently granular cycle length to capture the stopping rules for the intervention and comparators without excessive computational programming
Half-cycle correction	NR	Yes	No	Cycle length is sufficiently short in context of time horizon to not warrant a half-cycle correction
Perspective	NHS/PSS	NHS/PSS	NHS/PSS	In line with NICE reference case[100]
Source of utilities	• Non-linear algorithm developed by Pfizer to map BASDAI and BASFI scores to the EQ-5D	• Linear algorithm based on MEASURE 1 and MEASURE 2 data translating BASDAI and BASFI scores to EQ-5D was used in the base case	• Linear algorithms based on COAST-V, COAST-W and COAST-X developed for each population to map BASDAI and BASFI scores to EQ-5D-5L values • EQ-5D-5L scores cross-walked to -3L values using van Hout *et al*.	In line with NICE reference case[100] and previous models in axSpA[24, 25]

			(2012) algorithm	
Source of costs	Acquisition costs: • Source: BNF 2014 • PAS' included for CZP and GOL • Biosimilar costs not included for IFX Administration costs: • SC therapies: AG included one-off cost of nurse training for self-administration (£49; PSSRU 2013) • IV therapy (IFX): Committee's preferred infusion cost was £159 (national tariff for delivering simple parenteral chemotherapy 2012–13) Initiation and monitoring costs: • Resource use assumptions sourced from TA199 (York Model for PSA) • CRP test cost was derived from Henriksson 2010 • Specialist visits were costed using NHS References Costs 2012–13 • Initiation and costs applied for 12 weeks and monitoring costs applied quarterly Long-term management costs: • Exponential BASFI linear algorithm based on OASIS data (long-term study of clinical and economic outcomes in AS) • Committee deemed BASFI only to be a predictor of cost as it reflects long-term progression (whilst BASDAI does not increase over time) AE resource use and costs: • Serious infections and TB	Acquisition costs: • Source: BNF 2015 • PAS' included for SEC, CZP and GOL • Biosimilar costs included for IFX (Remsima and Inflectra) Administration costs: • SC therapies: one-off cost (1-hour training session with nurse [£43]; PSSRU 2015) • IV therapy (IFX): per administration cost (£326.43; NHS Reference Costs 2014–15, HRG SB15Z) Monitoring costs: • Medical visits and laboratory resource to monitor SEC and TNF-alpha inhibitors, based on TA383 • Medical visit costs sourced from PSSRU 2015 (GP visit) and NHS Reference Costs (2014–15; WF01A) • Laboratory test costs sourced from TA199 and inflated using HCHS PSSRU 2015	Acquisition costs: • Source: MIMS 2019 • PAS included for CZP. PAS for GOL was not considered, as the 100 mg dose was not included in the NMA or model, as this dose is only recommended in patients weighing >100 kg who do not adequately respond to the 50 mg dose.[24] PAS for SEC was not included as it is confidential and is not known to the company • Biosimilar costs included for IFX, ETA and ADA Administration costs: • SC therapies: one-off cost (1-hour training session with nurse [£43]: PSSRU 2018) • IV therapy (IFX): per administration costs (£289.00; NHS Reference Costs 2017-18, SB15Z) Initiation and monitoring costs: • Medical visits and laboratory resource to monitor IXE, SEC and TNF-alpha inhibitor treatments • Medical visit costs	In line with NICE reference case[100] and previous models in axSpA[24, 25]

	reactivation included in the AG model only • Excess AE rates vs conventional care sourced from the Cochrane review of TNF-alpha inhibitor AEs • Cost of serious infection sourced from Pfizer MTA submission (weighted average of relevant NHS Reference Cost 2012–13 codes [WA03C, DZ23G, LA04M, PA16B, DZ22J, DZ21U]) • Cost of TB reactivation sourced from weighted average of NHS reference cost codes of different severity (DZ14C, DZ14D, DZ14E)	index Health state costs: • Disease management costs estimated based on an exponential BASFI regression model, as per York model AE resource use and costs: • Serious infections and TB reactivation included in the model only, as per the York model • Cost of serious infection sourced from weighted average of NHS Reference Costs (2014–15) codes WJ06J, DZ23N, LA04M, DZ22Q and DZ65J • Cost of TB reactivation sourced from weighted average of NHS Reference Costs (2014–15) codes DZ14F, DZ14G, DZ14H and DZ14J	sourced from NHS Reference Costs (2015–16; WF01A) • Laboratory test costs sourced from National Schedule of Reference Costs (2017–18; DAPS05) AE resource use and costs: • Cost of serious infection sourced from weighted average of NHS Reference Costs (2017–18) codes WJ06A–H, WJ06J, DZ23H, DZ23J–N, LA04H, LA04J–N, LA04P–S, HC31H, HC31J–N, DZ22K–Q and DZ65A–C • Cost of TB reactivation sourced from weighted average of NHS Reference Costs (2017–18) codes DZ14F, DZ14G, DZ14H and DZ14J	

Abbreviations: ADA: adalimumab; AE: adverse event; AG: Assessment Group; AS: ankylosing spondyloarthritis; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BNF: British National Formulary; CRP: C-reactive protein; CZP: certolizumab pegol; EQ-5D: EuroQol-Five Dimensions; ETA: etanercept; GOL: golimumab; GP: general practitioner; HCHS: Hospital & Community Health Services; HRG: health resource group; IFX: infliximab; IV; intravenous; MIMS: Monthly Index of Medical Specialities; MTA: multiple technology appraisal; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NR: not recorded; PAS: patient access scheme; PSA: probabilistic sensitivity analysis; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year; TA: technology appraisal; TB: tuberculosis; TNF: tumour necrosis factor; SC: subcutaneous; SEC: secukinumab.

B.3.2.3 Intervention technology and comparators

The intervention assessed in the model is ixekizumab 80 mg Q4W, following an 80 mg LD in rad-axSpA biologic-naïve and nr-axSpA biologic-naïve patients and a 160 mg LD in rad-axSpA biologic-experienced patients, reflecting the doses of ixekizumab anticipated to be licensed and most commonly used in clinical practice. The comparator interventions included for each patient population align with those presented in the final scope Section B.1.1, and are presented in Table 97.

The comparator doses included in the model are aligned with their licensed indications and approved doses in prior NICE submission.[23-25, 27, 32, 50, 101-105] The stopping rules for the comparators are aligned with the length of trial period and the stopping rules included in their NICE recommendations, as described in detail in Section B.1.3.[24, 25, 50]

As described in Section B.1.3, the licence for secukinumab has recently been extended. According to the wording of the licence extension, based on clinical response, patients may have their dose increased from the 150 mg dose to 300 mg.[25] This licence extension has not been appraised by NICE, however, as described in Section B.1.3, a dose utilisation study conducted by Lilly in the UK,
[redacted]

Table 97: Interventions included in the analysis

Intervention	Length of trial period in model	Rad-axSpA biologic-naïve	Rad-axSpA biologic-experienced	Nr-axSpA biologic-naïve
		Dosing schedule		
Intervention				
Ixekizumab	16 weeks[2, 3, 5]	80 mg Q4W (LD: 80 mg)[32]	80 mg Q4W (LD: 160 mg)[32]	80 mg Q4W (LD: 80 mg)[32]
Comparators				
Adalimumab	12 weeks[24]	40 mg Q2W[103]	40 mg Q2W[103]	40 mg Q2W[103]
Certolizumab pegol	12 weeks[24]	400 mg at Weeks 0, 2 and 4, followed by maintenance dosing of 200 mg Q2W *or* 400 mg Q4W[101]	400 mg at Weeks 0, 2 and 4, followed by maintenance dosing of 200 mg every 2 weeks or 400 mg every 4 weeks[101]	400 mg at Weeks 0, 2 and 4, followed by maintenance dosing of 200 mg every 2 weeks or 400 mg every 4 weeks[101]
Etanercept	12 weeks[24]	25 mg Q2W *or* 50 mg QW[102]	25 mg Q2W *or* 50 mg QW[102]	25 mg Q2W *or* 50 mg QW[102]
Golimumab	12 weeks[24]	50 mg once monthly[105]	50 mg once monthly[105]	50 mg once monthly[105]
Infliximab	12 weeks[24]	5 mg/kg at Weeks 0, 2, and 6; thereafter every 6–8 weeks (assume every 7 weeks on average)[104] See Section B.3.3.1 for mean weight included in the model	5 mg/kg at Weeks 0, 2, and 6; thereafter every 6–8 weeks (assume every 7 weeks on average)[104] See Section B.3.3.1 for mean weight included in the model	Not a comparator in the analysis of the specified patient population
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conventional care	NA	Patients are assumed to continue conventional care alongside biologic therapy, therefore specific interventions are not explicitly modelled	Patients are assumed to continue conventional care alongside biologic therapy, therefore specific interventions are not explicitly modelled	Patients are assumed to continue conventional care alongside biologic therapy, therefore specific interventions are not explicitly modelled

[redacted]

Abbreviations: LD: loading dose; NA: not applicable; nr-axSpA: non-radiographic axial spondyloarthritis; Q2W: every two weeks; Q4W: every four weeks; QW: every week; rad-axSpA: radiographic axial spondyloarthritis.

B.3.3 *Clinical parameters and variables*

As discussed in Section B.3.2.1, three populations were considered in the economic analysis base case: rad-axSpA biologic-naïve patients, rad-axSpA biologic-experienced patients and nr-axSpA biologic-naïve patients. In the base case analysis, the clinical parameters for BASDAI50, BASDAI cfb and BASFI cfb were derived from the NMA sensitivity analysis (see Section B.2.9), for which data were sourced from the clinical SLR (Section B.2.1). However, due to data availability limitations in the literature, the NMA was not able to provide input data to populate the model for all comparators across all three clinical outcomes.

Accordingly, in the base case, for TNF-alpha inhibitors, for comparators where clinical input data were missing, the average value across TNF-alpha inhibitors for which NMA sensitivity analysis data were available was calculated. This aligns with the approach taken in TA407 to populate data gaps for TNFi.[25]

Efficacy inputs for secukinumab 150 mg were missing for BASDAI50 and BASFI cfb from the NMA. [redacted]

[redacted]

The data sources for the clinical parameters for each patient population in the base case and scenario analyses are presented in Table 98.

Table 98: Data sources for clinical parameters

Clinical parameter	Rad-axSpA biologic-naïve	Rad-axSpA biologic-experienced	Nr-axSpA biologic-naïve

BASDAI50 **BASDAI cfb** **BASFI cfb**	NMA (sensitivity analysis) based on clinical efficacy SLR in rad-axSpA and COAST-V trial Averages of TNF-alpha inhibitor data taken as needed	NMA (sensitivity analysis) based on clinical efficacy SLR in rad-axSpA and COAST-W trial Averages of TNF-alpha inhibitor data taken as needed	NMA (sensitivity analysis) based on clinical efficacy SLR in rad-axSpA and COAST-X trial Averages of TNF-alpha inhibitor data taken as needed
[redacted]	[redacted]		
Scenario analysis: **BASDAI cfb conditional on BASDAI50 response**	COAST-V[2]	COAST-W[3]	COAST-X[5]
Scenario analysis: **BASFI cfb conditional on BASDAI50 response**	COAST-V[2]	COAST-W[3]	COAST-X[5]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; NMA: network meta-analysis; nr-axSpA: non-radiographic axial spondyloarthritis; rad-axSpA: radiographic axial spondyloarthritis; SLR: systematic literature review.

B.3.3.1 Starting patient characteristics

The base case inputs for the model in terms of patient age, gender distribution and weight for each patient population are detailed in Table 99.

Table 99: Patient characteristics in the model

Model parameter	Value	Source
Rad-axSpA biologic-naïve		
Mean age, years	41.7	COAST-V[2]
Percentage male	80.9%	COAST-V[2]
Mean weight, kg	78.1	COAST-V[2]
Rad-axSpA biologic-experienced		
Mean age, years	46.1	COAST-W[3]
Percentage male	80.1%	COAST-W[3]
Mean weight, kg	83.2	COAST-W[3]
Nr-axSpA biologic-naïve		
Mean age, years	40.3	COAST-X[5]
Percentage male	47.2%	COAST-X[5]
Mean weight, kg	77.5	COAST-X[5]

Abbreviations: nr-axSpA: non-radiographic axial spondyloarthritis; rad-axSpA: radiographic axial spondyloarthritis.

The baseline BASDAI and BASFI scores in each population are presented in Table 100. In the base case analysis, the baseline BASDAI and BASFI scores are unconditional on responder status and on intervention received.

Table 100: Baseline BASDAI and BASFI scores

Population	Baseline BASDAI score	Baseline BASFI score	Source
Biologic-naïve rad-axSpA	6.75	6.23	COAST-V trial[2]
Biologic-experience rad-axSpA	7.43	7.27	COAST-W trial[3]
Biologic-naïve nr-axSpA	7.16	6.52	COAST-X trial[5, 6]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; nr-axSpA: non-radiographic axial spondyloarthritis; rad-axSpA: radiographic axial spondyloarthritis.

B.3.3.2 Response rate

As discussed in Section B.3.2.2, the BASDAI50 response at the end of trial period (Week 12 or Week 16) was used to determine whether patients continued on the same treatment they were assigned to in the trial period during the maintenance period, or whether they switched to conventional care.

The BASDAI50 response rates for each treatment were determined from the estimates for each intervention from the NMA analysis, which was informed by the clinical SLR. As described in Section B.3.3, published BASDAI50 response rates were not identified for secukinumab 150 mg at the time that the clinical SLR update was conducted in all three included populations, therefore secukinumab is not included in the base case. For TNF-alpha inhibitors with missing data points (adalimumab and golimumab in biologic-experienced patients), an unweighted average over other TNF-alpha inhibitors were calculated. The base case BASDAI50 inputs are presented in Table 101.

Table 101: BASDAI50 response applied in the model base case

Intervention (95% CrI)	Rad-axSpA biologic-naïve	Rad-axSpA biologic-experienced	Nr-axSpA biologic-naïve
Ixekizumab Q4W (80 mg LD)	[redacted]	[redacted]	[redacted]
Ixekizumab Q4W (160 mg LD)	Not a comparator in the analysis of the specified patient population	[redacted]	Not a comparator in the analysis of the specified patient population
Ixekizumab (overall)	Not a comparator in the analysis of the specified patient population	Not a comparator in the analysis of the specified patient population	Not a comparator in the analysis of the specified patient population
Adalimumab	[redacted]	[redacted]	[redacted]
Certolizumab pegol[a]	[redacted]	[redacted]	[redacted]
Etanercept[a]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]

	[redacted]		[redacted]
Infliximab	[redacted]	[redacted]	Not a comparator in the analysis of the specified patient population
Secukinumab	NA	NA	Not a comparator in the analysis of the specified patient population
Conventional care	[redacted]	[redacted]	[redacted]

[a] Values for pooled doses for etanercept and certolizumab pegol are presented.
[b] Unweighted average over available data points from TNF-alpha inhibitors.
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; LD: loading dose; NA: not applicable; nr-axSpA: non-radiographic axial spondyloarthritis; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis.

B.3.3.3 Short-term change in BASDAI and BASFI

In line with the York model, the value by which patients' BASDAI and BASFI scores improve (reduce) upon treatment is dependent upon whether they are classified as a responder or non-responder according to their BASDAI50 assessment at the end of the trial period.[24] This was important as BASDAI50 response at the end of trial period determined whether or not patients continued with the therapy assigned in the trial period.

Estimates of mean cfb in BASDAI and BASFI scores conditional on response status (defined by achievement of BASDAI50) were not available from the NMA. Conditional data from the ixekizumab trial and other published sources were available, and these data were used to calculate the relationship between conditional BASDAI and BASFI cfb values in responders and non-responders, through the division of 'responder cfb data' by 'non-responder cfb data'. In the rad-axSpA population, proportions of responder/non-responder cfb data were available for adalimumab[87], golimumab[87], ixekizumab[2, 3] and secukinumab.[25] For all treatments except conventional care, an average of available responder/non-responder relationships was then calculated.[25, 87] In the nr-axSpA population, conditional cfb data were available for adalimumab,[87] golimumab[87] and ixekizumab,[6] and an equivalent responder/non-responder relationship value calculated.[107] In order to generate conditional cfb data for all interventions, the relationship values were then inputted into a set of equations, along with data for the overall proportion of responders and overall cfb values for BASDAI and BASFI for each intervention, as sourced from the NMA, in order to generate conditional values. These equations are presented in in Appendix M.

The conditional cfb in BASDAI and BASFI scores are presented in Table 102 and Table 103, respectively. In the rad-axSpA population, for TNF-alpha inhibitors with missing overall cfb BASDAI and BASFI values from the NMA (golimumab and infliximab in biologic-naïve patients and golimumab, etanercept and adalimumab in biologic-experienced patients), an unweighted average over other TNF treatments were calculated. Similarly, as NMA data on cfb for BASDAI and BASFI was not available for adalimumab and golimumab in patients with nr-axSpA, an average of the estimates of certolizumab pegol and etanercept was used to fill these gaps and enable a comparison with these treatments.

Table 102: Conditional Cfb in BASDAI

Intervention	Rad-axSpA biologic-naïve		Rad-axSpA biologic-experienced		Nr-axSpA biologic-naïve	
	Responders	Non-responders	Responders	Non-responders	Responders	Non-responders
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Average over available data points of TNF-alpha inhibitors.[b] Values for pooled doses for etanercept and certolizumab pegol are presented.
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; NA: not applicable; nr-axSpA: non-radiographic axial spondyloarthritis; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA data sensitivity 2

Table 103: Conditional Cfb in BASFI

Intervention	Rad-axSpA biologic-naïve		Rad-axSpA biologic-experienced		Nr-axSpA biologic-naïve	
	Responders	Non-responders	Responders	Non-responders	Responders	Non-responders
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Average over available data points of TNF-alpha inhibitors.[b] Values for pooled doses for etanercept and certolizumab pegol are presented.
Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; NA: not applicable; nr-axSpA: non-radiographic axial spondyloarthritis; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA data sensitivity 2

B.3.3.4 Long-term changes in BASDAI and BASFI

In addition to the short-term changes in BASDAI and BASFI described in Section B.3.3.3, patients who responded to biologic treatment were assumed to experience a slower rate of disease progression (as measured by BASFI) during treatment, in comparison to the natural history of axSpA whilst receiving conventional care. This approach was based on models used in previous NICE submissions in axSpA (TA383 and TA407),[24, 25] and is detailed below.

In a targeted literature review performed by the Assessment Group in TA383, the identified evidence, including a UK registry study (SIRAS),[108] indicated that disease activity (as measured by BASDAI) in rad-axSpA and nr-axSpA typically remains stable over time and does not progress.[24] However, the captured evidence suggests that patients' functional impairment (as measured by BASFI) progressively worsens over time. Landewe *et al.* (2009) identified that physical function impairment is independently affected by both disease activity (i.e. BASDAI) and bony progression, which is assessed using mSASSS.[81]

Given that the effect of disease activity on BASFI is accounted for through mean change in BASDAI and BASFI scores according to patients' classification as a responder or non-responder based on their BASDAI50 response, the model correlates BASFI progression to bony progression (mSASSS) in alignment with the York model.[24] This was done separately for rad-axSpA and nr-axSpA:

Rad-axSpA

In alignment with the findings of Landewe *et al.* (2009) and the York model in rad-axSpA, the ixekizumab model assumes that long-term progression of BASFI is a function of disease activity (e.g. BASDAI) and the extent of and progression of radiographic disease (e.g. mSASSS).[24] The association between BASDAI and BASFI is already accounted for in the short-term changes in BASDAI and BASFI scores, as described in Section B.3.3.3, and the differences in BASDAI from baseline were assumed to remain constant in the long-term as long as patients continued on the same treatment. Therefore, long-term changes in BASFI are modelled as a function of mSASSS scores only.

The annual rate of BASFI change can be determined through the following calculation:

Annual rate of BASFI change = annual rate of mSASSS change x BASFI change with 1 unit change in mSASSS

The annual rate of change in mSASSS in rad-axSpA patients was identified to be 1.440, based on the annual rate of change in a subgroup of patients with baseline mSASSS of ≥10 (who were eligible for TNF-alpha inhibitor treatment) in the Ramiro *et al.* (2013) study.[79] The Ramiro *et al.* (2013) study analysed 12 year data from the Outcome in Ankylosing Spondylitis International Study (OASIS), and therefore was able to assess the long-term relationship between disease activity and radiographic damage.[79] The independent effect of a 1 unit change in mSASSS on BASFI used was 0.057, which was taken from the multivariate relationship reported Landewe *et al.* (2009), based on longitudinal assessments of BASFI, BASDAI and mSASSS in patients with rad-axSpA in the OASIS cohort.[81]

The above calculation estimates the annual rate of BASFI change independent of any biologic treatment slowing the rate of progression, and is the rate of progression assumed for

conventional care. The model further assumed that there was a treatment effect of biologic therapies on relative rate of mSASSS change, and therefore, on BASFI change. The effect of biologic treatment on radiographic progression (relative rate) was identified to be 0.42, which was taken from Haroon *et al.* (2013).[80] Haroon *et al.* (2013) was a cohort study which assessed the effect of TNF-alpha inhibitors on progressive spinal damage in patients with rad-axSpA, and reported relative effect measures for TNF-alpha inhibitors and historical controls. The treatment effect was assumed to be the same across all biologic therapies, including TNF-alpha inhibitors, secukinumab and ixekizumab.

In the model, the treatment effect of ixekizumab, secukinumab and TNF-alpha inhibitors on disease progression is applied from the end of the trial period (e.g. from the start of maintenance treatment). This is aligned the NICE Committee preference in TA383, where the Committee chose to consider results presented in a scenario analysis where the treatment effect of progression was applied from the start of treatment, rather than after 4 years of treatment.[24, 25]

A summary of the parameters used to model long-term changes in BASFI is provided in Table 104.

Table 104: Summary of parameters used to estimate long-term changes in BASFI in rad-axSpA

Parameter	Value	Source
Annual rate of mSASSS change	1.44	Ramiro *et al.* (2013)[79]
BASFI change associated with a 1 unit change in mSASSS	0.057	Landewe *et al.* (2013)[81]
Effect of biologic treatment on radiographic progression (relative rate)	0.42	Haroon *et al.* (2013)[80]
Timepoint from which effect of biologic treatment introduced	Maintenance treatment initiation	Assumption

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; mSASSS: Modified Stoke Ankylosing Spondylitis Spinal Score; rad-axSpA: radiographic axial spondyloarthritis.

Nr-axSpA

For patients with nr-axSpA, a similar underlying disease process was assumed as for patients with rad-axSpA, and long-term changes in BASFI were calculated using the same equation as above.

The annual rate of change in mSASSS in nr-axSpA patients was identified to be 0.69, based on the annual rate of change in a subgroup of patients with baseline mSASSS of <10 (who were eligible for TNF-alpha inhibitor treatment) in the Ramiro *et al.* (2013) study.[79] As for the rad-axSpA population, the independent effect of a 1 unit change in mSASSS on BASFI used was 0.057, which was taken from the multivariate relationship reported Landewe *et al.* (2009).[81]

Similarly to the rad-axSpA population, the effect of biologic treatment on radiographic progression (relative rate) was identified to be 0.42, which was taken from Haroon *et al.* (2013).[80] The treatment effect of ixekizumab, secukinumab and TNF-alpha inhibitors on disease progression is applied from the end of the trial period (e.g. from the start of maintenance treatment), in alignment with NICE Committee preference in TA383.[24, 25]

Table 105: Summary of parameters used to estimate long-term changes in BASFI in nr-axSpA

Parameter	Value	Source
Annual rate of mSASSS change	0.69	Ramiro *et al.* (2013)[79]
BASFI change associated with a 1 unit change in mSASSS	0.057	Landewe *et al.* (2013)[79, 81]
Effect of biologic treatment on radiographic progression (relative rate)	0.42	Haroon *et al.* (2013)[80]
Timepoint from which effect of biologic treatment introduced	Maintenance treatment initiation	Assumption

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; mSASSS: Modified Stoke Ankylosing Spondylitis Spinal Score; nr-axSpA: non-radiographic axial spondyloarthritis.

A scenario in which the rate of BASFI progression for nr-axSpA patients is aligned with that of rad-axSpA patients is described in Section B.3.7.

B.3.3.5 Rebound in BASDAI and BASFI

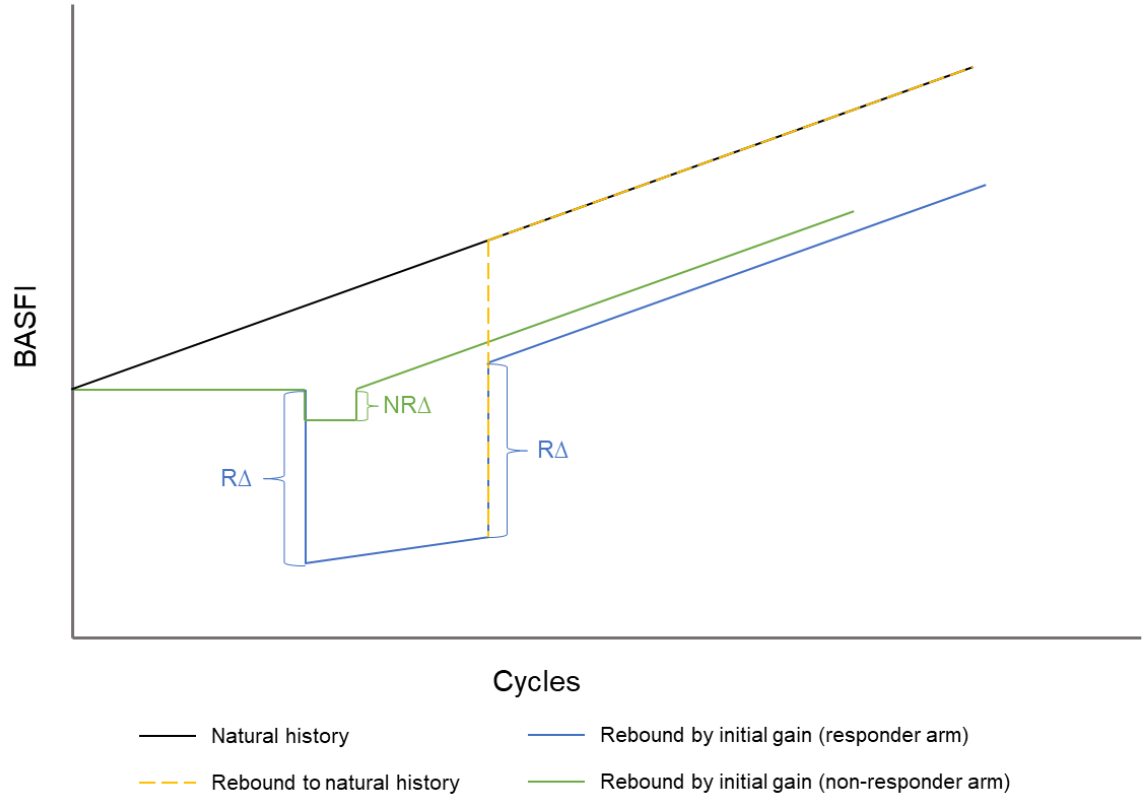
As described in Sections B.3.3.3 and B.3.3.4, the initial mean changes in BASDAI and BASFI were assumed to be maintained whilst patients remained on biologic treatment, and patients who remained on biologic treatment experienced a slowed rate of BASFI progression in comparison to disease natural history (as modelled by conventional care). The baseline BASDAI and BASFI values for each population were derived from the COAST trials and are the same for all comparators and are unconditional on BASDAI50 response, as described in Section B.3.3.3.

Upon discontinuation of treatment, patients are assumed to lose their treatment response and their corresponding gains in BASDAI and BASFI. Given that patients' BASDAI score is assumed not to progress over time, upon discontinuation, patients' BASDAI score will revert to their baseline value. However, two possible alternatives exist for BASFI scores, which progress over time. The two possible BASFI score rebound scenarios to model patients' loss of response included in the model are:

1. Rebound by initial gain – following treatment discontinuation, BASFI deteriorates by the amount equal to the improvement achieved during response to biologic therapy, in addition to the amount of deterioration which occurred during maintenance treatment.
2. Rebound to natural history – following treatment discontinuation, BASFI deteriorates to the level and subsequent trajectory that would have occurred had the patient not initially responded to therapy.

An illustration of the two rebound options is presented in Figure 30. The method of calculating the rate of BASFI progression according to disease natural history is described in detail in Section B.3.3.4.

Figure 30. Illustration of BASFI rebound by initial gain



Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; NR: non-responder; R: responder.
Note: For non-responders to treatment, there is no disease progression whilst on treatment as it is assumed progression is captured following the trial period.

In the base case, the 'rebound to initial gain' scenario was selected, with 'rebound to natural history' being explored in a scenario analysis (see Section B.3.8.3).

As per Committee preferences in TA383, different baseline scores for responders and non-responders were not incorporated into the ixekizumab model.[24] The same average BASDAI and BASFI scores were assumed for responders and non-responders, as described in Section B.3.3.1.

Patients entering conventional care at the end of the trial period (i.e. non-responders) experience a transient treatment response corresponding to placebo response, in line with the York model. After the first cycle of conventional care, non-responder patients will revert to their baseline values.

B.3.3.6 AEs

The AEs included in the model were tuberculosis reactivation and severe infections. These AEs were included based on a Cochrane review of AEs in adults receiving TNF-alpha inhibitors, which found that the only specific AEs that were with statistically significantly more frequent in patients treated with TNF-alpha inhibitors compared to conventional care were tuberculosis reactivation and other serious infections.[99] In line with the York model, and due to lack of data in the literature, AEs in the model were not associated with any loss in utility.[24]

Treatment specific absolute risks of tuberculosis reactivation and severe infections are employed in the model, as described in Table 106. For conventional care these were conservatively assumed to be zero. The model applies AE rates for the whole treatment period. This is a conservative estimate in comparison to the York model, which assumed that AE rates would only occur in the first year of treatment, which is explored in a scenario analysis (see Section B.3.8.3).[24] The risk of AEs was assumed to be consistent across all three populations modelled in the base case.

Table 106: Risk of AEs

Risk of AEs, rate/patient year	Tuberculosis reactivation	Severe infections	Source
Ixekizumab	0.0000	0.0150	SmPC;[109] Romiti *et al.* (2017)[110]
Adalimumab	0.0022	0.0400	SmPC;[111] Dixon *et al.* (2010)[112]
Certolizumab pegol[a]	0.0020	0.0700	SmPC;[113] Sieper *et al.* (2015)[114]
Etanercept[a]	0.0005	0.0600	Dixon *et al.* (2006);[115] Dixon *et al.* (2010)[112]
Golimumab	0.0017	0.0250	SmPC;[116] Kay *et al.* (2013)[117]
Infliximab	0.0012	0.0552	Dixon *et al.* (2006);[115] Dixon *et al.* (2010)[112]
Secukinumab	0.0000	0.0150	SmPC;[118] Cantini *et al.* (2017)[119]
Conventional care	0.0000	0	Assumption

[a] Values for pooled doses for etanercept and certolizumab pegol are presented.
Abbreviations: AE: adverse event; EMA: European Medicines Agency; EPAR: European public assessment report.

B.3.3.7 Withdrawal from biologic therapy

During maintenance treatment, responder patients are in each cycle at risk of dropping out of treatment and, as a consequence, transition to conventional care. Discontinuations are assumed to happen as a consequence of severe AEs or loss of response. The drop-out rate is assumed to be constant over time, with yearly drop-out rates of 11% and 5% in the rad-axSpA and nr-axSpA populations, respectively, and in line with the estimates used in the York model.[24] Additionally, the drop-out rate is assumed to be the same for all treatments. The annual drop-out rate estimates were based on a parametric function (exponential distribution) estimated from BASDAI50 responders at Week 12 in the open-label extensions of the 311-EU, 312-EU and 907-studies for the rad-axSpA population and study 1031 for the nr-axSpA population.[24]

B.3.3.8 Mortality

The model includes normal UK population mortality in the base case. The general population mortality rates were determined by a Gompertz curve fitted to the general population life tables from the Office for National Statistics 2016–2018 dataset, in order to reflect general mortality rates of the UK population.[120]

An increased risk of death in patients with axSpA compared to the normal population is explored in a scenario analysis (see Section B.3.8.3). Within this scenario, in line with the York model, the ixekizumab model has separate standardised mortality ratios (SMRs) for men and women which are derived from a study by Bakland *et al.* (2011) (Table 107).[43] Bakland *et al.* (2011) was a large

regional study in Norway which investigated standardised mortality ratios in patients with rad-axSpA compared to gender, age and postal area controls from the general population.[43] In the scenario analysis, these ratios are applied to gender-specific background mortality rates for the UK and applied to both the rad-axSpA and the nr-axSpA populations. The percentage of patients assumed to be male and female in each population assessed in the model is described in Table 99 in Section B.3.3.1.

Table 107: Relative risks of death applied in the scenario analysis

Input	Standardised mortality ratio	Source
Men	1.63	Bakland *et al.* (2011)[43]
Women	1.38	Bakland *et al.* (2011)[43]

Source: Bakland *et al.* (2011)[43]

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

As described in Section 0, the COAST-V, -W and -X trials collected HRQoL outcomes via the EQ-5D-5L health utilities instrument.

In line with the NICE reference case, the EQ-5D-5L scores collected in the COAST-V, -W and -X trials were cross-walked to EQ-5D-3L values using the van Hout *et al.* (2012) approach and converted to utility values using the UK value set.[121]

B.3.4.2 Mapping

Given that the COAST trials collected EQ-5D-5L data, no mapping to other HRQoL measures was required.

B.3.4.3 Health-related quality-of-life studies

Studies reported relevant HRQoL model inputs were identified as part of the SLR described in Section B.3.1. Studies reported relevant HRQoL model inputs were identified as part of the SLR described in Section B.3.1. A total of 638 records (including 15 records identified through a hand search) were selected for full-text review against the study eligibility criteria. Subsequently, 121 records were included and selected for data extraction. Of those included in the original and updated review, 93 were categorised as HRQoL studies (77 studies in the original SLR and 16 studies in the update). The methodology for the systematic search of HRQoL model inputs, are presented in Appendix G, and an extraction grid summarising the included HRQoL studies can be found in the reference pack.

B.3.4.4 Adverse reactions

As described in Section B.3.3.6, the AEs included in the model were tuberculosis reactivation or other serious infection. In line with the York model, and due to lack of data in the literature, AEs in the model are not associated with any loss in utility.[24]

B.3.4.5 HRQoL data used in the cost-effectiveness analysis

Within the cost-effectiveness analyses, patients' health state utility is calculated using an algorithm, similarly to previous models of axSpA.[24] There are a number of available algorithms, which consist of a regression model to calculate utility (as measured by EQ-5D scores) incorporating a number of covariates, including BASDAI and BASFI scores, age, gender, race and disease duration.

In the base case, each population in the model (biologic-naïve rad-axSpA, biologic-experienced rad-axSpA and biologic-naïve nr-axSpA) uses an ordinary least-square utility regression model that was derived from the COAST-V, COAST-W or COAST-X data, respectively. The regression model was developed between BASDAI/BASFI data and EQ-5D-3L values cross-walked from EQ-5D-5L values, as described in Section B.3.4.1. The model therefore links disease activity and function to quality of life, and quality of life varies as patients' BASDAI and BASFI scores change.

In the biologic-naïve rad-axSpA population, with an adjusted R^2 of 0.5801, the linear algorithm based on COAST-V data was as follows:

Expected EQ-5D-3L = 0.9893 – 0.0320 x BASDAI – 0.0270 x BASFI

In the biologic-experienced rad-axSpA population, with an adjusted R^2 of 0.4391, the linear algorithm based on COAST-W data was as follows:

Expected EQ-5D-3L = 1.0022 – 0.0474 x BASDAI – 0.0182 x BASFI

The parameters of the regression model are presented in Table 108 and Table 109.

In addition to the base case mapping algorithm, the model includes the most recent and relevant publicly available regression models, the parameters of which are presented in Table 108 and Table 109, and are explored in scenario analyses (see Section B.3.8.3). All regression models are linear. The models available have been employed in the York model and reported in the secukinumab NICE submission.[24, 87]

The parameters for the utility regression models included in the cost-effectiveness analysis for rad-axSpA are presented in Table 108.

Table 108. Utility regression models used in the cost-effectiveness analysis for rad-axSpA

Parameters	Ixekizumab regression model (biologic-naïve)	Ixekizumab regression model (biologic-experienced)	Secukinumab NICE submission, 2016[25]	Schering-Plough model, McLeod *et al.* (2007)[88]	Wailoo *et al.* (2015)[122]
Intercept	0.9893	1.0022	0.9610	0.8772	0.722
BASFI (BASFI/100 in Wailoo)	−0.0270	−0.0182	−0.0330	−0.0384	−0.214
BASDAI	−0.0320	−0.0474	−0.0442	−0.0323	-
Sex (male)	-	-	−0.0111	−0.0279	-
Age	-	-	0.0005	0.0017	0.003
$(BASFI/100)^2$	-	-	-	-	−0.233
$(BASDAI/100)^2$	-	-	-	-	−0.47

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; NICE: National Institute for Health and Care Excellence; rad-axSpA: radiographic axial spondyloarthritis.

In the biologic-naïve rad-axSpA population, with an adjusted R^2 of 0.4573, the linear algorithm based on COAST-X data was as follows:

Expected EQ-5D-3L = 0.9573 – 0.0291 x BASDAI – 0.0275 x BASFI

The parameters for the regression models included in the cost-effectiveness analysis for nr-axSpA are presented in Table 109.

Table 109. Utility regression models used in the cost-effectiveness analysis for nr-axSpA

	Ixekizumab regression model (biologic-naïve nr-axSpA patients)	AbbVie MTA submission according to Corbett *et al.* (2016)[87]
Intercept	0.09573	0.922
BASFI	−0.0275	−0.04117
BASDAI	−0.0291	−0.03924

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; nr-axSpA: non-radiographic axial spondyloarthritis.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

Studies reporting relevant cost and resource use model inputs were identified as part of the SLR described in Section B.3.1. In total, eight publications (six in the original SLR and two in the update) reporting UK cost and resource use information were included. Details of the studies identified in the SLR that report cost and resource use data and are relevant to the submission can be found in the extraction grid included in the reference pack, and the methodology for the systematic search of cost and resource use model inputs, are presented in Appendix G.

The following cost categories are included in the model:

- Drug acquisition costs (Section B.3.5.1)
- Administration costs (Section B.3.5.1)
- Treatment initiation and monitoring resource use (Section B.3.5.1)
- Disease-related costs (Section B.3.5.2)
- AEs (Section B.3.5.3)

Costs were considered from an NHS/PSS perspective and were inflated to 2019 values where required using the Personal Social Services Research Unit (PSSRU) Hospital & Community Health Services Price and Pay index.[123] NHS Reference Costs 2017–18 were used to source cost inputs for treatment initiation and monitoring and treatment of AEs. NHS Reference Costs were selected over Payment by Results (PbR) tariffs due to the granularity provided for the Reference Costs compared to PbR National Tariffs, and also to align with the approach taken in the York model and TA407.[24, 25]

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition

In the model, patients incur treatment and monitoring costs which differ depending on whether patients are in a trial period, on maintenance treatment, or receiving conventional care. Drug acquisition cost is calculated based on the total number of doses for the trial period, number of doses yearly for the maintenance period and the unit cost (cost per dose). The unit costs for each medication have been derived from the Monthly Index for Medical Specialities (MIMS) database,[124] excluding the cost of acquisition for adalimumab, which is reimbursed under a nationally set reference price.[125] Certolizumab pegol is subject to a publicly available PAS in which the first 12 weeks of certolizumab pegol (equivalent to ten 200 mg vials) are provided to the NHS free of charge, therefore in the model there are no drug acquisition costs included for certolizumab pegol for the trial period.[24] Golimumab is also subject to a publicly available PAS, which applies only to NHS patients who weigh more than 100 kg and whose disease does not show an adequate clinical response after three or four doses of golimumab. For these patients, the treating clinician may recommend to increase the dose of golimumab from 50 mg to 100 mg, In this case, the 100 mg dose of golimumab will be provided to the NHS at the same price as the 50 mg dose. The golimumab PAS was not explicitly modelled as the mean weight for all three populations was less than 100 kg. It was deemed that modelling different weight distributions to capture patients greater than 100 kg would make little difference to the cost-effectiveness results, given that the cost of the 50 mg and 100 mg doses is equivalent when the PAS is applied.

The trial period duration, number of doses during trial period and annual maintenance period for ixekizumab and comparators are provided in Table 110. The treatment doses and dose costs, and the resulting drug costs per trial period and year whilst on maintenance treatment, are provided in Table 111. The cost of acquisition for adalimumab is presented in **Table** 112.

Table 110: Trial period duration, number of doses during trial period and annual maintenance period

Treatment	Trial period duration, cycles	Trial period number of doses	Maintenance number of doses per year	Method of administration	Dosing regimen	Indication(s)
Ixekizumab (rad-axSpA biologic-naïve and nr-axSpA biologic-naïve)	4	4	13	SC	80 mg Q4W (LD: 80 mg for rad-axSpA biologic-naïve and nr-axSpA biologic-naïve patients)[32]	Rad-axSpA, nr-axSpA
Ixekizumab (rad-axSpA biologic-experienced)	4	5	13	SC	80 mg Q4W (LD: 160 mg for rad-axSpA biologic-experienced patients)[32]	Rad-axSpA
Adalimumab	3	6	26	SC	40 mg Q2W[103]	Rad-axSpA, nr-axSpA
Certolizumab pegol	3	10	26	SC	400 mg at Weeks 0, 2 and 4, followed by maintenance dosing of 200 mg Q2W *or* 400 mg Q4W[101]	Rad-axSpA, nr-axSpA
Etanercept (50 mg Q2W)[a]	3	12	52	SC	50 mg QW (*or* 25 mg Q2W)[102]	Rad-axSpA, nr-axSpA
Golimumab	3	3	12	SC	50 mg once monthly[105]	Rad-axSpA, nr-axSpA
Infliximab	3	3	8	IV	5 mg/kg at Weeks 0, 2, and 6; thereafter every 6–8 weeks (assume every 7 weeks on average)[104] See Section B.3.3.1 for mean weight	Rad-axSpA
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Etanercept is also available under a 25 mg Q2W dosing regimen

Abbreviations: IV: intravenous; LD: loading dose; nr-axSpA: non-radiographic axial spondyloarthritis; Q2W: every two weeks; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SC: subcutaneous.

Table 111: Treatment doses and costs

Treatment	Dose[a]	Unit size	Pack size (No. units)	Cost per pack (£)	Cost per unit (£)	Cost per trial period (£)	Cost per year in maintenance period (£)
Ixekizumab (80 mg LD; PAS price)	80 mg	80 mg	1	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab (160 mg LD; PAS price)	80 mg	80 mg	1	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	200 mg/400 mg	200 mg	2	715.00	357.50	0[b]	9,295
Etanercept (25 mg)	25 mg	25 mg	4	328.00	82.00	1,931	8,366
Etanercept (50 mg)	50 mg	50 mg	4	656.00	164.00	1,931	8,366
Golimumab	50 mg	50 mg	1	762.97	762.97	2,289	9,156
Infliximab	5 mg/kg[c]	100 mg	1	377.00	377.00	4,524	12,064
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] For dosing frequencies please see Table 97, Section B.3.2.3.
[b] Certolizumab pegol is subject to a publicly available PAS in which the first 12 weeks of certolizumab pegol (equivalent to ten 200 mg vials) are provided to the NHS free of charge, therefore in the model there are no drug acquisition costs included for certolizumab pegol for the trial period.[24]
[c] Dose is weight dependent. See Section B.3.3.1 for mean weight used in the model for each patient population.
[redacted]197[redacted]
Abbreviations: PAS: patient access scheme.
Sources: MIMS 2019[124]

Table 112: Adalimumab acquisition costs

Treatment	Annual UK reference price (£)	Weekly price	Cost per trial period (£)	Cost per year in maintenance period (£)
Adalimumab	£3,550.00	£68.27	£819.23	£3,550.00

Source: NHS Improvement and NHS England[125]

Administration costs

The drug administration costs included in the model are provided in Table 113.

The majority of resource use estimates associated with administration were sourced from the York model,[87] which was based on assumptions included in the York model for psoriatic arthritis (NICE TA199).[126] The assumptions related to laboratory testing conform to guidelines from the BSR for the use of biologics.[42]

The administration cost for intravenous administered infliximab is assumed to be similar to a regular chemotherapy cost, as sourced from the NHS Reference Costs 2017–18 (health resource group [HRG] code SB15Z, deliver subsequent elements of a chemotherapy cycle).[24, 87, 127] All subcutaneous treatments are assigned a one-time cost for an administration training session after which it is assumed that the treatment is self-administered.[127] The cost of the training is based on one hour of nurse time.

Table 113: Drug administration costs

Administration method	Cost (£)	Source
Subcutaneous injection	42.00	Nurse (GP practice, cost per hour including qualifications), Unit Costs of Health and Social Care 2018, PSSRU[127]
Intravenous injection	289.00	National Schedule of NHS Reference Costs 2017–18, Chemotherapy (CHEM), Outpatient, SB15Z, Deliver Subsequent Elements of a Chemotherapy Cycle[127]

Abbreviations: GP: general practitioner; NHS: National Health Service; PSSRU: Personal Social Services Research Unit.
Source: NHS Reference Costs 2017/18[127]

Initiation and monitoring costs

The drug initiation and monitoring costs included in the model are provided in

Table 114.

During the trial period, treatment with ixekizumab, TNF-alpha inhibitors and secukinumab is assigned two specialist visits, and two visits per year thereafter. Routine laboratory tests are assumed to occur at initiation, at 12 weeks to evaluate response and every three months for monitoring during maintenance treatment. The routine laboratory tests are full blood count (FBC), liver function test (LFT), erythrocyte sedimentation rate (ESR) and urea and electrolytes (U&E). All patients also receive an X-ray, tuberculosis Heaf test, antinuclear antibodies test and DNA

double strand test at initiation. Patients with nr-axSpA are assumed to receive additional MRI and CRP tests at initiation as well as yearly X-rays for monitoring radiographic progression.

The unit costs for laboratory tests were obtained from NHS Reference Costs 2017/18.[127] The cost for a tuberculosis Heaf test was obtained from Rodgers *et al.* (2011).[128] The cost of a specialist visit was taken from NHS Reference Costs 2017/18 (Cost per a consultant-led, non-admitted face to face attendance, follow-up, WF01A Rheumatology).[127]

Table 114: Drug initiation and monitoring costs

Cost parameter	Rad-axSpA resource use		Nr-axSpA resource use		Unit cost (£)	Source
	Trial period	Maintenance (yearly)	Trial period	Maintenance (yearly)		
Medical visits						
Specialist visit	2	2	2	2	137.00	NHS Reference Costs 2017–18, code WF01A, Rheumatology[127]
Laboratory tests						
FBC	2	4	2	4	2.51	DAPS05, National Schedule of Reference Costs 2017–18[127]
LFT	2	4	2	4	1.11	DAPS04, National Schedule of Reference Costs 2017–18[127]
ESR	2	4	2	4	2.51	DAPS05, National Schedule of Reference Costs 2017–18[127]
U&E	2	4	2	4	1.11	DAPS04, National Schedule of Reference Costs 2017–18[127]
Chest radiograph (X-ray)	1	0	1	1	31.00	DAPF, National Schedule of Reference Costs 2017–18[127]
THT	1	0	1	0	8.91	Rodgers *et al.* (2011)[128]
Antinuclear antibodies	1	0	1	0	2.51	DAPS05, National Schedule of Reference Costs 2017–18[127]
DNA double-strand test	1	0	1	0	2.51	DAPS05, National Schedule of Reference Costs 2017–18[127]
CRP	0	0	1	0	0.00	NA
MRI	0	0	1	0	149.69	Weighted average, National Schedule of Reference Costs 2017–18[127]

Abbreviations: CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FBC: full blood count; HCHS: Hospital & Community Health Services; LFT: liver function test; MRI: magnetic resonance imaging; NA: not applicable; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; THT: tuberculosis Heaf test; U&E: urea & electrolytes.
Source: NHS Reference Costs 2017/18[127]

B.3.5.2 Health-state unit costs and resource use

In alignment with the York model and the model used in TA407, health state costs were modelled as disease management costs, estimated based on an exponential BASFI regression model.[24, 25] Therefore, the more severe the patient's disease is (as measured by BASFI score), the higher the cost of disease management will be. The equation used in the regression model is:

Cost of disease management = £1,349.68 × exp (0.213 × *BASFI score*)

The regression model was originally developed in one of the manufacturer's submissions in TA383, and uses data from the international OASIS cohort which has been re-analysed using 2013 published tariffs.[24, 87] These values were then inflated from 2014/15 to 2017/18 using New Health Service Index (PSSRU 2018).[123]

B.3.5.3 Adverse reaction unit costs and resource use

The costs of tuberculosis reactivation and severe infections are included in the model accordingly, as described in Section B.3.3.6.

Treatment-specific absolute risks of severe infections are employed in the model and provided in Table 106, Section B.3.3.6. The risk of severe infections when receiving conventional care was assumed to be zero. In the model, the AE rates are conservatively applied for the whole treatment period. This is in contrast to the York model, where relative risks versus conventional care were applied, and these risks were assumed to only occur in the first year of treatment.[24]

The cost of a serious infection and a tuberculosis reactivation episode are presented in Table 115. These are weighted averages of relevant HRG costs from NHS Reference Costs 2017/18.

Table 115: Cost of tuberculosis reactivation and severe infection

HRG code	HRG description	Activity, number of FCEs	National average unit cost
Tuberculosis reactivation			
DZ14F	Pulmonary, Pleural or Other Tuberculosis, with Interventions	548	£5,273.89
DZ14G	Pulmonary, Pleural or Other Tuberculosis, without Interventions, with CC Score 7+	666	£4,144.78
DZ14H	Pulmonary, Pleural or Other Tuberculosis, without Interventions, with CC Score 3-6	635	£3,527.60
DZ14J	Pulmonary, Pleural or Other Tuberculosis, without Interventions, with CC Score 0-2	626	£2,692.45
Weighted average cost		£3,869.10	
Serious infection			
WJ06A	Sepsis with Multiple Interventions, with CC Score 9+	2877	£9,250.40
WJ06B	Sepsis with Multiple Interventions, with CC Score 5-8	4021	£7,083.64
WJ06C	Sepsis with Multiple Interventions, with CC Score 0-4	1905	£5,408.57
WJ06D	Sepsis with Single Intervention, with CC Score 9+	5934	£5,220.72
WJ06E	Sepsis with Single Intervention, with CC Score 5-8	10752	£4,242.39

WJ06F	Sepsis with Single Intervention, with CC Score 0-4	6218	£3,415.76
WJ06G	Sepsis without Interventions, with CC Score 9+	31949	£3,251.30
WJ06H	Sepsis without Interventions, with CC Score 5-8	84455	£2,562.65
WJ06J	Sepsis without Interventions, with CC Score 0-4	73040	£1,947.55
DZ23H	Bronchopneumonia with Multiple Interventions	161	£6,943.02
DZ23J	Bronchopneumonia with Single Intervention, with CC Score 11+	392	£4,682.79
DZ23K	Bronchopneumonia with Single Intervention, with CC Score 0-10	325	£2,828.76
DZ23L	Bronchopneumonia without Interventions, with CC Score 11+	2539	£3,201.76
DZ23M	Bronchopneumonia without Interventions, with CC Score 6-10	3085	£2,185.89
DZ23N	Bronchopneumonia without Interventions, with CC Score 0-5	1679	£1,591.41
LA04H	Kidney or Urinary Tract Infections, with Interventions, with CC Score 12+	1223	£6,683.25
LA04J	Kidney or Urinary Tract Infections, with Interventions, with CC Score 9-11	2298	£5,333.37
LA04K	Kidney or Urinary Tract Infections, with Interventions, with CC Score 6-8	3539	£3,996.29
LA04L	Kidney or Urinary Tract Infections, with Interventions, with CC Score 3-5	3543	£3,098.34
LA04M	Kidney or Urinary Tract Infections, with Interventions, with CC Score 0-2	2169	£2,335.72
LA04N	Kidney or Urinary Tract Infections, without Interventions, with CC Score 13+	3766	£4,226.60
LA04P	Kidney or Urinary Tract Infections, without Interventions, with CC Score 8-12	22854	£3,113.54
LA04Q	Kidney or Urinary Tract Infections, without Interventions, with CC Score 4-7	43698	£2,225.71
LA04R	Kidney or Urinary Tract Infections, without Interventions, with CC Score 2-3	20488	£1,694.93
LA04S	Kidney or Urinary Tract Infections, without Interventions, with CC Score 0-1	14066	£1,464.54
HC31H	Spinal Infection with Interventions, with CC Score 6+	437	£11,613.16
HC31J	Spinal Infection with Interventions, with CC Score 0-5	537	£8,621.60
HC31K	Spinal Infection without Interventions, with CC Score 10+	277	£6,280.29
HC31L	Spinal Infection without Interventions, with CC Score 6-9	469	£5,063.71
HC31M	Spinal Infection without Interventions, with CC Score 3-5	510	£4,305.60
HC31N	Spinal Infection without Interventions, with CC Score 0-2	446	£3,231.83
DZ22K	Unspecified Acute Lower Respiratory Infection with Interventions, with CC Score 9+	1494	£4,179.23
DZ22L	Unspecified Acute Lower Respiratory Infection with Interventions, with CC Score 0-8	1283	£2,876.05
DZ22M	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 13+	4085	£3,067.75
DZ22N	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 9-12	13068	£2,316.21

DZ22P	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 5-8	20913	£1,840.80
DZ22Q	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 0-4	15172	£1,435.02
DZ65A	Chronic Obstructive Pulmonary Disease or Bronchitis, with Multiple Interventions, with CC Score 9+	523	£4,731.87
DZ65B	Chronic Obstructive Pulmonary Disease or Bronchitis, with Multiple Interventions, with CC Score 0-8	484	£3,319.00
DZ65C	Chronic Obstructive Pulmonary Disease or Bronchitis, with Single Intervention, with CC Score 9+	2713	£3,311.29
DZ65D	Chronic Obstructive Pulmonary Disease or Bronchitis, with Single Intervention, with CC Score 5-8	3,354	£2,454
DZ65E	Chronic Obstructive Pulmonary Disease or Bronchitis, with Single Intervention, with CC Score 0-4	2,297	£2,077
DZ65F	Chronic Obstructive Pulmonary Disease or Bronchitis, without Interventions, with CC Score 13+	4,813	£2,948
DZ65G	Chronic Obstructive Pulmonary Disease or Bronchitis, without Interventions, with CC Score 9-12	17,074	£2,281
DZ65H	Chronic Obstructive Pulmonary Disease or Bronchitis, without Interventions, with CC Score 5-8	35,364	£1,820
DZ65J	Chronic Obstructive Pulmonary Disease or Bronchitis, without Interventions, with CC Score 0-4	36,526	£1,493
DZ65K	Chronic Obstructive Pulmonary Disease or Bronchitis, with length of stay 1 day or less, Discharged Home	1,684	£1,154
Weighted average cost		£3,060.65	

Abbreviations: CC: conventional care; FCE: finished case episode; HRG: Health Resource Group.

B.3.5.4 Miscellaneous unit costs and resource use

There are no further unit costs or resource use included in the model.

B.3.6 *Summary of base-case analysis inputs and assumptions*

B.3.6.1 Summary of base-case analysis inputs

A summary of the variables applied in the model is in the biologic-naïve and biologic-experienced rad-axSpA populations and the biologic naïve nr-axSpA population is provided in Table 116.

Table 116: Summary of variables applied in the economic model

Type of variable	Variable	Value	Reference to section in submission	Reference
Global model assumptions	Start age	Biologic-naïve rad-axSpA: 41.7 Biologic-experienced rad-axSpA: 46.1 Biologic-naïve nr-axSpA: 40.3	Section B.3.3.1	COAST-V trial[2] COAST-W trial[3] COAST-X trial[5, 6]
	Proportion male (%)	Biologic-naïve: 80.9 Biologic-experienced: 80.1 Biologic-naïve nr-axSpA: 47.2	Section B.3.3.1	COAST-V trial[2] COAST-W trial[3] COAST-X trial[5, 6]
	Mean weight (kg)	Biologic-naïve: 78.1 Biologic-experienced: 83.2 Biologic-naïve nr-axSpA: 77.5	Section B.3.3.1	COAST-V trial[2] COAST-W trial[3] COAST-X trial[5, 6]
	Discount rate costs (%)	3.5	Section B.3.2.2	NICE reference case[100]
	Discount rate effects (%)	3.5	Section B.3.2.2	NICE reference case[100]
	Modelling time horizon	Lifetime	Section B.3.2.2	NICE reference case[100]
	Include mortality	Yes	Section B.3.3.8	NA
	Withdrawal of biologic therapy	Rad-axSpA: 11% Nr-axSpA: 5%	Section B.3.3.7	NICE TA407[25]
Disease progression	Definition of responders	BASDAI50	Section B.3.3.2	NMA
	Baseline BASDAI	Biologic-naïve rad-axSpA: 6.75 Biologic-experienced rad-axSpA: 7.43 Biologic-naïve nr-axSpA: 7.16	Section B.3.3.1	COAST-V trial[2] COAST-W trial[3] COAST-X trial[5, 6]
	Baseline BASFI	Biologic-naïve rad-axSpA: 6.23 Biologic-experienced rad-axSpA: 7.27 Biologic-naïve nr-axSpA: 6.52	Section B.3.3.1	COAST-V trial[2] COAST-W trial[3] COAST-X trial[5, 6]
	Cfb baseline BASDAI and BASFI	Conditional on BASDAI50 response/non-response	Section B.3.3.3	COAST-V trial[2] COAST-W trial[3] COAST-X trial[5, 6] NICE TA407[25] York model[87]

	Annual rate of mSASSS change:	Rad-axSpA: 1.44 Nr-axSpA: 0.69	Section B.3.3.4	Ramiro *et al.* (2013)[79]
	BASFI change with 1 unit mSASSS change	0.057	Section B.3.3.4	Landewe *et al.* (2013)[81]
	Treatment effect for biologics on progression	0.42	Section B.3.3.4	Haroon *et al.* (2013)[80]
	Rebound method for BASDAI and BASFI	Initial gain	Section B.3.3.5	Assumption
Utilities	Algorithm to determine patient utilities	Ixekizumab EQ-5D-3L algorithm	Section B.3.4.5	COAST-V trial[2] COAST-W trial[3] COAST-X trial[5, 6]
	Adverse events	Not included	Section B.3.4.4	NICE TA407[25]
Costs	Acquisition	Biosimilar costs, PASs and national reference price applied where applicable	Section B.3.5.1	MIMS,[124] NICE TA407,[25] ADA price reference[125]
	Administration	SC administration training costs, IV costs	Section B.3.5.1	NICE TA407[25]
	Initiation and monitoring costs	Applied for biologic treatments	Section B.3.5.1	NICE TA407[25]
	Disease management	Cost of disease management algorithm based on BASFI score	Section B.3.5.2	NICE TA407[25]
	Include cost of AEs	On treatment	Section B.3.5.3	NA
	AEs	Serious infections and tuberculosis reactivation	Section B.3.5.3	NHS Reference Costs

Abbreviations: AE: adverse event; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; EQ-5D: EuroQol-Five Dimensions; IV: intravenous; mSASSS: modified Stroke Ankylosing Spondylitis Spine Score; NHS: National Health Service; NMA: network meta-analysis; nr-axSpA: non-radiographic axial spondyloarthritis; PAS: patient access scheme; rad-axSpA: radiographic axial spondyloarthritis; SC: subcutaneous.

B.3.6.2 Assumptions

The assumptions included in the model, and their justifications, are provide in Table 117.

Table 117: List of model assumptions and their justifications

Model assumption	Justification
BASDAI was assumed to remain constant over time and does not progress in the long-term.	A targeted literature review was performed by the Assessment Group in TA383 and the identified evidence, including a UK registry study (SIRAS),[108] indicated that disease activity (as measured by BASDAI) in rad-axSpA and nr-axSpA typically remains stable over time and does not progress.[24]
BASFI was assumed to progressively worsen over time. The model assumed that long-term progression of BASFI is a function of disease activity (e.g. BASDAI) and the extent and progression of radiographic disease (e.g. mSASSS).	A target literature review performed by the Assessment Group in TA383 indicated that patients' functional impairment (as measured by BASFI) progressively worsens over time.[24] This approach is in alignment with the findings of Landewe *et al.* (2009) and the York model in rad-axSpA.[24, 81]
Patients who responded to biologic treatment were assumed to experience a slower rate of disease progression (as measured by BASFI) during treatment, in comparison to the natural history of axSpA whilst receiving conventional care	This approach is consistent with models used in previous NICE submissions in axSpA (TA383 and TA407).[24, 25]
Where data were missing for TNF-alpha inhibitors for BASDAI50, cfb BASDAI and cfb BASFI, an unweighted average of available data from other TNF-alpha inhibitors was used.	This approach is consistent with the model used in TA407.[25]
The relationship between cfb BASFI and BASDAI values in responders and non-responders is assumed to be equivalent between interventions.	This approach was required due to the lack of availability of conditional values for all interventions. This approach is consistent with the model used in TA407, where this assumption was validated by two clinical experts.[25]
[redacted]	[redacted]
The treatment effect of ixekizumab, secukinumab and TNF-alpha inhibitors on mSASSS is assumed to be the same.	This approach is consistent with models used in previous NICE submissions in axSpA (TA383 and TA407).[24, 25]
The treatment effect of ixekizumab and comparators on disease progression is applied from the end of the trial period (e.g. from the start of the maintenance health state)	This approach is consistent with the base case approach in TA407 and is aligned the NICE Committee preference in TA383, where the Committee chose to consider results presented in a scenario analysis where the treatment effect of progression was applied from the start of treatment, rather than after 4 years of treatment.[24, 25]
Upon discontinuation of treatment and transfer to the conventional care health state, patients are assumed	This is a conservative estimate in comparison to the NICE Committee

to lose their treatment response on BASDAI and BASFI. In the case of BASDAI, patients will rebound to their baseline value. In the case of BASFI, patients are assumed to 'rebound by initial gain'.	preference in TA383 and the base case approach in TA407 where the base case rebound scenario is "rebound to baseline". An alternative rebound scenario, "rebound to natural history" is explored in a scenario analysis.
Baseline characteristics (including BASDAI and BASFI values) are unconditional upon response, that is, baseline values are the same for responders and non-responders	This approach aligns with the NICE Committee preference in TA383.[24] The use of conditional baselines is explored in a scenario analysis.
It is assumed that the probability of transition from any of the other health states to death is equal within each cycle and in the base case patients experience normal UK mortality rates	This is a conservative assumption in comparison to the York model, which assumed that mortality rate was greater than the UK population average in patients with axSpA. An increased mortality rate with rad-axSpA and nr-axSpA is explored in a scenario analysis.[24]
The drop-out rate is assumed to be constant over time and is assumed to be the same for all treatments.	This approach is consistent with models used in previous NICE submissions in axSpA (TA383 and TA407).[24, 25]
Conventional care is assumed to continue alongside biologic treatment, and is therefore costed at £0.00, and was not associated with any AEs	This is a conservative assumption and the assumption of no AEs with conventional care is consistent with previous NICE submissions in axSpA.[25]
All subcutaneous treatments are assigned a one-time cost for an administration training session, after which it is assumed that the treatment is self-administered.	This approach is consistent with models used in previous NICE submissions in axSpA (TA383 and TA407).[24, 25]
The model assumes that AE rates apply for the whole treatment period.	This is a conservative estimate in comparison to the York model, which assumed that AE rates would only occur in the first year of treatment, which is explored in a scenario analysis (see Section B.3.8.3).[24]
The model assumes that there is no disutility associated with tuberculosis reactivation or severe infections.	This approach is consistent with models used in previous NICE submissions in axSpA (TA383 and TA407).[24, 25]

Abbreviations: AE: adverse event; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CI: confidence interval; EQ-5D: EuroQol-Five Dimensions; IV: intravenous; mSASSS: modified Stroke Ankylosing Spondylitis Spine Score; NHS: National Health Service; NMA: network meta-analysis; nr-axSpA: non-radiographic axial spondyloarthritis; PAS: patient access scheme; rad-axSpA: radiographic axial spondyloarthritis; SC: subcutaneous; TNF: tumour necrosis factor

B.3.7 *Base-case results*

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The summary of results in the base case analysis are presented in Table 118 for the rad-axSpA biologic-naïve population, Table 119 for the rad-axSpA biologic-experienced population and Table 120 for the nr-axSpA biologic-naïve population. All results incorporate the PAS for ixekizumab that is established in the NHS for psoriasis and psoriatic arthritis. The clinical outcomes and disaggregated base case cost-effectiveness results are presented in Appendix J.

Biologic-naïve rad-axSpA

The results of the incremental analysis demonstrate that adalimumab dominated all biologic treatments. In the pairwise comparisons for ixekizumab Q4W versus each comparator, ixekizumab Q4W dominated all biologic treatments with the exception of adalimumab. These results demonstrate that ixekizumab Q4W would be a cost-effective addition to the physician's armamentarium of treatments for biologic-naïve rad-axSpA patients.

As described in Section B.1, the relevant comparators for patients who are contraindicated to TNF inhibitors are conventional care and secukinumab. As described in Section B.3.3, due to the limited availability of efficacy data from the NMA, it was not possible to include secukinumab in the base case for this population. [redacted].3.8.3 The pairwise result for ixekizumab Q4W versus conventional care shows that the ICER is slightly greater than the £30,000 per QALY threshold.

Table 118: Base case results – rad-axSpA biologic-naïve (with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER ixekizumab Q4W vs comparator (£/QALY)
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	-	£34,301
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£4,387	Dominated
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant

Life years gained are equivalent between technologies (interventions do not impact mortality in the model) and are therefore not presented. Results are presented here for ixekizumab 80 mg Q4W (LD: 80 mg). As described in Section B.3.3, results for secukinumab 150 mg are not presented for the base case due to relevant efficacy inputs being unavailable from the NMA. Results for pooled doses for etanercept and certolizumab pegol are presented.
Abbreviations: ICER: incremental cost-effectiveness ratio; LD: loading dose; QALYs: quality-adjusted life years

Biologic-experienced rad-axSpA

The results of the incremental analysis demonstrate that adalimumab dominated all biologic treatments, with the exception of infliximab (ICER of £860,378 per QALY). In the pairwise comparisons for ixekizumab Q4W versus each comparator, with the exception of the comparison to adalimumab (in which adalimumab was dominant), the ICERs for ixekizumab Q4W fell into the south-west quadrant of the cost-effectiveness plane, indicating that ixekizumab generated fewer QALYs and accrued fewer costs versus the comparator. For ICERs falling into this quadrant, ICERs greater than the £30,000 per QALY threshold may be considered cost-effective. As such, the pairwise ICERs for ixekizumab Q4W versus etanercept, certolizumab pegol, golimumab and infliximab may be considered meet to the £30,000 cost-effectiveness threshold. [redacted]

Table 119: Base case results – rad-axSpA biologic-experienced (with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER ixekizumab Q4W vs comparator (£/QALY)
Conventional care	[redacted]	[redacted]	-	-	-	£1,603,221
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£56,119	Dominated
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£41,794*
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£954,573*
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£96,133*
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	£860,378	£287,583*

Life years gained are equivalent between technologies (interventions do not impact mortality in the model) and are therefore not presented. Results are presented here for ixekizumab 80 mg Q4W (LD: 160 mg). As described in Section B.3.3, results for secukinumab 150 mg and 300 mg are not presented for the base case due to relevant efficacy inputs being unavailable from the NMA. Results for pooled doses for etanercept and certolizumab pegol are presented. *ICERs are located in the south-west quadrant of the cost-effectiveness plane (ICERs > £30,000 per QALY may be considered cost-effective).
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Biologic-naïve nr-axSpA

Company evidence submission template for ixekizumab for the treatment of people with axSpA for whom NSAIDs, or anti-TNFs have been inadequately effective or not tolerated [ID1532]

The results of the incremental analysis demonstrate that adalimumab was the most cost-effective of all biologic treatments. In the pairwise comparisons for ixekizumab Q4W versus each comparator, ixekizumab Q4W dominated golimumab, and had ICERs within the cost-effective range versus etanercept (£16,672 per QALY) and conventional care (£29,687 per QALY). These results demonstrate that ixekizumab Q4W would be a cost-effective addition to the physician's armamentarium of treatments for biologic-naïve nr-axSpA patients, including those who are contraindicated to TNF inhibitors.

Table 120: Base-case results (list price) – nr-axSpA biologic-naïve (with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER ixekizumab Q4W vs comparator (£/QALY)
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	-	£29,687
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£4,809	£423,916
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£16,672
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	£75,056	£14,435*

Life years gained are equivalent between technologies (interventions do not impact mortality in the model) and are therefore not presented. Results are presented here for ixekizumab 80 mg Q4W (LD: 80 mg). Results for pooled doses for etanercept and certolizumab pegol are presented. *ICERs are located in the south-west quadrant of the cost-effectiveness plane (ICERs > £30,000 per QALY may be considered cost-effective).
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analyses (PSAs) with 1,000 iterations were performed for each pairwise comparison in each of the three patient populations, in order to assess the uncertainty associated with model input parameters. The input parameters varied in the PSAs and the distributions associated with each parameter are presented in Appendix J.2.

The probabilistic base case results, cost-effectiveness acceptability curves and cost-effectiveness plane scatterplots for the biologic-naïve rad-axSpA, biologic-experienced rad-axSpA and biologic-naïve nr-axSpA populations are presented below.

Table 121: Probabilistic base case results – rad-axSpA biologic-naïve (with-PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER ixekizumab Q4W vs comparator (£/QALY)
Conventional care	[redacted]	[redacted]	-	-	-	£31,265
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£1,627	Dominated
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant

Life years gained are equivalent between technologies (interventions do not impact mortality in the model) and are therefore not presented. Results are presented here for ixekizumab 80 mg Q4W (LD: 80 mg). As described in Section B.3.3, results for secukinumab are not presented for the base case due to relevant efficacy inputs being unavailable from the NMA. Results for pooled doses for etanercept and certolizumab pegol are presented.
Abbreviations: ICER: incremental cost-effectiveness ratio; LD: loading dose; QALYs: quality-adjusted life years

Table 122: Probabilistic base case results – rad-axSpA biologic-experienced (with-PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER ixekizumab Q4W vs comparator (£/QALY)
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	-	£1,635,912
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£44,867	Dominated
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£36,784*
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£1,117,054*
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£91,220*
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	£816,669	£272,720*

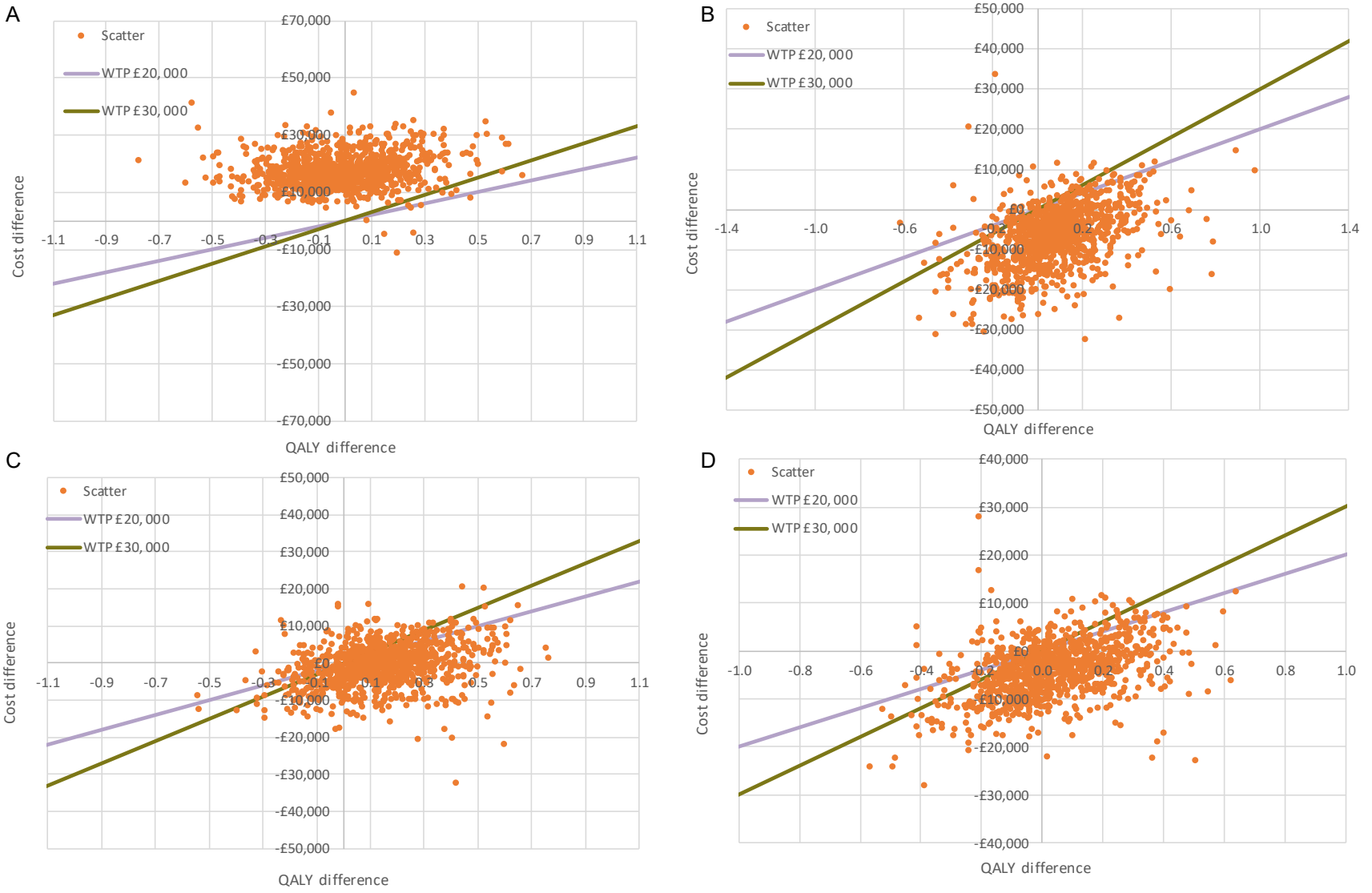
Life years gained are equivalent between technologies (interventions do not impact mortality in the model) and are therefore not presented. Results are presented here for ixekizumab 80 mg Q4W (LD: 160 mg). As described in Section B.3.3, results for secukinumab are not presented for the base case due to relevant efficacy inputs being unavailable from the NMA. Results for pooled doses for etanercept and certolizumab pegol are presented. *ICERs are located in the south-west quadrant of the cost-effectiveness plane (ICERs > £30,000 per QALY may be considered cost-effective).
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

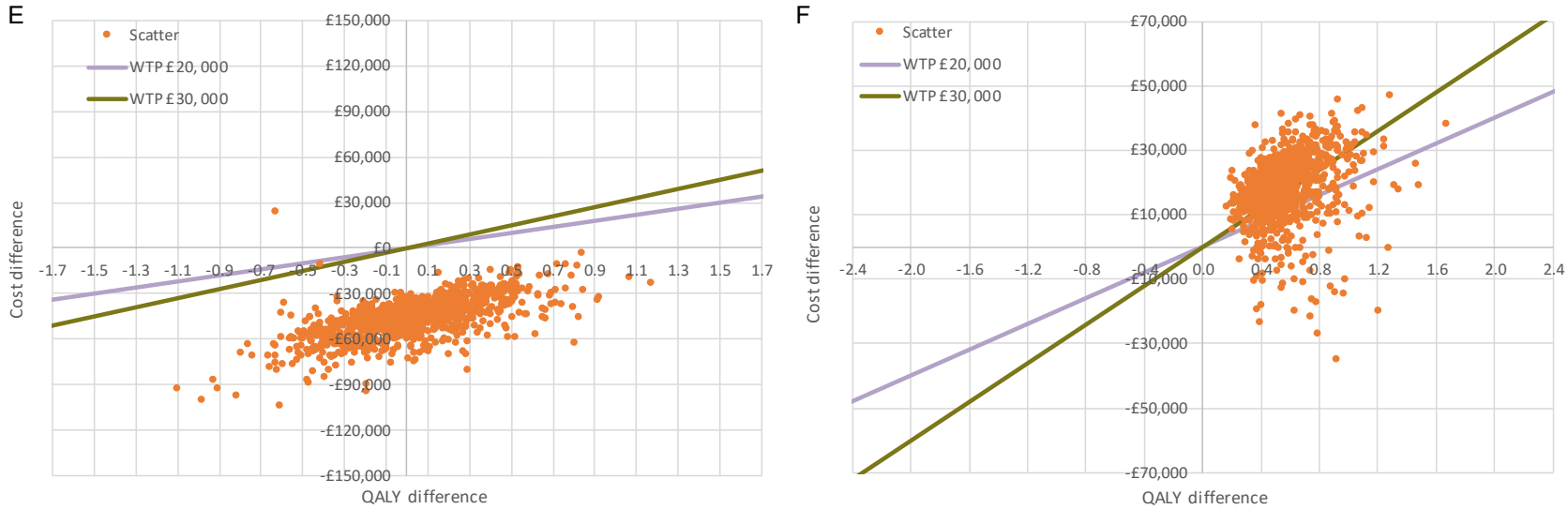
Table 123: Probabilistic base case results – nr-axSpA biologic-naive (with-PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER ixekizumab Q4W vs comparator (£/QALY)
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	-	£27,250
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£2,285	£559,570
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£14,026
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	£73,610	£12,851*

Life years gained are equivalent between technologies (interventions do not impact mortality in the model) and are therefore not presented. Results are presented here for ixekizumab 80 mg Q4W (LD: 80 mg). Results for pooled doses for etanercept and certolizumab pegol are presented. *ICERs are located in the south-west quadrant of the cost-effectiveness plane (ICERs > £30,000 per QALY may be considered cost-effective).
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

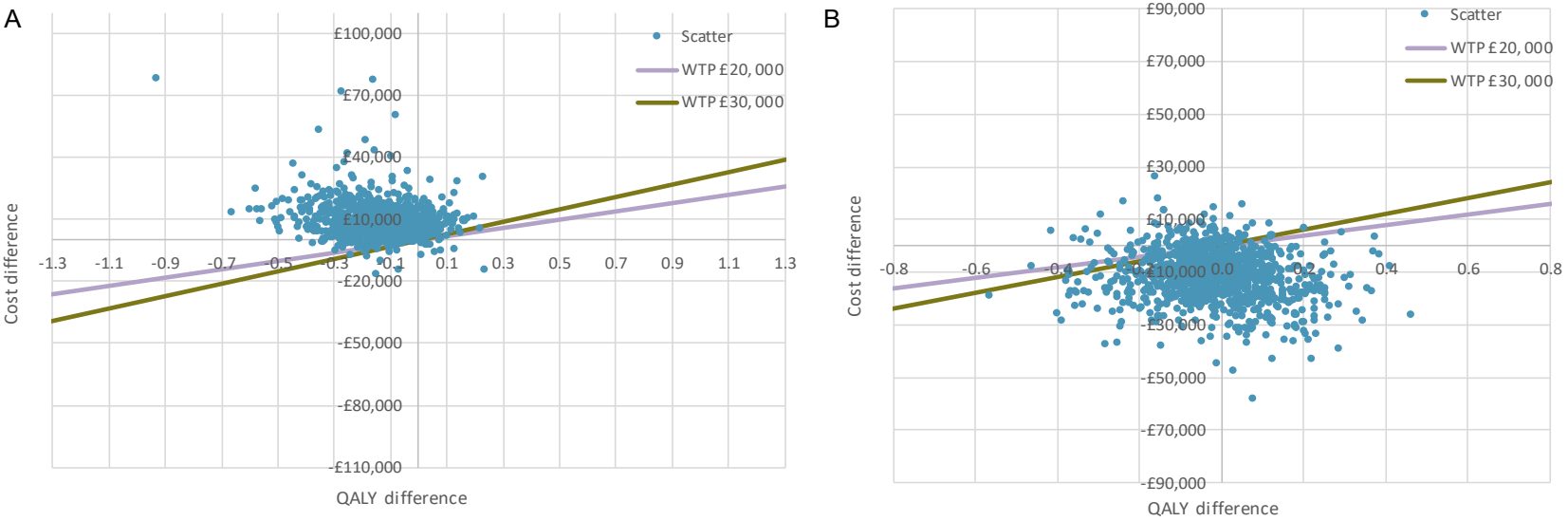
Figure 31: Biologic-naïve rad-axSpA pairwise PSA results for IXE vs A) ADA B) CZP C) ETA D) GOL E) IFX F) CC





ADA: adalimumab; CC: conventional care; CZP: certolizumab; ETA: etanercept; GOL: golimumab; IFX: infliximab; IXE: ixekizumab WTP: willingness-to-pay

Figure 32: Biologic-experienced rad-axSpA pairwise PSA results for IXE vs A) ADA B) CZP C) ETA D) GOL E) IFX F) CC



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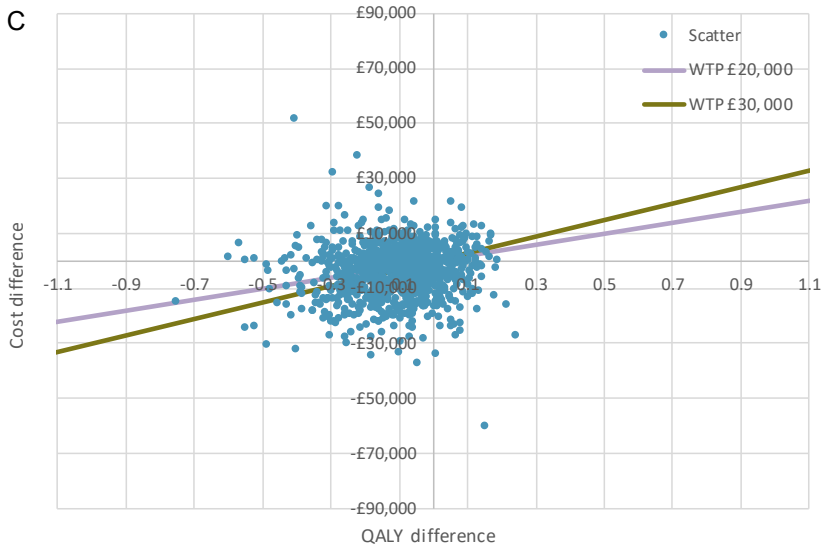

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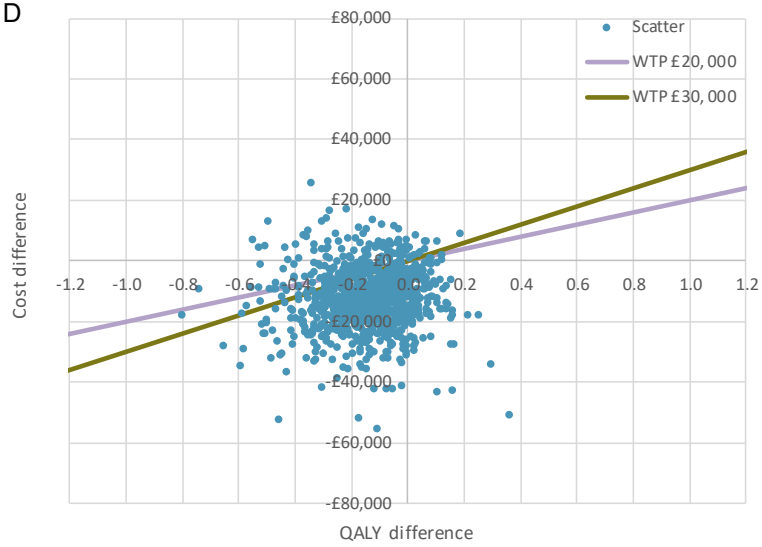

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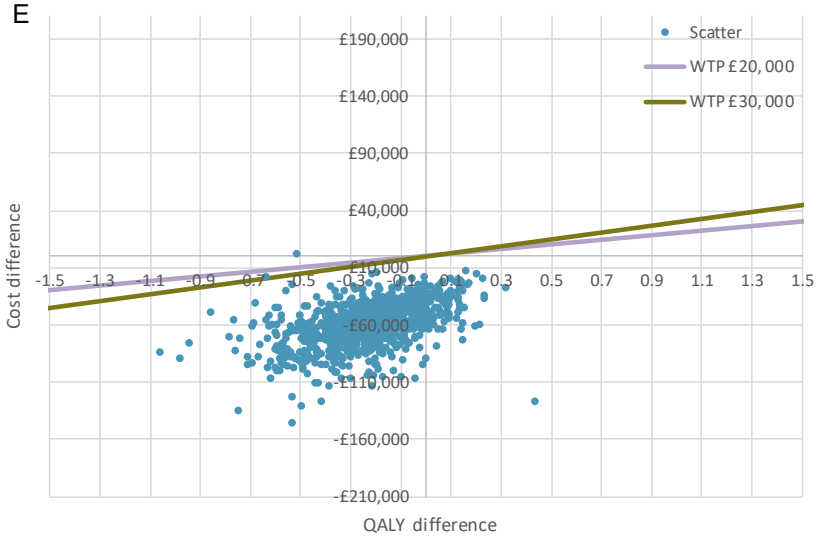
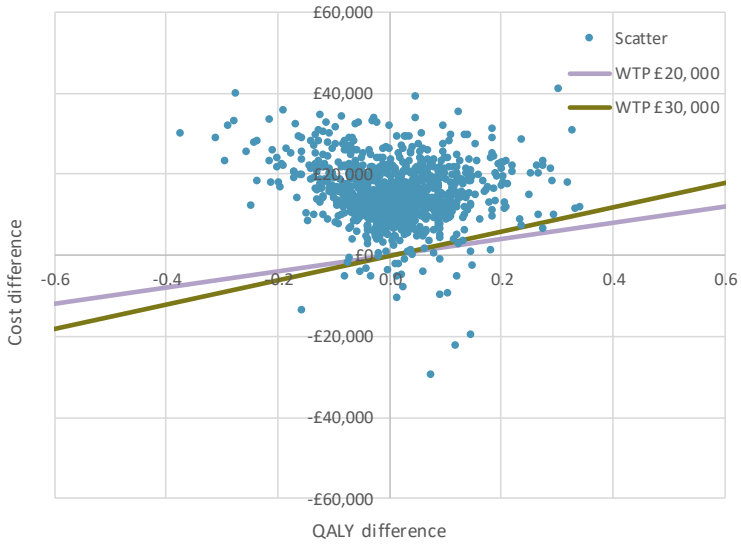
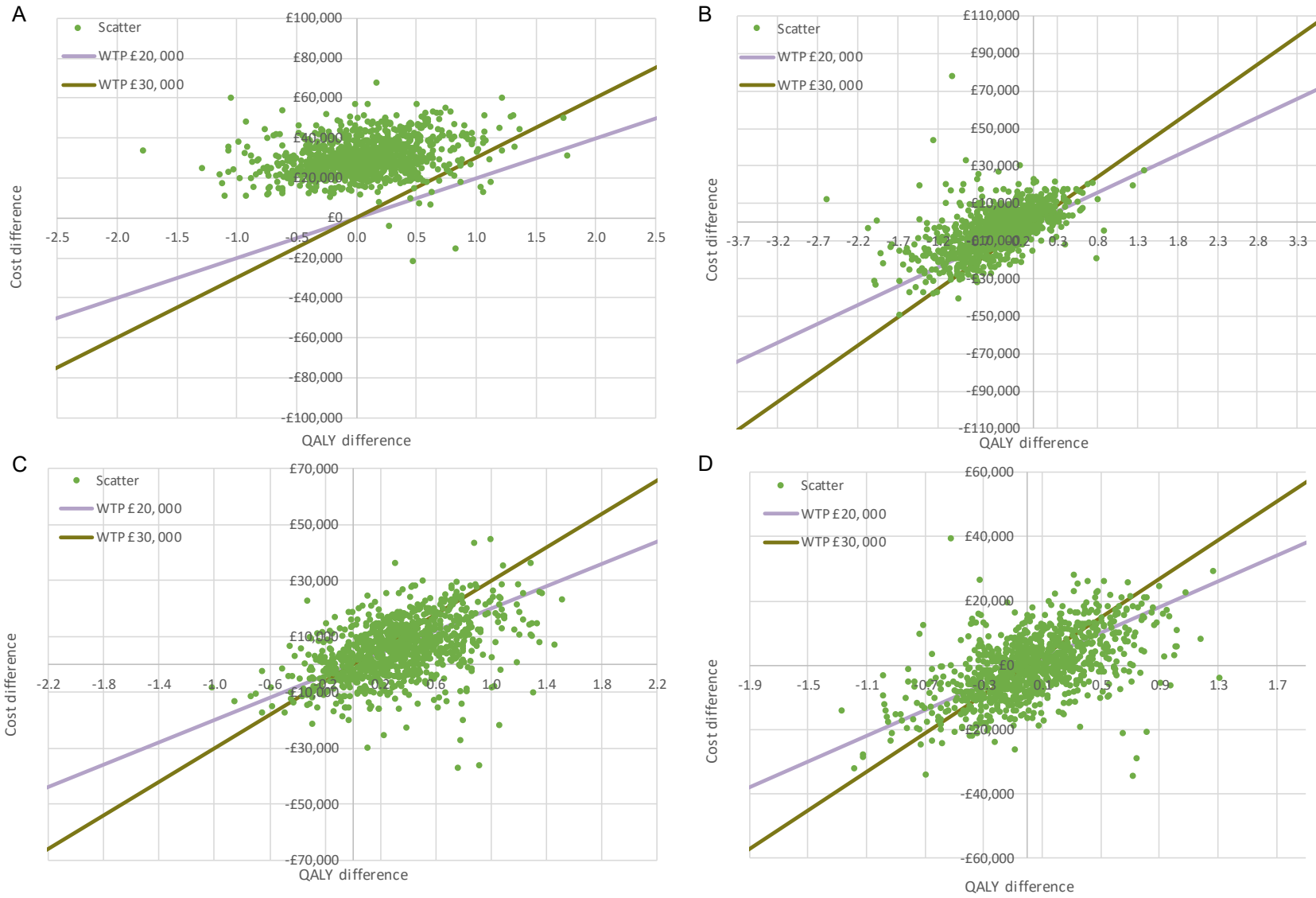


F



Abbreviations: ADA: adalimumab; CC: conventional care; CZP: certolizumab; ETA: etanercept; GOL: golimumab; IFX: infliximab; IXE: ixekizumab WTP: willingness-to-pay

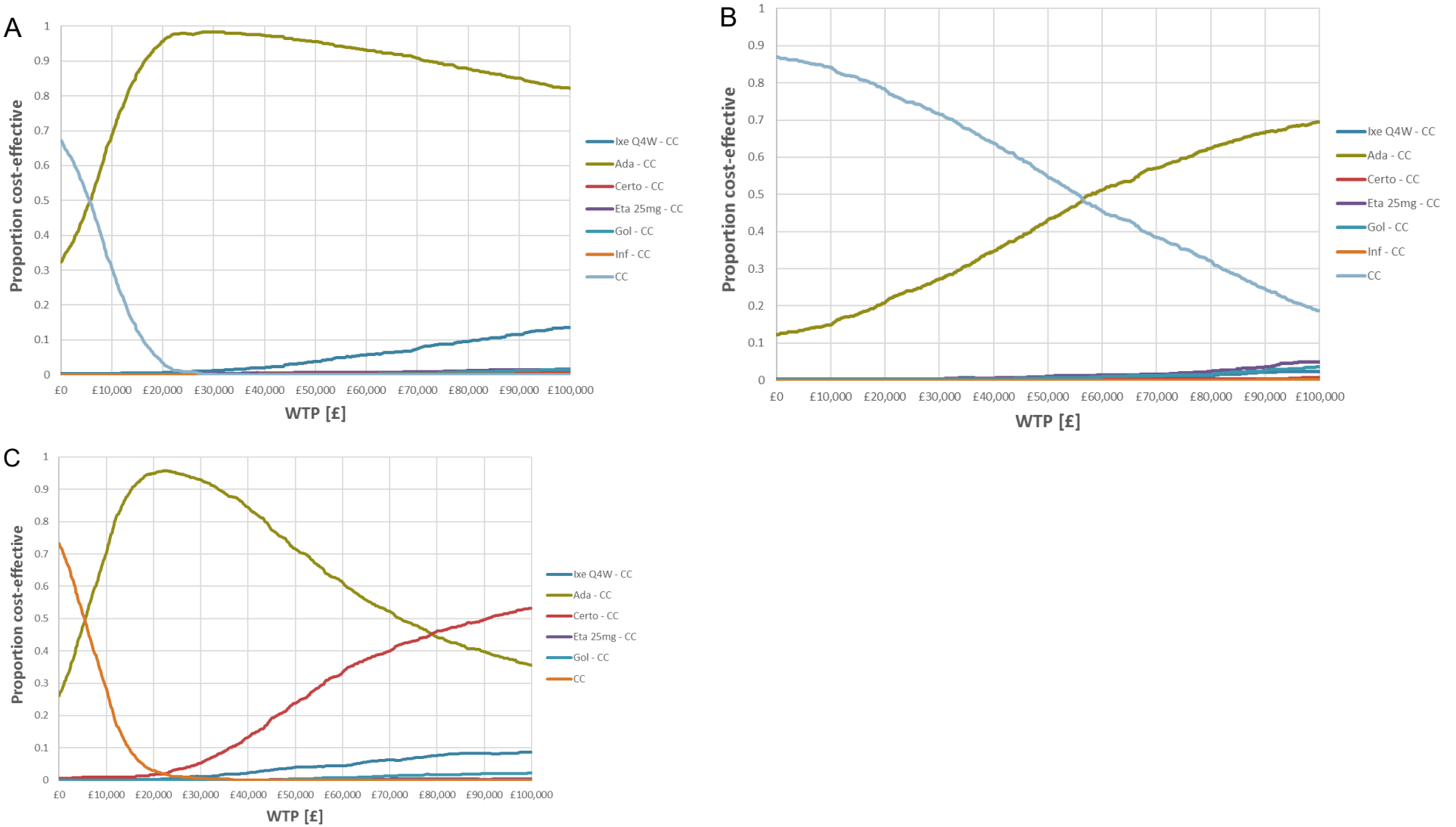
Figure 33: Biologic-naive nr-axSpA pairwise PSA results for IXE vs A) ADA B) CZP C) ETA D) GOL E) CC



E

Abbreviations: ADA: adalimumab; CC: conventional care; CZP: certolizumab; ETA: etanercept; GOL: golimumab; IXE: ixekizumab WTP: willingness-to-pay

Figure 34: Cost-effectiveness acceptability curves for A) biologic-naïve rad-axSpA B) biologic-experienced rad-axSpA C) biologic-naïve nr-axSpA



Abbreviations: ADA: adalimumab; CC: conventional care; CERTO: certolizumab; ETA: etanercept; GOL: golimumab; IXE: ixekizumab; WTP: willingness-to-pay

B.3.8.2 Deterministic sensitivity analysis

Input parameters for the three populations were varied individually in DSAs. The inputs varied and their variations can be found in Appendix J. The results of the deterministic sensitivity analyses (DSA) for pairwise comparisons of ixekizumab Q4W vs comparators within the biologic-naive rad-axSpA (Table 124), biologic-experienced rad-axSpA and biologic-naive nr-axSpA populations are presented below. Within the tables, results for the 16 most influential parameters are presented.

Table 124: Deterministic sensitivity analysis results - Biologic-naïve rad-axSpA population

Adalimumab			Certolizumab		
Base case	Dominated		Base case	Dominant	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**	**Treatment parameter**	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Discount rate QALYs	Dominated	Dominated	Certolizumab - BASDAI reduction for responders	Dominant	£584,179*
Adalimumab - BASDAI reduction for responders	£257,047	Dominated	Ixekizumab Q4W - BASFI reduction for responders	£561,236*	Dominant
Ixekizumab Q4W - BASFI reduction for responders	Dominated	£151,590	Certolizumab - BASFI reduction for responders	Dominant	Dominant
Ixekizumab Q4W - BASDAI reduction for responders	Dominated	£149,144	Ixekizumab Q4W - BASDAI reduction for responders	£283,685*	Dominant
Adalimumab - Response rate	Dominated	Dominated	Certolizumab - Response rate	£12,794	£173,338*
Ixekizumab Q4W - Response rate	Dominated	Dominated	Ixekizumab Q4W - Response rate	£110,141*	£467
Adalimumab - BASFI reduction for responders	Dominated	Dominated	Discount rate costs	Dominant	Dominant
Utility BASFI coefficient	Dominated	Dominated	Discount rate QALYs	Dominant	Dominant
Discount rate costs	Dominated	Dominated	Utility BASDAI coefficient	Dominant	Dominant
Annual discontinuation rate	Dominated	Dominated	Certolizumab: No. physician visits - maintenance (annually)	Dominant	Dominant
Ixekizumab Q4W - BASDAI reduction for non-responders	Dominated	Dominated	Utility BASFI coefficient	Dominant	Dominant
Ixekizumab Q4W - BASFI reduction for non-responders	Dominated	Dominated	Annual discontinuation rate	Dominant	Dominant
Adalimumab - BASDAI reduction for non-responders	Dominated	Dominated	Ixekizumab Q4W: No. physician visits - maintenance (annually)	Dominant	Dominant
Adalimumab - BASFI reduction for non-responders	Dominated	Dominated	Certolizumab: Rate of severe infections/patient year	Dominant	Dominant
Ixekizumab Q4W – No. physician visits - maintenance (annually)	Dominated	Dominated	BASFI coefficient	Dominant	Dominant
Adalimumab – No. physician visits - maintenance (annually)	Dominated	Dominated	Certolizumab: Number of physician visits - trial	Dominant	Dominant

Infliximab			Golimumab		
Base case	Dominant		Base case	Dominant	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**	**Treatment parameter**	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Discount rate QALYs	Dominant	Dominant	Golimumab - Response rate	£8,997	£103,055
Infliximab - BASDAI reduction for non-responders	Dominant	Dominant	Golimumab - BASDAI reduction for responders	Dominant	£72,538
Annual discontinuation rate	£5,983,522*	Dominant	Ixekizumab Q4W - Response rate	£64,043*	£9,806
Infliximab - BASFI reduction for non-responders	Dominant	Dominant	Ixekizumab Q4W - BASDAI reduction for responders	£59,198*	Dominant
Infliximab - BASDAI reduction for responders	Dominant	£777,847*	Golimumab - BASFI reduction for responders	Dominant	£45,459*
Ixekizumab Q4W - BASFI reduction for responders	£622,165*	Dominant	Ixekizumab Q4W - BASFI reduction for responders	£16,902*	Dominant
Infliximab - BASFI reduction for responders	Dominant	£571,364*	Discount rate costs	Dominant	Dominant
Ixekizumab Q4W - BASDAI reduction for responders	£534,277*	Dominant	Utility BASDAI coefficient	Dominant	Dominant
Ixekizumab Q4W - Response rate	£288,747*	Dominant	Discount rate QALYs	Dominant	Dominant
Infliximab - Response rate	Dominant	£163,707*	Golimumab - Physician visits costs: number of visits - maintenance (annually)	Dominant	Dominant
Utility BASDAI coefficient	Dominant	Dominant	Ixekizumab Q4W - Physician visits costs: number of visits - maintenance (annually)	Dominant	Dominant
Discount rate costs	Dominant	Dominant	Golimumab - Physician visits costs: number of visits - trial	Dominant	Dominant
Cost of physician visit for IV	Dominant	Dominant	Ixekizumab Q4W - Physician visits costs: number of visits - trial	Dominant	Dominant
Utility BASFI coefficient	Dominant	Dominant	Golimumab - AEs: Rate of severe infections/patient year	Dominant	Dominant
Proportion male	Dominant	Dominant	Annual discontinuation rate	Dominant	Dominant
Infliximab - Admin Costs: Number of visits - maintenance	Dominant	Dominant	Golimumab - Admin Costs: Number of visits - trial	Dominant	Dominant

Etanercept			Conventional care		
Base case	Dominant		Base case	£34,301	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**	**Treatment parameter**	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Etanercept - Response rate	£16,539	Dominant	Ixekizumab Q4W - BASFI reduction for responders	£49,209	£25,218
Ixekizumab Q4W - Response rate	£97,363*	£16,577	BASFI coefficient	£41,345	£23,795
Ixekizumab Q4W - BASFI reduction for responders	£63,745	Dominant	Ixekizumab Q4W - BASDAI reduction for responders	£43,805	£28,165
Etanercept - BASFI reduction for responders	Dominant	£61,174	Discount rate QALYs	£24,890	£40,704
Etanercept - BASDAI reduction for responders	Dominant	Dominant	Utility BASDAI coefficient	£38,608	£30,858
Ixekizumab Q4W - BASDAI reduction for responders	Dominant	Dominant	BASFI intercept	£37,895	£30,706
BASFI coefficient	Dominant	Dominant	Utility BASFI coefficient	£37,628	£31,514
Discount rate costs	Dominant	Dominant	Ixekizumab Q4W - Response rate	£37,118	£33,022
Ixekizumab Q4W - Physician visits costs: Number of visits - maintenance (annually)	Dominant	Dominant	Discount rate costs	£34,556	£32,487
Etanercept - Physician visits costs: Number of visits - maintenance (annually)	Dominant	Dominant	Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£33,553	£35,049
BASFI intercept	Dominant	Dominant	Annual discontinuation rate	£33,675	£34,980
Discount rate QALYs	Dominant	Dominant	Cost of Office visit (MD)	£33,902	£34,699
Etanercept - Physician visits costs: Number of visits - trial	Dominant	Dominant	Ixekizumab Q4W - Physician Visits Costs: Number of visits - trial	£34,052	£34,549
Ixekizumab Q4W - Physician visits costs: Number of visits - trial	Dominant	Dominant	Proportion male	£34,195	£34,405
Utility BASDAI coefficient	Dominant	Dominant	Ixekizumab Q4W - Admin Costs: Number of visits - trial	£34,225	£34,377
Etanercept - AEs: Rate of severe infections/patient year	Dominant	Dominant	Ixekizumab Q4W - Chest radiograph (X-ray) - trial	£34,245	£34,357

Pairwise results are presented for ixekizumab Q4W vs comparator. *ICERs fall into the SW quadrant of the cost-effectiveness plane. **Abbreviations:** BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ICER: Incremental cost-effectiveness ratio; IV: Intravenous; Q4W: Once every 4 weeks; QALY: Quality-adjusted life year

Table 125: Deterministic sensitivity analysis results - Biologic-experienced rad-axSpA population

Adalimumab			Certolizumab		
Base case	Dominated		Base case	£954,573*	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**	**Treatment parameter**	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Adalimumab - BASDAI reduction for responders	£1,127,257	Dominated	Certolizumab pegol - BASFI reduction for responders	Dominant	£106,323*
Ixekizumab Q4W - BASDAI reduction for responders	Dominated	£458,844	Ixekizumab Q4W - BASFI reduction for responders	£101,971*	Dominant
Adalimumab - Response rate	Dominated	Dominated	Certolizumab pegol - Response rate	Dominated	£1,270,742*
Ixekizumab Q4W - Response rate	Dominated	Dominated	Ixekizumab Q4W - BASDAI reduction for responders	£74,081*	Dominant
Discount rate costs	Dominated	Dominated	Certolizumab pegol - BASDAI reduction for responders	Dominant	£70,672*
Adalimumab - BASFI reduction for responders	Dominated	Dominated	Ixekizumab Q4W - Response rate	£1,528,538*	£190,272*
Discount rate QALYs	Dominated	Dominated	Utility BASDAI coefficient	£1,564,621*	£686,792*
Utility BASDAI coefficient	Dominated	Dominated	Discount rate QALYs	£473,395*	£1,498,965*
BASFI coefficient	Dominated	Dominated	Discount rate costs	£1,184,086*	£829,436*
Ixekizumab Q4W - BASFI reduction for responders	Dominated	Dominated	Utility BASFI coefficient	£802,228*	£1,178,342*
Adalimumab - Physician Visits Costs: Number of visits - maintenance (annually)	Dominated	Dominated	Ixekizumab Q4W - BASDAI reduction for non-responders	£878,472*	£1,045,079*
BASFI intercept	Dominated	Dominated	Certolizumab pegol - BASDAI reduction for non-responders	£995,033*	£917,387*
Annual discontinuation rate	Dominated	Dominated	Ixekizumab Q4W - BASFI reduction for non-responders	£918,699*	£993,239*
Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	Dominated	Dominated	Certolizumab pegol - Physician Visits Costs: Number of visits - maintenance (annually)	£919,859*	£989,287*
Utility BASFI coefficient	Dominated	Dominated	Annual discontinuation rate	£987,878*	£926,226*
Adalimumab - Physician Visits Costs: Number of visits - trial	Dominated	Dominated	Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£975,554*	£933,592*

Infliximab			Golimumab		
Base case	£287,583*		Base case	£96,133*	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**	**Treatment parameter**	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Infliximab - Response rate	Dominant	£206,655*	Golimumab - BASDAI reduction for responders	Dominated	£46,823*
Ixekizumab Q4W - BASDAI reduction for responders	£168,993*	£963,509*	Ixekizumab Q4W - BASDAI reduction for responders	£45,281*	Dominated
Infliximab - BASDAI reduction for responders	£856,335*	£171,985*	Golimumab - BASFI reduction for responders	£225,743*	£47,804*
Infliximab - BASFI reduction for responders	£435,833*	£207,827*	Ixekizumab Q4W - BASFI reduction for responders	£42,030*	£218,411*
Ixekizumab Q4W - BASFI reduction for responders	£208,001*	£420,090*	Golimumab - Response rate	Dominated	£129,503*
Infliximab - BASDAI reduction for non-responders	£227,623*	£392,111*	Ixekizumab Q4W - Response rate	£148,815*	£23,857*
Discount rate costs	£353,135*	£255,333*	Discount rate QALYs	£71,667*	£113,200*
Utility BASDAI coefficient	£340,870*	£248,703*	Utility BASDAI coefficient	£116,012*	£82,070*
Infliximab - BASFI reduction for non-responders	£247,759*	£338,995*	Discount rate costs	£113,456*	£86,174*
Ixekizumab Q4W - Response rate	£320,622*	£242,469*	BASFI coefficient	£102,404*	£85,831*
Annual discontinuation rate	£260,147*	£322,674*	Golimumab - Physician Visits Costs: Number of visits - maintenance (annually)	£92,685*	£99,581*
Discount rate QALYs	£262,446*	£313,071*	Utility BASFI coefficient	£98,969*	£93,456*
Utility BASFI coefficient	£300,716*	£275,549*	BASFI intercept	£98,950*	£93,317*
Cost of physician visit for IV	£277,295*	£297,870*	Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£98,116*	£94,151*
BASFI coefficient	£294,136*	£277,490*	Golimumab - Physician Visits Costs: Number of visits - trial	£95,080*	£97,187*
Infliximab - Admin Costs: Number of visits - maintenance	£281,674*	£293,491*	Ixekizumab Q4W - Physician Visits Costs: Number of visits - trial	£97,187*	£95,080*

Etanercept			Conventional care		
Base case	£41,794*		Base case	£1,603,221	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**	**Treatment parameter**	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Etanercept - BASDAI reduction for responders	Dominant	£20,312	Utility BASDAI coefficient	£826,786	£26,325,545
Etanercept - Response rate	Dominated	£100,984*	Utility BASFI coefficient	Dominated	£749,484
Ixekizumab Q4W - BASFI reduction for responders	Dominated	£185,178*	Ixekizumab Q4W - BASFI reduction for responders	Dominated	£176,586
Ixekizumab Q4W - BASDAI reduction for responders	£16,730*	Dominant	Discount rate QALYs	£593,428	£3,556,583
Ixekizumab Q4W - Response rate	£112,017*	Dominated	Ixekizumab Q4W - BASDAI reduction for responders	Dominated	£97,453
Etanercept - BASFI reduction for responders	£131,742*	£9,736*	Ixekizumab Q4W - Response rate	£867,066	£2,585,215
Utility BASDAI coefficient	£52,105*	£34,890*	Annual discontinuation rate	£1,958,517	£1,377,160
Discount rate QALYs	£32,174*	£48,456*	BASFI coefficient	£1,813,386	£1,266,877
Discount rate costs	£51,124*	£36,535*	Ixekizumab Q4W - BASDAI reduction for non-responders	£1,806,756	£1,440,945
Etanercept - Physician Visits Costs: Number of visits - maintenance (annually)	£38,331*	£45,257*	Discount rate costs	£1,743,030	£1,503,468
Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£44,439*	£39,149*	BASFI intercept	£1,700,740	£1,505,702
BASFI coefficient	£43,177*	£39,312*	Ixekizumab Q4W - BASFI reduction for non-responders	£1,685,890	£1,527,635
Annual discontinuation rate	£43,426*	£40,158*	Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£1,575,938	£1,630,504
Etanercept - Number of physician visits - trial	£40,388*	£43,199*	Proportion male	£1,580,120	£1,626,668
Ixekizumab Q4W - Physician Visits Costs: Number of visits - trial	£43,199*	£40,389*	Cost of Office visit (MD)	£1,586,508	£1,619,934
Etanercept - Rate of severe infections/patient year	£40,920*	£42,668*	Ixekizumab Q4W - Number of physician visits - trial	£1,588,722	£1,617,720

Pairwise results are presented for ixekizumab Q4W vs comparator. *ICER is in the south-west quadrant (<£30,000 per QALY may be considered cost-effective).
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ICER: Incremental cost-effectiveness ratio; IV: Intravenous; Q4W: Once every 4 weeks; QALY: Quality-adjusted life year

Table 126: Deterministic sensitivity analysis results - Biologic-naïve nr-axSpA population

Adalimumab			Certolizumab		
Base case	£423,916		Base case	£14,435*	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**	**Treatment parameter**	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Adalimumab - BASFI reduction for responders	£140,117	Dominated	Ixekizumab Q4W - Response rate	£21,210*	£123,157
Ixekizumab Q4W - BASFI reduction for responders	Dominated	£88,675	Ixekizumab Q4W - BASFI reduction for responders	£22*	£54,405*
Adalimumab - BASDAI reduction for responders	£107,619	Dominated	Certolizumab pegol - Response rate	£48,702	£20,936*
Ixekizumab Q4W - BASDAI reduction for responders	Dominated	£100,119	Ixekizumab Q4W - BASDAI reduction for responders	£9,266*	£32,956*
Adalimumab - Response rate	£63,123	Dominated	Certolizumab pegol - BASDAI reduction for responders	£29,583*	£9,559*
Ixekizumab Q4W - Response rate	Dominated	£79,929	Certolizumab pegol - BASFI reduction for responders	£28,050*	£7,178*
Discount rate costs	£616,843	£347,017	Discount rate costs	£23,480*	£10,732*
Discount rate QALYs	£253,164	£561,562	BASFI coefficient	£18,435*	£9,107*
Utility BASFI coefficient	£480,419	£379,305	Discount rate QALYs	£9,635*	£17,896*
Utility BASDAI coefficient	£461,977	£391,649	BASFI intercept	£16,837*	£12,034*
BASFI coefficient	£433,645	£409,538	Certolizumab pegol - Physician Visits Costs: Number of visits - maintenance (annually)	£12,248*	£16,622*
Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£412,549	£435,282	Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£16,410*	£12,460*
Adalimumab - Physician Visits Costs: Number of visits - maintenance (annually)	£433,900	£413,932	Utility BASDAI coefficient	£16,131*	£13,062*
BASFI intercept	£428,867	£418,964	Utility BASFI coefficient	£15,949*	£13,184*
Adalimumab - BASDAI reduction for non-responders	£421,290	£426,569	Certolizumab pegol - AEs: Rate of severe infections/patient year	£13,724*	£15,147*
Ixekizumab Q4W - Chest radiograph (X-ray) - maintenance	£421,344	£426,488	Annual discontinuation rate	£15,055*	£13,794*

Etanercept			Golimumab		
Base case	£16,672		Base case	Dominant	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**	**Treatment parameter**	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Etanercept - Response rate	£23,764	£27,065,509	Golimumab - Response rate	£23,497	£36,873*
Ixekizumab Q4W - BASFI reduction for responders	£92,849	£2,148	Ixekizumab Q4W - Response rate	£32,993*	£22,604
Ixekizumab Q4W - Response rate	£54,976	£22,706	Ixekizumab Q4W - BASFI reduction for responders	Dominated	Dominant
Ixekizumab Q4W - BASDAI reduction for responders	£50,546	£9,953	Golimumab - BASFI reduction for responders	Dominant	Dominated
Etanercept - BASDAI reduction for responders	£10,120	£47,204	Golimumab - BASDAI reduction for responders	Dominant	£4,706*
Etanercept - BASFI reduction for responders	£3,627	£43,442	Ixekizumab Q4W - BASDAI reduction for responders	£4,194*	Dominant
BASFI coefficient	£22,701	£8,187	BASFI coefficient	Dominant	Dominant
Discount rate QALYs	£10,743	£21,086	Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	Dominant	£1,797
Discount rate costs	£21,784	£14,209	Discount rate costs	Dominant	Dominant
BASFI intercept	£19,995	£13,349	Golimumab - Physician Visits Costs: Number of visits - maintenance (annually)	£306	Dominant
Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£14,299	£19,045	BASFI intercept	Dominant	Dominant
Utility BASFI coefficient	£18,614	£15,097	Discount rate QALYs	Dominant	Dominant
Etanercept - Physician Visits Costs: Number of visits - maintenance (annually)	£18,498	£14,846	Ixekizumab Q4W - Chest radiograph (X-ray) - maintenance	Dominant	Dominant
Utility BASDAI coefficient	£18,435	£15,217	Golimumab - Chest radiograph (X-ray) - maintenance	Dominant	Dominant
Ixekizumab Q4W - Chest radiograph (X-ray) - maintenance	£16,135	£17,209	Golimumab - Magnetic resonance imaging (MRI) - trial	Dominant	Dominant
Etanercept - Magnetic resonance imaging (MRI) - trial	£17,128	£16,216	Ixekizumab Q4W - Magnetic resonance imaging (MRI) - trial	Dominant	Dominant

Conventional care		
Base case	£29,687	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Ixekizumab Q4W - BASFI reduction for responders	£42,218	£21,948
Discount rate QALYs	£19,140	£37,473
Discount rate costs	£40,138	£25,059
BASFI coefficient	£35,475	£21,389
Ixekizumab Q4W - BASDAI reduction for responders	£36,676	£24,905
Utility BASDAI coefficient	£33,383	£26,727
BASFI intercept	£32,787	£26,586
Utility BASFI coefficient	£32,596	£27,254
Ixekizumab Q4W - Response rate	£31,331	£28,977
Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£29,012	£30,361
Cost of Office visit (MD)	£29,369	£30,004
Annual discontinuation rate	£29,436	£29,951
Ixekizumab Q4W - Chest radiograph (X-ray) - maintenance	£29,534	£29,839
Ixekizumab Q4W - Magnetic resonance imaging (MRI) - trial	£29,557	£29,816
Ixekizumab Q4W - Physician Visits Costs: Number of visits - trial	£29,568	£29,805
Ixekizumab Q4W - AEs: Rate of severe infections/patient year	£29,639	£29,734

*ICERs are located in the south-west quadrant of the cost-effectiveness plane (ICERs > £30,000 per QALY may be considered cost-effective).
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ICER: Incremental cost-effectiveness ratio; IV: Intravenous; Q4W: Once every 4 weeks; QALY: Quality-adjusted life year

B.3.8.3 Scenario analysis

A number of scenario analyses were explored in which model assumptions or parameters were altered. The scenario analyses carried out are presented in Table 127.

Table 127: Summary of scenario analyses

#	Scenario analysis	Base case value	Rationale
1	Discount rate for costs and benefits (combined)		
a	*0.0%*	3.5%	To determine the impact of alternative discount rates for costs and benefits
b	*6.0%*	3.5%	
2	Time horizon: 10 years	Lifetime	To determine the impact of a shorter time horizon
3	Utility sources		
a	*Wailoo et al. (2015) algorithm*[122]	Ixekizumab EQ-5D-3L algorithm	To explore the impact of alternative algorithms to map BASDAI, BASFI and other patient parameters to EQ-5D utility values (see Section B.3.4.5).
b	*McLeod et al. (2007) algorithm*[88]		
c	*Secukinumab NICE submission, 2016 algorithm*[25]		
d	*Ixekizumab EQ-5D-5L algorithm*		
4	Rebound for BASFI – natural history	Initial gain	To explore the impact of an alternative assumption for the rebound of BASFI scores following loss of treatment response, see Section B.3.3.5.
5	Response definition		
a	*BASDAI50 pooled dose*	BASDAI50 sensitivity analysis NMA	Ixekizumab BASDAI50 NMA data pooled by loading dose informing BASDAI50 response in the model
[redacted]	[redacted]		[redacted].3.3
6	Increased mortality in axSpA patients	Equivalent mortality to the general UK population	To explore the impact of increased mortality in axSpA patients, see Section B.3.3.8.
7	Costs of AEs applied in the first year only	Costs of adverse events applied whilst patients are on treatment	To explore alignment of assumption regarding duration of AEs with the York model, see Section B.3.5.3.
8	Baseline BASFI and BASDAI values conditional on BASDAI50 treatment response	Baseline BASFI and BASDAI values not conditional on BASDAI50 treatment response	To explore alignment of BASDAI and BASFI baseline values with assumptions made in the York model by the Assessment Group in TA383 and the manufacturer in TA407.[24, 25] Conditional baseline BASDAI and BASFI values are sourced from the COAST trials.
9	Biologic-experienced nr-axSpA population	Not included	To explore the cost-effectiveness of ixekizumab in the biologic-experienced nr-axSpA population. A modification factor was derived from the relative efficacy of ixekizumab between biologic-naïve and

			biologic-experienced rad-axSpA patients, as measured by BASDAI50 at Week 16. Due to the lack of biologic-experienced nr-axSpA efficacy data for all interventions, this modification factor was applied to the efficacy estimates for biologic-naïve nr-axSpA for all interventions, in order to generate biologic-experienced estimates.
10	Progression rate in biologic-naive nr-axSpA patients	Annual rate of mSASSS progression sourced from patients with a baseline mSASSS of <10.[79]	Annual rate of mSASSS progression sourced from patients with a baseline mSASSS of ≥10 to align with the assumption made in rad-axSpA patients, see Section B.3.3.4.[79]
[redacted]	[redacted]	[redacted]	[redacted] .3.3

Abbreviations: 3L: three levels; 5L: five levels; AE: adverse events; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; NMA: network meta-analysis; nr-axSpA: non-radiographic axial spondyloarthritis; PAS: patient access scheme.

The results of the scenario analyses for each population are presented in the tables below.

Table 128: Biologic-naïve rad-axSpA scenario analyses - results

	Adalimumab			Certolizumab			Etanercept			Golimumab			Infliximab			Conventional care		
Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£34,301
1a	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£25,076
1b	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	1,318	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	750,244	[redacted]	[redacted]	£38,551
2	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	3,206	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£46,175
3a	[redacted]	[redacted]	£2,798,792	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£20,640
3b	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£28,638
3c	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£26,165
3d	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£32,425
4	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	138	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£42,970
5a	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£38,938
5b	[redacted]	[redacted]	£64,133	[redacted]	[redacted]	£39,614*	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	102,941*	[redacted]	[redacted]	212,355*	[redacted]	[redacted]	£16,616
6	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	67,709*	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£35,310
7	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	1,876	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£34,075
8	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£27,255*	[redacted]	[redacted]	125,015*	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	143,739*	[redacted]	[redacted]	£23,356

Pairwise comparisons for ixekizumab Q4W versus each comparator are presented. *Indicates ICERs in the south-west quadrant of the cost-effectiveness plane
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Table 129: Biologic-experienced rad-axSpA scenario analyses – results

	Adalimumab			Certolizumab			Etanercept			Golimumab			Infliximab			Conventional care		
Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£954,573*	[redacted]	[redacted]	41,794*	[redacted]	[redacted]	96,133*	[redacted]	[redacted]	287,583*	[redacted]	[redacted]	£1,603,221
1a	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£587,216*	[redacted]	[redacted]	39,356*	[redacted]	[redacted]	84,581*	[redacted]	[redacted]	322,268*	[redacted]	[redacted]	£645,178
1b	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£1,302,462*	[redacted]	[redacted]	42,359*	[redacted]	[redacted]	101,473*	[redacted]	[redacted]	277,963*	[redacted]	[redacted]	£3,335,291
2	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£6,757,833*	[redacted]	[redacted]	45,507*	[redacted]	[redacted]	114,909*	[redacted]	[redacted]	260,067*	[redacted]	[redacted]	Dominated
3a	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£1,542,203*	[redacted]	[redacted]	27,343*	[redacted]	[redacted]	54,994*	[redacted]	[redacted]	166,489*	[redacted]	[redacted]	£145,510
3b	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	50,938*	[redacted]	[redacted]	101,398*	[redacted]	[redacted]	281,854*	[redacted]	[redacted]	£254,962
3c	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£9,916,515*	[redacted]	[redacted]	44,376*	[redacted]	[redacted]	90,808*	[redacted]	[redacted]	255,674*	[redacted]	[redacted]	£269,517
3d	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	95,112*	[redacted]	[redacted]	125,774*	[redacted]	[redacted]	303,260*	[redacted]	[redacted]	£111,625
4	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£954,573*	[redacted]	[redacted]	49,542*	[redacted]	[redacted]	116,083*	[redacted]	[redacted]	332,435*	[redacted]	[redacted]	Dominated
5a	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£203,396*	[redacted]	[redacted]	17,604*	[redacted]	[redacted]	64,856*	[redacted]	[redacted]	243,344*	[redacted]	[redacted]	Dominated
5b	[redacted]	[redacted]	£61,117	[redacted]	[redacted]	£23,459*	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	62,857*	[redacted]	[redacted]	165,069*	[redacted]	[redacted]	£13,235
6	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£1,025,585*	[redacted]	[redacted]	42,159*	[redacted]	[redacted]	97,558*	[redacted]	[redacted]	283,002*	[redacted]	[redacted]	£1,863,580
7	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£910,876*	[redacted]	[redacted]	39,016*	[redacted]	[redacted]	93,775*	[redacted]	[redacted]	284,838*	[redacted]	[redacted]	£1,594,983
8	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£289,450*	[redacted]	[redacted]	27,289*	[redacted]	[redacted]	63,997*	[redacted]	[redacted]	194,262*	[redacted]	[redacted]	-£80,953

Pairwise comparisons for ixekizumab Q4W versus each comparator are presented. *Indicates ICERs in the south-west quadrant of the cost-effectiveness plane
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Table 130: Biologic-naive nr-axSpA scenario analyses - results

	Adalimumab			Certolizumab			Etanercept			Golimumab			Conventional care		
Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	£423,916	[redacted]	[redacted]	£14,435*	[redacted]	[redacted]	16,672	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£29,687
1a	[redacted]	[redacted]	£368,382	[redacted]	[redacted]	£15,672*	[redacted]	[redacted]	14,037	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£25,878
1b	[redacted]	[redacted]	£459,694	[redacted]	[redacted]	£13,304*	[redacted]	[redacted]	17,971	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£31,632
2	[redacted]	[redacted]	£543,013	[redacted]	[redacted]	£11,321*	[redacted]	[redacted]	20,629	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£35,558
3a	[redacted]	[redacted]	£183,983	[redacted]	[redacted]	£10,976*	[redacted]	[redacted]	10,141	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£17,491
3b	[redacted]	[redacted]	£343,700	[redacted]	[redacted]	£11,547*	[redacted]	[redacted]	13,411	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£23,669
3c	[redacted]	[redacted]	£318,406	[redacted]	[redacted]	£10,555*	[redacted]	[redacted]	12,327	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£21,566
3d	[redacted]	[redacted]	£393,911	[redacted]	[redacted]	£12,944*	[redacted]	[redacted]	15,171	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£26,390
4	[redacted]	[redacted]	£448,995	[redacted]	[redacted]	£14,970*	[redacted]	[redacted]	18,074	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£31,763
5a	[redacted]	[redacted]	-£106,601	[redacted]	[redacted]	£15,003*	[redacted]	[redacted]	12,434	[redacted]	[redacted]	£22,568*	[redacted]	[redacted]	£34,514
5b	[redacted]	[redacted]	£65,863	[redacted]	[redacted]	£55,448*	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£109,122*	[redacted]	[redacted]	£19,162
6	[redacted]	[redacted]	£429,466	[redacted]	[redacted]	£14,396*	[redacted]	[redacted]	16,946	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£30,072
7	[redacted]	[redacted]	£429,235	[redacted]	[redacted]	£11,748*	[redacted]	[redacted]	17,903	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£29,474
8	[redacted]	[redacted]	£263,230	[redacted]	[redacted]	£12,054*	[redacted]	[redacted]	8,690	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£17,572
9	[redacted]	[redacted]	£432,106	[redacted]	[redacted]	£10,598*	[redacted]	[redacted]	17,512	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£31,243
10	[redacted]	[redacted]	£360,644	[redacted]	[redacted]	£12,879*	[redacted]	[redacted]	£11,963	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£23,876

Pairwise comparisons for ixekizumab Q4W versus each comparator are presented. *Indicates ICERs in the south-west quadrant of the cost-effectiveness plane (ICERs >£30,000 may be deemed cost-effective)

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

[redacted]

[redacted]

[redacted] 131 [redacted]

[redacted]

[redacted]

B.3.8.4 Summary of sensitivity analyses results

Biologic-naïve rad-axSpA population

The probabilistic base case results closely aligned with the deterministic base case, showing that ixekizumab is cost-effective in pairwise comparisons versus a number of biologic treatments. The majority of iterations on the pairwise PSA scatterplots were grouped closely around the base case ICER. As determined by the pairwise DSAs, the most influential parameters on the cost-effectiveness results were BASDAI50 response rate, BASFI reduction for responders and BASDAI reduction for responders, which consistently fell in the top five most influential parameters. The pairwise scenario analyses were aligned with the base case in the vast majority of cases, reaching the same conclusion regarding the cost-effectiveness of ixekizumab in each

pairwise comparison. [redacted]

Biologic-experienced rad-axSpA population

The probabilistic base case results closely aligned with the deterministic base case, showing that ICERs for ixekizumab fell into a cost-effective range with the south-west quadrant of the cost-effectiveness plane, compared to four biologic comparators. The majority of iterations on the pairwise PSA scatterplots were grouped closely around the base case ICER. As determined by the pairwise DSAs, the most influential parameters on the cost-effectiveness results were BASDAI50 response rate, BASFI reduction for responders and BASDAI reduction for responders, which consistently fell in the top five most influential parameters. The pairwise scenario analyses were aligned with the base case in the vast majority of cases, reaching the same conclusion regarding the cost-effectiveness of ixekizumab in each pairwise comparison. [redacted]

Biologic-naïve nr-axSpA population

The probabilistic base case results closely aligned with the deterministic base case, showing that ixekizumab is cost-effective in pairwise comparisons versus two biologic treatments recommended by NICE. The majority of iterations on the pairwise PSA scatterplots were grouped closely around the base case ICER. As determined by the pairwise DSAs, the most influential parameters on the cost-effectiveness results were BASDAI50 response rate, BASFI reduction for responders and BASDAI reduction for responders, which consistently fell in the top five most influential parameters. The pairwise scenario analyses were aligned with the base case in the vast majority of cases, reaching the same conclusion regarding the cost-effectiveness of ixekizumab in each pairwise comparison.

Of note, the scenario analysis investigating the cost-effectiveness of ixekizumab in biologic-experienced nr-axSpA patients suggested that ixekizumab was likely to be a cost-effective treatment option in this population, achieving cost-effective pairwise ICERs versus two biologic treatments recommended by NICE.

Altogether these results demonstrate the robustness of the model to uncertainty in all three populations.

B.3.9 *Subgroup analysis*

No further subgroup analyses were carried out beyond the analysis of rad-axSpA biologic-naïve patients, rad-axSpA biologic-experienced patients, nr-axSpA biologic-naïve patients and nr-axSpA biologic-experienced patients (scenario analysis), as described above.

B.3.10 *Validation*

B.3.10.1 Validation of cost-effectiveness analysis

The model methodology was designed to align with NICE's preferred methods. The model was built to align with the NICE reference case, and used an NHS and PSS perspective and discount

rates for costs and benefits of 3.5%.[100] The model used a lifetime time horizon in order to capture all costs and QALY gains associated with the interventions. In line with the NICE reference case, the EQ-5D-5L scores collected in the COAST-V, -W and -X trials were cross-walked to EQ-5D-3L values using the van Hout *et al.* (2012) approach and converted to utility values using the UK value set.[121]

The model structure is closely aligned with the 'York model', which was developed by the Assessment Group for use in the MTA TA383 for the evaluation of the cost-effectiveness of TNF-alpha inhibitors in rad-axSpA and nr-axSpA, and the model developed for use in TA407 for the evaluation of secukinumab in nr-axSpA. The model structure takes into account comments made by the NICE Committees assessing TA383 and TA407.[24, 25] The model structure and assumptions were also validated by an independent health economics expert.

B.3.11 *Interpretation and conclusions of economic evidence*

Summary of cost-effectiveness

In the deterministic base case for the biologic-naïve rad-axSpA population, ixekizumab was either cost-effective or dominant (accumulated fewer costs and greater QALYs) in pairwise comparisons against all biologic treatments recommended by NICE in this population, with the exception of adalimumab. The probabilistic base case was aligned with the deterministic base case, and the results of the DSAs and scenario analyses similarly found this result to be robust. [redacted]

In the deterministic base case for the biologic-experienced rad-axSpA population, pairwise ICERs for ixekizumab versus four biologic comparators fell into the south-west quadrant of the cost-effectiveness plane (i.e. ixekizumab accumulated less QALYs but also less costs compared to comparators). ICERs falling into this quadrant that are greater than the £20,000–£30,000 per QALY threshold may be deemed cost-effective. Accordingly, given the four previously mentioned base case ICERs were all greater than this threshold, ixekizumab may also be considered a cost-effective option in this patient population. The probabilistic base case was aligned with the deterministic base case, and the results of the DSAs and scenario analyses similarly found this result to be robust. It should be further noted that that efficacy inputs for ixekizumab were sourced from a highly refractory population (COAST-W), and as such, the NMA efficacy outputs for ixekizumab may have resulted in an underestimation of QALYs likely to be experienced by patients in clinical practice. Accordingly, ixekizumab may also comprise another treatment option for patients for whom an initial biologic treatment has been either inadequately effective or intolerated. [redacted]

In the deterministic base case for the biologic-naïve nr-axSpA population, ixekizumab was found to be cost-effective versus two biologic treatments recommended by NICE in this population as well as conventional care, indicating ixekizumab would also be a suitable option for patients contraindicated to TNF-alpha inhibitors. The probabilistic base case was aligned with the deterministic base case, and the results of the DSAs and scenario analyses similarly found this result to be robust.

A scenario analysis was additionally performed to explore the cost-effectiveness of ixekizumab in the biologic-experienced nr-axSpA population. As described in B.1, studies have demonstrated that patients with nr-axSpA experience a comparable disease burden to those with rad-axSpA in terms of disease activity and functional impairment. As such, it is important that treatment options are available for nr-axSpA patients for whom initial biological treatment has failed. The results of this scenario analysis demonstrated that ixekizumab may comprise a cost-effective treatment option, with cost-effective or dominant ICERs versus two biologic treatments recommended by NICE.

The results of the cost-effectiveness analysis demonstrate that ixekizumab offers physicians an additional cost-effective option in their armamentarium of biologic therapies to treat patients either biologic-naïve or experienced rad- or nr-axSpA, including patients who are contraindicated to TNF-alpha inhibitors.

Strengths

The cost-effectiveness model developed for this submission has a number of strengths. Firstly, the model was built to align with the York model, a cost-effectiveness model built by the Assessment Group as part of TA383 to assess the cost-effectiveness of TNF-alpha inhibitors in axSpA.[24] Built by an academic group, the structure and inputs of the York model were informed by evidence from the literature. The cost-effectiveness model built to assess secukinumab in rad-axSpA in TA407 also aligned closely to the York model.[25] As such, during the development of the model for ixekizumab, key criticisms and Committee preferences based on these two appraisals were taken into account to build as methodologically rigorous model as possible.

As described in Section B.3.2.2, the model closely aligns with the treatment pathway developed by NICE; the model is capable of modelling interventions at both the biologic-naïve and -experienced lines of therapy, and takes into account the stopping rules recommended by NICE.

Finally, the model was built to align with the NICE reference case, adopting an NHS and PSS perspective, a lifetime time horizon to fully capture all costs and QALY gains associated with the interventions, and discount rates for costs and benefits of 3.5%. Finally, in the development of a utilities algorithm dependent on BASDAI and BASFI scores, COAST trial data were cross-walked from the EQ-5D-5L to the 3L, in line with NICE's position statement on this topic.

Limitations

Key limitations associated with the cost-effectiveness analysis largely pertain to evidence gaps, in which required data were not available in the literature. Among these evidence gaps were:

- Comprehensive comparator data in the base case NMA (including efficacy inputs for secukinumab 150 and 300 mg)
- Conditional BASDAI and BASFI cfb data
- Data for biologic-experienced nr-axSpA patients
- Data for patients contraindicated to TNF-alpha inhibitors

These evidence gaps represent a limitation of the axSpA disease area in general and are not limited to the case of ixekizumab. Solutions to fill these data gaps are described within the submission and explored in scenario analyses.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ixekizumab for the treatment of people with axial spondyloarthritis for whom nonsteroidal anti-inflammatory drugs, or TNF-alpha inhibitors have been inadequately effective or not tolerated [ID1532]

Appendix of Evidence to Support Licensed Loading Doses for Ixekizumab (Biologic-Naïve Populations)

May 2020

File name	Version	Contains confidential information	Date
1532_Ixekizumab in AxSpA_Revised Analyses_Final LDs_REDACTED	N/A	Yes	22/05/2020

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Abbreviations

Abbreviation	Definition
ADA	Adalimumab
AE	Adverse event
ASAS	Assessment of Ankylosing Spondylitis International Society
axSpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
CEM	Cost-effectiveness model
CERTO	Certolizumab
cfb	Change from baseline
CHMP	The Committee for Medicinal Products for Human Use
CrI	Credible interval
CZP	Certolizumab
DSA	Deterministic sensitivity analysis
EQ-5D	EuroQol Five Dimensions
ETA	Etanercept
ETN	Etanercept
GOL	Golimumab
ICER	Incremental cost-effectiveness ratio
IFX	Infliximab
INF	Infliximab
INX	Infliximab
ITC	Indirect treatment comparison
IV	Intravenous
IXE	Ixekizumab
LD	Loading dose
MIMS	Monthly Index of Medical Specialities
MRI	Magnetic resonance imaging
mSASSS	Modified Stroke Ankylosing Spondylitis Spine Score
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analyses
nr-axSpA	Non-radiographic axial spondyloarthritis
NSAID	Non-steroidal anti-inflammatory drug
PAS	Patient access scheme
PBO	Placebo
PSA	Probabilistic sensitivity analysis
Q2W	Every two weeks

Q4W	Every four weeks
QALY	Quality-adjusted life year
QW	Once a week
rad-axSpA	Radiographic axial spondyloarthritis
SC	Subcutaneous
SD	Standard deviation
SEC	Secukinumab
SW	South-west
TA	Technology appraisal
TNF	Tumour necrosis factor
UK	United Kingdom
WTP	Willingness-to-pay

Introduction

Following the original submission to NICE for ixekizumab for the treatment of axial spondyloarthritis (axSpA) in January 2020, the loading doses (LDs) for ixekizumab to be licensed for each population (of biologic-naïve radiographic [rad]-axSpA, biologic-experienced rad-axSpA and biologic-naïve non-radiographic [nr]- axSpA) have been confirmed by EMA in the positive opinion received on May 1st 2020.

Specifically, it has been confirmed that the following LDs will be licensed for each population:

- Biologic-naïve rad-axSpA patients: **160 mg** (*previously 80 mg in the company submission*)
- Biologic-experienced rad-axSpA patients: **160 mg** *(no change from company submission)*
- Biologic-naïve nr-axSpA patients: **160 mg** (*previously 80 mg in the company submission*)

The maintenance dose of 80 mg Q4W remains the same for all three populations, as per the original company submission.

For the biologic-naïve rad-axSpA and biologic-naïve nr-axSpA populations (but not the biologic-experienced rad-axSpA population), the revised LDs do not align with the LDs for which indirect treatment comparison and cost-effectiveness evidence were submitted in the original company submission. (The full set of efficacy and safety data for both potential loading doses [80 mg or 160 mg] was provided for COAST-V and COAST-X in the original submission.)

Accordingly, this appendix has been developed in order to provide supplementary indirect treatment comparison and cost-effectiveness results for the confirmed LDs of the biologic-naïve rad-axSpA and nr-axSpA populations.

Indirect comparison and cost-effectiveness results are presented in the sections that follow.

Overall, the difference in the indirect comparison and cost-effectiveness results between the 160 mg and 80 mg LDs in the biologic-naïve rad-axSpA population are minimal, due to the marginal differences in cost and efficacy results.

In the biologic-naïve nr-axSpA population, however, there were more notable differences in the indirect treatment comparison and cost-effectiveness results, with the 160 mg LD appearing to demonstrate reduced efficacy and cost-effectiveness compared with the 80 mg LD results presented in the original submission.

This result is counterintuitive, given that it would be expected that an increased dose would result in greater efficacy (and therefore similar or increased cost-effectiveness). This anomalous result may be due to heterogeneity in the baseline characteristics of those randomised to receive an 80 mg LD compared to those randomised to receive an 160 mg LD. At baseline in COAST-X, the mean BASDAI score was higher in patients randomised to receive the 160 mg LD versus the 80 mg LD group ([redacted] and [redacted], respectively).[1] Of note, the proportion of patients with very high disease activity, as defined by a BASDAI score ≥6 was [redacted]) in the patients who received an 160 mg LD versus [redacted]) in patients who received the 80 mg LD.[1]

Importantly, the COAST-X trial was powered to show differences between treatment arms in their entirety; 100 patients per treatment arm were required to generate 98% power to detect the superiority of ixekizumab Q2W versus placebo for ASAS40 at Week 16. The LD subgroups were not powered to detect a statistical difference between them. However, the statistical models developed to analyse the data by LD included an interaction term to evaluate whether LD had an effect on BASDAI50 response rate. The interaction term was negative ([redacted], non-significant), thereby indicating that the response did not differ statistically between the 80 mg LD and 160 mg LD groups.

In summary, whilst the efficacy data for the 160 mg LD are numerically inferior to the 80 mg LD data in COAST-X trial, these differences are likely to be due to variations in baseline characteristics, and it cannot be concluded that there is a statistical difference in efficacy between the two subgroups.

Indirect and mixed treatment comparisons

An NMA was performed to assess the comparative effectiveness of ixekizumab versus comparators relevant to the decision problem of this appraisal. The full methodology of the NMA is provided in Appendix D to the company submission and remains unchanged. The results of the original NMA are presented in Section B.2.9 of the company submission, and Appendix D.

The results of the indirect comparisons with the revised LDs for the biologic-naïve rad-axSpA and nr-axSpA populations are presented in the sections below. In line with the company submission, results from the NMA sensitivity analysis, rather than the base case, have been provided.

Results of the network meta-analysis: biologic-naïve rad-axSpA

For the biologic-naïve rad-axSpA population, all analyses were carried out for ixekizumab 80 mg Q4W, with a LD of 160 mg.

ASAS40

The mean posterior rates for ASAS40 are presented in Table 1 below.

Table 1: Mean posterior rates (with 95% CrI); ASAS40 response at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Mean posterior rate	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
INX 5 mg/kg	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]
ETN pooled	[redacted]	[redacted]	[redacted]
SEC 150 mg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: ixekizumab; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.

The pairwise results for this analysis are presented in Table 2. The forest plot for all treatments compared with ixekizumab Q4W is provided in Figure 1.

Table 2: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (with 95% CrI); ASAS40 response at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	OR (95% CrI) vs IXE 80 mg Q4W
Placebo	[redacted]
INX 5 mg/kg	[redacted]
ADA 40 mg	[redacted]
GOL 50 mg	[redacted]
ETN pooled	[redacted]
SEC 150 mg	[redacted]
CZP pooled	[redacted]

Notes: * Significant difference (favours IXE)
Abbreviations: ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: ixekizumab; OR: odds ratio; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.

Figure 1: Forest plot of ORs of ixekizumab 80 mg Q4W relative to placebo and active comparators; ASAS40 response at 12–18 weeks, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Abbreviations: ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; OR: odds ratio; Q4W; every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.

BASDAI50

The mean posterior rates for BASDAI50 response in the biologic-naïve rad-axSpA population are presented in Table 3.

Table 3: Mean posterior rates (with 95% CrI); BASDAI50 response at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Mean posterior rate	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]
ETN pooled	[redacted]	[redacted]	[redacted]
INX 5 mg/kg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: Ixekizumab; NMA: network meta-analysis; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.

The pairwise results for this analysis are presented in Table 4. The forest plot for all treatments compared with ixekizumab Q4W is provided in Figure 2.

Table 4: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (with 95% CrI); BASDAI50 response at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Column vs. Row	OR (95% CrI) vs IXE 80 mg Q4W
Placebo	[redacted]
ADA 40 mg	[redacted]
GOL 50 mg	[redacted]
ETN pooled	[redacted]
INX 5 mg/kg	[redacted]
CZP pooled	[redacted]

Notes: * Significant difference, favours IXE
Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: Ixekizumab; OR: odds ratio; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.

Figure 2: Forest plot of ORs of ixekizumab 80 mg Q4W relative to placebo and active comparators; BASDAI50 at 12–18 weeks, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; OR: odds ratio; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.

BASDAI change from baseline

The mean posterior outcomes for cfb in BASDAI score in the biologic-naïve population are presented in Table 5.

Table 5: Mean posterior outcomes (with 95% CrI); BASDAI change from baseline at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Mean posterior outcome	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
INX 5 mg/kg	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]
ETN pooled	[redacted]	[redacted]	[redacted]
SEC 150 mg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; INX: infliximab; IXE: Ixekizumab; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.

The pairwise results for this analysis are presented in Table 6. The forest plot for all treatments compared with ixekizumab is provided in Figure 3.

Table 6: Relative treatment effect of pairwise comparisons (with 95% CrI); BASDAI change from baseline at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Posterior median treatment difference (95% CrI) IXE 80 mg Q4W vs comparator
Placebo	[redacted]
INX 5 mg/kg	[redacted]
ADA 40 mg	[redacted]
ETN pooled	[redacted]
SEC 150 mg	[redacted]
CZP pooled	[redacted]

Notes: * Significant difference, favours IXE
Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CrI: credible interval; CZP: Certolizumab Pegol; ETN: etanercept; INX: infliximab; IXE: Ixekizumab; OR: odds ratio; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.

Figure 3: Forest plot of posterior median treatment effect of ixekizumab 80 mg Q4W relative to placebo and active comparators; biologic-naïve rad-axSpA population, BASDAI change from baseline at Week 12–18, fixed-effects model, (sensitivity analysis)

Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CZP: Certolizumab Pegol; ETN: etanercept; INX: infliximab; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.

BASFI

The mean posterior outcomes for BASFI cfb in the biologic-naïve rad-axSpA population are presented in Table 7.

Table 7: Mean posterior outcomes (with 95% CrI); BASFI change from baseline at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Mean posterior outcomes	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
INX 5 mg/kg	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]
ETN pooled	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; BASFI: Bath Ankylosing Spondylitis Functional Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: ixekizumab; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis.

The pairwise results for the fixed-effects model for this analysis are presented in Table 8. The forest plot for all treatments compared with ixekizumab is provided in Figure 4.

Table 8: Relative treatment effect of pairwise comparisons (with 95% CrI); BASFI change from baseline at Week 12–18, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Posterior median treatment difference (95% CrI) IXE 80 mg Q4W vs comparator
Placebo	[redacted]
INX 5 mg/kg	[redacted]
GOL 50 mg	[redacted]
ADA 40 mg	[redacted]
CZP pooled	[redacted]
ETN pooled	[redacted]

Notes: * Significant difference: favourable for IXE
Abbreviations: ADA: adalimumab; BASFI: Bath Ankylosing Spondylitis Functional Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: ixekizumab; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.

Figure 4: Forest plot of posterior median relative treatment effect of ixekizumab 80 mg Q4W relative to placebo and active comparators; biologic-naïve rad-axSpA population, BASFI change from baseline at 12–18 weeks, fixed-effects model (sensitivity analysis)

Abbreviations: ADA: adalimumab; BASFI: Bath Ankylosing Spondylitis Functional Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis.

Results of the network meta-analysis: biologic-naïve nr-axSpA population

For the biologic-naïve nr-axSpA population, all analyses were carried out for the ixekizumab 80 mg Q4W arm, with a LD of 160 mg.

ASAS40

The mean posterior rates for ASAS40 response in the biologic-naïve nr-axSpA population are displayed in Table 9.

Table 9: Mean posterior rates (with 95% CrI); ASAS40 response at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Event rate	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]
ETN 50 mg QW	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.

The pairwise results for this analysis are presented in Table 10. The forest plot for all treatments compared with ixekizumab is provided in Figure 5.

Table 10: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (with 95% CrI); ASAS40 response at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	OR (95% CrI) vs IXE 80 mg Q4W
Placebo	[redacted]
ADA 40 mg	[redacted]
CZP pooled	[redacted]
ETN 50 mg QW	[redacted]
GOL 50 mg	[redacted]

[redacted]

Abbreviations: ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; OR: odds ratio; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.

Figure 5: Forest plot of ORs of ixekizumab 80 mg Q4W relative to placebo and active comparators; ASAS40 at 12–18 weeks, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Abbreviations: ADA: adalimumab; ASAS: Assessment of Spondyloarthritis International Society; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; OR: odds ratio; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly.

BASDAI50

The mean posterior rates for BASDAI50 response in the biologic-naïve nr-axSpA population are displayed in Table 11.

Table 11: Posterior rates (with 95% CrI); BASDAI50 response at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Event rate	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]
ETN 50 mg	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: Ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; Q4W: every four weeks.

The pairwise results for this analysis are presented in Table 12. The forest plot for all treatments compared with ixekizumab Q4W is provided in Figure 6.

Table 12: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (with 95% CrI); BASDAI50 response at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	OR (95% CrI) vs IXE 80 mg Q4W
Placebo	[redacted]
ADA 40 mg	[redacted]
ETN 50 mg QW	[redacted]
GOL 50 mg	[redacted]
CZP pooled	[redacted]

Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: Ixekizumab; OR: odds ratio; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.

Figure 6: Forest plot of ORs of ixekizumab 80 mg Q4W relative to placebo and active comparators; BASDAI50 at 12–18 weeks, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; OR: odds ratio; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.

BASDAI change from baseline

The mean posterior outcomes for cfb in BASDAI score in the biologic-naïve population are presented in Table 13.

Table 13: Posterior outcomes (with 95% CrI); BASDAI cfb at Week 12–18; biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Treatment effect	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
ETN 50 mg QW	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; IXE: Ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; Q4W: every four weeks.

The pairwise results for this analysis are presented in Table 14. The forest plot for all treatments compared with ixekizumab is provided in Figure 7.

Table 14: Posterior median relative treatment effect (with 95% CrI); BASDAI cfb at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Posterior median treatment difference (95% CrI) IXE 80 mg Q4W vs comparator
Placebo	[redacted]
ETN 50 mg QW	[redacted]
CZP pooled	[redacted]

Notes: [redacted]
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CrI: credible interval; CZP: Certolizumab Pegol; ETN: etanercept; IXE: Ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.

Figure 7: Forest plot of posterior median treatment effect of ixekizumab 80 mg Q4W relative to placebo and active comparators; BASDAI change from baseline at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CZP: Certolizumab Pegol; ETN: etanercept; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.

BASFI change from baseline

The mean posterior outcomes for BASFI cfb in the biologic-naïve nr-axSpA population are presented in Table 15.

Table 15: Posterior outcomes (with 95% CrI); BASFI cfb at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Treatment effect	95% CrI lower limit	95% CrI upper limit
Placebo	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]
ETN 50 mg QW	[redacted]	[redacted]	[redacted]

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.

The pairwise results for the fixed-effects model for this analysis are presented in Table 16. The forest plot for all treatments compared with ixekizumab is provided in Figure 8.

Table 16: Posterior median relative treatment effect of pairwise comparisons (with 95% CrI); BASFI cfb at Week 12–18, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Intervention	Posterior median treatment difference (95% CrI) IXE 80 mg Q4W vs comparator
Placebo	[redacted]
CZP pooled	[redacted]
ETN 50 mg QW	[redacted]

Notes: [redacted]
Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.

Figure 8: Forest plot of posterior median relative treatment effect of ixekizumab 80 mg Q4W relative to placebo and active comparators; BASFI cfb at 12–18 weeks, biologic-naïve nr-axSpA population, fixed-effects model (sensitivity analysis)

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; nr-axSpA: non-radiographic axial spondyloarthritis; QW: weekly; Q4W: every four weeks.

Cost effectiveness

Economic analysis

Intervention technology and comparators

The model structure and methodology are described in detail in Document B (Section B.3.2). As described above, following the update to the anticipated licensed dose of ixekizumab, results are presented below for 80 mg Q4W, following an 160 mg LD in rad-axSpA biologic-naïve and nr-axSpA biologic-naïve patients.

The comparator interventions included for each patient population align with those presented in the final scope (Document B Section B.1.1) and are presented in Table 17. The comparator doses included in the model are aligned with their licensed indications and approved doses in the original prior NICE submission.[2-12] The stopping rules for the comparators are aligned with the length of trial period and the stopping rules included in their NICE recommendations, as described in detail in Document B, Section B.1.3.[10-12]

Table 17: Interventions included in the analysis

Intervention	Length of trial period in model	Rad-axSpA biologic-naïve	Rad-axSpA biologic-experienced	Nr-axSpA biologic-naïve
		Dosing schedule		
Intervention				
Ixekizumab	16 weeks[1, 13, 14]	80 mg Q4W (LD: 160 mg)[8]	80 mg Q4W (LD: 160 mg)[8]	80 mg Q4W (LD: 160 mg)[8]
Comparators				
Adalimumab	12 weeks[10]	40 mg Q2W[5]	40 mg Q2W[5]	40 mg Q2W[5]
Certolizumab pegol	12 weeks[10]	400 mg at Weeks 0, 2 and 4, followed by maintenance dosing of 200 mg Q2W *or* 400 mg Q4W[2]	400 mg at Weeks 0, 2 and 4, followed by maintenance dosing of 200 mg every 2 weeks or 400 mg every 4 weeks[2]	400 mg at Weeks 0, 2 and 4, followed by maintenance dosing of 200 mg every 2 weeks or 400 mg every 4 weeks[2]
Etanercept	12 weeks[10]	25 mg Q2W *or* 50 mg QW[4]	25 mg Q2W *or* 50 mg QW[4]	25 mg Q2W *or* 50 mg QW[4]
Golimumab	12 weeks[10]	50 mg once monthly[7]	50 mg once monthly[7]	50 mg once monthly[7]
Infliximab	12 weeks[10]	5 mg/kg at Weeks 0, 2, and 6; thereafter every 6–8 weeks (assume every 7 weeks on average)[6] See Section B.3.3.1 for mean weight included in the model	5 mg/kg at Weeks 0, 2, and 6; thereafter every 6–8 weeks (assume every 7 weeks on average)[6] See Section B.3.3.1 for mean weight included in the model	Not a comparator in the analysis of the specified patient population
Conventional care	NA	Patients are assumed to continue conventional care alongside biologic therapy, therefore specific interventions are not explicitly modelled	Patients are assumed to continue conventional care alongside biologic therapy, therefore specific interventions are not explicitly modelled	Patients are assumed to continue conventional care alongside biologic therapy, therefore specific interventions are not explicitly modelled

Abbreviations: LD: loading dose; NA: not applicable; nr-axSpA: non-radiographic axial spondyloarthritis; Q2W: every two weeks; Q4W: every four weeks; QW: every week; rad-axSpA: radiographic axial spondyloarthritis.

Response rate

The BASDAI50 response rate for ixekizumab Q4W (160 mg LD) and comparators for which data were available for the biologic naïve rad- and nr-axSpA are presented in Table 18.

Table 18: BASDAI50 response applied in the model base case

Intervention	Rad-axSpA biologic-naïve (95% CrI)	Nr-axSpA biologic-naïve (95% CrI)
Ixekizumab Q4W (80 mg LD)	Not a comparator in the analysis of the specified patient population	Not a comparator in the analysis of the specified patient population
Ixekizumab Q4W (160 mg LD)	[redacted]	[redacted]
Ixekizumab (overall)	Not a comparator in the analysis of the specified patient population	Not a comparator in the analysis of the specified patient population
Adalimumab	[redacted]	[redacted]
Certolizumab pegol[a]	[redacted]	[redacted]
Etanercept[a]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Infliximab	[redacted]	Not a comparator in the analysis of the specified patient population
Conventional care	[redacted]	[redacted]

[a] Values for pooled doses for etanercept and certolizumab pegol are presented.
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CrI: credible interval; LD: loading dose; NA: not applicable; nr-axSpA: non-radiographic axial spondyloarthritis; Q4W: every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis.

[Please note that these model inputs were obtained from the original running of the NMA. They differ slightly from the new values generated in the NMA section in this appendix as the Bayesian NMA is non-deterministic, so it is not unusual to get slightly differing results from run to run, but this does not change the conclusions in this case as they only differ after the decimal point.]

Short-term change in BASDAI and BASFI

The conditional cfb in BASDAI and BASFI scores for ixekizumab 80 mg Q4W (160 mg LD) and comparator treatments are presented in Table 19 and Table 20, respectively.

Table 19: Conditional Cfb in BASDAI

Intervention	Rad-axSpA biologic-naïve		Nr-axSpA biologic-naïve	
	Responders	Non-responders	Responders	Non-responders
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol[b]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept[b]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]

[a] Average over available data points of TNF-alpha inhibitors.
[b] Values for pooled doses for etanercept and certolizumab pegol are presented.
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; NA: not applicable; nr-axSpA: non-radiographic axial spondyloarthritis; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA data sensitivity 2

Table 20: Conditional Cfb in BASFI

Intervention	Rad-axSpA biologic-naïve		Nr-axSpA biologic-naïve	
	Responders	Non-responders	Responders	Non-responders
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol[b]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept[b]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]

[a] Average over available data points of TNF-alpha inhibitors.
[b] Values for pooled doses for etanercept and certolizumab pegol are presented.
Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; NA: not applicable; nr-axSpA: non-radiographic axial spondyloarthritis; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA data sensitivity 2

Cost and healthcare resource use identification, measurement and valuation

Intervention and comparators' costs and resource use

Drug acquisition

The 160 mg LD is equivalent to two 80 mg doses at the start of the trial period, followed by 80 mg doses Q4W, as summarised in Table 21. The treatment doses and dose costs, and the resulting drug costs per trial period and year whilst on maintenance treatment, are provided in Table 22. The cost of acquisition for adalimumab is presented in Table 23. It was not possible to include secukinumab in the cost-effectiveness analyses due to the lack of efficacy data available in the literature.

Table 21: Trial period duration, number of doses during trial period and annual maintenance period

Treatment	Trial period duration, cycles	Trial period number of doses	Maintenance number of doses per year	Method of administration	Dosing regimen	Indication(s)
Ixekizumab (rad-axSpA biologic-naïve and nr-axSpA biologic-naïve)	4	5	13	SC	80 mg Q4W (LD: 160 mg for biologic-naïve rad-axSpA and biologic-naïve nr-axSpA patients)[8]	Rad-axSpA, nr-axSpA
Adalimumab	3	6	26	SC	40 mg Q2W[5]	Rad-axSpA, nr-axSpA
Certolizumab pegol	3	10	26	SC	400 mg at Weeks 0, 2 and 4, followed by maintenance dosing of 200 mg Q2W *or* 400 mg Q4W[2]	Rad-axSpA, nr-axSpA
Etanercept (50 mg Q2W)[a]	3	12	52	SC	50 mg QW (*or* 25 mg Q2W)[4]	Rad-axSpA, nr-axSpA
Golimumab	3	3	12	SC	50 mg once monthly[7]	Rad-axSpA, nr-axSpA
Infliximab	3	3	8	IV	5 mg/kg at Weeks 0, 2, and 6; thereafter every 6–8 weeks (assume every 7 weeks on average)[6]	Rad-axSpA

[a] Etanercept is also available under a 25 mg Q2W dosing regimen

Abbreviations: IV: intravenous; LD: loading dose; nr-axSpA: non-radiographic axial spondyloarthritis; Q2W: every two weeks; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SC: subcutaneous.

Table 22: Treatment doses and costs

Treatment	Dose[a]	Unit size	Pack size (No. units)	Cost per pack (£)	Cost per unit (£)	Cost per trial period (£)	Cost per year in maintenance period (£)
Ixekizumab (80 mg Q4W; LD: 160 mg; PAS price)	80 mg	80 mg	1	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	200 mg/400 mg	200 mg	2	715.00	357.50	0[b]	9,295
Etanercept (25 mg)	25 mg	25 mg	4	328.00	82.00	1,931	8,366
Etanercept (50 mg)	50 mg	50 mg	4	656.00	164.00	1,931	8,366
Golimumab	50 mg	50 mg	1	762.97	762.97	2,289	9,156
Infliximab	5 mg/kg[c]	100 mg	1	377.00	377.00	4,524	12,064

[a] For dosing frequencies please see Table 17.
[b] Certolizumab pegol is subject to a publicly available PAS in which the first 12 weeks of certolizumab pegol (equivalent to ten 200 mg vials) are provided to the NHS free of charge, therefore in the model there are no drug acquisition costs included for certolizumab pegol for the trial period.[10]
[c] Dose is weight dependent. See Section B.3.3.1 of the company submission for mean weight used in the model for each patient population.
Abbreviations: LD: loading dose; PAS: patient access scheme.
Sources: Monthly Index of Medical Specialities (MIMS) 2019[15]

Table 23: Adalimumab acquisition costs

Treatment	Annual UK reference price (£)	Weekly price	Cost per trial period (£)	Cost per year in maintenance period (£)
Adalimumab	£3,550.00	£68.27	£819.23	£3,550.00

Source: NHS Improvement and NHS England[16]

Base-case results

Base-case incremental cost-effectiveness analysis results

Biologic-naïve rad-axSpA

Table 24: Base case results – rad-axSpA biologic-naïve (with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER ixekizumab Q4W vs comparator (£/QALY)
Conventional care	[redacted]	[redacted]	-	-	-	£39,851
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£4,387	Dominated
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£11,029
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant

Life years gained are equivalent between technologies (interventions do not impact mortality in the model) and are therefore not presented. Results are presented here for ixekizumab 80 mg Q4W (LD: 160 mg). Results for pooled doses for etanercept and certolizumab pegol are presented.
Abbreviations: ICER: incremental cost-effectiveness ratio; LD: loading dose; QALYs: quality-adjusted life years

Biologic-naïve nr-axSpA

Table 25: Base-case results – nr-axSpA biologic-naïve (with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER ixekizumab Q4W vs comparator (£/QALY)
Conventional care	[redacted]	[redacted]	-	-	-	£44,434
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£4,809	Dominated
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£14,372*
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£18,676*
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	£75,056	£15,163*

Life years gained are equivalent between technologies (interventions do not impact mortality in the model) and are therefore not presented. Results are presented here for ixekizumab 80 mg Q4W (LD: 160 mg). Results for pooled doses for etanercept and certolizumab pegol are presented. *ICERs are located in the south-west quadrant of the cost-effectiveness plane (ICERs > £30,000 per QALY may be considered cost-effective).
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Sensitivity analyses

Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analyses (PSAs) with 1,000 iterations were performed for each pairwise comparison in the biologic-naïve rad-axSpA and nr-axSpA patient populations, in order to assess the uncertainty associated with model input parameters. The input parameters varied in the PSAs and the distributions associated with each parameter are presented in Appendix J.2.

The probabilistic base case results, cost-effectiveness acceptability curves and cost-effectiveness plane scatterplots for the two populations are presented below.

Table 26: Probabilistic base case results – rad-axSpA biologic-naïve (with-PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER ixekizumab Q4W vs comparator (£/QALY)
Conventional care	[redacted]	[redacted]	-	-	-	£36,031
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£861	Dominated
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£8,839
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant

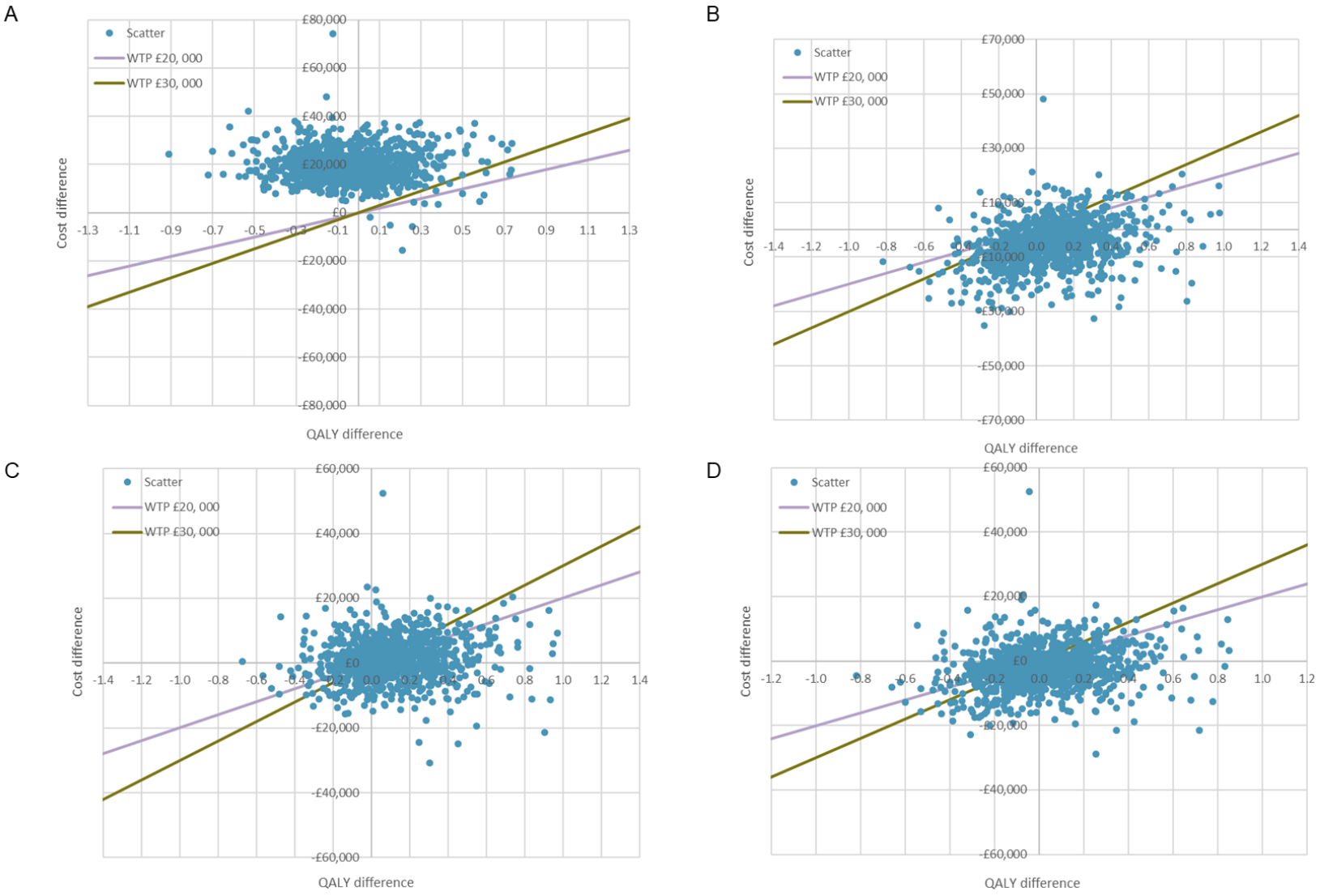
Life years gained are equivalent between technologies (interventions do not impact mortality in the model) and are therefore not presented. Results are presented here for ixekizumab 80 mg Q4W (LD: 160 mg). Results for pooled doses for etanercept and certolizumab pegol are presented.
Abbreviations: ICER: incremental cost-effectiveness ratio; LD: loading dose; QALYs: quality-adjusted life years

Table 27: Probabilistic base case results – nr-axSpA biologic-naive (with-PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER ixekizumab Q4W vs comparator (£/QALY)
Conventional care	[redacted]	[redacted]	-	-	-	£42,705
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£2,285	Dominated
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£10,580*
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£15,753*
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	£73,610	£12,652*

Life years gained are equivalent between technologies (interventions do not impact mortality in the model) and are therefore not presented. Results are presented here for ixekizumab 80 mg Q4W (LD: 160 mg). Results for pooled doses for etanercept and certolizumab pegol are presented. *ICERs are located in the south-west quadrant of the cost-effectiveness plane (ICERs > £30,000 per QALY may be considered cost-effective).
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Figure 9: Biologic-naïve rad-axSpA multiple pairwise PSA results for IXE vs A) ADA B) CZP C) ETA D) GOL E) INF F) CC



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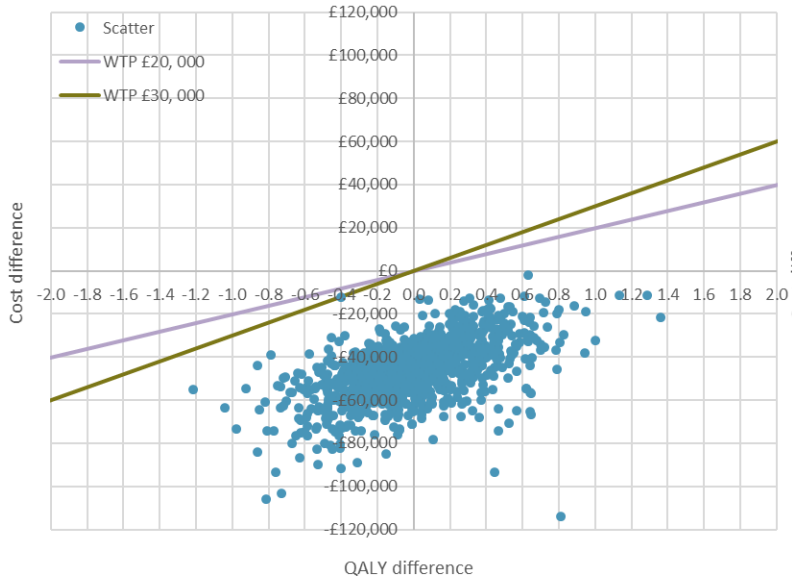

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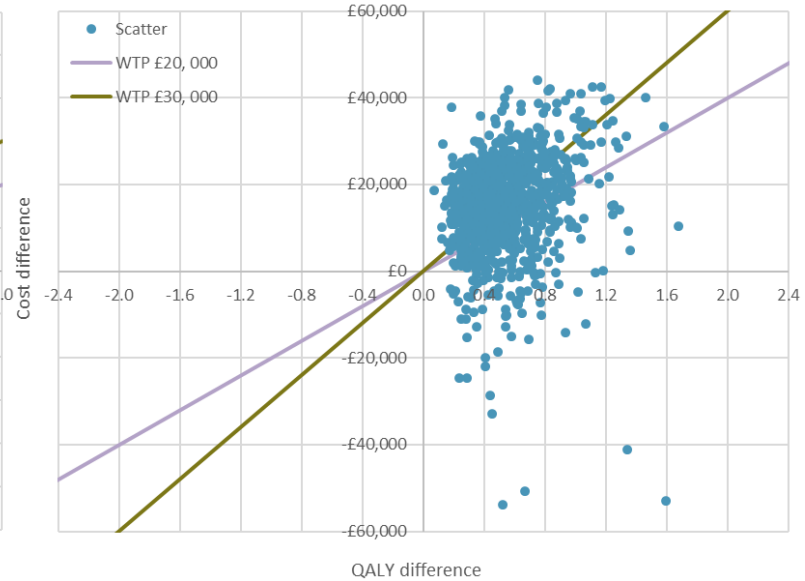
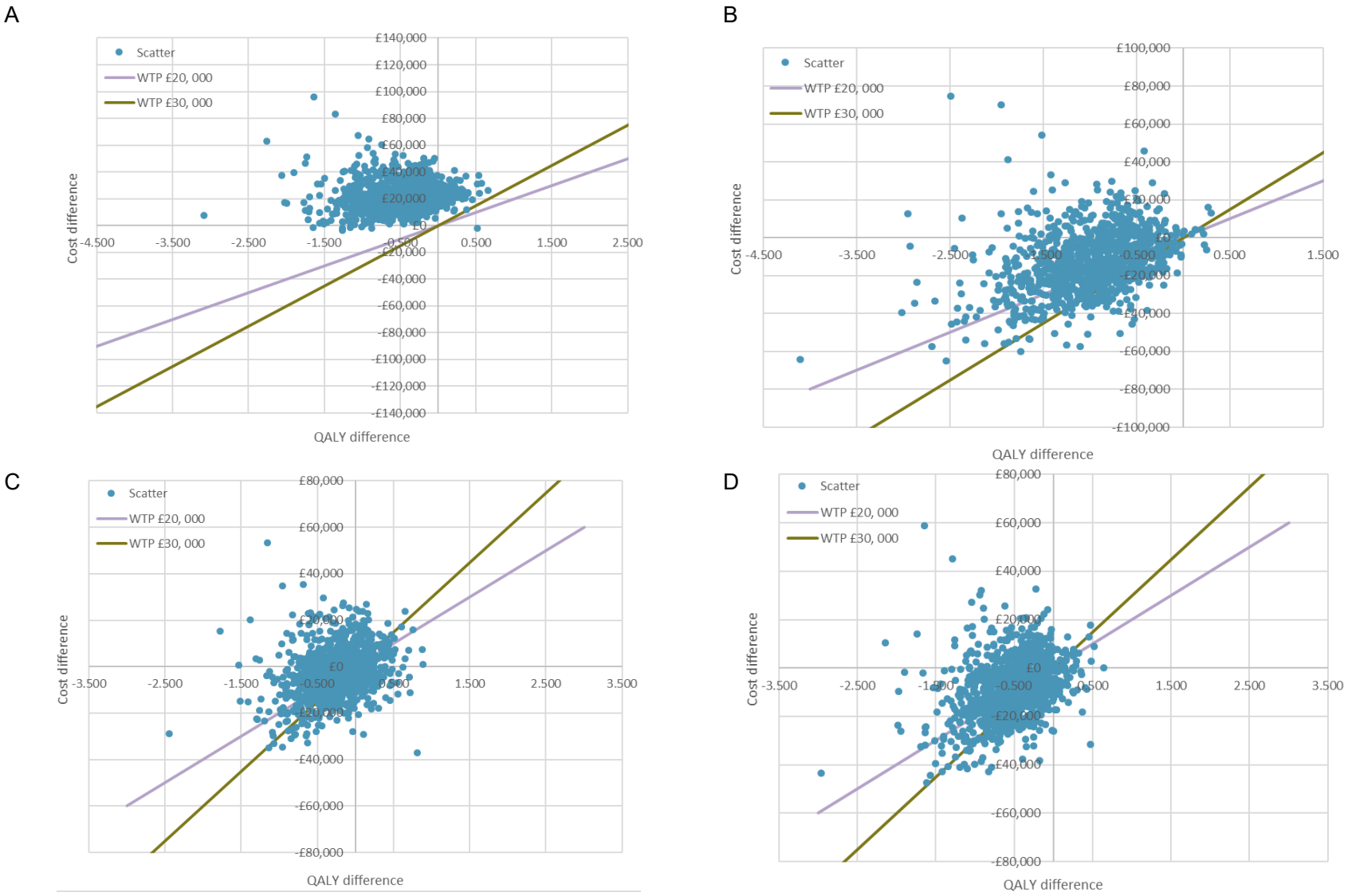


Abbreviations: ADA: adalimumab; CC: conventional care; CZP: certolizumab; ETA: etanercept; GOL: golimumab; INF: infliximab; IXE: ixekizumab WTP: willingness-to-pay

Figure 10: Biologic-naive nr-axSpA multiple pairwise PSA results for IXE vs A) ADA B) CZP C) ETA D) GOL E) CC



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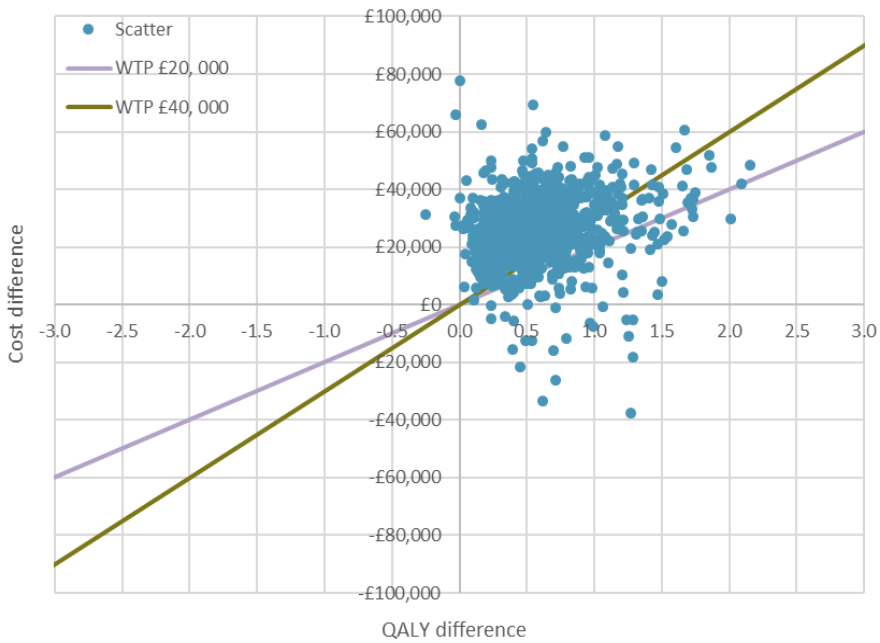
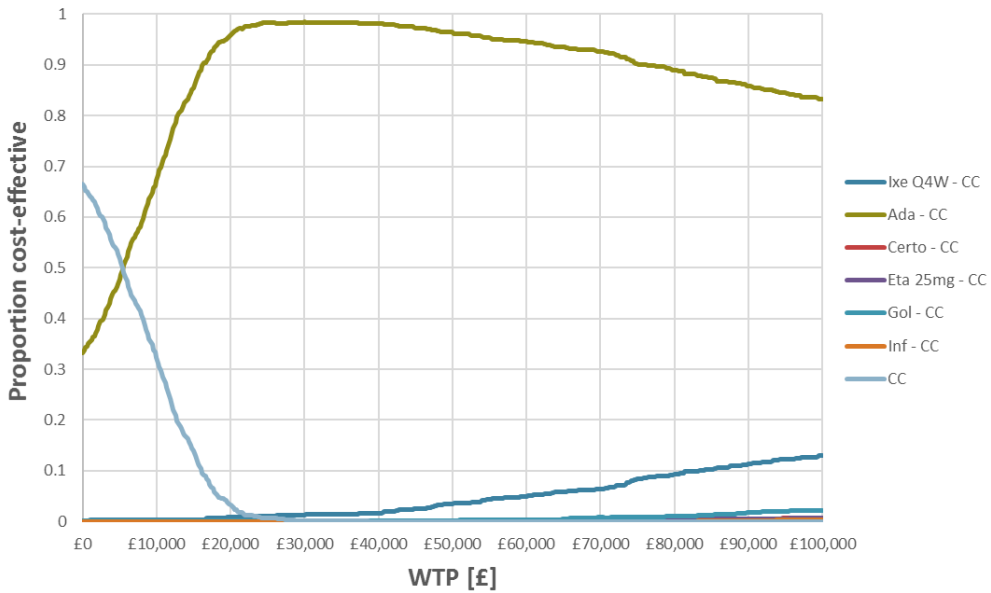


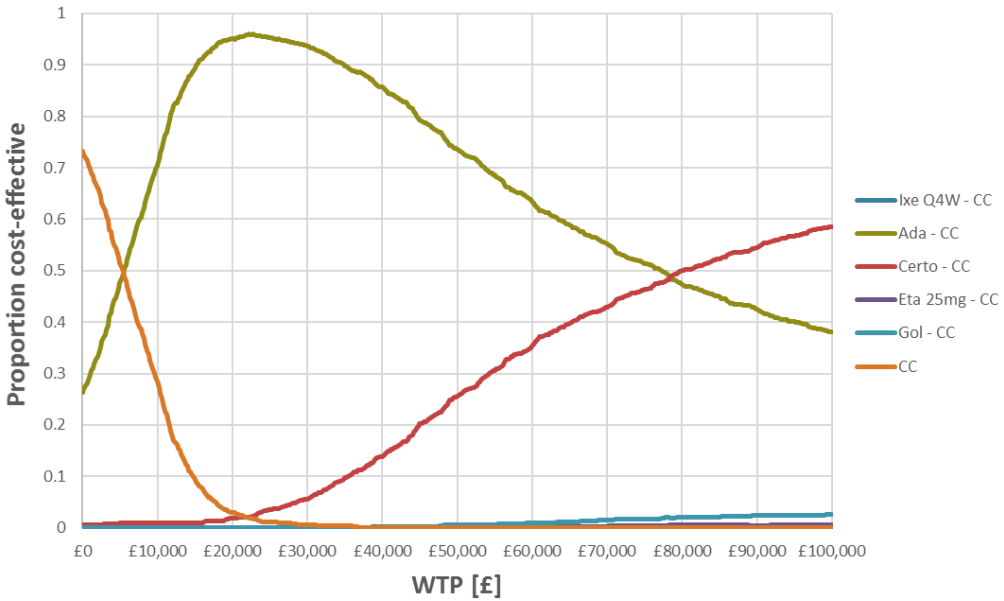
Abbreviations: ADA: adalimumab; CC: conventional care; CZP: certolizumab; ETA: etanercept; GOL: golimumab; IXE: ixekizumab WTP: willingness-to-pay

Figure 11: Cost-effectiveness acceptability curves for A) biologic-naïve rad-axSpA B) biologic-naïve nr-axSpA

A)



B)



Abbreviations: ADA: adalimumab; CC: conventional care; CERTO: certolizumab; ETA: etanercept; GOL: golimumab; IXE: ixekizumab; WTP: willingness-to-pay

Deterministic sensitivity analysis

Table 28: Deterministic sensitivity analysis results - Biologic-naïve rad-axSpA population

Adalimumab			Certolizumab		
Base case	Dominated		Base case	Dominant	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**	**Treatment parameter**	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Adalimumab - BASDAI reduction for responders	£523,033	Dominated	Certolizumab pegol - Response rate	£21,877	£120,361*
Adalimumab - Response rate	£216,514	Dominated	Certolizumab pegol - BASDAI reduction for responders	Dominant	£116,996*
Ixekizumab Q4W - Response rate	Dominated	£156,256	Certolizumab pegol - BASFI reduction for responders	Dominant	£96,142*
Adalimumab - BASFI reduction for responders	£111,926	Dominated	Ixekizumab Q4W - Response rate	£86,524*	£7,827
Ixekizumab Q4W - BASFI reduction for responders	Dominated	£92,704	Ixekizumab Q4W - BASDAI reduction for responders	£55,320*	Dominant
Ixekizumab Q4W - BASDAI reduction for responders	Dominated	£87,252	Ixekizumab Q4W - BASFI reduction for responders	£16,864*	Dominant
Utility BASDAI coefficient	Dominated	Dominated	Discount rate costs	Dominant	Dominant
Discount rate costs	Dominated	Dominated	Discount rate QALYs	Dominant	Dominant
Discount rate QALYs	Dominated	Dominated	Utility BASFI coefficient	Dominant	Dominant
Annual discontinuation rate	Dominated	Dominated	Annual discontinuation rate	Dominant	Dominant
BASFI coefficient	Dominated	Dominated	Certolizumab pegol - Physician Visits Costs: Number of visits - maintenance (annually)	Dominant	Dominant
Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	Dominated	Dominated	BASFI coefficient	Dominant	Dominant
Adalimumab - Physician Visits Costs: Number of visits - maintenance (annually)	Dominated	Dominated	Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	Dominant	Dominant
Ixekizumab Q4W - BASDAI reduction for non-responders	Dominated	Dominated	Utility BASDAI coefficient	Dominant	Dominant

Adalimumab			Certolizumab		
Ixekizumab Q4W - BASFI reduction for non-responders	Dominated	Dominated	BASFI intercept	Dominant	Dominant
Adalimumab - BASDAI reduction for non-responders	Dominated	Dominated	Certolizumab pegol - AEs: Rate of severe infections/patient year	Dominant	Dominant

Infliximab			Golimumab		
Base case	Dominant		Base case	Dominant	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**	**Treatment parameter**	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Infliximab - BASFI reduction for non-responders	£2,154,584*	Dominant	Golimumab - Response rate	£22,249	£64,816*
Discount rate QALYs	Dominant	£1,688,643*	Ixekizumab Q4W - Response rate	£50,260*	£20,985
Infliximab - BASDAI reduction for non-responders	£1,685,465*	Dominant	Golimumab - BASDAI reduction for responders	Dominant	£25,221*
Annual discontinuation rate	£1,173,025*	Dominant	Ixekizumab Q4W - BASDAI reduction for responders	£16,414*	Dominant
Infliximab - BASDAI reduction for responders	Dominant	£499,648*	Golimumab - BASFI reduction for responders	Dominant	Dominated
Infliximab - BASFI reduction for responders	Dominant	£394,531*	Ixekizumab Q4W - BASFI reduction for responders	Dominated	Dominant
Ixekizumab Q4W - BASFI reduction for responders	£348,784*	Dominant	Discount rate costs	Dominant	Dominant
Ixekizumab Q4W - BASDAI reduction for responders	£297,353*	Dominant	Discount rate QALYs	Dominant	Dominant
Ixekizumab Q4W - Response rate	£258,966*	Dominant	Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	Dominant	Dominant
Infliximab - Response rate	Dominant	£147,072*	Golimumab - Physician Visits Costs: Number of visits - maintenance (annually)	Dominant	Dominant
Discount rate costs	Dominant	Dominant	BASFI coefficient	Dominant	Dominant
Proportion male	Dominant	Dominant	Utility BASDAI coefficient	Dominant	Dominant
Utility BASFI coefficient	Dominant	Dominant	Utility BASFI coefficient	Dominant	Dominant
Ixekizumab Q4W - BASDAI reduction for non-responders	Dominant	Dominant	Annual discontinuation rate	Dominant	Dominant
Ixekizumab Q4W - BASFI reduction for non-responders	Dominant	Dominant	Golimumab - Physician Visits Costs: Number of visits - trial	Dominant	Dominant
Cost of physician visit for IV	Dominant	Dominant	Ixekizumab Q4W - Physician Visits Costs: Number of visits - trial	Dominant	Dominant

Etanercept			Conventional care		
Base case	£11,029		Base case	£39,851	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**	**Treatment parameter**	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Etanercept 25 mg - BASFI reduction for responders	Dominant	£841,593	Ixekizumab Q4W - BASFI reduction for responders	£61,199	£23,289
Ixekizumab Q4W - BASFI reduction for responders	Dominated	Dominant	Ixekizumab Q4W - BASDAI reduction for responders	£56,274	£26,984
Etanercept 25 mg - Response rate	£26,965	£324,657*	BASFI coefficient	£47,676	£28,166
Etanercept 25 mg - BASDAI reduction for responders	£5,149	Dominated	Discount rate QALYs	£28,627	£47,499
Ixekizumab Q4W - Response rate	£63,637*	£25,717	Utility BASDAI coefficient	£44,409	£36,141
Ixekizumab Q4W - BASDAI reduction for responders	Dominated	£3,442	Utility BASFI coefficient	£44,148	£36,315
BASFI coefficient	£16,286	£3,382	BASFI intercept	£43,835	£35,866
Discount rate costs	£7,109	£11,861	Ixekizumab Q4W - Response rate	£43,497	£38,241
Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£7,131	£14,927	Discount rate costs	£40,249	£37,755
Etanercept 25 mg - Physician Visits Costs: Number of visits - maintenance (annually)	£14,608	£7,450	Annual discontinuation rate	£39,027	£40,741
Discount rate QALYs	£8,193	£12,990	Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£39,007	£40,694
BASFI intercept	£13,810	£8,248	Cost of Office visit (MD)	£39,409	£40,293
Utility BASDAI coefficient	£12,577	£9,821	Ixekizumab Q4W - Physician Visits Costs: Number of visits - trial	£39,589	£40,113
Annual discontinuation rate	£9,664	£12,418	Proportion male	£39,724	£39,975
Etanercept 25 mg - Physician Visits Costs: Number of visits - trial	£12,240	£9,818	Ixekizumab Q4W - BASFI reduction for non-responders	£39,908	£39,763

Ixekizumab Q4W - Physician Visits Costs: Number of visits - trial	£9,818	£12,240	Ixekizumab Q4W - Admin Costs: Number of visits - trial	£39,770	£39,931

Pairwise results are presented for ixekizumab Q4W vs comparator. *ICERs fall into the SW quadrant of the cost-effectiveness plane.

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ICER: Incremental cost-effectiveness ratio; IV: Intravenous; Q4W: Once every 4 weeks; QALY: Quality-adjusted life year

Table 29: Deterministic sensitivity analysis results - Biologic-naïve nr-axSpA population

Adalimumab			Certolizumab		
Base case	Dominated		Base case	£15,163*	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**	**Treatment parameter**	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Ixekizumab Q4W - Response rate	Dominated	Dominated	Ixekizumab Q4W - BASFI reduction for responders	£7,735*	£30,902*
Adalimumab - Response rate	Dominated	Dominated	Certolizumab pegol - Response rate	£420*	£18,923*
Ixekizumab Q4W - BASDAI reduction for responders	Dominated	Dominated	Ixekizumab Q4W - Response rate	£20,461*	£1,217*
Adalimumab - BASDAI reduction for responders	Dominated	Dominated	Ixekizumab Q4W - BASDAI reduction for responders	£12,428*	£24,192*
Ixekizumab Q4W - BASFI reduction for responders	Dominated	Dominated	Discount rate costs	£22,385*	£12,025*
Discount rate costs	Dominated	Dominated	BASFI coefficient	£20,197*	£8,200*
Discount rate QALYs	Dominated	Dominated	Discount rate QALYs	£9,964*	£18,956*
BASFI coefficient	Dominated	Dominated	Certolizumab pegol - BASFI reduction for responders	£19,689*	£11,747*
Utility BASDAI coefficient	Dominated	Dominated	Certolizumab pegol - BASDAI reduction for responders	£19,069*	£12,593*
Utility BASFI coefficient	Dominated	Dominated	BASFI intercept	£18,015*	£12,312*
Adalimumab - BASFI reduction for responders	Dominated	Dominated	Utility BASDAI coefficient	£16,905*	£13,747*
BASFI intercept	Dominated	Dominated	Utility BASFI coefficient	£16,792*	£13,823*
Adalimumab - Physician Visits Costs: Number of visits - maintenance (annually)	Dominated	Dominated	Certolizumab pegol - Physician Visits Costs: Number of visits - maintenance (annually)	£14,288*	£16,038*
Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	Dominated	Dominated	Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£15,644*	£14,682*
Annual discontinuation rate	Dominated	Dominated	Annual discontinuation rate	£15,478*	£14,839*

Adalimumab			Certolizumab		
Adalimumab - Chest radiograph (X-ray) - maintenance	Dominated	Dominated	Certolizumab pegol - AEs: Rate of severe infections/patient year	£14,879*	£15,448*

Etanercept			Golimumab		
Base case	£14,372*		Base case	£18,676*	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**	**Treatment parameter**	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Ixekizumab Q4W - BASFI reduction for responders	Dominated	Dominant	Ixekizumab Q4W - BASFI reduction for responders	£5,588*	£69,644*
Etanercept 50 mg - Response rate	£199,880	£24,042*	Ixekizumab Q4W - Response rate	£25,611*	Dominated
Ixekizumab Q4W - Response rate	£26,909*	£94,139	Ixekizumab Q4W - BASDAI reduction for responders	£13,262*	£60,673*
Etanercept 50 mg - BASDAI reduction for responders	£74,674*	£7,955*	Golimumab - Response rate	Dominated	£23,124*
Ixekizumab Q4W - BASDAI reduction for responders	£7,878*	Dominant	Golimumab - BASFI reduction for responders	£31,225*	£11,401*
Etanercept 50 mg - BASFI reduction for responders	£57,412*	£1,869*	Golimumab - BASDAI reduction for responders	£30,216*	£13,522*
BASFI coefficient	£19,713*	£6,859*	Discount rate costs	£26,793*	£15,186*
Discount rate costs	£21,495*	£11,240*	BASFI coefficient	£23,879*	£11,441*
Discount rate QALYs	£9,458*	£17,935*	Discount rate QALYs	£12,288*	£23,326*
BASFI intercept	£17,309*	£11,436*	BASFI intercept	£21,592*	£15,760*
Etanercept 50 mg - Physician Visits Costs: Number of visits - maintenance (annually)	£12,095*	£16,649*	Utility BASDAI coefficient	£20,851*	£16,912*
Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£16,174*	£12,571*	Utility BASFI coefficient	£20,652*	£17,045*
Utility BASDAI coefficient	£16,133*	£12,958*	Golimumab - Physician Visits Costs: Number of visits - maintenance (annually)	£17,379*	£19,973*
Utility BASFI coefficient	£15,809*	£13,175*	Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£19,568*	£17,784*
Etanercept 50 mg - Magnetic resonance imaging (MRI) - trial	£13,804*	£14,940*	Golimumab - Chest radiograph (X-ray) - maintenance	£18,382*	£18,970*

Ixekizumab Q4W - Magnetic resonance imaging (MRI) - trial	£14,940*	£13,804*	Golimumab - Magnetic resonance imaging (MRI) - trial	£18,395*	£18,957*

Conventional care		
Base case	£44,434	
Treatment parameter	**Lower bound ICER (£/QALY)**	**Upper bound ICER (£/QALY)**
Ixekizumab Q4W - BASFI reduction for responders	£79,096	£21,739
Ixekizumab Q4W - BASDAI reduction for responders	£72,296	£26,873
Discount rate QALYs	£28,387	£56,330
Discount rate costs	£59,556	£37,846
BASFI coefficient	£50,291	£35,880
Ixekizumab Q4W - Response rate	£51,709	£41,862
Utility BASDAI coefficient	£50,510	£39,664
Utility BASFI coefficient	£48,283	£41,154
BASFI intercept	£47,483	£41,386
Ixekizumab Q4W - Physician Visits Costs: Number of visits - maintenance (annually)	£43,592	£45,277
Annual discontinuation rate	£43,808	£45,092
Cost of Office visit (MD)	£44,000	£44,869
Ixekizumab Q4W - Magnetic resonance imaging (MRI) - trial	£44,169	£44,700
Ixekizumab Q4W - Physician Visits Costs: Number of visits - trial	£44,191	£44,678
Ixekizumab Q4W - Chest radiograph (X-ray) - maintenance	£44,244	£44,625
Ixekizumab Q4W - BASFI reduction for non-responders	£30,188	£30,284

ICERs are located in the south-west quadrant of the cost-effectiveness plane (ICERs > £30,000 per QALY may be considered cost-effective).
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ICER: Incremental cost-effectiveness ratio; IV: Intravenous; Q4W: Once every 4 weeks; QALY: Quality-adjusted life year.

Scenario analysis

A number of scenario analyses were explored in which model assumptions or parameters were altered. The scenario analyses carried out are presented in Table 30.

Table 30: Summary of scenario analyses

#	Scenario analysis	Base case value	Rationale
1	Discount rate for costs and benefits (combined)		
a	*0.0%*	3.5%	To determine the impact of alternative discount rates for costs and benefits
b	*6.0%*	3.5%	
2	Time horizon: 10 years	Lifetime	To determine the impact of a shorter time horizon
3	Utility sources		
a	*Wailoo et al. (2015) algorithm*[17]	Ixekizumab EQ-5D-3L algorithm	To explore the impact of alternative algorithms to map BASDAI, BASFI and other patient parameters to EQ-5D utility values
b	*McLeod et al. (2007) algorithm*[18]		
c	*Secukinumab NICE submission, 2016 algorithm*[11]		
d	*Ixekizumab EQ-5D-5L algorithm*		
4	Rebound for BASFI – natural history	Initial gain	To explore the impact of an alternative assumption for the rebound of BASFI scores following loss of treatment response
5	Response definition		
a	*BASDAI50 pooled dose*	BASDAI50 sensitivity analysis NMA	Ixekizumab BASDAI50 NMA data pooled by loading dose informing BASDAI50 response in the model
6	Increased mortality in axSpA patients	Equivalent mortality to the general UK population	To explore the impact of increased mortality in axSpA patients.
7	Costs of AEs applied in the first year only	Costs of adverse events applied whilst patients are on treatment	To explore alignment of assumption regarding duration of AEs with the York model
8	Baseline BASFI and BASDAI values conditional on BASDAI50 treatment response	Baseline BASFI and BASDAI values not conditional on BASDAI50 treatment response	To explore alignment of BASDAI and BASFI baseline values with assumptions made in the York model by the Assessment Group in TA383 and the manufacturer in TA407.[10, 11] Conditional baseline BASDAI and BASFI values are sourced from the COAST trials.
9	Biologic-experienced nr-axSpA population	Not included	To explore the cost-effectiveness of ixekizumab in the biologic-experienced nr-axSpA population. A modification factor was derived from the relative efficacy of ixekizumab between biologic-naïve and biologic-experienced rad-axSpA

			patients, as measured by BASDAI50 at Week 16. Due to the lack of biologic-experienced nr-axSpA efficacy data for all interventions, this modification factor was applied to the efficacy estimates for biologic-naïve nr-axSpA for all interventions, in order to generate biologic-experienced estimates.
10	Progression rate in biologic-naive nr-axSpA patients	Annual rate of mSASSS progression sourced from patients with a baseline mSASSS of <10.[19]	Annual rate of mSASSS progression sourced from patients with a baseline mSASSS of ≥10 to align with the assumption made in rad-axSpA patients.

Abbreviations: 3L: three levels; 5L: five levels; AE: adverse events; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; NMA: network meta-analysis; nr-axSpA: non-radiographic axial spondyloarthritis; PAS: patient access scheme.

The results of the scenario analyses for each population are presented in the tables below.

Table 31: Biologic-naïve rad-axSpA scenario analyses - results

	Adalimumab			Certolizumab			Etanercept			Golimumab			Infliximab			Conventional care		
Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£11,029	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£39,851
1a	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£5,281	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£28,913
1b	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£13,970	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,473,159*	[redacted]	[redacted]	£45,002
2	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£18,333	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£54,327
3a	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£7,218	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£23,122
3b	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£9,206	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£33,279
3c	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£8,355	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£30,564
3d	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£10,356	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£37,869
4	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£13,608	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£50,321
5a	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£13,376	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£40,142
6	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£11,591	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£41,055
7	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£13,551	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£39,596
8	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£295,889	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£127,306*	[redacted]	[redacted]	£26,624

Pairwise comparisons for ixekizumab Q4W versus each comparator are presented. *Indicates ICERs in the south-west quadrant of the cost-effectiveness plane. Scenarios 9 and 10 are not relevant for this population.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Table 32: Biologic-naive nr-axSpA scenario analyses - results

	Adalimumab			Certolizumab			Etanercept			Golimumab			Conventional care		
Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£15,163*	[redacted]	[redacted]	£14,372*	[redacted]	[redacted]	£18,676*	[redacted]	[redacted]	£44,434
1a	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£14,710*	[redacted]	[redacted]	£14,146*	[redacted]	[redacted]	£17,628*	[redacted]	[redacted]	£38,048
1b	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£15,033*	[redacted]	[redacted]	£14,026*	[redacted]	[redacted]	£18,967*	[redacted]	[redacted]	£47,978
2	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£14,900*	[redacted]	[redacted]	£13,499*	[redacted]	[redacted]	£19,618*	[redacted]	[redacted]	£55,145
3a	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£10,119*	[redacted]	[redacted]	£9,028*	[redacted]	[redacted]	£12,180*	[redacted]	[redacted]	£24,999
3b	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£12,145*	[redacted]	[redacted]	£11,470*	[redacted]	[redacted]	£14,947*	[redacted]	[redacted]	£35,230
3c	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£11,114*	[redacted]	[redacted]	£10,460*	[redacted]	[redacted]	£13,669*	[redacted]	[redacted]	£31,926
3d	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£13,640*	[redacted]	[redacted]	£12,808*	[redacted]	[redacted]	£16,767*	[redacted]	[redacted]	£38,933
4	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£16,159*	[redacted]	[redacted]	£15,575*	[redacted]	[redacted]	£19,759*	[redacted]	[redacted]	£47,486
5a	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£14,085*	[redacted]	[redacted]	£26,128*	[redacted]	[redacted]	£19,893*	[redacted]	[redacted]	£35,254
6	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£15,262*	[redacted]	[redacted]	£14,464*	[redacted]	[redacted]	£18,814*	[redacted]	[redacted]	£45,051
7	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£13,991*	[redacted]	[redacted]	£12,471*	[redacted]	[redacted]	£17,789*	[redacted]	[redacted]	£44,169
8	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£9,712*	[redacted]	[redacted]	£7,814*	[redacted]	[redacted]	£12,597*	[redacted]	[redacted]	£26,086
9	[redacted]	[redacted]	£446,954	[redacted]	[redacted]	£7,974*	[redacted]	[redacted]	£20,645	[redacted]	[redacted]	£7,374	[redacted]	[redacted]	£32,136
10	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£12,126*	[redacted]	[redacted]	£11,226*	[redacted]	[redacted]	£15,579*	[redacted]	[redacted]	£36,382

Pairwise comparisons for ixekizumab Q4W versus each comparator are presented. *Indicates ICERs in the south-west quadrant of the cost-effectiveness plane (ICERs >£30,000 may be deemed cost-effective)

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Clarification questions

February 2020

File name	Version	Contains confidential information	Date
ID1532 ixekizumab ERG clarification questions to the company_Response_v2_REDACTED.docx	FINAL	Yes	24/02/2020

Notes for company

Highlighting in the template

Square brackets and [redacted] highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [redacted] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

COAST trials

A1. Please provide the protocols and statistical analysis plans (SAPs) for each of the COAST trials.

The protocols and statistical analysis plans for COAST-V, -W and -X have been provided alongside this document.

A2. On page 37 of the CS, it is stated that for the COAST-X trial, "If patients did not require a rescue dose, they remained in their original treatment group until Week 52. Patients who did receive rescue therapy were regarded as non-responders and were not included in analysis". However, in Appendix L of the CS (Table 100), it is stated that "patients who (...) used rescue ixekizumab 80 mg Q2W were analysed as non-responders for the Week 52 analysis." These two statements are contradictory; please clarify whether patients who received rescue therapy were included in analyses at week 52 as non-responders or excluded from analyses at week 52.

Apologies for the contradicting statements in the submission. The second statement above (quoted from Appendix L) is accurate. In COAST-X, analysis of categorical efficacy and health outcomes at Week 52 was assessed using the non-responder imputation (NRI) method. Non-responders were defined as patients who did not meet the clinical response criteria or had missing clinical response data at the timepoint under consideration (in this case, Week 52). Any patient who received a dose of rescue ixekizumab 80 mg every two weeks (Q2W) was considered a non-responder and therefore, as per the NRI method, these patients were analysed as non-responders.[1]

A3. Please clarify the strategy for handling missing data in the analyses presented in: Table 17, Table 22, Figure 9, Table 31, Figure 12, Table 36, Figure 13, Table 46, Figure 15, Table 48 and Figure 16 of the CS.

Missing data in the tables listed above, which all present data for the Week 16 timepoint, (company submission [CS] Section B.2.6) were accounted for using a mixed-effects model of repeated measures (mixed models repeated measure [MMRM] analysis). Tables 46 and 48 additionally present data for the Week 52 timepoint (Section B.2.6.3), where missing data were imputed using the modified baseline observation carried forward (mBOCF) method. For all figures listed in the question, MMRM analysis was used to impute missing data, for data presented up to Week 16 and Week 52.

Table 1: Summary of handling of missing data in the company evidence submission, section B.2.6

Table or Figure	Title	Method for handling missing data
Table 17	BASDAI least squares mean change from baseline in the ITT population, MMRM, COAST-V, Week 16	Week 16: MMRM
Table 22	BASFI least squares mean change from baseline in the ITT population, MMRM, COAST-V, Week 16	Week 16: MMRM
Table 31	BASDAI least squares mean change from baseline in the ITT population, MMRM, COAST-W, Week 16	Week 16: MMRM
Table 36	BASFI least squares mean change from baseline in the ITT population, MMRM, COAST-W, Week 16	Week 16: MMRM
Table 46	BASDAI least squares mean change from baseline in the ITT population, COAST-X, Week 16 (MMRM) and Week 52 (mBOCF, ANCOVA)	Week 16: MMRM Week 52: mBOCF
Table 48	BASFI least squares mean change from baseline in the ITT population, COAST-X, Week 16 (MMRM) and Week 52 (mBOCF ANCOVA)	Week 16: MMRM Week 52: mBOCF
Figure 9	BASFI score least squares mean change from baseline in the ITT population, MMRM analysis, COAST-V, up to Week 16	Up to Week 16: MMRM
Figure 12	BASDAI score least squares mean change from baseline in the ITT population, MMRM analysis, COAST-W, up to Week 16	Up to Week 16: MMRM
Figure 13	BASFI score least squares mean change from baseline in the ITT population, MMRM analysis, COAST-W, up to Week 16	Up to Week 16: MMRM
Figure 15	BASDAI least squares mean change from baseline in the ITT population, COAST-X, Week 16 and Week 52 (MMRM)	Up to Week 52: MMRM
Figure 16	BASFI score least squares mean change from baseline in the ITT population, MMRM analysis, COAST-X, up to Week 52	Up to Week 52: MMRM

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ITT: intent-to-treat; mBOCF: missing baseline observation carried forward; MMRM: mixed models repeated measure analysis.

A4. The results presented in Table 22 of the CS are not from a logistic regression analysis. Please provide a corrected set of footnotes for Table 22.

Thank you for highlighting this error. The footnote to Table 22 should read "[redacted]."

A5. It is stated on p117 of the clinical study report for the COAST-X trial that:

[redacted]. Please provide justification for presenting results of the secondary analysis (mBOCF ANCOVA) rather than results from the primary analysis in Table 46 and Table 48 of the CS.

In COAST-X, the primary analysis was performed using the MMRM analysis from Week 0 to Week 52, due to a regulatory requirement from the US Food and Drug Administration (FDA) for the primary endpoint analysis to take place at Week 52, as described in the COAST-X clinical study report (CSR).[2] In the COAST-V and COAST-W trials, the [redacted], as described in Appendix L.2, Table 100 of the CS. mBOCF results were therefore presented in Tables 46 and 48 of the CS (Section B.2.6.3) for COAST-X, in order to present data with a consistent data imputation method across the three clinical trials.

The results of the MMRM analysis were numerically similar to those that were presented in Tables 46 and 48 of the CS. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) least squares mean difference versus placebo (Table 46 of the CS) was −1.13 using MMRM and [redacted] using mBOCF to impute missing data in the ixekizumab every four weeks (Q4W) arm, and was –1.29 using MMRM and [redacted] using mBOCF in the ixekizumab Q2W arm. Bath Ankylosing Spondylitis Functional Index (BASFI) least squares mean difference versus placebo (Table 48 of the CS) was −1.06 using MMRM and [redacted] using mBOCF in the ixekizumab Q4W arm, and was –1.18 using MMRM and [redacted] using mBOCF in the ixekizumab Q2W arm. Furthermore, BASDAI and BASFI least squares mean change from baseline were statistically significantly greater compared to placebo in both the ixekizumab Q2W and Q4W arms with both analysis types. Therefore, the presentation of the mBOCF data did not have an impact on the overall conclusions made for these outcomes in the COAST-X trial. For completeness, results of the MMRM analysis at Week 52 for BASDAI and BASFI are presented in Table 2 and Table 3, respectively.

Table 2: BASDAI least squares mean change from baseline in the ITT population, COAST-X, Week 52 (MMRM)

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p-value
PBO (N=105)	–1.76 (0.31)	-	-

IXE Q4W (N=96)	–2.89 (0.27)	–1.13 (–1.92; –0.33)	0.0058
IXE Q2W (N=102)	–3.04 (0.27)	–1.29 (–2.08; –0.49)	0.0017

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cfb: change from baseline; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; MMRM: mixed models repeated measure analysis; N: number of patients in the analysis population; PBO: placebo; SE: standard error.
Source: Deodhar *et al.* (2019)[3]

Table 3: BASFI least squares mean change from baseline in the ITT population, COAST-X, Week 52 (MMRM)

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p-value
PBO (N=105)	–1.57 (0.33)	-	-
IXE Q4W (N=96)	–2.63 (0.29)	–1.06 (–1.93; –0.18)	0.0180
IXE Q2W (N=102)	–2.75 (0.29)	–1.18 (–2.05; –0.31)	0.0082

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CI: confidence interval; ITT: intent-to-treat; IXE Q2W: ixekizumab every 2 weeks; IXE Q4W: ixekizumab every 4 weeks; LSM: least squares mean; MMRM: mixed models repeated measure analysis; N: number of patients in the analysis population; PBO: placebo; SE: standard error.
Source: Deodhar *et al.* (2019)[3]

A6. Details relating to the COAST-W trial are provided on p65 of the CS and on this page it is stated that: "a significantly higher proportion of patients achieved an ASAS40 response from as early as [redacted] in the ixekizumab Q4W arm (p=[redacted]) and the ixekizumab Q2W arm (p≤[redacted]) compared to placebo [redacted]." Please clarify why the p-value from the Fisher's exact test was used for week 1 data instead of the p-value from logistic regression analysis.

In the COAST-W trial, Fisher's exact test was the predetermined test to analyse categorical outcomes in the event that the logistic regression model did not converge due to sparse data, as specified in the SAP and described in Appendix L.2 of the CS, Table 100.[4] For Assessment of Ankylosing Spondylitis International Society 40 (ASAS40) response at Week 1 in COAST-W, there were [redacted] in the ixekizumab Q4W and Q2W arms, respectively, and [redacted] in the placebo arm, as presented in Section B.2.6.2, Figure 11. Therefore, the logistic regression model did not converge and the Fisher's exact test was used in this case.[5]

Network meta-analyses

A7. The information presented in Section D.1.3 of the Appendices to the CS is contradictory in several places, as described in the table that follows this question. Please provide clarification on the total number of publications (full publications and

conference abstracts) and independent studies that were included in the original, updated and final SLRs for both the rad-axSpA and nr-axSpA populations.

	Number of full publications/conference abstracts/ independent studies	
	rad-axSpA	**nr-axSpA SLR**
Original SLR	p28: 66 full publications (31 independent studies) + 14 conference abstracts (2 new independent studies) This is consistent with Figure 1 Contradictory to Table 12 which includes 75 full publications + 25 conference abstracts	p28: 10 full publications (6 independent studies) + 13 conference abstracts (0 new independent studies) This is consistent with Figure 3 Contradictory to Table 14 which includes 14 full publications + 13 conference abstracts
Updated SLR	p28: 12 full publications + 13 conference abstracts (4 new studies not included in the original SLR) This is consistent with Figure 2 Contradictory to Table 13 which includes 5 full publications + 2 conference abstracts	p28: 5 full publications + 13 conference abstracts (2 new studies not included in the original SLR) Contradictory to Figure 4 which says 5 full publications + 12 conference abstracts Contradictory to Table 15 which includes 2 full publications + 12 conference abstracts
Final SLR (original + updated)	p28: 66 full publications + 14 conference abstracts (33 independent studies). It seems unlikely that these numbers are correct, as 66 full publications and 14 abstracts were included in the original SLR (according to the text on p28 and Figure 1), before adding the additional records from the updated SLR	p28: 10 full publications + 13 conference abstracts (6 independent studies). It seems unlikely that these numbers are correct, as 10 full publications and 13 abstracts were included in the original SLR (according to the text on p28 and Figure 3), before adding the additional records from the updated SLR

Thank you for highlighting these inconsistencies. A corrected table detailing the number of full publications, conference abstracts and independent studies included in the original, updated and final systematic literature reviews (SLRs) for both the radiographic axial spondyloarthritis (rad-axSpA) and non-radiographic axial spondyloarthritis (nr-axSpA) populations is provided in Table **4**. The references included in the original and updated rad-axSpA SLR are provided in **Error! Reference source not found.** and **Error! Reference source not found.**, respectively. The references included in the original and updated nr-axSpA SLR are provided in **Error! Reference source not found.** and **Error! Reference source not found.**, respectively. Below each of these tables a reference list containing the full citation details of all included studies is provided.

Table 4: Number of full publications/conference abstracts/independent studies included in the rad-axSpA and nr-axSpA SLRs

	Number of full publications/conference abstracts/ independent studies	
	rad-axSpA	**nr-axSpA SLR**
Original SLR	66 full publications + 14 conference abstracts (33 independent studies)	10 full publications + 13 conference abstracts (6 independent studies)

Updated SLR	12 full publications + 10 conference abstracts (4 new studies not included in the original SLR)	5 full publications + 12 conference abstracts (2 new studies not included in the original SLR)
Final SLR (original + updated)	78 full publications + 24 conference abstracts (37 independent studies)	15 full publications + 25 conference abstracts (8 independent studies)

Table 5. Original rad-axSpA SLR – included studies

Study ID	Primary publication	Clinical trial number	Associated publications/ conference proceedings
ASSERT	van der Heijde 2005[19]	NCT00207701	Braun 2008[20] Visvanathan 2008[21]
ATLAS	van der Heijde 2006[22]	NCT00085644	Davis 2007[23]; van der Heijde 2009a[24]; van der Heijde 2009b[25]; Sieper 2012[26]; van der Heijde 2015[27] Revicki 2008[28] Maksymowych 2010[29]
Baeten 2013	Baeten 2013[30]	NCT00809159	-
Bao 2014	Bao 2014[31]	NCT01248793	-
Barkham 2010	Barkham 2010[32]	-	-
Brandt 2003	Brandt 2003[33]	-	-
Braun 2002	Braun 2002[34]	-	Braun 2003[35]; Braun 2005a[36]; Braun 2005b[37]; Baraliakos 2007[38]; Braun 2007[39]; Baraliakos 2011[40]
BUILDER-1	Sieper 2014[41]	NCT01209702	
Calin 2004	Calin 2004[42]	NCT00421980	Djikmans 2009[43]; Martin-Mola 2010[44]
CANDLE	Inman 2010[45]	-	
Cantini 2013	Cantini 2013[46]	-	
Davis 2003	Davis 2003[47]	-	Davis 2005[48]; Boonen 2008[49]; Davis 2008[50] Davis 2005[51]
Giardina 2010	Giardina 2010[52]	-	-
GO-ALIVE (Deodhar ACR/ARHP 2016)	Conference abstract Deodhar ACR/ARHP 2016[53]	-	-
GO-RAISE	Inman 2008[54]	NCT00265083	Braun 2012[55]; van der Heijde 2013[56]; van der Heijde 2014[57]; Braun 2014[58]; Deodhar 2015[59]
Gorman 2002	Gorman 2002[60]	-	Davis 2004[61]
HEEL	Dougados 2010[62]	NCT00420303	-
Hu 2012	Hu 2012[63]	-	-
Huang 2014	Huang 2014[64]	NCT01114880	-
Lambert 2007	Lambert 2007[65]	NCT00195819	Maksymowych 2008[66]

LOADET	Navarro-Sarabia 2011[67]	NCT00873730	-
Marzo-Ortega 2005	Marzo-Ortega 2005[68]	-	-
MEASURE 1	Baeten 2015*[69]	NCT01358175	Deodhar 2016[70] Conferences: Baeten ACR/ARHP 2015a[71]**; Wei EULAR 2015[72]; Baeten ACR/ARHP 2015b[73]; Emery EULAR 2016[74] Baralakios ACR/ARHP 2015 [75]
MEASURE 2	Baeten 2015*[69]	NCT01649375	Sieper 2016[76] Conferences Baeten ACR/ARHP 2015a[71]**; Braun EULAR 2015[77]; Deodhar EULAR 2015[78]; Marzo-Ortega EULAR 2016[79];
Pathan 2013	Pathan 2013[80]	NCT00944658	-
PLANETAS	Park 2013[81]	NCT01220518	Park 2016[82]
RAPID-axSpA	Landewe 2014[83]	NCT01087762	Sieper 2015a[84]; Sieper 2015b[85] Conferences van der Heijde EULAR 2016[86]; van der Heijde ACR/ARHP 2016[87] Braun EULAR 2015[88]
SPINE	Dougados 2011[89]	NCT00420238	Dougados 2012[90] Dougados 2012[91]
Tam 2014	Tam 2014[92]	NCT01212653	-
van den Bosch 2002	Van den Bosch 2002[93]	-	-
van der Heijde 2006	Van der Heijde 2006[94]	-	Braun 2007[95]
van der Heijde ACR/ARHP 2015	Conference abstract van der Heijde ACR/ARHP 2015[96]	NCT01786668	Conferences Maksymowych ACR/ARHP 2016[97]
Yates 2015	Yates 2015[98]	-	-

Notes: *Refers to the same Baeten 2015 journal publication[69] **Refers to the same Baeten 2015 conference abstract[71]

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83. Landewe R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Annals of the Rheumatic Diseases 2014;**73**(1):39-47.
84. Sieper J, Landewe R, Rudwaleit M, et al. Effect of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis: Results from a phase III randomized trial. Arthritis and Rheumatology 2015;**67**(3):668-77.
85. Sieper J, Kivitz A, Van Tubergen A, et al. Impact of Certolizumab Pegol on Patient-Reported Outcomes in Patients with Axial Spondyloarthritis. Arthritis Care and Research 2015;**67**(10):1475-80.
86. Certolizumab pegol for the treatment of axial spondyloarthritis: 4-year outcomes from the rapid-axSpA trial. EULAR; 2016.
87. Four Year Imaging Outcomes in Patients with Axial Spondyloarthritis Treated with Certolizumab Pegol, Including Patients with Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis. acr/arhp; 2016.
88. Braun et al. OP0171 Achievement of Remission of Inflammation in the Spine and Sacroiliac Joints Measured by Magnetic Resonance Imaging (MRI) in Patients with Axial Spondyloarthritis, and Associations Between MRI and Clinical Remission, Over 96 Weeks of Treatment with Certolizumab Pegol. EULAR 2015; 2015.
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96. Van der Heijde et al. Tofacitinib in patients with ankylosing spondylitis: A phase 2, 16-week, randomized, placebo-controlled, dose-ranging study. . ACR/ARHP; 2015.

97. Maksymowych et al. Treatment with Tofacitinib Is Associated with Clinically Meaningful Reductions in Axial MRI Inflammation in Patients with Ankylosing Spondylitis. ACR/ARHP; 2016.
98. Yates M, Hamilton LE, Elender F, et al. Is etanercept 25 mg once weekly as effective as 50 mg at maintaining response in patients with ankylosing spondylitis? a randomized control trial. Journal of Rheumatology 2015;**42**(7):1177-85.

Table 6. Updated rad-axSpA SLR – included studies

Study ID	Primary publication	Clinical trial number	Associated publications/ conference proceedings
GO-ALIVE (Deodhar ACR/ARHP 2016)	Deodhar 2018[54]		Conference abstracts Deodhar ACR/ARHP 2017a[55]; Deodhar ACR/ARHP 2017b[56]; Reveille ACR/ARHP 2017a[59]; Reveille ACR/ARHP 2017b[60]; Reveille ACR/ARHP 2017c[61];
MEASURE 1	Baraliakos 2018a[78]; Braun 2017a[79]	NCT01358175	Conference abstracts Baraliakos ACR/ARHP 2018b[86]; Baraliakos ACR/ARHP 2017b[87]
MEASURE 2	Sieper 2017[88] Marzo-Ortega 2017[89]	NCT01649375	Conference abstracts Kivitz ACR/ARHP 2017a[94];
PLANETAS	Park 2017[99]	NCT01220518	
van der Heijde ACR/ARHP 2015	van der Heijde 2017a[115]	NCT01786668	
COAST V	van der Heijde 2018a[118]	NCT02696785	van der Heijde 2018c[119]
COAST W	Deodhar 2019[120]	NCT02696798	
MEASURE 3	Pavelka 2017a[121]	NCT02008916	Conferences Pavelka ACR/ARHP 2017b[122] Kivitz ACR/ARHP 2018b[95]
MEASURE 4	Kivitz 2018a[123]	NCT02159053	

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55. Deodhar A, Reveille JD, Chan EK, et al. Improvements in sleep problems and pain in patients with active ankylosing spondylitis treated with intravenous golimumab: 28-week results of the phase III go-alive trial. *Annals of the Rheumatic Diseases* 2017;76 (Supplement 2):341. doi: http://dx.doi.org/10.1136/annrheumdis-2017-eular.5325
56. Deodhar A, Reveille JD, Harrison DD, et al. Safety and efficacy of intravenous golimumab in adult patients with active ankylosing spondylitis: Results through week 28. *Annals of the Rheumatic Diseases* 2017;76 (Supplement 2):335. doi: http://dx.doi.org/10.1136/annrheumdis-2017-eular.1020
59. Reveille JD, Deodhar A, Chan EK, et al. Effects of intravenous golimumab on patient-reported outcomes in active ankylosing spondylitis: 28-week results of the phase iii go-alive trial. *Annals of the Rheumatic Diseases* 2017;76 (Supplement 2):1295-96. doi: http://dx.doi.org/10.1136/annrheumdis-2017-eular.6145
60. Reveille JD, Deodhar A, Li N, et al. The effect of golimumab, an anti-TNFa monoclonal antibody, on general health status, daily activity and work productivity in subjects with active ankylosing spondylitis: 28-week results of the phase III go alive trial. *Value in Health* 2017;20 (5):A151.

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78. Baraliakos X, Kivitz AJ, Deodhar AA, et al. Long-term effects of interleukin-17A inhibition with secukinumab in active ankylosing spondylitis: 3-year efficacy and safety results from an extension of the Phase 3 MEASURE 1 trial. *Clinical and Experimental Rheumatology* 2018;36(1):50-55.
79. Braun J, Baraliakos X, Deodhar A, et al. Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study. *Annals of the Rheumatic Diseases* 2017;76(6):1070-77. doi: http://dx.doi.org/10.1136/annrheumdis-2016-209730
86. Baraliakos X, Braun J, Deodhar A, et al. Secukinumab demonstrates low radiographic progression and sustained efficacy through 4 years in patients with active ankylosing spondylitis. *Annals of the Rheumatic Diseases* 2018;77 (Supplement 2):997-98. doi: http://dx.doi.org/10.1136/annrheumdis-2018-eular.1396
87. Baraliakos X, Kivitz AJ, Deodhar A, et al. Secukinumab provides sustained improvements in the signs and symptoms of active ankylosing spondylitis: 3-year results from a phase 3 extension trial (measure 1). *Annals of the Rheumatic Diseases* 2017;76 (Supplement 2):357-58. doi: http://dx.doi.org/10.1136/annrheumdis-2017-eular.1195
88. Sieper J, Deodhar A, Marzo-Ortega H, et al. Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: Results from the MEASURE 2 Study. *Annals of the Rheumatic Diseases* 2017;76(3):571-75. doi: http://dx.doi.org/10.1136/annrheumdis-2016-210023
89. Marzo-Ortega H, Sieper J, Kivitz A, et al. Secukinumab and Sustained Improvement in Signs and Symptoms of Patients With Active Ankylosing Spondylitis Through Two Years: Results From a Phase III Study. *Arthritis Care and Research* 2017;69(7):1020-29. doi: http://dx.doi.org/10.1002/acr.23233
94. Kivitz et al. High retention rate and sustained responses with secukinumab 150mg in patients with active ankylosing spondylitis: 3-year results from a phase 3 study. *Arthritis and rheumatology*;Conference:american college of rheumatology/association of rheumatology health professionals annual scientific meeting.
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99. Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. *Annals of the Rheumatic Diseases* 2017;76(2):346-54. doi: http://dx.doi.org/10.1136/annrheumdis-2015-208783
115. Van Der Heijde D, Deodhar A, Wei JC, et al. Tofacitinib in patients with ankylosing spondylitis: A phase II, 16-week, randomised, placebo-controlled, dose-ranging study. *Annals of the Rheumatic Diseases* 2017;76(8):1340-47. doi: http://dx.doi.org/10.1136/annrheumdis-2016-210322
118. van der Heijde D, Cheng-Chung Wei J, Dougados M, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. *Lancet* 2018;392(10163):2441-51. doi: https://dx.doi.org/10.1016/S0140-6736(18)31946-9
119. Van Der Heijde D, Wei JCC, Dougados M, et al. Ixekizumab significantly improves signs, symptoms, and spinal inflammation of active ankylosing spondylitis/radiographic axial spondyloarthritis: 16-week results of a phase 3 randomized, active and placebo-controlled trial. *Arthritis and Rheumatology* 2018;70 (Supplement 9):2074-76. doi: http://dx.doi.org/10.1002/art.40700
120. Deodhar A, Poddubnyy D, Pacheco-Tena C, et al. Efficacy and Safety of Ixekizumab in the Treatment of Radiographic Axial Spondyloarthritis: Sixteen-Week Results From a Phase III Randomized, Double-Blind, Placebo-Controlled Trial in Patients With Prior Inadequate Response to or Intolerance of Tumor Necrosis Factor Inhibitors. *Arthritis Rheumatol* 2019;71(4):599-611.

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122. Pavelka K, Kivitz AJ, Dokoupilova E, et al. Secukinumab provides sustained improvements in the signs and symptoms of active ankylosing spondylitis: 2-year results from a phase 3 study. *Arthritis and Rheumatology Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP* 2017;69(Supplement 10)
123. Kivitz AJ, Wagner U, Dokoupilova E, et al. Efficacy and Safety of Secukinumab 150 mg with and Without Loading Regimen in Ankylosing Spondylitis: 104-week Results from MEASURE 4 Study. *Rheumatology and Therapy* 2018;5(2):447-62. doi: http://dx.doi.org/10.1007/s40744-018-0123-5

Table 7. Original nr-axSpA SLR – included studies

Study ID	Primary publication	Clinical trial number	Associated publications/ conference proceedings
ABILITY-1	Sieper 2013[21]	NCT00939003	Conferences Baraliakos EULAR 2015 [22]
Barkham 2009	Barkham 2009[23]	-	-
EMBARK	Dougados 2014[24]	NCT01258738	Dougados 2015[25] Maksymowych 2016[26] Conferences Brown ACR/ARHP 2015[27] Dougados ACR/ AHRP 2015[43] Van Den Bosch ACR/ARHP 2015[29]
GO-AHEAD	Sieper 2015[30]	NCT01453725	Conferences Sieper EULAR 2015[31] Maksymowych EULAR 2015[32] Dougados ACR/AHRP 2015[28] van der Heijde ACR/AHRP 2015[33] Maksymowych ACR/AHRP 2015 [34] Sieper ACR /ARHP 2016[35]
Haibel 2008	Haibel 2008[36]	NCT00235105	-
RAPID-axSpA	Landewe 2014[37]	NCT01087762	Sieper 2015a[38] Sieper 2015b[39] Conferences van der Heijde EULAR 2016[40] van der Heijde ACR/ARHP 2016[41] Braun EULAR 2015[42]

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22. Baraliakos EULAR 2015. Clinically active non-radiographic axial spondyloarthritis patients who initially have a negative MRI and normal CRP may develop a positive MRI or elevated CRP at a later time point. 2015.
23. Barkham N, Keen HI, Coates LC, et al. Clinical and imaging efficacy of infliximab in HLA-B27-positive patients with magnetic resonance imaging-determined early sacroiliitis. Arthritis and Rheumatism 2009;**60**(4):946-54.

24. Dougados M, Van Der Heijde D, Sieper J, et al. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: A multicenter, randomized, double-blind, placebo-controlled trial. Arthritis and Rheumatology 2014;**66**(8):2091-102.
25. Dougados M, Tsai WC, Saaibi DL, et al. Evaluation of health outcomes with etanercept treatment in patients with early nonradiographic axial spondyloarthritis. Journal of Rheumatology 2015;**42**(10):1835-41.
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27. Brown ACR ARHP 2015. Baseline mri and CRP as predictors of response to etanercept in the management of patients with non-radiographic axial spondyloarthritis (nr-axspa). (EMBARK). 2015.
28. Dougados ACR ARHP 2015. Baseline Demographic and Disease Characteristics Associated with Response to Golimumab in Patients with Active Nonradiographic Axial Spondyloarthritis: GO-AHEAD.
29. van den Bosch ACR ARHP 2015. Long-term effects of etanercept on patient-reported outcomes in early non-radiographic axial spondyloarthritis: 104-week results of a phase III study. (EMBARK). 2015.
30. Sieper J, van der Heijde D, Dougados M, et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. Arthritis & rheumatology (Hoboken, NJ) 2015;**67**(10):2702-12.
31. Sieper EULAR 2015. Randomized, Double-Blind, Placebo-Controlled, 16-Week Study of Subcutaneous Golimumab in Patients with Active Nonradiographic Axial Spondyloarthritis: GO AHEAD, 2015.
32. Maksymowych EULAR 2015. Quality of life in Patients with Active Nonradiographic Axial Spondyloarthritis After 16 Weeks of Golimumab Treatment: GO AHEAD. 2015.
33. Van der Heijde ACR AHRP 2015. Long-Term Tolerability and Efficacy of Golimumab in Active Nonradiographic Axial Spondyloarthritis: Results from the Open-Label Extension of a Randomized, Double-Blind Study. 2015.
34. Maksymowych ACR AHRP 2016. Patient-Reported Quality of Life in Patients with Baseline Objective Signs of Inflammation and Active Nonradiographic Axial Spondyloarthritis Treated with Golimumab: Results of the Open-Label Extension of a Randomized, Double-Blind Study GO AHEAD. 2016.
35. Sieper ACR ARHP 2016. Efficacy of golimumab for nonradiographic axial spondyloarthritis (nraxspa): Subgroup analysis by baseline MRI and C-reactive protein status. 2016.
36. Haibel H, Rudwaleit M, Listing J, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: Results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. Arthritis and Rheumatism 2008;**58**(7):1981-91.
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38. Sieper J, Landewe R, Rudwaleit M, et al. Effect of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis: Results from a phase III randomized trial. Arthritis and Rheumatology 2015;**67**(3):668-77.
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40. Van der Heijde et al. Certolizumab pegol for the treatment of axial spondyloarthritis: 4-year outcomes from the rapid-axSpA trial. EULAR; 2016.
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Table 8. Nr-axSpA SLR update – included studies

Study ID	Primary publication	Clinical trial number	Associated publications/ conference proceedings
EMBARK	Dougados 2017[25] Maksymowych 2018[26]	NCT01258738	
RAPID-axSpA	Braun 2017b[40] van der Heijde 2018a[41]	NCT01087762	
C-axSpAnd	Conference abstract Deodhar 2018a[47]	NCT02552212	
ABILITY-3	Landewe 2018a[48]	NCT01808118	Conferences Kwantra 2018[49] Kwatra 2018[50] Landewe 2017a[51] Landewe 2017b[52] Landewe 2017d[53] Landewe 2018b[54] Landewe 2018c[55] Landewe 2018d[56] Sieper 2017a[57] Sieper 2017b[58] Sieper 2018[59]

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26. Maksymowych WP, Wichuk S, Dougados M, et al. Modification of structural lesions on MRI of the sacroiliac joints by etanercept in the EMBARK trial: A 12-week randomised placebo-controlled trial in patients with non-radiographic axial spondyloarthritis. *Annals of the Rheumatic Diseases* 2018;77(1):78-84. doi: http://dx.doi.org/10.1136/annrheumdis-2017-211605

40. Braun J, Baraliakos X, Hermann KG, et al. Effect of certolizumab pegol over 96 weeks of treatment on inflammation of the spine and sacroiliac joints, as measured by MRI, and the association between clinical and MRI outcomes in patients with axial spondyloarthritis. *RMD Open* 2017;3 (1) (no pagination)(e000430) doi: http://dx.doi.org/10.1136/rmdopen-2017-000430

41. van der Heijde D, Sieper J, Maksymowych WP, et al. Clinical and MRI remission in patients with nonradiographic axial spondyloarthritis who received long-term open-label adalimumab treatment: 3-year results of the ABILITY-1 trial. *Arthritis Research and Therapy* 2018;20 (1) (no pagination)(61) doi: http://dx.doi.org/10.1186/s13075-018-1556-5

47. Deodhar AA, Gensler LS, Kay J, et al. Efficacy and safety outcomes in patients with non-radiographic axial spondyloarthritis treated with certolizumab pegol: Results from the first 52-week randomized placebo-controlled study (NCT02552212). *Arthritis and Rheumatology* 2018;70 (Supplement 9):2082-83. doi: http://dx.doi.org/10.1002/art.40700

48. Landewe R, Sieper J, Mease P, et al. Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. *Lancet* 2018;392(10142):134-44. doi: https://dx.doi.org/10.1016/S0140-6736(18)31362-X

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50. Kwatra NV, Magrey M, Mease PJ, et al. Adalimumab serum concentration fails to predict achievement of sustained remission or absence of flare for patients with nonradiographic axial spondyloarthritis in the ability-3 study. *Annals of the Rheumatic Diseases* 2018;77 (Supplement 2):63. doi: http://dx.doi.org/10.1136/annrheumdis-2018-eular.6515
51. Landewe R, Sieper J, Inman R, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: Results from the 28-week open-label period of the ability-3 study. *Annals of the Rheumatic Diseases* 2017;76 (Supplement 2):353-54. doi: http://dx.doi.org/10.1136/annrheumdis-2017-eular.6119
52. Landewe R, Sieper J, Inman R, et al. Efficacy and safety of adalimumab (ADA) in patients with nonradiographic axial spondyloarthritis (nr-axSpA): Open-label period results from the ABILITY-3 study. *International Journal of Rheumatic Diseases* 2017;20 (Supplement 1):99. doi: http://dx.doi.org/10.1111/1756-185X.13178
53. Landewe R et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results from the 28-week open-label period of the ability-3 study. *Annals of the rheumatic diseases* 2017;76:353-54.
54. Landewe R, Sieper J, Kiltz U, et al. Potential differences in axial spondyloarthritis disease activity categorization using different minimum values for high-sensitivity CRP in ankylosing spondylitis disease activity score calculation and different definitions of disease flare. *Annals of the Rheumatic Diseases* 2018;77 (Supplement 2):173. doi: http://dx.doi.org/10.1136/annrheumdis-2018-eular.2636
55. Landewe R, Sieper J, Mease P, et al. Efficacy and safety of continuing versus withdrawing adalimumab (ADA) in maintaining remission in patients with non-radiographic axial spondyloarthritis (Nr-AXSPA). *Annals of the Rheumatic Diseases* 2018;77 (Supplement 2):213. doi: http://dx.doi.org/10.1136/annrheumdis-2018-eular.2641
56. Landewe R, Sieper J, Mease P, et al. Efficacyand safetyof continuing versus withdrawing adalimumab in maintaining remission in patients with non-radiographic axial spondyloarthritis. *Journal of Clinical Rheumatology* 2018;24 (3 Supplement 1):S3.
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59. Sieper J, Landewe R, Magrey M, et al. Predictors of remission maintenance and successful therapy discontinuation in patients with non-radiographic axial spondyloarthritis (NR-AXSPA) who achieved sustained remission on open-label adalimumab (ADA) treatment. *Annals of the Rheumatic Diseases* 2018;77 (Supplement 2):995. doi: http://dx.doi.org/10.1136/annrheumdis-2018-eular.2632

A8. The ERG notes that two randomised controlled trials (RCTs) (Giardina 2010 and PLANETAS) that were cited in TA383 (TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis) have been excluded from the NMAs conducted for the current appraisal for being an open-label study and pilot study, respectively. The company has also excluded phase II studies from the NMAs

that were conducted for the current appraisal. Please provide justification for excluding these types of RCTs from the NMAs.

As noted in the question, Giardina 2010 was not included in the network meta-analysis (NMA) as it was an open-label study. The rationale for excluding open-label trials was to avoid the introduction of bias into the NMA due to the lack of treatment blinding undertaken in such studies. The only reported endpoint in Giardina 2010 that could be included in the NMA was ASAS40, and, as patient-reported outcomes are included as part of this composite endpoint (see CS, page 40), the open-label design of this study was deemed to risk the introduction of significant bias into the NMA.[6]

As also noted in the question, PLANETAS was not included in the NMA as it was a pilot study. The rationale for excluding pilot studies was due to the small-scale nature of such trials, and thus insufficiently small sample sizes to detect treatment effects. As a result of this, pilot studies are not hypothesis testing in nature.[7] This study type was therefore seen as unsuitable for inclusion in the NMA. It should however be noted that this study would also not have informed the network, as it compared originator infliximab with a biosimilar version of infliximab, a comparison which was not informative to the decision problem for this appraisal.

Furthermore, both Giardina 2010 and PLANETAS were excluded from the NMA in the Assessment Group report of TA383.[8] Giardina 2010 was excluded as it was redundant in a class effect model (and was unblinded) and PLANETAS was excluded as it did not include any of the relevant comparators needed for the meta-analysis.

The rationale for excluding phase II studies was that such trials are also frequently of small sample size and thus lack statistical power to detect a treatment effect. It should however be noted that all studies that were excluded from the NMA due to classification as a phase II study also fulfilled other exclusion criteria, as detailed below:

- Baeten 2013 utilised off-label dosing
- BUILDER-1 evaluated an intervention not licensed for axSpA (tocilizumab)
- Pathan 2013 evaluated an intervention not licensed for axSpA (apremilast)
- Van der Heijde ACR/ARHP 2015 and van der Heijde 2017a evaluated an intervention not licensed for axSpA (tofacitinib)

In summary, the inclusion of Giardina 2010, PLANETAS and phase II studies would not have altered the networks analysed in the submission, and thus the relative efficacy conclusions drawn from the analyses remain the same.

A9. The ERG notes that for the Hu 2012 (adalimumab) and van den Bosch 2002 (infliximab) trials, it is stated in Appendix D to the CS (Table 40) that results are not reported for any of the outcomes. However, the ERG notes that results from these RCTs are reported in the published papers and the data were also input into NMAs for cfb BASDAI and cfb BASFI outcomes in TA383. Please clarify whether the data

have been omitted in error in the company's NMAs. If these data have been omitted in error, please also update the relevant NMAs.

The Hu 2012 and van den Bosch 2002 trials have not been omitted in error.

The van den Bosch 2002 trial was not included in the NMA as only median values and ranges for BASDAI and BASFI scores are presented in the published paper, and these data do not allow for inclusion in the NMA (specifically, the mean change from baseline [cfb] value and accompanying standard deviation [SD] or the baseline and final mean values and accompanying SD are required for input into the analysis). Furthermore, van den Bosch 2002 included a population of mixed aetiology, of which there were only 21 patients with rad-axSpA. This included patient number is too small to determine whether the patient population would be comparable to another study from which to derive variance measures.

Within the published Hu 2012 paper, cfb BASDAI and BASFI values were not reported; only baseline and final values were included. According to the NMA protocol, in trials where this was the case, cfb was to be calculated from the final value minus the baseline value, which was possible to undertake in this case. However, to derive the corresponding SD for the cfb values for Hu 2012, a comparable study with the same treatment arm was required to inform the calculation of the SDs. Two other studies in the NMA included adalimumab arms: ATLAS and Huang 2014. ATLAS was not comparable with Hu 2012 as the patients were on average greater than 10 years older at baseline (mean baseline age: 28.2 years [adalimumab arm]/27.4 years [placebo arm] in Hu 2012 versus 41.7 years [adalimumab arm]/43.4 years [placebo arm] in ATLAS). Additionally, the vast majority of patients included in ATLAS were Caucasian (97.1% [adalimumab arm]/92.5% [placebo arm]), whereas 100% of patients included in Hu 2012 were Asian. It was similarly deemed unreliable to transfer the SD from Huang 2014 to Hu 2012, as the paper for Hu 2012 reported too few baseline characteristics to make an informed decision as to whether the two study populations were sufficiently comparable to transfer a SD. Additionally, the study population for Huang 2014 is biologic-naïve, whereas this status is unclear for Hu 2012.

Due to these difficulties and the risk of introducing of uncertainty into the NMA, it was decided to exclude Hu 2012. Finally, whilst ATLAS and Huang 2014 together contribute 659 patients to the adalimumab versus placebo comparison within the rad-axSpA NMA, Hu 2012 would have only contributed 46 patients to the analysis. It is therefore unlikely that the inclusion of Hu 2012 would have changed the conclusion of the analyses.

A10. For the ad-hoc NMA that is presented in Appendix M to the CS, please provide:

a) The data inputs (and their sources) used in the NMA for each outcome.

Please see the response to part b.

b) Relative treatment effects for the whole population, responders and non-responders for each comparator in comparison to ixekizumab (i.e., odds ratios and 95% confidence intervals for BASDAI50; posterior median treatment difference and 95% confidence intervals for cfb BASDAI and cfb BASFI).

[redacted]

[redacted]

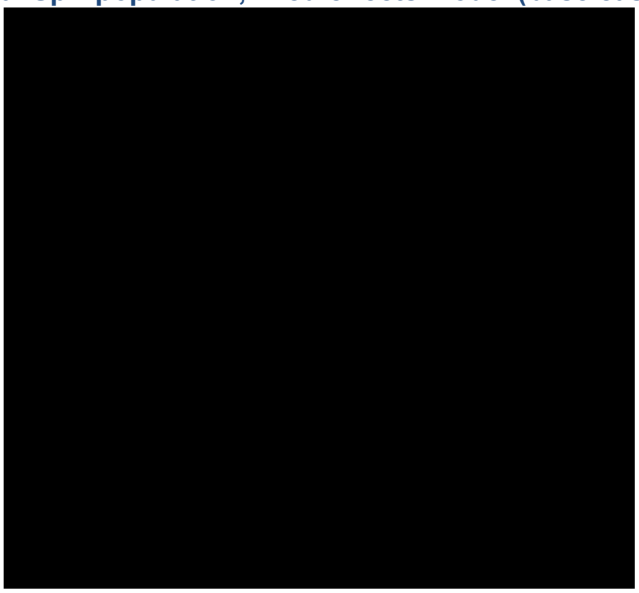
Section B: Clarification on cost-effectiveness data

B1. The company sensitivity analysis NMAs for BASDAI50, cfb BASDAI and cfb BASFI have generated credible intervals that do not support ixekizumab being superior to any other treatments considered in the CS. Please provide any additional scientific evidence that would support ixekizumab being superior, equivalent or non-inferior to comparator treatments.

In addition to ASAS40, BASDAI50 and cfb in BASDAI and BASFI, additional efficacy and safety outcomes were evaluated in the NMA. As described in Section B.2.9 of the CS, the aforementioned outcomes were selected for presentation in the submission due to ASAS40 being the primary endpoint of the COAST trials and BASDAI50 and cfb in BASDAI and BASFI being included as outcomes in the cost-effectiveness model.

However, evidence of superiority for ixekizumab versus biologic comparators was additionally identified for the outcome of cfb in Ankylosing Spondylitis Disease Activity Score (ASDAS) C-reactive protein (CRP) in the biologic-naïve rad-axSpA population in both the base case and sensitivity analysis, as presented in Figure 1 and Figure 2, respectively. In both analyses, ixekizumab was found to be superior to golimumab and etanercept, and additionally to certolizumab pegol in the sensitivity analysis. A statistically significant improvement in ASDAS CRP is clinically meaningful as it represents a reduction in disease activity.

Figure 1: Forest plot of median treatment difference of ixekizumab 80 mg Q4W relative to placebo and active comparators; ASDAS CRP cfb at 12–18 weeks, biologic-naïve rad-axSpA population, fixed-effects model (base case analysis)



Abbreviations: ADA: adalimumab; ASDAS: Ankylosing Spondylitis Disease Activity Score; CrI: credible interval; ETN: etanercept; GOL: golimumab; Q4W; every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis.
Source: NMA report, rad-axSpA[12]

Figure 2: Forest plot of median treatment difference of ixekizumab 80 mg Q4W relative to placebo and active comparators; ASDAS CRP cfb at 12–18 weeks, biologic-naïve rad-axSpA population, fixed-effects model (sensitivity analysis)

Abbreviations: ADA: adalimumab; ASDAS: Ankylosing Spondylitis Disease Activity Score; CrI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: Ixekizumab; NMA: network meta-analysis; OR: odds ratio; Q4W; every 4 weeks; rad-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab.
Source: NMA report, rad-axSpA[12]

Lilly are not aware of any further statistical analyses in axSpA above those presented in the CS comparing ixekizumab to comparators relevant to the decision problem, which demonstrate either statistical superiority, equivalence or non-inferiority of ixekizumab. However, given the analogous mechanism of action to secukinumab (IL-17 inhibition), a treatment which has been recommended by NICE for the treatment of rad-axSpA,[13] it is anticipated that ixekizumab is, as a minimum, non-inferior to secukinumab. The role of IL-17 in the pathogenesis of axSpA has been well-researched and documented.[14-16] In line with this, it should be noted that ixekizumab was found to be statistically significantly superior to secukinumab in the biologic-naïve rad-axSpA population for the outcomes of ASAS40 and BASDAI cfb, as presented in Section B.2.9.1 in the CS.

Numerical evidence to support the non-inferiority of ixekizumab versus adalimumab is additionally available from the COAST-V trial (biologic-naïve rad-axSpA patients), in which adalimumab was included as a reference arm.[17] In the intent-to-treat population, ixekizumab 80 mg Q4W was identified to be numerically superior to adalimumab at Week 16 across a number of outcomes, including ASAS40, ASAS20, BASDAI50 and least squares mean change from baseline in BASFI.[17] Whilst the trial was not powered to perform a statistical comparison between ixekizumab and adalimumab, both treatments were used in the same randomised controlled setting, allowing for a fair comparison. This evidence therefore suggests that ixekizumab performed at least as well as adalimumab in this study.

It is Lilly's view that if ixekizumab were to be recommended by NICE, it would offer physicians an additional treatment option in their armamentarium of therapies for patients with rad- and nr-axSpA. In the rad-axSpA population, there is currently only one treatment with an alternative mechanism of action to TNF-alpha inhibition (secukinumab; an IL-17A inhibitor), whilst in the nr-axSpA population, there are currently no treatments with an alternative mechanism of action.

This unmet need in clinical practice for a treatment with a novel mechanism of action was highlighted in a recently published paper of findings from the BSRBR-AS cohort of axSpA patients (n=335), in which response to TNF-alpha inhibition varied between just 33–52% after a median of 14 weeks of treatment in biologic-naïve patients.[18] Of note, patients in the COAST-W trial were highly refractory and had experienced a prior inadequate response to up to two TNF-alpha inhibitor treatments.[5] Despite this, ixekizumab met the primary endpoint of this trial and was statistically significant versus placebo across a range of outcomes spanning disease activity, functional ability pain and inflammation, as described in the CS.[5]

Finally, a variety of available treatment options is beneficial for patients. As described in the recommendations in TA383,[8] the choice of treatment should consider any associated conditions the patient may have such as extra-articular manifestations (e.g. psoriasis). Ixekizumab has demonstrated statistically significantly improved efficacy compared to TNF-alpha inhibitors in related inflammatory skin conditions. In two head-to-head trials of ixekizumab versus etanercept in moderate-to-severe psoriasis and versus adalimumab in active psoriatic arthritis, respectively, ixekizumab met its primary efficacy endpoint and demonstrated improved efficacy.[19, 20] Additionally, in a systematic review and network meta-analysis of immunomodulators for moderate-to-severe psoriasis, IL-17 inhibitors were found to be generally more effective than TNF-alpha inhibitors,[21]

B2. Please provide any technical manual or design report that will help us to navigate the economic model (if available, please provide immediately).

A model user guide, and 2 separate XL documents for the rad- and nr-axSpA models containing model variables lists and the model worksheets and VBA modules are provided alongside this response document.

B3. Please provide mean index values at baseline by trial arms (EQ-5D-5L cross-walked to EQ-5D-3L) alongside the numbers of patients completing the questionnaire at baseline and at all other subsequent time points.

The baseline EQ-5D index values are presented in Table 9.

Table 9: Baseline EQ-5D values for COAST-V, -W and -X (cross-walked from 5L to 3L)

Mean (SD)	COAST-V	COAST-W	COAST-X
PBO	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]
ADA 40 mg Q2W	[redacted]	[redacted]	[redacted]

Abbreviations: 3L: three levels; 5L: five levels; EQ-5D: EuroQoL Five Dimensions; NA: not applicable; PBO: placebo; Q2W: every two weeks; Q4W: every four weeks.

Patients in the COAST trials completed EQ-5D-5L questionnaires at baseline, Week 16 and Week 52. The number of patients completing the questionnaire at each timepoint is presented in Table 10 to Table 12.

Table 10: Number of patients completing the EQ-5D-5L questionnaire in COAST-V (ITT population)

Timepoint	Number of respondents					
	PBO/IXE	ADA40 Q2W/IXE	IXE/IXE	Total IXE80 Q4W	Total IXE80 Q2W	Total
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16 (Visit 8) (Observed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 (Visit 15) (Observed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; EQ-5D-5L: EuroQol Five Dimensions Five Levels; ITT: intention-to-treat; IXE: ixekizumab; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation.
Source: COAST-V CSR: Week 52 Report[22]

Table 11: Number of patients completing EQ-5D-5L questionnaire in COAST-W (ITT population)

Timepoint	Number of respondents						
	PBO/IXE80 Q4W	PBO/ IXE80 Q2W	IXE80 Q4W/IXE80 Q4W	IXE80 Q2W/IXE80 Q2W	PBO/IXE	IXE/IXE	Total
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16 (Visit 8) (Observed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Week 52 (Visit 15) (Observed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-5L: EuroQol Five Dimensions Five Levels; ITT: intention-to-treat; IXE: ixekizumab; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation.
Source: COAST-W CSR: Week 52 Report[23]

Table 12: Number of patients completing EQ-5D-5L questionnaire in COAST-X (ITT population)

Timepoint	Number of respondents				
	PBO	IXE80 Q4W	IXE80 Q2W	Total IXE	Total
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16 (Visit 8) (Observed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 (Visit 15) (Observed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-5L: EuroQol Five Dimensions Five Levels; ITT: intention-to-treat; IXE: ixekizumab; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation.
Source: COAST-X CSR: Week 16 and Week 52 Report[2]

B4. We cannot source the values shown in Tables 102 and 103 of the CS.

a) Please could you provide us with your report entitled "Network meta-analysis of Ixekizumab with comparators in patients with radiographic Axial Spondyloarthritis (Ankylosing spondylitis)" (CS, Reference 57).

As described in the response to part b) below, the inputs for the cost-effectiveness model were sourced from the NMA analysis described in the CS, however, adjustments to the data were required to ensure they were in the format required for the model, which are described in the CS and in part b below. The NMA report does not contain the adjusted data used for inputs into the model, and as such has not been provided.

b) In addition, if this report does not contain the NMA outputs used within the economic models, please clarify the source of the NMA outputs used within the economic models.

For BASDAI50 inputs in the model, data were sourced directly from the NMA sensitivity analysis presented in Section B.2.9 of the CS. Where BASDAI50 data were missing for any TNF-alpha inhibitors, the protocol was to take an unweighted average value of all other TNF-alpha inhibitors. The only TNF-alpha inhibitor with missing BASDAI50 NMA data across all three populations was adalimumab in the biologic-experienced rad-axSpA population.

For change from baseline in BASDAI and BASFI, the NMAs for these outcomes were performed for the whole population, and not individually for populations of responders or non-responders (according to BASDAI50), due to limited data availability in these populations. However, cfb BASDAI and BASFI data by response or non-response were required for the cost-effectiveness model inputs to align with methodology previously undertaken in TA383 and TA407.[8, 13] As such, it was necessary to perform additional calculations using the data outputs from the NMA to derive cfb data according to response or non-response. The methodology undertaken and equations

used to perform this transformation are presented in Section B.3.3.3 and Appendix M of the CS, respectively, and repeated here for ease of understanding:

Summary conditional cfb data for BASDAI and BASFI from the ixekizumab trial and other published sources were available, and these data were used to calculate the relationship between conditional BASDAI and BASFI cfb values in responders and non-responders, through the division of 'responder cfb data' by 'non-responder cfb data'. In the rad-axSpA population, proportions of responder/non-responder cfb data were available for adalimumab[24], golimumab[24], ixekizumab[5, 17] and secukinumab.[13] For all treatments except conventional care, an average of available responder/non-responder relationships was then calculated.[13, 24] In the nr-axSpA population, conditional cfb data were available for adalimumab,[24] golimumab[24] and ixekizumab,[3] and an equivalent responder/non-responder relationship value calculated.[25] In order to generate conditional cfb data for all interventions, the relationship values were then inputted into a set of equations, along with data for the overall proportion of responders and overall cfb values for BASDAI and BASFI for each intervention, as sourced from the NMA, in order to generate conditional values. These equations utilised are as follows:

Calculation of response proportions from trial data:

$$CFB_R / CFB_{NR} = Pr$$

Rearranged to:

$$CFB_R = Pr \times CFB_{NR}$$

Relationship between % responders, % non-responders, total CFB, responder CFB and non-responder CFB:

$$CFB_T = CFB_R \times \%_R + CFB_{NR} \times \%_{NR}$$

$$\%_{NR} = 1 - \%_R$$

For treatments where only CFB_T and %R are known, CFB_{NR} and CFB_R are calculated as following:

$$CFB_T = Pr \times CFB_{NR} \times \%_R + CFB_{NR} \times (1 - \%_R)$$

Rearranged, solving CFB_{NR}:

$$CFB_{NR} = \frac{CFB_T}{Pr \times \%_R + 1 - \%_R}$$

Calculating CFB_R

$$CFB_R = CFB_{NR} \times Pr$$

CFB: change from baseline; NR: non-responders; R: responders; Pr: proportion; T: total arm.

As with BASDAI50, cfb in BASDAI and BASFI NMA output data in the whole population were not available for all TNF-alpha inhibitors included within the cost-effectiveness analyses. In these cases, an unweighted average of the cfb values from other TNF-alpha inhibitors from the whole population NMAs was taken (before adjustment for response or non-response was subsequently undertaken).

To conclude, the BASDAI and BASFI cfb inputs utilised in the model are based on data sourced from the NMA, but have been adjusted according to response or non-response. As noted in the question, these data are presented in Tables 102 and 103 of the CS.

c) Please provide the BASDAI change from baseline and BASFI change from baseline NMA outputs (base case and sensitivity analysis) by BASDAI50 responders and BASDAI50 non-responders.

Searches were performed for suitable BASDAI/BASFI cfb data and corresponding SDs for the comparators of interest in order to perform the requested analyses, but unfortunately these data were not available in the literature and therefore it was not possible to conduct the analyses.

B5. In scenario 8 (see CS, p197 for details), differential baseline BASDAI and baseline BASFI estimates are used, please provide details of how these were calculated:

- by treatment
- by treatment and response

In the base case, baseline BASDAI and BASFI values are equivalent between interventions, and do not differ between responders or non-responders. In contrast, in scenario 8, patients' baseline values vary according to whether they are subsequent BASDAI50 responders or not. The sources of baseline data conditional upon response differ between the rad-axSpA and nr-axSpA populations, as follows:

Rad-axSpA

In the biologic-naïve rad-axSpA population, conditional baseline data for ixekizumab and adalimumab were taken from the respective arms of the COAST-V trial. For the remaining biologic interventions, conditional baseline data were derived through the averaging of the ixekizumab and adalimumab conditional baseline data. For conventional care, conditional baseline data were sourced from the placebo arm of COAST-V trial. The data used in the scenario for the biologic-naïve rad-axSpA population are presented in Table 13.

For the biologic-experienced rad-axSpA population, conditional baseline data for all biologic interventions were derived from the ixekizumab arm of the COAST-W trial, whilst conditional baseline data for conventional care were derived from the placebo arm. The data used in the scenario for the biologic-experienced rad-axSpA population are presented in Table 14.

Table 13. Conditional BASDAI and BASFI baseline scores (biologic-naïve rad-axSpA)

COAST-V Mean (SD)	Baseline BASDAI score		Baseline BASFI score	
	Responders	Non-responders	Responders	Non-responders
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; IXE: ixekizumab; PBO: placebo; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SD: standard deviation.

Table 14. Conditional BASDAI and BASFI baseline scores (biologic-experienced rad-axSpA)

COAST-W Mean (SD)	Baseline BASDAI score		Baseline BASFI score	
	Responders	Non-responders	Responders	Non-responders
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; IXE: ixekizumab; PBO: placebo; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SD: standard deviation.

Nr-axSpA

In the biologic-naïve nr-axSpA population, conditional baseline data for all biologic interventions were derived from the ixekizumab arm of the COAST-X trial, whilst conditional baseline data for conventional care were derived from the placebo arm. The data used in the scenario for the biologic-naive nr-axSpA population are presented in Table 15.

Table 15. Conditional BASDAI and BASFI baseline scores (biologic-naive nr-axSpA)

COAST-X Mean (SD)	Baseline BASDAI score		Baseline BASFI score	
	Responders	Non-responders	Responders	Non-responders
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; PBO: placebo; Q4W: every four weeks; SD: standard deviation.

Section C: Textual clarification and additional points

C1. The data for TEAEs possibly related to study drug data for COAST-X is missing from Table 90 of the CS. For completeness, and to be consistent with the equivalent tables for COAST-V and COAST-W, please provide this information.

Thank you for highlighting this omission from Table 90. The corrected version of Table 90 is presented in Table 16 below.

Table 16: Summary of safety analysis in COAST-X (safety population; Week 52; prior to biologic rescue of ixekizumab Q2W)

AE, n (%)	Ixekizumab Q2W (N=102)	Ixekizumab Q4W (N=96)	Ixekizumab total (N=198)	Placebo (N=104)
TEAEs	**79 (77.5)***	**63 (65.6)**	**142 (71.7)**	**60 (57.7)**
[redacted]				
[redacted]				
Severe	7 (6.9)	1 (1.0)	8 (4.0)	4 (3.8)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Anaphylactoid reaction	0	0	0	1 (1.0)
Death	0	0	0	0
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Anaphylactoid reaction	0	0	0	1 (1.0)

*p<0.05 versus placebo
Abbreviations: AE: adverse event; ALT: alanine aminotransferase; Q2W: every 2 weeks; Q4W: every 4 weeks; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: Deodhar *et al.* (2019),[3] COAST-X CSR: Week 16 and Week 52 Report (Table RHBX.12.2, Table RHBX.12.6, Table RHBX.12.9 and Table RHBX.14.119)[2]

C2. In the appendices to the CS, Table 30, there appears to be a missing footnote (‡) for the following column: Proportion of patients with concomitant NSAIDs (%). Please clarify.

Thank you for highlighting this omission. The footnote text that should be included here is: '‡ Note that the proportions of patients receiving concomitant glucocorticoids or methotrexate during the study was not reported in any of the publications'.

C3. In the appendices to the CS, Table 34 to Table 36, please clarify what is meant by the heading of the following column: 'CRP or ESR?'.

The column 'CRP or ESR?' indicates whether the study calculated the ASDAS score on the basis of CRP levels or erythrocyte sedimentation rate (ESR).

C4. In Section B.3.4.1 of the CS, it is stated that "As described in Section B.2.6, the COAST-V, -W and -X trials collected HRQoL outcomes via the EQ-5D-5L health utilities instrument." However, these data are not described in Section B.2.6 and nor

are EQ-5D-5L data presented for the trials in the clinical effectiveness section of the CS (Section 2.6). Please provide available summary EQ-5D-5L results.

EQ-5D-5L assessments were carried out at baseline, Week 16 and Week 52 in COAST-V, COAST-W and COAST-X. The EQ-5D-5L UK population-based index scores (observed) at baseline, Week 16 and Week 52 in COAST-V, COAST-W and COAST-X are presented in Table 17, Table 18 and Table 19, respectively.

Table 17: EQ-5D-5L UK population-based index score in COAST-V (Extended Treatment Period population)

	PBO/ IXE80 Q4W	PBO/IXE 80 Q2W	ADA40 Q2W/IXE 80 Q4W	ADA40 Q2W/IXE 80 Q2W	IXE80 Q4W/IXE 80 Q4W	IXE80 Q2W/IXE 80 Q2W	PBO/IXE	ADA 40 Q2W /IXE	IXE/IXE	Total IXE Q80 Q4W	Total IXE 80 Q2W	Total
Baseline												
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16 (Observed)												
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 (Observed)												
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: adalimumab; EQ-5D-5: EuroQol Five Dimensions Five Levels; IXE: ixekizumab; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation.
Source: COAST-V CSR: Week 52 Report[22]

Table 18: EQ-5D-5L UK population-based index score in COAST-W (Extended Treatment Period population)

	PBO/IXE80 Q4W	PBO/IXE80 Q2W	IXE80 Q4W/IXE80 Q4W	IXE80 Q2W/IXE80 Q2W	PBO/IXE	IXE/IXE	Total
Baseline							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16 (Observed)							

n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 (Observed)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-5: EuroQol Five Dimensions Five Levels; IXE: ixekizumab; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation.
Source: COAST-W CSR: Week 52 Report[23]

Table 19: EQ-5D-5L UK population-based index score in COAST-X (ITT population)

	PBO	IXE80 Q4W	IXE80 Q2W	Total IXE	Total
Baseline					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16 (Observed)					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 (Observed)					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-5: EuroQol Five Dimensions Five Levels; IXE: ixekizumab; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation.
Source: COAST-X CSR: Week 16 and Week 52 Report[2]

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Professional organisation submission

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Spondyloarthritis Special Interest Group (SIG) ([redacted])**
2. Name of organisation	**British Society for Rheumatology Spondyloarthritis SIG**

3. Job title or position	**Consultant Rheumatologist**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**British Society for Rheumatology Spondyloarthritis Special Interest Group (SIG)**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve clinical outcomes, Quality Of Life (QOL) and productivity. Reduce pain, improve mobility, reduce disability
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Improved outcome scores of >=50% Reduction in spinal pain VAS and BASDAI by >= 2 points

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Unmet need in nr-axSpA only as biologic treatment has been limited to TNF inhibitors thus far. Yes – some patients do not tolerate or respond to NSAIDs and available biologic therapies
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	NSAIDS x 2, cheapest biologic (allocate anti-TNF), then other cheaper anti-TNF or secukinumab – for radiographic AXSpA only, not nr-AxSpA
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines NICE CG 65 Spondyloarthritis in over 16s NICE QS 170
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Well-defined with clear national and international clinical guidelines but there are lots of variation depending on local commissioner agreements

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Offer additional therapeutic options. Increase options available for nr-AXSpA
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	This provides a new mode of action (IL-17 inhibition) for nr-AxSpA
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and specialist AxSpA clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Use of current facilities. Use of existing homecare service and delivery

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Not aware of data
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – improvements seen in clinical trials in ASAS Health Index and SF-36 PCS
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This treatment will benefit patients with nr-AxSpA
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No change expected from current care pathway
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As per NICE Guidance on biologics in AxSpA Failure to achieve reduction in spinal pain VAS and BASDAI by at least 2 points
15. Do you consider that the use of the technology will result in any substantial health-	

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Offer additional therapeutic option for patients who do not tolerate or respond to NSAID, TNF inhibitor or secukinumab

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Use caution in inflammatory bowel disease Most frequent adverse event is infection – usually minor – consistent with previously reported data
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	ASAS40, BASDAI50, ASDAS, MRI data, ASAS-HI, SF-36 PCS Yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any data
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No
21. How do data on real-world experience compare with the trial data?	Not yet in routine clinical use – limited real world data
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Increase treatment options for patients with AxSpA
- Provide a new mode of action (IL-17 inhibition) in nr-AxSpA
- Improved clinical outcomes from clinical trials
- No additional or new safety signals from the clinical trials beyond what is known about IL-17 inhibitors
- Improvement in patient reported outcome measures and quality of life

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	National Axial Spondyloarthritis Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	NASS is the only charity in the UK solely dedicated to supporting people living with axial spondyloarthritis (axial SpA) including ankylosing spondylitis. We provide information and support to people with the condition, as well as campaigning for better treatment and care. NASS is funded by a variety of voluntary sources including membership, individual fundrasisers, charitable trusts, legacies and industry funding. We receive no statutory or government funding. NASS currently has 3,547 members, the majority of which have axial SpA (AS).
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	None from the manufacturers **Novartis** £30,000 - Aspiring to Excellence quality improvement programme £11,000 – Part funding for secretariat of All-Party Parliamentary Group for Axial Spondyloarthritis £40,000 – NASS Voices and Members Day (patient information days) **Abbvie** £30,000 - Aspiring to Excellence quality improvement programme **UCB Pharma** £36,250 - Aspiring to Excellence quality improvement programme **Biogen** £60,000 - Aspiring to Excellence quality improvement programme (2 years' funding 2019 to 2020)

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We conducted a survey of people with axial spondyloarthritis (axial SpA) including ankylosing spondylitis (AS) and their carers which ran from 20 November 2019 to 2 December 2019. We received 330 responses. The questions were based on the questions asked in this submission. 303 valid responses were received with automatic exclusions applied to those who did not live in England and were neither a person living with axial SpA (AS) or a carer of a person with axial SpA (AS).
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Axial Spondyloarthritis (axial SpA) refers to inflammatory disease where the main symptom is back pain, and where the x-ray changes of sacroiliitis *may or may not* be present. Within axial SpA there are two groups: **Ankylosing Spondylitis (AS):** Where the x-ray changes are clearly present. **Non-radiographic axial spondyloarthritis (nr-axSpA):** Where x-ray changes are *not* present but you have symptoms. Around 7 in 10 in this group have visible inflammation which shows on an MRI. 3 in 10 may not have any change visible on the MRI despite symptoms of back pain and other symptoms of inflammatory disease including: • Episodes of uveitis (inflammation in the eyes) • Crohn's disease or ulcerative colitis (inflammatory bowel disease) • Psoriasis • Inflammation in the heel of the foot • Inflammation in the fingers or toes • Elevated markers of inflammation in blood tests

	• HLA-B27+ Axial SpA is an inflammatory condition of the spine which often produces pain, stiffness, deformity and disability throughout adult life. It is a chronic progressive disease. It is characterised by periods of fluctuating intensity, leading to slowly increasing spinal and peripheral joint damage. The key symptom in early disease is inflammatory back pain (IBP). The onset of back pain and stiffness is usually gradual, being especially severe at night and following immobility. For many people sleep is disturbed, often causing them to get out of bed in the night to move around so as to improve their back pain and stiffness. Pain and stiffness in AS are commonly at their worst first thing in the morning and may improve considerably with stretching and light exercise. Persistence of the disease leads to progressive spinal stiffness which may be accompanied by deformity. Up to 25% of people with axial SpA eventually develop complete fusion of the spine which leads to substantial disability and restriction. 50% of people with axial SpA also suffer from associated disorders at sites distant from the spine. In particular, 40% experience episodic eye inflammation (iritis), 16% develop psoriasis and 10% inflammatory bowel disease. Symptoms of axial SpA usually begin in adolescence or early adulthood, a critical period in terms of education, work and establishment of social frameworks and relationships. Symptoms are often present for a long time (7-10 years) before the diagnosis is made. Although most people with axial SpA live a normal lifespan, there is an increased risk of premature death from cardiovascular disease in particular. Since many people with axial SpA are neither deformed nor have peripheral joint abnormalities, much of the burden of living with axial SpA is invisible. The spectrum of severity means that although many people with axial SpA live active and rewarding lives, others experience progressive spinal pain, immobility and functional impairment. Work disability is a major problem with more than 50% of people who are affected suffering work instability. The average age of diagnosis is 24, a prime time for establishing a career. In addition, one-third of people with axial SpA give up work before normal retirement age and another 15% reduce or change their work because of axial SpA. The work capacity of people with axial SpA in the middle decades of life is similar to that of people with rheumatoid arthritis.

	Being unable to work has important consequences for the individual and his/her family through both loss of earnings and the loss of self-esteem that a career and income provide. People with axial SpA are more likely to be divorced or never to have married and women with axial SpA are less likely to have children. Many people with axial SpA suffer with issues including depression, fatigue and poor sleep during their lives. All of these problems exert a profound influence on their quality of life. Q11 Describe in your own words what it is like to live with axial spondyloarthritis / ankylosing spondylitis, or what it is like to care for someone with the condition.  Carers commented that they felt frustration at missing out on life and opportunities, but also watching someone young suffer in so much pain left them feeling useless.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	269 people answered this question. Of those 45% believed that current treatments available are sufficient, 55% believed that they are not. When asked why they did not believe the treatment to be sufficient, some common themes did occur: • For some individuals, no medication developed so far has been effective • Some patients may not be able to tolerate any of the current treatments available due to underlying conditions • Efficacy of treatment can wear off over time or it can take a long time to find an effective treatment • Worries about possible side effects • Concerns for patients who do not meet the criteria for biologic therapy but who display severe symptoms We also asked if care was sufficient on the NHS. Of the 269 that answered, 43% believed that it is and 57% that it isn't. The reasons cited for this included: • Insufficient staffing in rheumatology and physiotherapy • A lack of specialist rheumatology physiotherapy • Insufficient knowledge amongst some rheumatologists / a lack of specialist axial SpA (AS) clinics as opposed to general rheumatology clinics • Dwindling access to hydrotherapy • No direct access to help when in a flare • A lack of information on the condition provided when diagnosed and throughout disease course **Many of the older patients acknowledged that whilst options for the treatment of axial SpA (AS) had improved, there was still more to be done.**
8. Is there an unmet need for patients with this condition?	Those surveyed believed that more research was needed into the causes of axial SpA (AS). Inequalities in care around England also mean that inadequate care is the norm in some areas. In a recent FOI enquiry sent to all NHS Trusts in England, of the 88% of trusts who responded, less than half offered a specialist axial SpA (AS) clinic.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	When asked if they thought that ixekizumab should be available for the treatment of axial spondyloarthritis (axial SpA), 88% responded positively. Respondents were enthusiastic that any drug that can improve the quality of life be available for people with axial SpA. They were also keen that all possible options for treatment be made available to patients to ensure the best possible care for everyone living with the condition. A common response was also the impact that effective treatment could have on the wider economy; if people are treated with the drug that suits them the best then they are more likely to be able to stay in work and contribute more fully to society.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Many others said they didn't feel they had enough technical knowledge to fully comment on the possible disadvantages.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Currently the only biologic drugs available for non-radiographic axial spondyloarthritis (nr-axSpA) are TNF-alpha inhibitors. Any patient who has not responded to this type of drug with nr-axSpA could potentially benefit from this drug, with improved symptoms allowing for a better quality of life. Ixekizumab is an IL17-a inhibitor which works differently to TNF-alpha inhibitors and as such could be hugely beneficial to whole new group of patients. There is currently one other IL17-a inhibitor available for ankylosing spondylitis (changes on x-ray) but it is not available for nr-axSpA, although it is currently also undergoing a NICE technology appraisal, namely secukinumab. However, it has been well documented that patients respond to the various types of TNF-alpha inhibitors in different ways, with some finding that not all brands work for every individual and often the efficacy can wear off. Ixekizumab would give the option of an additional IL17-a inhibitor to those who do not respond to TNF-alpha inhibitors or secukinumab.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Axial spondyloarthritis is a painful and debilitating condition which can often lead to social isolation at a young age if left untreated.
- All patients within the axial sponyloarthritis deserve the opportunity to the full range of treatment for the condition.
- The technology could significantly improve the quality of life of those with non-radiographic axial spondyloarthritis which has an equal if not greater disease burden than radiographic axial SpA / ankylosing spondylitis.
- There are no other IL17-a biologic drugs currently available for nr-axSpA as an alternative to TNF-alpha inhibitors, although there is currently a technology appraisal underway for secukinumab.
- The vast majority of patients surveyed (88%) would like to see ixekizumab available for nr-axSpA.

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Clinical expert statement

Single Technology Appraisal (STA)

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Helena Marzo-Ortega**

2. Name of organisation	**Leeds Teaching Hospitals Trust and University of Leeds**
3. Job title or position	**Consultant Rheumatologist and Honorary Clinical Associate Professor**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment in axial Spondyloarthritis is to control signs and symptoms of disease, improving quality of life and ultimately arrest disease progression, which is directly linked to functional impairment and disability.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Complete resolution of symptoms. Current measures of disease activity and improvement in clinical practice such as the BASDAI or spinal pain assessment on visual analogue scales are not specific enough for this condition and may be influenced by other factors. ASDAS utilises CRP and is a better tool, as can reflect disease status even in those patients who many never have an abnormal CRP.
9. In your view, is there an unmet need for patients and	Yes, there are many unmet needs. • Lack of understanding at the molecular level makes it difficult to stratify treatment, ie no immunological biomarkers of treatment response; ie when to choose an Il-17i rather a TNFi for

healthcare professionals in this condition?	example. This knowledge is essential to understand primary and secondary non-response, and so to avoid unnecessary cycling of therapies. • The main unmet need for patients remains the unacceptable long delay in diagnosis, which averages 8.5 years in the UK. Lack of awareness among primary care and MSK interface clinicians and HCPs, and the general public is a significant limitation. • Lack of pathonomonic symptoms and signs of disease, as the majority of patients will present with (inflammatory) back pain. Radiographs take an average of 10 years to show diagnostic change (ie erosions, new bone formation), and only 60% patients will be identified on MRI when presenting with inflammatory back pain symptoms. These will be a primarily male, HLA-B27+ve, which means is largely HLA-B27-ve and/or female patients who may have a longer diagnostic delay. This delay contributes to work instability per year of delay, and accrual of co-morbidities including extra-articular manifestations. • Further, data suggest that earlier treatment initiation (ie shorter disease duration) leads to better disease control, ie achievement of inactive disease. However disease activity returns in majority of cases when treatment is withdrawn. This is one of the main issues for patients, mainly of young age.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	First line of treatment is NSAIDs, physiotherapy and regular exercise. If symptoms persist, ie disease activity (BASDAI>4, VAS spinal pain>4, high CRP, positive MRI), treatment with biologic therapy can be considered. This is the case in 60% of people with axSpA.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	• NICE biologics for axial SpA guideline TA383 • BSR and BHPR guideline for the treatment of axSpA (including AS) with biologics • NICE clinical guidance for the diagnosis and management of SpA [NG65] • NICE Quality Standards for axial SpA [QS170] • ASAS/EULAR guidelines recommendations for the management of axial SpA • ASAS Quality Standards for SpA

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined both in the UK and abroad. However, health inequities may lead to some countries taking longer to commence biologic therapy, and considering options such as sulphasalazine, which has very limited data in the context of primary axial, rather than axial and peripheral involvement. Other variation may be due to differences in regulatory use of drugs, for example there are less technologies approved for nr-axSpA in Australia, and use is restricted to the subgroup with both high CRP and positive MRI.
• What impact would the technology have on the current pathway of care?	It will contribute a second alternative option to TNFi in axSpA. Compared to PsA, and RA, the drug armamentarium in axSpA remains very limited, with only 2 biologic options available.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes.
• How does healthcare resource use differ between the technology and current care?	It is not expected to differ.
• In what clinical setting should the technology be used? (For example,	Secondary and tertiary care.

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None beyond data dissemination through HCPs.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect the technology to increase length of life more than current care?	No, the expectation is that it will be comparable with biologic therapies currently available.
• Do you expect the technology to increase health-related quality of life more than current care?	The expectation is to be comparable with biologic therapies currently available.

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It is expected that this technology would be easy to use, and comparable with other technologies currently available (both IL-17i and TNFi).

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes, the data from axSpA and PsA trials suggest that the efficacy of this drug on skin psoriasis is excellent, and enhanced from other available IL-17i.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No in axSpA.
• Does the use of the technology address any particular unmet need of the patient population?	It offers a second option within the class of TNFi.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effect profile for ixekizumab is no different than from other IL-17i and is probably better than that seen in TNFi.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, inclusion criteria was that of current NICE recommendations for biologic therapies in axSpA, ie: patients who have responded inadequately to ≥2 NSAIDs or are intolerant of NSAIDs. The patient sample was quite mixed with UK participating in COAST-W, only.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	One strength of the data is the number of studies performed, as efficacy of ixekizumab in axSpA has been demonstrated in 3 Phase III, multicentre, double-blind, randomised controlled trials, reporting for up to 52 weeks: COAST-V: r-axSpA patients biologic-naïve patients; COAST-W: r-axSpA biologic-experienced patients (ie previously responding inadequately to or were intolerant to one to two TNF-alpha inhibitors; COAST-X: r-axSpA biologic-naïve patients. The primary endpoint of the COAST trials was the proportion of patients achieving an ASAS40 response at Week 16, which is current requirement by EMA. Other outcomes included imaging (SPARCC), BASDAI50, quality of life instruments.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	N/A

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	N/A
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance **TA383, TA497, TA407**	N/A
22. How do data on real-world experience compare with the trial data?	There are not much data published on real life with IL-17i. Data from my service (Leeds, unpublished) on secukinumab suggest efficacy and survival comparable with that of clinical trials.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	The main equality issue will come from price, and the restrictions attached to these differences.

23b. Consider whether these issues are different from issues with current care and why.	It is possible that regional/local differences in access may exist depending on individual treatment protocols and/or algorithms, which are almost always cost driven.
Topic-specific questions	
24a. We would like to understand more about the clinical need for new treatments for patients with axSpA and the likely place of ixekizumab in therapy. • Can you explain how/when you expect ixekizumab to be used in the treatment of axSpa? First line, second line etc. • When it is likely to be used in preference to or	Based on efficacy, TNFi will remain the first line of treatment due to the wider indications (ie uveitis, inflammatory bowel disease and pregnancy indications). IL-17i are superior in skin psoriasis but this is not the main area of need in axSpA, where psoriasis if present tends to be milder than that seen in the context of psoriatic arthritis. Biosimilar availability is also a main factor when choosing first therapy. Further, response and drug survival are more significant with the first biologic drug used, meaning that a significant proportion of patients will remain on a TNFi. IL-17i are therefore desirable in the 30-40% of patients with primary non-response to TNFi or have had tolerability issues or contraindications, ie risk of TB, or those with secondary non-response to 2 or more TNFi. Data from current studies (COAST V/X) show proven efficacy as first line treatment and the only limitation not to use ixekizumab first line would be cost.

instead of an anti-TNF-alpha inhibitor? • Do you think ixekuzumab/IL-17a inhibitors have specific advantages for some patients over TNF-alpha inhibitors? 24b. What percentage of patients currently treated with secukinumab in the NHS receive a 300mg dose?	Any axSpA (either bDMARD naïve or experienced) would be eligible, presence of moderate to severe skin psoriasis would make it preferred. Loading dose and 4 weekly injection regime will be desirable for patients. IL-17i have comparable efficacy in the joints, more efficacy in the skin, and have a favourable side effect profile (mild infections, no strong signal for TB), but are no proven effect on uveitis or IBD. 10-15%
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Ixekizumab trial data show efficacy and safety in bDMARD naïve and bDMARD experienced axSpA patients
- Safety profile is acceptable, although trial data show a high number of TEAs, these appear mild.
- It would be desirable to have the possibility of accessing ixekizumab as first line therapy. This will allow for experience to be developed with drug use, which will otherwise not be possible if only used post TNFi. The loading dose and four weekly injection regime will be desirable for patients.
- Head to head trials between IL-17i and TNFi with molecular studies are needed. Although COAST-V used adalimumab as a comparator treatment arm, the study was not powered to show superiority. These data would have been extremely useful and remains highly needed.
-

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Single Technology Appraisal (STA)

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Louise Warburton**
2. Name of organisation	**Shropshire Community NHS Trust**

3. Job title or position	**GPwSI in Rheumatology and Associate Medical Director**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐**x** other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ **x** nothing to add

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Prevent axial Spondyloarthritis from progressing.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in functional scores such as BASDAI
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Oral traditional DMARDS such as MTX and SLZ
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE SpA guideline.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Not well defined for Spa and when to introduce biologics.
• What impact would the technology have on the current pathway of care?	It would broaden the choice of drugs which can be used to treat SPA
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not sure

• How does healthcare resource use differ between the technology and current care?	It is a different class of treatments from usual care (biologics)
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil; all present already in clinical settings.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	yes
• Do you expect the technology to increase length of life more than current care?	Not sure

• Do you expect the technology to increase health-related quality of Not surelife more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	no
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Will be very similar to existing care

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not sure
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	no
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes, it will provide an alternative for people who do not respond to more traditional therapies such as anti-TNFs

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, increases the choice of drugs available.
• Does the use of the technology address any particular unmet need of the patient population?	There are a group of people who do not respond to anti-TNFs and this group of people will benefit.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are relatively rare.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	I don't have knowledge of this
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	n/a
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	n/a
20. Are you aware of any relevant evidence that might	no

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance **TA383, TA497, TA407**	no
22. How do data on real-world experience compare with the trial data?	n/a
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	no

23b. Consider whether these issues are different from issues with current care and why.	n/a
Topic-specific questions	
24a. We would like to understand more about the clinical need for new treatments for patients with axSPa and the likely place of ixekizumab in therapy. • Can you explain how/when you expect ixekizumab to be used in the treatment of axSpa? First line, second line etc. • When it is likely to be used in preference to or	As mentioned above , this drug could be used for people who have not responded to he more traditional an ti-TNF treatements. It might be preferable to use of an anti- TNF in patients who have co-morbidities which are worsened by anti- TNFS such as iritis. I think the risk of infection is lower as well, so in patients with poorly controlled diabetes for example, it would be safer to use IL17 inhibitor.

instead of an anti-TNF-alpha inhibitor? • Do you think ixekuzumab/IL-17a inhibitors have specific advantages for some patients over TNF-alpha inhibitors? 24b. What percentage of patients currently treated with secukinumab in the NHS receive a 300mg dose?	
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Increases the choice of treatments available to patients with SPA who do not respond to anti-TNF
- Safer in some co-morbidities.
-
-
-
-

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ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number NIHR 17/156/08

Completed 23rd March 2020

CONTAINS [redacted] AND [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

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Contributions of authors:

Janette Greenhalgh	Co-project lead, critical appraisal of the clinical evidence and supervised the final report
Nigel Fleeman	Co-project lead, critical appraisal of the clinical evidence
Rachel Houten	Critical appraisal of the economic evidence
Marty Chaplin	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
James Mahon	Critical appraisal of the economic model
Yenal Dundar	Checking the company's literature search strategy
Ashley Marsden	Critical appraisal of the company submission
Tom Kennedy	Clinical advice and critical appraisal of the clinical sections of the company submission
Nicola Goodson	Clinical advice and critical appraisal of the clinical sections of the company submission

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List of abbreviations

ADA	adalimumab
AE	adverse event
AESI	adverse event of special interest
ASAS	Assessment of Ankylosing Spondylitis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
axSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BIA	Budget Impact Assessment
cfb	change from baseline
CrI	credible interval
COAST-V	Company's main trial discussed the company submission (ixekizumab versus placebo)
COAST-W	Company's main trial discussed the company submission (ixekizumab versus placebo)
COAST-X	Company's main trial discussed the company submission (ixekizumab versus placebo)
CRP	C-reactive protein
CS	company submission
CSR	clinical study report
CZP	certolizumab
DIC	deviance information criterion
EQ-5D	EuroQol-five dimensions
ERG	Evidence Review Group
ETA	etanercept
GOL	golimumab
HRG	Health Resource Group
HRQoL	health-related quality of life
ICER	incremental cost effectiveness ratio
INF	Infliximab
IL	interleukin
ITT	intent-to-treat
IV	intravenous
IXE	ixekizumab
LD	loading dose
LSM	least squares mean
mBOCF	modified baseline observation carried forward
MIMS	Monthly Index of Medical Specialities
MMRM	mixed effect model repeat measurement
MRI	magnetic resonance imaging
mSASSS	modified Stroke Ankylosing Spondylitis Spine Score
MTA	multiple technology appraisal
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported
nr-axSpA	non-radiographic axial spondyloarthritis
NRS	numeric rating scale
NSAID	non-steroidal anti-inflammatory drug
PAS	Patient Access Scheme
PBO	placebo
PCS	physical component summary
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
Q2W	every two weeks
Q4W	every four weeks
QALY	quality adjusted life year
rad-axSpA	radiographic axial spondyloarthritis
RCT	randomised controlled trial
SAE	serious adverse event
SEC	secukinumab
SF-36	Short Form-36
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event

TNF	tumour necrosis factor
VAS	visual analogue scale
VBA	Visual Basic for Applications

1 EXECUTIVE SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by the company (Eli Lilly and Company Ltd) in support of the use of ixekizumab (Taltz®) for treating axial spondyloarthritis (axSpA) after non-steroidal anti-inflammatory drugs (NSAIDs).

Ixekizumab is not currently licensed for use in the UK. The European Medicines Agency Committee for Medicinal Products for Human Use decision is expected in April 2020 and the European marketing authorisation is expected in June 2020.

Direct clinical effectiveness data were provided in the company submission (CS) from three trials relating to three populations with axSpA: i) patients with radiographic axSpA previously untreated with tumour necrosis factor (TNF)-alpha inhibitors (biologic-naïve rad-axSpA, COAST-V trial); ii) patients with radiographic axSpA previously treated with TNF-alpha inhibitors (biologic-experienced rad-axSpA, COAST-W trial) and iii) patients with non-radiographic axSpA previously untreated with TNF-alpha inhibitors (biologic-naïve nr-axSpA, COAST-X trial).

Each of the COAST trials included a placebo arm. Data were also collected for the TNF-alpha inhibitor adalimumab as an active reference arm in COAST-V. Data from the placebo arms in these trials can be considered as a proxy for established clinical practice for treatment-naïve patients. Comparative clinical effectiveness evidence for ixekizumab versus all comparator biological treatments, in these three populations, was generated using network meta-analyses (NMAs).

All three COAST trials included two ixekizumab treatment arms (every 2 weeks [Q2W] and every 4 weeks [Q4W]). This ERG report has focussed on the outcomes of patients who were treated with ixekizumab Q4W as this is the anticipated licensed dose of ixekizumab. In addition, patients were randomised to receive two different loading doses of ixekizumab (80mg and 160mg). Outcomes are reported in the CS at Week 16 and at Week 52.

1.1 Critique of the decision problem in the company's submission

As highlighted in Section 2.5 of this ERG report, the decision problem addressed by the company is largely in accordance with the final scope issued by NICE; ERG comments relating to the decision problem addressed by the company are summarised in Table 1.

Table 1 ERG comments relating to the decision problem addressed by the company

Parameter	Final scope issued by NICE	ERG comments on company decision problem
Population	People with axSpA for whom NSAIDs or TNF-alpha inhibitors have been inadequately effective or not tolerated, or are contraindicated.	There is no specific evidence to demonstrate the clinical effectiveness of ixekizumab in people with axSpA for whom NSAIDs or TNF-alpha inhibitors have not been tolerated or are contraindicated. Nor is there any evidence to support the clinical effectiveness of ixekizumab in biologic-experienced patients with rad-axSpA who have failed treatment with more than two biologics or in biologic-experienced patients with nr-axSpA.
Comparators	TNF-alpha inhibitors, IL-17 inhibitors (only for patients with rad-axSpA) and established clinical practice.	In the CS, placebo was considered to be a proxy for established clinical practice.
Outcomes	• disease activity • functional capacity • disease progression • pain • peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) • adverse effects of treatment • HRQoL	Direct clinical effectiveness evidence (ixekizumab versus placebo) is available from the CS for all outcomes except disease progression, peripheral symptoms and extra-articular manifestations. The company states that peripheral symptoms and extra-articular manifestations are not presented in the CS as priority was given to presenting outcomes relevant to the economic model and those that were relevant to previous appraisals of treatments for axSpA (CS, Table 1). The outcomes estimated by the company NMAs were disease activity, progression and functional capacity (as measured by ASAS40, BASDAI50, BASDAI score cfb and BASFI score cfb).
Subgroups to be considered	If the evidence allows the subgroups of people who have had or not had TNF-alpha inhibitors will be considered.	Clinical effectiveness evidence is not available for the biologic-experienced nr-axSpA patient population. However, the company has considered this patient population in a scenario analysis in the cost effectiveness section.

ASAS40=Assessment of Ankylosing Spondylitis International Society 40; axSpA=axial spondyloarthritis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI= Bath Ankylosing Spondylitis Functional Index; cfb=change from baseline; HRQoL=health-related quality of life; NMA=network meta-analysis; nr-axSpA=non-radiographic axial spondyloarthritis; NSAIDs=non-steroidal anti-inflammatory drugs; rad-axSpA=radiographic axial spondyloarthritis; TNF=tumour necrosis factor

1.2 Summary of the key issues in the clinical effectiveness evidence

Overall, the ERG considers that the methods used to conduct the company's systematic search and selection of clinical effectiveness evidence were carried out to a good standard (ERG report, Section 3.1).

1.2.1 Direct evidence

The COAST-V, COAST-W and COAST-X trials are good quality randomised controlled trials that recruited substantial numbers of patients. [redacted]). The baseline characteristics of the patients recruited to the COAST trials (ERG report, Section 3.2.1) appear to be similar to the characteristics of patients treated in the National Health Service (NHS).

Week 16 results from the COAST trials show that treatment with ixekizumab (Q4W) was statistically significantly more effective than placebo in terms of Assessment of Anklyolsing Spondylitis International Society 40 (ASAS40) response, [redacted] intention-to-treat (ITT) populations (ERG report, Section 3.3.1).

Comparative effectiveness data from the COAST-V and COAST-W trials were only available at Week 16 since patients randomised to the placebo arms of these trials received ixekizumab after 16 weeks. Comparative data (Week 16 and Week 52) were available from the COAST-X trial as patients who did not require rescue treatment remained on placebo from Week 16 to Week 52.

A comparison of the health-related quality of life (HRQoL) results, as measured using the Short Form (SF)-36 questionnaire, showed that, at Week 16, there was [redacted] in cfb scores for patients treated with ixekizumab compared with patients treated with placebo across all of the COAST trials. The results of the COAST-V and COAST-W trials showed that [redacted] Data from the COAST-X trial showed that [redacted] (ERG report, Section 3.4).

Safety data from all the COAST trials suggest that ixekizumab is well-tolerated by all patient subgroups. However, clinical advice to the ERG is that adverse events (AEs) arising from treatment with IL-17A inhibitors (such as ixekizumab and secukinumab) require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of biologic therapy related AEs, and that this can place a high burden on NHS staff and systems (ERG report, Section 3.5).

As highlighted in Section 3.7 of this ERG report, axSpA is a lifelong disease and the ERG notes that the clinical effectiveness evidence presented in the CS is relatively short term; the duration of the randomised phase of the COAST-V and COAST-W trials was 16 weeks with an extension phase up to 52 weeks, while for the COAST-X trial, the randomised phase was 52 weeks.

1.2.2 Indirect evidence

The company carried out NMAs to facilitate comparison of the effectiveness of ixekizumab versus the comparator drugs listed in the final scope issued by NICE. The company conducted base case and sensitivity NMAs for each patient population for the following outcomes: ASAS40, BASDAI50, BASDAI score cfb and BASFI score cfb. The base case NMAs only included studies known to be conducted in the relevant patient population. The sensitivity NMAs included all of the studies included in the base case NMAs and also studies with unclear or mixed populations. The ERG considers that the methods used by the company to conduct the NMAs were appropriate (ERG report, Section 3.6.2).

For patients with rad-axSpA, the relevant comparators were TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), secukinumab and established clinical practice (represented by placebo). For patients with nr-axSpA, the comparators were TNF alpha-inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab) and established clinical practice (represented by placebo). Clinical advice to the ERG is that established clinical practice is only an appropriate comparator for biologic-naive patients in the nr-axSpA population when TNF-alpha inhibitors are not tolerated or contraindicated, and only for biologic-experienced patients in the rad-axSpA and nr-axSpA populations when biological treatment options are exhausted.

Established clinical practice may not be an appropriate treatment for biologic-naïve patients in the rad-axSpA population, (even when TNF-alpha inhibitors are not tolerated or are contraindicated) as secukinumab is a treatment option for patients who cannot tolerate TNF-alpha inhibitors or for whom TNF-alpha inhibitors are contraindicated, or for biologic-

experienced patients as biologic-naïve patients will be offered a biological treatment (ERG report, Section 2.5).

Results from sensitivity NMAs: all patients

[redacted] (ERG report, Section 3.6.3).

Results from sensitivity NMAs: biologic-naïve patients

[redacted] (ERG report, Section 3.6.3).

Results from sensitivity NMAs: biologic-experienced patients

[redacted] (ERG report, Section 3.6.3).

For all populations, the ERG cautions that a comparison of base case and sensitivity NMA absolute effect results showed that, for some outcomes, there were large differences depending on which network had been used to inform the NMA. The ERG considers the absolute effect estimates generated by the base case NMAs are likely to be more reliable than those generated by the sensitivity NMAs as the risk of population heterogeneity is lower in the smaller network. The ERG does not consider that the absolute effect estimates generated by the sensitivity NMAs for BASDAI score cfb and BASFI score cfb in the biologic-naïve rad-axSpA population, or for BASDAI score cfb in the biologic-experienced rad-axSpA to be suitable for decision-making purposes (ERG report, Section 3.6.3).

It was not possible for the ERG to investigate the robustness of results from the sensitivity NMAs where there were no base case results available (ERG report, Section 3.6.3).

1.3 Summary of the key issues in the cost effectiveness evidence

The company was only able to generate cost effectiveness results for three populations: the biologic-naïve rad-axSpA, biologic-experienced rad-axSpA and biologic-naïve nr-axSpA populations. Further, due to an absence of evidence, it was not possible for the company to carry out any analyses to compare the cost effectiveness of ixekizumab versus secukinumab in any population.

The structure of the company models is similar to that of models used to inform previous NICE Technology Appraisals of TNF-alpha inhibitors of treatments for rad-axSpA and nr-axSpA (TA3831 and TA4072). The major issues, identified by the ERG, in relation to the company model are:

- Treatment sequencing was not modelled, nor were there sufficient data available to estimate the clinical effectiveness of sequential biological treatment use. Clinical advice to the ERG is that, in practice, patients receive may receive several lines of treatment (ERG report, Section 4.4.1).

- The relationship between BASDAI, BASFI and HRQoL is uncertain and complicated by the non-linear disease process which can include frequent flares for many patients (ERG report, Section 4.4.1).

- Clinical advice to the ERG is that the influence of biological treatments on radiographic change is uncertain. Variation in treatment effect could have important implications when estimating the relative cost effectiveness of different biological treatments (ERG report, Section 4.4.1).

- In the company models, patients are categorised as responders or non-responders based on BASDAI50 which is assessed at the end of a 12 (or 16) week trial period. In contrast, NICE guidelines suggest that response should be assessed by BASDAI change (BASDAI50 or BASDAI change from baseline of 2 points) and a change in pain visual analogue scale (VAS) of 2cm (ERG report, Section 4.5.3).

- The treatment trial period in the economic models is limited to 12 or 16 weeks. In contrast, in NHS clinical practice, a longer period may be used to assess response to treatment (ERG report, Section 4.5.4).

- Estimates of health care resource use are based on the experience of patients in three European countries and these data were collected more than 20 years ago. Clinical

advice to the ERG is that these data do not reflect current NHS care provision (ERG report, Section 4.5.5).

The ERG considers that these aspects are critical when assessing the cost effectiveness of treatments for axSpA. However, there is no alternative clinical evidence available and the company's choice of model structure means that it has not been possible to resolve any of these issues.

1.4 Summary of ERG's preferred assumptions and resulting ICER per QALY gained

The ERG does not have a preferred set of modelling assumptions but has presented the results from three scenarios that demonstrate how sensitive the incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) are to the incorporation of different modelling assumptions (ERG report, Section 4.6).

1. **BASFI scores after treatment discontinuation**

The amount by which a patient's BASFI score increases (i.e., function deteriorates) upon discontinuation of treatment is uncertain. The ERG presents the company's results using the 'rebound to natural history' assumption i.e., the patient returns to the level of function they would have had if they not received the biological treatment (ERG report, Section 4.6.1).

2. **Alternative estimates of utility**

In the company models, utility values were estimated based on regression equations developed from EQ-5D data collected in the COAST trials. Several published equations are also available and the ERG has presented the company's results using the regression equation that, on average, generates the lowest utility estimates (ERG report, Section 4.6.2).

3. **Nr-axSpA population clinical effectiveness estimates**

[redacted] Therefore, the ERG has presented a de novo scenario in which the magnitude of these outcomes does not vary by treatment (all are set to equal the effectiveness estimates associated with treatment with ixekizumab) (ERG report, Section 4.6.3).

1.5 Summary of ERG's preferred assumptions and resulting ICER per QALY gained

The ERG does not have a preferred set of modelling assumptions and has not presented a preferred ICER per QALY gained. The ERG considers the aspects that would have the biggest influence on the cost effectiveness estimates for ixekizumab versus any comparator are aspects that the ERG has been unable to test.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

Spondyloarthritis (SpA) encompasses a group of related inflammatory rheumatic conditions that can affect either the axial or peripheral joints.[1] Axial spondyloarthritis (axSpA) primarily affects the sacroiliac joints (the joints between the sacrum and the ilium bones of the pelvis) and the spine.[1] Physical symptoms include chronic back pain, stiffness, arthritis, enthesitis (inflammation of sites where a bone joins a tendon) and dactylitis (swelling of the fingers due to inflammation of the tendons and synovial sheaths).[1,2] Extra-articular symptoms include inflammatory bowel disease, uveitis (inflammation of the eye) and psoriasis.[2,3] AxSpA is also associated with co-morbidities, including cardiovascular disease, diabetes and osteoporosis,[4-6] and can lead to spinal deformaties.[7] Consequently, axSpA has been found to affect health-related quality of life (HRQoL).[7-9] Studies have shown that, compared with the general population, people with axSpA have increased risk of clinical depression (by 50% in men[7] and by 80% in women[7]) and mortality (by approximately 50%[5]). It has also been reported that 95% of people with axSpA are under 45 years old when their symptoms start[10] and, therefore, axSpA can have significant health[7,11] and economic[12,13] implications for patients during the most productive years of their life (company submission [CS], p22).

AxSpA can be considered to comprise two subtypes:[2]

1. radiographic axSpA (rad-axSpA), in which inflammatory changes of the sacroiliac joints can be detected via X-ray
2. non-radiographic axSpA (nr-axSpA), in which inflammatory changes of the sacroiliac joints are not detected via X-ray.

Rad-axSpA is more common in men than women, and nr-axSpA is equally common in both sexes.[3] Patients with nr-axSpA may subsequently develop rad-axSpA (approximately 10% of patients within 2 years, and approximately 50% of patients within 10 years[14,15]). Despite a lack of evidence of radiographic changes, patients with nr-axSpA report disease activity and functional impairments comparable to patients with rad-axSpA.[3,11]

The focus of this appraisal is on patients with rad-axSpA or nr-axSpA for whom non-steroidal anti-inflammatory drugs (NSAIDs) have been inadequately effective, are contraindicated or are not tolerated. Patients may have been previously treated with a tumour necrosis factor (TNF)-alpha inhibitor and/or interleukin (IL)-17A inhibitor (defined as biologic-experienced) or they may have received neither of these drugs (defined as biologic-naïve).

2.2 Company's overview of current service provision

As highlighted by the company (CS, p20), in non-specialist settings, axSpA is often misdiagnosed as mechanical lower back pain. Thus, in the UK, there is an average delay of 8.5 years between symptom onset and diagnosis, with only approximately 15% of patients receiving a diagnosis within 3 months of initial presentation.[16,17]

Following diagnosis, the conventional treatment recommended by the National Institute for Health and Care Excellence (NICE) for patients with axSpA is NSAIDs (at the lowest effective dose[18]) and physical therapies.[18] If an NSAID, taken at the maximum tolerated dose for 2 to 4 weeks, does not provide adequate pain relief, then switching to another NSAID should be considered.[18,19] Up to 40% of patients taking NSAIDs have an inadequate response to treatment or develop adverse events (AEs).[14,20,21] The AEs include renal and gastrointestinal toxicity.[2,5]

Following treatment with NSAIDs, a biologic therapy (TNF-alpha inhibitor and/or the IL-17A inhibitor, secukinumab) is recommended by NICE (Table 2);[14,18,21] the TNF-alpha inhibitors that may be prescribed are adalimumab, certolizumab pegol, etanercept, golimumab and infliximab. However, infliximab and secukinumab are only recommended treatment options for patients with rad-axSpA, they are not recommended for patients with nr-axSpA.[14,18,21]

Table 2 Biologic drugs recommended by NICE for treating axSpA*

Drug	Information on administration/dose	NICE TA report: axSpA subtype for whom treatment is recommended
TNF-alpha inhibitors		
Adalimumab	Subcutaneous injection: 40mg every other week	TA383[14] rad-axSpA and nr-axSpA
Certolizumab pegol	Subcutaneous injection: 400mg at weeks 0, 2 and 4200mg every other week or 400mg every 4 weeks	TA383[14] rad-axSpA and nr-axSpA
Etanercept	Subcutaneous injection: 25mg twice weekly or 50mg once per week	TA383[14] rad-axSpA and nr-axSpA
Golimumab	Subcutaneous injection: 50mg once per month	TA383[14] rad-axSpA TA497[22] nr-axSpA
Infliximab	Intravenous infusion: 5mg/kg infusion at weeks 0, 2 and 6, then every 6–8 weeks	TA383[14] rad-axSpA only
IL-17A inhibitor		
Secukinumab	Subcutaneous injection: 150mg once per week at weeks 0, 1, 2 and 3; followed by a maintenance dose once per month starting at week 4**	TA407[21] rad-axSpA only

nr-axSpA=non-radiographic axial spondyloarthritis; IL-17A=interleukin 17A; rad-axSpA=radiographic axial spondyloarthritis TA=technology assessment; TNF=tumour necrosis factor
*All drugs are treatment options following treatment with NSAIDs. All drugs (except those which have previously been used) are also potential treatment options following treatment with a TNF-alpha inhibitor
** As noted in the CS (Figure 2), in line with a recent licence extension, depending on their clinical response, patients treated with a 150mg dose of secukinumab in NHS clinical practice may have their dose up titrated to 300mg per month[23] but this dose has not been appraised for patients with rad-axSpA by NICE
Source: Information extracted from NICE guidance: TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (TA383);[14] Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors (TA407);[20] Golimumab for treating non-radiographic axial spondyloarthritis (TA497)[22]

When choosing a TNF-alpha inhibitor, NICE guidance (TA383[14]) states that the advantages and disadvantages of the treatments available should be discussed, particularly in light of any associated conditions such as extra-articular manifestations. Clinical advice to the ERG is that discussions about treatment choice also include method and frequency of treatment administration and possible AEs. The TA383[14] guidance advises that if more than one TNF-alpha inhibitor is considered suitable, the least expensive (taking into account administration costs and any Patient Access Scheme [PAS] discounts) should be chosen.[14] Moreover, as there are infliximab biosimilars available to the NHS, infliximab is recommended only if treatment is started with the least expensive infliximab product.[14] The ERG notes that since the publication of TA383,[14] biosimilar versions of etanercept and adalimumab have also become available.

After 12 weeks of treatment with a TNF-alpha inhibitor, or 16 weeks of treatment with secukinumab, treatment response is usually assessed and treatment only continued if a patient is found to be responding to treatment.[14,19,21]Treatment response is defined as a 50% reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score

(BASDAI50) compared with the pre-treatment value (or a reduction by ≥2 units) and a reduction in the spinal pain visual analogue scale (VAS) by ≥2cm.[14,19,21] Clinical advice to the ERG is that in the NHS, response to TNF-alpha inhibitors is assessed at 12 weeks and if adequate response criteria are not met, patients are reassessed at regular intervals up until 6 months.

If patients with rad-axSpA fail to respond to treatment with a TNF-alpha inhibitor they may receive treatment with a different TNF-alpha inhibitor.[14,19]Alternatively, they can receive secukinumab.[19,21]Patients who fail to respond to treatment with secukinumab may receive a TNF-alpha inhibitor.

If patients with nr-axSpA fail to respond to treatment with a TNF-alpha inhibitor, they may receive treatment with a different TNF-alpha inhibitor.[14,19]Secukinumab is not currently a recommended treatment option for patients with nr-axSpA.

Clinical advice to the ERG is that, in the process of trying to achieve adequate response, patients may be offered up to three biologic therapies in sequence and that more than three biologic therapies may be tried if a patient discontinues treatment due to AEs arising from treatment. However, advice to the ERG is that it is sometimes difficult to determine whether switching has been instigated due to a lack of efficacy or if it was due to the occurrence of AEs as the two reasons can be interconnected.

The ERG notes that the Assessment Group for TA383[14] (a multiple technology appraisal [MTA] of TNF-alpha inhibitors) analysed data from 12 registry studies and found that the proportions of patients who continued to take their first TNF-alpha inhibitor were approximately 70% to 80% after 1 year, 65% to 75% after 2 years, 70% after 3 years, and 55% after 5 years.[14]

The last step in the treatment pathway (CS, Figure 1) is surgery. As highlighted in the CS (p26), this relates to spinal deformity correction and should only be considered if the spinal deformity is significantly affecting HRQoL and is severe or progressing despite optimal non-surgical management, including physiotherapy.

2.3 Ixekizumab

As summarised by the company (CS, Table 2 and p22):

- Ixekizumab is a monoclonal antibody which selectively binds to IL-17A, preventing its binding to the IL-17 receptor and thereby reducing the inflammatory signalling that leads to the symptoms of axSpA[23]

- Ixekizumab has been shown to be efficacious and safe in psoriatic arthritis and plaque psoriasis and has a licence for use in these indications in the European Union[24]

- Ixekizumab is anticipated to be licensed for the treatment of adult patients with active rad-axSpA who have had an inadequate response to, or are intolerant to NSAIDs. Ixekizumab is also anticipated to be licensed for patients with active nr-axSpA defined as elevated C-reactive protein (CRP) and/or [evidence of sacroiliitis on] magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs

- Ixekizumab is expected to be a treatment option for patients who have not received a biologic treatment or are contraindicated to or who cannot tolerate TNF-alpha inhibitors, in addition to patients whose disease has not responded to treatment with a first TNF-alpha inhibitors, or whose disease has stopped responding after an initial response

- The anticipated ixekizumab dosing regimen is:

    - biologic-naïve: 80mg loading dose (LD) by subcutaneous injection (one injection) at Week 0, followed by 80mg every 4 weeks (Q4W)

    - biologic-experienced: 80mg LD or 160mg LD by subcutaneous injection (one or two injections) at clinician discretion at Week 0, followed by 80mg (one injection) Q4W

- Contraindications to ixekizumab are:

    - serious hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the Summary of Product Characteristics (SmPC)[24]

    - clinically important active infections such as active tuberculosis.

If recommended by NICE, ixekizumab may become the first IL-17A inhibitor available to patients with nr-axSpA (the NICE appraisal of secukinumab[27] for the treatment of patients with nr-axSpA is ongoing).

2.4 Number of patients eligible for treatment with ixekizumab

Given the lifelong nature of axSpA, the number of patients potentially eligible for treatment with ixekizumab can be estimated from prevalence data. However, as noted by the company (CS, p21), due to the difficulties associated with the diagnosis of axSpA, and the different

clinical classification criteria, estimates of axSpA prevalence vary. The company has estimated the number of patients potentially eligible for treatment with ixekizumab in its budget impact assessment (BIA) report. The summary BIA report estimates are provided in Table 3. Data provided in the BIA report (Tables 5 and 6) show that most patients with rad-axSpA are treated with adalimumab, etanercept or secukinumab (approximately [redacted], [redacted] and [redacted] respectively). Data in the BIA report (Table 7) also show that patients with nr-axSpA receive adalimumab (approximately [redacted]) or etanercept (approximately [redacted]). [redacted]

Table 3 Number of patients potentially eligible for treatment with ixekizumab

Population	Proportion	Number	Source/Assumption
Adult population, England and Wales		46,531,406	ONS (18+, mid-2018 estimate[25])
rad-axSpA			
Prevalence of rad-axSpA	0.238%	110,745	NICE Resource Impact Report (TA407)[26]
Proportion of patients with rad-axSpA who do not respond to conventional therapy	40.000%	44,298	NICE Resource Impact Report (TA407)[26]
Proportion of patients with rad-axSpA who do not respond to conventional therapy who go on to receive biologic therapy (biologic-naïve patients)	60.000%	26,579	NICE Resource Impact Report (TA407)[26]
Proportion of patients with rad-axSpA who do not respond to first-line biological treatment (biologic-experienced patients)	30.000%	7974	NICE TA407;[26] Lord 2010[20]
nr-axSpA			
Prevalence of nr-axSpA	0.150%	69,797	NICE Resource Impact Report (TA383)[27]
Proportion of patients with nr-axSpA who meet BSR guidelines for TNF-alpha inhibitor treatment	38.000%	26,523	NICE Resource Impact Report (TA383)[27]

BSR=British Society for Rheumatology; nr-axSpA=non-radiographic axial spondyloarthritis; ONS=Office for National Statistics; rad-axSpA=radiographic axial spondyloarthritis TA=technology assessment; TNF=tumour necrosis factor
Source: BIA report, Table 2

2.5 Critique of company's definition of the decision problem

A summary of the ERG's comparison of the decision problem outlined in the final scope[28] issued by NICE and that addressed within the CS is presented in Table 4.

Table 4 Comparison between the final scope issued by NICE and the decision problem addressed in the company submission

Parameter	Final scope issued by NICE (original wording)	Decision problem addressed in the company submission with rationale	ERG comment
Intervention	Ixekizumab	• Biologic-naïve patients: ixekizumab 80mg by SC injection (one injection) at Week 0, followed by 80mg every 4 weeks • Biologic-experienced patients: Ixekizumab 80mg or 160mg by SC injection (one or two injections – at clinician discretion) at Week 0, followed by 80mg (one injection) every 4 weeks	The company sought and presented evidence for the anticipated licensed doses of ixekizumab.
Population	People with axial spondyloarthritis for whom non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors have been inadequately effective or not tolerated, or are contraindicated.	As per scope	As highlighted by the company, clinical effectiveness evidence is not available for biologic-experienced nr-axSpA patients or for patients with contra-indications to TNF-alpha inhibitors. Evidence is presented for the following populations: biologic-naïve rad-axSpA, biologic-experienced rad-axSpA and biologic-naïve nr-axSpA

Parameter	Final scope issued by NICE (original wording)	Decision problem addressed in the company submission with rationale	ERG comment
Comparator(s)	**Radiographic axial spondyloarthritis** • TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) • IL-17A inhibitors (secukinumab) • Established clinical management without biological treatments **Non-radiographic axial spondyloarthritis** • TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab) • Established clinical management without biological treatments	As per scope	As highlighted by the company, the comparators for biologic-naïve patients are the same as those for biologic-experienced patients (comparators only differ between patients with rad-axSpA and patients with nr-axSpA). In the RCTs of ixekizumab (COAST-V, COAST-W and COAST-X), the comparator is placebo. The ERG accepts that placebo can be considered a proxy for established clinical management but only for biologic-naive patients in the nr-axSpA population when TNF-alpha inhibitors are not tolerated or contraindicated and for biologic-experienced patients in the rad-axSpA and nr-axSpA populations when biological treatment options are exhausted. Established clinical practice may not be an appropriate treatment for biologic-naïve patients in the rad-axSpA population, (even when TNF-alpha inhibitors are not tolerated or are contraindicated) as secukinumab is a treatment option. To compare ixekizumab with TNF-alpha inhibitors and secukinumab, NMAs were conducted. When conducting the NMAs, placebo was considered to be a proxy for established clinical management without biological treatments. The ERG considers that this approach is reasonable. Further information about the NMAs is presented in Section 3.6 of this ERG report.

Outcomes	The outcome measures to be considered include: • disease activity • functional capacity • disease progression • pain • peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) • adverse effects of treatment • health-related quality of life (HRQoL)	• Composite outcome (ASAS40[29]) • Disease activity (ASDAS<2.1, BASDAI50,[30] BASDAI score cfb) • Functional capacity (BASFI[30]) • Inflammation (SPARCC MRI spine and sacroiliac joint scores) • Pain (spinal pain from BASDAI question 2) • Adverse effects of treatment • HRQoL (SF-36 PCS[31]) Given the amount of clinical data to be presented for the three COAST trials, priority was given to outcomes presented in the economic model and presented for axSpA in prior NICE submissions. As such peripheral symptoms and extra-articular manifestations are not presented in the submission. The impact of ixekizumab on dactylitis, enthesitis and peripheral arthritis has previously been documented in the NICE appraisal of ixekizumab in psoriatic arthritis (TA537[32]). Similarly, the impact of ixekizumab on psoriasis has been documented in TA442.[33] Disease progression is additionally assessed in the economic analysis through modelling the link between BASFI and the mSASSS.	Along with the ASAS-HI,[34] the outcomes specified in the company's decision problem were also highlighted as being the most important outcomes in the professional organisation submission to NICE from the British Society for Rheumatology Spondyloarthritis Special Interest Group.[35] ASAS-HI data were collected in the COAST trials; results were not presented in the CS but were provided in the CSRs.[36-40] The outcomes from the NMAs are: • Composite outcome (ASAS40) • Disease activity (BASDAI50, BASDAI score cfb) • Functional capacity (BASFI) ASAS40 is the primary efficacy outcome from the COAST trials and clinical advice to the ERG is that this is a clinically meaningful outcome. In the COAST trials, ASAS40 was assessed at weeks 1, 2, 4, 8, 12 and 16. The primary endpoint of the COAST trials was the proportion of patients achieving an ASAS40 at Week 16. ASAS40 is not an outcome measure used in clinical practice nor was the company's cost effectiveness base case analysis informed by ASAS40 outcomes. The outcomes of peripheral symptoms and extra-articular manifestations are not addressed in the CS. Response to treatment in clinical practice is defined as achievement of a BASDAI50 response (or fall in BASDAI of ≥2 units), in addition to a reduction in the spinal pain VAS ≥2cm after 12 weeks (16 weeks for patients with a diagnosis of rad-axSpA who are treated with secukinumab).[4,14,19,20] While mean spinal pain NRS data are presented in the CS, data are not presented for the number of patients who achieved VAS ≥2cm, nor the number who achieved this in combination with the associated BASDAI criteria required for treatment response. ASAS40, BASDAI50, BASDAI score cfb and BASFI score cfb are the outcomes focussed on in Section 3 of this ERG report. BASDAI50, BASDAI score cfb and BASFI score cfb are the outcomes used to inform the company's cost effectiveness economic analyses.

Parameter	Final scope issued by NICE (original wording)	Decision problem addressed in the company submission with rationale	ERG comment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per scope	As specified in the final scope[28] issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per QALY gained. Outcomes were assessed over a lifetime horizon and costs were considered from an NHS perspective.
Subgroups to be considered	If the evidence allows the subgroups of people who have had or not had TNF-alpha inhibitors will be considered.	As per scope	

Parameter	Final scope issued by NICE (original wording)	Decision problem addressed in the company submission with rationale	ERG comment
Other considerations	The availability and cost of biosimilar products should be taken into account.	As per scope	In the company's cost effectiveness analyses, the costs of infliximab, etanercept and adalimumab have been estimated using the lowest price of the biosimilar drugs for each of these treatments. Ixekizumab, certolizumab pegol, golimumab and secukinumab are all available to the NHS at discounted PAS prices. The PAS prices for certolizumab pegol and golimumab are publicly available and are included, along with the confidential PAS for ixekizumab, in the company base case cost effectiveness analyses. The PAS price for secukinumab is confidential and is, therefore, not included in the company's analyses. The company has not identified any equity issues. The ERG considers that the company has (appropriately) not put forward a case for ixekizumab to be considered under NICE's End of Life treatment criteria.

ASAS40=Assessment of Ankylosing Spondylitis International Society 40 ASAS-HI= Assessment of Ankylosing Spondylitis International Society Health Index; ASDAS=Ankylosing Spondylitis Disease Activity Score; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; cfb=change from baseline; CSR=clinical study report; HRQoL=health related quality of life; IL-17A=interleukin 17A; MRI=magnetic resonance imaging; mSASSS=modified Stroke Ankylosing Spondylitis Spine Score; MRI=magnetic resonance imaging; NMA=network meta-analysis; nr-axSpA=non-radiographic axial spondyloarthritis; ONS=Office for National Statistics; PAS=Patient Access Scheme; QALY=quality adjusted life year; rad-axSpA=radiographic axial spondyloarthritis; RCT=randomised controlled trial; SC=subcutaneous; SPARCC=Spondyloarthritis Research Consortium of Canada; TA=technology assessment; TNF=tumour necrosis factor; VAS=visual analogue scale

Source: Final scope[28] issued by NICE, CS Table 1 and Section B.1.4

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the process and methods used by the company to identify and select the clinical evidence relevant to ixekizumab are presented in Appendix D to the CS. Overall, the ERG considers that these process and methods were generally satisfactory (Table 5).

Table 5 ERG appraisal of systematic review methods

Review process	ERG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix D.1.2, Table 11
Were appropriate sources searched?	Yes	Sources included MEDLINE, Embase, the Cochrane Library and searches of trial registries for ongoing trials. Manual searches of abstracts from conference proceedings were also conducted
Was the timespan of the searches appropriate?	Yes	Searches were conducted in November 2016 and updated in February 2019
Were appropriate search terms used?	Yes	No additional ERG comments
Were the eligibility criteria appropriate to the decision problem?	Partially	The ERG questioned (via the clarification process) the company's a priori exclusion of pilot studies, phase I/II studies and open-label studies from the NMAs. The ERG's critique of the company's response is discussed in Section 3.6 of this ERG report
Was study selection applied by two or more reviewers independently?	Yes	This improves the accuracy of study selection and reduces study selection bias
Was data extracted by two or more reviewers independently?	Unclear	Details about how data from studies included in the clinical effectiveness review were extracted are not reported. However, equivalent details about how data were extracted for the cost effectiveness, HRQoL, cost and healthcare resource identification, measurement and valuation reviews are provided in Appendix G.1.2, Appendix H.1.2 and Appendix I.1.2 to the CS; in all cases, data from studies included in these reviews were extracted by one reviewer and quality checked by another
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	The company conducted a quality assessment exercise using the University of York Centre for Reviews and Dissemination guidance[44] (CS, Table 13 and Appendix D.1.8, Table 44 and Table 45)
Was the quality assessment conducted by two or more reviewers independently?	Unclear	Responsibility for quality assessment was not reported in the CS
Were attempts to synthesise evidence appropriate?	Yes	NMAs were required to facilitate a comparison of ixekizumab with all appropriate comparators. For full details of the NMAs, see Sections 3.6 of this ERG report

HRQoL=health-related quality of life; NMA=network meta-analysis
Source: LRiG in-house checklist

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

3.2.1 Included trials

Three randomised controlled trials (RCTs) that provide clinical effectiveness evidence of ixekizumab versus placebo were identified, namely the COAST-V,[36,39,41] COAST-W[37,40,42] and COAST-X trials.[38,43] The ERG considers that the placebo treatment in the three COAST trials can be considered to be a proxy for established 'clinical management without biological treatments'.

To compare the clinical effectiveness of treatment with ixekizumab versus biological treatments listed in the final scope[28] issued by NICE, the company conducted NMAs. The NMAs were conducted for patients with rad-axSpA or nr-axSpA who had received previous treatment with biologic drugs (biologic-experienced) or had not received previous treatment with biologic drugs (biologic-naïve). Bibliographic details of the trials included in the company's NMAs and the associated sensitivity analyses are listed in Appendix 6.1 of this ERG report. The ERG's critique and discussion of the company's NMAs are presented in Section 3.6 of this ERG report.

Characteristics of the included trials of ixekizumab

The key characteristics of the COAST-V, COAST-W and COAST-X trials are summarised in Table 6.

All three COAST trials are phase III, international, double-blind, placebo-controlled trials. [redacted] Clinical advice to the ERG is that the treatment of axSpA in Europe may not be comparable to the treatment of axSpA in the NHS.

Each of the COAST trials recruited a different patient population. The COAST-V trial recruited biologic-naïve patients with rad-axSpA, the COAST-W trial recruited biologic-experienced patients with rad-axSpA and the COAST-X trial recruited biologic-naïve patients with nr-axSpA.

The COAST-V and COAST-W trials consisted of a 16-week treatment phase and a 36-week extension phase. The COAST-X trial consisted of a randomised treatment period of 52 weeks. During the 16-week treatment phase patients in the COAST-W and COAST-X trials were randomised to receive treatment with ixekizumab 80mg Q2W, ixekizumab 80mg Q4W or

placebo. In addition, patients within the Q2W and Q4W arms were also randomised to receive a LD of ixekizumab, either 80mg or 160mg. The dosing schedule for patients in the placebo arm was Q2W.

The design of the COAST-V trial was the same as that of the COAST-W and COAST-X trials, except that patients were randomised to receive treatment with ixekizumab 80mg Q2W, ixekizumab 80mg Q4W, placebo or adalimumab (40mg Q2W). The purpose of the adalimumab treatment arm (CS, p34) was to provide a reference to the placebo arm and the company highlights (CS, p32) that the trial was not powered to statistically test for differences between treatment with adalimumab and ixekizumab.

Clinical advice to the ERG is that some patients treated in the NHS do not achieve an adequate response to TNF-alpha inhibitor drugs after 12 weeks of treatment; however, they may have a good response after a further 6 weeks of treatment. Likewise, some patients treated with IL-17A inhibitors may not achieve an adequate response after 16 weeks of treatment; however, a good response may be achieved after a further 6 weeks of treatment. Clinical advice to the ERG is that treatment outcomes measured at 6 months (26 weeks) might better reflect the outcomes of patients treated in the NHS.

During the extension period (Week 16 to Week 52) of the COAST-V and COAST-W trials, patients receiving ixekizumab continued to receive treatment according to their randomised assignment. All other patients were randomised to receive ixekizumab, either 80mg Q2W or 80mg Q4W, with a LD of 160mg.

During the extension period (Week 16 to Week 36) of the COAST-X trial, patients continued to receive treatment according to their randomised assignment. In the COAST-X trial, patients who were considered by the investigator to be non-responders could be administered a ‘rescue treatment’ of ixekizumab at a dose of 80mg Q2W (LD 80mg).

Anticipated licensed dose of ixekizumab

The company anticipates (CS, Table 2) that the licensed dose of ixekizumab for patients with rad-axSpA and nr-axSpA not previously treated with TNF-alpha inhibitors, will be 80mg Q4W, with a LD of 80mg. For patients previously treated with TNF-alpha inhibitors, the company anticipates that the licensed dose will be 80mg Q4W with a LD of 80mg or 160mg. The ERG notes (Table 6), that within the COAST trials, not all patients were treated with the doses of ixekizumab that are likely to be licensed.

The company considers (CS, p149) that if ixekizumab is recommended for use in the NHS, then it is most likely that patients previously treated with TNF-alpha inhibitors will be treated

with a LD of 160mg (49 patients received this dosing regimen). Clinical advice to the ERG supports this opinion.

Table 6 Key characteristics of the COAST-V, COAST-W and COAST-X trials

Trial parameters	COAST-V	COAST-W	COAST-X
Design	International, phase III, multi-centre, double-blind RCT with active control and placebo control	International, phase III, multi-centre, double-blind placebo controlled RCT	International, phase III, multi-centre, double-blind placebo controlled RCT
Number of patients and setting	N=341 Czech Republic, Germany, [redacted], the Netherlands, [redacted], Japan, South Korea, [redacted], Taiwan, USA	N=316 Argentina, Brazil, Canada, Finland, France, Germany, Israel, Italy, Republic of Korea, Mexico, Netherlands, Poland, Spain, UK, USA	N=303 Argentina, Austria, Brazil, Canada, Czech Republic, Finland, Germany, Japan, Republic of Korea, Mexico, Netherlands, Poland, Romania, Russian Federation, USA
Patient population	• Adults with rad-axSpA fulfilling ASAS criteria • Received ≥12 weeks therapy for axSpA • Inadequate response to, or intolerant of NSAIDs • No prior TNF-alpha inhibitors	• Adults with rad-axSpA fulfilling ASAS criteria • Received ≥12 weeks therapy for axSpA • Inadequate response to, or intolerant of NSAIDs and TNF-alpha inhibitors	• Adults with nr-axSpA fulfilling ASAS 2009 criteria who show sacroiliitis on MRI or elevated CRP • Received ≥12 weeks therapy for axSpA • Inadequate response to, or intolerant of NSAIDs • No prior TNF-alpha inhibitors
Design and trial treatments	Week 0 to Week 16 • Ixekizumab -80mg Q2W+LD 80mg (n=45) -80mg Q2W+LD 160mg (n=38) -80mg Q4W+LD 80mg (n=42) -80mg Q4W+LD 160mg (n=39) • Adalimumab 40mg Q2W (n=90) • Matched placebo Q2W (n=87) Week 16 to Week 52 • Patients in the ixekizumab arm continued with assigned treatments • Patients in the adalimumab and placebo arms were randomised to treatment with ixekizumab (80mg Q2W or 80mg Q4W). The LD of ixekizumab was 160mg Week 52 onwards Optional 2-year extension study	Week 0 to Week 16 • Ixekizumab -80mg Q2W+LD 80mg (n=48) -80mg Q2W+LD 160mg (n=50) -80mg Q4W+LD 80mg (n=60) -80mg Q4W+LD 160mg (n=54) • Matched placebo Q2W (n=104) Week 16 to Week 52 • Patients in the ixekizumab arm continued with assigned treatments • Patients in the placebo arm were randomised to treatment with ixekizumab (80mg Q2W or 80mg Q4W). The LD of ixekizumab was 160mg Week 52 onwards Optional 2-year extension study	Week 0 to Week 16 • Ixekizumab -80mg Q2W+LD 80mg (n=50) -80mg Q2W+LD 160mg (n=52) -80mg Q4W+LD 80mg (n=47) -80mg Q4W+LD 160mg (n=49) • Matched placebo Q2W (n=105) Week 16 to Week 52 • Patients continued with assigned treatments • Patients identified as inadequate responders could be administered a rescue treatment of ixekizumab 80 mg Q2W (80 mg LD). Week 52 onwards Optional 2-year extension study

Trial parameters	COAST-V	COAST-W	COAST-X
Primary outcome	Proportion of patients achieving ASAS40 response at Week 16	Proportion of patients achieving ASAS40 response at Week 16	Proportion of patients achieving ASAS40 response at Week 16
Company base-case	Ixekizumab 80mg Q4W+80mg LD	Ixekizumab 80mg Q4W+160mg LD	Ixekizumab 80mg Q4W+80mg LD
Expected licensed dose	Ixekizumab 80mg Q4W+80mg LD	Ixekizumab 80mg Q4W+80mg or 160mg LD	Ixekizumab 80mg Q4W+80mg LD
ERG comment	[redacted] • The trial was not powered to statistically test for differences between adalimumab and ixekizumab • Only 42 patients randomised to ixekizumab received the anticipated licensed dosing regimen of 80mg Q4W+80mg LD	[redacted] • Only 114 of the patients randomised to ixekizumab received the anticipated licensed dosing regimen of 80mg Q4W with a LD of 80mg or 160mg • The company considers that in the NHS, most patients will receive a LD of 160mg	[redacted] • Only the 47 patients randomised to ixekizumab received the anticipated licensed dosing regimen of 80mg Q4W+80mg LD

ASAS=Assessment of Ankylosing Spondylitis International Society; CRP=C-reactive protein; LD=loading dose; MRI=magnetic resonance imaging; nr-axSpA=non-radiographic ankylosing spondylitis; NSAID=non-steroidal anti-inflammatory drug; rad-axSpA=radiographic ankylosing spondylitis; TNF=tumour necrosis factor; Q2W=every 2 weeks; Q4W=every 4 weeks; RCT=randomised controlled trial; vs=versus
Source: Adapted from Table 3 and Table 11 of the CS

Baseline characteristics of patients recruited to the ixekizumab trials

The baseline characteristics of patients recruited to the included trials are presented in the CS in Table 8 (COAST-V), Table 9 (COAST-W) and Table 10 (COAST-X). Clinical advice to the ERG is that the patients in the COAST trials are generally representative of patients treated in the NHS. The ERG agrees with the company (CS, p41) that, within each trial, patient baseline characteristics were well-balanced across the trial arms.

3.2.2 Risk of bias assessment in the COAST trials

The company conducted a quality assessment of the COAST-V, COAST-W and COAST-X trials using the University of York Centre for Reviews and Dissemination guidance[44] (CS, Table 13). The ERG agrees with the company that the risk of bias is low for the COAST-V, COAST-W and COAST-X trials.

3.2.3 Statistical approach adopted for the trials of ixekizumab

Information relevant to the statistical approach taken by the company has been extracted from the trial statistical analysis plans (TSAPs),[44-46] clinical study reports (CSRs),[36-40] and from the CS. A summary of the additional checks made by the ERG in relation to the pre-planned statistical approach used by the company to analyse data from the included trials is provided in Table 7. Having carried out these checks, the ERG is satisfied with the pre-planned statistical approach employed by the company.

Table 7 ERG assessment of statistical approaches used in the ixekizumab trials

Item	ERG assessment	Statistical approach with ERG comments
Were all analysis populations clearly defined and pre-specified?	Yes	The definitions of all study populations analysed in the COAST-V, -W and -X trials are presented in Table 12 of the CS. The ERG is satisfied that these analysis populations were pre-specified in the TSAPs (COAST-V trial TSAP, pp22-23; COAST-W trial TSAP, pp22-23; COAST-X trial TSAP, pp19-20)
Was an appropriate sample size calculation pre-specified?	Yes	The sample size calculations for the COAST-V, -W and -X trials are provided in Table 100 of Appendix L to the CS. The ERG is satisfied that these sample size calculations are appropriate and were pre-specified in the TSAPs (COAST-V trial TSAP, p16; COAST-W trial TSAP, p16; COAST-X trial TSAP, p17)
Were all protocol amendments made prior to analysis?	Yes	Protocol amendments are listed in: • COAST-V trial Week 16 CSR (p101) • COAST-V trial Week 16 and Week 52 CSR (pp95-96) • COAST-W trial Week 16 and Week 52 CSR (pp93-94) • COAST-X trial Week 16 and Week 52 CSR (pp156-157) The first data cut-off dates were: COAST-V trial, 31st Jan 2018 (analysis of Week 16 data); COAST-W trial, 19th Jun 2018 (analysis of Week 16 data); COAST-X trial, 1st Apr 2019 (analysis of Week 16 and Week 52 data). Protocol amendments in all trials were made prior to the date of the first data cut. Amendments were, therefore, not driven by results from the analyses. In the COAST-V trial, the only change in the planned analyses after 31st Jan 2018 was the addition of a post-hoc analysis of the percentage of patients achieving ASDAS <2.1. There were no changes in the planned analyses of data from the COAST-W trial after 19th Jun 2018, or the COAST-X trial after 1st Apr 2019
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	In the CS, results are presented for the primary efficacy outcome in each of the COAST trials, ASAS40, and for the following key secondary efficacy outcomes: BASDAI, BASDAI50, ASDAS <2.1, BASFI, spinal pain NRS score and SPARCC sacroiliac and spine scores. Definitions for each of these outcomes are provided in the CS (Table 7). The analysis approach for the primary and secondary efficacy outcomes is reported in Appendix L to the CS (Table 100). The company employed a graphical multiple testing procedure for each of the COAST trials to control the family-wise type I error rate at a 2-sided α level of 0.05 (COAST-V trial Week 16 CSR, pp77-81; COAST-W trial Week 16 CSR, pp77-81; COAST-X trial Week 16 and Week 52, p124). The ERG is satisfied that the primary and secondary efficacy outcome definitions and analysis approaches were pre-specified in the TSAPs (COAST-V trial TSAP, pp30-34, 42-70; COAST-W trial TSAP, pp30-34, 42-71; COAST-X trial TSAP, pp31-37, 46-70) and that the definitions and analysis approaches are appropriate
Was the analysis approach for HRQoL outcomes appropriate and pre-specified?	Yes	In the COAST-V, -W and –X trials, HRQoL was measured using the SF-36 PCS and the EQ-5D-5L questionnaire. The ERG is satisfied that appropriate analysis approaches for SF-36 PCS and EQ-5D-5L were pre-specified in the TSAPs for each of the COAST trials (COAST-V trial TSAP, pp74-82, 133; COAST-W trial TSAP, pp75-85, 138; COAST-X trial TSAP, pp74-81, 136)

Item	ERG assessment	Statistical approach with ERG comments
Was the analysis approach for AEs appropriate and pre-specified?	Yes	In the COAST-V, -W and –X trials, the safety of ixekizumab was assessed through evaluations of TEAS, SAEs, AESIs, and rates and reasons for discontinuation (CS, p109). The ERG is satisfied that an appropriate analysis approach for AEs was pre-specified in the TSAPs for each of the COAST trials (COAST-V TSAP, pp85-98; COAST-W TSAP, pp88-102; COAST-X TSAP, pp84-98)
Was a suitable approach employed for handling missing data?	Yes	The approaches used to handle missing data in the COAST-V, -W and -X trials are provided in Table 100 of Appendix L to the CS. The ERG is satisfied that the approaches used were appropriate
Were all subgroup and sensitivity analyses pre-specified?	Yes	The company summarises results from subgroup analyses for ASAS40 for various demographic and baseline characteristics for each of the COAST trials (CS, Table 52). Full results for the analyses where statistically significant subgroup effects (p<0.1) were observed are provided in the CSRs (COAST-V trial Week 16 CSR, Table RHBV.14.71; COAST-W trial Week 16 CSR, Table RHBW.14.68; COAST-X trial Week 16 and Week 52 CSR, Table RHBX.14.106). For subgroup analyses, a pre-specified list of the demographic and baseline characteristics of interest was provided in the TSAPs for each of the COAST trials (COAST-V trial TSAP, pp115-116; COAST-W trial TSAP, pp120-121; COAST-X trial TSAP, pp116-118) The company does not present results of sensitivity analyses for any of the COAST trials in the CS

AE=adverse event; AESI=adverse event of special interest; ASAS=Assessment of SpondyloArthritis International Society; ASDAS=Ankylosing Spondylitis Disease Activity Score; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; CSR=clinical study report; EQ-5D-5L=EuroQol-five dimensions-five levels; HRQoL=health-related quality of life; NRS=numeric rating score; PCS=physical component summary; SAE=serious adverse event; SF-36=Short Form-36; SPARCC=Spondyloarthritis Research Consortium of Canada; TEAE=treatment-emergent adverse event; TSAP=trial statistical analysis plan
Source: CS, COAST-V trial TSAP, COAST-W trial TSAP, COAST-X trial TSAP, COAST-V trial Week 16 CSR, COAST-V trial Week 16 and Week 52 CSR, COAST-W trial Week 16 CSR, COAST-W trial Week 16 and Week 52 CSR, COAST-X trial Week 16 and Week 52 CSR, and ERG comment
Source: ERG in-house checklist

3.3 Efficacy results from the trials of ixekizumab

The primary outcome of all three COAST trials was the proportion of patients achieving an ASAS40 response at Week 16. Results for the primary outcome and three key secondary outcomes (BASDAI50, BASDAI score change from baseline [cfb], and BASFI score cfb) are presented in this section. Clinical advice to the ERG is that these four outcomes are clinically important. Data relating to the three key secondary outcomes are used in the company's economic models. Results for other secondary outcomes from the three COAST trials (ASDAS score <2.1, Spondyloarthritis Research Consortium of Canada MRI score cfb and spinal pain NRS [numeric rating scale] score cfb) are presented in the CS.

Throughout this section, results are presented for patients in the COAST trials who received ixekizumab Q4W. Results for patients in the COAST trials who received ixekizumab Q2W are available in the CS but are not presented in this ERG report. Furthermore, since the COAST-V trial was not powered to statistically test for differences between treatment with ixekizumab and treatment with adalimumab, clinical effectiveness results for patients treated with adalimumab are provided in the CS.

3.3.1 Week 16 data

Results for ASAS40, BASDAI50, BASDAI score cfb and BASFI score cfb at Week 16 in each of the COAST trials are presented in Table 8 to Table 11.

Table 8 ASAS40 response for the ITT population with non-responder imputation, COAST-V, COAST-W and COAST-X trials, Week 16

Dosing schedule	Response, n (%)	Difference versus placebo or 80mg LD, % (95% CI)	p-value
COAST-V			
PBO (N=87)	**16 (18.4)**	**-**	**-**
IXE Q4W (N=81)	**39 (48.1)**	**29.8 (16.2 to 43.3)**	**<0.0001[a]**
IXE Q4W 80mg LD ([redacted])	[redacted]	-	-
IXE Q4W 160mg LD (n[redacted])	[redacted]	[redacted]	[redacted]
COAST-W			
PBO (N=104)	**13 (12.5)**	**-**	**-**
IXE Q4W (N=114)	**29 (25.4)**	**12.9 (2.7 to 23.2)**	**0.017[a]**
IXE Q4W 80mg LD ([redacted])	[redacted]	-	
IXE Q4W 160mg LD (n[redacted])	[redacted]	[redacted]	[redacted][b]
COAST-X			
PBO (N=105)	**20 (19.0)**	**-**	**-**
IXE Q4W (N=96)	**34 (35.4)**	[redacted]	**0.0094[a]**
IXE Q4W 80mg LD ([redacted])	[redacted]	-	-
IXE Q4W 160mg LD ([redacted])	[redacted]	[redacted]	[redacted][b]

Notes: emboldened text used for thePBO arm and pooled loading doses for the IXE arm
[a] p-value compared to PBO
[b] p-value compared to 160mg and 80mg LD
ASAS=Assessment of Spondylo Arthritis International Society; CI=confidence interval; ITT=intention-to-treat; IXE=ixekizumab; LD=loading dose; PBO=placebo; Q4W=every 4 weeks
Source: Adapted from CS, Table 14, Table 28, Table 43 and Table 44

Table 9 BASDAI50 response in the ITT population, with non-responder imputation, COAST-V, COAST-W and COAST-X, Week 16

Treatment arm	Response, n (%)	Difference versus PBO, % (95% CI)	p-value
COAST-V			
PBO (N=87)	15 (17.2)	-	-
IXE Q4W (N=81)	34 (42.0)	24.7 (11.4 to 38.1)	0.0003
COAST-W			
PBO (N=104)	[redacted]	-	-
IXE Q4W (N=114)	[redacted]	[redacted]	[redacted]
COAST-X			
PBO (N=105)	[redacted]	-	-
IXE Q4W (N=96)	[redacted]	[redacted]	[redacted]

BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; CI=confidence interval; ITT=intention-to-treat; IXE=ixekizumab; PBO=placebo; Q4W=every 4 weeks
Source: Adapted from CS, Table 16, Table 30 and Table 45

Table 10 BASDAI score least squares mean cfb in the ITT population, MMRM, COAST-V, COAST-W and COAST-X, Week 16

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p−value
COAST-V			
PBO (N=[redacted])	[redacted]	–	–
IXE Q4W (N=[redacted])	[redacted]	[redacted]	[redacted]
COAST-W			
PBO (N=[redacted])	[redacted]	-	-
IXE Q4W (N=[redacted])	[redacted]	[redacted]	[redacted]
COAST-X			
PBO (N=[redacted])	−1.51 (0.22)	-	-
IXE Q4W (N=[redacted])	−2.18 (0.22)	−0.67 (−1.28 to −0.06)	0.031

For the Ns, the ERG here uses the number of patients included in the analysis (as reported in COAST-V Week 16 CSR Table RHBV.14.32, COAST-W Week 16 CSR Table RHBW.14.32 and COAST-X CSR Table RHBX.14.38), rather than the number of patients randomised to each treatment arm (as presented in the CS, Table 17, Table 31 and Table 46).
BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; cfb=change from baseline; CI=confidence interval; CSR=clinical study report; ITT=intention-to-treat; IXE=ixekizumab; LSM=least squares mean; MMRM=mixed models repeated measure analysis; PBO=placebo; Q4W=every 4 weeks; SE=standard error
Source: Adapted from CS, Table 17, Table 31 and Table 46; COAST-V Week 16 CSR Table RHBV.14.32; COAST-W Week 16 CSR Table RHBW.14.32; COAST-X CSR Table RHBX.14.38

Table 11 BASFI score least squares mean cfb in the ITT population, MMRM, COAST-V, COAST-W, and COAST-V, Week 16

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p-value
COAST-V			
PBO (N=[redacted])	−1.16 (0.22)	-	-
IXE Q4W (N=[redacted])	−2.39 (0.22)	−1.22 (−1.83 to −0.62)	<0.0001
COAST-W			
PBO (N=[redacted])	[redacted]	-	-
IXE Q4W (N=[redacted])	[redacted]	[redacted]	[redacted]
COAST-X			
PBO (N=[redacted])	−1.34 (0.23)	-	-
IXE Q4W (N=[redacted])	−2.01 (0.23)	−0.67 (−1.31; 0.03)	0.040

For the Ns, the ERG here uses the number of patients included in the analysis (as reported in COAST-V Week 16 CSR Table RHBV.14.28, COAST-W Week 16 CSR Table RHBW.14.28 and COAST-X CSR Table RHBX.14.48), rather than the number of patients randomised to each treatment arm (as presented in the CS, Table 22, Table 36 and Table 48).
BASFI=Bath Ankylosing Spondylitis Functional Index; cfb=change from baseline; CI=confidence interval; CSR=clinical study report; ITT=intention-to-treat; IXE=ixekizumab; LSM=least squares mean; MMRM=mixed models repeated measure analysis; PBO=placebo; Q4W=every 4 weeks; SE=standard error
Source: Adapted from CS, Table 22, Table 36 and Table 48; COAST-V Week 16 CSR, Table RHBV.14.28; COAST-W Week 16 CSR Table RHBW.14.28; COAST-X CSR Table RHBX.14.48

[redacted] (Table 8 of this ERG report; Appendix D to the CS, Table 101 to Table 108, Figure 35 and Figure 36).

Most outcomes were [redacted] in the ixekizumab Q4W arm (pooled 80mg and 160mg LDs) in comparison to the placebo arm by [redacted] in the trials; statistical significance was reached for all outcomes by [redacted] (CS, pp55-79).

3.3.2 Week 52 data

COAST-V and COAST-W trials

At Week 16 in the COAST-V and COAST-W trials, all patients from the placebo arm were randomised to receive either ixekizumab Q2W or ixekizumab Q4W. It is, therefore, not possible to compare ixekizumab Q4W with placebo at Week 52 in either of these trials; it is, however, possible to compare outcomes for patients treated with ixekizumab at Week 52 with those at Week 16. The results for ASAS40, BASDAI50, BASDAI score cfb and BASFI score cfb at Week 52 in the COAST-V and COAST-W trials are presented in Table 12 to Table 15.

Table 12 ASAS40 response in the ITT population who were initially randomised to ixekizumab Q4W, with non-responder imputation, COAST-V and COAST-W, Week 52

Treatment arm	Response, n (%)	95% CI for response rate (%)
COAST-V		
IXE Q4W ([redacted])	[redacted]	[redacted]
COAST-W		
IXE Q4W ([redacted])	[redacted]	[redacted]

ASAS=Assessment of SpondyloArthritis International Society; CI=confidence interval; ITT=intention-to-treat; IXE=ixekizumab; Q4W=every 4 weeks
Source: Adapted from CS, Table 15 and Table 29

Table 13 BASDAI50 response in the ITT population who were initially randomised to ixekizumab Q4W, with non-responder imputation, COAST-V and COAST-W, Week 52

Treatment arm	Response, n (%)	95% CI for response rate (%)
COAST-V		
IXE Q4W ([redacted])	[redacted]	[redacted]
COAST-W		
IXE Q4W ([redacted])	[redacted]	[redacted]

BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; CI=confidence interval; ITT=intention-to-treat; IXE=ixekizumab; Q4W=every 4 weeks
Source: Adapted from CS, Table 18 and Table 32

Table 14 BASDAI score mean change from baseline in the ITT Population who were originally randomised to receive ixekizumab, mBOCF, COAST-V and COAST-W, Week 52

Treatment arm	Cfb, mean (SD)
COAST-V	
IXE Q4W ([redacted])	[redacted]
COAST-W	
IXE Q4W ([redacted])	[redacted]

BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; cfb=change from baseline; ITT=intention-to-treat; IXE=ixekizumab; mBOCF=modified baseline observation carried forward; Q4W=every four weeks; SD=standard deviation.
Source: Adapted from CS, Table 19 and Table 33

Table 15 BASFI score mean change from baseline in the ITT Population who were originally randomised to receive ixekizumab, mBOCF, COAST-V and COAST-W, Week 52

Treatment arm	Cfb, mean (SD)
COAST-V	
IXE Q4W ([redacted])	[redacted]
COAST-W	
IXE Q4W ([redacted])	[redacted]

BASFI=Bath Ankylosing Spondylitis Functional Index; cfb=change from baseline; ITT=intention-to-treat; IXE=ixekizumab; mBOCF=modified baseline observation carried forward; Q4W=every four weeks; SD=standard deviation.
Source: Adapted from CS, Table 23 and Table 37

A comparison of the results in Table 12 and Table 13 with those in Table 8 and Table 9, shows that ASAS40 and BASDAI50 response rates were [redacted] for the ixekizumab Q4W arm in both the COAST-V and COAST-W trials. Similarly, a comparison of the results in Table 14 and Table 15 with those in Table 10 and Table 11, shows that treatment with ixekizumab leads to [redacted] in BASDAI score and BASFI score up to Week 52.

COAST-X trial

As described in Section 3.2.1, in the COAST-X trial, from Week 16 to Week 52, any patient who was deemed to be an inadequate responder by investigators could receive rescue treatment with ixekizumab 80mg Q2W. Patients who received rescue treatment were analysed as non-responders in the analysis of ASAS40 and BASDAI50 response data for Week 52 of the COAST-X trial (Appendix L to the CS, Table 100). For BASDAI score cfb and BSFI score cfb, missing data were imputed using the modified baseline observation carried forward (mBOCF) method. For patients who received rescue treatment, [redacted] (Appendix L to the CS, Table 100). The results fo the ASAS40, BASDAI50, BASDAI score cfb and BASFI score cfb at Week 52 in the COAST-X trial are presented in Table 16 to Table 19.

Table 16 ASAS40 response for the ITT population with non-responder imputation, COAST-X, Week 52

Dosing schedule	Response rate, n (%)	Percentage difference versus PBO or 80mg LD, (95% CI)	p-value
PBO (N=105)	**14 (13.3)**	**-**	**-**
IXE Q4W (N=96)	**29 (30.2)**	[redacted]	**0.0045[a]**
IXE Q4W 80mg LD ([redacted])	[redacted]	-	-
IXE Q4W 160mg LD ([redacted])	[redacted]	[redacted]	[redacted][b]

Notes: emboldened text used for the PBO arm and pooled loading doses for the IXE arm
[a] p-value comparing to PBO
[b] p-value comparing 160mg and 80mg LD
ASAS=Assessment of Ankylosing Spondylitis International Society; CI=confidence interval; CRP=C-reactive protein; ITT=intention-to-treat; IXE=ixekizumab; MRI=magnetic response imaging; PBO=placebo; Q4W=every 4 weeks
Source: Adapted from CS, Table 43 and COAST-X CSR, Table RHBX.14.103

Table 17 BASDAI50 response for the ITT population with non-responder imputation, COAST-X, Week 52

Dosing schedule	Response rate, n (%)	Percentage difference versus PBO (95% CI)	p-value
PBO (N=105)	[redacted]	-	-
IXE Q4W (N=96)	[redacted]	[redacted]	[redacted]

BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; CI=confidence interval; ITT=intention-to-treat; IXE=ixekizumab; PBO=placebo; Q4W=every 4 weeks
Source: Adapted from CS, Table 45

Table 18 BASDAI least squares mean cfb in the ITT population, COAST-X, Week 52 (mBOCF, ANCOVA)

Treatment arm	Cfb, LSM (SE)	Difference versus PBO, (95% CI)	p-value
PBO (N=[redacted])	[redacted]	-	-
IXE Q4W (N=[redacted])	[redacted]	[redacted]	[redacted]

For the Ns, the ERG here uses the number of patients included in the analysis (as reported in the COAST-X CSR Table RHBX.14.39), rather than the number of patients randomised to each treatment arm (as presented in the CS, Table 46)
ANCOVA=analysis of covariance; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; cfb=change from baseline; CI=confidence interval; CSR=clinical study report; ITT=intention-to-treat; IXE=ixekizumab; LSM=least squares mean; mBOCF=modified baseline observation carried forward; PBO=placebo; Q4W=every 4 weeks; SE=standard error
Source: Adapted from CS, Table 46; COAST-X CSR, Table RHBX.14.39

Table 19 BASFI least squares mean cfb in the ITT population, COAST-X, Week 52 (mBOCF ANCOVA)

Treatment arm	Cfb, LSM (SE)	Difference versus PBO (95% CI)	p−value
Week 52, mBOCF			
PBO (N=[redacted])	[redacted]	-	-
IXE Q4W (N=[redacted])	[redacted]	[redacted]	[redacted]

For the Ns, the ERG here uses the number of patients included in the analysis (as reported in the COAST-X CSR Table RHBX.14.49), rather than the number of patients randomised to each treatment arm (as presented in the CS, Table 48)
ANCOVA=analysis of covariance; BASFI=Bath Ankylosing Spondylitis Functional Index; cfb=change from baseline; CI=confidence interval; CSR=clinical study report; ITT=intention-to-treat; IXE=ixekizumab; LSM=least squares mean; mBOCF=modified baseline observation carried forward; PBO=placebo; Q4W=every 4 weeks; SE=standard error
Source: Adapted from CS, Table 48; COAST-X CSR, Table RHBX.14.49

[redacted]

There were [redacted] between the two LDs within the ixekizumab Q4W arm at Week 52 for ASAS40, BASDAI50, or BASDAI score cfb (Appendix L to the CS, Figure 35 and Figure 36). The company did not present results for BASFI score at Week 52 stratified by LD.

In total, [redacted] patients initially treated with ixekizumab Q4W ([redacted]) and [redacted] patients initially treated with placebo ([redacted]) were rescued with ixekizumab Q2W (CS, p76 and COAST-X CSR, p199). The company provides ASAS40 response rates for the patient population who remained on ixekizumab Q4W throughout the study ([redacted]) at Week 52, no imputation for missing data) and for those who received rescue therapy with ixekizumab Q2W ([redacted] at Week 52, no imputation for missing data) in Appendix L to the CS (Figure 34). [redacted] achieved an ASAS40 response at Week 52.

3.3.3 Subgroup analyses

In each of the COAST trials, pre-specified subgroup analyses were performed for the primary outcome, ASAS40 response at Week 16, for various demographic and baseline characteristics. The subgroup analyses for which statistically significant subgroup interactions (defined as p<0.10) were observed are listed in Table 20.

Table 20 Significant (p<0.10) treatment-by-subgroup interactions at Week 16 for the primary endpoint (ASAS40) in COAST-V, COAST-W and COAST-X

Outcome	COAST-V trial	COAST-W trial	COAST-X trial
[redacted]	[redacted]	[redacted]	[redacted]

ASAS=Assessment of SpondyloArthritis International Society; CRP=C-reactive protein; TNF=tumour necrosis factor; vs=versus
Source: CS, Table 52

Full results for the analyses where statistically significant subgroup effects were observed are provided in the CSRs (COAST-V trial Week 16 CSR, Table RHBV.14.71; COAST-W trial Week 16 CSR, Table RHBW.14.68; COAST-X trial Week 16 and Week 52 CSR, Table RHBX.14.106).

[redacted]

[redacted]

3.4 Patient reported outcomes from the trials of ixekizumab

HRQoL data were collected during the COAST-V (CS, p64), COAST-W (CS, p74) and COAST-X (CS, p83) trials using the physical component summary (PCS) of the SF-36[31] global health assessment measure. The PCS score is derived from four of the eight domains of the SF-36 instrument, including physical functioning, role-physical, bodily pain and general health scales. Patient responses to the instrument are recorded on a Likert scale. Summary scores range from 0 to 100, with 0 indicating the worst possible health state and 100 indicating the best possible health state. The company used Version 2 of the SF-36 instrument, which is designed for weekly recall. Data were collected at baseline, Week 4, Week 8, Week 16, Week 36 and Week 52.

HRQoL data were also collected during the COAST trials using the EQ-5D-5L[47] questionnaire. Patients completed the questionnaire at baseline, Week 16 and Week 52. The EQ-5D-5L scores collected in the COAST trials were cross-walked to EQ-5D-3L values using the van Hout[48] approach and converted to utility values using the UK[49] value set (CS, p161).

3.4.1 Summary of SF-36 data

In the CS, summary HRQoL data from the three COAST trials are reported from Week 16 (Table 21) and Week 52 (Table 22). The data from Week 16 were analysed using a mixed model repeated measure analysis (MMRM). The data from Week 52 were analysed using the modified baseline observation carried forward (mBOCF) method.

Change from baseline at Week 16

The SF-36 cfb scores at Week 16 are shown in Table 21. These data show that cfb scores at Week 16 for patients treated with ixekizumab Q4W [redacted] than those of patients treated with placebo. The ERG notes that [redacted] patients provided SF-36 data at Week 16.

Table 21 SF-36 PCS scores at Week 16 in the ITT population, COAST-V, COAST-W, COAST-X (MMRM analysis)

Trial and treatment arm (number of patients)	Number of patients completing questionnaire	CfB LSM (SE)	Difference versus PBO (95% CI)	p-value
COAST-V				
PBO ([redacted])	[redacted]	3.64 (0.75)	-	-
IXE Q4W ([redacted])	[redacted]	7.70 (0.78)	4.05 (1.94 to 6.16)	0.0002
COAST-W				
PBO ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]
IXE Q4W ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]
COAST-X				
PBO ([redacted])	[redacted]	5.21 (0.80)	[redacted]	-
IXE Q4W ([redacted])	[redacted]	8.06 (0.81)	[redacted]	0.013

CfB=change from baseline; CI=confidence interval; IXE=ixekizumab; LSM=least squares mean; PBO=placebo; Q4W=every four weeks; SE=standard error
For the Ns, the ERG here uses the number of patients included in the analysis (as reported in COAST-V Week 16 CSR Table RHBV.14.56, COAST-W Week 16 CSR Table RHBW.14.55, and COAST-X Week 16 and Week 52 CSR Table RHBX.14.42), rather than the number of patients randomised to each treatment arm (as presented in the CS, Table 26, Table 41 and Table 51)
Source: Adapted from CS, Table 26, Table 41 and Table 51,

Change from baseline at Week 52

At Week 16, in the COAST-V and COAST-W trials, all patients in the placebo arm were randomised to receive either ixekizumab Q2W or ixekizumab Q4W. It is, therefore, not possible to compare ixekizumab Q4W with placebo at Week 52 using data from either of these trials. The SF-36 results presented in Table 22 and Table 23 are derived from patients who were originally randomised to receive ixekizumab Q4W. The company reports (CS, p64 and p74) that in the COAST-V and COAST-W trials SF-36 cfb scores at Week 52 were [redacted] than at Week 16 for patients treated with ixekizumab Q4W. The company considers (CS, p64 and p74) that for patients treated with ixekizumab, improvements in HRQoL were [redacted] This finding applies to biologic-naïve rad-axSpA (COAST-V) biologic-experienced rad-axSpA (COAST-W) patients.

Table 22 SF-36 PCS scores at Week 52 in the ITT populations originally randomised to ixekizumab, COAST-V, COAST-W (mBOCF analysis)

Trial and treatment arm (number of patients)	Number of patients completing questionnaire	Mean cfb mean (SD)
COAST-V		
IXE Q4W ([redacted])	[redacted]	[redacted]
COAST-W		
IXE Q4W (N=114)	[redacted]	[redacted]

cfb=change from baseline; IXE=ixekizumab; Q4W=every 4 weeks; SD=standard deviation
Source: Adapted from CS, Table 27 and Table 42, COAST-V Week 16 and Week 52 CSR Table RHBV.14.22, COAST-W Week 16 and Week 52 CSR Table RHBW.14.43,

In the COAST-X trial, from Week 16 to Week 52, any patient who was deemed to be an inadequate responder by investigators could receive rescue treatment with ixekizumab 80mg Q2W. [redacted] (Appendix L to the CS, Table 100).

The SF-36 cfb score at Week 52 was [redacted] for patients in the ixekizumab arm compared with that for those in the placebo arm (Table 23). The company considers (CS, p82) that for patients treated with ixekizumab Q4W, [redacted]

Table 23 SF-36 PCS scores at Week 52 in the ITT population, COAST-X (mBOCF ANCOVA analysis)

Treatment arm	Number of patients completing questionnaire	SF-36 cfb, LSM (SE)	Difference versus PBO (95% CI)	p-value
Placebo ([redacted])	[redacted]	[redacted]	-	-
IXE Q4W (N=96)	[redacted]	[redacted]	[redacted]	[redacted]

CfB=change from baseline; IXE=ixekizumab; PBO=placebo; Q4W=every four weeks; SE=standard error
For the N in the placebo arm of the COAST-X trial, the ERG uses the number of patients included in the analysis (COAST-X Week 16 and Week 52 CSR Table RHBX.14.43) rather than the number of patients randomised to this treatment arm (as is presented in the CS, Table 51)
Source: Adapted from CS, Table 51 and COAST-X Week 16 and Week 52 CSR Table RHBX.14.43

The SF-36 scores at Week 16 demonstrate [redacted] in HRQoL for patients treated with ixekizumab compared to patients receiving placebo in the (i) biologic-naïve rad-axSpA population (COAST-V) (ii) biologic-experienced rad-axSpA population (COAST-W) and (iii) biologic-naïve nr-axSpA population (COAST-X). The [redacted] However, the ERG cautions that axSpA is a lifelong disease. The ERG also notes that there are no HRQoL data available for patients with nr-axSpA who have had previous treatment with biologics (biologic-experienced).

3.4.2 Summary of EQ-5D data

Details of the EQ-5D-5L data collected during the COAST trials were not included in the CS. The ERG asked the company (QB3 of the clarification letter) to provide mean index values at baseline by trial arms (EQ-5D-5L cross-walked to EQ-5D-3L). These results are reproduced in Table 24. The ERG also asked the company to provide details of the numbers of patients completing the questionnaire at baseline and at all other subsequent time points. These data (company clarification response Tables 10, 11 and 12) showed that [redacted].

Table 24 Baseline COAST-V, -W and -X EQ-5D values (cross-walked from 5L to 3L)

	COAST-V	COAST-W	COAST-X
	Mean (SD)		
PBO	[redacted]	[redacted]	[redacted]
IXE 80mg Q4W	[redacted]	[redacted]	[redacted]
ADA 40mg Q2W	[redacted]	[redacted]	[redacted]

3L=three levels; 5L=five levels; ADA=adalimumab; EQ-5D=EuroQol-five dimensions; IXE=ixekizumab; N/A=not applicable; PBO=placebo; Q2W= every 2 weeks; Q4W=every 4 weeks; SD=standard deviation
Source: Company clarification response, Table 9

3.5 Safety and tolerability results from ixekizumab studies

Clinical advice to the ERG is that AEs arising from treatment with ixekizumab and other IL-17A inhibitors require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of biologic therapy related AEs, and that this can place a high burden on NHS staff and systems.

Upper respiratory tract, varicella zoster and fungal infections are often classified as minor AEs in trials as they not life threatening and do not require hospital admission. However, severe and recurrent infections cause significant morbidity to patients and frequently increase clinical care interventions. Long-term specialist follow-up is needed to allow identification of effects of IL-17A inhibitions on late occurring events including CVD and malignancy.

Safety and tolerability data are presented in the CS from the three COAST trials (Section B.2.10.2). Week 16 (the end of the blinded treatment) and Week 52 (the end of the extended treatment) data are presented. The company defined the safety population as all randomised patients who received at least one dose of study treatment (CS, p109). The safety data discussed in this section of the ERG report were collected from patients treated with ixekizumab Q4W (pooled 80mg and 160mg LDs).

[redacted]

Treatment exposure

The Week 16 and Week 52 treatment exposure data from the COAST trials (CS, p109) are summarised in Table 25. The ERG agrees with the company (CS, p109) that in the COAST-V and COAST-W trials treatment exposure at Week 16 was [redacted]. Week 16 data from the COAST-X trial were not presented in the CS but were provided in the CSR.

The company observes (CS, p110) that in the COAST-V and COAST-W trials, treatment exposure at Week 52 was [redacted]. In the COAST-X trial, treatment exposure was [redacted] (CS, p110).

Table 25 Treatment exposure at Week 16 and Week 52, COAST-V, COAST-W and COAST-X trials

Trial	Ixekizumab Q4W Week 16	PBO Week 16	Ixekizumab Q4W Week 52	PBO Week 52
	Mean duration in days (N)	Mean duration in days (N)	Mean duration in days (N)	Mean duration in days (N)
COAST-V	[redacted] (81)	[redacted] (104)	[redacted] (81)	NA
COAST-W	[redacted] (114)	[redacted] 104)	[redacted] (114)	NA
COAST-X	[redacted]	[redacted]	[redacted]	[redacted]

NA=not applicable; NR=not reported; PBO=placebo; Q4W=every 4 weeks
Source: Adapted from CS, p109 and p110

3.5.1 Adverse events COAST-V and COAST-W

COAST-V trial (biologic-naïve rad-axSpA)

Week 16 AE results for patients randomised to treatment with ixekizumab Q4W and placebo in the COAST-V trial are summarised in Table 26. Data from Week 52 for patients who were initially randomised to treatment with ixekizumab Q4W are also presented in Table 26. There are no Week 52 data available for the placebo group as the trial design meant that all patients received ixekizumab after Week 16.

The ERG notes that at Week 16, the number of patients who experienced an AE was similar in the ixekizumab and placebo arms. One patient (in the placebo arm) experienced a severe treatment emergent adverse event (TEAE) and one patient in the ixekizumab arm experienced a severe adverse event (SAE). None of the patients in the trial discontinued treatment due to an AE. Infection was the most common AE of special interest (AESI), with frequencies of 9.8% and 15.1% in the ixekizumab and placebo arms, respectively. The company reports (CS, p111) that the [redacted]

At Week 52, almost [redacted] It is stated in the CS (p112) that [redacted] The company reports that [redacted]

Table 26 Summary of Week 16 and Week 52 adverse event results: COAST-V trial

	Ixekizumab Q4W N=81 n (%)	PBO N=104 n (%)	Ixekizumab Q4W N=81 n (%)
	Week 16	Week 16	Week 52
AEs			
Any TEAE	38 (42)	34 (39.5)	[redacted]
Severe TEAE	0	1 (1.2)	[redacted]
TEAE possibly related to study drug	10 (12.3)	14 (16.3)	[redacted]
Patients with ≥1 SAE	1 (1.2)	0	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
Death	[redacted]	[redacted]	[redacted]
Discontinuation due to AE	[redacted]	[redacted]	[redacted]
AESI*			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	1 (1.2)	1 (1.2)	[redacted]
[redacted]	16 (9.8)	13 (15.1)	[redacted]
[redacted]	3 (3.7)	4 (4.7)	[redacted]
[redacted]	3 (3.7)	1 (1.2)	[redacted]
[redacted]	3 (3.7)	1 (1.2)	[redacted]
[redacted]	1 (1.2)	0	[redacted]
[redacted]	0	0	[redacted]

AE=adverse event; AESI=adverse event of special interest; PBO=placebo; Q4W=treatment every 4 weeks; SAE=serious adverse event; TEAE=treatment emergent adverse event
*Only the AESIs experienced by patients treated with ixekizumab Q4W or placebo are included
Source: Adapted from CS, Table 80 and Table 81, Table 82 and Table 83

COAST-W trial (biologic-experienced rad-axSpA)

Week 16 AE results for patients randomised to treatment with ixekizumab Q4W and placebo in the COAST-W trial are summarised in Table 27. Week 52 data from patients who were initially randomised to treatment with ixekizumab Q4W are also presented in Table 27. There are no comparative data available from the placebo group at Week 52 as the trial design meant that all patients received ixekizumab after Week 16.

The ERG notes that at Week 16, more patients in the ixekizumab arm experienced a TEAE compared with patients in the placebo arm. The ERG agrees with the company (CS, p114) that the number of AEs considered to be [redacted] The ERG

notes that the incidence of [redacted]

At Week 52, [redacted] patients treated with ixekizumab had experienced a TEAE and [redacted] of the TEAEs were considered to be related to treatment with ixekizumab. [redacted] of the patients experienced an infection. The company reports (CS, p116) that the [redacted] and [redacted] (CS, p116).

Table 27 Summary of adverse events at Week 16 and Week 52, COAST-W

	Ixekizumab Q4W N=114 n (%)	PBO N=104 n (%)	Ixekizumab Q4W N=114 n (%)
	Week 16	Week 16	Week 52
AEs			
Any TEAE	73 (64.0)	51 (49.0)	[redacted]
Severe TEAE	4 (3.5)	7 (6.7)	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 SAE	4 (3.5)	5 (4.8)	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Discontinuation due to AE	10 (8.8)	2 (1.9)	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
AESI*			
Cytopenia			
Hepatic	5 (4.4)	2 (1.9)	
Infections	34 (29.8)	10 (9.6)	
Injection site reactions	9 (7.9)	6 (5.8)	
Allergic reactions and hypersensitivities	3 (2.6)	1 (1.0)	
Non-anaphylaxis	3 (2.6)	1 (1.0)	
Confirmed cerebrocardiovascular events	0	1 (1.0)	
Malignancies	1 (0.9)	0	
Depression	0	5 (4.8)	
Inflammatory bowel disease	3 (2.6)	1 (1.0)	

AE=adverse event; AESI=adverse event of special interest; NR=not reported; Q4W=treatment every 4 weeks; SAE=serious adverse event; TEAE=treatment emergent adverse event
Source: Adapted from CS, Table 84, Table 85, Table 86 and Table 87
*Only the AESI's experienced by patients treated with ixekizumab Q4W or placebo are included

COAST-X trial (biologic-naïve nr-axSpA)

The Week 16 AE results for patients randomised to treatment with ixekizumab Q4W and placebo in the COAST-X trial are summarised in Table 28. The ERG notes that similar numbers of patients in the ixekizumab and placebo arms experienced a TEAE and that [redacted] patients (all in the [redacted] arm) experienced a severe TEAE. Similar numbers of AEs in both trial arms were considered to be related to treatment. [redacted] (in the placebo arm) experienced a SAE and [redacted] (in the placebo arm) discontinued treatment due to an AE.

The most common AESIs were [redacted]

Table 28 Summary of adverse events at Week 16, COAST-X

	Ixekizumab Q4W N=96 n (%)	**PBO N=104 n (%)**

AEs		
Any TEAE	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]
TEAE possibly related to study drug	[redacted]	[redacted]
Patients with ≥1 SAE	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]
Discontinuation due to AE	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
AESI		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

AE=adverse event; AESI=adverse event of special interest; Q4W-treatment every 4 weeks; SAE=serious adverse event; TEAE=treatment emergent adverse event
Source: Adapted from CS, Table 88 and Table 89

The Week 52 AE results for patients initially randomised to treatment with ixekizumab Q4W or placebo are summarised in Table 29.

Similar numbers of TEAEs were experienced in the ixekizumab and placebo arms. The company reports (CS, p120) that, compared with the placebo arm, [redacted]. The most common AESI was infection. More patients in the ixekizumab experienced an infection compared with the placebo arm. The company reports (CS, p120) that the majority of infections and injection site reactions were considered to be mild or moderate.

Table 29 Summary of adverse events at Week 52, COAST-X

	Ixekizumab Q4W N=96 n (%)	**PBO N=104 n (%)**
AEs		
Any TEAE	63 (65.6)	60 (57.7)
Severe TEAE	1 (1.0)	4 (3.8)
TEAE possibly related to study drug	[redacted]	[redacted]
Patients with ≥1 SAE	[redacted]	[redacted]
Discontinuation due to AE	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]
Anaphylactoid reaction	0	1 (1.0)

Death	0	0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Anaphylactoid reaction	0	1 (1.0)
AESI		
[redacted]	[redacted]	[redacted]
Hepatic	3 (3.1)	6 (5.8)
Infections	38 (39.6)	30 (28.8)
Injection site reactions	18 (18.8)	7 (6.7)
Allergic reactions and hypersensitivities	4 (4.2)	4 (3.8)
potential anaphylaxis	0	1 (1.0)
non-anaphylaxis	4 (4.2)	3 (2.9)
Inflammatory bowel disease	0	1 (1.0)

AE=adverse event; AESI=adverse event of special interest; Q4W=treatment every 4 weeks; SAE=serious adverse event; TEAE=treatment emergent adverse event
Source: Adapted from CS, Table 88, Table 90, Table 91 and company clarification response

3.5.2 Summary of safety results

The company states (CS, 109) that Week 16 and Week 52 results show that most TEAEs experienced by patients in all treatment arms of the three COAST trials were mild to moderate in severity and that few patients experienced a SAE. [redacted] The company highlights that the safety profile of ixekizumab, as demonstrated by results from the COAST trials, is consistent with the safety profile of ixekizumab in other disease areas, including moderate to severe plaque psoriasis and psoriatic arthritis. The ERG agrees with the company (CS, p109) that data collected from patients in the COAST trials demonstrated that ixekizumab was a well-tolerated treatment.

3.6 ERG critique of the indirect evidence

The company performed a series of NMAs to establish the comparative efficacy of ixekizumab versus comparator treatments relevant to the final scope[28] issued by NICE. The company NMAs were conducted for each of the following populations:

- Biologic-naïve rad-axSpA population (including data from the COAST-V trial)
- Biologic-experienced rad-axSpA population (including data from the COAST-W trial)
- Biologic-naïve nr-axSpA population (including data from the COAST-X trial)

Within each of these populations, base case and sensitivity NMAs were performed. The base case NMAs included studies in which the patient population could clearly be classified into one of the three patient populations listed above. The sensitivity NMAs incorporated studies with either mixed or unclear patient populations in addition to the studies included in the base case NMAs.

The company performed NMAs for a variety of outcomes, including efficacy, safety and HRQoL (see CS Table 53, Table 62 and Table 71). However, the company only presents results from the NMAs for the following outcomes: ASAS40, BASDAI50, BASDAI score cfb and BASFI score cfb.

3.6.1 Critique of trials identified and included in the NMAs

The company applied eligibility criteria to the trials identified through their systematic search (Section 3.1) to determine which RCTs should be included in the NMAs. In brief, the company excluded the following from the base case NMAs:

- open label studies
- pilot studies
- phase I/II trials
- studies with unclear populations or mixed populations that did not report subgroup data for the population of interest (i.e., biologic-naïve rad-axSpA, biologic-experienced rad-axSpA and biologic-naïve nr-axSpA)
- studies of off-label use of drugs for the populations of interest.

The company only included studies in the NMAs that reported outcomes during the period between 12 weeks and 18 weeks. The ERG notes that all efficacy outcome data included in the company NMAs were reported at Week 12, Week 14 or Week 16 (Appendix D to the CS, Tables 20 to 22).

The ERG considered that the exclusion of pilot and phase I/II studies from the company NMAs is an unusual approach and, therefore, requested justification for this approach during the clarification process. The company responded that these types of studies often have small sample sizes and thus lack the statistical power to detect a treatment effect (company response to the ERG clarification letter, question A8). The ERG considers that having a sample size and a lack of statistical power are not adequate reasons for excluding studies from NMAs; indeed, one of the key purposes of synthesizing evidence from different studies is to increase statistical power. However, there were other valid reasons to exclude the seven identified pilot and phase I/II studies from the company NMAs. Three trials evaluated interventions that were not licensed for the treatment of axSpA,[50-52] and one study[53] used off-label dosing. Two other trials[54,55] evaluated comparisons which were not informative to this appraisal: the PLANETAS trial[55] compared infliximab with a biosimilar version of infliximab and the LOADET[56] trial compared golimumab with placebo in a rad-axSpA population. The ERG considers that this trial was eligible for inclusion in the company's NMAs; however, the publication did not include details of any of the relevant outcomes between Week 12 and Week

18. The ERG, therefore, considers that the exclusion of pilot, phase I and phase II studies from the company's NMAs is not an issue of concern.

Characteristics of the trials included in the biologic-naïve and/or biologic-experienced rad-axSpA NMAs are provided in Table 30, and characteristics of the trials included in the biologic-naïve nr-axSpA NMAs are provided Table 31.

Table 30 Studies included in the biologic-naïve and/or biologic-experienced rad-axSpA NMAs

Trial name	Tx 1	Tx 2	Tx 3	Prior biologic	Biologic-naïve NMA	Biologic-experienced NMA
Base-case NMAs						
ATLAS	ADA 40mg Q2W SC	PBO	NA	Naïve	Yes	No
Bao 2014	GOL 50mg Q4W SC	PBO	NA	Naïve	Yes	No
Calin 2004	ETN 25mg BIW SC	PBO	NA	Naïve	Yes	No
Cantini 2013[a]	ETN 50mg Q2W	ETN 50mg QW	NA	Experienced	No	Yes
COAST-V	IXE 80mg Q2W and Q4W SC	ADA 40mg Q2W SC	PBO	Naïve	Yes	No
COAST-W	IXE 80mg Q2W and Q4W SC	PBO	NA	Experienced	No	Yes
Davis 2003	ETN 25mg BIW SC	PBO	NA	Naïve	Yes	No
GO-RAISE	GOL 100mg Q4W SC	GOL 50mg Q4W SC	PBO	Naïve	Yes (100mg arm excluded)	No
HEEL	ETN 50mg QW SC	PBO	NA	Naïve	Yes	No
Huang 2014	ADA 40mg Q2W SC	PBO	NA	Naïve	Yes	No
MEASURE-2	SEC 75mg Q4W SC	SEC 150mg Q4W SC	PBO	Mixed	Yes (75mg arm excluded)	Yes (75mg arm excluded)
MEASURE-4	SEC 75mg Q4W SC	SEC 150mg Q4W SC	PBO	Mixed	Yes (75mg arm excluded)	Yes (75mg arm excluded)
SPINE	ETN 50mg QW SC	PBO	NA	Naïve	Yes	No
Van den Bosch 2002[b]	IFX 5mg/kg	PBO	NA	Naïve	Yes	No
Van der Heijde 2006	ETN 50mg QW SC	ETN 25mg BIW SC	PBO	Naïve	Yes	No
Additional studies included in sensitivity NMAs						
Barkham 2010	ETN 25mg BIW SC	PBO	NA	Unclear	Yes	Yes
Brandt 2003	ETN 25mg BIW SC	PBO	NA	Unclear	Yes	Yes
Gorman 2002[b]	ETN 25mg BIW SC	PBO	NA	Unclear	Yes	Yes
ASSERT	IFX 5mg/kg IV	PBO	NA	Unclear	Yes	Yes
Braun 2002	IFX 5mg/kg IV	PBO	NA	Unclear	Yes	Yes
RAPID-axSpA	CZP 200mg Q2W SC	CZP 400mg Q4W SC	PBO	Mixed	Yes	Yes
Hu 2012[b]	ADA 40mg	PBO	NA	Unclear	Yes	Yes
Lambert 2007[b]	ADA 40mg	PBO	NA	Unclear	Yes	Yes

ADA=adalimumab; BIW=bi-weekly; CZP=certolizumab pegol; ETN=etanercept; GOL=golimumab; IFX=infliximab; IV=intravenous; IXE=ixekizumab; NMA=network meta-analysis; PBO=placebo; QW=every week; Q2W=every 2 weeks; Q4W=every 4 weeks; rad-axSpA=radiographic axial spondyloarthritis; SC=subcutaneous; SEC=secukinumab; Tx=treatment

[a]This study was eligible for inclusion in the base case and sensitivity NMAs for the biologic-experienced rad-axSpA population but did not provide any useable data

[b]This study did not contribute data for any of the four key outcomes

Source: Adapted from Table 16 and Table 17 of Appendix D to the CS

Table 31 Studies included in the biologic-naïve nr-axSpA NMAs

Trial name	Tx 1	Tx 2	Tx 3	Prior biologic
Base-case NMAs				
EMBARK	ETN 50mg QW	PBO	NA	Naïve
ABILITY-1	ADA 40mg Q2W SC	PBO	NA	Naïve
GO-AHEAD	GOL 50mg Q2W SC	PBO	NA	Naïve
COAST-X	IXE 80mg Q2W and Q4W SC	PBO	NA	Naïve
Additional studies included in sensitivity NMAs				
Haibel 2008	ADA 40mg Q2W SC	PBO	NA	Unclear
RAPID-axSpA	CZP 200mg Q2W	CZP 400mg Q4W	PBO	Mixed
C-axSpAnd	CZP 200mg Q2W	CZP 400mg Q4W	PBO	Naïve Experienced (18/317)

ADA=adalimumab; ETN=etanercept; CZP=certolizumab pegol; GOL=golimumab; IXE=ixekizumab; NMA=network meta-analysis; nr-axSpA=non-radiographic axial spondyloarthritis; PBO=placebo; QW=every week; Q2W=every 2 weeks; Q4W=every 4 weeks; SC=subcutaneous; Tx=treatment
Source: Adapted from Table 18 and Table 19 of Appendix D to the CS

The company provides a summary showing which trials report data for each of the four key outcomes, and the corresponding time-point at which the outcome was assessed in Tables 20 to 22 of Appendix D to the CS. In the base case NMAs for the biologic-experienced rad-axSpA population, the time-point of assessment for all included studies was Week 16. For all other NMAs, the assessment time-points of the included studies ranged from Week 12 to Week 16. Treating patients for longer may increase the likelihood that patients will respond to treatment or experience AEs. The ERG, therefore, considers that differences in assessment time-points may introduce heterogeneity, potentially causing bias both for and against treatments that were investigated in studies with later assessment time-points. The ERG notes that all trials of secukinumab (MEASURE-2 and MEASURE-4) and ixekizumab (COAST-V, -W, and -X) report outcomes at Week 16, whereas the majority of studies investigating TNF-alpha inhibitors report outcomes at Week 12.

The company provides a summary of the methods used in each of the included trials in Table 25, Table 27 and Table 29 of Appendix D to the CS. All studies that contributed data to the NMAs were double-blind, and the majority were conducted internationally. The ERG notes that phase was not reported for many of the included studies (14 of 21 studies included in the biologic-naïve rad-axSpA NMAs, 8 of 12 studies included in the biologic-experienced rad-axSpA NMAs, and 1 of 7 studies included in the biologic-naïve nr-axSpA NMAs). This further demonstrates the inappropriateness of excluding studies from NMAs based on phase alone.

The company presents a summary of the treatment regimens, and concomitant medications, given to patients participating in each of the included trials (Table 26, Table 28 and Table 30 of Appendix D to the CS).

The company also provides summaries of baseline patient characteristics (Tables 31 to 33, Appendix D to the CS), baseline disease severity (Tables 34 to 36, Appendix D to the CS) and prior therapy (Tables 37 to 39, Appendix D to the CS) in the included trials.

The ERG notes that the company did not provide information on baseline CRP levels across the trials included in the NMAs. CRP level has previously been reported to be a key predictor of treatment response in patients with ankylosing spondylitis.[57] The ERG has summarised CRP levels across the trials included in the NMAs in Appendix 6.2. Clinical advice to the ERG is that variation in CRP levels may introduce heterogeneity into the network, but that there is no evidence to suggest that bias would be introduced in favour of any single treatment.

3.6.2 Methods used to conduct the NMAs

The NMAs were performed using two software programs developed by the company; the BATMAN tool was used to perform Bayesian NMAs and the CHEETAH tool was used to perform frequentist NMAs.

In the first instance, the company used a Bayesian approach to perform the NMAs and followed the methods described in the NICE Decision Support Unit (DSU) Technical Support Document 2.[58] If the Bayesian model did not converge for a NMA, a frequentist model NMA was performed using methods described by Rucker.[59]

The company modelled the baseline effect and relative treatment effect separately in all analyses, as recommended by Dias et al.[60] The company assessed both fixed and random effects models for each network and examined goodness of fit statistics (deviance, residual deviance and deviance information criterion [DIC]) to determine which model fitted the data most closely. Based on these statistics, the company concluded that it was appropriate to only present results from fixed effects models. The ERG considers that examining goodness of fit statistics is an appropriate method of choosing between fixed and random effects models. However, it is also important to note that fixed effects models may underestimate uncertainty in treatment effect estimates if there is variability in treatment effects between trials included in the network.

A Bayesian approach involves updating prior information about population parameters in light of new evidence to reflect the current state of knowledge. Prior distributions, which must be specified, are updated to reflect new evidence (i.e., evidence provided by the studies included in the NMA), resulting in posterior distributions. Results from using a Bayesian approach may, therefore, be sensitive to the chosen prior distribution. A lack of external data to inform the choice of prior distribution led the company to initially choose to use the same vague prior for

baseline treatment effect and relative treatment effect, namely a normal distribution with a mean of 0 and standard deviation of 100.

The ERG was unable to determine with certainty the priors used for the between trial variances (only applicable to the random effects models). During the clarification process the ERG asked the company to provide the NMA report; however, the company only provided the protocol which included contradictory information on the priors used to the information provided in Appendix D to the CS.

The company states (Appendix D to the CS, p78) that if a model appeared to be sensitive to the choice of vague priors, i.e., if unstable (wide) credible intervals (Crls) were observed, informative priors may have been used. These informative priors were chosen on a case by case basis.

The company provides information on the specification of initial values and the Markov Chain Monte Carlo (MCMC) settings used when conducting the NMAs in Appendix D to the CS (p79). Model convergence was assessed using trace plots as modified by Brooks and Gelman, monitoring the Monte Carlo error, Gelman Rubin diagnostics, auto-correlation plots and Gelman-Rubin statistics.

The ERG considers that the methods used by the company to conduct the NMAs were appropriate.

3.6.3 Results from the NMAs

As comparisons of base case and sensitivity NMA results showed that the two sets of results were generally similar. Only results from the ixekizumab sensitivity NMAs have been reproduced in this report (it is these results that have been used to populate the company economic model). Results from the base case NMAs are provided as part of the CS (Appendix D) and results for placebo versus each relevant treatment are provided in the main CS document.

Biologic-naïve rad-axSpA population

For the biologic-naïve rad-axSpA population, all analyses were carried out using data from the ixekizumab 80mg Q4W arm (80mg LD) of the COAST-V trial. A summary of the studies providing data for each outcome in the base case and sensitivity NMAs is provided in Table 32. All studies included in the base case NMAs were also included in the sensitivity NMAs.

Table 32 Summary of sources of outcome data from the studies included in the biologic-naïve rad-axSpA NMAs

Interventions	ASAS40	BASDAI50	BASDAI score: cfb	BASFI score: cfb
Base case analysis				
IXE Q4W LD 80mg vs ADA 40mg vs PBO	COAST-V	COAST-V	COAST-V	COAST-V
ADA 40mg vs PBO	ATLAS Huang 2014	ATLAS Huang 2014	ATLAS Huang 2014	Huang 2014
ETN pooled vs PBO	Davis 2003 SPINE Van der Heijde 2006	SPINE Van der Heijde 2006	HEEL SPINE	SPINE
GOL 50mg vs PBO	Bao 2014 GO-RAISE	Bao 2014 GO-RAISE		Bao 2014
SEC 150mg vs PBO	MEASURE-2 MEASURE-4		MEASURE-2 MEASURE-4	
Sensitivity analysis				
ETN pooled vs PBO		Barkham 2010 Brandt 2003		
CZP pooled vs PBO	RAPID-axSpA	RAPID-axSpA	RAPID-axSpA	RAPID-axSpA
IFX 5mg/kg vs PBO	ASSERT Braun 2002	Braun 2002	ASSERT Braun 2002	ASSERT Braun 2002

ADA=adalimumab; ASAS=Assessment of Spondyloarthritis International Society; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; cfb=change from baseline; CZP=certolizumab pegol; ETN=etanercept; GOL=golimumab; IFX=infliximab; IXE=ixekizumab; LD=loading dose; NMA=network meta-analysis; PBO=placebo; rad-axSpA=radiographic axial spondyloarthritis; Q4W=every four weeks; SEC=secukinumab
Source: Adapted from CS, Table 53

The ERG notes that data for certolizumab pegol and etanercept are pooled across different regimens. The RAPID-axSpA trial includes two certolizumab pegol arms: certolizumab pegol 400mg Q4W and certolizumab pegol 200mg Q2W. For the comparison of etanercept versus placebo, five trials included one etanercept arm (etanercept 25mg in Davis 2003, Barkham 2010, and Brandt 2002; etanercept 50mg in HEEL and SPINE), and one trial included two etanercept arms (etanercept 25mg and etanercept 50mg, Van der Heijde 2006).

Network diagrams for each outcome are provided in Appendix D to the CS (ASAS40: Figure 14; BASDAI50: Figure 15; BASDAI score cfb: Figure 16; BASFI score cfb: Figure 17). The absolute effects for each relevant treatment and the relative effects for ixekizumab versus each comparator are provided in Table 33. The company has also provided forest plots displaying the results of the pairwise comparisons (CS, Figure 17 to Figure 20).

Table 33 Results from the biologic-naïve rad-axSpA population sensitivity NMAs

Intervention	ASAS40		BASDAI50		BASDAI score cfb		BASFI score cfb	
	Mean posterior event rate (95% CrI)	Posterior median OR (95% CrI) IXE 80mg Q4W vs comparator	Mean posterior event rate (95% CrI)	Posterior median OR (95% CrI) IXE 80mg Q4W vs comparator	Mean posterior cfb (95% CrI)	Posterior median treatment difference (95% CrI) IXE 80mg Q4W vs comparator	Mean posterior cfb (95% CrI)	Posterior median treatment difference (95% CrI) IXE 80mg Q4W vs comparator
IXE 80mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INX 5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ADA=adalimumab; ASAS=Assessment of Spondyloarthritis International Society; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; cfb=change from baseline; CrI=credible interval; CZP=certolizumab pegol; ETN=etanercept; GOL=golimumab; INX=infliximab; IXE=ixekizumab; NMA=network meta-analysis; OR=odds ratio; Q4W=every 4 weeks; PBO=placebo; rad-axSpA=radiographic axial spondyloarthritis; SEC=secukinumab
Source: Adapted from CS, Table 54 to Table 61

Biologic-naïve rad-axSpA population sensitivity NMA results [redacted]

The ERG notes that all results for ASAS40 and BASDAI50 response from the company sensitivity NMAs were comparable to results from the base case NMAs (CS, Appendix D, Table 46 to Table 49). For BASDAI score cfb and BASFI score cfb, relative effects (i.e., treatment effect difference when comparing the effect of ixekizumab Q4W versus each comparator) were very similar across the base case NMAs (CS, Appendix D, Table 51 and Table 53) and the sensitivity NMAs.

However, results from the absolute effects (i.e., cfb for each comparator) base case NMAs (CS, Appendix D, Table 50 and Table 52) were considerably different to those from the sensitivity NMAs. For example, the mean posterior BASDAI score cfb for ixekizumab was [redacted] in the base case NMA and [redacted] in the sensitivity NMA. These large differences suggest that the absolute effect estimates are not robust when studies with mixed and unclear patient populations are added to the base case network of evidence. The ERG, therefore, considers the absolute effect results generated by the base case NMAs are likely to be more reliable than those from the sensitivity NMAs. The ERG does not consider that the BASDAI score cfb and BASFI score cfb absolute effect results from the sensitivity NMAs for the biologic-naïve rad-axSpA population provide a reliable basis for decision making.

The ERG highlights that results for the comparisons of ixekizumab versus infliximab and ixekizumab versus certolizumab pegol were only available from sensitivity NMAs and so it was not possible to compare these results with those from the base case NMAs. The source of certolizumab pegol data was the RAPID-axSpA trial (mixed biologic-naïve and biologic-experienced population) whilst the source of the infliximab data was the Braun 2002 and ASSERT trials (unclear populations). The ERG considers that the introduction of mixed and unclear populations is an important source of heterogeneity and advises that the robustness of both relative and absolute effect estimates for ixekizumab versus infliximab and ixekizumab versus certolizumab pegol in the biologic-naïve rad-axSpA cannot be investigated by the ERG.

Biologic-experienced rad-axSpA population

For the biologic-experienced rad-axSpA population, all analyses were carried out using data from the ixekizumab 80mg Q4W arm (80mg and 160mg LDs) of the COAST-W trial. Results for ixekizumab 80mg Q4W (160mg LD) are presented in the main body of the CS and are reproduced in this ERG report. Clinical advice to the ERG is that biologic-experienced rad-axSpA patients are likely to receive a LD of 160mg (see Section 3.2.1 of this ERG report). Results for ixekizumab 80mg Q4W (80mg LD) are presented as part of the CS (Appendix D). The ERG considers that results from the NMAs that incorporated data for ixekizumab 80mg Q4W (LD 80mg) are broadly comparable to results from the NMAs that incorporated data for ixekizumab 80mg Q4W (LD 160mg).

A summary of the studies providing data for each outcome (base case NMAs and sensitivity NMAs) is provided in Table 34. All studies included in the base case NMAs are also included in the sensitivity NMAs.

Table 34 Summary of sources of outcome data from the studies included in the biologic-experienced rad-axSpA NMAs

Interventions	ASAS40	BASDAI50	BASDAI score cfb	BASFI score cfb
Base-case analysis				
IXE Q4W vs PBO	COAST-W	COAST-W	COAST-W	COAST-W
SEC 150mg vs PBO	MEASURE-2 MEASURE-4		MEASURE-2 MEASURE-4	
Sensitivity analysis				
CZP pooled vs PBO	RAPID-axSpA	RAPID-axSpA	RAPID-axSpA	RAPID-axSpA
IFX 5mg/kg vs PBO	ASSERT Braun 2002	Braun 2002	ASSERT Braun 2002	ASSERT Braun 2002
ETN 25mg BIW vs PBO		Barkham 2010 Brandt 2003		

ASAS=Assessment of Spondyloarthritis International Society; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BIW=bi-weekly; cfb=change from baseline; CZP=certolizumab pegol; ETN=etanercept; IFX=infliximab; IXE=ixekizumab; NMA=network meta-analysis; PBO=placebo; rad-axSpA=radiographic axial spondyloarthritis; Q4W=every 4 weeks; SEC=secukinumab
Source: Adapted from CS, Table 62

The ERG notes that data for certolizumab pegol were pooled across different regimens. The RAPID-axSpA trial includes two certolizumab pegol arms: certolizumab pegol 400mg Q4W and certolizumab pegol 200mg Q2W.

Network diagrams, for each outcome, for the biologic-experienced rad-axSpA population were provided as part of the CS (Appendix D [ASAS40: Figure 18; BASDAI50: Figure 19; BASDAI score cfb: Figure 20; BASFI score cfb: Figure 21]). The absolute effect results for each relevant treatment, and the relative effects results for ixekizumab versus each comparator are provided in Table 35. The company has also provided forest plots displaying the results of pairwise comparisons (CS, Figure 21 to Figure 24).

Table 35 Results from the biologic-experienced rad-axSpA population sensitivity NMAs

Intervention	ASAS40		BASDAI50		BASDAI score cfb		BASFI score cfb	
	Mean posterior event rate (95% CrI)	Posterior median OR (95% CrI) IXE 80mg Q4W vs comparator	Mean posterior event rate (95% CrI)	Posterior median OR (95% CrI) IXE 80mg Q4W vs comparator	Mean posterior cfb (95% CrI)	Posterior median treatment difference (95% CrI) IXE 80mg Q4W vs comparator	Mean posterior cfb (95% CrI)	Posterior median treatment difference (95% CrI) IXE 80mg Q4W vs comparator
IXE 80mg Q4W 160mg LD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INX 5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 25mg BIW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ASAS=Assessment of Spondyloarthritis International Society; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BIW=bi-weekly; cfb=change from baseline; CrI=credible interval; CZP=certolizumab pegol; ETN=etanercept; INX=infliximab; IXE=ixekizumab; LD=loading dose; NMA=network meta-analysis; OR=odds ratio; PBO=placebo; Q4W=every 4 weeks; rad-axSpA=radiographic axial spondyloarthritis; SEC=secukinumab
Source: Adapted from CS, Table 63 to Table 70

[redacted]

For ASAS40, the ERG notes that results from the sensitivity NMA are comparable to results from the base-case NMA (CS, Appendix D, Table 55 and Table 57). For BASDAI score cfb, relative effects results from the base case and sensitivity NMAs were very similar. However, the base case and sensitivity NMA absolute treatment effect results were markedly different. [redacted] The ERG considers the absolute effect estimates from the base case NMAs are likely to be more reliable than those from the sensitivity NMAs as the base case NMAs did not include trials with mixed or unclear patient populations. The ERG does not consider that the absolute effect estimates from the sensitivity NMAs for BASDAI score cfb are suitable for the purposes of decision-making.

The ERG highlights that results for the comparisons of ixekizumab versus infliximab and ixekizumab versus certolizumab pegol were only available from sensitivity NMAs and so it is not possible to compare these results with those from the base case NMAs. The source of certolizumab pegol data was the RAPID-axSpA trial (mixed biologic-naïve and biologic-experienced population) whilst the source of the infliximab data was the Braun 2002 and ASSERT trials (unclear populations). The ERG considers that the introduction of mixed and unclear populations is an important source of heterogeneity and advises that the robustness of both relative and absolute effect estimates for ixekizumab versus infliximab and ixekizumab versus certolizumab pegol in the biologic-naïve rad-axSpA cannot be investigated by the ERG.

It was not possible to conduct base case NMAs for BASDAI50 or BASFI score cfb as the base case network for the biologic-experienced rad-axSpA NMA for these outcomes only included the COAST-W trial. It was, therefore, not possible to investigate the robustness of results from the sensitivity NMAs with regards to the inclusion of studies conducted in mixed or unclear patient populations for these outcomes.

Biologic-naïve nr-axSpA population

For the biologic-naïve nr-axSpA population, all analyses were carried out using data from the ixekizumab 80mg Q4W arm (80mg LD) of the COAST-X trial. A summary of the studies providing data for each outcome in the base case NMAs and sensitivity NMAs is provided in Table 36. All studies included in the base case NMAs were also included in the sensitivity NMAs.

Table 36 Summary of sources of outcome data from the studies included in the biologic-naïve nr-axSpA NMAs

Interventions	ASAS40	BASDAI50	BASDAI score cfb	BASFI score cfb
Base-case analysis				
IXE Q4W LD 80mg vs PBO	COAST-X	COAST-X	COAST-X	COAST-X
ADA 40mg vs PBO	ABILITY-1	ABILITY-1		
ETN 50mg QW vs PBO	EMBARK	EMBARK	EMBARK	EMBARK
GOL 50mg vs PBO	GO-AHEAD	GO-AHEAD		
Sensitivity analysis				
ADA 40mg vs PBO	Haibel 2008			
CZP pooled vs PBO	RAPID-axSpA C-axSpAnd	RAPID-axSpA	RAPID-axSpA	RAPID-axSpA C-axSpAnd

ADA=adalimumab; ASAS=Assessment of Spondyloarthritis International Society; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; cfb=change from baseline; CZP=certolizumab pegol; ETN=etanercept; GOL=golimumab; LD=loading dose; IXE=ixekizumab; NMA=network meta-analysis; nr-axSpA=non-radiographic axial spondyloarthritis; PBO=placebo; QW=every week; Q4W=every four weeks
Source: Adapted from CS, Table 71

The ERG notes that data for certolizumab pegol were pooled across different dosing regimens. The RAPID-axSpA trial includes two certolizumab pegol arms: certolizumab pegol 400mg Q4W and certolizumab pegol 200mg Q2W; the C-axSpAnd trial includes one certolizumab pegol arm: certolizumab pegol 400mg at weeks 0, 2, and 4 (LD) followed by 200mg Q2W.

Network diagrams, for each outcome, for the biologic-experienced nr-axSpA population were provided as part of the CS (Appendix D [ASAS40: Figure 22; BASDAI50: Figure 23; BASDAI score cfb: Figure 24; BASFI score cfb: Figure 25]). The absolute effects results for each relevant treatment, and relative effects results for ixekizumab versus each comparator are provided in Table 37. The company has also provided forest plots displaying the results of pairwise comparisons in the CS (Figure 25 to Figure 28).

Table 37 Results from the biologic-naive nr-axSpA population sensitivity NMAs

Intervention	ASAS40		BASDAI50		BASDAI score cfb		BASFI score cfb	
	Mean posterior event rate (95% CrI)	Posterior median OR (95% CrI) IXE 80mg Q4W vs comparator	Mean posterior event rate (95% CrI)	Posterior median OR (95% CrI) IXE 80mg Q4W vs comparator	Mean posterior event rate (95% CrI)	Posterior median OR (95% CrI) IXE 80mg Q4W vs comparator	Mean posterior event rate (95% CrI)	Posterior median treatment difference (95% CrI) IXE 80mg Q4W vs comparator
IXE 80mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 50mg QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ADA=adalimumab; ASAS=Assessment of Spondyloarthritis International Society; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; cfb=change from baseline; CrI=credible interval; CZP=certolizumab pegol; ETN=etanercept; GOL=golimumab; IXE=ixekizumab; NMA=network meta-analysis; nr-axSpA=non-radiographic axial spondyloarthritis; OR=odds ratio; PBO=placebo; QW=weekly; Q4W=every 4 weeks
Source: Adapted from CS, Table 72 to Table 79

[redacted]

Results from the sensitivity NMAs were comparable to results from the base case NMAs. However, results for the comparison of certolizumab pegol versus ixekizumab were only available from the sensitivity NMAs and so it is not possible to compare these results with those from the base-case NMAs. It should be noted that all data for certolizumab pegol were sourced from the RAPID-axSpA and C-axSpAnd trials, both of which included mixed patient populations (biologic-naïve and biologic-experienced patients). The ERG considers that this is an important source of heterogeneity and advises that results for the comparison of ixekizumab versus certolizumab pegol may not be robust.

Indirect HRQoL and AE evidence

The company has not presented the results from its NMAs of AEs, SAEs, treatment discontinuations from AEs or HRQoL.

3.7 Conclusions of the clinical effectiveness section

3.7.1 Direct evidence

The company provided direct clinical effectiveness evidence from three trials, relating to three populations with axSpA: i) patients with radiographic axSpA previously untreated with tumour TNF-alpha inhibitors (biologic-naïve rad-axSpA, COAST-V trial); ii) patients with radiographic axSpA previously treated with TNF-alpha inhibitors (biologic-experienced rad-axSpA, COAST-W trial); iii) patients with non-radiographic axSpA previously untreated with TNF-alpha inhibitors (biologic-naïve nr-axSpA, COAST X trial). The comparator arm of all three COAST trials was placebo, although in the COAST-V trial, adalimumab was included as an active reference arm. Placebo can be considered as a proxy for standard of care (for patients previously treated with biologics). However, there is no direct evidence available to compare the effectiveness of ixekizumab versus any TNF-alpha inhibitors or versus secukinumab (the other comparators identified in the final scope[28] issued by NICE).

The ERG highlights that there is no specific evidence to demonstrate the clinical effectiveness of ixekizumab in people with axSpA for whom NSAIDs or TNF-alpha inhibitors have not been tolerated or are contraindicated. Nor is there any evidence to support the clinical effectiveness of ixekizumab in biologic-experienced patients with rad-axSpA who have failed treatment with more than two biologics or in biologic-experienced patients with nr-axSpA. Further, no evidence was presented in the CS for peripheral symptoms or symptoms of extra-articular manifestations, two of the outcomes listed in the final scope[28] issued by NICE.

The ERG considers that the three COAST trials are good quality randomised controlled trials. [redacted] The baseline characteristics of the patients recruited to the COAST trials suggest that these patients are similar to patients treated in the NHS.

The ERG highlights that axSpA is a lifelong condition and evidence is only available from the COAST trials for a maximum period of 52 weeks.

3.7.2 Indirect evidence

The company conducted base case and sensitivity NMAs for four key outcomes (ASAS40, BASDAI50, BASDAI score cfb and BASFI score cfb) reported between Week 12 and Week 16 in the included studies. The base case NMAs only included studies known to be conducted in the relevant patient population. The sensitivity NMAs included all of the studies included in the base case NMAs and also studies with unclear or mixed populations. The ERG considers that the methods used by the company to conduct the NMAs were appropriate.

A comparison of base case and sensitivity NMA absolute effect results showed that, for some outcomes, there were large differences depending on which network had been used to inform the NMA. The ERG considers the absolute effect estimates generated by the base case NMAs are likely to be more reliable than those generated by the sensitivity NMAs as the risk of population heterogeneity is lower in the smaller network. The ERG does not consider that the following absolute effects sensitivity NMA results, for all comparators, are a suitable basis for decision making:

- biologic-naïve rad-axSpA population for BASDAI score cfb and BASFI score cfb
- biologic-experienced rad-axSpA population for BASDAI score.

It was not possible for the ERG to investigate the robustness of the sensitivity NMAs where there were no base case results available.

3.7.3 Adverse events

Results from the COAST trials show that treatment with ixekizumab was well-tolerated. Clinical advice to the ERG is that AEs arising from treatment with ixekizumab and other IL-17A inhibitors require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of biologic therapy related AEs, and that this can place a high burden on NHS staff and systems.

4 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of the use of ixekizumab for treating axSpA after NSAIDs. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

4.1 Published cost effectiveness evidence

4.1.1 Objective of the company's literature searches

The company undertook systematic and targeted searches to identify studies evaluating the cost effectiveness of ixekizumab and other relevant interventions for the treatment of rad-axSpA and nr-axSpA.

1.1.1 Search strategy

The searches were carried out between January and March 2017 and were updated in October 2019. Relevant electronic databases (MEDLINE, Embase, the Cochrane Library and EconLit) were searched and the search terms used included combinations of index terms and free text words.

Manual searches of abstracts from conferences, including those held by the American College of Rheumatology (ACR/ARHP Annual Meeting), Asia Pacific Rheumatology Congress (APLAR) and the European League Against Rheumatism (EULAR), were also conducted to identify relevant abstracts published during the 2 years prior to the database searches. In addition, the websites of international health technology appraisal (HTA) agencies were searched to identify appraisals or assessments of relevant therapies for axSpA that included descriptions of cost effectiveness models.

4.1.2 Eligibility criteria used in study selection

The eligibility criteria were designed to identify cost effectiveness models that had been developed to estimate the cost effectiveness of biological treatments to treat adults with active axSpA.

Two researchers independently screened all publications according to their title and abstract content. Any discrepancies in terms of inclusion/exclusion decisions between the researchers were resolved through discussion. The same process was repeated for the full-length articles selected during the title and abstract screening process.

4.1.3 Findings from the company's cost effectiveness review

The company's selection strategy identified 26 publications reporting cost effectiveness models. However, none of these studies evaluated the cost effectiveness of treatment with ixekizumab in populations with rad-axSpA or nr-axSpA.

4.1.4 ERG comments

The ERG is satisfied with the company's cost effectiveness literature search and study selection methods and notes that this process did not identify any studies evaluating the cost effectiveness of treatment with ixekizumab in populations with rad-axSpA or nr-axSpA.

The searches used by the company to identify cost effectiveness models were also used by to identify HRQoL, resource and cost information that could be used to populate the company economic models. However, the study selection process for identifying these types of data differed, but only slightly, from the criteria used to identify the cost effectiveness studies.

4.2 NICE Reference Case and Drummond checklists

Table 38 NICE Reference Case checklist

Element of health technology assessment	Reference case	ERG comment on company submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource use based on European data collected over 20 years ago. NHS costs only
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

EQ-5D=EuroQol-5 dimensions; HRQoL=health-related quality of life; PSS=Personal Social Services; QALYs=quality adjusted life years

Table 39 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Clinical effectiveness in comparison to placebo was established in the COAST trials and in the NMAs for the rad-axSpA populations and for the biologic-naïve nr-axSpA population. However, heterogeneity in the sensitivity analysis NMAs for the rad-axSpA populations has resulted in uncertainty in the comparative clinical effectiveness of ixekizumab versus biological treatments.
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	Resource use was from a European source (data collected over 20 years ago); however, this was the best available evidence that could have been used in the company models.
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

NMA=network meta-analysis; nr-axSpA=non-radiographic axial spondylitis

4.3 ERG summary of the company models

4.3.1 Populations

The company has produced cost effectiveness results (incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained for three patient populations. A description of these populations and the baseline characteristics of the populations that were included in the company's three main RCTs are provided in Table 40.

Table 40 Model populations

	Mean age (years)	Proportion male (%)	Mean weight (kg)	Baseline BASDAI score	Baseline BASFI score	Source
Rad-axSpA						
Biologic-naive	47.1	80.9	78.1	6.75	6.23	COAST-V trial
Biologic-experienced	46.1	80.1	83.2	7.43	7.27	COAST-W trial
Nr-axSpA						
Biologic-naive	40.3	47.2	77.5	7.16	6.52	COAST-X trial

BASDAI=Bath ankylosing spondylitis disease activity index; BASFI=Bath ankylosing spondylitis functional index; nr-axSpA=non-radiographic axial spondyloarthritis; rad-axSpA=radiographic axial spondyloarthritis

4.3.2 Structure of the models

The company provided two MS Excel cohort Markov models that are driven by Visual Basic for Applications (VBA) code. One model is populated with data relating to the population with rad-axSpA and the other relates to the population with nr-axSpA. The company models are similar to models used to inform previous NICE Technology appraisals of TNF-alpha inhibitors of treatments for rad-axSpA and nr-axSpA (TA383[14] and TA407[21]).

The structure of the company model is shown in Figure 1. At the end of the initial trial period (12 or 16 weeks), the patient's response to treatment (defined by BASDAI50) was assessed. Patients who responded to treatment transitioned to the maintenance treatment health state; those who did not, transitioned to the conventional care health state.

The initial mean changes in BASDAI and BASFI scores that occurred during the initial trial phase were assumed to be maintained whilst patients remained on biological treatment (i.e., whilst in the maintenance treatment health state) and these patients experienced a slower rate of BASFI progression compared with those receiving conventional care (referred to in the CS as 'disease natural history'). The baseline BASDAI and BASFI values for each population were derived from the COAST trials.

Patients in the maintenance treatment health state were at risk of treatment discontinuation as a consequence of severe AEs or loss of response. The drop-out rate was assumed to be constant over time and across all treatments. On discontinuation of treatment, patients transition to the conventional care health state where they stay until death or until the end of the simulation. This means that biologic-naïve patients only receive one biological treatment over the course of their lifetime, and biologic-experienced patients only receive one further biological treatment regardless of the number of previous treatments.

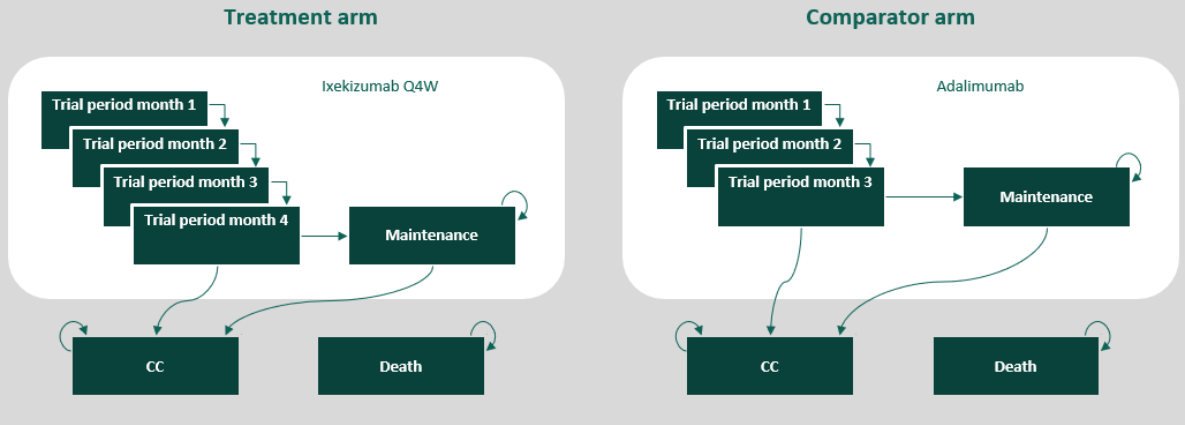

Figure 1 Company model structure

cc=conventional care
Source: CS, Figure 29 (p143)

4.3.3 Interventions and comparators

Intervention

The intervention is ixekizumab. In line with the product SmPC,[3] the modelled dose is 80mg Q4W, irrespective of underlying medical condition.

Comparators

Dosing schedules for the comparator treatments are provided in Table 41.

Table 41 Comparator treatments

Comparator	Length of trial period	Dosing schedule	Notes
Adalimumab	12 weeks[14]	400mg Q2W[61]	
Certolizumab pegol	12 weeks[14]	400mg at weeks 0, 2 and 4, followed by maintenance dosing of 200mg every 2 weeks or 400mg every 4 weeks[62]	
Etanercept	12 weeks[14]	25mg Q2W *or* 50mg QW[63]	
Golimumab	12 weeks[14]	50mg once monthly[64]	
Infliximab	12 weeks[14]	5mg/kg at weeks 0, 2, and 6; thereafter every 6 – 8 weeks (assume every 7 weeks on average)[65]	Not a comparator for the nr-axSpA population
Secukinumab	16 weeks[21]	150mg or 300mg at Weeks 0, 1, 2 and 3 followed by a maintenance dose once a month starting at Week 4[66]	Included in a scenario analysis only Not a comparator for the nr-axSpA population
Conventional care	NA	Patients are assumed to continue conventional care alongside biologic therapy, therefore specific interventions were not explicitly modelled	

nr-axSpA=non-radiographic axial spondyloarthritis; QW=every week; Q2W=every 2 weeks
Source: CS, Table 97

Secukinumab is listed as a relevant comparator in the final scope[28] issued by NICE for patients with rad-axSpA disease. The company did not include this drug as a comparator in their base case analysis due to insufficient effectiveness data; [redacted]

4.3.4 Perspective, time horizon and discounting

The company states that costs are considered from the perspective of the NHS and Personal Social Services. The model cycle length is 1 month (a half-cycle correction was not applied) and the model time horizon is 54 years for the rad-axSpA biologic-experienced population, 58 years for the rad-axSpA biologic-naïve population and 60 years for the nr-axSpA biologic-naïve population. Costs and outcomes were discounted at 3.5% per annum.

4.3.5 Clinical parameters and variables

The company base case model values for BASDAI50, BASDAI score cfb and BASFI score cfb were derived from the company's sensitivity NMAs. However, data were not available to populate all variables for all treatments for all three populations. In the base case, where parameter values were missing, average NMA results across the TNF-alpha inhibitors were used.

4.3.6 Response rates

Short-term changes in BASDAI and BASFI

The BASDAI50 values used in the company base case analyses were obtained from the company's sensitivity NMAs. Where the trial results inputs required to populate the NMAs were not available, the average inputs across all TNF-alpha inhibitors for which relevant inputs were available were used.

Due to BASDAI50 and BASFI score cfb efficacy inputs not being available from the rad-axSpA sensitivity NMA results, secukinumab 150mg (an IL-17A inhibitor) was not included as a comparator in the company base case cost effectiveness analyses. Further, due to the date of the licence extension which permitted use of a 300mg dose, systematic searches were not carried out to determine the efficacy of the 300mg dose. [redacted]

Estimates of mean BASDAI score cfb and BASFI score cfb that are conditional on response status (as defined by BASDAI50) were not available from the company's sensitivity NMAs for any of the treatment options. The company estimated the relationship between conditional BASDAI and BASFI using available trial data. Where treatment-specific trial data were not available, an average from available trial data (for active treatments, therefore excluding conventional care) was used. To generate the conditional values, the relationship values, as well as data relating to the overall proportion of responders and overall cfb values for BASDAI and BASFI for each intervention, were input into a set of equations (see CS, Appendix M). The conditional scores are presented in Table 102 (BASDAI) and Table 103 (BASFI) of the CS.

Long-term changes in BASDAI and BASFI

In line with the York rad-axSpA model, [14] the company has assumed that, as well as the short-term progression described in the previous section, patients experience long-term BASFI progression. This long-term progression was assumed to be a function of disease activity (as defined by BASDAI) and the extent of, and progression of, radiographic disease (modified stroke ankylosing spondylitis spine score [mSASSS]). The annual natural history without pharmacological treatment (conventional care) rate of BASFI change was modelled using the equation displayed in Box 1.

Box 1 Annual rate of BASFI change equation

Annual rate of BASFI change=annual rate of mSASSS change x BASFI change with 1 unit change in mSASSS

BASFI=Bath Ankylosing Spondylitis Functional Index; mSASSS=Modified Stroke Ankylosing Spondylitis Spine Score
Source: CS, p156

The company assumed that the annual rate of change of mSASSS was that reported by Ramiro[67] (1.44 for patients with rad-axSpA and 0.69 for patients with nr-axSpA) and the magnitude of the independent effect of a 1 unit change in mSASSS on BASFI was 0.057 (derived from the multivariate relationship reported by Landewe[68]). The annual rate of BASFI change for patients receiving a biological treatment was estimated to be 0.42 (reported by Haroon[69]) multiplied by the natural history (conventional care) rate of BASFI change. The treatment effect was applied from the start of the maintenance period.

Rebound in BADAI and BASFI

In the base case, upon discontinuation of treatment, patients were assumed to lose their treatment response and their BASDAI and BASFI scores reverted to baseline values.

Patients who entered conventional care at the end of the trial period (i.e., non-responders) were modelled to experience a transient treatment response (corresponding to placebo response) but, after the first cycle, BASDAI and BASFI reverted to baseline values.

4.3.7 Adverse events

Conventional care was assumed not to be associated with any AEs. For all other treatments, only two AEs were modelled: tuberculosis reactivation and severe infections. Treatment specific absolute risks were used; no differences between populations were modelled. The AE rates were applied for the whole treatment period and, due to a lack of data, the incidence of an AE was not associated with any utility loss.

4.3.8 Discontinuation of therapy

During each cycle, patients in the maintenance health state were at risk of discontinuing treatment, i.e., moving to the conventional care health state. The discontinuation rate was assumed to be the same for all treatments and constant over time. The annual discontinuation rates for the rad-axSpA and nr-axSpA populations were 11% and 5%, respectively. [14]

4.3.9 Mortality

General UK population mortality was modelled by fitting a Gompertz curve to Office for National Statistics (ONS) 2016-2018 life table data.[70]

4.3.10 Health-related quality of life

The COAST-V, -W and -X trials included the collection of HRQoL data using the EQ-5D-5L health utilities instrument. The collected EQ-5D-5L scores were cross-walked to EQ-5D-3L values using the van Hout 2012[48] approach and converted to utility values using the UK value set.[49] The company then developed regression models to link disease activity and function to HRQoL, so that utility varies as patients' BASDAI and BASFI scores change. Different models were developed for the three different populations (CS, Table 108 and Table 109). The effect of using utility values generated by regression models developed by other companies/authors[21,71,72] was explored using scenario analyses.

4.3.11 Resources and costs

Five categories of costs were included in the company model (Section B.3.5.1):

- drug acquisition costs
- administration costs
- trial period and maintenance health state monitoring costs
- health state costs
- AEs.

Where required, costs were inflated to 2019 values using the Personal Social Services Research Unit (PSSRU) Hospital & Community Health Service Prices and Pay index.[20]

Drug acquisition costs

The drug acquisition costs used in the company model are provided in Table 42. When calculating these costs, it was assumed that vials were not shared.

Ixekizumab is available to the NHS at a confidential PAS discounted price. Secukinumab is also available to NICE at confidential PAS discounted price, this price is not known to the company. The PAS scheme for golimumab and certolizumab pegol are not confidential and are as follows:

- Certolizumab pegol: first 12 weeks of stock free
- Golimumab: 100mg for the price of 50mg when patient weighs >100kg.

The company has not included the golimumab PAS discount in their model as the mean baseline weight of patients in the COAST-V, COAST-W and COAST-X trials was <100kg and it was considered that the discount would make little difference to model cost effectiveness results.

Acquisition costs were obtained from MIMS[21] (certolizumab, etanercept, golimumab and infliximab), NICE TA407[21] (secukinumab), and NHS England & NHS Improvement[73] (adalimumab). The cost of adalimumab used in the company model relates to regional groups except South London (the South London price for the 40mg dose is £3,662.23 per patient per year). Where biosimilar drugs are available, the company has used the lowest biosimilar price.

Table 42 Drug acquisition costs

Treatment[†]	Indication(s)	Dose[a]	Cost per trial period	Cost per year in maintenance period
Ixekizumab (80mg LD; PAS price)	rad-axSpA nr-axSpA	80mg	[redacted]	[redacted]
Ixekizumab (160mg LD; PAS price)	rad-axSpA	80mg	[redacted]	[redacted]
Certolizumab pegol	rad-axSpA nr-axSpA	200mg/400mg	0	£9,295
Etanercept (25mg)	rad-axSpA nr-axSpA	25mg	£1,931	£8,366
Etanercept (50mg)	rad-axSpA nr-axSpA	50mg	£1,931	£8,366
Golimumab	rad-axSpA nr-axSpA	50mg	£2,289	£9,156
Infliximab	rad-axSpA	5mg/kg[b]	£4,524	£12,064
Secukinumab (300mg)	rad-axSpA	300mg	£9,750	£14,625
Adalimumab	rad-axSpA nr-axSpA	40mg	£819.23	£3,550

[†] All drug costs have been obtained from MiMS 2019, except that for adalimumab
[a] Dosing frequencies are provided in the CS (Table 97)
[b] Dose is weight dependent – estimated based on mean dose (see Table 40 for population weights used in the company model)
nr-axSpA=non-radiographic axial spondyloarthritis; LD=loading dose; PAS=Patient Access Scheme; rad-axSpA=radiographic axial spondyloarthritis
Source: CS, Table 110 and Table 111

Administration costs

All drugs are administered subcutaneously, except infliximab, which is administered intravenously (IV).

The company has assumed that once patients have been taught to self-administer, there are no further administration costs associated with subcutaneous injections. The training was assumed to take one hour of nurse time (£42).[73]

The company has assumed that the cost of an IV infusion is the same as the cost of an IV chemotherapy infusion. The cost (£289.00 per administration) relates to NHS Reference Costs 2017-2018[74] health care resource (HRG) code SB15Z "deliver subsequent elements of a chemotherapy cycle".

Trial period and maintenance health state monitoring costs

Details of level of treatment monitoring included in the model are provided in Table 43. The cost of a specialist visit was taken from NHS Reference Costs 2017-18,[74] as were the unit costs for laboratory tests, except for the cost for a tuberculosis Heaf test, which was obtained from Rodgers 2011.[75]

Table 43 Health state monitoring resource use

Cost parameter	rad-axSpA resource use		nr-axSpA resource use	
	Trial period	Maintenance (yearly)	Trial period	Maintenance (yearly)
Medical visits				
Specialist visit	2	2	2	2
Laboratory tests				
FBC	2	4	2	4
LFT	2	4	2	4
ESR	2	4	2	4
U&E	2	4	2	4
Chest radiograph (X-ray)	1	0	1	1
THT	1	0	1	0
Antinuclear antibodies	1	0	1	0
DNA double-strand test	1	0	1	0
CRP	0	0	1	0
MRI	0	0	1	0

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; FBC=full blood count; LFT=liver function test; MRI=magnetic resonance imaging; THT=tuberculosis Heaf test; U&E=urea & electrolytes
Source: CS, Table 114

Health state costs

Health state costs were estimated using a regression model equation that was originally presented in one of the company submissions for TA383.[14] This regression model includes BASFI score as a parameter. It was originally developed using data from the international OASIS cohort which has been re-analysed using 2013 published tariffs.[76] The company inflated the resultant costs to 2019 prices.

Adverse event costs

The costs of a serious infection and a tuberculosis reactivation episode used in the company model are the weighted averages of relevant Health Resource Group costs from NHS Reference Costs 2017-18. [74]The cost of treating a serious infection has been estimated to be £3,060.65 per episode and the cost of treating a tuberculosis reactivation episode has been estimated to be £3,869.10.

4.3.12 Results

Company base case results

Incremental and pairwise company base case cost effectiveness results for patients with rad-axSpA are provided in Table 44 (biologic-naive) and Table 45 (biologic-experienced) whilst those for patients with nr-axSpA are provided in Table 46 (biologic-naïve).

Table 44 Company base case ICERs per QALY gained for rad-axSpA biologic-naïve patients (PAS prices for ixekizumab and certolizumab pegol)

Comparator	Total		Incremental		ICER per QALY gained	
	Costs	QALYs	Costs	QALYs	Incremental	Pairwise (ixekizumab vs comparator)
Conventional care	[redacted]	[redacted]	-	-	-	£34,301
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£4,387	IXE Dominated
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	IXE Dominant
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	IXE Dominant
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	IXE Dominant
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	IXE Dominant

ICER=incremental cost effectiveness ratio; IXE=ixekizumab; QALY=quality adjusted life year; Q4W=every 4 weeks
Source: CS, Table 118

Table 45 Company base case ICERs per QALY gained for rad-axSpA biologic-experienced patients (PAS prices for ixekizumab and certolizumab pegol)

Comparator	Total		Incremental		ICER per QALY gained	
	Costs	QALYs	Costs	QALYs	Incremental	Pairwise (ixekizumab vs comparator)
Conventional care	[redacted]	[redacted]	-	-	-	£1,603,221
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£56,119	IXE Dominated
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£41,794*
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£954,573*
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£96,133*
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	£860,378	£287,583*

ICER=incremental cost effectiveness ratio; IXE=ixekizumab; QALY=quality adjusted life year; Q4W=every 4 weeks
* ICERs per QALY gained are located in the south-west quadrant of the cost effectiveness plane (ICERs per QALY gained > threshold value indicate intervention is cost effective)
Source: CS, Table 119

Table 46 Company base case ICERs per QALY gained for nr-rad-axSpA biologic-naïve patients (PAS prices for ixekizumab and certolizumab pegol)

Comparator	Total		Incremental		ICER per QALY gained	
	Costs	QALYs	Costs	QALYs	Incremental	Pairwise (ixekizumab vs comparator)
Conventional care	[redacted]	[redacted]	-	-	-	£29,687
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£4,809	£423,916
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£16,672
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	IXE Dominant
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	£75,056	£14,435*

ICER=incremental cost effectiveness ratio; IXE=ixekizumab; QALY=quality adjusted life year; Q4W=every 4 weeks
* ICER per QALY gained located in the south-west quadrant of the cost effectiveness plane (ICERs per QALY gained > threshold value indicate intervention is cost effective).
Source: CS, Table 120

Probabilistic sensitivity analysis

The company carried out probabilistic sensitivity analyses (PSAs) for each pairwise comparison, for each of the populations (1,000 iterations). The ICERs per QALY gained generated by the company's PSAs were similar for the rad-axSpA biologic-naïve population for all pairwise comparisons; differences (>£5,000) for the rad-axSpA biologic-experienced and nr-axSpA biologic-naïve patients are shown in Table 47.

Table 47 Differences (>£5,000) between deterministic and probabilistic pairwise (versus ixekizumab) cost effectiveness results (PAS prices for ixekizumab and certolizumab pegol)

Comparator	ICERs per QALY gained (ixekizumab vs comparator)		
	Deterministic analysis	Probabilistic analysis	Difference
Rad-axSpA: biologic-experienced			
Conventional care	£1,603,221	£1,635,912	£32,691
Certolizumab pegol	£954,573	£1,117,054	£162,481
Infliximab	£287,583	£272,720	-£14,863
Nr-axSpA: biologic-naive			
Adalimumab	£423,916	£559,570	£135,654

ICER=incremental cost effectiveness ratio; nr-axSpA=non-radiographic axial spondyloarthritis; rad-axSpA=radiographic axial spondyloarthritis; QALY=quality adjusted life year
Source: CS, Table 119, Table 120, Table 122 and Table 123

4.3.13 Deterministic sensitivity analyses

The company undertook a wide range of deterministic sensitivity analyses. For all three populations, the most influential parameters were BASDAI50 response rate, BASFI reduction for responders and BASDAI reduction for responders; these parameters were consistently placed in the list of top five most influential parameters for all comparisons.

4.3.14 Scenario analyses

The company also carried out a wide range of scenario analyses and concluded that these results aligned with their pairwise base case cost effectiveness results in the vast majority of cases.

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	-	-	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

4.3.15 Model validation

The company reports that the model was built to align with the NICE Reference Case[74]and that the structure of the model closely aligns with the model built by the Assessment Group for use in TA383.[14] In addition, the company reports that the model structure and assumptions were validated by an independent health economics expert.

4.4 ERG critique of the company models

4.4.1 The modelling of axial spondyloarthritis

The company submitted two cost effectiveness models, built in MS Excel, largely driven by VBA code. The company highlights (CS, p142) that a cohort Markov structure was used and is the same structure that was used in the MTA model (the 'York model') that compared TNF-alpha inhibitors (TA383[14]) with conventional care for the treatment of rad-axSpA and nr-axSpA.

The model is a modified decision tree, the duration of the initial treatment phase is 12 weeks and response at the end of 12 weeks is determined by BASDAI50. After the initial treatment phase, patients experience an improvement in BASDAI and BASFI; the magnitude of this improvement is estimated from results of an evidence synthesis conducted for the MTA by the original Assessment Group. BASDAI score cfb and BASFI score cfb values are estimated for responders and non-responders as two separate groups. Prior to the York model, BASDAI score cfb and BASFAI score cfb were included in economic models of axSpA using data from the whole population.

Patients' BASFI scores change over time and the rate of change is slowed whilst patients are on treatment. Patients who initially respond, but later fail treatment, have their BASFI scores increased to reflect the deterioration in disease function once treatment has been discontinued. Whether patients lose their initial BASFI gain only, or return to the same point they would have been reached via the natural history trajectory (without treatment), is explored by the company.

Patients were modelled to only receive one line of treatment. For the biologic-naïve populations, this means patients are modelled to only receive one treatment over the whole of their remaining lifetime. Clinical advice to the ERG is that this assumption is unrealistic as there are a number of treatments available to treat axSpA. Allowing only one treatment per remaining lifetime is a limitation of the company models as the totality of the downstream consequences of introducing ixekizumab to the treatment pathway are not modelled. The models have the functionality to include subsequent lines of treatment; however, there is insufficient effectiveness evidence to facilitate the modelling of treatment sequencing.

Clinical advice to the ERG is that the disease process of axSpA is non-linear and is complicated by flares that may temporarily influence a patient's BASDAI score. Also, permanent spinal deformity can mean that functional improvement (as measured by BASFI) becomes very difficult. The relationship between BASDAI and BASFI and HRQoL is uncertain; attempts to model these relationships have produced varied results (see Section 4.6.2).

Clinical advice to the ERG is that evidence of the impact of biologic drugs on radiographic progression is uncertain. If this impact varies between treatments, this could have important implications for the relative cost effectiveness of the treatments being compared. In the models, the company incorporates the published evidence that is available to estimate this relationship; however, the ERG considers this is another area of uncertainty in the company models.

In line with the results of previous appraisals of health economic modelling in this patient population (TA383[14] & TA407[2]), the ERG considers that there are evidence gaps that mean that any economic modelling is reliant on the incorporation of uncertain assumptions. Some of these assumptions are fundamental to the estimates of cost effectiveness, but little can be done to reduce this uncertainty. The ERG considers that use of a model based on the available data and using the same structural assumptions as have been employed in previous appraisals does, however, create a level playing field for the appraisal of the cost effectiveness of ixekizumab versus treatments previously recommended by NICE.

4.4.2 ERG validation of the company models

The algorithms in the company models are coded in Visual Basic and are therefore difficult to check. The model manual and technical guide provided by the company during and after clarification provided insufficient information to facilitate a comprehensive validation of the company model. The ERG stress tested the model and also checked that the variable references in the Visual Basic code pointed to the correct input parameters in the model Excel sheets. No Visual Basic errors were detected. Whilst the results from stress testing the model suggest that the model algorithms are correctly specified and that the model results reflect the company's choice of input parameters and structural assumptions, the ERG cannot be fully confident that the model algorithms are error free.

The company states that their estimates of BASDAI score cfb and BASFI score cfb are based on published values that have been used to describe the relationship between response of (i) responders and (ii) non-responders. The ERG asked for further details of these calculations at the clarification stage but the company did not provide sufficient detail for the ERG to be confident that the published values used in the models were appropriate.

4.5 Model parameters and assumptions

4.5.1 Robustness of efficacy data to populate the rad-axSpA model

As stated in Section 3.6.3 of this report, the ERG considers that the some of the results from the sensitivity NMAs for the rad-axSpA populations (BASDAI score cfb and BASFI score cfb for the biologic-naïve, and BASDAI score cfb for the biologic-experienced) are not suitable for decision making. As these values are used in the company model for the rad-axSpA populations, the cost effectiveness results generated by the company model for the rad-axSpA populations are also not suitable for decision making.

In their clarification response, the company stated that [redacted]

The ERG agrees with the company that there are currently insufficient data available in the public domain to allow a comparison of either the clinical or cost effectiveness of ixekizumab versus secukinumab.

4.5.2 Conventional care as a comparator

Clinical advice to the ERG is that conventional management is an appropriate comparator for biologic-naive patients in the nr-axSpA population when TNF-alpha inhibitors are not tolerated or contraindicated and for biologic-experienced patients in the rad-axSpA and nr-axSpA populations when biological treatment options are exhausted.

Established clinical practice may not be an appropriate treatment for biologic-naïve patients in the rad-axSpA population, (even when TNF-alpha inhibitors are not tolerated or are contraindicated) as secukinumab is a treatment option.

4.5.3 Response to treatment

It is stated in NICE guidance[1,2] that response to biological treatment is determined by:

- a 50% reduction in BASDAI score or a reduction in BASDAI score by 2 units from the pre-treatment value
  and
- a reduction in spinal pain VAS by 2cm or more.

In the company economic models, response to treatment was determined only if there was a 50% reduction in BASDAI score during the initial 'trial phase'. This means that the response rate used in the models may not reflect the response rate seen in NHS clinical practice. The company collected BASDAI50 and VAS data during the COAST trials; however, as both BASDAI50 and VAS data are not available for patients treated with all of the drugs of interest in this appraisal, this information could not be incorporated into the company economic models. The company's approach (using only BASDAI50 data) has also been used in previously published models that were developed to assess the relative cost effectiveness of treatments for axSpA (TA383[1] and TA407[2]).

The result of using this modelling approach is likely to be an overestimation of the response rate as there may be some patients who achieve a 50% reduction in BASDAI but do not meet the pain VAS criterion. The exact level of overestimation of response cannot be determined for each treatment. In the absence of evidence, it is not known whether the level of overestimation is similar across all treatments.

4.5.4 Trial period in the economic models

Clinical advice to the ERG is that although there is a pre-defined period during which the responsiveness of patients to the biologic drugs is measured (12 or 16 weeks),[1,2] in reality, determining whether a patient is going to be a long-term responder may take more time. For example, clinical advice to the ERG is that it could take up to 6 months for patients to show adequate response to treatment. The percentage of responders and therefore effectiveness of specific treatments in the company models may therefore be underestimated.

4.5.5 Health state resource use and costs

The company economic models use a regression equation to derive health state costs according to patients' BASFI scores. The data source used in the regression equation is the OASIS study[77]; the OASIS study was conducted in France, Netherlands and Belgium in 1998. The equation was derived by Abbvie as part of their TA383[1] submission. Clinical advice to the ERG is that basing resource use on the BASFI score is a reasonable approach. However,

clinicians also advised that current NHS practice differs significantly from the clinical practice experienced by the OASIS cohort and also from the resource use described in the company model. The resource use described in the company model suggests that:

- patients with the highest BASFI scores are assumed to have a physiotherapy appointment every week; in contrast, clinical advice to the ERG is that, on average, patients in the NHS are offered six physiotherapy sessions per year
- the number of patients hospitalised is much higher than the number of NHS patients hospitalised
- the number of specialist visits for people with a BASFI score of 5-6 is much higher than it is for people in NHS clinical practice.

These assumptions are all likely to lead to an overestimation of healthcare resource use by BASFI status in the company models.

4.5.6 Biologic-experienced nr-axSpA patients

Clinical effectiveness evidence is not available for the biologic-experienced nr-axSpA patients. The company presents a scenario analysis for this population. This scenario has been rung by populating the nr-axSpA company model with data from the biologic-naïve nr-axSpA population. The biologic-naïve data have been adjusted using a 'modification factor' that reflects the relationship between the BASDAI50 results for the biologic-naïve and biologic-experienced rad-axSpA populations. The modification factor (61.43%) is applied to each of the BASDAI50 response rates for the nr-axSpA biologic-naïve treatments. The company stated that the sources of evidence used to derive this modification factor were the COAST-V and COAST-W trials, however, the calculations used by the company to generate this value were not clear.

There is no evidence that the relationship between the biologic-naïve and biologic-experienced nr-axSpA populations is the same as the relationship between the biologic-naïve and biologic-experienced rad-axSpA populations. Therefore, the ERG considers that using effectiveness evidence based on this assumption is problematic and that the results of the company scenario analysis (scenario 9) for biologic-experienced nr-axSpA patients are not suitable for decision making.

4.6 Exploratory and sensitivity analyses presented by the ERG

The ERG has highlighted that there are several structural and data weaknesses (see Section 3.6.3, 4.4.1 and 4.5) in the company's economic models. Unfortunately, the ERG is unable to resolve any of these issues. To illustrate how sensitive the company's models can be to small changes in costs and QALYs, the ERG has explored three scenarios where it is possible to make appropriate changes to the company models.

4.6.1 Company scenario (4)/ ERG scenario (S1): BASFI scores after treatment discontinuation

In the company base case, the economic models assume that after treatment is discontinued, patients' BASFI scores increase (function deteriorates) by the same amount as the initial gain (the 'rebound by initial gain assumption'). The rebound by initial gain assumption implies some of the functional improvement from the use of biological treatment is maintained after treatment has been discontinued.

In the company models there is an alternative to the 'rebound by initial gain' assumption, namely the 'rebound to natural history' assumption. The 'rebound to natural history' assumption returns the patient to the level of function they would have had if they not received the biological treatment.

Clinical advice to the ERG is that there is no strong evidence to support either assumption. The ERG considers that the reality may lie somewhere in between these two assumptions i.e., that the rebound to natural history assumption implies there is no benefit beyond the end of treatment (likely worst case) and the rebound by initial gain assumption implies that all of the initial gain from treatment is maintained beyond treatment discontinuation (likely overestimating the gains of treatment). The ERG has presented the company's results from the rebound to natural history scenario to demonstrate the effect of using this alternative assumption on company base case cost effectiveness results.

4.6.2 Company scenario (3a)/ERG scenario (S2): utility estimates

In the company base case, regression equations were used to generate utility values from HRQoL data collected as part of the COAST trials using EQ-5D-5L questionnaires. Utility values were estimated using six different regression equations. These equations varied depending on whether they were developed using EQ-5D-5L data or EQ-5D-5L data that had been cross walked to EQ-5D-3L data, and whether the underlying data were sourced from biologic-naive or biologic-experienced patients. All six regression equations included BASDAI and BASFI scores as parameters.

The company models included options that allowed results from other published regression equations to be used to estimate utility values. These equations all take into account BASDAI and BASFI scores, and some equations also considered age and sex.[21,72] Figure 2 shows the utility values generated by the different equations included in the company models for a population with a BASDAI score of 7 and BASFI scores that vary over time. The variation in the results from the equations tends to increase as BASFI levels increase (i.e., as patients' levels of function deteriorate).

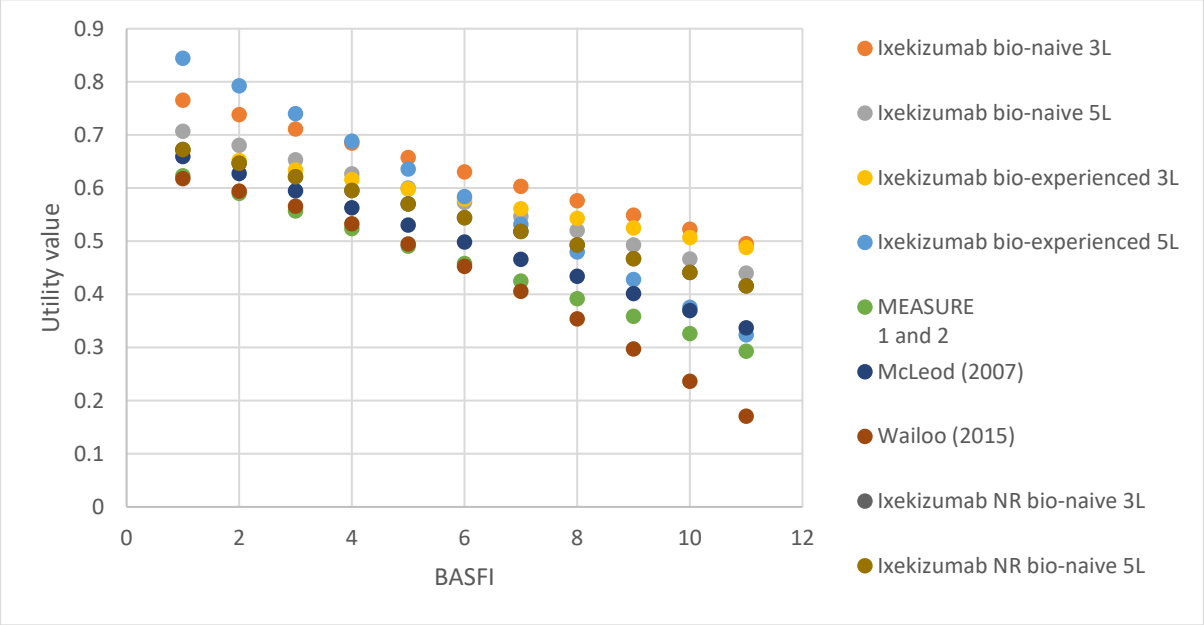

Figure 2 Comparison of utility estimates generated by different regression equations

The ERG highlights that the estimates of utility generated by the company's approach are all higher than the estimates generated using the other published regression equations. The ERG has, therefore, presented a scenario analysis in which the Wailoo 2015[71] regression equation is used to estimate utilities; of the nine equations considered in the CS, this equation generally generates the lowest utility estimates. A scenario using the Wailoo 2015[71] regression equation provides lower life time QALY estimates which contrast with the higher QALY estimates generated using the company's approach.

4.6.3 ERG scenario (S3): clinical effectiveness

In the CS and in the response to clarification, the company provided evidence of the superiority of ixekizumab versus some of the comparator treatments; this evidence of superiority was not based on any of the effectiveness outcomes used within the company economic models. Where ixekizumab was not demonstrated to be superior to comparator treatments, testing the equivalence or non-inferiority of ixekizumab was not carried out by the company.

The ERG highlights that [redacted]. The ERG considers that, in comparisons when (some) effectiveness outcomes have not been demonstrated to be statistically significant, a scenario should be run in which the magnitude of these outcomes is modelled to be the same for all treatment options. The ERG presents a de novo scenario for the biologic-naïve nr-axSpA population using the ixekizumab effectiveness results from the company's sensitivity NMAs for the biological treatment comparators. The placebo sensitivity NMA estimates were used to represent conventional care were not amended as the sensitivity NMAs demonstrated superiority of ixekizumab over placebo. Scenario results for the rad-axSpA populations are not presented due to irregularities in the results of some of the outcomes assessed in the sensitivity NMAs (see Section 3.6.3 for details).

4.7 Impact on the ICER of additional clinical and economic analyses presented by the ERG

The ERG has presented results from three scenario analyses:

- BASFI rebound to natural history upon treatment discontinuation (S1)
- Alternative method of modelling utility (Wailoo 2015[71] regression equation) (S2)
- Non-statistically significantly different outcomes from the NMAs assumed to demonstrate no evidence of superiority (S3).

Two sets of pairwise cost effectiveness comparisons (ixekizumab versus conventional care and ixekizumab versus adalimumab) for three of the four subpopulations (Table 49 to Table 54) are presented in the main body of this report; the ERG has not been able to present cost effectiveness estimates for biologic-experienced nr-axSpA patients (due to the lack of NMA results).

The ERG has presented the results of ixekizumab versus conventional care and ixekizumab versus adalimumab in the main body of the report. Clinical advice to the ERG is that adalimumab is the most commonly used biological treatment (and it is the comparator that presents the greatest challenge, from a cost effectiveness perspective, to ixekizumab). The pairwise results for ixekizumab versus the other comparators modelled by the company and the fully incremental results are presented in Appendices 3 to 7.

Details of all Microsoft Excel revisions carried out by the ERG to the company model are provided in Appendices 8 to 10.

Table 49 Biologic naïve rad-axSpA (ixekizumab compared to conventional care), PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Conventional care		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]						£34,301	-
S1. BASFI rebound to natural history	[redacted]						£42,970	+£8,670
S2. Alternative utility calculations (Wailoo)	[redacted]						£20,640	-£13,661
S1+S2	[redacted]						£26,622	-£7,679

ICER=incremental cost effectiveness ratio: PAS=patient access scheme; QALY=quality adjusted life year

Table 50 Biologic naïve rad-axSpA (ixekizumab compared to adalimumab), PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Adalimumab		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]						IXE dominated	-
S1. BASFI rebound to natural history	[redacted]						IXE dominated	+£440,399
S2. Alternative utility calculations (Wailoo)	[redacted]						£2,798,792	+£4,473,895
S1+S2	[redacted]						IXE dominated	-£6,214,398

ICER=incremental cost effectiveness ratio, IXE=ixekizumab; PAS=patient access scheme; QALY=quality adjusted life year

Table 51 Biologic experienced rad-axSpA (ixekizumab compared to conventional care), PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Conventional care		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]		[redacted]		[redacted]		£1,603,221	-
S1. BASFI rebound to natural history	[redacted]		[redacted]		[redacted]		IXE dominated	-£4,160,121
S2. Alternative utility calculations (Wailoo)	[redacted]		[redacted]		[redacted]		£145,510	-£1,457,711
S1+S2	[redacted]		[redacted]		[redacted]		£335,837	-£1,267,384

*This is the value from the company model
ICER=incremental cost effectiveness ratio, IXE=ixekizumab; PAS=patient access scheme; QALY=quality adjusted life year

Table 52 Biologic experienced rad-axSpA (ixekizumab compared to adalimumab), PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Adalimumab		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]		[redacted]		[redacted]		IXE dominated	-
S1. BASFI rebound to natural history	[redacted]		[redacted]		[redacted]		IXE dominated	+£4,750
S2. Alternative utility calculations (Wailoo)	[redacted]		[redacted]		[redacted]		IXE dominated	+£4,090
S1+S2	[redacted]		[redacted]		[redacted]		IXE dominated	+£23,685

*This is the value from the company model

ICER=incremental cost effectiveness ratio, IXE=dominated; PAS=patient access scheme; QALY=quality adjusted life year

Table 53 Biologic naïve nr-rad-axSpA (ixekizumab compared to conventional care), PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Conventional care		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,687	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,763	+£2,076
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,491	-£12,195
S3. Non-superior non-statistically significant outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,687	£0*
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,815	-£10,871
S1+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,763	£2,076
S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,491	-£12,195
S1+S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,815	-£10,871

ICER=incremental cost effectiveness ratio, PAS=patient access scheme; QALY=quality adjusted life year
*Superiority of ixekizumab compared to conventional care in the sensitivity NMAs. Therefore, the scenario of equivalence does not apply to this comparison ,is only presented for completeness

Table 54 Biologic naïve nr-rad-axSpA (ixekizumab compared to adalimumab), PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Adalimumab		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£423,916	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£448,995	£25,080
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£183,983	-£239,933
S3. Non-superior non-statistically significant outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominated	-£15,289,196
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£193,739	-£230,177.00
S1+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominated	-£16,614,096
S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominated	-£10,906,065
S1+S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominated	-£12,353,647

ICER=incremental cost effectiveness ratio; IXE=ixekizumab; PAS=patient access scheme; QALY=quality adjusted life year
*Ixekizumab is dominated as there is a small difference in the QALYs in favour of the comparator arm due to the different lengths of trial periods

4.8 Conclusions of the cost effectiveness section

The company was only able to generate cost effectiveness results for three populations: the biologic-naïve rad-axSpA, the biologic-experienced rad-axSpA and the biologic-naïve nr-axSpA populations. Further, due to an absence of evidence, it was not possible for the company to carry out any analyses to compare the cost effectiveness of ixekizumab versus secukinumab in any population.

The company models are driven by Visual Basic code. The ERG was not able to comprehensively validate the models due to a lack of detail provided in the model manual and technical guide provided by the company. However, basic checks carried out by the ERG (including stress testing the models) did not identify any errors.

However, the ERG has identified six areas of concern relating to the structure and to the data inputs used in the company model:

- There is insufficient evidence to determine, with any certainty, the influence of biological treatments on radiographic change
- Treatment sequencing was not modelled; clinical advice to the ERG is that, in practice, NHS patients may receive several lines of treatment
- The treatment trial period is limited to 12 (or 16) weeks in the company model; however, in NHS practice, a longer period may be required
- The method used in the model (only using BASDAI data) to categorise patients as responders or non-responders to treatment does not reflect clinical guidelines
- The relationship between BASDAI, BASFI and HRQoL is uncertain and complicated which casts doubt on the reliability of the utility values used in the company models
- Estimates of healthcare resource use are based on very old data collected in mainland Europe and clinical advice to the ERG is that these data do not reflect current NHS practice.

The limited nature of the current evidence base and/or the company's choice of model structure means that it has not been possible to resolve these issues. As a consequence, the ERG does not have a preferred set of modelling assumptions. The ERG has, however, examined in detail two of the scenario analyses presented by the company:

- BASFI rebound to natural history upon treatment discontinuation (S1)
- Use of an alternative (generally the most pessimistic) method of modelling utility (Wailoo 2015[71]) (S2)

The ERG has also run the following scenario:

- Where NMA results are not statistically significantly different between treatments, no difference is modelled (S3)

Results from the cost effectiveness analyses show that some of the scenarios result in very small incremental QALY gains. Where this occurs, the ICERs per QALY gained are very susceptible to the number of decimal points used when calculating [redacted]

The ERG considers the aspects that would have the biggest influence on the cost effectiveness estimates for ixekizumab are those aspects that the ERG is unable to test within the model due to a lack of relevant data and the it is beyond the ERG's remit to make structural changes to the model.

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6 APPENDICES

6.1 Appendix 1: Main references to trials included in the company NMAs

Table 55 Bibliographic details of trials included in the company NMAs

Trial	Bibliographic details
ABILITY-1	Sieper J, Landewe R, Rudwaleit M, et al. Effect of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis: Results from a phase III randomized trial. Arthritis and Rheumatology 2015;67(3):668-77. doi: http://dx.doi.org/10.1002/art.38973
ASSERT	van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: Results of a randomized, placebo-controlled trial (ASSERT). Arthritis & Rheumatism. 2005;52(2):582-91.
ATLAS	Revicki DA, Luo MP, Wordsworth P, et al. Adalimumab reduces pain, fatigue, and stiffness in patients with ankylosing spondylitis: Results from the adalimumab trial evaluating long-term safety and efficacy for ankylosing spondylitis (ATLAS). Journal of Rheumatology 2008;35(7):1346-53.
Bao 2014	Bao C, Huang F, Khan MA, et al. Safety and efficacy of golimumab in Chinese patients with active ankylosing spondylitis: 1-year results of a multicentre, randomized, double-blind, placebo-controlled phase III trial. Rheumatology (United Kingdom) 2014;53(9):1654-63. doi: http://dx.doi.org/10.1093/rheumatology/keu132
Barkham 2010	Barkham N, Coates LC, Keen H, et al. Double-blind placebo-controlled trial of etanercept in the prevention of work disability in ankylosing spondylitis. Annals of the Rheumatic Diseases 2010;69(11):1926-28. doi: http://dx.doi.org/10.1136/ard.2009.121327
Brandt 2003	Brandt J, Khariouzov A, Listing J, et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis and rheumatism 2003; 48(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/180/CN-00438180/frame.html
Braun 2002	Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet (London, England) 2002; 359(9313). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/593/CN-00379593/frame.html
C-axSpAnd	Deodhar A, Gensler LS, Kay J, Maksymowych WP, Haroon N, Landewé N, et al. A Fifty-Two–Week, randomized, placebo-controlled trial of certolizumab pegol in nonradiographic axial spondyloarthritis. Arthritis & Rheumatology. 2019;71(7):1101-11.
Calin 2004	Calin A, Dijkmans BAC, Emery P, et al. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. Annals of the Rheumatic Diseases 2004;63(12):1594-600. doi: http://dx.doi.org/10.1136/ard.2004.020875
Cantini 2013	Cantini F, Niccoli L, Cassara E, et al. Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis: A randomized, prospective, long-term, follow-up study. Biologics: Targets and Therapy 2013;7(1):1-6. doi: http://dx.doi.org/10.2147/BTT.S31474
Davis 2003	Davis Jr JC, Van Der Heijde D, Braun J, et al. Recombinant Human Tumor Necrosis Factor Receptor (Etanercept) for Treating Ankylosing Spondylitis: A Randomized, Controlled Trial. Arthritis and Rheumatism 2003;48(11):3230-36. doi: http://dx.doi.org/10.1002/art.11325
EMBARK	Dougados M, Van Der Heijde D, Sieper J, et al. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: A multicenter, randomized, double-blind, placebo-controlled trial. Arthritis and Rheumatology 2014;66(8):2091-102. doi: http://dx.doi.org/10.1002/art.38721
GO-AHEAD	Sieper J, van der Heijde D, Dougados M, et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active

	nonradiographic axial spondyloarthritis. Arthritis & rheumatology (Hoboken, NJ) 2015;67(10):2702-12. doi: http://dx.doi.org/10.1002/art.39257
Trial	**Bibliographic details**
GO-RAISE	Braun J, Baraliakos X, Hermann KG, et al. The effect of two golimumab doses on radiographic progression in ankylosing spondylitis: results through 4 years of the GO-RAISE trial. Annals of the rheumatic diseases 2014; 73(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/481/CN-00997481/frame.html
Gorman 2002	Gorman JD, Sack KE, Davis Jr JC. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. New England Journal of Medicine 2002;346(18):1349-56. doi: http://dx.doi.org/10.1056/NEJMoa012664
Haibel 2008	Haibel H, Rudwaleit M, Listing J, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: Results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. Arthritis and Rheumatism 2008;58(7):1981-91. doi: http://dx.doi.org/10.1002/art.23606
HEEL	Dougados M, Combe B, Braun J, et al. A randomised, multicentre, double-blind, placebo controlled trial of etanercept in adults with refractory heel enthesitis in spondyloarthritis: The HEEL trial. Annals of the Rheumatic Diseases 2010;69(8):1430-35. doi: http://dx.doi.org/10.1136/ard.2009.121533
Hu 2012	Hu Z, Xu M, Li Q, et al. Adalimumab significantly reduces inflammation and serum DKK-1 level but increases fatty deposition in lumbar spine in active ankylosing spondylitis. Int J Rheum Dis 2012; 15(4). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/214/CN-00840214/frame.html
Huang 2014	Huang F, Gu J, Zhu P, et al. Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: results of a randomised, controlled trial. Annals of the rheumatic diseases 2014; 73(3). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/790/CN-00977790/frame.html
Lambert 2007	Lambert RGW, Salonen D, Rahman P, et al. Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: A multicenter, randomized, double-blind, placebo-controlled study. Arthritis and Rheumatism 2007;56(12):4005-14. doi: http://dx.doi.org/10.1002/art.23044
MEASURE-2	Sieper J, Deodhar A, Marzo-Ortega H, et al. Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: results from the MEASURE 2 Study. Annals of the Rheumatic Diseases 2016;31:31. doi: http://dx.doi.org/10.1136/annrheumdis-2016-210023
MEASURE-4	Kivitz AJ, Wagner U, Dokoupilova E, et al. Efficacy and Safety of Secukinumab 150 mg with and Without Loading Regimen in Ankylosing Spondylitis: 104-week Results from MEASURE 4 Study. *Rheumatology and Therapy* 2018;5(2):447-62. doi: http://dx.doi.org/10.1007/s40744-018-0123-5
RAPID-axSpA	Landewe R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Annals of the Rheumatic Diseases 2014;73(1):39-47. doi: http://dx.doi.org/10.1136/annrheumdis-2013-204231
SPINE	Dougados M, Braun J, Szanto S, et al. Efficacy of etanercept on rheumatic signs and pulmonary function tests in advanced ankylosing spondylitis: Results of a randomised double-blind placebo-controlled study (SPINE). Annals of the Rheumatic Diseases 2011;70(5):799-804. doi: http://dx.doi.org/10.1136/ard.2010.139261
Van den Bosch 2002	Van Den Bosch F, Kruithof E, Baeten D, et al. Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (infliximab) versus placebo in active spondylarthropathy. Arthritis and Rheumatism 2002;46(3):755-65. doi: http://dx.doi.org/10.1002/art.511
Van der Heijde 2006	Van Der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: Results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis and Rheumatism 2006;54(7):2136-46. doi: http://dx.doi.org/10.1002/art.21913

6.2 Appendix 2: Summary of CRP values in trials included in the company's NMAs

Table 56 Mean CRP in studies included in the NMAs for biologic-naïve rad-axSpA population

Endpoint	Trial name	Treatment arm	Mean CRP (SD) or median (mg/L)	
			Treatment arm	Placebo arm
ASAS40	ATLAS	ADA 40mg Q2W SC	18	22
	Huang 2014	ADA 40mg Q2W SC	22.4 (24)	23 (30)
	COAST-V	ADA 40mg Q2W SC IXE 80mg Q4W	12.5 (17.6) 12.2 (13.3)	16.0 (21.0)
	Calin 2004	ETN 25mg BIW SC	*154*	*97*
	Davis 2003	ETN 25mg BIW SC	19	20
	SPINE	ETN 25mg BIW SC	25 (31)	17 (19)
	Van der Heijde 2006	ETN 25mg BIW SC	19.8 (20.8)	22 (22.9)
	Bao 2014	GOL 50mg Q4W SC	20.6	18.6
	GO-RAISE	GOL 50mg Q4W SC	11	11.5
	MEASURE-2	SEC 150mg Q4W SC	*7.5*[a]	*8.3*[a]
	MEASURE-4	SEC 150mg with l starting dose SC	*6.25*[a]	*5.40*[a]
	ASSERT	INX 5mg/kg	15	17
	Braun 2002	INX 5mg/kg	24	18
	RAPID-axSpA	CZP 200mg CZP 400mg	*14* *12.9*	*16.6*
BASDAI50	ATLAS	ADA 40mg Q2W SC	18	22
	Huang 2014	ADA 40mg Q2W SC	22.4 (24)	23 (30)
	COAST-V	ADA 40mg Q2W SC IXE 80mg Q4W	12.5 (17.6) 12.2 (13.3)	16.0 (21.0)
	SPINE	ETN 25mg BIW SC	25 (31)	17 (19)
	Van der Heijde 2006	ETN 50mg QW SC ETN 25mg BIW SC	21.7 (24.6) 19.8 (20.8)	22 (22.9)
	Bao 2014	GOL 50mg Q4W SC	20.6	18.6
	GO-RAISE	GOL 50mg Q4W SC	11	11.5
	Barkham 2010	ETN 25mg BIW	NR	NR
	Brandt 2003	ETN 25mg BIW	19 (17)	NR
	Braun 2002	INX 5mg/kg	24	18
	RAPID-axSpA	CZP 200mg CZP 400mg	*14* *12.9*	*16.6*
BASDAI cfb	ATLAS	ADA 40mg Q2W SC	18	22
	Huang 2014	ADA 40mg Q2W SC	22.4 (24)	23 (30)
	COAST-V	ADA 40mg Q2W SC IXE 80mg Q4W	12.5 (17.6) 12.2 (13.3)	16.0 (21.0)
	HEEL	ETN 50mg QW SC	NR	NR
	SPINE	ETN 25mg BIW SC	25 (31)	17 (19)
	MEASURE-2	SEC 150mg Q4W SC	*7.5*[a]	*8.3*[a]
	MEASURE-4	SEC 150mg with l starting dose SC	*6.25*[a]	*5.40*[a]
	ASSERT	INX 5mg/kg	15	17

Endpoint	Trial name	Treatment arm	Mean CRP (SD) or median (mg/L)	
			Treatment arm	Placebo arm
	Braun 2002	INX 5mg/kg	24	18
	RAPID-axSpA	CZP 200mg CZP 400mg	*14* *12.9*	*16.6*
BASFI cfb	Huang 2014	ADA 40mg Q2W SC	22.4 (24)	23 (30)
	COAST-V	ADA 40mg Q2W SC IXE 80mg Q4W	12.5 (17.6) 12.2 (13.3)	16.0 (21.0)
	SPINE	ETN 25mg BIW SC	25 (31)	17 (19)
	Bao 2014	GOL 50mg Q4W SC	20.6	18.6
	ASSERT	INX 5mg/kg	15	17
	Braun 2002	INX 5mg/kg	24	18
	RAPID-axSpA	CZP 200mg CZP 400mg	*14* *12.9*	*16.6*

ADA=adalimumab; CRP=C-reactive protein; CZP=certolizumab pegol; ETN=etanercept; GOL=golimumab; INX=infliximab; IXE=ixekizumab; QW=every week; Q2W=every two weeks; Q4W=every four weeks; SC=subcutaneous; SD=standard deviation
[a] high sensitivity median CRP
Source: AG report for TA383,[14] Table 3; original trial papers

Table 57 Mean CRP in studies included in the NMAs for biologic-experienced rad-axSpA population

Endpoint	Trial name	Treatment arm	Mean CRP (SD) or *median* mg/L	
			Treatment arm	Placebo arm
ASAS40	COAST-W	IXE 80mg Q4W SC	20.2 (34.3)	16.0 (22.3)
	MEASURE-2	SEC 150mg Q4W SC	*7.5*[a]	*8.3*[a]
	MEASURE-4	SEC 150mg with l starting dose SC	*6.25*[a]	*5.40*[a]
	ASSERT	INX 5mg/kg	15	17
	Braun 2002	INX 5mg/kg	24	18
	RAPID-axSpA	CZP 200mg CZP 400mg	*14* *12.9*	*16.6*
BASDAI50	COAST-W	IXE 80mg Q4W SC	20.2 (34.3)	16.0 (22.3)
	Braun 2002	INX 5mg/kg	24	18
	RAPID-axSpA	CZP 200mg CZP 400mg	*14* *12.9*	*16.6*
	Barkham 2010	ETN 25mg BIW	NR	NR
BASDAI cfb	COAST-W	IXE 80mg Q4W SC	20.2 (34.3)	16.0 (22.3)
	MEASURE-2	SEC 150mg Q4W SC	*7.5*[a]	*8.3*[a]
	MEASURE-4	SEC 150mg with l starting dose SC	*6.25*[a]	*5.40*[a]
	ASSERT	INX 5mg/kg	15	17
	Braun 2002	INX 5mg/kg	24	18
	RAPID-axSpA	CZP 200mg CZP 400mg	*14* *12.9*	*16.6*
BASFI cfb	COAST-W	IXE 80mg Q4W SC	20.2 (34.3)	16.0 (22.3)
	ASSERT	INX 5mg/kg	15	17
	Braun 2002	INX 5mg/kg	24	18
	RAPID-axSpA	CZP 200mg CZP 400mg	*14* *12.9*	*16.6*

ADA=adalimumab; BIW=bi-weekly; CRP=C-reactive protein; CZP=certolizumab pegol; ETN=etanercept; GOL=golimumab; INX=infliximab; IXE=ixekizumab; QW=every week; Q2W=every two weeks; Q4W=every four weeks; SC=subcutaneous; SD=standard deviation

[a] high sensitivity median CRP

Source: AG report for TA383,[14] Table 3; original trial papers

Table 58 Mean CRP in studies included in the NMAs for biologic-naïve nr-axSpA population

Endpoint	Trial name	Treatment arm	Mean CRP (SD) or *median* mg/L	
			Treatment arm	Placebo arm
ASAS40	ABILITY-1	ADA 40mg Q2W SC	8.6 (13.1)	9.3 (10.9)
	EMBARK	ETN 50mg QW	6.8	6.4
	GO-AHEAD	GOL 50mg Q2W SC	1.5 (2.9)[a]	1.3 (2.0)[a]
	COAST-X	IXE 80mg Q4W SC	12.4 (18.0)	14.3 (24.4)
	C-axSpAnd	CZP 200mg	15.8 (17.8)	15.8 (17.7)
	Haibel 2008	ADA 40mg	6.2 (5.8)	7.8 (7.0)
	RAPID-axSpA	CZP 200mg CZP 400mg	*10* *12.1*	*13.5*
BASDAI50	GO-AHEAD	GOL 50mg Q2W SC	1.5 (2.9)[a]	1.3 (2.0)[a]
	EMBARK	ETN 50mg QW	6.8	6.4
	ABILITY-1	ADA 40mg Q2W SC	8.6 (13.1)	9.3 (10.9)
	COAST-X	IXE 80mg Q4W SC	12.4 (18.0)	14.3 (24.4)
	RAPID-axSpA	CZP 200mg CZP 400mg	*10* *12.1*	*13.5*
BASDAI cfb	EMBARK	ETN 50mg QW	6.8	6.4
	COAST-X	IXE 80mg Q4W SC	12.4 (18.0)	14.3 (24.4)
	RAPID-axSpA	CZP 200mg CZP 400mg	*10* *12.1*	*13.5*
BASFI cfb	EMBARK	ETN 50mg QW	6.8	6.4
	COAST-X	IXE 80mg Q4W SC	12.4 (18.0)	14.3 (24.4)
	C-axSpAnd	CZP 200mg	15.8 (17.8)	15.8 (17.7)
	RAPID-axSpA	CZP 200mg CZP 400mg	*10* *12.1*	*13.5*

ADA=adalimumab; BIW=bi-weekly; CRP=C-reactive protein; CZP=certolizumab pegol; ETN=etanercept; GOL=golimumab; INX=infliximab; IXE=ixekizumab; QW=every week; Q2W=every two weeks; Q4W=every four weeks; SC=subcutaneous; SD=standard deviation

[a] Measured in mg/dL

Source: AG report for TA383,[14] Table 3; original trial papers

6.3 Appendix 3: Ixekizumab versus comparators, ERG's ICER per QALY gained tables

Table 59 Biologic naïve rad-axSpA (ixekizumab compared to certolizumab pegol), using PAS prices for ixekizumab and certolizumab pegol

Scenario/ERG amendment	Ixekizumab		Certolizumab pegol		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£68,666]	
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£67,996]	£670
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£62,707]	£5,959
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£57,850]	£10,816

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 60 Biologic naïve rad-axSpA (ixekizumab compared to etanercept), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Etanercept		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£4,663]	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£4,357]	£306
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£3,510]	£1,153
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£3,291]	£1,372

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 61 Biologic naïve rad-axSpA (ixekizumab compared to golimumab), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Golimumab		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£78,750]	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£77,967]	£783
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£77,175]	£1,575
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£72,927]	£5,823

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 62 Biologic naïve rad-axSpA (ixekizumab compared to infliximab), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Infliximab		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£1,340,851]	
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£770,987]	£569,864
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£373,579]	£967,272
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£258,320]	£1,082,531

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 63 Biologic experienced rad-axSpA (ixekizumab compared to certolizumab pegol), using PAS prices for ixekizumab and certolizumab pegol

Scenario/ERG amendment	Ixekizumab		Certolizumab pegol		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£954, 573*	
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,891,107*	£5,936,534
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,542,203*	£587,630
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£455,422	-£1,409,995

*SW quadrant
BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 64 Biologic experienced rad-axSpA (ixekizumab compared to etanercept), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Etanercept		Incremental		*ICER*	
	Cost*	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,794*	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,542*	£7,748
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,343*	-£14,451
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,703*	-£7,090

*SW quadrant
BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 65 Biologic experienced rad-axSpA (ixekizumab compared to golimumab), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Golimumab		Incremental		*ICER*	
	Cost*	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£96,133*	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£116,083*	£19,950
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,994*	-£41,139
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£116,083*	-£19,950

*SW quadrant
BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 66 Biologic experienced rad-axSpA (ixekizumab compared to infliximab), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Infliximab		Incremental		*ICER*	
	Cost*	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£287,583**	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£332,435**	£44,852
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£166,489**	-£121,094
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£217,126**	-£70,457

*SW quadrant
BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life yea

Table 67 Biologic naïve nr-rad-axSpA (ixekizumab compared to certolizumab pegol), using PAS prices for ixekizumab and certolizumab pegol

Scenario/ERG amendment	Ixekizumab		Certolizumab pegol		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,435 *	
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,970*	£535
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,976*	-£3,459
S3. Non-superior non-statistically significant outcomes*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,468,914*	£2,454,479
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,434*	-£3,001
S1+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,694,750*	£2,680,315
S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,740,937*	£1,726,502
S1+S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,985,626*	£1,971,191

*SW quadrant
BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year
**The ICER is large because there is a small difference in the QALYs in favour of the comparator arm due to the different lengths of trial periods

Table 68 Biologic naïve nr-rad-axSpA (ixekizumab compared to etanercept), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Etanercept		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,672	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,074	£1,402
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,141	-£6,531
S3. Non-superior non-statistically significant outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£469,740*	£453,068
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,050	-£5,622
S1+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£516,728*	£500,056
S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£331,234*	£314,562
S1+S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£380,751*	£364,079

*SW quadrant
BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year
**The ICER is large because there is a small difference in the QALYs in favour of the comparator arm due to the different lengths of trial periods

Table 69 Biologic naïve nr-rad-axSpA (ixekizumab compared to golimumab), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Golimumab		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£11,199]	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£8,877]	£2,322
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£4,673]	£6,526
S3. Non-superior non-statistically significant outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,979,337*	£2,990,536
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£3,674]	£7,525
S1+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,250,836*	£3,262,035
S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,100,859*	£2,112,058
S1+S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,395,378*	£2,406,577

*SW quadrant
BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year
**The ICER is large because there is a small difference in the QALYs in favour of the comparator arm due to the different lengths of trial periods

6.4 Appendix 4: Biologic naïve rad-axSpA, ERG's fully incremental results

Table 70 ERG Scenario 1: ICERs per QALY gained for patients with biologic-naïve rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully Incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£42,970
Adalimumab	[redacted]	[redacted]	£9,715	IXE dominated by ADA
Ixekizumab	[redacted]	[redacted]	Dominated	
Etanercept	[redacted]	[redacted]	Dominated	IXE dominates
Golimumab	[redacted]	[redacted]	Dominated	IXE dominates
Certolizumab pegol	[redacted]	[redacted]	Dominated	IXE dominates
Infliximab	[redacted]	[redacted]	Dominated	IXE dominates

ADA=adalimumab; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 71 ERG Scenario 2: ICERs per QALY gained for patients with biologic-naïve rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£20,640
Adalimumab	[redacted]	[redacted]	£2,704	£2,798,792
Ixekizumab	[redacted]	[redacted]	£2,798,792	
Etanercept	[redacted]	[redacted]	Dominated	IXE dominates
Golimumab	[redacted]	[redacted]	Dominated	IXE dominates
Certolizumab pegol	[redacted]	[redacted]	Dominated	IXE dominates
Infliximab	[redacted]	[redacted]	Dominated	IXE dominates

ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 72 ERG Scenario 1&2: ICERs per QALY gained for patients with biologic-naïve rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£26,622
Adalimumab	[redacted]	[redacted]	£6,164	IXE dominated by ADA
Ixekizumab	[redacted]	[redacted]	Dominated	
Etanercept	[redacted]	[redacted]	Dominated	IXE dominates
Golimumab	[redacted]	[redacted]	Dominated	IXE dominates
Certolizumab pegol	[redacted]	[redacted]	Dominated	IXE dominates
Infliximab	[redacted]	[redacted]	Dominated	IXE dominates

ADA=adalimumab; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

6.5 Appendix 5: Biologic experienced rad-axSpA, ERG's fully incremental results

Table 73 ERG Scenario 1: ICERs per QALY gained for patients with biologic-experienced rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		IXE dominated by CC
Adalimumab	[redacted]	[redacted]	£95,596	IXE dominated by ADA
Ixekizumab	[redacted]	[redacted]	Dominated	
Etanercept	[redacted]	[redacted]	Dominated	£49,542*
Certolizumab pegol	[redacted]	[redacted]	Dominated	£6,891,107*
Golimumab	[redacted]	[redacted]	Dominated	£116,083*
Infliximab	[redacted]	[redacted]	£994,747	£332,435*

*SW quadrant
ADA=adalimumab; CC=conventional care; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 74 ERG Scenario 2: ICERs per QALY gained for patients with biologic-experienced rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£145,510
Adalimumab	[redacted]	[redacted]	£23,619	IXE dominated by ADA
Ixekizumab	[redacted]	[redacted]	Dominated	
Etanercept	[redacted]	[redacted]	Dominated	£27,343*
Certolizumab pegol	[redacted]	[redacted]	Dominated	£1,542,203*
Golimumab	[redacted]	[redacted]	Dominated	£54,994*
Infliximab	[redacted]	[redacted]	£508,258	£166,489*

*SW quadrant
ADA=adalimumab; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 75 ERG Scenario 1&2: ICERs per QALY gained for patients with biologic-experienced rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£335,837*
Adalimumab	[redacted]	[redacted]	£45,079	IXE dominated by ADA
Ixekizumab	[redacted]	[redacted]	Dominated	
Etanercept	[redacted]	[redacted]	Dominated	£34,703*
Certolizumab pegol	[redacted]	[redacted]	Dominated	IXE dominates
Golimumab	[redacted]	[redacted]	Dominated	£73,439*
Infliximab	[redacted]	[redacted]	£688,160	£217,126*

*SW quadrant ADA=adalimumab; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

6.6 Appendix 6: Biologic naïve nr-rad-axSpA, ERG's fully incremental results

Table 76 ERG Scenario 1: ICERs per QALY gained for patients with biologic-naïve nr-rad-axSpA, using PAS price for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£31,763
Adalimumab	[redacted]	[redacted]	£6,174	£448,995
Etanercept	[redacted]	[redacted]	Dominated	£18,074
Ixekizumab	[redacted]	[redacted]	Extendedly dominated	
Golimumab	[redacted]	[redacted]	Dominated	IXE dominates
Certolizumab pegol	[redacted]	[redacted]	£76,886	£14,970*

*SW quadrant
ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 77 ERG Scenario 2 ICERs per QALY gained for patients with biologic-naïve nr-rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£17,491
Adalimumab	[redacted]	[redacted]	£2,899	£183,983
Etanercept	[redacted]	[redacted]	Dominated	£10,141
Ixekizumab	[redacted]	[redacted]	Extendedly dominated	
Golimumab	[redacted]	[redacted]	Dominated	IXE dominates
Certolizumab pegol	[redacted]	[redacted]	£51,354	£10,976*

*SW quadrant
ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 78 ERG Scenario 3: ICERs per QALY gained for patients with biologic-naïve nr-rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£29,687
Adalimumab	[redacted]	[redacted]	£5,541	IXE is dominated by ADA
Ixekizumab	[redacted]	[redacted]	Dominated	
Etanercept	[redacted]	[redacted]	Dominated	£469,740*
Certolizumab pegol	[redacted]	[redacted]	Dominated	£2,468,914*
Golimumab	[redacted]	[redacted]	Dominated	£2,979,337*

*SW quadrant
ADA=adalimumab; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 79 ERG Scenario 1&2: ICERs per QALY gained for patients with biologic-naïve nr-rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully Incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£18,815
Adalimumab	[redacted]	[redacted]	£3,743	£193,739
Etanercept	[redacted]	[redacted]	Dominated	£11,050
Ixekizumab	[redacted]	[redacted]	Extendedly dominated	
Golimumab	[redacted]	[redacted]	Dominated	IXE dominates
Certolizumab pegol	[redacted]	[redacted]	£52,913	£11,434*

*SW quadrant
ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 80 ERG Scenario 2&3: ICERs per QALY gained for patients with biologic-naïve nr-rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£17,491
Adalimumab	[redacted]	[redacted]	£3,266	IXE is dominated by ADA
Ixekizumab	[redacted]	[redacted]	Dominated	
Etanercept	[redacted]	[redacted]	Dominated	£331,234*
Certolizumab pegol	[redacted]	[redacted]	Dominated	£1,740,937*
Golimumab	[redacted]	[redacted]	Dominated	£2,100,859*

*SW quadrant
ADA=adalimumab; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 81 ERG Scenario 1&3: ICERs per QALY gained for patients with biologic-naïve nr-rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE versus comparator)
Conventional care	[redacted]	[redacted]		£31,763
Adalimumab	[redacted]	[redacted]	£7,024	IXE is dominated by ADA
Ixekizumab	[redacted]	[redacted]	Dominated	
Etanercept	[redacted]	[redacted]	Dominated	£516,728*
Certolizumab pegol	[redacted]	[redacted]	Dominated	£2,694,750*
Golimumab	[redacted]	[redacted]	Dominated	£3,250,836*

*SW quadrant
ADA=adalimumab; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 82 ERG All scenarios combined (1-3): ICERs per QALY gained for patients with biologic-naïve nr-rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE comparator)
Conventional care	[redacted]	[redacted]		£18,815
Adalimumab	[redacted]	[redacted]	£4,162	IXE dominated by ADA
Ixekizumab	[redacted]	[redacted]	Dominated	
Etanercept	[redacted]	[redacted]	Dominated	£380,751*
Certolizumab pegol	[redacted]	[redacted]	Dominated	£1,985,626*
Golimumab	[redacted]	[redacted]	Dominated	£2,395,378*

*SW quadrant
ADA=adalimumab; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

6.7 Appendix 7: Biologic-naïve rad-axSpA – Instructions for running ERG scenario (S1)

Rad-axSpA model: "Main" sheet:

Ensure the model has biologic-naïve as population in cell D24.

1. Scenario 1
    - In the sheet "Main":
        i. Change the switch in column L next to 'rebound method for BASDAI and BASFI' from 'initial gain' to 'natural history'
        ii. Click the 'run model' button in column N
2. Scenario 2
    - In the sheet "Main":
        i. Change the switch in column L next to 'utility estimation' from 'ixekizumab bio-naïve 3L' to 'Wailoo et al'
        ii. Click the 'run model' button in column N

ERG revision number and description	Sheet	Cells	Modified formulae
S1 BASFI scores after treatment discontinuation	Main	L10	Change switch from 'initial gain' to 'natural history'
S2 Utility estimates year one unless reaching EDSS 7	Main	L18	Change switch from 'ixekizumab bio-naïve 3L' to 'Wailoo et al'

6.8 Appendix 8: Biologic-experienced rad-axSpA – Instructions for running ERG scenario (S2)

Rad-axSpA model: "Main" sheet:
Ensure the model has biologic-experienced as population in cell D24.
Change "Input Data" cell value E46 to 2, as more initial doses required for biologic-experienced population.

1. Scenario 1
    - In the sheet "Main":
        i. Change the switch in column L next to 'rebound method for BASDAI and BASFI' from 'initial gain' to 'natural history'
        ii. Click the 'run model' button in column N
2. Scenario 2
    - In the sheet "Main":
        i. Change the switch in column L next to 'utility estimation' from 'ixekizumab bio-naïve 3L' to 'Wailoo et al'
        ii. Click the 'run model' button in column N

ERG revision number and description	Sheet	Cells	Modified formulae
S1 BASFI scores after treatment discontinuation	Main	L10	Change switch from 'initial gain' to 'natural history'
S2 Utility estimates year one unless reaching EDSS 7	Main	L18	Change switch from 'ixekizumab bio-naïve 3L' to 'Wailoo et al'

6.9 Appendix 9: Biologic-naive nr-axSpA – Instructions for running ERG scenario (S3)

Nr-axSpA model: “Main” sheet:
Ensure the model has biologic-naïve as population in cell D24.

1. Scenario 1
    - In the sheet “Main”:
        i. Change the switch in column L next to ‘rebound method for BASDAI and BASFI’ from ‘initial gain’ to ‘natural history’
        ii. Click the ‘run model’ button in column N
2. Scenario 2
    - In the sheet “Main”:
        i. Change the switch in column L next to ‘utility estimation’ from ‘ixekizumab bio-naïve 3L’ to ‘Wailoo et al’
        ii. Click the ‘run model’ button in column N
3. Scenario 3
    - In the sheet “Input data”:
        i. Change the response rates of the comparators as equal to IXE (J17:J21)
        ii. Change the BASDAI reduction of the comparators as equal to IXE (K17:J21)
        iii. Change the BASFI reduction of the comparators as equal to IXE (M17:J21)

ERG revision number and description	Sheet	Cells	Modified formulae
S1 BASFI scores after treatment discontinuation	Main	L10	Change switch from 'initial gain' to 'natural history'
S2 Utility estimates year one unless reaching EDSS 7	Main	L18	Change switch from 'ixekizumab bio-naïve 3L' to 'Wailoo et al'
S3 Clinical effectiveness	Input data	J17	=J16
		J18	=J16
		J19	=J16
		J20	=J16
		J21	=J16
		K17	=K16
		K18	=K16
		K19	=K16
		K20	=K16
		K21	=K16
		L17	=L16
		L18	=L16
		L19	=L16
		L20	=L16
		L21	=L16
		M17	=M16
		M18	=M16
		M19	=M16
		M20	=M16
		M21	=M16
		N17	=N16
		N18	=N16
		N19	=N16
		N20	=N16
		N21	=N16

ERG STA REPORT Addendum 1

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number NIHR 17/156/08

Completed 7 July 2020

CONTAINS COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 ERG REVIEW OF SUPPLEMENTARY DATA

Following the original company submission to NICE for ixekizumab for the treatment of axial spondyloarthritis (axSpA) in January 2020, the licensed loading doses (LDs) for ixekizumab for each population (of biologic-naïve radiographic [rad]-axSpA, biologic-experienced rad-axSpA and biologic-naïve non-radiographic [nr]-axSpA) were confirmed by the EMA in the positive opinion issued on 1 May 2020.

Specifically, the following LDs for each population were confirmed:

- Biologic-naïve rad-axSpA patients: 160mg (previously 80mg in the company submission)
- Biologic-experienced rad-axSpA patients: 160mg (no change from company submission)
- Biologic-naïve nr-axSpA patients: 160mg (previously 80mg in the company submission)

As a result, the company produced an appendix to their submission which included updated sensitivity network meta-analyses (NMAs) and updated cost effectiveness results for the biologically naïve rad-axSpA and the biologically naïve nr-axSpA populations.

Changes to the clinical and/or cost effectiveness evidence for the biologically experienced rad-axSpA population were not necessary as the loading dose used in the original company submission (160mg) was approved by the EMA. Also, as in the original company submission, the ERG was not able to comment on the company's cost effectiveness estimates for the fourth population described in the NICE scope (the biologic-experienced nr-axSpA patients), due to the lack of NMA results.

In an email dated 16th June, NICE asked the ERG to review the supplementary data submitted by the company and update the ERG report (via this addendum).

1.1 ERG comment on network meta-analyses presented in the company's appendix

The methods used by the company to perform the NMAs presented in their appendix are the same as the methods used to perform the NMAs presented in the original company submission. The ERG considers that these methods are appropriate (see ERG report, Section 3.6.2).

In the company's original submission, some of the absolute effect estimates generated by the sensitivity NMAs differed from the absolute effect estimates generated by the base case NMAs (see ERG Report, Section 3.6.3). The ERG considers that the absolute effect estimates generated by the base case NMAs are likely to be more reliable than those generated by the

sensitivity NMAs as the risk of population heterogeneity is lower in the smaller (base case) network. Nevertheless, the ERG considers that the following absolute effects sensitivity NMA results, for all comparators, should not be used to inform decision making:

- biologic-naïve rad-axSpA population for BASDAI score cfb and BASFI score cfb
- biologic-experienced rad-axSpA population for BASDAI score.

The appendix to the company submission only includes results from their updated sensitivity NMAs; it is, therefore, not possible to compare these results with results obtained from the latest base case NMAs and/or assess their relative reliability.

1.2 ERG comment on cost effectiveness results presented in the company's appendix

In the original ERG report it was highlighted that there were several structural and data weaknesses in the company's economic models (see ERG Report, Section 3.6.2, 4.4.1 and 4.5). Unfortunately, the ERG was unable to resolve any of these issues. However, to illustrate how sensitive the company's models were to small changes in costs and QALYs, the ERG explored three scenarios where it is was possible to make appropriate changes to the company models:

- BASFI rebound to natural history upon treatment discontinuation (S1)
- Alternative method of modelling utility (Wailoo 2015[1] regression equation) (S2)
- Non-statistically significantly different outcomes from the NMAs assumed to demonstrate no evidence of superiority (S3).

The ERG has re-run these three scenario analyses, using PAS prices where appropriate, and using the higher LD for the biologic-naïve rad-axSpA patients and the biologic-naïve nr-axSpA patients as specified in the company's appendix. The results from these analyses are presented in Section 1.3.

1.3 Cost effectiveness results generated by the ERG

The impact on cost effectiveness results of implementing the new (160mg) ixekizumab loading dose is presented in this Section. Pairwise incremental analyses for the biologic-naïve rad-axSpA and nr-axSpA populations are presented in Sections 1.3.1 and Section 1.3.2 respectively. Fully incremental cost effectiveness analyses for the biologic-naïve rad-axSpA and nr-axSpA populations are presented in Sections 1.3.3 and 1.3.4 respectively.

Scenario 3 only applies to the biologic-naïve nr-axSpA population due to irregularities in the results of some of the outcomes assessed in the sensitivity NMAs for this population (see ERG report, Section 3.6.3 for details).

1.3.1 Biologic-naïve rad-axSpa pairwise cost effectiveness results

Table 1 Biologic-naïve rad-axSpA (ixekizumab compared to conventional care), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Conventional care		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,851	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,321	+£10,470
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,122	-£16,728
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,034	-£9,816

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness ratio; PAS=patient access scheme; QALY=quality adjusted life year

Table 2 Biologic-naïve rad-axSpA (ixekizumab compared to adalimumab), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Adalimumab		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominated [-£474,177]	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominated [-£411,658]	£62,519
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominated [-£1,842,745]	-£1,368,568
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominated [-£753,932]	-£279,755

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness ratio; IXE=ixekizumab; PAS=patient access scheme; QALY=quality adjusted life year

Table 3 Biologic-naïve rad-axSpA (ixekizumab compared to certolizumab pegol), using PAS prices for ixekizumab and certolizumab pegol

Scenario/ERG amendment	Ixekizumab		Certolizumab pegol		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£69,790]	
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£69,153]	£637
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£52,497]	£17,293
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£50,005]	£19,785

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 4 Biologic-naïve rad-axSpA (ixekizumab compared to etanercept), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Etanercept		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,029	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,608	£2,579
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,218	-£3,811
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,045	-£1,984

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 5 Biologic-naïve rad-axSpA (ixekizumab compared to golimumab), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Golimumab		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£95,110]	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£96,724]	-£1,614
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£58,405]	£36,705
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£60,254]	£34,856

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 6 Biologic-naïve rad-axSpA (ixekizumab compared to infliximab), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Infliximab		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£8,438,539]	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£1,539,265]	£6,899,274
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£411,222]	£8,027,317
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£281,842]	£8,156,697

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year

1.3.2 Biologic-naïve nr-axSpA pairwise cost effectiveness results

Table 7 Biologic-naïve nr-axSpA (ixekizumab compared to conventional care), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Conventional care		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,434	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,486	+ £3,051
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,999	-£19,435
S3. Non-superior non-statistically significant outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,434	£0*
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,851	-£17,584
S1+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,486	+ £3,051
S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,999	-£19,435
S1+S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,851	-£17,584

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness ratio; PAS=patient access scheme; QALY=quality adjusted life year
*Superiority of ixekizumab compared to conventional care in the sensitivity NMAs. Therefore, the scenario of equivalence does not apply to this comparison and is only presented for completeness

Table 8 Biologic-naïve nr-axSpA (ixekizumab compared to adalimumab), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Adalimumab		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominated [-£37,852]	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominated [-£37,631]	£220
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominated [-£24,718]	£13,133
S3. Non-superior non-statistically significant outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£272,838,090	£272,875,942
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominated [-£24,703]	£13,149
S1+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£113,497,020	£113,534,871
S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,678,813	£35,716,665
S1+S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,731,385	£25,769,237

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness ratio; IXE=ixekizumab; PAS=patient access scheme; QALY=quality adjusted life year
*There is a small difference in the QALYs in favour of the ixekizumab arm due to the different lengths of trial periods

Table 9 Biologic-naïve nr-axSpA (ixekizumab compared to certolizumab pegol), using PAS prices for ixekizumab and certolizumab pegol

Scenario/ERG amendment	Ixekizumab		Certolizumab pegol		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,163*	
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,159*	£996
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,119*	-£5,045
S3. Non-superior non-statistically significant outcomes*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£18,716,613]	-£18,731,776
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,843*	-£4,321
S1+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£7,820,680]	-£7,835,843
S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£2,447,556]	-£2,462,719
S1+S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£1,773,059]	-£1,788,222

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year
*SW quadrant
**Ixekizumab dominates because there is a small difference in the QALYs in favour of the ixekizumab arm due to the different lengths of trial periods

Table 10 Biologic-naïve nr-axSpA (ixekizumab compared to etanercept), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Etanercept		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,372*	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,575*	£1,203
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,028*	-£5,344
S3. Non-superior non-statistically significant outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,235,833	£4,221,461
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,836*	-£4,536
S1+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,729,974	£1,715,602
S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£553,916	£539,544
S1+S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£392,210	£377,837

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year
*SW quadrant
**The ICER per QALY gained is large because there is a small difference in the QALYs in favour of the ixekizumab arm due to the different lengths of trial periods

Table 11 Biologic-naïve nr-axSpA (ixekizumab compared to golimumab), using PAS price for ixekizumab

Scenario/ERG amendment	Ixekizumab		Golimumab		Incremental		*ICER*	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,676*	-
S1. BASFI rebound to natural history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,759*	£1,083
S2. Alternative utility calculations (Wailoo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,180*	-£6,496
S3. Non-superior non-statistically significant outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£40,708,675]	-£40,727,351
S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,954*	-£5,723
S1+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£16,971,712]	-£16,990,388
S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£5,323,440]	-£5,342,116
S1+S2+S3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE dominates [-£3,847,728]	-£3,866,404

BASFI=Bath Ankylosing Spondylitis Functional Index; ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year
*SW quadrant
**Ixekizumab dominates because there is a small difference in the QALYs in favour of the ixekizumab arm due to the different lengths of trial periods

1.3.3 Biologic-naïve rad-axSpA, ERG's fully incremental results

Table 12 ERG Scenario 1 ICERs per QALY gained for patients with biologic-naïve rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully Incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£50,321
Adalimumab	[redacted]	[redacted]	£9,715	IXE dominated by ADA
Etanercept 50 mg	[redacted]	[redacted]	Dominated	£13,608
Ixekizumab Q4W	[redacted]	[redacted]	Dominated	
Golimumab	[redacted]	[redacted]	Dominated	IXE dominates
Certolizumab pegol	[redacted]	[redacted]	Dominated	IXE dominates
Infliximab	[redacted]	[redacted]	Dominated	IXE dominates

ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 13 ERG Scenario 2 ICERs per QALY gained for patients with biologic-naïve rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£23,122
Adalimumab	[redacted]	[redacted]	£2,704	IXE dominated by ADA
Etanercept 50 mg	[redacted]	[redacted]	Dominated	£7,218
Ixekizumab Q4W	[redacted]	[redacted]	Dominated	
Golimumab	[redacted]	[redacted]	Dominated	IXE dominates
Certolizumab pegol	[redacted]	[redacted]	Dominated	IXE dominates
Infliximab	[redacted]	[redacted]	Dominated	IXE dominates

ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 14 ERG Scenario 1 & 2 ICERs per QALY gained for patients with biologic-naïve rad-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£30,034
Adalimumab	[redacted]	[redacted]	£6,164	IXE dominated by ADA
Etanercept 50 mg	[redacted]	[redacted]	Dominated	£9,045
Ixekizumab Q4W	[redacted]	[redacted]	Dominated	
Golimumab	[redacted]	[redacted]	Dominated	IXE dominates
Certolizumab pegol	[redacted]	[redacted]	Dominated	IXE dominates
Infliximab	[redacted]	[redacted]	Dominated	IXE dominates

ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year

1.3.4 Biologic-naïve nr-axSpA, ERG's fully incremental results

Table 15 ERG Scenario 1 ICERs per QALY gained for patients with biologic-naïve nr-axSpA, using PAS price for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£47,486
Adalimumab	[redacted]	[redacted]	£6,174	IXE dominated by ADA
Ixekizumab	[redacted]	[redacted]	Dominated	
Etanercept	[redacted]	[redacted]	Dominated	£15,575*
Golimumab	[redacted]	[redacted]	Extendedly dominated	£19,759*
Certolizumab pegol	[redacted]	[redacted]	£76,886	£16,159*

ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year
*SW quadrant

Table 16 ERG Scenario 2 ICERs per QALY gained for patients with biologic-naïve nr-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£24,999
Adalimumab	[redacted]	[redacted]	£2,899	IXE dominated by ADA
Ixekizumab	[redacted]	[redacted]	Dominated	
Etanercept	[redacted]	[redacted]	Dominated	£9,028*
Golimumab	[redacted]	[redacted]	Extendedly dominated	£12,180*
Certolizumab pegol	[redacted]	[redacted]	£51,354	£10,119*

ICER=incremental cost effectiveness data; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life year
*SW quadrant

Table 17 ERG Scenario 3 ICERs per QALY gained for patients with biologic-naïve nr-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£44,434
Adalimumab	[redacted]	[redacted]	£12,076	£272,838,090**
Etanercept	[redacted]	[redacted]	Dominated	£4,235,833*
Ixekizumab	[redacted]	[redacted]	Extendedly dominated by ADA	
Certolizumab pegol	[redacted]	[redacted]	Dominated	IXE dominates**
Golimumab	[redacted]	[redacted]	Dominated	IXE dominates**

ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year
*SW quadrant
**Large ICER because there is a small difference in the QALYs in favour of the ixekizumab arm due to the different lengths of trial periods

Table 18 ERG Scenario 1&2 ICERs per QALY gained for patients with biologic-naïve nr-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully Incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£26,851
Adalimumab	[redacted]	[redacted]	£3,743	IXE dominated by ADA
Ixekizumab	[redacted]	[redacted]	Dominated	
Etanercept	[redacted]	[redacted]	Dominated	£9,836
Golimumab	[redacted]	[redacted]	Extendedly dominated	£12,954
Certolizumab pegol	[redacted]	[redacted]	£52,913	£10,843

*SW quadrant
ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 19 ERG Scenario 1&3 ICERs per QALY gained for patients with biologic-naïve nr-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE versus comparator)
Conventional care	[redacted]	[redacted]		£47,486
Adalimumab	[redacted]	[redacted]	£14,148	£113,497,020
Etanercept	[redacted]	[redacted]	Dominated	£1,729,974
Ixekizumab	[redacted]	[redacted]	£113,497,020**	
Certolizumab pegol	[redacted]	[redacted]	Dominated	IXE dominates
Golimumab	[redacted]	[redacted]	Dominated	IXE dominates

ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year
*SW quadrant
**Large ICER per QALY gained because there is a small difference in the QALYs in favour of the ixekizumab arm due to the different lengths of trial periods

Table 20 ERG Scenario 2&3 ICERs per QALY gained for patients with biologic-naïve nr-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE vs comparator)
Conventional care	[redacted]	[redacted]		£24,999
Adalimumab	[redacted]	[redacted]	£6,797	£35,678,813
Etanercept	[redacted]	[redacted]	Dominated	£553,916
Ixekizumab	[redacted]	[redacted]	£35,678,813**	
Certolizumab pegol	[redacted]	[redacted]	Dominated	IXE dominates
Golimumab	[redacted]	[redacted]	Dominated	IXE dominates

ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year
*SW quadrant
**Large ICER per QALY gained because there is a small difference in the QALYs in favour of the ixekizumab arm due to the different lengths of trial periods

Table 21 ERG All scenarios combined (1-3) ICERs per QALY gained for patients with biologic-naïve nr-axSpA, using PAS prices for ixekizumab and certolizumab pegol

	Total costs	Total QALYs	ICER per QALY gained	
			Fully incremental	Pairwise (IXE comparator)
Conventional care	[redacted]	[redacted]		[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]	[redacted]	
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness data; PAS=Patient Access Scheme; QALY=quality adjusted life year
*SW quadrant
**Large ICER per QALY gained because there is a small difference in the QALYs in favour of the ixekizumab arm due to the different lengths of trial periods

2 REFERENCES

1 Wailoo A, Hernandez M, Philips C, et al. Modeling Health State Utility Values in Ankylosing Spondylitis: Comparisons of Direct and Indirect Methods. Value Health 2015;18:425-31.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Thursday 9 April 2020** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Expected dates for marketing authorisation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 11: "The European Medicines Agency Committee for Medicinal Products for Human Use decision is expected in [redacted] and the European marketing authorisation is expected in [redacted]."	Please amend as follows: "The European Medicines Agency Committee for Medicinal Products for Human Use decision is expected in [redacted] and the European marketing authorisation is expected in [redacted].	The anticipated dates for Committee for Medicinal Products for Human Use decision and marketing authorisation have shifted.	The ERG report has been updated as requested.

Issue 2 Comparator arm description for the COAST trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 11 and Page 68: "The comparator arm in all three of the COAST trials was placebo"	Please amend as follows: The comparator arm in all three of the COAST trials was placebo. **Data were also collected for the TNF-alpha inhibitor adalimumab as an active reference arm in COAST-V, however, the trial was not powered to assess statistical superiority or non-inferiority of adalimumab compared to ixekizumab"**	The Company would like to clarify that although all three trials were powered to assess efficacy of ixekizumab compared to placebo, data for the efficacy of adalimumab as a reference treatment arm were collected in the COAST-V trial.	Amended as follows: Each of the COAST trials included a placebo arm. Data were also collected for the TNF-alpha inhibitor adalimumab as an active reference arm in COAST-V.

Issue 3 Description of COAST-X trial design

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 11: "Outcomes are reported in the CS at Week 16 (randomised phase) and at Week 52 (extension phase)."	Please amend as follows: "Outcomes are reported in the CS at Week 16 ~~(randomised phase)~~ and at Week 52 ~~(extension phase)~~."	The statement is misleading, as although in the COAST-V and -W trials there was a 16-week randomised phase and an extension phase (16–52), for the COAST-X trial, the randomised double-blind phase of the trial included Weeks 0–52. Therefore, to describe the data at Week 52 as the "extension phase" is inaccurate.	Thank you. The ERG report has been amended as suggested.
Page 16: "As highlighted in Section 3.7 of this ERG report, axSpA is a lifelong disease and the ERG notes that the clinical effectiveness evidence presented in the CS is relatively short term; the duration of the randomised phase of the COAST trials was 16 weeks with an extension phase up to 52 weeks."	Please amend as follows: "As highlighted in Section 3.7 of this ERG report, axSpA is a lifelong disease and the ERG notes that the clinical effectiveness evidence presented in the CS is relatively short term; the duration of the randomised phase of the COAST**-V and -W** trials was 16 weeks with an extension phase up to 52 weeks, **while for COAST-X the randomised phase was 52 weeks**."	The amended statement makes clear that the randomised phase for the COAST-X trial was 52 weeks, as opposed to a 16-week randomised phase followed by an extension phase up to 52 weeks.	Thank you. The ERG report has been amended as suggested.
Page 31: "The COAST trials consisted of a 16-week treatment phase and a 36-week extension phase."	Please amend as follows: "The COAST**-V and -W** trials consisted of a 16-week treatment phase and a 36-week extension phase, **and the COAST-X trial is a randomised, double-blind study with a 52-week duration**."	The amended statement makes it clear that the randomised phase for the COAST-X trial was 52 weeks, as opposed to a 16-week randomised phase followed by an extension phase of 36 weeks.	Thank you. The ERG report has been amended to read: The COAST-V and COAST-W trials consisted of a 16-week treatment phase and a 36-week extension phase. The COAST-X trial consisted of a

			randomised treatment period of 52 weeks.

Issue 4 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15: “patients who cannot tolerate TNF-alpha inhibitors or for whom TNF-alpha inhibitors are contraindicated, or for biologic-experienced patients as biologic-naïve patients will be offered a biological treatment (ERG report, Section 2.5).”	Please amend structure of sentence.	The sentence is incomplete and should be updated to allow the reader to understand the sentence meaning clearly.	An editorial issue – a sentence was inappropriately split (p14 and p15). Amended to: Established clinical practice may not be an appropriate treatment for biologic-naïve patients in the rad-axSpA population, (even when TNF-alpha inhibitors are not tolerated or are contraindicated) as secukinumab is a treatment option, for patients who cannot tolerate TNF-alpha inhibitors or for whom TNF-alpha inhibitors are contraindicated, or for biologic-experienced patients as biologic-naïve patients will be offered a biological treatment (ERG report, Section 2.5).

Issue 5 Anticipated licensed population for ixekizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 23: "Ixekizumab is anticipated to be licensed for the treatment of adult patients with active rad-axSpA and nr-axSpA defined as elevated C-reactive protein (CRP) and/or [evidence of sacroiliitis on] magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs"	Please amend as follows: "Ixekizumab is anticipated to be licensed for the treatment of adult patients with active rad-axSpA **who have had an inadequate response to, or are intolerant to NSAIDs**. ~~and~~ **Ixekizumab is also anticipated to be licensed for patients with active** nr-axSpA defined as elevated C-reactive protein (CRP) and/or [evidence of sacroiliitis on] magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs"	The Company suggest updating this text to make it clear that the requirements of elevated CRP and MRI evidence will only be required for nr-axSpA. These will not be required for rad-axSpA patients.	Thank you. The ERG report has been amended as suggested.

Issue 6 Position of ixekizumab in the clinical pathway of care

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 23: "Ixekizumab is expected to be a treatment option for patients who are contraindicated to TNF-alpha inhibitors"	Please amend as follows: "Ixekizumab is expected to be a treatment option for patients who **have not received a biologic treatment** or are contraindicated to **or who cannot tolerate TNF-alpha inhibitors, in addition to patients whose disease has not responded to treatment with a first** TNF-alpha inhibitor~~s~~, **or whose disease has stopped responding after an initial response**"	The Company would like to update this text to make clear that ixekizumab is expected to be a treatment option for patients who are biologic naïve or inadequate responders or those who are intolerant to TNF-alpha inhibitors, in addition to patients who are contraindicated (i.e. in line with the anticipated licensed indications).	Thank you. The ERG report has been amended as suggested.

Issue 7 Description of outcomes assessed in the COAST trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 27 (Table 4): "In the COAST trials, ASAS40 was assessed weekly. The primary endpoint of the COAST trials was ASAS40 cfb at Week 16. ASAS40 is not an outcome measure used in clinical practice nor was the Company's cost effectiveness base case analysis informed by ASAS40 outcomes.	Please amend as follows: "In the COAST trials, ASAS40 was assessed ~~weekly~~ at weeks **1, 2, 4, 8, 12 and 16**. The primary endpoint of the COAST trials was **the proportion of patients achieving an** ASAS40 **response** ~~cfb~~ at Week 16. ASAS40 is not an outcome measure used in clinical practice nor was the company's cost effectiveness base case analysis informed by ASAS40 outcomes."	The time points for ASAS40 were incorrectly reported. The primary endpoint was also incorrectly reported as cfb in ASAS40 and should be reported as ASAS40 response rate.	Thank you. The ERG report has been amended as suggested.
Page 27 (Table 4): "Response to treatment in clinical practice is defined as achievement of a BASDAI50 response (or fall in BASDAI of ≥2 units), in addition to a reduction in the spinal pain VAS ≥2cm after 12 weeks (16 weeks for patients with a diagnosis of rad-axSpA who are treated with secukinumab).[4,14,19,20]"	Please amend as follows: "Response to treatment in clinical practice is defined as achievement of a BASDAI50 response (or fall in BASDAI of ≥2 units), in addition to a reduction in the spinal pain VAS ≥2cm after 12 weeks (16 weeks for patients with a diagnosis of rad-axSpA who are treated with secukinumab **[and for ixekizumab according to the anticipated licence]**).[4,14,19,20]"	The Company would like to clarify here that response is expected to be assessed every 16 weeks in patients treated with ixekizumab, based on the anticipated licence.	This is not a factual error. The statement in Table 4 is a reference to current practice in the NHS. Ixekizumab is not part of current practice in the NHS. No change required.
Page 27 (Table 4): "While mean spinal pain VAS data are presented in the CS, data are not presented for the number of patients who achieved VAS ≥2cm, nor the number who achieved this in combination with the associated BASDAI criteria required for treatment response."	Please amend as follows: "While mean spinal pain ~~VAS~~ NRS data are presented in the CS, data are not presented for the number of patients who achieved VAS ≥2cm, nor the number who achieved this in combination with the associated BASDAI criteria required for treatment response."	The rating scale for spinal pain is incorrectly reported. In the COAST trials, spinal pain was measured on a numeric rating scale (NRS) as opposed to a visual analogue scale (VAS).	Thank you. The ERG report has been amended as suggested.

Issue 8 COAST-X trial design and treatment arms

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 33 (Table 6): "Week 0 to Week 16 Ixekizumab -80mg Q2W+LD 80mg (n=50) -80mg Q2W+LD 160mg (n=47) -80mg Q4W+LD 80mg (n=50) -80mg Q4W+LD 160mg (n=47) Matched placebo Q2W (n=105)"	Please amend as follows: Week 0 to Week 16 Ixekizumab -80mg Q2W+LD 80mg (n=50) -80mg Q2W+LD 160mg (n=~~47~~52) -80mg Q4W+LD 80mg (n=~~50~~47) -80mg Q4W+LD 160mg (n=~~47~~49) Matched placebo Q2W (n=105)"	Patient numbers in loading dose groups were incorrectly reported.	Thank you. The ERG report has been amended as suggested.
Page 33 (Table 6): "Week 16 to Week 52 Patients in the ixekizumab arm continued with assigned treatments Patients identified as inadequate responders could be administered a rescue treatment of ixekizumab 80 mg Q2W (80 mg LD)."	Please amend as follows: "Week 16 to Week 52 Patients in ~~the ixekizumab~~ all treatment arms continued with assigned treatments Patients identified as inadequate responders could be administered a rescue treatment of ixekizumab 80 mg Q2W (80 mg LD)."	The Company would like to clarify that all patients remained on their initial treatment arm in COAST-X, including those treated with placebo, with the exception of those who were deemed inadequate responders and received rescue therapy.	Thank you. The ERG report has been amended to: Patients continued with assigned treatments

Issue 9 Confidentiality highlighting in Section 3.3 and 3.4

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Sections 3.3 and 3.4: Confidentiality highlighting on clinical efficacy data added from CSRs have been added as [redacted]	Please amend all confidentiality highlighting of clinical efficacy data from the CSRs to [redacted]	Incorrect confidentiality highlighting.	Thank you. The ERG report has been amended as suggested.

Issue 10 Data labelling error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 39 (Table 12): The second row of data is labelled as "COAST-V"	Please amend as follows: "COAST-~~V~~ -W"	Data incorrectly labelled.	Thank you. The ERG report has been amended as suggested.
Page 39 (Table 13): The second row of data is labelled as "COAST-V"	Please amend as follows: "COAST-~~V~~ -W"	Data incorrectly labelled.	Thank you. The ERG report has been amended as suggested.

Issue 11 Reporting of ixekizumab rescue therapy in COAST-X

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 40: "As described in Section 3.2.1, in the COAST-X trial, from Week 16 to Week 52, any patient who was deemed to be an inadequate responder by investigators could receive rescue treatment with ixekizumab 80mg Q2W. Patients who received rescue treatment were analysed as non-responders in the analysis of ASAS40 and BASDAI50 response data from Week 52 of the COAST-X trial (Appendix L to the CS, Table 100)."	Please amend as follows: "As described in Section 3.2.1, in the COAST-X trial, from Week 16 to Week 52, any patient who was deemed to be an inadequate responder by investigators could receive rescue treatment with ixekizumab 80mg Q2W. Patients who received rescue treatment were analysed as non-responders in the analysis of ASAS40 and BASDAI50 response data ~~from~~ for Week 52 of the COAST-X trial (Appendix L to the CS, Table 100)."	Changing this one word changes the meaning of the sentence. The Company would like to clarify that patients who received rescue therapy were analysed as non-responders from the point of rescue therapy initiation up to and including Week 52, not "from" Week 52.	Thank you. The ERG report has been amended as suggested.

Issue 12 Patient numbers in the COAST-X trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 41 (Table 18): "PBO (N=[redacted])"	Please amend as follows: "PBO (N=[redacted])"	N for the placebo arm incorrectly reported.	Thank you. The ERG has made the suggested changes but highlights that the numbers in the ERG report were extracted from the CSR rather than the CS.
Page 41 (Table 19): "PBO (N=[redacted])"	Please amend as follows: "PBO (N=[redacted])"	N for the placebo arm incorrectly reported.	
Page 45 (Table 23): "PBO (N=[redacted])"	Please amend as follows: "PBO (N=[redacted])"	N for the placebo arm incorrectly reported.	

Issue 13 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 43: "HRQoL data were collected during the COAST-V, COAST-W (p74) and COAST-X (p83) trials using the physical component summary (PCS) of the SF-36[31]"	Please amend as follows: "HRQoL data were collected during the COAST-V **(p64)**, COAST-W (p74) and COAST-X (p83) trials using the physical component summary (PCS) of the SF-36[31]"	This addition will help the reader to locate the data in the company submission (CS).	Thank you. The ERG report has been amended as suggested.

Issue 14 Time points for SF-36 PCS

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 43: "Data were collected at baseline, Week 4, Week 8, Week 16, Week 32 and Week 52."	Please amend as follows: "Data were collected at baseline, Week 4, Week 8, Week 16, Week ~~32~~ 36 and Week 52."	The time points for measuring SF-36 PCS scores were incorrectly reported.	Thank you. The ERG report has been amended as suggested.

Issue 15 Typographic error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 43: "The company defined the safety population as all randomised patients who received at least one dose of study treatment (CS, p100)."	Please amend as follows: "The company defined the safety population as all randomised patients who received at least one dose of study treatment (CS, p10~~0~~9)."	This addition will help the reader to locate the data in the CS.	Thank you. The ERG report has been amended as suggested.

Issue 16 Reporting of safety results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 47 (Table 25): Data reported for PBO Week 52, COAST-X "[redacted]"	Please amend as follows: Data reported for PBO Week 52, COAST-X "[redacted]"	The data was incorrectly copied from the CS.	Thank you. The ERG report has been amended as suggested.
Page 47: "The company reports (CS, p111) that the [redacted]	Please amend as follows: "The company reports (CS, p111) that the [redacted]	The wording from p111 of the CS was incorrectly reported, the Company would like to clarify that most injection site reactions were mild in severity.	Thank you. The ERG report has been amended as suggested.
Page 47: [redacted] It is stated in the CS (p112) that [redacted]	Please amend as follows: [redacted] It is stated in the CS (p112) that [redacted]	The additions suggested by the Company make it clear that in the ixekizumab Q4W arm, [redacted]% of patients experienced a TEAE. In the ixekizumab Q2W arm this percentage was lower ([redacted]%) and therefore overall, in patients treated with ixekizumab the percentage TEAEs were [redacted]% ([redacted]%). The company would also like to note that the number of patients experiencing an infection was 33 (20.1%) at Week 16 and 30 ([redacted]%) at Week 52, which the Company does not believe to be a substantial increase in the number of patients.	These are not factual errors. The ERG report is concerned only with reporting on the safety outcomes of patients treated with the anticipated licensed dose and regimen of ixekizumab (80mg Q4W). See ERG report p46. The safety data for this population are correctly reported. No changes required.

<table>
<tr>
<td>Page 48 (Table 26):
Confidentiality highlighting:
<table><tr><td>1 (1.2)</td><td></td></tr><tr><td>[redacted]</td><td>[redacted]</td></tr><tr><td>[redacted]</td><td>[redacted]</td></tr><tr><td></td><td></td></tr><tr><td>[redacted]</td><td>[redacted]</td></tr><tr><td>[redacted]</td><td>[redacted]</td></tr><tr><td>[redacted]</td><td>[redacted]</td></tr><tr><td>[redacted]</td><td>[redacted]</td></tr><tr><td>[redacted]</td><td>[redacted]</td></tr><tr><td>[redacted]</td><td>[redacted]</td></tr><tr><td>[redacted]</td><td>[redacted]</td></tr><tr><td>[redacted]</td><td>[redacted]</td></tr><tr><td>[redacted]</td><td>[redacted]</td></tr></table></td>
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<td>Confidentiality highlighting corrected.</td>
<td>Thank you. The ERG report has been amended as suggested.</td>
</tr>
<tr>
<td>Page 48:
“The ERG agrees with the company (CS, p114) that the number of AEs considered to be [redacted] and that more patients in the ixekizumab arm discontinued treatment due to AEs.”</td>
<td>Please amend confidentiality highlighting as follows:
“The ERG agrees with the company (CS, p114) that the number of AEs considered to be [redacted].”</td>
<td>Confidentiality highlighting corrected.</td>
<td>Thank you. The ERG report has been amended as suggested.</td>
</tr>
<tr>
<td>Page 49:
“The company reports (CS, p118) that [redacted] of the infections were classified as [redacted] The company also</td>
<td>Please amend as follows:
“The company reports (~~CS, p118 4) that~~ [redacted] ~~of the infections were classified as~~ [redacted] ~~The company also reports~~</td>
<td>The conclusions in the CS on p118 are referring to the COAST-X trial. The amendment includes the conclusions from p114 for the COAST-W trial.</td>
<td>Thank you. The ERG report has been amended as suggested.</td>
</tr>
</table>

reports (CS, p118) that [redacted]	~~(CS, p118) that~~ [redacted] (CS, p114)"		
Page 49: "The company reports (CS, p116) that the [redacted]"	Please amend as follows: "The company reports (CS, p116) that the [redacted]"	Results inaccurately copied from p116 of the CS.	Thank you. The ERG report has been amended as suggested.
Page 50 (Table 27): Week 52 results reported as: "non-anaphylaxis: [redacted] Confirmed cerebrocardiovascular events: [redacted]"	Please amend as follows: "non-anaphylaxis: [redacted] Confirmed cerebrocardiovascular events: [redacted]"	Incorrect reporting of results.	Thank you. The ERG report has been amended as suggested.
Page 51: [redacted]	Please amend as follows: [redacted]	The Company would like to clarify that the statement also applies to infections in COAST-X.	Thank you. The ERG report has been amended as suggested.
Page 51 (Table 28): PBO results are reported as: "Anaphylactoid reaction: [redacted]"	Please amend as follows: "Anaphylactoid reaction: [redacted]"	Incorrect reporting of data.	Thank you. The ERG report has been amended as suggested.

Page 51: "More patients in the ixekizumab experienced an infection compared with the placebo arm. The company reports (CS, p120) that the majority of infections were considered to be mild or moderate and none caused patients to discontinue treatment. The company also reports that the majority of injection site reactions were considered to be mild."	Please amend as follows: "More patients in the ixekizumab **Q4W arm** experienced an infection compared with the placebo arm. The company reports (CS, p120) that the majority of infections **and injection site reactions** were considered to be mild**-to-**~~or~~ moderate ~~and none caused patients to discontinue treatment~~. ~~The company also reports that the majority of injection site reactions were considered to be mild~~."	Correcting this typographical error makes the sentence meaning clearer. The company would also like to clarify the wording reported on p120 of the CS.	Thank you. The ERG report has been amended as suggested.
Page 52 (Table 29): PBO results reported as: "Hepatic: 6 (5.)"	Please amend as follows: "Hepatic: 6 (5.8)"	Typographic error in results reporting.	Thank you. The ERG report has been amended as suggested.

Issue 17 Priors in the NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 58: "During the clarification process the ERG asked the company to provide the NMA report; however, the company only provided the protocol which included contradictory information on the priors used to the information provided in Appendix D to the CS."	Please amend as follows: "During the clarification process the ERG asked the company to provide the NMA report; however, the company only provided the protocol which included contradictory information on the priors used to the information provided in Appendix D to the CS **due to the fact that the protocol contained updated, corrected prior values**."	The Company would like to clarify that the protocol contained updated information and the priors included in the protocol are the correct ones that were used in the analysis.	Thank you for the clarification. No change required.

Issue 18 Conclusions of the clinical effectiveness evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 68: "The comparator arm of all three COAST trials was placebo. Placebo can be considered as a proxy for standard of care (for patients previously treated with biologics). However, there is no direct evidence available to compare the effectiveness of ixekizumab versus any TNF-alpha inhibitors or versus secukinumab (the other comparators identified in the final scope[28] issued by NICE)."	Please amend as follows: "The comparator arm of all three COAST trials was placebo, **although in COAST-V adalimumab was included as an active reference arm.** Placebo can be considered as a proxy for standard of care (for patients previously treated with biologics). However, there is no direct evidence available to compare the effectiveness of ixekizumab versus any TNF-alpha inhibitors or versus secukinumab (the other comparators identified in the final scope[28] issued by NICE)."	The Company would like to clarify that adalimumab data were collected as part of the COAST-V trial design.	Thank you. The ERG report has been amended as suggested.

Issue 19 Redaction of information about [redacted]

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
[redacted]	[redacted]	[redacted]	Highlight added

[redacted]	[redacted]	[redacted]	Highlight added
[redacted] **Error! Reference source not found.** [redacted]	[redacted]	[redacted]	Highlight added
[redacted]	[redacted]	[redacted]	Highlight added

		[redacted]	

Issue 20 Numerical error for annual rate of mSASSS change in nr-axSpA patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 77: There is a numerical error in the annual rate of change of mSASSS for nr-axSpA patients from Ramiro 2013. The ERG report states this value is "0.069" and the correct value is "0.69"	Please amend as follows: "0.~~0~~69"	This change is to ensure the correct number is provided in the report.	Text amended

Issue 21 Modelling of sequential treatments

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 85: The ERG report states that "The structure of the models means that patients are only able to receive a single line of treatment."	Please amend this sentence as follows: "Patients were modelled to only receive one line of treatment."	The ixekizumab models have the functionality to model sequential treatments; this option can be optionally selected. However, due to the lack of available clinical data for the sequential treatment of axSpA patients, this option was not selected for presentation in the CS. The original wording suggests that modelling sequential treatments is not possible with the ixekizumab models.	Text amended

Issue 22 Modification factor for the biologic-experienced nr-axSpA scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 89: The ERG report states that "The source of the evidence used to derive this modification factor is not clear." This refers to the modification factor used to generate efficacy estimates for the scenario analysis for biologic-experienced nr-axSpA patients.	Please amend as follows: "The source of evidence used to derive this modification factor was the COAST-V and COAST-W trials."	The data source for the calculation of the modification factor was BASDAI50 data at Week 16 for ixekizumab from the COAST-V (data for biologic-naive patients) and COAST-W (data for biologic-experienced) trials.	Text amended to: "The company stated that the sources of evidence used to derive this modification factor were the COAST-V and COAST-W trials; however, the calculations used by the company to generate this value were not clear"

Issue 23 Total cost of ixekizumab in biologic-experienced rad-axSpA cost-effectiveness results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 94 (Table 51 and Table 52): A value of £[redacted] has been used for the total cost of ixekizumab for the company base case, which the ERG note has been sourced from the company model. This value is incorrect; the value in the CS on page 177 is correct. The source of the ERG's error is not increasing the number of initial doses to 2 in cell E46 on the 'Input Data' sheet	Please correct value to £[redacted]. Should this error have been carried forward in any other of the ERG's analyses of the biologic-experienced rad-axSpA population, these should be corrected.	The current total cost for ixekizumab in the cost-effectiveness results for the biologic-experienced rad-axSpA population is incorrect.	Values in tables changed, including corresponding tables in the Appendices. Also added a line of instruction to Appendix 9 to ensure this change to the initial doses is carried through.
Page 112–113 (Tables 63, 64, 65 and 66): A value of £[redacted] has been used for the total cost of	Please correct value to £[redacted]. Should this error have been carried forward in any other of the ERG's analyses of the biologic-	The current total cost for ixekizumab in the cost-effectiveness results for the	Values in tables changed.

ixekizumab for the company base case, which the ERG note has been sourced from the company model. This value is incorrect; the value in the CS on page 177 is correct. The source of the ERG's error is not increasing the number of initial doses from 1 to 2 in cell E46 on the 'Input Data' sheet of the company model.	experienced rad-axSpA population, these should be corrected.	biologic-experienced rad-axSpA population is incorrect.	

Issue 24 Appendix headings

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 117: An error to the numbering of Appendix headings has been made from this point onwards.	Please amend the numbering of the Appendix headings.	The numbering of the Appendix headings is currently incorrect.	Thank you. The numbering has been corrected.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Ixekizumab for treating axial spondyloarthritis after nonsteroidal anti-inflammatory drugs

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: December 2020

Topic background

Disease background

Axial spondyloarthritis (axSpA) is a chronic rheumatic condition, characterised by inflammation at the sacroiliac joint and spine. AxSpA is an umbrella term, encompassing both:

- Radiographic (rad-axSpA) (also known as ankylosing spondylitis): inflammatory changes in the sacroiliac joints or spine can be determined on X-ray
- Non-radiographic (nr-axSpA): absence of visible structural damage on X-ray, although inflammation may be observed on MRI (magnetic resonance imaging).

Clinical symptoms are variable, but generally include chronic back pain, stiffness, fatigue, poor sleep quality and night-time waking. Joint and tendon pain, arthritis and swelling of the fingers are also common, resulting in significantly reduced physical function. Extra-articular symptoms such as psoriasis, inflammatory bowel disease and inflammation of the eye occur in around 40% of cases. AxSpA is also associated with comorbidities such as cardiovascular disease, diabetes and osteoporosis. The burden of disease (in terms of functionality and self-reported disease activity) is similar for radiographic and non-radiographic axSpA. Approximately 12% of nr-axSpA progresses to rad-axSpA over a patient's lifetime.

The prevalence of axSpA is uncertain, but it is estimated that around 62,650 people are currently living with nr-axSpA and 100,815 with rad-axSpA in England. The average age on onset is 24. The difficulty in distinguishing inflammation from other causes of back pain contributes to an average diagnostic delay in the UK of 8.5 years from symptom onset.

AxSpA is caused by dysregulation of the immune system, resulting in inflammation at the axial joints. The influx of inflammatory cells can lead to dysregulation of bone maintenance: uncontrolled breakdown can damage the axial joint, whilst the over-

production of cells that produce new bone leads to abnormal bone formation and, ultimately, fusing of the sacroiliac joints and spine. The tumor necrosis factor (TNF)-alpha and interleukin (IL)-17 cytokine families are thought to play a key role in symptom production and are therefore important therapeutic targets.

The Assessment of Spondyloarthritis International Society (ASAS) response criteria (range 0-100) is a clinical tool to assess and monitor axSpA and is based on four domains:

1. Patient global assessment of disease activity (10cm visual analogue scale (VAS) score)
2. Spinal pain (10cm VAS score)
3. Physical function (Bath Ankylosing Spondylitis Functional Index (BASFI) score; range 0-100)
4. Inflammation (mean score of items 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); both 10 cm VAS)

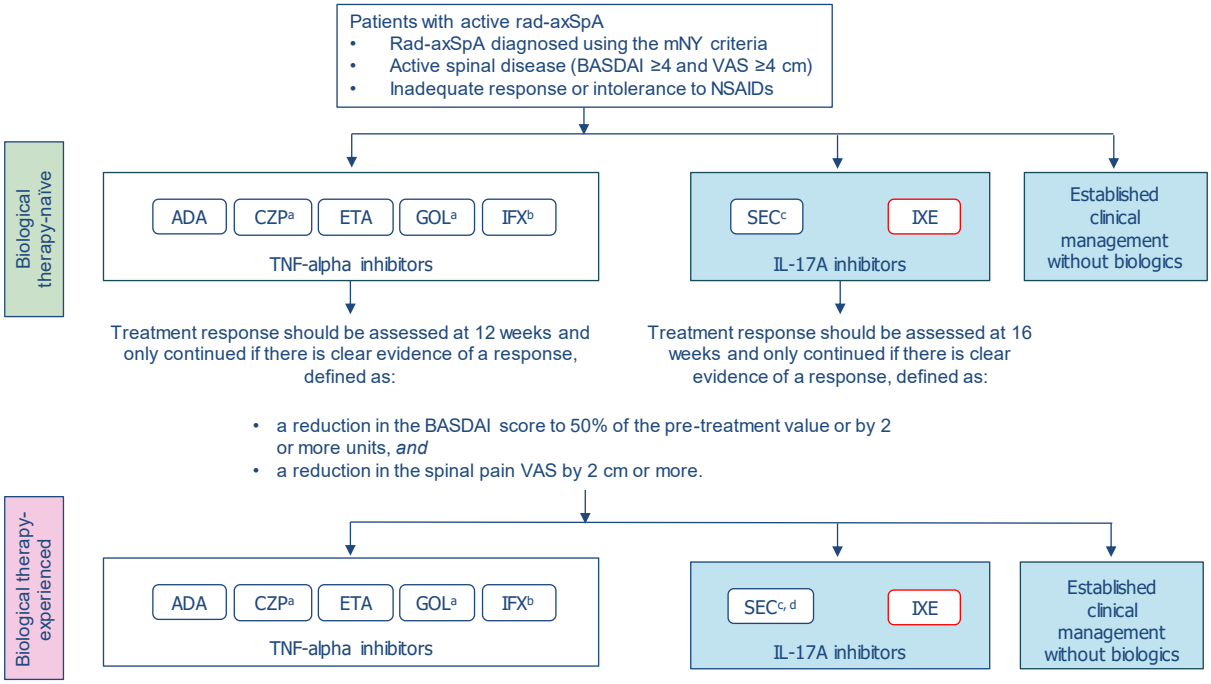
ASAS40 response is defined as improvement from baseline of ≥ 40% and absolute improvement from baseline of ≥ 2 units in at least 3 domains without any worsening in the remaining domains.

Treatment pathway

There is no cure for axSpA. Treatment aims to relieve pain and stiffness, prevent joint and organ damage and preserve joint function and mobility. Following diagnosis, NICE guideline 65 recommends conventional treatment with physical therapies and first-line pharmacological treatment non-steroidal anti-inflammatory drugs (NSAIDs) at the lowest effective dose.

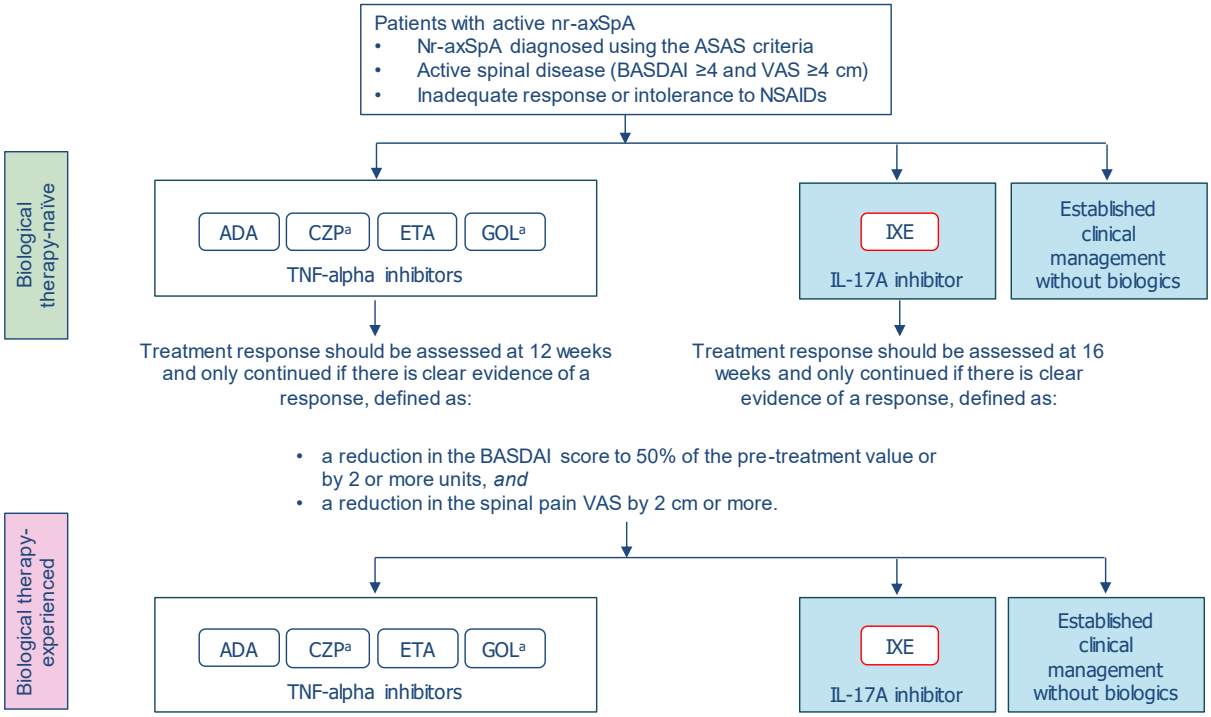
Figures 1 & 2 summarise the treatment pathways for people with rad-ax-SpA and nr-ax-SpA whose disease has not responded to, or who cannot tolerate NSAIDs.

Figure 1 -NICE-recommended treatment pathway for patients with rad-axSpA who have responded inadequately to, or cannot tolerate, NSAIDs or TNF-alpha inhibitors



Source CS, B. 1.2.3, figure 3
Boxes coloured **blue** indicate treatments that are **also** options for patients who are **contraindicated to TNF-alpha inhibitors.** Red squares indicate anticipated position of ixekizumab in the treatment pathway. [a]Manufacturer submitted with a patient access scheme in TA383; [b]Recommended only if treatment is started with the least expensive infliximab product; [c]Manufacturer submitted with a patient access scheme in TA407 for SEC 150 mg. [d]A recent licence extension for SEC permits up-titration to a dose of 300 mg based on clinical response to the 150 mg dose (this dose has not been appraised by NICE in rad-axSpA).[8]
Abbreviations: ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CZP: certolizumab pegol; ETA: etanercept; GOL: golimumab; IFX: infliximab; IXE: ixekizumab; IL-17A: interleukin 17A; mNY: modified New York; NSAID: non-steroidal anti-inflammatory drug; rad-axSpA: radiographic axSpA; SEC: secukinumab; TNF: tumour necrosis factor; VAS: visual analogue scale

Figure 2: NICE-recommended treatment pathway for patients with nr-axSpA who have responded inadequately to, or cannot tolerate, NSAIDs or TNF-alpha inhibitors



Source CS, B. 1.2.3, figure 3
Boxes coloured **blue** indicate treatments that are **also** options for patients who are **contraindicated to TNF-alpha inhibitors** (in addition to being options for patients who do not have any contraindications). Red squares indicate anticipated position of ixekizumab in the treatment pathway. [a]Manufacturer submitted with a patient access scheme in TA383.
Abbreviations: ADA: adalimumab; ASAS: Assessment of SpondyloArthritis International Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CZP: certolizumab pegol; ETA: etanercept; GOL: golimumab; IXE: ixekizumab; IL-17A: interleukin 17A; mNY: Modified New York; NSAID: non-steroidal anti-inflammatory drug; rad-axSpA: radiographic axSpA; TNF: tumour necrosis factor; VAS: visual analogue scale

Existing NICE recommendations

From TA383 (MTA of TNF-alpha inhibitors, 2016)

- TNF-alpha inhibitors recommended when disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs as follows:
  - Rad-axSpA: **Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab**
  - NR-axSpA: **Adalimumab, certolizumab pegol and etanercept**
- If more than 1 treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen.
- Treatment with another TNF-alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response

From TA407 (STA, 2016)

- **Secukinumab** is recommended for treating rad-Ax-Spa when disease has responded inadequately to conventional therapy (non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors).

From TA497 (Cost comparison FTA, 2018)

- **Golimumab** is recommended for treating NR-Ax-Spa in adults whose disease has responded inadequately to, or who cannot tolerate, nonsteroidal anti-inflammatory drugs.
- If golimumab is one of a range of suitable treatments, including adalimumab, etanercept and certolizumab pegol, the least expensive (taking into account administration costs and patient access schemes) should be chosen.

The technology: Ixekizumab

UK approved name and brand name	Ixekizumab (Taltz, Eli Lilly)
Mechanism of action	Humanised monoclonal antibody which selectively binds interleukin-17A and inhibits the release of pro-inflammatory cytokines, chemokines and prostaglandins responsible for the clinical symptoms of axSpA.
Marketing authorisation	• Treatment of adult patients with active ankylosing spondylitis (rad-axSpA) who have responded inadequately to conventional therapy • Treatment of adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs). Also licensed for plaque psoriasis and psoriatic arthritis (either alone or in combination with methotrexate), see TA537 and TA442.

Dosing regimen and trial period	• 160 mg SC (two 80 mg injections) at week 0, followed by 80 mg SC every 4 weeks. • Consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks

Price	Confidential simple discount PAS has been agreed with NHSE and is included in the company's model
	List price:
	• 80 mg/ml solution for injection pre-filled pen: £1,125.00
	• Per annum cost
	  ○ First year: 15 injections - £16,875
	  ○ Second year: 13 injections - £14,625

Decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	ERG/technical team comment
Intervention	Ixekizumab	160mg loading dose by SC injection (two injections) at Week 0, followed by 80mg (one injection) every 4 weeks	Reflects the licensed dose of ixekizumab and the company's updated evidence submission from June 2020
Population	People with axial spondyloarthritis for whom non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors have been inadequately effective or not tolerated, or are contraindicated.	As per scope	No results reported for the overall population. Clinical and cost effectiveness evidence presented for 3 subgroups defined by disease type and prior treatment exposure as follows: • People with rad-axSpA who have responded inadequately to two or more NSAIDs, or have shown intolerance of NSAIDs (rad-axSpa biologic-naïve subgroup) • People with rad-axSpA who have responded inadequately to or were intolerant to one to two TNF-alpha inhibitors, following inadequate response to two or more NSAIDs, or intolerance of NSAIDs (rad-axSpa biologic-experienced subgroup) • People with nr-axSpA who have responded inadequately to two or more NSAIDs, or are intolerant of NSAIDs (nr-axSpA biologic-naïve subgroup) Clinical effectiveness evidence not available for people with: • Contra-indications to TNF-alpha inhibitors • People with nr-axSpA and previous exposure to biological therapies

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	ERG/technical team comment
Comparator(s)	**Radiographic axial spondyloarthritis** • TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) • IL-17A inhibitors (secukinumab) • Established clinical management without biological treatments **Non-radiographic axial spondyloarthritis** • TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab) • Established clinical management without biological treatments	As per scope	Company comparators for the biologic-naïve population are the same as those for biologic-experienced population (comparators only differ between patients with rad-axSpA and patients with nr-axSpA). ERG accepts that placebo can be considered a proxy for established clinical management but only for biologic-naive patients in the nr-axSpA population when TNF-alpha inhibitors are not tolerated or contraindicated and for biologic-experienced patients in the rad-axSpA and nr-axSpA populations when biological treatment options are exhausted. Established clinical practice may not be an appropriate treatment for biologic-naïve patients in the rad-axSpA population, (even when TNF-alpha inhibitors are not tolerated or are contraindicated) as secukinumab is a treatment option. To compare ixekizumab with TNF-alpha inhibitors and secukinumab, NMAs were conducted. When conducting the NMAs, placebo was considered to be a proxy for established clinical management without biological treatments. The ERG considers that this approach is reasonable.
Outcomes	The outcome measures to be considered include: • disease activity • functional capacity • disease progression • pain • peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) • adverse effects of treatment • health-related quality of life (HRQoL)	• Composite outcome (ASAS40) • Disease activity (ASDAS<2.1, BASDAI50, BASDAI score change from baseline) • Functional capacity (BASFI) • Inflammation (SPARCC MRI spine and sacroiliac joint scores) • Pain (spinal pain from BASDAI question 2)[1] • Adverse effects of treatment • HRQoL (SF-36 PCS)	ASAS40 primary efficacy outcome in COAST trials but not used in clinical practice or company's cost effectiveness base case analysis. Company conducted NMAs for: • Composite outcome (ASAS40) • Disease activity (BASDAI50, BASDAI score change from baseline) • Functional capacity (BASFI) Company cost effectiveness analysis informed by • BASDAI50 • BASDAI score change from baseline • BASFI score change from baseline. The outcomes of peripheral symptoms and extra-articular manifestations are not addressed in the CS.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	ERG/technical team comment
Subgroups to be considered	If the evidence allows the subgroups of people who have had or not had TNF-alpha inhibitors will be considered.	As per scope	

[1] Response to treatment in clinical practice is defined as achievement of a BASDAI50 response (or fall in BASDAI of ≥2 units), in addition to a reduction in the spinal pain VAS ≥2cm after 12 weeks (16 weeks for patients with a diagnosis of rad-axSpA who are treated with secukinumab). While mean spinal pain NRS data are presented in the CS, data are not presented for the number of patients who achieved VAS ≥2cm, nor the number who achieved this in combination with the associated BASDAI criteria required for treatment response.

Clinical evidence

The COAST trials

The clinical trial evidence for ixekizumab comes from three international randomised controlled trials (RCTs). A brief description of each is given in the table below. The baseline characteristics of patients recruited to the included trials are presented in the CS in Table 8 (COAST-V), Table 9 (COAST-W) and Table 10 (COAST-X). Clinical experts advising the ERG confirmed that the patients in the COAST trials are generally representative of patients treated in the NHS. The ERG agreed with the company that, within each trial, patient baseline characteristics were well-balanced across the trial arms (ERG report section 3.2.1).

Trial parameters	COAST-V	COAST-W	COAST-X
Number of patients	N=341[1]	N=316[1]	N=303[1]
Patient population	• Adults with rad-axSpA • Inadequate response to, or intolerant of NSAIDs • No prior TNF-alpha inhibitors	• Adults with rad-axSpA • Inadequate response to, or intolerant of NSAIDs and TNF-alpha inhibitors	• Adults with nr-axSpA • Inadequate response to, or intolerant of NSAIDs • No prior TNF-alpha inhibitors
Design and trial treatments	Week 0 to Week 16 • 6 arms in total - 4 x ixekizumab arms, 1x adalimumab arm, 1 x placebo arm Week 16 to Week 52 • Patients in the ixekizumab arms continued with assigned treatments • Patients in the adalimumab and placebo arms were randomised to treatment with ixekizumab[3] Week 52 onwards • Optional 2-year extension study	Week 0 to Week 16 5 arms in total - 4 x ixekizumab arms, 1 x placebo arm Week 16 to Week 52 • Patients in the ixekizumab arms continued with assigned treatments • Patients in the placebo arm were randomised to treatment with ixekizumab[3] Week 52 onwards • Optional 2-year extension study	Week 0 to Week 16 5 arms in total - 4 x ixekizumab arms, 1 x placebo arm Week 16 to Week 52 • Patients continued with assigned treatments • Patients identified as inadequate responders could be administered ixekizumab as rescue treatment[4] Week 52 onwards • Optional 2-year extension study
Primary outcome	Proportion of patients achieving ASAS40 response at Week 16	Proportion of patients achieving ASAS40 response at Week 16	Proportion of patients achieving ASAS40 response at Week 16

[1] All three trials were international studies, only COAST-W included any UK patients (N=[redacted])
[2] The four ixekizumab regimens were as follows
- Loading dose 80mg, then 80mg once every 2 weeks
- Loading dose 160mg, then 80mg once every 2 weeks
- Loading dose 80mg, then 80mg once every 4 weeks
- Loading dose 160mg, then 80mg once every 4 weeks [Licenced dose/regimen]
[3]Patients re-randomised to ixekizumab received either:
- Loading dose 160mg, then 80mg once every 2 weeks
- Loading dose 160mg, then 80mg once every 4 weeks [Licenced dose/regimen]
[4] Ixekizumab rescue regimen was loading dose 80mg, then 80mg once every 2 weeks
Source: adapted from ERG report, table 6

Network Meta-Analysis

A network meta-analysis was conducted for ixekizumab versus comparators in the decision problem. Placebo was used as the common comparator, as there were no clinical trials directly comparing the active treatments.

The company conducted separate NMAs for the biologic-naïve and -experienced rad-axSpA populations, and the biologic-naïve nr-axSpA population, in line with the COAST-V, COAST-W and COAST-X trials, respectively.

Two NMAs were performed for each subgroup:

- a base case NMA (only included studies known to be conducted in the relevant patient population)
- a sensitivity NMA (included all of the studies included in the base case NMAs and also studies with mixed populations and populations where prior treatment was unclear).

Only data from patients assigned to doses anticipated to be licensed were inputted.

Data from patients having the anticipated licensed dose of ixekizumab were included in the original analyses. The company updated its analyses after the licensed loading dose for each of the three populations was confirmed to be 160 mg.

Key results from the COAST trials

Week 16 data

Results for the primary outcome ASAS40 at week 16 in each of the COAST trials are presented in the table below. Results are reported for the ITT population (which included patients receiving either the 80 mg or 160 mg loading doses) and for subgroups based on the loading doses received.

Equivalent results for the key secondary outcomes of BASDAI50, BASDAI score change from baseline and BASFI score change from baseline at week 16 are presented for the ITT only (see ERG report section 3.3.1, tables 9 to 11)

COAST-V, COAST-W and COAST-X: ASAS40 response for the ITT population with non-responder imputation, Week 16

Dosing schedule	Response, n (%)	Difference versus placebo or 80mg LD, % (95% CI)	p-value
COAST-V			
PBO (N=87)	**16 (18.4)**	**-**	**-**
IXE every 4 weeks (N=81)	**39 (48.1)**	**29.8 (16.2 to 43.3)**	**<0.0001[a]**
ADA every 2 weeks (N=90)	**32 (35.6)**	**17.2 (4.4; 30.0)**	**0.0053[a]**
IXE every 4 weeks 80mg LD ([redacted])	[redacted]	-	-
IXE every 4 weeks 160mg LD (n[redacted])	[redacted]	[redacted]	[redacted]
COAST-W			
PBO (N=104)	**13 (12.5)**	**-**	**-**
IXE every 4 weeks(N=114)	**29 (25.4)**	**12.9 (2.7 to 23.2)**	**0.017[a]**
IXE every 4 weeks 80mg LD ([redacted])	[redacted]	-	
IXE every 4 weeks 160mg LD (n[redacted])	[redacted]	[redacted]	[redacted][b]
COAST-X			
PBO (N=105)	**20 (19.0)**	**-**	**-**
IXE every 4 weeks (N=96)	**34 (35.4)**	[redacted]	**0.0094[a]**
IXE every 4 weeks 80mg LD ([redacted])	[redacted]	-	-
IXE every 4 weeks 160mg LD ([redacted])	[redacted]	[redacted]	[redacted][b]

Notes: emboldened text used for thePBO arm and pooled loading doses for the IXE arm
[a] p-value compared to PBO
[b] p-value compared to 160mg and 80mg LD
ASAS=Assessment of Spondylo Arthritis International Society; CI=confidence interval; ITT=intention-to-treat; IXE=ixekizumab; LD=loading dose; PBO=placebo
Source: Adapted from ERG report table 8 and CS, section B.2.6.1 table 14

In all three studies, there were [redacted] loading doses for the

primary outcome of ASAS40. However, in COAST-W the 160 mg loading dose resulted in a faster onset and a numerically greater response rate.

Week 52 data

It is not possible to compare ixekizumab every 4 weeks with placebo at Week 52 in either COAST-V or COAST-W due to the re-randomised trial designs. Therefore, a within-arm comparison in patients treated with ixekizumab was performed (response at Week 52 versus response at week 16). Results for ASAS40 are presented in the table below and equivalent results for the key secondary outcomes of BASDAI50, BASDAI score change from baseline and BASFI score change from baseline are presented in ERG report section 3.3.2, tables 13-15.

COAST-V and COAST-W: ASAS40 response in the ITT population who were initially randomised to ixekizumab every 4 weeks , with non-responder imputation, Week 52		
Treatment arm	**Response, n (%)**	**95% CI for response rate (%)**
COAST-V		
IXE every 4 weeks ([redacted])	[redacted]	[redacted]
COAST-W		
IXE every 4 weeks ([redacted])	[redacted]	[redacted]

ASAS=Assessment of SpondyloArthritis International Society; CI=confidence interval; ITT=intention-to-treat; IXE=ixekizumab
Source: ERG report, table 12

The design of the COAST-X trial allowed for comparison of ixekizumab every 4 weeks with placebo at week 52 (for a more detailed description of the methods underpinning the analysis, see ERG report section 3.3.2, p.40 ‘COAST-X trial’). Results for ASAS40 are presented in the table below and equivalent results for the key secondary outcomes of BASDAI50, BASDAI score change from baseline and BASFI score change from baseline are presented in ERG report section 3.3.2, tables 13-15.

COAST-X: ASAS40 response for the ITT population with non-responder imputation, Week 52			
Dosing schedule	**Response rate, n (%)**	**Percentage difference versus PBO or 80mg LD, (95% CI)**	**p-value**
PBO (N=105)	**14 (13.3)**	**-**	**-**
IXE every 4 weeks (N=96)	**29 (30.2)**	[redacted]	**0.0045[a]**
IXE every 4 weeks 80mg LD ([redacted])	[redacted]	-	-
IXE every 4 weeks 160mg LD ([redacted])	[redacted]	[redacted]	[redacted][b]
Notes: emboldened text used for the PBO arm and pooled loading doses for the IXE arm [a] p-value comparing to PBO [b] p-value comparing 160mg and 80mg LD ASAS=Assessment of Ankylosing Spondylitis International Society; CI=confidence interval; CRP=C-reactive protein; ITT=intention-to-treat; IXE=ixekizumab; MRI=magnetic response imaging; PBO=placebo Source: ERG report table 12			

Network Meta-Analysis results

The number of studies (including the COAST trials) that met the inclusion criteria for each of the company NMAs is presented in the table below (it has been assumed that the number of included studies remained the same when the company updated its analysis to reflect the licensed loading dose of ixekizumab).

Outcome	Rad-axSpA				Nr-axSpA	
	Biologic-naïve		Biologic-experienced		Biologic-naïve	
	Base case	Sensitivity	Base case	Sensitivity	Base case	Sensitivity
ASAS40	10	13	3	6	4	7
BADAI50	7	11	1	5	4	5
BASDAI change from baseline	7	10	3	5	2	3
BASFI change from baseline	4	7	1	4	2	4
Source: ERG report tables 32, 34 & 36						

The company used the results of the sensitivity NMAs to inform its economic model. The result of these analyses are summarised below.

Rad-axSpA population

[redacted]

Results against active comparators varied across the treatment exposure subgroups and outcomes as follows:

- Biologic-naïve population
  - ASAS40 response
  - [redacted] BASDAI150 response
  - [redacted] BASDAI score change from baseline
  - [redacted] BASFI score change from baseline
- [redacted] Biologic-experienced population
  - [redacted] ASAS40 response, BASDAI score change from baseline and BASDAI150 response
  - [redacted] BASFI score change from baseline

[redacted]

Nr-axSpA population

NMAs results are only available for the biologic-naïve population and varied by outcome as follows.

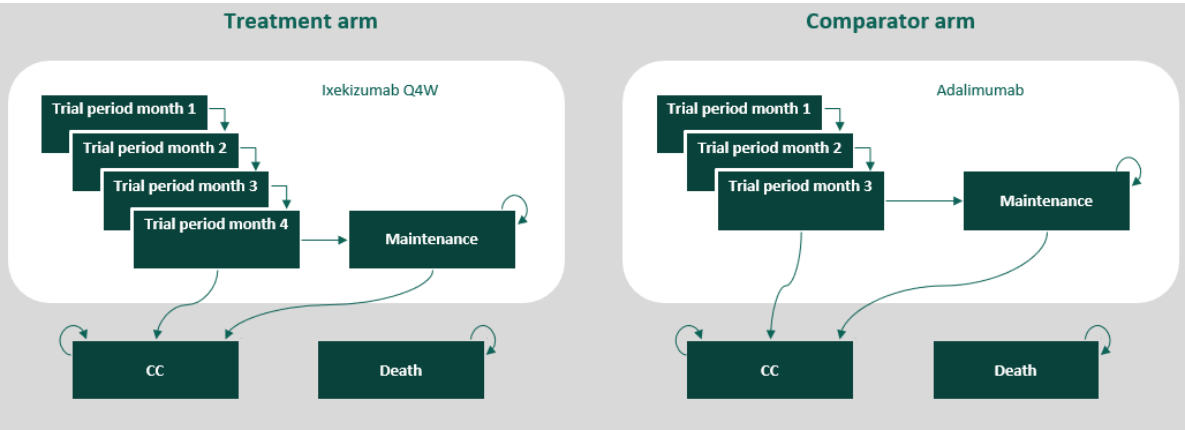
- ASAS40 response
- [redacted]
  BASDAI150 response,
- [redacted]
  BASDAI score change from baseline
- [redacted]
  BASFI score change from baseline

[redacted]

Model structure

The key features of the economic analysis are detailed in **Figure 2**.

Figure 2 - Diagram of cost-effectiveness model for ixekizumab



The model aligns with the *de-novo* model ('York model') developed for use in TA383 to evaluate the cost-effectiveness of multiple TNF-alpha inhibitors in axSpA. This differs from a traditional Markov model as it incorporates a 'trial period', represented by a set of tunnel states which are visited once in a fixed sequence. The duration of this period is determined by the stopping rule in the technology assessment for each comparator (i.e. the point at which response to treatment is assessed (12 or 16 weeks)). In line with the models used in TA383 and TA407, response criteria are determined by BASDAI50 score, with responders transitioning to 'maintenance treatment' and non-responders to 'conventional care'. BASFI is used to model disease progression over time.

Patients in the 'maintenance treatment' state are modelled to receive continuous treatment, with risk of discontinuation due to adverse events or lack of response. Once transitioned to 'conventional care', patients remain in this state until death or the end of the simulation.

Key model assumptions

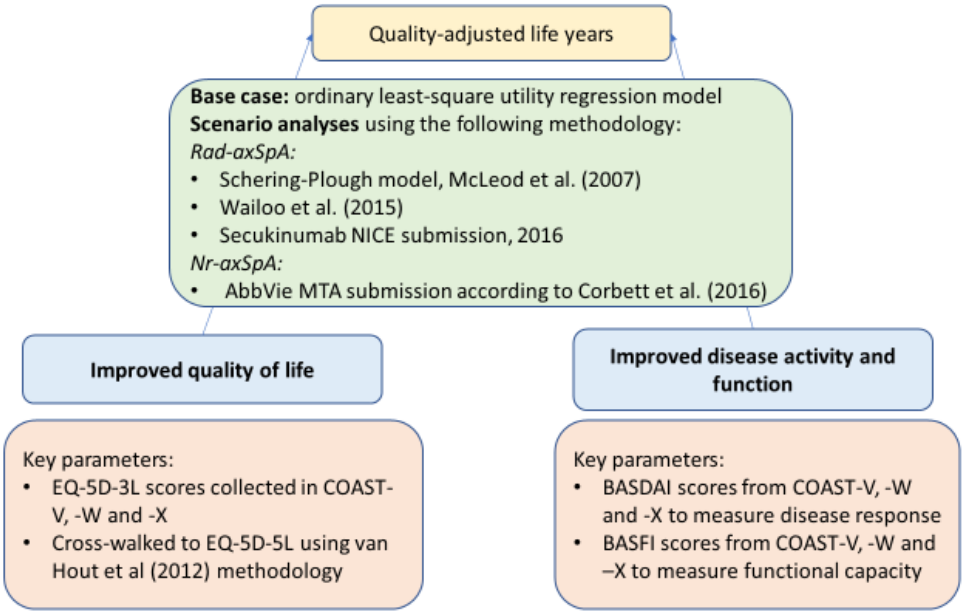
Category	Model assumption
Population	Rad-axSpA - biologic-naïve population from COAST-V trial - biologic-experienced population from COAST-W trial Nr-axSpA - biologic-naïve population from COAST-X trial - biological-experienced population based on scenario analysis using data for the biologic-naïve population
Efficacy	Data for each intervention were derived from NMA sensitivity analyses (BASDAI50 response and change from baseline in BASDAI and BASFI).
Progression of treatment	- BASDAI remains constant over time, whilst BASFI progressively worsens. - Biologic treatment responders have a slower rate of progression (as measured by BASFI) during treatment versus the natural history of axSpA on conventional care - Treatment effect of ixekizumab and comparators on disease progression applies from the end of the trial period until the patient comes off-treatment - Upon treatment discontinuation and transfer to conventional care, patients lose their BASDAI and BASFI treatment response. BASDAI - rebound to baseline, BASFI - 'rebound by initial gain' - Baseline characteristics including BASDAI and BASFI are unconditional upon response i.e. values are the same for responders and non-responders

Adverse effects	AEs included in the model were tuberculosis reactivation and severe infections. Rates apply for the whole treatment period. AEs were not associated with any loss of utility due to lack of data.
Time horizon	Lifetime (54 years rad-axSpA biologic-experienced; 58 years rad-axSpA biologic-naïve; 60 years nr-axSpA biologic-naïve population)
Cycle length	1 month
Utilities	Calculated using an algorithm, similar to previous axSpA models. This consists of a regression model to calculate utility (from EQ-5D-5L scores from COAST trials cross walked to EQ-5D-3L) and incorporates a number of covariates including BASDAI and BASFI scores, age, sex, race and disease duration
Costs and resource use	Includes acquisition, administration, initiation and monitoring costs and long-term management costs. Includes the PAS price for ixekizumab and certolizumab pegol (publicly available) but not for golimumab as does not affect the results. Cost of infliximab, was derived from MIMs and is the same as the BNF list price for the lowest cost biosimilar Cost of etanercept was derived from MIMs and does not match BNF list price of either originator or biosimilar. Cost of adalimumab based on NHS reference costs 2017/18 and unit price was NR. Disease related costs used to model health state costs were based on BASFI score using a regression equation from TA383.

Overview of how quality-adjusted life years accrue in the model

Quality adjusted life years were calculated in a similar manner to previous axSpA appraisals, as summarised in **Figure 3**.

Figure 3 - Quality adjusted life year (QALY) inputs



Summary of the technical report

3.1 In summary, the technical team considered the following:

Issue 1 The company's approach of presenting cost effectiveness results for subgroups defined by disease subtype and prior treatment exposure contributes to the uncertainty in the model estimates. Further analysis and clinical opinion is requested to understand if looking at less specific populations is appropriate.

Issue 2 The company's current analysis of the relative effectiveness of ixekizumab and secukinumab is not robust. Secukinumab is an important scope comparator so further analysis is requested to inform better estimates of the relative clinical and cost effectiveness of the IL-17A inhibitors.

Issue 3 The company's network meta-analyses for the rad-axSpA population are not robust. Further analyses using more inclusive and connected networks are requested to explore the uncertainty in the current estimates

and provide a broader range clinical inputs for cost effectiveness scenario testing.

Issue 4 Evidence on the long-term effectiveness of ixekizumab and secukinumab is available that has not yet been presented by the company. These results are requested to validate the model assumptions and outcomes.

Issue 5 The ERG has highlighted the impact of the company's assumptions regarding the modelling of BASFI scores following treatment discontinuation. Clinical opinion on the validity of the company's approach is requested.

Issue 6 The company approach to estimating utilities is similar in principle to approaches used in other previous axSpA technology appraisals but is based on EQ-5D data collected in the COAST trials. It has explored the impact of using different data sets in scenario analyses which would need to be run again for any new cost effectiveness results presented at engagement.

Issue 7 Currently, the only estimates of the cost effectiveness of ixekizumab for people with nr-axSpA and prior exposure to biologics comes from one very uncertain company scenario (scenario 9). Clarification of the calculations underpinning this scenario are requested. It is also noted that the new analyses requested at engagement may provide a more robust basis for decision making for this population.

3.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

3.2.1 There is no specific evidence to demonstrate the clinical effectiveness of ixekizumab in people with axSpA for whom NSAIDs or TNF-alpha inhibitors have not been tolerated or are contraindicated.

3.2.2 There is no evidence to on the clinical effectiveness of ixekizumab in biologic-experienced patients with rad-axSpA in whom more than 2 biologics have failed.

3.2.3 There is no evidence to on the clinical effectiveness of ixekizumab in biologic-experienced patients with nr-axSpA.

3.2.4 Patients were modelled to only receive one line of treatment but in clinical practice patients frequently receive multiple lines of treatment. The models have the functionality to include subsequent lines of treatment; however, there is insufficient effectiveness evidence to facilitate the modelling of treatment sequencing.

3.3 The cost-effectiveness results include a commercial arrangement (patient access scheme) for ixekizumab. Some of the relevant discounted prices for comparator treatments are not in the public domain so all of the current cost effectiveness estimates (i.e. both the company's and ERG's) must be considered illustrative.

3.4 The technical team recognise the limitations of the clinical data and has been unable to identify any alternative assumptions that are obviously preferable to those chosen by the company based on the current evidence. However, as outlined in this report, the technical team believe further evidence/analysis should be presented to explore the uncertainty in the current estimates. The technical team considers that once a wider range of scenario analysis are available, it may be possible to construct an alternative base case to inform committee decision making (see table 1).

3.5 No equality issues were identified.

Key issues for consideration

Issue 1 – Impact of disease subtype and prior exposure to biologic therapy on the clinical effectiveness of ixekizumab

Background/description of issue	The company has only presented clinical and cost effectiveness analyses for specific subgroups within the overarching population covered by the NICE scope. • Patients with rad-axSpA who have had no prior exposure to biologic treatments (referred to hereafter as the rad-axSpA biologic naïve subgroup) • Patients with rad-axSpA who have had prior exposure to biologic treatments (referred to hereafter as the rad-axSpA biologic experienced subgroup) • Patients with nr-axSpA who have had no prior exposure to biologic treatments (referred to hereafter as the nr-axSpA biologic naïve subgroup) The company stated that its approach is aligned to the design/inclusion criteria of the COAST trials, but it is unclear if its approach makes best use of the available data overall. The evidence for ixekizumab versus placebo in biologic experienced patients is very limited. In current practice, patients with rad-axSpA can receive up to 6 biologics (5 TNF-alpha inhibitors and 1 other IL-17A-inhibitor) and patients with nr-axSpA can receive up to 4 TNF-alpha inhibitors. COAST-W didn't include any patients with nr-axSpA or any patients with rad-axSpA who had experience of more than two biologics or previous experience with sekukinumab. Also the results of COAST-W may not provide an accurate estimate of how effective ixekizumab is versus placebo at any specific subsequent treatment line. In addition, comparator evidence related to the subgroups prioritised by the company is very limited; most of the available studies are in biologic naïve or mixed populations, or populations where prior treatment is unclear. To date, the company has not provided any NMA results that relate solely to patients with previous biologic experience, and the company's sensitivity NMAs (which informed the cost effectiveness analysis) included

	studies with mixed and 'unclear' populations, even though these incremental cost effectiveness ratios (ICERs) are presented as being specific to biologic naïve/experienced patients.
	In NICE's previously published axSpA appraisals, separate analyses have always been conducted for rad- and nr-axSpA, but the extent to which prior treatment exposure has been explored through data analysis or impacted decision making has varied as follows:
	• TA497 Golimumab for treating non-radiographic axial spondyloarthritis (2018)
	  ○ The only available data came from a trial that excluded patients previously treated with TNF-targeted therapies, any biologic agent or cytotoxic drug.
	  ○ The committee considered one set of ICERs that were based on an NMA of studies that included biologic naïve and experienced patients
	  ○ The committee made one overarching recommendation that covered both populations
	• TA407, Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors (2016)
	  ○ The committee considered separate ICERs for biologic naïve and experienced patients; the ICERs for the biologic naïve subgroup were based on data for biologic-naïve patients only, but the ICERs for the biologic-experienced subgroup were based on data for a mixed population of patients with and without prior exposure to biological therapies due to lack of subgroup-specific data.
	  ○ The committee concluded that the ICERs indicated that secukinumab was cost effective in both biologic-naïve and -experienced patients and made one overarching recommendation that covered both populations
	• TA383 TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis
	  ○ The committee considered one set of ICERs for each disease subtype (rad-axSpA or nr-axSpA)
	  ○ In the cost effectiveness analyses it was assumed that all the TNF-inhibitors were equally effective
	  ○ This assumption was based on the results of NMAs of studies that included biologic-naïve and -experienced patients which showed there were no statistically significant differences between the 5 TNF-alpha inhibitors for efficacy outcomes at 10–16 weeks.
	  ○ The committee made one overarching recommendation that covered both populations

	The company did not comment on the strength of the evidence for a difference in treatment effect across the subgroups it prioritised or conduct any meta-analysis of the COAST trials. The ERG accepted the company's approach to analysing data for biologic-naïve and -experienced patients separately but also noted that the current approach does not accurately capture the impact of treatment sequencing in any group. Pooling the clinical evidence across the rad-axSpA and nr-axSpA populations and biologic-naïve and -experienced populations is potentially possible but has not yet been explored.
Why this issue is important	The company's decision to pursue a subgroup approach has a big impact on the inclusion criteria for the NMAs which are the key driver of cost effectiveness. The company's current NMA results are highly uncertain. Combining the available data in larger, more connected networks has the potential to make the results more robust. To understand whether this is appropriate, the similarity of the underlying trial populations and consistency in the relative treatment effects across the component trial needs to be evaluated. Comparator data have been combined in previous appraisals within each disease subtype but so far none of the COAST trials have been combined.
Questions for engagement	a) Is ixekizumab most likely to be used in people with previous exposure to at least one TNF-alpha inhibitor or would it also be offered to people who have never had a TNF-alpha inhibitor? b) Is there a clinical rationale for why treatment outcomes with ixekizumab would be likely to vary based on disease subtype (rad-axSpA versus nr-axSpA) or prior exposure to *any* biologic treatment? If so, is there a clinical rationale why the number or type of prior biologic treatments received previously would impact on the efficacy of ixekizumab? c) How many people would receive more than two biological therapies prior to ixekizumab in clinical practice? d) What is the clinical effectiveness of ixekizumab versus placebo in the patients with rad-axSpA regardless of prior treatment exposure (i.e. the average effect across COAST-V and COAST-W)
Technical team preliminary judgement and rationale	Given the limitations of the subgroup data, the company should meta-analyse the COAST trials to explore the clinical effectiveness of ixekizumab in rad-axSpa populations that are not differentiated by prior treatment exposure. These analyses should include appropriate statistically testing for heterogeneity. Clinical feedback on whether the effectiveness of ixekizumab would be expected to vary by disease type or prior treatment exposure would be welcome to assist with the interpretation of the current and additional analyses.

Issue 2 – Clinical effectiveness estimates for ixekizumab versus secukinumab

Background/description of issue	Secukinumab is licenced in the same population as ixekizumab and is currently recommended by NICE as an option for treating active ankylosing spondylitis in adults whose disease has responded inadequately to conventional therapy (non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors) (NICE TA407) Secukinumab was therefore included as a comparator in the NICE scope for rad-axSpA population in the current appraisal. However, secukinumab is not included in the company's current base case estimates for any population, only in separate scenario analyses that were conducted for the rad-axSpA population. This is because the company's estimates for the clinical effectiveness of ixekizumab versus secukinumab are derived from a separate set of underlying NMA analyses. The reasons for this are complicated. The company included the pivotal secukinumab studies used in TA407 (MEASURE 2 and MEASURE 4) in its original systematic literature review. These studies provided data for two of the four key outcomes for which NMAs were originally conducted by the company. The NMA results showed that ixekizumab was [redacted] secukinumab 150 mg for the outcome of ASAS40 but [redacted] ixekizumab and secukinumab 150 mg for the outcome of BASDAI score change from baseline. However, neither of the MEASURE trials reported BASDAI50 or BASFI change from baseline so the company's original NMAs for these outcomes did not include any data that would allow for comparisons to be made between ixekizumab and secukinumab. The MA for secukinumab changed during the appraisal to allow for use of an escalated 300mg dose. This prompted the company to run additional targeted searches for secukinumab data. The company's reporting regarding the number of additional secukinumab studies identified via these searches is inconsistent. In the CS it refers to two studies by [redacted] respectively. In, its clarification response it refers to three studies: [redacted]. In the CS, the company states that all the additional studies were specific to biologic naive patients and the recommended starting dose of 150 mg (i.e. not the newly licensed 300 mg dose). The company did not provide a clear explanation for why these studies had not been identified in the original searches/systematic literature review. [redacted] At the clarification stage the company noted that [redacted] However, the response did not make clear if further analysis is possible using some the other identified studies (MEASURE 2 and 4, [redacted]).

	The ERG concluded that 'there are currently insufficient data available in the public domain to allow a comparison of either the clinical or cost effectiveness of ixekizumab versus secukinumab' but it is unclear if this conclusion relates to the lack of available ITC data or lack of sufficient trial data. Overall, it is unclear whether the company has managed to identify and analyse appropriately all the relevant secukinumab studies related to the rad-axSpA population. In addition, since the company's most recent submission, another randomised controlled trial of secukinumab, which looks at the use of secukinumab in the nr-axSpA population has been published: Deodhar, A., et al, (2020), Improvement of Signs and Symptoms of Nonradiographic Axial Spondyloarthritis in Patients Treated With Secukinumab: Primary Results of a Randomized, Placebo-Controlled Phase III Study. Arthritis Rheumatol. https://doi.org/10.1002/art.41477. This study will not provide any of the currently missing outcome data for the rad-axSpA population, but it may provide sufficient evidence for further NMAs to be conducted in the nr-axSpA. These results, in combination with either the existing or any further analysis in the rad-axSpA population, may provide sufficient evidence to draw conclusions about whether it is reasonable to assume a class effect across the IL-17A inhibitors. This would however, be contingent on the assumption that effects in the nr-axSpA population can be extrapolated to the rad-axSpA population (see issue 1). If such an assumption is considered viable, then there would be sufficient data in the COAST trials to generate all the clinical and cost effectiveness estimates required by the scope of the appraisal.
Why this issue is important	Secukinumab is an important comparator. It is licenced in the same population at ixekizumab and holds a significant amount of the market for rad-axSpA, with the 150mg dose estimated to be used in [redacted] for the biologic-naive and [redacted] of the biologic-experienced population in 2020.
Questions for engagement	a. Is the company able to provide any revised estimates of the clinical and cost effectiveness of ixekizumab compared with secukinumab?
Technical team preliminary judgement and rationale	If data exist to allow for cost effectiveness estimates to be generated for the comparison of ixekizumab versus secukinumab, these should be included in the company's main NMAs and base case analyses. Based on the evidence presented currently, it is not possible to conclude definitively whether ixekizumab is superior to secukinumab, but no evidence has been presented to suggest that it is any less effective in the rad-axSpA population. Therefore, if the current estimates cannot be improved on, it would be reasonable and conservative to assume a class effect across the IL-17A inhibitors and use the COAST data to inform the economic modelling of both ixekizumab and secukinumab.

	Although the NICE scope does not cover the cost effectiveness of ixekizumab versus secukinumab in the nr-axSpA population, it may potentially be appropriate to consider the newly published evidence of secukinumab in nr-axSpA, to further explore the evidence base for a class effect across the IL-17A inhibitors

Issue 3 – Limitations in the network meta-analysis

Background/ description of issue	Base-case and sensitivity NMAs were performed for each of the subgroups prioritised by the company for four key outcomes. The company only included studies conducted in the exact population of interest in their base case NMAs, whilst studies with 'unclear' or mixed populations were included in the sensitivity NMAs. The ERG concluded that three of the sensitivity NMAs for the rad-axSpa population were not suitable for decision making and that the cost effectiveness results that relied on these findings (all of the company's current ICERs for the rad-axSpA population) are therefore not robust. The ERG's conclusion was based on the large differences in the absolute effects estimated by the base case and sensitivity models. In its original report the ERG noted that these large differences suggest that the absolute effect estimates are not robust when studies with mixed and 'unclear' patient populations are added to the base case network of evidence. The ERG,

	therefore, considers the absolute effect results generated by the base case NMAs are likely to be more reliable than those from the sensitivity NMAs. The ERG was unable to comment on whether this conclusion held true in relation to the company's updated analysis as updated results for the base case NMAs were not reported. The ERG also noted that difference in the timing of outcome measurement was another important source of heterogeneity in the company's NMAs. The company's base case NMAs are too sparsely populated with studies to generate results for all relevant comparator treatments. Specifically: • In the biologic-naïve subgroup, results from the base case NMAs only provide results for ixekizumab versus placebo, adalimumab, etanercept and golimumab (i.e. no results are available for comparison of ixekizumab versus certolizumab pegol or infliximab). • In the biologic-experienced subgroup, the base case networks do not provide results for any of the comparisons of interest, and even if the company is able to provide further data for secukinumab (see issue 2), base case NMA results could not be generated for any TNF-alpha-inhibitor. In addition, considering the results of the sensitivity NMAs the ERG concluded were appropriate for decision making, [redacted]. The ERG presented a de novo scenario for the biologic-naïve nr-axSpA population using the ixekizumab effectiveness results from the company's sensitivity NMAs for the biological treatment comparators (the placebo sensitivity NMA estimates were used to represent conventional care). However, the ERG's scenario does not solve the issue of there being no reliable estimates of clinical or cost effectiveness in the rad-axSpA population. Further class effects NMAs are potentially feasible but have not yet been explored. Class analysis may be justifiable because: • TA383 and TA497 both concluded that the TNF inhibitors have similar clinical efficacy (and average TNF-alpha inhibitor scores are already used in the company's model to substitute for missing values) • There is currently insufficient evidence to conclude definitively that clinical efficacy varies across the IL-17A inhibitors (see issue 2) or between the TNF-alpha and IL-17A inhibitors Also, conducting NMAs for populations undifferentiated by disease subtype or prior treatment exposure is potentially feasible and, given that the current approach has not led to robust results being available for all subgroups, this more inclusive approach may be justified (although this is contingent on the extent to which the clinical effectiveness of ixekizumab differs in these populations – see issue 1)

Why this issue is important	The NMA results are a major driver of cost effectiveness. There is currently only one set of NMA estimates available for the rad-axSpa population and the ERG concluded these results are not robust meaning there is a high chance of decision error in this population.
Questions for engagement	a) Is it reasonable to assume equal efficacy across all TNF-alpha inhibitors in rad-axSpa biologic naïve patients? If so, should the same assumption be applied in all other subgroups? b) Is it reasonable to assume equal efficacy across all IL-17-1A inhibitors in rad-axSpa biologic naïve patients? If so, should the same assumption be applied in all other subgroups? c) Is it reasonable to assume equal efficacy across all comparators and in all populations given the limited evidence to demonstrate that ixekizumab is more or less effective than other currently available treatments?
Technical team preliminary judgement and rationale	Any NMA results for the rad-axSpA population are likely to be limited by heterogeneity. Combining the existing evidence in more inclusive networks may increase the heterogeneity in the networks overall, but given that heterogeneity is already a problem, it's not clear whether being more inclusive will lead to results that are substantively less reliable. Also, conducting further, more inclusive, NMAs would: • Provide an alternative set of clinical effectiveness estimates which may help to characterise the level of uncertainty in the current results • Help to better understand whether extrapolating results across comparators or populations is reasonable • Potentially reduce the number of separate cost effectiveness analyses that need to be presented to committee The following additional analyses should therefore be conducted: • Analysis that assumes that a class effect exists across: o the TNF-alpha inhibitors o the IL-17A inhibitors • Analysis that assumes that a class effect exists across all the biologic treatments • If appropriate (based on the response to issue 1) analysis that includes all studies regardless of prior treatment exposure The source data included in each new analysis should be reported in full. For each new analysis consideration should be given to whether fixed or random effects NMA models are most appropriate with results for both models reported in full. Additional cost effectiveness scenarios should be run using the results of each of any new analyses conducted.

Issue 4 – Long-term effectiveness of ixekizumab

Background/description of issue	During maintenance treatment, responder patients are in each cycle at risk of dropping out of treatment due to severe AEs or loss of response. The drop-out rate is assumed to be constant over time, with yearly drop-out rates of 11% and 5% in the rad-axSpA and nr-axSpA populations, respectively, with the same drop-out rate applied for all treatments (CS section B.3.3.7). This means the company has effectively assumed that all the treatments included in the model have the same long-term clinical effectiveness during the maintenance phase. This approach aligns to TA383 and TA407. There is a lack of randomised data for the comparison of ixekizumab to placebo past week 16 in the rad-axSpA population and evidence for both the rad-axSpA and nr-axSpA populations is limited to a maximum period of 52 weeks. The results of the COAST-Y study were due to be published in March 2020 and if available, would provide useful evidence on the longer-term effectiveness of maintenance ixekizumab. The ERG also noted that the trials used to inform decision making in TA407 (MEASURE 1 and 2 trials) followed people for two and five years and so these provide another potential evidence source to validate the model outputs.
Why this issue is important	The cost effectiveness estimates are based on a model with a lifetime time horizon therefore it is important to know whether the projected estimates of clinical effectiveness are plausible. So far, the company has provided limited evidence to support any conclusions about the long-term effectiveness of ixekizumab.
Questions for engagement	a) Can the company supply the results of the COAST-Y study? b) Can the company comment on the extent to which the currently available evidence supports the projected estimates of long-term treatment effects derived from the economic model?
Technical team preliminary judgement and rationale	The lack of long-term comparative data and short follow-up period in the COAST trials increases the uncertainty surrounding the difference in efficacy between placebo and ixekizumab.. If further data exist to validate the model assumptions or outputs regarding the long-term effectiveness of ixekizumab or its comparators, it should be presented in the company's response to engagement.

Issue 5 – Modelling of BASFI scores after treatment discontinuation

Background/description of issue	The company assumed that when treatment is discontinued, function (measured by BASFI scores) begins to decline (BASFI scores increase or 'rebound'). In its base case, the company assumed that the BASFI score would deteriorate by the same amount as was initially gained i.e. patients return to their baseline level of function. Because untreated disease would be expected to progress, this approach essentially assumes that there is some ongoing functional improvement after discontinuing treatment. The committee for TA383 considered the 'rebound by initial gain' approach appropriate as clinical experts stated people were unlikely to deteriorate to a poorer state of health than their baseline level. The company also explored use of the 'rebound to natural history' assumption in a scenario analysis. This assumption returns the BASFI level to that which would be expected had the biological treatment not been given. The ERG reported the key finding for the rebound to natural history scenario in its own report. The most substantive impact was in the rad-axSpA biologic-naïve population for the comparison of ixekizumab compared to conventional care: the QALY gains associated with ixekizumab reduced from [redacted] to [redacted] (difference of [redacted]) (source: ERG addendum July 2020, section 1.3.2, table 1). For all other comparisons the alternative scenario had little impact on the incremental cost and QALY gains associated with ixekizumab. Despite its decision to present the same scenario as the company, the ERG ultimately concluded that the treatment effect would most likely fall between that calculated using the 'rebound by initial gain' and 'rebound to natural history' approach, noting that the former is likely to overestimate the effects of treatment post discontinuation and the latter probably reflects a worst case scenario.
Why this issue is important	The correct functional effect following discontinuation of biological treatment is important for determining downstream costs.
Questions for engagement	a) When treatment is discontinued, is it reasonable to assume that patients return to their baseline level of function?
Technical team preliminary judgement and rationale	The technical team agrees with the company's 'rebound by initial gain' approach as it reflects the views of the clinical experts that contributed to TA383.

Issue 6 – Choice of utility regression equation

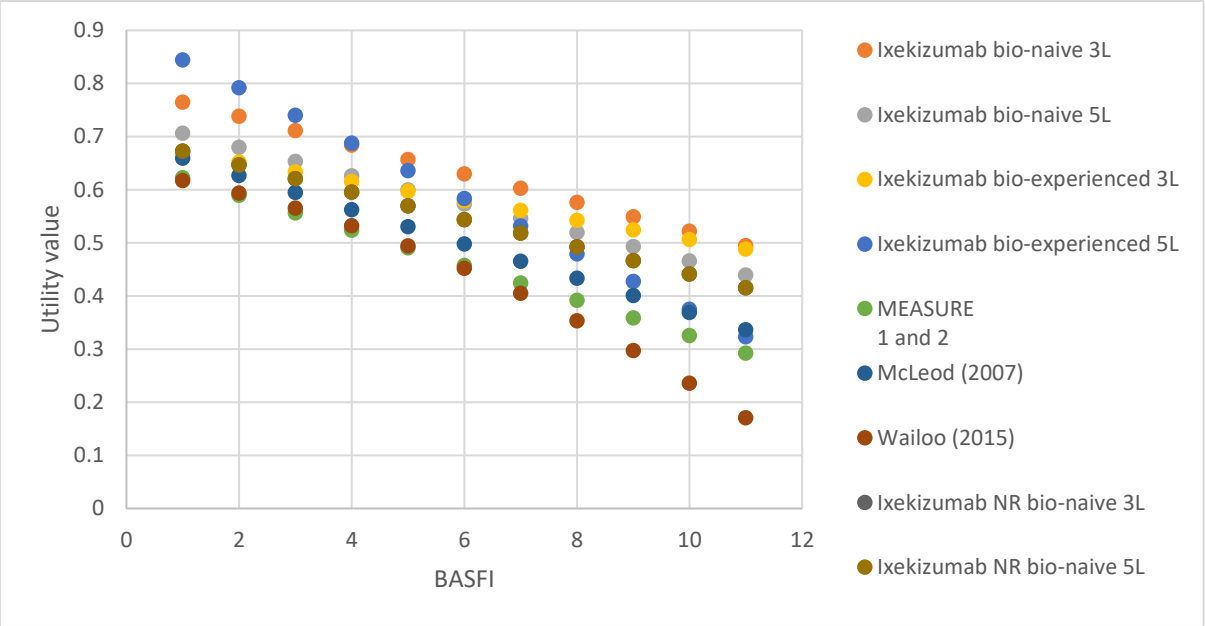
Background/description of issue	The company's overall approach to estimating utility values is similar to methods used in other previously published axSpA appraisals. In the base case, an ordinary least-square utility regression model was developed for each population in the model (biologic-naïve rad-axSpA, biologic-experienced rad-axSpA and biologic-naïve nr-axSpA) that was derived from the COAST-V, COAST-W or COAST-X data, respectively. The regression model was developed between BASDAI/BASFI data and EQ-5D-3L utility values cross-walked from EQ-5D-5L data collected in the trials. The company tested the use of four alternative approaches in scenario analysis (a-d summarised below). Company scenarios 3a-c used other previously published equations that were based on a different combination of covariates and had been tested in previous NICE appraisals. The Wailoo et. al 2015 and Company scenario 3c were both considered in the previously published secukinumab appraisal TA407 – the different scenarios had

only a small impact on the cost effectiveness results. Company scenario 3d used the same regression equation as in the company base case but with the original EQ-5d-5L data instead of the cross-walked data.

3	Scenario utility source	Base case utility source	Purpose of scenario
a	Wailoo et al. (2015) algorithm	Ixekizumab EQ-5D-3L algorithm	To explore the impact of alternative algorithms to map BASDAI, BASFI and other patient parameters to EQ-5D utility values (see Section **Error! Reference source not found.**).
b	McLeod et al. (2007) algorithm		
c	Algorithm used in company model for TA407 (2016)		
d	Ixekizumab EQ-5D-5L algorithm		
Source: CS, section B.3.8.3, table 127 Mcleod et. al 2007 and Wailoo et al. 2015 have both been explored in scenario analysis in TA383 or TA407			

The company also made reference to another published model that was used in the AbbVie MTA submission (Corbett et al. 2016) but no scenario testing was conducted using this source.

The ERG noted that a large variation in the utilities was produced by using different regression models. This is demonstrated in the Figure below, which shows the range of utilities produced with a BASDAI score of 7 and varying BASFI scores.



The ERG noted that the range of results calculated by the different regression equations increases with the BASFI score (representing functional deterioration). Furthermore, the utility equations used in the company submission produced higher results than the other regression equations tested. The approach associated with the lowest values was the Wailoo 2015 regression equation. The ERG presented the company's Wailoo 2015 scenario for the biologic naïve subgroups in its report. The impact of the changes varied by comparator – for some comparisons, the incremental QALYs associated with ixekizumab increased, in others they declined.

In the rad-axSpA population, for the comparisons with conventional care and etanercept the QALY gains from ixekizumab treatment increased as follows, causing the ICERs to fall:

Comparator	**QALYs gained with IXE**	
	Company base case utilities	**Wailoo 2015 scenario utilities**

	Conventional care	[redacted]	[redacted]
	Etanercept	[redacted]	[redacted]
	Source: ERG addendum July 2020, tables 1-6		

For all other comparisons ixekizumab was either dominant or dominated by the comparator in the base case and the scenario did not change these findings.

In the nr-axSpA population, for the comparisons with conventional care, certolizumab pegol and golimumab, the QALY gains from ixekizumab treatment increased as follows:

Comparator	**QALYs gained with IXE**	
	Company base case utilities	**Wailoo 2015 scenario utilities**
Conventional care	[redacted]	[redacted]
Source: ERG addendum July 2020, tables 1-6		

For all other comparisons ixekizumab was less effective than the comparator in the base case and the scenario did not change these findings.

Why this issue is important	Varying the regression model influences the cost-effectiveness estimates for some comparisons
Questions for engagement	a) What are the results of the utilities scenario analysis (company scenarios 3a-d) when tested in the new population/class scenario analyses requested by the technical team in issues 3?
Technical team preliminary judgement and rationale	The alternative regression models tested by the company were all compared in TA407 and the ERG for that appraisal concluded that using alternative regression models resulted in relatively minor differences in the total number of QALYs per treatment and had no impact on the conclusions. In the current appraisal, the findings of the scenario analyses were variable with a greater impact on total QALY gains seen in some subgroups. The technical team have requested several new analyses in this report for different populations/drug-class combinations. The current utility scenario analyses will need to be repeated for all new cost effectiveness analyses presented by the company following technical engagement before any definitive conclusions can be drawn regarding the magnitude of difference between each possible approach.

Issue 7 – Company's cost effectiveness scenario for patients with nr-axSpA that have had prior exposure to biologic treatments

Background/description of issue	There is no clinical evidence for the effectiveness of ixekizumab in people with nr-rad-axSpa with prior exposure to biological treatments (see issue 3). To deal with this evidence gap, the company conducted a scenario analysis (scenario 9) in which the model was populated with the available data for the biologic-naïve nr-axSpA population, which was then adjusted using a 'modification factor'. The modification factor ([redacted]%) is applied to each of the BASDAI50 response rates for the nr-axSpA biologic-naïve treatments. The company stated that the modification factor reflects the relationship between the BASDAI50 results for the biologic-naïve and biologic-experienced rad-axSpA populations. It also stated that the sources of evidence used to derive this modification factor were the COAST-V and COAST-W trials. The ERG noted that the calculations used by the company to generate the modification factor from the COAST-V and COAST-W trials were not clear. It also stated that no evidence exists to suggest the relationship between biologic-naive and -experienced patients in the rad-axSpA population would apply to the nr-axSpA population. Furthermore, the source of the modification factor was not stated in the company's submission. The ERG concluded that the scenario analysis for the biologic-experienced population was unsuitable for decision making.
Why this issue is important	The marketing authorisation and NICE decision problem covers all nr-axSpA but it is not clear whether the assumptions underlying the cost effectiveness estimates for the biologic-experienced population are robust
Questions for engagement	a) Can the company clarify how it calculated the modification factor used in its scenario analysis for the biologic-experienced nr-axSpA population?
Technical team preliminary judgement and rationale	Scenario 9 is currently highly uncertain. Responses to key issues 1-3 should help to clarify whether evidence for patients with specific disease subtypes and or different levels of biologic treatment exposure can be extrapolated to other groups. The reliability of the company's modification factor calculations and scenario 9 needs to be considered with reference to these responses.

Issues for information

Tables 1 to 6 are provided to stakeholders for information only and not included in the technical report comments table provided.

Cost effectiveness results

Table 1: Company base case results (probabilistic) – rad-axSpA biologic-naïve (with-PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER ixekizumab Q4W vs comparator (£/QALY)
Conventional care	[redacted]	[redacted]	-	-	-	£36,031
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£861	Dominated
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£8,839
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant

Source: CS, Revised Analysis, June 2020, table 26

Life years gained are equivalent between technologies (interventions do not impact mortality in the model) and are therefore not presented. Results are presented here for ixekizumab 80 mg Q4W (LD: 160 mg). Results for pooled doses for etanercept and certolizumab pegol are presented.

Abbreviations: ICER: incremental cost-effectiveness ratio; LD: loading dose; QALYs: quality-adjusted life years

Table 2: Company base case results (probabilistic) – rad-axSpA biologic-experienced (with-PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER ixekizumab Q4W vs comparator (£/QALY)
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	-	£1,635,912
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£44,867	Dominated
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£36,784*
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£1,117,054*
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£91,220*
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	£816,669	£272,720*

Source: CS, section B.3.8.1, table 122

Life years gained are equivalent between technologies (interventions do not impact mortality in the model) and are therefore not presented. Results are presented here for ixekizumab 80 mg Q4W (LD: 160 mg). As described in Section **Error! Reference source not found.**, results for secukinumab are not presented for the base case due to relevant efficacy inputs being unavailable from the NMA. Results for pooled doses for etanercept and certolizumab pegol are presented. *ICERs are located in the south-west quadrant of the cost-effectiveness plane (ICERs > £30,000 per QALY may be considered cost-effective).

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Table 3: Company base case results (probabilistic) – nr-axSpA biologic-naive (with-PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER ixekizumab Q4W vs comparator (£/QALY)
Conventional care	[redacted]	[redacted]	-	-	-	£42,705
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£2,285	Dominated
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£10,580*
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£15,753*
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	£73,610	£12,652*

Source: CS, Revised Analysis, June 2020, table 27

Life years gained are equivalent between technologies (interventions do not impact mortality in the model) and are therefore not presented. Results are presented here for ixekizumab 80 mg Q4W (LD: 160 mg). Results for pooled doses for etanercept and certolizumab pegol are presented. *ICERs are located in the south-west quadrant of the cost-effectiveness plane (ICERs > £30,000 per QALY may be considered cost-effective).

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 4: Technical team preferred assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	ICER	Change from base case
To be confirmed	The ERG concluded that it is not possible to resolve any of the key clinical or cost effectiveness issues and consequently did not specify a preferred set of modelling assumptions. The technical team recognise the limitations of the clinical data and has also been unable to identify any alternative assumptions that are obviously preferable to those chosen by the company based on the current evidence. However, as outlined in issues 1-4 in this report, the technical team believe further evidence/analysis should be presented to explore the uncertainty in the current estimates. The technical team considers that once a wider range of scenario analysis are available, it may be possible to construct an alternative base case to inform committee decision making. In addition, the technical team note that all the comparator treatments included in the model are available in the NHS at discounted prices. In some cases, the available discount applies to the originator form of the drug and in other cases to the biosimilar version. In some cases, there are discounts available for both the originator and the biosimilar. Some discounts apply to products that are available nationally, others to products that are only available in specific regions of England. The cheapest nationally available prices should be used to inform decision making (see paragraphs 5.5.1 and 5.5.2 of the NICE Guide to the methods of technology appraisal 2013), however, because some of the relevant discounted prices are not in the public domain and have not been available to the ERG to date, all of the current cost effectiveness estimates (i.e. both the company's and ERG's) must be considered illustrative. Analysis incorporating all the relevant commercial in confidence discounts will be conducted by the ERG post engagement and presented to committee.	**To be confirmed**	**To be confirmed**

Table 5: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
There is no specific evidence to demonstrate the clinical effectiveness of ixekizumab in people with axSpA for whom NSAIDs or TNF-alpha inhibitors have not been tolerated or are contraindicated.	Populations covered by marketing authorisation	Unknown
There is no evidence on the clinical effectiveness of ixekizumab in biologic-experienced patients with rad-axSpA who have failed treatment with more than two biologics.		
There is no evidence on the clinical effectiveness of ixekizumab in biologic-experienced patients with nr-axSpA.		
Patients were modelled to only receive one line of treatment but in clinical practice patients frequently receive multiple lines of treatment. The models have the functionality to include subsequent lines of treatment; however, there is insufficient effectiveness evidence to facilitate the modelling of treatment sequencing.		

Table 6: Other issues for information

Issue	Comments
Limited clinical evidence for patients receiving care in the UK	Out of the 3 trials presented by the company to support the clinical effectiveness of ixekizumab, only one (COAST-W) included UK patients and these represented a small proportion of the overall sample (n=[redacted]/N=316). However, the ERG noted that the patients included in the COAST trials were likely to be similar to UK patients.
Health state resource use and costs	The ERG concluded that the company's approach to modelling health state resource use and costs is likely to lead to an overestimation of healthcare resource use by BASFI status in the company models. This would affect all model arms equally though so is unlikely to have a major impact on the ICER
Measuring response to treatment	The method used in the model (only using BASDAI data) to categorise patients as responders or non-responders to treatment does not reflect clinical guidelines but the same approach has also been used in previously published models that were developed to assess the relative cost effectiveness of treatments for axSpA (TA3831 and TA4072).
Flares in BASDAI score	Clinical experts advised that the disease process of axSpA may include flares associated with temporary increases in BASDAI score, which were not included in the company models.
Impact of biological treatment on radiographic progression	Clinical evidence of the impact of biologics on radiographic progression is lacking. The company has included the available data in the model, but any variation in effect between biologicals could significantly impact the cost-effectiveness estimate.
Validation of model	The model manual and technical guide provided by the company was not sufficient for the ERG to perform a comprehensive validation of the model, although a stress test and check of the variable references in the code did not identify any errors.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

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Technical engagement response form

ID1532 Ixekizumab for treating axial spondyloarthritis after nonsteroidal anti-inflammatory drugs

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Friday 29 January 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text:

'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Eli Lilly and Company
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Summary for Committee

Issue 1

Treatment Position of Ixekizumab

- Lilly consider that if recommended, ixekizumab will be used in the following manner in UK clinical practice:
  - In **rad-axSpA** patients, ixekizumab will be used for the treatment of adults who have responded inadequately to, or have not tolerated, non-steroidal anti-inflammatory drugs (NSAIDs) and **at least two biological DMARDs (bDMARDs),** or are contra-indicated or otherwise unsuitable for TNF-alpha inhibitor treatment.
  - In **nr-axSpA** patients, ixekizumab will be used for the treatment of adults who have responded inadequately to, or have not tolerated, NSAIDs and **at least one TNF-alpha inhibitor treatment**, or are contra-indicated or otherwise unsuitable for TNF-alpha inhibitor treatment.
- It is important for ixekizumab to be available for use in the axSpA population of the UK as there is still a significant unmet need for effective treatments for patients. The Company acknowledge that TNF-alpha inhibitors will likely be used as first line treatment in UK clinical practice. However, response rates to first-line TNF-alpha inhibition in axSpA have been estimated to be between 33–52%, and real-world studies have consistently confirmed lower effectiveness of sequential TNF-alpha inhibitors in rad-axSpA patients.[1-4] There is also a need for clinician flexibility for primary and secondary non-responders to TNF-alpha inhibitors.
- UK guidance recommend switching to a biologic with a new mechanism of action following treatment failure.[5] In **rad-axSpA,** secukinumab is the only available biologic with a mechanism of action distinct from TNF-alpha inhibition.
  - In **rad-axSpA**, ixekizumab is therefore anticipated to be used following attempt of one TNF-alpha inhibitor and one bDMARD with a distinct mechanism of action (for primary TNF-alpha inhibitor non-responders), or following two TNF-alpha inhibitors in patients with secondary loss of response to their second TNF-alpha inhibitor.
  - In **nr-axSpA**, no treatment options with a distinct mechanism of action to TNF-alpha inhibition are currently available. Therefore, the Company consider that for nr-axSpA patients, ixekizumab would primarily be used following one TNF-alpha inhibitor in TNF-alpha inhibitor primary non-responders, or following two TNF-alpha inhibitors in TNF-alpha inhibitor secondary non-responders
  - Lilly consider that ixekizumab should be an option for rad- and nr-axSpA patients who are **contraindicated to TNF-alpha inhibitors**, given these patients have extremely limited biologic treatment options

Evidence Availability in Subgroups

- The Company acknowledge the Technical Team's wish to minimise uncertainty associated with the presentation of subgroups by prior biologic-exposure, but consider that, based on clinical rationale and statistical evidence and NICE TSD guidance, meta-analysing biologic-naive and -experienced data would not offer greater decision-making certainty for the Committee due to the introduction of significant heterogeneity between patient populations into the analysis.
- NICE has previously recommended the use of the comparator biologic agents (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol and secukinumab) in the biologic-experienced patient population. However, there are no published Phase 3 clinical trial data for the TNF-alpha inhibitors solely in a biologic-experienced population (and none at the time of NICE review). Published evidence from randomised controlled trials of secukinumab includes data from only 59 patients in MEASURE-2 and MEASURE-4 (within subgroups), in which patients could have received a maximum of one prior TNF-alpha inhibitor.[6, 7]
- The Company note that ixekizumab is the only biologic agent to have been studied in a large randomised controlled trial and to have demonstrated efficacy and safety in a specific biologic experienced, intent-to-treat patient population. The COAST-W clinical trial included rad-axSpA patients with an inadequate response to up to two TNF-alpha inhibitors, with no limitations on reasons for prior failure. Patients had long-standing disease duration, which is representative of biologic-experienced patients observed in the UK.
    - The Company therefore believe that COAST-W offers strong evidence to support a recommendation of ixekizumab in the biologic-experienced population.
- With regards to the generalisability of treatment effects between rad- and nr-axSpA, as accepted by the Committee in TA383, the Company consider there to be significant clinical validation of the assumption that clinical efficacy results are generalisable between the rad- and nr-axSpA populations, given that these conditions represent either end of a continuous spectrum of the same disease and thus have the same underlying pathophysiology and similar burden on patients.[8-10]

Issue 2

Comparison to secukinumab

- As requested by the technical team, the Company have been able to conduct an NMA in the nr-axSpA population that incorporates the PREVENT secukinumab study.
- The results found no statistically significant difference between ixekizumab and secukinumab for any of the outcomes assessed, whilst the 95% credible intervals (CrIs) for all of the biologic treatments versus placebo, as well as the posterior median outcomes per treatment arm, overlap substantially for the outcomes assessed.

- The Company therefore consider that the results for ASAS40, BASDAI50, BASDAI cfb and BASFI cfb support a class effect among IL-17 inhibitors and TNF-alpha inhibitors that could be generalised across rad- and nr-axSpA patients.

Issue 3

Class effects among TNF-alpha inhibitors

- The Company consider it reasonable to assume equal efficacy across all TNF-alpha inhibitors within the rad-axSpA biologic-naïve population and further that this assumption may be applied *within* rad-axSpA biologic-experienced and nr-axSpA biologic-naive and -experienced subgroups.
  - An assumption of class effects among TNF-alpha inhibitors is in line with conclusions made by the NICE Committee in TA383, and is supported by clinical evidence that TNF-alpha is a key driver of the pathophysiology of axSpA (all treatments target soluble TNF-alpha) and the substantial overlap of the 95% CrIs in the comparison of TNF-alpha inhibitors versus placebo in the NMAs presented by the Company, together with the substantial overlap of the 95% CrIs for the posterior median outcomes.

Class effects among IL-17A inhibitors

- The Company consider it reasonable to assume equal efficacy across IL-17A inhibitors within the rad-axSpA biologic-naïve population and further that this assumption may be applied *within* rad-axSpA biologic-experienced and nr-axSpA biologic-naive and -experienced subgroups based on current evidence.
  - An assumption of class effects among IL-17A inhibitors is supported by clinical evidence that IL-17A is a key driver of the pathophysiology of axSpA; both secukinumab and ixekizumab target the A variant of the IL-17 cytokine superfamily. Statistical evidence from the NMA presented in response to Issue 2 illustrates no significant differences identified between ixekizumab and secukinumab for any outcomes assessed (ASAS40, BASDAI50, BASDAI cfb and BASFI cfb).

Class effects among all biologics indicated for axSpA

- For the purposes of decision-making, the Company ultimately deem it reasonable to assume class effects amongst all biologics for the rad and nr-axSpA indications.
  - This finding is in alignment with the conclusion of the NICE Committee in the appraisal of secukinumab (TA407) that "secukinumab has a similar efficacy to the TNF-alpha inhibitors".[6]
  - Studies demonstrate that axSpA is driven by cytokine dysregulation, with both the TNF-alpha and IL-17A cytokines playing key roles.

Cost-effectiveness results

- In order to provide a revised economic analysis for the Committee assuming class effects among all biologics, the Company have adopted a non-complex approach, which we deem makes use of the most robust data available to inform decision-making.

- Specifically, an analysis was conducted in the biologic-experienced rad-axSpA population (to support the intended treatment position of ixekizumab in this population) with all biologic treatments adopting the same efficacy inputs from COAST-W as ixekizumab. In lieu of a biologic-experienced model to support the intended position of ixekizumab in the nr-axSpA treatment pathway, a second analysis was conducted using the biologic-naïve nr-axSpA model, with all biologic treatments adopting the same efficacy inputs from COAST-X as ixekizumab.
    - Given the uncertainties raised by the ERG regarding the NMA results, it was deemed that the highly internally valid COAST trials would comprise the most appropriate inputs for these analyses.
- The results of the economic analysis in **rad-axSpA** illustrate that over a lifetime horizon, ixekizumab is associated with either a comparable or less expensive total cost compared to **5/6** biologic treatments recommended by NICE for biologic-experienced patients, namely certolizumab pegol, etanercept, secukinumab 150 mg (N.B. it was not possible to consider the confidential PAS in the analysis), golimumab and infliximab, a result which supports the proposed use of ixekizumab after attempt of NSAIDs and at least two bDMARDs.
- The results of the economic analysis in **nr-axSpA,** illustrate that over a lifetime horizon, ixekizumab is associated with a less expensive total cost compared to **3/4** biologic treatments recommended by NICE, namely etanercept, certolizumab pegol and golimumab, supporting its use after attempt of NSAIDs and at least one prior biologic.

In conclusion, based on the assumptions utilised in this analysis, as informed by the responses provided in Issues 1 to 3, the Company believe that ixekizumab comprises a valuable treatment option for biologic-experienced patients across the full spectrum of axSpA.

Issue 1: Impact of disease subtype and prior exposure to biologic therapy on the clinical effectiveness of ixekizumab	
a) Is ixekizumab most likely to be used in people with previous exposure to at least one TNF-alpha inhibitor or would it also be offered to people who have never had a TNF-alpha inhibitor?	The Company thank the ERG and NICE Technical Team for the feedback received throughout this appraisal. Following this feedback, the Company consider that in UK clinical practice ixekizumab will be used as follows: • In **rad-axSpA** patients, ixekizumab will be used for the treatment of adults who have responded inadequately to, or have not tolerated, NSAIDs and at least two bDMARDs, or are contra-indicated or otherwise unsuitable for TNF-alpha inhibitor treatment. • In **nr-axSpA** patients, ixekizumab will be used for the treatment of adults who have responded inadequately to, or have not tolerated, NSAIDs and at least one TNF-alpha inhibitor treatment, or are contra-indicated or otherwise unsuitable for TNF-alpha inhibitor treatments. Therefore, in both disease subtypes, the Company believe ixekizumab will primarily be used in biologic-experienced patients. The exception is patients in the nr-axSpA population contra-indicated to TNF-alpha inhibitors who may be

biologic-treatment naïve at the point of ixekizumab commencement given that no biologic with a mechanism distinct from TNF-alpha inhibition is currently available in the nr-axSpA population.

Positioning in the rad-axSpA population

- The positioning of ixekizumab in rad-axSpA patients following inadequate response to, or intolerance to, NSAIDs and at least two bDMARDs, or in the case of patients who are contra-indicated or otherwise unsuitable for anti-TNF-alpha treatment, permits necessary clinician flexibility within the treatment pathway. In particular, it is expected that treatment decisions will differ for patients who exhibit primary non-response (no response following treatment initiation) or secondary non-response (initial response to treatment followed by loss of response) to TNF alpha inhibition.
- The Company acknowledge that long-standing TNF-alpha inhibitor treatments such as adalimumab will be used as first line treatment in rad-axSpA patients in UK clinical practice. However, response rates to first-line TNF-alpha inhibition in axSpA have been estimated at 33–52% depending on the criteria used, suggesting approximately 48–67% of patients may be primary or secondary non-responders.[1] Furthermore, recently published evidence suggests that patients who discontinue their first TNF-alpha inhibitor due to primary non-response may be less likely to show a response to their second TNF-alpha inhibitor, based on outcomes such as the Ankylosing Spondylitis Disease Activity Score Inactive Disease (ASDAS-ID).[11, 12]
- In addition, real world studies have confirmed lower effectiveness of sequential TNF-alpha inhibitors in rad-axSpA patients. Glintborg *et al* (2013) and colleagues reported the proportion of rad-axSpA patients (N=1,436, of whom 432 [30%] had a second TNF-alpha inhibitor) achieving BASDAI 50%/20 mm response within 6 months on their first TNF was 54% (NNT=1.9). Corresponding rates during the second and third treatment course were 37% (NNT=2.7) and 30% (NNT=3.4), respectively.[2] Similarly, Heinenon *et al* (2015) reported on a study including 543 rad-axSpA patients (123 patients commenced a second TNF inhibitor). BASDAI response at 6 months was achieved by 52% and 25% of the users of the first and the second TNF inhibitors, respectively.[3] In a UK-based study, mean drug survival in 651 axSpA patients fell from 10.2 years for the first TNF-alpha inhibitor to 5.5 years for the second.[4]
- In line with these clinical observations of diminishing efficacy in subsequent therapies of the same mechanism following prior failure, the Regional Medicines Optimisation Committee (RMOC) recommends switching to a biologic with a new mechanism of action following treatment failure.[5] Similarly, in the case of primary non-

response to the first TNF-alpha inhibitor in rad-axSpA patients, the ACR recommends switching to an IL-17A inhibitor (Recommendation 12).[13]

- The Company acknowledge that in current UK clinical practice, secukinumab is the only available biologic with a mechanism of action distinct from TNF-alpha inhibition, and thus would likely be used second line following primary treatment failure on one TNF-alpha inhibitor. Therefore, based on these clinical observations and regulatory guidelines, the Company consider that for rad-axSpA patients, to optimise patient care, ixekizumab would primarily be used in clinical practice following attempt of NSAIDs and at least two prior bDMARDs: following one TNF-alpha inhibitor and another bDMARD with a distinct mechanism of action in TNF-alpha inhibitor primary non-responders, and following two TNF-alpha inhibitors in patients with a secondary loss of response to prior TNF-alpha inhibitors (secondary non-responders). The Company further note that in the case of TNF-alpha contraindication, such as in patients with demyelinating disease or Stage III–IV heart failure, ixekizumab is anticipated to provide a welcome second-line treatment option in the case of secukinumab failure given that no further biologic options currently exist for these patients.
- It is therefore anticipated that positioning of ixekizumab following NSAIDs and at least two bDMARDs treatments or in the case of TNF-alpha contraindication would provide an additional treatment option for patients in the rad-axSpA population who have exhibited a primary or secondary treatment failure to TNF-alpha inhibition, or are contraindicated or otherwise unsuitable for TNF-alpha inhibition.

Positioning in the nr-axSpA population

- The positioning of ixekizumab in nr-axSpA patients following inadequate response to, or intolerance to, NSAIDs and at least one TNF-alpha inhibitor, or in the case of patients who are contra-indicated or otherwise unsuitable for anti-TNF alpha treatment, allows clinician flexibility within the treatment pathway and addresses a significant unmet need in these patients.
- As discussed above, two or more TNF-alpha inhibitors may be used sequentially following secondary non-response, although clinical evidence suggests diminishing response efficacy at each subsequent line. For primary non-responders, it is recommended by the ACR that patients with active nr-axSpA and primary non-response to the first TNF-alpha inhibitor switch to a treatment with an alternative mechanism of action (Recommendation 63).[13] However, in the UK, no treatment options with a distinct mechanism of action to TNF-alpha inhibition are currently recommended for patients with nr-axSpA. Similarly, no biologic treatment options are currently available for patients with nr-axSpA who are contraindicated to, or otherwise unsuitable to receive, TNF-alpha inhibitors.

- Therefore, the Company consider that for nr-axSpA patients, to optimise patient care, ixekizumab would primarily be used in clinical practice from second line: following one TNF-alpha inhibitor in TNF-alpha inhibitor primary non-responders, or following two TNF-alpha inhibitors in TNF-alpha inhibitor secondary non-responders. In patients with nr-axSpA who cannot receive TNF-alpha inhibitors, ixekizumab would represent a first-line biologic option in UK clinical practice.
- It is therefore anticipated that the positioning of ixekizumab following NSAIDs and at least one biologic treatment or in the case of TNF-alpha contraindication would be unique in providing a treatment option for patients in the nr-axSpA population who have exhibited a primary or secondary treatment failure to TNF-alpha inhibition, or are contraindicated or otherwise unsuitable for TNF-alpha inhibition.

Ixekizumab addresses an unmet need

- As outlined above, the Company understands there to be a significant unmet need remaining in axSpA patients in the UK despite other available biologics. Despite the availability of six biologics for rad-axSpA patients (five TNF-alpha inhibitors and one other IL-17A-inhibitor) and four TNF-alpha inhibitors for nr-axSpA patients (as noted by the Technical Team, Technical Engagement Report, page 23), patient feedback collected by the National Axial Spondyloarthritis Society during this Technical Engagement process (Technical Engagement Papers, pages 315–324) indicated that 55% of patients feel that treatment options currently available to patients on the NHS are insufficient (page 320), and that overall, patients felt strongly that offering as many treatment options as possible would be beneficial to ensure the best care possible is provided to those living with the condition (page 321). This unmet need is heightened in nr-axSpA patients as reflected by feedback from patients during this Technical Engagement process, who highlighted introduction of ixekizumab would be of significant advantage to patients with nr-axSpA to whom no non-TNF-alpha inhibitor biologics are currently available (Technical Engagement Papers, page 322).
- The NICE Guideline for the diagnosis and management of spondyloarthritis in over 16s (NG65) provides guidance for clinicians on selecting the appropriate biologic for use based on individual patient factors, including the frequency of injections and the administration route.[14] It further states that "*clinical comorbidities, such as previous malignancy, infection risk or presence of demyelinating disease*" should be taken into account, while moderate to severe heart failure is a contraindication for use of adalimumab, certolizumab pegol, golimumab and infliximab but is not for ixekizumab use.[14-19]

	• Together, these guidelines and patient feedback reinforce the necessity of increasing treatment options available to clinicians to permit patient-specific treatment decisions and highlight how the introduction of ixekizumab into UK clinical practice may address the current unmet needs faced by axSpA patients.[14] **Conclusion** Based on this, the Company consider placement of ixekizumab in the treatment pathway for rad-axSpA patients who have not responded to NSAIDs and at least two bDMARDs and for nr-axSpA patients who have not responded to NSAIDs and at least one TNF-alpha inhibitor, or for any axSpA patient who is contraindicated or otherwise unsuitable for TNF-alpha inhibitor use, to be clinically plausible and to address a current treatment need within UK clinical practice.
b) Is there a clinical rationale for why treatment outcomes with ixekizumab would be likely to vary based on disease subtype (rad-axSpA versus nr-axSpA) or prior exposure to *any* biologic treatment? If so, is there a clinical rationale why the number or type of prior biologic treatments received previously would impact on the efficacy of ixekizumab?	**Rad-axSpA versus nr-axSpA** • The Company do **not** consider there to be a clinical rationale to support differential treatment effects in biologics including ixekizumab the rad- and nr-axSpA populations. • Previous clinical trials of rad- and nr-axSpA have been conducted separately given that they have traditionally been considered as two distinct disease entities. However, clinical practice has more recently moved towards consideration of axSpA as a spectrum of disease, with the rad- and nr- subtypes representing either end of a continuous spectrum.[20, 21] This clinical view is supported by whole body MRIs, which identify that the number of inflammatory lesions in the spine and in the sacroiliac joint do not differ between rad- and nr-axSpA.[9] Furthermore, the patient and clinical experts in the NICE appraisal of TNF-alpha inhibitors (TA383) made clear that rad- and nr-axSpA are distinguishable conditions within a single disease spectrum and that disease severity and patient experiences of pain, functioning and quality of life are similar across both subtypes, as has been reported elsewhere.[8-10] • Therefore, that subtypes of the same disease driven by the same pathophysiology and with similar clinical presentation and HRQoL impact for patients should show a generalisable treatment effect retains clinical plausibility. This is supported by clinical evidence: the ESTHER trial, which assessed the response rates in patients with rad- and nr-axSpA after one year of treatment with etanercept, identified no differences in symptom duration or disease activity between the two groups, while the phase 3 RAPID-axSpA trial identified similar improvements with CZP treatment in rad- and nr-axSpA patients at 24 weeks.[22, 23] • A conclusion of generalisability between rad- and nr-axSpA is aligned with the conclusions of the clinical experts and the Appraisal Committee in TA383 that a differential response to treatment between rad- and nr-axSpA

patients would not be expected and that a similar benefit of treatment was likely to be observed between these two patient populations.[8] It is further supported by a published meta-analysis of TNF-alpha inhibitors which identified no differences in effect sizes between the rad- and nr-axSpA populations, and by an indirect comparison between IL-17 and TNF-alpha inhibitors in which it was concluded that "*although all these newer drugs were tested in AS, it can be assumed that efficacy results can also be extrapolated to nr-axSpA*".[24, 25]

- Given the above, the Company consider that treatment outcomes with ixekizumab are likely to be generalisable between the rad- and nr-axSpA populations.

Biologic-naïve versus biologic experienced

- The Company **do** consider there to be a clinical rationale for why response to biologics such as ixekizumab would vary by prior biologic use and provide supportive evidence from the COAST trials that show prior biologic use is a treatment effect modifier.
- The COAST-V and COAST-W trials represent large populations of biologic-naïve and -experienced rad-axSpA patients, respectively. Despite the same underlying disease, these two trial populations differ in terms of their baseline characteristics. As presented in Section B.2.3.3 of Document B of the Company Submission, patients at baseline in the COAST-W trial (biologic-experienced) had mean ASDAS and BASDAI scores of approximately 4.2 and 7.4, respectively, as compared with approximately 3.8 and 6.8, respectively, in the COAST-V trial (biologic-naïve). Mean duration of symptoms since axSpA onset was longer in the COAST-W population as compared with COAST-V (16.5–19.9 years versus 15.6–16.6 years, respectively) and this is reflected in the older average age of patients (44.2–47.4 years in COAST-W as compared with 41.0–42.7 years in COAST-V). Together, these data indicate that the biologic-experienced patients in the COAST-W trial had more severe disease at baseline, and their increased age and longer duration of symptoms are treatment effect modifiers which clinically indicate a poorer response likelihood.[26, 27]
- These differences at baseline are suggestive of clinical heterogeneity between biologic-naïve and -experienced patients with the same disease subtype. This translates to evidence of varying efficacy at Weeks 16 and 52 across several key outcomes between the COAST-V and -W trials, as summarised in Table 1.

Table 1: Key efficacy outcome responses at Week 16 and 52 in the COAST-V and COAST-W populations

Outcome	COAST-V (biologic-naïve)		COAST-W (biologic-experienced)	
	PBO (N=87)	IXE Q4W (N=81)	PBO (N=104)	IXE Q4W (N=114)
Week 16				
ASAS40, n (%)	16 (18.4)	39 (48.1)	13 (12.5)	29 (25.4)
BASDAI50, n (%)	15 (17.2)	34 (41.9)	[redacted]	[redacted]
BASDAI, cfb LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
BASFI, cfb LSM (SE)	−1.16 (0.22)	−2.39 (0.22)	[redacted]	[redacted]
ASDAS <2.1	11 (12.6)	35 (43.2)	[redacted]	[redacted]
ASDAS<1.3	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
ASAS40	-	[redacted]	-	[redacted]
BASDAI50	-	[redacted]	-	[redacted]
BASDAI cfb	-	[redacted]	-	[redacted]
BASFI cfb	-	[redacted]	-	[redacted]
ASDAS <2.1	-	[redacted]	-	[redacted]
ASDAS<1.3	-	[redacted]	-	[redacted]

Abbreviations: ASAS: Assessment of SpondyloArthritis International Society; BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; IXE: ixekizumab; PBO: placebo; Q4W: every four weeks.

- In turn, this indicates that meta-analysis is unlikely to be meaningful between these two populations. In support of this, prior biologic use was shown to represent a treatment effect modifier upon attempting meta-analysis of the COAST- V and -W trials, (i.e. attempting meta-analysis between biologic-naïve and biologic-experienced patients). This analysis is discussed further in response to Part D of this question, where pooling between biologic-naïve and -experienced patients is concluded to be clinically and statistically inappropriate. This is in alignment with the recommendations of NICE Technical Support Document 1 (TSD1) where an assumption of equal efficacy across naïve and experienced populations is described as "*highly implausible*". In rheumatoid arthritis, an

	inflammatory disease similar to axSpA, TSD1 further concludes: "*one cannot assess the relative efficacy of biologics by combining trials of biologics in patients who have failed on standard therapies, with trials of patients who have failed on biologics. Summaries of effect sizes in these cases lack validity because… patients who are naïve to biologics and those who have failed on them represent different clinical populations and require different decisions, informed by different summaries of treatment effects*."[28] • Therefore, the Company acknowledge the Technical Team's wish to minimise uncertainty associated with the presentation of subgroups by prior biologic-exposure, but considered that, based on this clinical rationale and statistical evidence, meta-analysing biologic naive and experience data would not offer greater decision-making certainty for the Committee. **Number of prior biologic treatments** • The Company consider there may be a clinical rationale for why response to biologics such as ixekizumab would vary by number of prior biologic treatments. • As discussed above, disease duration is a prognostic indicator of response in axSpA patients, with increased time since symptom onset associated with a reduced probability of response. It is clinically plausible to extrapolate that patients with an increased disease duration, and thus a lower probability of response, are more likely to have had more previous biologics than those with short disease duration. **Type of prior biologic treatments** • With regards to a differential response by biologic type, as described in response to Part A, to optimise patient care, physicians may opt to switch classes to a treatment with a different mechanism of action following primary treatment failure based on the recommendation by the ACR and RMOC.[5, 13] However, the Company believe there is **no further** clinical rationale for why type of prior treatment would affect the efficacy of ixekizumab at later lines.
c) How many people would receive more than two biological therapies prior to ixekizumab in clinical practice?	• The Company provide evidence to suggest [redacted]% of axSpA patients in UK clinical practice would receive more than two bDMARDs prior to ixekizumab based on data collected from patients in current UK clinical practice who are receiving, or have previously received, secukinumab. As an alternative IL-17A inhibitor, secukinumab was selected as a proxy for this estimate. • As discussed further in response to Part A of this question, treatment guidelines suggest that selection of the appropriate biologic should be individualised based on several patient factors. This individualised treatment in UK clinical practice makes this question difficult to comment on, but as an illustrative example of where an IL-17

	inhibitor might be used in clinical practice, the Company provide evidence derived from real-world evidence from patients in current UK clinical practice and collected as part of the Disease Specific Programmes of Adelphi Real World. These data, sourced from Adelphi DSP Plus 2019, with Patient Record Form Completion between April and August 2019, are presented in Table 8. • These data show that patients in UK clinical practice receive secukinumab following [redacted] prior biologics, with [redacted] receiving at least two prior biologics before secukinumab commencement. Assuming an equal market share between secukinumab and ixekizumab, these data suggest [redacted] of patients may receive ixekizumab after two or more prior biologics. This is in line with the unmet clinical need in biologic-experienced patients highlighted in response to Part A of this question.
d) What is the clinical effectiveness of ixekizumab versus placebo in the patients with rad-axSpA regardless of prior treatment exposure (i.e. the average effect across COAST-V and COAST-W)	• While the Company acknowledges the limitations raised by the technical team with regards to conducting NMAs within patient subgroups, they do not consider it statistically appropriate to synthesise treatment effect estimates for ixekizumab versus placebo regardless of prior treatment exposure by conducting a meta-analysis between the biologic-naïve rad-axSpA patients of COAST-V and the biologic-experienced rad-axSpA patients of COAST-W. This is due to heterogeneity in the populations with respect to their baseline characteristics and evidence of prior biologic use representing a treatment effect modifier. Such heterogeneity would introduce further uncertainty in the estimate of treatment effect for ixekizumab and render any results inappropriate for decision making. • As discussed further in response to Part B of this question, the COAST-V and COAST-W trial populations differ in terms of their baseline characteristics and these differences show that patients in COAST-W trial had more severe disease at baseline. The presence of significant clinical heterogeneity increases the risk of inconsistency and thus renders evidence synthesis inappropriate.[28, 29] • In order to determine whether prior biologic experience represents a treatment effect modifier, the Company attempted a meta-analysis of the ixekizumab versus placebo treatment effect from the COAST-V (rad-axSpA, biologic naïve) and COAST-W (rad-axSpA, biologic experienced) trials, utilizing the ITT populations and pooled loading doses (80 mg and 160 mg). Even though no heterogeneity was apparent when assessing the heterogeneity of the relative risks by means of the I^2 statistic for the endpoints ASAS40, BASDAI50, ASDAS<2.1 and ASDAS<1.3, and despite the known low power of the statistical test to detect heterogeneity, the meta-analysis identified substantial to considerable heterogeneity for these endpoints when comparing the risk difference between ixekizumab and placebo between the two studies (ASAS40 [I^2: [redacted], p[redacted]], BASDAI50 [I^2: [redacted], p[redacted]], ASDAS<2.1 [I^2: [redacted], p[redacted]], ASDAS<1.3 [I^2: [redacted], p[redacted]]. (It is noted that an I^2 value of >50% may be considered indicative that heterogeneity between studies can primarily be explained by systematic differences between

	studies (e.g. in terms of prognostic patient characteristics) rather than random sampling error within studies). This lends further strong support, beside the already presented clinical rationale, that a treatment effect in these patient populations is different, and advises against a pooling of these different patient populations. • Therefore, based on these findings, the Company conclude that significant heterogeneity in the study populations makes performance of a meta-analysis between biologic-naïve and biologic-experienced rad-axSpA patients inappropriate and that any estimates of treatment effect for ixekizumab obtained would be not meaningful, rendering them inappropriate for decision making. • In addition to being statistically inappropriate to perform, the Company further note that use of this meta-analysis to inform the comparison between ixekizumab and other comparator trials which contain mixed biologic-experienced and naïve data would produce misleading relative treatment effect estimates given the difference in treatment effect likely to be achieved by biologic-naïve and -experienced patients. This is due to the higher proportion of biologic-experienced patients in the combined COAST-V and -W trials ([redacted]%, with [redacted]% having received 2 prior TNF alpha inhibitors) as compared with the patient populations in the key clinical trials of secukinumab, MEASURE-2 and -4 (39% and 27–28%, respectively, none of whom had received more than one prior biologic) that include both biologic-naïve and -experienced patients, as shown in Table 9 below. Disease duration of patients in the MEASURE-2 and -4 trials has not been reported, but patients in the pooled COAST-V and -W trials had an average time since disease diagnosis of [redacted] years, as compared with 6.4–8.4 years in the MEASURE-2 and -4 trials (see Table 9). Overall, these data are suggestive of a harder-to-treat population in the COAST trials as compared with in the MEASURE trials, which would lead to misleading results.
Issue 2: Clinical effectiveness estimates for ixekizumab versus secukinumab	
a) Is the company able to provide any revised estimates of the clinical and cost effectiveness of ixekizumab compared with secukinumab?	• The Company provide estimates for the clinical efficacy of ixekizumab compared with secukinumab in nr-axSpA using data published since completion of the original submission documents and have identified no significant differences between these treatment options. • As suggested by the NICE Technical Team, the Company have included the PREVENT study, which reports the efficacy of secukinumab versus placebo in an nr-axSpA population, in the NMA.[30] The Company acknowledge that secukinumab is not a relevant comparator in the nr-axSpA population as per the final NICE scope. However, as discussed further in response to Issue 1, the Company considers the relative efficacy between ixekizumab and these results to be generalisable to a rad-axSpA population, given that these subtypes represent each end of a

	continuous spectrum of the same disease, and such an analysis may provide insight on a potential class effect amongst IL-17A inhibitors, and among biologic treatments more generally. • Therefore, the ITT population of this trial was incorporated into the networks for the ASAS40, BASDAI50, BASDAI change from baseline (cfb) and BASFI cfb to permit estimation of the relative efficacy of ixekizumab (pooled 80 mg and 160 mg loading doses) and secukinumab in the nr-axSpA population. The Company considered pooling of these loading doses to be suitable given that the COAST trials were designed and powered to detect a difference between the ixekizumab treatment arms (Q4W and Q2W) pooled by loading dose versus placebo, and efficacy loading dose analyses did not appear to have any meaningful impact on the treatment effect at week 16. In line with the original submission to NICE, the fixed effects model was selected as the random effects model did not converge. As discussed above, the Company acknowledge the limitations associated with the 'sensitivity analysis' NMAs, therefore results for the 'base case' NMA approach are presented, with sensitivity analysis results provided for completeness only as they provide results for a greater number of outcomes. • The results derived from the updated NMAs are presented in Table 10 and Table 11 (base case) and Table 12 and Table 13 (Sensitivity Analysis) below. The results found no statistically significant difference between ixekizumab and secukinumab for any of the outcomes assessed: ASAS40, BASDAI50, BASDAI cfb and BASFI cfb. Furthermore, an overlap between the credible intervals and posterior median outcomes of ixekizumab and secukinumab in their comparison versus placebo was observed, which was also the case for all of the biologic treatments for the outcomes assessed. • Based on these results, the Company consider a class effect between IL-17 inhibitors amongst rad- and nr-axSpA patients. The clinical and statistical justifications for assumption of class effects are discussed in more detail in response to Issue 3, alongside updated cost-effectiveness estimates in which these class effects are considered. • Due to a conclusion of a class effects amongst IL-17 inhibitors, a revised cost-effectiveness analysis between ixekizumab and secukinumab based on these NMA results has not be conducted. However, a cost-effectiveness analysis based on the assumption of class effects has been conducted (please see response to Issue 3, Part C for further details). **Secukinumab 300 mg dose** • As described in the Company Submission, an extension was made to the licence for secukinumab in ankylosing spondylitis (rad-axSpA) in October 2019, which states that "based on clinical response, the dose can be increased to 300 mg" following an initial dosing schedule with 150 mg. The cost-effectiveness of this dose in rad-axSpA

	patients has not been evaluated by NICE, however, real-world evidence demonstrates that there is substantial usage of this more expensive dose in UK clinical practice, as both a starting and maintenance treatment. • An analysis of the Adelphi AxSpA Plus Disease Specific Programme, a cross-sectional anonymised database, demonstrated that between April and August 2019 in the UK, [redacted]% of rad-axSpA patients in the database were currently receiving, or had been receiving prior to discontinuation, secukinumab at a dose of 300 mg either weekly ([redacted]%) or monthly ([redacted]%). It was further identified that a proportion of patients ([redacted]%) had been initiated on the 300 mg dose for the loading dose phase of treatment. • Given that a substantial proportion of patients are treated with the 300 mg dose of secukinumab in UK clinical practice, a scenario analysis was conducted to demonstrate the impact of the 300 mg secukinumab dose on the likely costs to the NHS (see Issue 3, Part C).
Issue 3: Limitations in the network meta-analysis	
a) Is it reasonable to assume equal efficacy across all TNF-alpha inhibitors in rad-axSpa biologic naïve patients? If so, should the same assumption be applied in all other subgroups?	• The Company consider it reasonable to assume equal efficacy across all TNF-alpha inhibitors within the rad-axSpA biologic-naïve population given their same mechanism of action within the pathophysiology of axSpA, and further that this assumption may be applied within rad-axSpA biologic-experienced and nr-axSpA biologic-naive and -experienced subgroups. • Molecular and immunologic research has repeatedly supported the key role of cytokine dysregulation in the pathophysiology of axSpA. Studies show that patients with axSpA demonstrate overexpression of TNF-alpha in the sacroiliac joints and high levels of circulating soluble TNF receptors. This, combined with the significant improvements in axSpA symptoms following treatment with TNF-alpha inhibitors, implicates this cytokine as a key driver in the pathophysiology of the disease. Whilst minor differences in pharmacological properties between TNF-alpha inhibitors exist, which may influence the pharmacokinetics of each drug in the body, in clinical practice, selection of TNF-alpha inhibitor is not driven by differences in relief of axSpA symptoms, but rather the effects these differences have on comorbidities to axSpA, such as psoriasis, or factors including the patient's preferred mode of administration or desire to bear children.[31, 32] Accordingly, the common mechanism of these therapies, neutralisation of soluble TNF-alpha, may be considered to explain the class effect results observed statistically for key clinical outcomes in axSpA. • In addition to the clinical validity of a class effect across treatments with the same mechanism of action, no significant differences were identified between TNF-alpha inhibitors in either the NMAs presented in the original

	Company submission nor the updated NMA to include secukinumab as a comparator in the nr-axSpA population using data from the PREVENT trial (see response to Issue 2 and Table 10 and Table 11 below). • The Company are therefore aligned with the assertion made by the Technical Team (Technical Report, page 28) that combined with a biologic rationale, a lack of statistically significant difference between treatments provides reasonable grounds to assume a class effect among TNF-alpha inhibitors in the rad-axSpA biologic-naïve population. This is in line with the conclusion of the Committee in TA383 final appraisal determination (FAD) that "*given the lack of difference in effect between [the TNF-alpha inhibitors], they should be considered as a class with broadly similar, even if not completely identical, effects*."[8] The Company are of the view that this assumption can be generalised to the rad-axSpA biologic-experienced population; whilst the evidence presented in response to Issue 1 illustrates that prior biologic experience represents a treatment effect modifier, the Company deem it reasonable to assume that a reduction in treatment effect between naïve and experienced patients would apply in a similar manner across TNF-alpha inhibitors. As described in response to Part B of Issue 1, it was concluded by the Assessment Group in TA383 that a decrease in response rates over sequential lines of TNF-alpha inhibitor therapy as a class takes place in clinical practice, which is supported by evidence from a UK-based study in which mean drug survival was substantially shorter for the second TNF-alpha inhibitor as compared with the first.[4, 8] • For these reasons, the Company consider the assumption of a class effect amongst TNF-alpha inhibitors to be reasonable. However, as described further in response to Part C of this question, the Company consider it reasonable to extend this class effect assumption to all biologics. • Furthermore, as described in response to Issue 1, Part B, based on the underlying pathophysiology of each disease subtype, the Company consider it reasonable to assume that the assumption of class effects among TNF-alpha inhibitors may plausibly be applied *within* the other subpopulations of relevance to this appraisal.
b) Is it reasonable to assume equal efficacy across all IL-17-1A inhibitors in rad-axSpa biologic naïve patients? If so, should the same assumption be applied in all other subgroups?	• As above, the Company consider it reasonable to assume equal efficacy across IL-17A inhibitors in the rad-axSpA biologic-naïve population, given their same mechanism of action, and further that this assumption can be applied within the rad-axSpA biologic-experienced and nr-axSpA subgroups. • As described in response to Part A, cytokine dysregulation has been shown to be a major driver of pathophysiology in axSpA, and this extends to the IL-17 cytokine pathway.[33] In healthy individuals, the IL-17 superfamily of cytokines (IL-17A–IL-17F) functions in host defence against a range of bacterial and fungal pathogens. IL-17-A has been implicated in the pathophysiology of axSpA and other inflammatory diseases through *in vitro* and animal studies, with this role substantiated by high response rates to IL-17A inhibitors in clinical trials.[34] Whilst clinicians have not yet had the opportunity to prescribe both secukinumab and ixekizumab in routine clinical practice in

	axSpA, both treatments selectively neutralise IL-17A, and it is therefore reasonable to assume that they would result in similar relief of axSpA symptoms. Accordingly, it is deemed clinically reasonable that a class effect should exist in axSpA among IL-17A inhibitors. • The results of the NMA incorporating the PREVENT study (presented in response to Issue 2) identified no statistically significant differences between ixekizumab and secukinumab for any of the outcomes assessed (BASDAI50, BASDAI cfb, BASFI cfb and ASAS40). • As described in response to Issue 1, Part B, based on the underlying pathophysiology of each disease subtype, it is considered that class effects observed within the nr-axSpA population may be considered to similarly exist within the rad-axSpA (biologic-naive and -experienced) populations. • For these reasons, the Company consider the assumption of a class effect of IL-17A inhibitors to be reasonable. However, as described further in response to Part C of this question, the Company consider it reasonable to extend this class effect assumption to all biologics.
c) Is it reasonable to assume equal efficacy across all comparators and in all populations given the limited evidence to demonstrate that ixekizumab is more or less effective than other currently available treatments?	• The Company consider it reasonable to assume equal efficacy across all biologics in the rad-axSpA biologic-naïve population and further that this assumption can be applied within rad-axSpA biologic-experienced and nr-axSpA biologic-naive and -experienced subgroups. • As described in response to Parts A and B, evidence demonstrates that the pathophysiology of axSpA is strongly driven by dysregulation of inflammatory cytokines, in which TNF-alpha and IL-17 play key roles. • The results of the NMA incorporating the PREVENT study (presented in response to Issue 2) identified no evidence for differences between TNF-alpha inhibitors and IL-17A inhibitors for any of the outcomes assessed. This finding is in alignment with the conclusion of the NICE Committee in the appraisal of secukinumab (TA407) that "*secukinumab has a similar efficacy to the TNF-alpha inhibitors*".[6] • The Company note that the class effects analysis suggested by the NICE Technical Team comprising TNF-alpha inhibitors versus IL-17A inhibitors versus placebo, and any subsequent cost-effectiveness analyses, could not be performed in the rad- or nr-axSpA populations. This is due to the fact that to synthesise an input for the TNF-alpha inhibitor group in such an analysis for the populations of interest (biologic-experienced rad-axSpA and biologic-naïve nr-axSpA), data from trials including unclear or mixed populations (i.e. those originally informing the sensitivity analysis NMAs) would need to be utilised. Given the clinical and statistical implausibility of assuming

	generalisability of efficacy for biologics across biologic-naïve and biologic-experienced patient populations (as discussed further in response to Issue 1, Part B), it was deemed this approach was unsuitable. • Therefore, the Company present cost-effectiveness analysis in which a class effect across all biologics is assumed in the rad-axSpA biologic-experienced and nr-axSpA biologic-naïve populations only. The biologic-experienced population has been selected on the basis of the response to Issue 1, Part A, that ixekizumab would primarily be used after TNF-alpha inhibitors have been attempted, whilst the biologic-naïve nr-axSpA population has been selected in lieu of biologic-experienced data in this population (where ixekizumab is anticipated to be used), but with the assumption made that a class effects analysis would apply in a nr-axSpA biologic-experienced population (as discussed above). This analysis was implemented by assuming efficacy for all biologics is equal to the efficacy of ixekizumab in the COAST-W and -X trials for the rad-axSpA biologic-experienced and nr-axSpA biologic-naïve populations, respectively, for three efficacy inputs informing the model (BASDAI50, BASDAI cfb and BASFI cfb). Data from the COAST trials represent the most appropriate inputs for use, given that they are derived from well-powered, internally valid clinical trials and therefore remove the uncertainty associated with the NMA (see Issue 2 for further discussion). Economic analysis results produced following implementation of these relative efficacy estimates are presented for the rad-axSpA biologic-experienced and nr-axSpA biologic-naïve populations in Table 14 and Table 16, respectively. • The results of these analyses show that in the rad-axSpA population, over a lifetime horizon, ixekizumab is associated with either a comparable or less expensive total cost compared to five of the six biologic treatments recommended by NICE for these patients: certolizumab pegol, etanercept, secukinumab 150 mg (N.B. it was not possible to consider the confidential PAS in the analysis), golimumab and infliximab. These results support the positioning of ixekizumab after NSAIDs and at least two prior bDMARDs in rad-axSpA patients. Furthermore, a freedom of information request by the Company to determine the current biologic use in rad-axSpA patients in hospitals in the UK between June and August 2020 identified that a higher proportion of patients were receiving one of these five biologics that are comparable or more expensive than ixekizumab (combined 55.9%) than those who were receiving adalimumab (31.6%). This real world evidence reinforces that ixekizumab represents a cost-effective use of NHS resources in the rad-axSpA population. • An additional analysis is presented in Table 15 including the 300 mg dose of secukinumab (without confidential PAS), which, as noted in the response to Issue 2, is being prescribed frequently in clinical practice. The results show ixekizumab results in less expensive overall costs compared to secukinumab 300 mg.

	• In the nr-axSpA population, ixekizumab is associated with fewer total costs than three of the four relevant comparators, certolizumab pegol, etanercept and golimumab, which supports the positioning of ixekizumab after NSAIDs and at least one biologic in the nr-axSpA population.
Issue 4: Long-term effectiveness of ixekizumab	
a) Can the company supply the results of the COAST-Y study?	The COAST-Y study is an ongoing, multicentre, Phase 3, long-term extension study of 104 week to evaluate the maintenance of treatment effect of ixekizumab in patients with axial spondyloarthritis. COAST-Y provides patients with an opportunity to continue ixekizumab treatment for up to 2 additional years. COAST-Y includes patients who completed any of the originating studies of COAST-V, -X and -W.[35, 36] At present, data are available for patients who have received treatment with ixekizumab Q4W from Week 0 of the originating studies through Week 64 of COAST-Y (totalling 116 weeks of continuous ixekizumab treatment). Results are provided below for ASAS40, BASDAI50 and change from baseline in BASDAI and BASFI. Overall, the results support that the treatment effect of ixekizumab observed at Week 16 is maintained or improved for at least 116 weeks. **ASAS40 response at Week 64 of COAST-Y** ASAS40 responses for patients treated with ixekizumab 80 mg Q4W at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y are presented in Table 2. With ixekizumab 80 mg Q4W treatment, ASAS40 responses were maintained or increased from Week 16 to Week 116 of continuous ixekizumab treatment. **Table 2: ASAS40 response (observed) at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y (Week 116 of ixekizumab 80 mg Q4W treatment)** **Timepoint (duration of ixekizumab treatment)** / **N** / **n (%)** **Week 16** / 157 / 64 (40.8) **Week 52** / 156 / 82 (52.6) **Week 116** / [redacted] / [redacted] **BASDAI50 response at Week 64 of COAST-Y**

BASDAI50 responses for patients treated with ixekizumab 80 mg Q4W at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y are presented in Table 3. With ixekizumab 80 mg Q4W treatment, BASDAI50 responses were maintained or increased from Week 16 to Week 116 of continuous ixekizumab treatment.

Table 3: BASDAI50 response (observed) at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y (Week 116 of ixekizumab 80 mg Q4W treatment)

Timepoint (duration of ixekizumab treatment)	N	n (%)
Week 16	157	58 (36.9)
Week 52	156	78 (50.0)
Week 116	[redacted]	[redacted]

BASDAI change from baseline at Week 64 of COAST-Y

Change from baseline in BASDAI score for patients treated with ixekizumab 80 mg Q4W at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y are presented in Table 4. With ixekizumab 80 mg Q4W treatment, changes from baseline were maintained or improved from Week 16 to Week 116 of continuous ixekizumab treatment.

Table 4: BASDAI change from baseline (observed) at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y (Week 116 of ixekizumab 80 mg Q4W treatment)

Timepoint (duration of ixekizumab treatment)	N	Mean (SD)
Week 16	157	−2.8 (2.1)
Week 52	156	−3.4 (2.2)
Week 116	[redacted]	[redacted]

BASFI change from baseline at Week 64 of COAST-Y

Change from baseline in BASFI score for patients treated with ixekizumab 80 mg Q4W at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y are presented in Table 5. With ixekizumab 80 mg Q4W treatment, changes from baseline were maintained or improved from Week 16 to Week 116 of continuous ixekizumab treatment.

Table 5: BASFI change from baseline (observed) at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y (Week 116 of ixekizumab 80 mg Q4W treatment)

Timepoint (duration of ixekizumab treatment)	N	Mean (SD)
Week 16	157	–2.2 (2.2)
Week 52	156	–2.9 (2.3)
Week 116	[redacted]	[redacted]

b) Can the company comment on the extent to which the currently available evidence supports the projected estimates of long-term treatment effects derived from the economic model?

As described in response to part a, the COAST-Y study includes patients derived from the three originating COAST studies, -V, -W and -X. Accordingly, since the COAST-Y data cover patients from across the spectrum of axSpA patients from these studies, and the cost-effectiveness models have been developed to focus on individual patient populations by disease subtype and prior biologic exposure, any conclusions drawn from a comparison between the COAST-Y data and the cost-effectiveness models must be interpreted with caution. Similarly, it should be considered that the model considers that only responders continue treatment, whereas COAST-Y data is derived from responders and non-responders to ixekizumab treatment. It may nevertheless be useful to examine the general trend of the treatment effect estimates across the two sources, rather than precise numerical differences.

Long-term projections of BASDAI and BASFI may be extracted from the model in which BASFI scores change over time but responders to treatment are assumed to maintain their BASDAI score, which is based on the Week 16 data, over time. A comparison of long-term model outcomes in 16-week increments between Week 52 and 116 are presented in Table 6 and Table 7 in order to allow observation of the trend in results for BASDAI cfb and BASFI cfb, respectively.

The COAST-Y results show that the benefits to patients in terms of disease activity and function are consistently maintained up to Week 116. This maintenance of response aligns with the trend observed in the two sets of model predictions for biologic-experienced rad-axSpA patients and biologic-naïve nr-axSpA patients, although for the reasons discussed above, the values presented are illustrative only.

Table 6. BASDAI change from baseline (observed) in COAST-Y vs model predictions

Timepoint (duration of ixekizumab treatment)	COAST-Y Mean (SD)	Model prediction	
		Biologic-experienced rad-axSpA (IXE responders)	Biologic-naive nr-axSpA (IXE responders)
Week 52, cycle 12	–2.8 (2.1)	–4.89	–4.27
Week 68, cycle 17	[redacted]	–4.89	–4.27
Week 84, cycle 21	[redacted]	–4.89	–4.27
Week 100, cycle 25	[redacted]	–4.89	–4.27
Week 116, cycle 29	[redacted]	–4.89	–4.27

Abbreviations: BASDAI: Bath AS Disease Activity Index; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; rad-axSpA: radiographic axial spondyloarthritis; SD: standard deviation.

Table 7. BASFI change from baseline (observed) in COAST-Y vs model predictions

Timepoint (duration of ixekizumab treatment)	COAST-Y Mean (SD)	Model prediction	
		Biologic-experienced rad-axSpA (IXE responders)	Biologic-naive nr-axSpA (IXE responders)
Week 52, cycle 12	–2.9 (2.3)	–3.68	–3.84
Week 68, cycle 17	[redacted]	–3.67	–3.84
Week 84, cycle 21	[redacted]	–3.66	–3.83
Week 100, cycle 25	[redacted]	–3.64	–3.82
Week 116, cycle 29	[redacted]	–3.63	–3.82

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; rad-axSpA: radiographic axial spondyloarthritis; SD: standard deviation.

Issue 5: Modelling of BASFI scores after treatment discontinuation

a) When treatment is discontinued, is it reasonable to assume that patients return to their baseline level of function?	• The Company are aligned with the technical team on this issue and consider it reasonable to assume that patients return to their baseline level of function, as measured by BASFI score, following treatment discontinuation. • As noted by the Technical Team, this is in alignment with clinical expert opinion provided during TA383 that following treatment discontinuation, patients would not be expected to deteriorate to a functional level more severe than that experienced prior to commencing biologic treatment. • An equivalent assumption was similarly adopted in the manufacturer's model in TA407, which evaluated secukinumab in ankylosing spondylitis (the assumption was not discussed by the Committee in this appraisal).[6]
Issue 6: Choice of utility regression equation	
a) What are the results of the utilities scenario analysis (company scenarios 3a-d) when tested in the new population/class scenario analyses requested by the technical team in issues 3?	• The Company explored the utilities scenario analyses (scenarios 3a–d in the original company submission) when the full biologics class effects analysis described in Issue 3 (Part C) is implemented. • For illustrative purposes, the results for one of these scenarios (scenario 3c in the original submission in which utility values are sourced from Wailoo *et al* [2015]), are presented for the rad-axSpA biologic experienced and nr-axSpA biologic naïve populations in Table 17 and Table 18, respectively. As shown, the results found the incremental QALYs to remain identical across all interventions when a class effect is assumed. • As described in Section B.3.4.5 of Document B of the original company submission, the health state utility of patients within the model is calculated using an algorithm which produces a relationship between disease activity and function, as measured by BASDAI and BAFSI scores change, and expected patient quality of life as an EQ-5D-3L score, incorporating a number of covariates including gender, race and disease duration. Due to these covariates, the relationship between efficacy and HRQoL (and therefore utility values implemented in the model) is not mathematically linear, but these scenario analyses show it to be close enough to linear as to be functionally a linear relationship. Therefore, an assumption of equal efficacy across all biologics results in the same expected quality of life for all patients within the model, and thus identical incremental QALYs. • Therefore, assumption of a class effect removes the relevance of these utility scenarios from further discussion.
Issue 7: Company's cost effectiveness scenario for patients with nr-axSpA that have had prior exposure to biologic treatments	

a) Can the company clarify how it calculated the modification factor used in its scenario analysis for the biologic-experienced nr-axSpA population?	• In the absence of data for the efficacy of ixekizumab in the biologic-experienced nr-axSpA population, a modification factor was derived in order to estimate this efficacy value from the available data from the biologic-naïve nr-axSpA population in the COAST-X trial. The use of a modification factor to estimate the efficacy of ixekizumab was based on the premise described in response to Issue 1: that prior biologic use has a significant impact on treatment efficacy, where disease subtype differences do not. • The BASDAI50 results at Week 16 for ixekizumab were compared between the biologic-naïve (COAST-V: 42.0%) and biologic-experienced (COAST-W: [redacted]) rad-axSpA patients to produce a modification factor associated with prior biologic use of [redacted]. This factor was applied to the BASDAI50 result at Week 16 for ixekizumab in the biologic-naïve nr-axSpA population (COAST-X: [redacted]) to produce an estimated efficacy of ixekizumab in the biologic-experienced nr-axSpA population of [redacted].

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Appendix

Issue 1

Table 8: Number of prior biologics received by patients on any biologics and received by patients on secukinumab, derived from real-world evidence from patients in current UK clinical practice and collected as part of the Disease Specific Programmes of Adelphi Real World

Number of prior biologics	axSpA patients on any biologic, n (%) [N=[redacted]][b]	axSpA patients on secukinumab, n (%) [a] [N=[redacted]][c]
0 (first line)	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]

Data are derived from real-world evidence
[a] Includes patients who are currently receiving secukinumab and those who have previously received and discontinued from secukinumab. Number of prior biologics received at the time of secukinumab commencement is presented.
[b] Adelphi DSP IV: Patient Record Form, Completion July–December 2018
[c] Adelphi DSP Plus: Patient Record Form, Completion April–August 2019
Abbreviations: axSpA: axial spondyloarthritis.

Table 9: Proportion of patients in the key clinical trials of ixekizumab and its relevant comparators in the rad-axSpA population

Characteristic at baseline	COAST-V and COAST-W, pooled			MEASURE 2		MEASURE 4	
	IXE Q2W	IXE Q4W	PBO	SEC 150 mg	PBO	SEC 150 mg	PBO
Biologic-naïve, n (%)	[redacted]	[redacted]	[redacted]	44 (61)	45 (61)	85 (73)	83 (71)
Biologic experienced, n (%)	[redacted]	[redacted]	[redacted]	28 (39)	29 (39)	31 (27)	34 (29)
≥1 prior TNF-alpha inhibitor	[redacted]	[redacted]	[redacted]	28 (39)	29 (39)	31 (27)	34 (29)
≥2 prior TNF-alpha inhibitor	[redacted]	[redacted]	[redacted]	0 (0)	0 (0)	0 (0)	0 (0)
Time since diagnosis, years (SD)	[redacted]	[redacted]	[redacted]	7.0 + 8.2	6.4 + 8.9	8.4 + 10.84	7.1 + 9.23
Mean time since symptom onset, years (SD)	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR

Abbreviations: IXE: ixekizumab; NR: not reported; PBO: placebo; Q2W: every two weeks; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SD: standard deviation; SEC: secukinumab; TNF: tumour necrosis factor.

Table 10: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (binary endpoints) or MDs (continuous endpoints) (with 95% CrI) versus placebo at Week 12–18 in the nr-axSpA population following inclusion of the PREVENT trial in the NMAs, fixed-effect model (base case analysis)

Intervention	ASAS40			BASDAI50			BASDAI cfb			BASFI cfb		
	OR	95% CrI Lower limit	95% CrI Upper limit	OR	95% CrI Lower limit	95% CrI Upper limit	MD	95% CrI Lower limit	95% CrI Upper limit	MD	95% CrI Lower limit	95% CrI Upper limit
IXE (pooled LD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
ETN 50 mg QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
SEC 150 mg	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC	NC	NC	NC

Abbreviations: ADA: adalimumab; ASAS: Assessment of SpondyloArthritis International Society; BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; MD: median difference; NC: not calculable; NMA: network meta-analysis; nr-ax-SpA: non-radiographic axial spondyloarthritis; NRI: non-responder imputation; OR: odds ratio; Q4W: every four weeks; QW: weekly.

Table 11: Median posterior outcomes (with 95% CrI) at Week 12–18 in the nr-axSpA population following inclusion of the PREVENT trial in the NMAs, fixed-effect model (base case analysis)

Intervention	ASAS40			BASDAI50			BASDAI cfb			BASFI cfb		
	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
ETN 50 mg QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
SEC 150 mg	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC	NC	NC	NC

Table 12: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (binary endpoints) or MDs (continuous endpoints) (with 95% CrI) versus placebo at Week 12–18 in the nr-axSpA population following inclusion of the PREVENT trial in the NMAs, fixed-effect model (sensitivity analysis)

Intervention	ASAS40			BASDAI50			BASDAI cfb			BASFI cfb		
	OR	95% CrI Lower limit	95% CrI Upper limit	OR	95% CrI Lower limit	95% CrI Upper limit	MD	95% CrI Lower limit	95% CrI Upper limit	MD	95% CrI Lower limit	95% CrI Upper limit
IXE (pooled LD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
CZP pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 50 mg QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
SEC 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For completeness, these results are presented to supplement the base case NMA results in Table 10 to enable comparison for a greater number of outcomes. However, the Company acknowledge the SA is associated with limitations, as highlighted previously by the ERG.

Abbreviations: ADA: adalimumab; ASAS: Assessment of SpondyloArthritis International Society; BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; MD: median difference; NC: not calculable; NMA: network meta-analysis; nr-ax-SpA: non-radiographic axial spondyloarthritis; NRI: non-responder imputation; OR: odds ratio; Q4W: every four weeks; QW: weekly.

Table 13: Median posterior outcomes (with 95% CrI) at Week 12–18 in the nr-axSpA population following inclusion of the PREVENT trial in the NMAs, fixed-effect model (sensitivity analysis)

Intervention	ASAS40			BASDAI50			BASDAI cfb			BASFI cfb		
	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
CZP pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 50 mg QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
SEC 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For completeness, these results are presented to supplement the base case NMA results in Table 11 to enable comparison for a greater number of outcomes. However, the Company acknowledge the SA is associated with limitations, as highlighted previously by the ERG.
Abbreviations: ADA: adalimumab; ASAS: Assessment of SpondyloArthritis International Society; BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; MD: median difference; NC: not calculable; NMA: network meta-analysis; nr-ax-SpA: non-radiographic axial spondyloarthritis; NRI: non-responder imputation; OR: odds ratio; Q4W: every four weeks; QW: weekly.

Issue 3

Table 14: Economic analysis results with assumed class effects: biologic-experienced rad-axSpA (with ixekizumab PAS)

Technologies	Rad-axSpA biologic-experienced	
	Total costs (£)	Incremental costs (£)
Adalimumab	[redacted]	-
Conventional care	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]
Etanercept 25/50 mg	[redacted]	[redacted]
Ixekizumab Q4W	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]

Abbreviations: nr-axSpA: non-radiographic axial spondyloarthritis; PAS: patient access scheme; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.

Table 15: Economic analysis results with assumed class effects: biologic-experienced rad-axSpA (with ixekizumab PAS)

Technologies	Rad-axSpA biologic-experienced	
	Total costs (£)	Incremental costs (£)
Adalimumab	[redacted]	-
Conventional care	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]
Etanercept 25/50 mg	[redacted]	[redacted]

Technologies	Rad-axSpA biologic-experienced	
	Total costs (£)	Incremental costs (£)
Ixekizumab Q4W	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]

Abbreviations: nr-axSpA: non-radiographic axial spondyloarthritis; PAS: patient access scheme; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.

Table 16: Economic analysis results with assumed class effects: biologic-naive nr-axSpA (with ixekizumab PAS)

Technologies	Nr-axSpA biologic-naïve	
	Total costs (£)	Incremental costs (£)
Conventional care	[redacted]	-
Adalimumab	[redacted]	[redacted]
Ixekizumab Q4W	[redacted]	[redacted]
Etanercept 25/50 mg	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]

Abbreviations: nr-axSpA: non-radiographic axial spondyloarthritis; PAS: patient access scheme; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.

Issue 6

Table 17: Scenario analyses in the biologic-experienced rad-axSpA population with utility values sourced from Wailoo *et al* (2015)[37] in the original company submission and updated to consider the results of the all-biologics class effect assumption presented in Technical Engagement Issue 3c

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Adalimumab	[redacted]	[redacted]	-	-	-
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab

Etanercept 25/50 mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Ixekizumab Q4W	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab

Pairwise comparisons for ixekizumab Q4W versus each comparator are presented. *Indicates ICERs in the south-west quadrant of the cost-effectiveness plane.
Abbreviations: ICER: incremental cost-effectiveness ratio; NC: not calculated; QALYs: quality-adjusted life years; rad-ax-SpA: radiographic axial spondyloarthritis.

Table 18: Scenario analyses in the biologic-naïve nr-axSpA population with utility values sourced from Wailoo *et al* (2015)[37] in the original company submission and updated to consider the results of the all-biologics class effect assumption presented in Technical Engagement Issue 3c

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional care	[redacted]	[redacted]	-	-	-
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£1,955
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Etanercept 25/50 mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab

Pairwise comparisons for ixekizumab Q4W versus each comparator are presented. *Indicates ICERs in the south-west quadrant of the cost-effectiveness plane.
Abbreviations: ICER: incremental cost-effectiveness ratio; NC: not calculated; QALYs: quality-adjusted life years.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ixekizumab for the treatment of people with axial spondyloarthritis for whom nonsteroidal anti-inflammatory drugs, or TNF-alpha inhibitors have been inadequately effective or not tolerated [ID1532]

Technical Engagement Modelling Analyses

February 2021

File name	Version	Contains confidential information	Date
1532_Ixekizumab in AxSpA_Technical Engagement Analyses_ACIC	FINAL	Yes	04/02/2021

Technical Engagement Modelling Analyses

In order to conduct the class effects modelling analyses in Lilly's response to the technical engagement report, the following adaptations were made to the rad-axSpA and nr-axSpA models provided at Lilly's original submission to NICE in January 2020. Lilly have provided the revised models used to conduct the analyses, which are entitled: 1532_Ixekizumab in Rad-AxSpA_CEM_TE_290121 and 1532_Ixekizumab in Nr-AxSpA_CEM_TE_290121.

Rad-axSpA biologic-experienced population

The class effects analysis in the biologic-experienced rad-axSpA population was conducted utilising the same base case inputs and settings as described in the Company submission for this population, with the exception of the following:

- On the 'Input data' and 'Input data default' tabs, the following efficacy inputs were adjusted for all biologic treatments in the model to be equal to the values for ixekizumab, which were sourced from the COAST-W trial:
    - Response rate (mean proportion and 95% confidence intervals [standard error was calculated])
    - BASDAI reduction; responders and non-responders (least squares mean and 95% confidence intervals [standard errors were calculated]). To calculate BASDAI cfb by response, the formulae described in Appendix M of the company submission were utilised. For all interventions, the proportion of responders and non-responders (according to BASDAI50) used to inform the formulae were sourced from COAST-W.
    - BASFI reduction; responders and non-responders (least squares mean and 95% confidence intervals [standard errors were calculated]). To calculate BASFI cfb by response, the formulae described in Appendix M of the company submission were utilised. For all interventions, the proportion of responders and non-responders (according to BASDAI50) used to inform the formulae were sourced from COAST-W.
    - Efficacy inputs sourced from COAST-W are presented in Table 1.
- As noted in the technical engagement response, in the interest of utilising data with high statistical power to inform the analyses, data from the ixekizumab Q4W arm of the COAST-W trial (which included patients treated with either the 80 mg or 160 mg loading dose) were used to inform the analysis. COAST-W was not powered to detect a statistically significant difference between the 160 mg and 80 mg loading dose groups. In the attached models, the 'BASDAI50 pooled dose' option of the 'main' tab is therefore selected.
- The class effects analysis assumes that the efficacy of all biologics is equal. Accordingly, timing of response would similarly be expected to be the same for all treatments. As such, the trial period duration was made to be equal to ixekizumab for all biologic interventions in the model: Week 16.

Nr-axSpA biologic-experienced population

The class effects analysis supporting the biologic-experienced nr-axSpA population was conducted utilising the same base case inputs and settings as described in the Company

submission for the biologic-naïve nr-axSpA population (in lieu of biologic-experienced nr-axSpA model), with the exception of the following:

- On the 'Input data' and 'Input data default' tabs, the following efficacy inputs were adjusted for all biologic treatments in the model to be equal to the values for ixekizumab, which were sourced from the COAST-X trial:
    - Response rate (mean proportion and 95% confidence intervals [standard error was calculated])
    - BASDAI reduction; responders and non-responders (least squares mean and 95% confidence intervals [standard errors were calculated]). To calculate BASDAI cfb by response, the formulae described in Appendix M of the company submission were utilised. For all interventions, the proportion of responders and non-responders (according to BASDAI50) used to inform the formulae were sourced from COAST-X.
    - BASFI reduction; responders and non-responders (least squares mean and 95% confidence intervals [standard errors were calculated]). To calculate BASFI cfb by response, the formulae described in Appendix M of the company submission were utilised. For all interventions, the proportion of responders and non-responders (according to BASDAI50) used to inform the formulae were sourced from COAST-X.
    - Efficacy inputs sourced from COAST-X are presented in Table 2.
- As noted in the technical engagement response, in the interest of utilising data with high statistical power to inform the analyses, data from the ixekizumab Q4W arm of the COAST-X trial (which included patients treated with either the 80 mg or 160 mg loading dose) were used to inform the analysis. COAST-X was not powered to detect a statistically significant difference between the 160 mg and 80 mg loading dose groups. In the attached models, the 'BASDAI50 pooled dose' option of the 'main' tab is therefore selected.
- The class effects analysis assumes that the efficacy of all biologics is equal. Accordingly, timing of response would similarly be expected to be the same for all treatments. As such, the trial period duration was made to be equal to ixekizumab for all biologic interventions in the model: Week 16.

Table 1. COAST-W Model Efficacy Input Data

Treatment	Proportion BASDAI50 responders			BASDAI mean change from baseline			BASFI mean change from baseline		
	Proportion	Lower 95% CI	Upper 95% CI	LSM	Lower 95% CI	Upper 95% CI	LSM	Lower 95% CI	Upper 95% CI
Placebo	0.096	[redacted]	[redacted]	-0.92	[redacted]	[redacted]	-0.64	[redacted]	[redacted]
Ixe 80 mg Q4W	0.219	[redacted]	[redacted]	-2.17	[redacted]	[redacted]	-1.69	[redacted]	[redacted]

Source: Lilly Data on File.
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CI: confidence interval; LSM: least squares mean; Q4W: every 4 weeks
Statistical analyses: BASDAI50: Week 16 (NRI); BASDAI cfb: Week 16 (MMRM); BASFI cfb: Week 16 (MMRM)

Table 2. COAST-X Model Efficacy Input Data

Treatment	Proportion BASDAI50 responders			BASDAI mean change from baseline			BASFI mean change from baseline		
	Proportion	Lower 95% CI	Upper 95% CI	LSM	Lower 95% CI	Upper 95% CI	LSM	Lower 95% CI	Upper 95% CI
Placebo	[redacted]	[redacted]	[redacted]	-1.51	[redacted]	[redacted]	-1.34	[redacted]	[redacted]
Ixe 80 mg Q4W	[redacted]	[redacted]	[redacted]	-2.18	[redacted]	[redacted]	-2.01	[redacted]	[redacted]

Source: Lilly Data on File.
Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CI: confidence interval; LSM: least squares mean; Q4W: every 4 weeks
Statistical analyses: BASDAI50: Week 16 (NRI); BASDAI cfb: Week 16 (MMRM); BASFI cfb: Week 16 (MMRM)

NICE National Institute for Health and Care Excellence

Technical engagement response form

ID1532 Ixekizumab for treating axial spondyloarthritis after nonsteroidal anti-inflammatory drugs

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- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Novartis Pharmaceuticals UK Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Impact of disease subtype and prior exposure to biologic therapy on the clinical effectiveness of ixekizumab	
a) Is ixekizumab most likely to be used in people with previous exposure to at least one TNF-alpha inhibitor or would it also be offered to people who have never had a TNF-alpha inhibitor?	Ixekizumab is likely to be option alongside biologic treatments already recommended by NICE (TA 487, TA 407 and TA 383). We anticipate the majority of usage of ixekizumab will be second line given the established presence of anti-TNFs in axial SpA, and an existing IL-17 option (secukinumab) for patients with rad-axSpA.
b) Is there a clinical rationale for why treatment outcomes with ixekizumab would be likely to vary based on disease subtype (rad-axSpA versus nr-axSpA) or prior exposure to *any* biologic treatment? If so, is there a clinical rationale why the number or type of prior biologic treatments received previously would impact on the efficacy of ixekizumab?	If the committee decides to assume that treatment effects in the nr-axSpA population can be extrapolated to the rad-axSpA population, a consistent approach should also be taken for secukinumab which is currently being appraised in the nr-axSpA population. i.e. in the ongoing appraisal ID1419, evidence from MEASURE 1 and 2, and the TA407 recommendation of secukinumab in rad-axSpA should also be considered, alongside PREVENT. There is evidence to suggest that treatment efficacy diminishes as the number of lines of treatment increases for all biologics.
c) How many people would receive more than two biological therapies prior to ixekizumab in clinical practice?	No comment.
d) What is the clinical effectiveness of ixekizumab versus placebo in the patients with rad-axSpA regardless of prior treatment exposure (i.e. the average effect across COAST-V and COAST-W)	No comment.

Issue 2: Clinical effectiveness estimates for ixekizumab versus secukinumab	
a) Is the company able to provide any revised estimates of the clinical and cost effectiveness of ixekizumab compared with secukinumab?	We agree with the ERG that secukinumab is an important comparator for ixekizumab so further analysis to inform better estimates of the relative clinical and cost effectiveness of the IL-17A inhibitors is important. Eli Lilly claims superiority of ixekizumab vs secukinumab only for one outcome (ASAS40) in one population (biologic-naive rad-axSpA) out of 4 outcomes across three populations. Superiority of ixekizumab over secukinumab is highly unlikely given the similarity of the mode of action and the similar efficacy reported in MEASURE 1 and 2 and COAST-V.
Issue 3: Limitations in the network meta-analysis	
a) Is it reasonable to assume equal efficacy across all TNF-alpha inhibitors in rad-axSpa biologic naïve patients? If so, should the same assumption be applied in all other subgroups?	No comment.
b) Is it reasonable to assume equal efficacy across all IL-17-1A inhibitors in rad-axSpa biologic naïve patients? If so, should the same assumption be applied in all other subgroups?	Yes it is reasonable, please see comment above on issue 2. Please note the following sentence on page 26 in the Technical Report is incorrect; *"neither of the MEASURE trials reported BASDAI50 or BASFI change from baseline so the company's original NMAs for these outcomes did not include any data that would allow for comparisons to be made between ixekizumab and secukinumab."* Please see Table 51 on page 167 of the company submission, available in the Committee Papers section on the NICE website; https://www.nice.org.uk/guidance/ta407/documents/committee-papers.

c) Is it reasonable to assume equal efficacy across all comparators and in all populations given the limited evidence to demonstrate that ixekizumab is more or less effective than other currently available treatments?	No comment.
Issue 4: Long-term effectiveness of ixekizumab	
a) Can the company supply the results of the COAST-Y study?	No comment.
b) Can the company comment on the extent to which the currently available evidence supports the projected estimates of long-term treatment effects derived from the economic model?	Estimates of long term treatment effects should be based on licensed dosing regimens only. The committee should be consistent in its approach to data from unlicensed treatment regimens across ID1419 and ID1532.
Issue 5: Modelling of BASFI scores after treatment discontinuation	
a) When treatment is discontinued, is it reasonable to assume that patients return to their baseline level of function?	No comment.
Issue 6: Choice of utility regression equation	
a) What are the results of the utilities scenario analysis (company scenarios 3a-d) when tested in the new population/class scenario analyses requested by the technical team in issues 3?	No comment.

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About you

Your name	**BSR Spondyloarthritis Special Interest Group**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Society for Rheumatology**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

Questions for engagement

Issue 1: Impact of disease subtype and prior exposure to biologic therapy on the clinical effectiveness of ixekizumab	
a) Is ixekizumab most likely to be used in people with previous exposure to at least one TNF-alpha inhibitor or would it also be offered to people who have never had a TNF-alpha inhibitor?	**Yes**
b) Is there a clinical rationale for why treatment outcomes with ixekizumab would be likely to vary based on disease subtype (rad-axSpA versus nr-axSpA) or prior exposure to *any* biologic treatment? If so, is there a clinical rationale why the number or type of prior biologic treatments received previously would impact on the efficacy of ixekizumab?	**Length of disease duration, inflammatory burden, degree of radiographic damage eg. fusion in both radiographic and non-radiographic axSpA is likely to affect the treatment outcome with Ixekizumab as these are heterogenous groups.**
c) How many people would receive more than two biological therapies prior to ixekizumab in clinical practice?	**10% of patients. Ixekizumab is more likely to be used earlier in treatment.**
d) What is the clinical effectiveness of ixekizumab versus placebo in the patients with rad-axSpA regardless of prior treatment exposure (i.e. the average effect across COAST-V and COAST-W)	

Issue 2: Clinical effectiveness estimates for ixekizumab versus secukinumab	
a) Is the company able to provide any revised estimates of the clinical and cost effectiveness of ixekizumab compared with secukinumab?	
Issue 3: Limitations in the network meta-analysis	
a) Is it reasonable to assume equal efficacy across all TNF-alpha inhibitors in rad-axSpa biologic naïve patients? If so, should the same assumption be applied in all other subgroups?	**It is a reasonable assumption and may be used in the analysis**
b) Is it reasonable to assume equal efficacy across all IL-17-1A inhibitors in rad-axSpa biologic naïve patients? If so, should the same assumption be applied in all other subgroups?	**This is not known and is an area for further research and study**
c) Is it reasonable to assume equal efficacy across all comparators and in all populations given the limited evidence to demonstrate that ixekizumab is more or less effective than other currently available treatments?	**This is an area for further research and study**
Issue 4: Long-term effectiveness of ixekizumab	
a) Can the company supply the results of the COAST-Y study?	
b) Can the company comment on the extent to which the currently available evidence	

supports the projected estimates of long-term treatment effects derived from the economic model?	
Issue 5: Modelling of BASFI scores after treatment discontinuation	
a) When treatment is discontinued, is it reasonable to assume that patients return to their baseline level of function?	**They may return to baseline or may have worsening disease**
Issue 6: Choice of utility regression equation	
a) What are the results of the utilities scenario analysis (company scenarios 3a-d) when tested in the new population/class scenario analyses requested by the technical team in issues 3?	

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Eli Lilly and Company
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Summary for Committee

Issue 1

Treatment Position of Ixekizumab

- Lilly consider that if recommended, ixekizumab will be used in the following manner in UK clinical practice:
  - In **rad-axSpA** patients, ixekizumab will be used for the treatment of adults who have responded inadequately to, or have not tolerated, non-steroidal anti-inflammatory drugs (NSAIDs) and **at least two biological DMARDs (bDMARDs),** or are contra-indicated or otherwise unsuitable for TNF-alpha inhibitor treatment.
  - In **nr-axSpA** patients, ixekizumab will be used for the treatment of adults who have responded inadequately to, or have not tolerated, NSAIDs and **at least one TNF-alpha inhibitor treatment**, or are contra-indicated or otherwise unsuitable for TNF-alpha inhibitor treatment.
- It is important for ixekizumab to be available for use in the axSpA population of the UK as there is still a significant unmet need for effective treatments for patients. The Company acknowledge that TNF-alpha inhibitors will likely be used as first line treatment in UK clinical practice. However, response rates to first-line TNF-alpha inhibition in axSpA have been estimated to be between 33–52%, and real-world studies have consistently confirmed lower effectiveness of sequential TNF-alpha inhibitors in rad-axSpA patients.[1-4] There is also a need for clinician flexibility for primary and secondary non-responders to TNF-alpha inhibitors.
- UK guidance recommend switching to a biologic with a new mechanism of action following treatment failure.[5] In **rad-axSpA,** secukinumab is the only available biologic with a mechanism of action distinct from TNF-alpha inhibition.
  - In **rad-axSpA**, ixekizumab is therefore anticipated to be used following attempt of one TNF-alpha inhibitor and one bDMARD with a distinct mechanism of action (for primary TNF-alpha inhibitor non-responders), or following two TNF-alpha inhibitors in patients with secondary loss of response to their second TNF-alpha inhibitor.
  - In **nr-axSpA**, no treatment options with a distinct mechanism of action to TNF-alpha inhibition are currently available. Therefore, the Company consider that for nr-axSpA patients, ixekizumab would primarily be used following one TNF-alpha inhibitor in TNF-alpha inhibitor primary non-responders, or following two TNF-alpha inhibitors in TNF-alpha inhibitor secondary non-responders
  - Lilly consider that ixekizumab should be an option for rad- and nr-axSpA patients who are **contraindicated to TNF-alpha inhibitors**, given these patients have extremely limited biologic treatment options

Evidence Availability in Subgroups

- The Company acknowledge the Technical Team's wish to minimise uncertainty associated with the presentation of subgroups by prior biologic-exposure, but consider that, based on clinical rationale and statistical evidence and NICE TSD guidance, meta-analysing biologic-naive and -experienced data would not offer greater decision-making certainty for the Committee due to the introduction of significant heterogeneity between patient populations into the analysis.
- NICE has previously recommended the use of the comparator biologic agents (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol and secukinumab) in the biologic-experienced patient population. However, there are no published Phase 3 clinical trial data for the TNF-alpha inhibitors solely in a biologic-experienced population (and none at the time of NICE review). Published evidence from randomised controlled trials of secukinumab includes data from only 59 patients in MEASURE-2 and MEASURE-4 (within subgroups), in which patients could have received a maximum of one prior TNF-alpha inhibitor.[6, 7]
- The Company note that ixekizumab is the only biologic agent to have been studied in a large randomised controlled trial and to have demonstrated efficacy and safety in a specific biologic experienced, intent-to-treat patient population. The COAST-W clinical trial included rad-axSpA patients with an inadequate response to up to two TNF-alpha inhibitors, with no limitations on reasons for prior failure. Patients had long-standing disease duration, which is representative of biologic-experienced patients observed in the UK.
    - The Company therefore believe that COAST-W offers strong evidence to support a recommendation of ixekizumab in the biologic-experienced population.
- With regards to the generalisability of treatment effects between rad- and nr-axSpA, as accepted by the Committee in TA383, the Company consider there to be significant clinical validation of the assumption that clinical efficacy results are generalisable between the rad- and nr-axSpA populations, given that these conditions represent either end of a continuous spectrum of the same disease and thus have the same underlying pathophysiology and similar burden on patients.[8-10]

Issue 2

Comparison to secukinumab

- As requested by the technical team, the Company have been able to conduct an NMA in the nr-axSpA population that incorporates the PREVENT secukinumab study.
- The results found no statistically significant difference between ixekizumab and secukinumab for any of the outcomes assessed, whilst the 95% credible intervals (CrIs) for all of the biologic treatments versus placebo, as well as the posterior median outcomes per treatment arm, overlap substantially for the outcomes assessed.

- The Company therefore consider that the results for ASAS40, BASDAI50, BASDAI cfb and BASFI cfb support a class effect among IL-17 inhibitors and TNF-alpha inhibitors that could be generalised across rad- and nr-axSpA patients.

Issue 3

Class effects among TNF-alpha inhibitors

- The Company consider it reasonable to assume equal efficacy across all TNF-alpha inhibitors within the rad-axSpA biologic-naïve population and further that this assumption may be applied *within* rad-axSpA biologic-experienced and nr-axSpA biologic-naive and -experienced subgroups.
  - An assumption of class effects among TNF-alpha inhibitors is in line with conclusions made by the NICE Committee in TA383, and is supported by clinical evidence that TNF-alpha is a key driver of the pathophysiology of axSpA (all treatments target soluble TNF-alpha) and the substantial overlap of the 95% CrIs in the comparison of TNF-alpha inhibitors versus placebo in the NMAs presented by the Company, together with the substantial overlap of the 95% CrIs for the posterior median outcomes.

Class effects among IL-17A inhibitors

- The Company consider it reasonable to assume equal efficacy across IL-17A inhibitors within the rad-axSpA biologic-naïve population and further that this assumption may be applied *within* rad-axSpA biologic-experienced and nr-axSpA biologic-naive and -experienced subgroups based on current evidence.
  - An assumption of class effects among IL-17A inhibitors is supported by clinical evidence that IL-17A is a key driver of the pathophysiology of axSpA; both secukinumab and ixekizumab target the A variant of the IL-17 cytokine superfamily. Statistical evidence from the NMA presented in response to Issue 2 illustrates no significant differences identified between ixekizumab and secukinumab for any outcomes assessed (ASAS40, BASDAI50, BASDAI cfb and BASFI cfb).

Class effects among all biologics indicated for axSpA

- For the purposes of decision-making, the Company ultimately deem it reasonable to assume class effects amongst all biologics for the rad and nr-axSpA indications.
  - This finding is in alignment with the conclusion of the NICE Committee in the appraisal of secukinumab (TA407) that "secukinumab has a similar efficacy to the TNF-alpha inhibitors".[6]
  - Studies demonstrate that axSpA is driven by cytokine dysregulation, with both the TNF-alpha and IL-17A cytokines playing key roles.

Cost-effectiveness results

- In order to provide a revised economic analysis for the Committee assuming class effects among all biologics, the Company have adopted a non-complex approach, which we deem makes use of the most robust data available to inform decision-making.

- Specifically, an analysis was conducted in the biologic-experienced rad-axSpA population (to support the intended treatment position of ixekizumab in this population) with all biologic treatments adopting the same efficacy inputs from COAST-W as ixekizumab. In lieu of a biologic-experienced model to support the intended position of ixekizumab in the nr-axSpA treatment pathway, a second analysis was conducted using the biologic-naïve nr-axSpA model, with all biologic treatments adopting the same efficacy inputs from COAST-X as ixekizumab.
    - Given the uncertainties raised by the ERG regarding the NMA results, it was deemed that the highly internally valid COAST trials would comprise the most appropriate inputs for these analyses.
- The results of the economic analysis in **rad-axSpA** illustrate that over a lifetime horizon, ixekizumab is associated with either a comparable or less expensive total cost compared to **5/6** biologic treatments recommended by NICE for biologic-experienced patients, namely certolizumab pegol, etanercept, secukinumab 150 mg (N.B. it was not possible to consider the confidential PAS in the analysis), golimumab and infliximab, a result which supports the proposed use of ixekizumab after attempt of NSAIDs and at least two bDMARDs.
- The results of the economic analysis in **nr-axSpA,** illustrate that over a lifetime horizon, ixekizumab is associated with a less expensive total cost compared to **3/4** biologic treatments recommended by NICE, namely etanercept, certolizumab pegol and golimumab, supporting its use after attempt of NSAIDs and at least one prior biologic.

In conclusion, based on the assumptions utilised in this analysis, as informed by the responses provided in Issues 1 to 3, the Company believe that ixekizumab comprises a valuable treatment option for biologic-experienced patients across the full spectrum of axSpA.

ERG's interpretation of the company's positioning of ixekizumab, and relevant cost effectiveness comparators

Table A rad-axSpA populations considered in the company submission and company response to technical engagement, and ERG comment

Population	Location	Treatments offered prior to IXE	Relevant comparators to IXE as determined by the ERG	Cost effectiveness results versus IXE presented by the company
Biologic-naïve	CS	NSAIDs	CC All TNF-alpha inhibitors SEC	Company approach: The company presented cost effectiveness results or IXE vs all TNF-alpha inhibitors and CC. IXE vs SEC results were presented as a scenario analysis ERG comment: The company withdrew their IXE vs SEC cost effectiveness results (scenario analysis) due to data issues during clarification
	CS	NSAIDs	SEC	Company approach:

Contraindicated to TNF-alpha inhibitors				Cost effectiveness analyses were presented versus the relevant comparators (SEC [scenario analysis] and CC [biologic-naïve results]). These comparisons were discussed in the company's decision problem table but not in the discussion of cost effectiveness results ERG comment: Clinical advice to the ERG (ERG report, p87) is that CC is not a relevant comparator as SEC is a treatment option for this population. The company withdrew their SEC cost effectiveness results (scenario analysis) due to data issues during clarification It is not clear whether clinical effectiveness evidence for a biologic-naïve population reflects the experience of a TNF-alpha contraindicated population	
	TE	NSAIDs	SEC	Company approach: No results have been discussed or presented for the TNF-alpha inhibitor contraindicated population ERG comment: If the biologic-naïve population is the same as the contraindicated population, under the new assumption that clinical effectiveness demonstrated in a biologic-naïve nr-axSpA population is mirrored in a biologic-naïve rad-axSpA population, then company cost effectiveness results have been provided for IXE vs all the TNF-alpha inhibitors The ERG considers that the relevant comparators for this population are SEC and CC. However, the (biologic-naïve) results generated by the company do not include SEC and only costs have been provided for the comparison of IXE vs CC. An ICER per QALY gained for the comparison of IXE vs CC is required The TNF-alpha contraindicated population is a subset of the biologic-naïve population and this renders consideration of the TNF-alpha inhibitors redundant It is not clear whether clinical effectiveness evidence for a biologic-naïve population reflects the experience of a TNF-alpha contraindicated population	

Biologic-experienced	CS	NSAIDs followed by ≥ one TNF-alpha inhibitor	CC All TNF-alpha inhibitors SEC	Company approach: The company presented cost effectiveness results for all TNF-alpha inhibitors, SEC (scenario analysis) and CC ERG comment: The company withdrew their SEC cost effectiveness results (scenario analysis) due to data issues
Biologic experienced: two TNF-alpha inhibitors	TE	NSAIDs followed by two TNF-alpha inhibitors	CC SEC	Company approach: The company has not presented results separately for these two populations, only results for the whole biologic-experienced population are presented Results for IXE vs TNF-alpha inhibitors, SEC and CC have been provided ERG comment: The available clinical effectiveness evidence for IXE relates to failure after one or two TNF-alpha inhibitors in the rad-axSpA population. The populations considered by the company are those who have received two TNF-alpha inhibitors (relevant comparators: CC and SEC) and those who have received one TNF-alpha inhibitor and SEC (relevant comparator: CC). An ICER per QALY gained for the comparison of IXE vs CC is required
Biologic-experienced: one TNF-alpha inhibitor and SEC		NSAIDs followed by one TNF-alpha inhibitor and then SEC	CC	

Table B nr-axSpA populations considered in the company submission and company response to technical engagement, and ERG comment

Population	Location	Treatments offered prior to IXE	Relevant comparators to IXE as determined by the ERG	Cost effectiveness results versus IXE presented by the company
Biologic-naïve	CS	NSAIDs	CC All TNF-alpha inhibitors	Company approach: The company provided cost effectiveness results for IXE vs CC and for IXE vs all TNF-alpha inhibitors ERG comment: No comment.
Contraindicated to TNF-alpha inhibitors	CS	NSAIDs	CC	Company approach: No specific results were presented for the TNF-alpha contraindicated population, however, the company stated that the results from the

				biologic-naïve population can be used to infer the cost effectiveness of ixekizumab in the TNF-alpha inhibitor contraindicated population ERG comment: No comment
	TE	NSAIDs	CC	Company approach: No specific results have been presented for the TNF-alpha contraindicated population (the company only presents results for the biologic-naïve population) ERG comment: If the biologic-naïve population is the same as the contraindicated population, then company cost effectiveness results have been provided for IXE vs all the TNF-alpha inhibitors and CC. The ERG considers that the relevant comparator for this population is CC. An ICER per QALY gained for the comparison of IXE vs CC is required The TNF-alpha contraindicated population is a subset of the biologic-naïve population and this renders consideration of the TNF-alpha inhibitors redundant It is not clear whether clinical effectiveness evidence for a biologic-naïve population reflects the experience of a TNF-alpha contraindicated population
Biologic-experienced: ≥ one TNF-alpha inhibitors	CS	≥ one TNF-alpha inhibitors	CC All TNF-alpha inhibitors	Company approach: No cost effectiveness results were presented for the nr-axSpA biologic-experienced population ERG comment: None
	TE	≥ one TNF-alpha inhibitor	CC All TNF-alpha inhibitors	Company approach: No specific results have been presented for the nr-axSpA biologic-experienced population (the company only presents results for the rad-axSpA biologic-experienced population)

				ERG comment: Under the new assumption that clinical effectiveness demonstrated in a biologic-experienced rad-axSpA population is mirrored in a biologic-experienced nr-axSpA population, then company cost effectiveness results have been provided for IXE vs all the TNF-alpha inhibitors and CC. An ICER per QALY gained for the comparison of IXE vs CC is required

Issue 1: Impact of disease subtype and prior exposure to biologic therapy on the clinical effectiveness of ixekizumab	
a) Is ixekizumab most likely to be used in people with previous exposure to at least one TNF-alpha inhibitor or would it also be offered to people who have never had a TNF-alpha inhibitor?	The Company thank the ERG and NICE Technical Team for the feedback received throughout this appraisal. Following this feedback, the Company consider that in UK clinical practice ixekizumab will be used as follows: • In **rad-axSpA** patients, ixekizumab will be used for the treatment of adults who have responded inadequately to, or have not tolerated, NSAIDs and at least two bDMARDs, or are contra-indicated or otherwise unsuitable for TNF-alpha inhibitor treatment. • In **nr-axSpA** patients, ixekizumab will be used for the treatment of adults who have responded inadequately to, or have not tolerated, NSAIDs and at least one TNF-alpha inhibitor treatment, or are contra-indicated or otherwise unsuitable for TNF-alpha inhibitor treatments. Therefore, in both disease subtypes, the Company believe ixekizumab will primarily be used in biologic-experienced patients. The exception is patients in the nr-axSpA population contra-indicated to TNF-alpha inhibitors who may be biologic-treatment naïve at the point of ixekizumab commencement given that no biologic with a mechanism distinct from TNF-alpha inhibition is currently available in the nr-axSpA population. **Positioning in the rad-axSpA population** • The positioning of ixekizumab in rad-axSpA patients following inadequate response to, or intolerance to, NSAIDs and at least two bDMARDs, or in the case of patients who are contra-indicated or otherwise unsuitable for anti-TNF-alpha treatment, permits necessary clinician flexibility within the treatment pathway. In particular, it is expected that treatment decisions will differ for patients who exhibit primary non-response (no response following treatment initiation) or secondary non-response (initial response to treatment followed by loss of response) to TNF alpha inhibition.

	• The Company acknowledge that long-standing TNF-alpha inhibitor treatments such as adalimumab will be used as first line treatment in rad-axSpA patients in UK clinical practice. However, response rates to first-line TNF-alpha inhibition in axSpA have been estimated at 33–52% depending on the criteria used, suggesting approximately 48–67% of patients may be primary or secondary non-responders.[1] Furthermore, recently published evidence suggests that patients who discontinue their first TNF-alpha inhibitor due to primary non-response may be less likely to show a response to their second TNF-alpha inhibitor, based on outcomes such as the Ankylosing Spondylitis Disease Activity Score Inactive Disease (ASDAS-ID).[11, 12] • In addition, real world studies have confirmed lower effectiveness of sequential TNF-alpha inhibitors in rad-axSpA patients. Glintborg *et al* (2013) and colleagues reported the proportion of rad-axSpA patients (N=1,436, of whom 432 [30%] had a second TNF-alpha inhibitor) achieving BASDAI 50%/20 mm response within 6 months on their first TNF was 54% (NNT=1.9). Corresponding rates during the second and third treatment course were 37% (NNT=2.7) and 30% (NNT=3.4), respectively.[2] Similarly, Heinenon *et al* (2015) reported on a study including 543 rad-axSpA patients (123 patients commenced a second TNF inhibitor). BASDAI response at 6 months was achieved by 52% and 25% of the users of the first and the second TNF inhibitors, respectively.[3] In a UK-based study, mean drug survival in 651 axSpA patients fell from 10.2 years for the first TNF-alpha inhibitor to 5.5 years for the second.[4] • In line with these clinical observations of diminishing efficacy in subsequent therapies of the same mechanism following prior failure, the Regional Medicines Optimisation Committee (RMOC) recommends switching to a biologic with a new mechanism of action following treatment failure.[5] Similarly, in the case of primary non-response to the first TNF-alpha inhibitor in rad-axSpA patients, the ACR recommends switching to an IL-17A inhibitor (Recommendation 12).[13] • The Company acknowledge that in current UK clinical practice, secukinumab is the only available biologic with a mechanism of action distinct from TNF-alpha inhibition, and thus would likely be used second line following primary treatment failure on one TNF-alpha inhibitor. Therefore, based on these clinical observations and regulatory guidelines, the Company consider that for rad-axSpA patients, to optimise patient care, ixekizumab would primarily be used in clinical practice following attempt of NSAIDs and at least two prior bDMARDs: following one TNF-alpha inhibitor and another bDMARD with a distinct mechanism of action in TNF-alpha inhibitor primary non-responders, and following two TNF-alpha inhibitors in patients with a secondary loss of response to prior TNF-alpha inhibitors (secondary non-responders). The Company further note that in the case of TNF-alpha contraindication, such as in patients with demyelinating disease or Stage III–IV heart failure, ixekizumab is

anticipated to provide a welcome second-line treatment option in the case of secukinumab failure given that no further biologic options currently exist for these patients.

- It is therefore anticipated that positioning of ixekizumab following NSAIDs and at least two bDMARDs treatments or in the case of TNF-alpha contraindication would provide an additional treatment option for patients in the rad-axSpA population who have exhibited a primary or secondary treatment failure to TNF-alpha inhibition, or are contraindicated or otherwise unsuitable for TNF-alpha inhibition.

Positioning in the nr-axSpA population

- The positioning of ixekizumab in nr-axSpA patients following inadequate response to, or intolerance to, NSAIDs and at least one TNF-alpha inhibitor, or in the case of patients who are contra-indicated or otherwise unsuitable for anti-TNF alpha treatment, allows clinician flexibility within the treatment pathway and addresses a significant unmet need in these patients.
- As discussed above, two or more TNF-alpha inhibitors may be used sequentially following secondary non-response, although clinical evidence suggests diminishing response efficacy at each subsequent line. For primary non-responders, it is recommended by the ACR that patients with active nr-axSpA and primary non-response to the first TNF-alpha inhibitor switch to a treatment with an alternative mechanism of action (Recommendation 63).[13] However, in the UK, no treatment options with a distinct mechanism of action to TNF-alpha inhibition are currently recommended for patients with nr-axSpA. Similarly, no biologic treatment options are currently available for patients with nr-axSpA who are contraindicated to, or otherwise unsuitable to receive, TNF-alpha inhibitors.
- Therefore, the Company consider that for nr-axSpA patients, to optimise patient care, ixekizumab would primarily be used in clinical practice from second line: following one TNF-alpha inhibitor in TNF-alpha inhibitor primary non-responders, or following two TNF-alpha inhibitors in TNF-alpha inhibitor secondary non-responders. In patients with nr-axSpA who cannot receive TNF-alpha inhibitors, ixekizumab would represent a first-line biologic option in UK clinical practice.
- It is therefore anticipated that the positioning of ixekizumab following NSAIDs and at least one biologic treatment or in the case of TNF-alpha contraindication would be unique in providing a treatment option for patients in the nr-axSpA population who have exhibited a primary or secondary treatment failure to TNF-alpha inhibition, or are contraindicated or otherwise unsuitable for TNF-alpha inhibition.

Ixekizumab addresses an unmet need

	• As outlined above, the Company understands there to be a significant unmet need remaining in axSpA patients in the UK despite other available biologics. Despite the availability of six biologics for rad-axSpA patients (five TNF-alpha inhibitors and one other IL-17A-inhibitor) and four TNF-alpha inhibitors for nr-axSpA patients (as noted by the Technical Team, Technical Engagement Report, page 23), patient feedback collected by the National Axial Spondyloarthritis Society during this Technical Engagement process (Technical Engagement Papers, pages 315–324) indicated that 55% of patients feel that treatment options currently available to patients on the NHS are insufficient (page 320), and that overall, patients felt strongly that offering as many treatment options as possible would be beneficial to ensure the best care possible is provided to those living with the condition (page 321). This unmet need is heightened in nr-axSpA patients as reflected by feedback from patients during this Technical Engagement process, who highlighted introduction of ixekizumab would be of significant advantage to patients with nr-axSpA to whom no non-TNF-alpha inhibitor biologics are currently available (Technical Engagement Papers, page 322). • The NICE Guideline for the diagnosis and management of spondyloarthritis in over 16s (NG65) provides guidance for clinicians on selecting the appropriate biologic for use based on individual patient factors, including the frequency of injections and the administration route.[14] It further states that "*clinical comorbidities, such as previous malignancy, infection risk or presence of demyelinating disease*" should be taken into account, while moderate to severe heart failure is a contraindication for use of adalimumab, certolizumab pegol, golimumab and infliximab but is not for ixekizumab use.[14-19] • Together, these guidelines and patient feedback reinforce the necessity of increasing treatment options available to clinicians to permit patient-specific treatment decisions and highlight how the introduction of ixekizumab into UK clinical practice may address the current unmet needs faced by axSpA patients.[14] **Conclusion** Based on this, the Company consider placement of ixekizumab in the treatment pathway for rad-axSpA patients who have not responded to NSAIDs and at least two bDMARDs and for nr-axSpA patients who have not responded to NSAIDs and at least one TNF-alpha inhibitor, or for any axSpA patient who is contraindicated or otherwise unsuitable for TNF-alpha inhibitor use, to be clinically plausible and to address a current treatment need within UK clinical practice.
b) Is there a clinical rationale for why treatment outcomes with ixekizumab would be likely to vary based on disease subtype	**Rad-axSpA versus nr-axSpA** • The Company do **not** consider there to be a clinical rationale to support differential treatment effects in biologics including ixekizumab the rad- and nr-axSpA populations.

(rad-axSpA versus nr-axSpA) or prior exposure to *any* biologic treatment? If so, is there a clinical rationale why the number or type of prior biologic treatments received previously would impact on the efficacy of ixekizumab?	• Previous clinical trials of rad- and nr-axSpA have been conducted separately given that they have traditionally been considered as two distinct disease entities. However, clinical practice has more recently moved towards consideration of axSpA as a spectrum of disease, with the rad- and nr- subtypes representing either end of a continuous spectrum.[20, 21] This clinical view is supported by whole body MRIs, which identify that the number of inflammatory lesions in the spine and in the sacroiliac joint do not differ between rad- and nr-axSpA.[9] Furthermore, the patient and clinical experts in the NICE appraisal of TNF-alpha inhibitors (TA383) made clear that rad- and nr-axSpA are distinguishable conditions within a single disease spectrum and that disease severity and patient experiences of pain, functioning and quality of life are similar across both subtypes, as has been reported elsewhere.[8-10] • Therefore, that subtypes of the same disease driven by the same pathophysiology and with similar clinical presentation and HRQoL impact for patients should show a generalisable treatment effect retains clinical plausibility. This is supported by clinical evidence: the ESTHER trial, which assessed the response rates in patients with rad- and nr-axSpA after one year of treatment with etanercept, identified no differences in symptom duration or disease activity between the two groups, while the phase 3 RAPID-axSpA trial identified similar improvements with CZP treatment in rad- and nr-axSpA patients at 24 weeks.[22, 23] • A conclusion of generalisability between rad- and nr-axSpA is aligned with the conclusions of the clinical experts and the Appraisal Committee in TA383 that a differential response to treatment between rad- and nr-axSpA patients would not be expected and that a similar benefit of treatment was likely to be observed between these two patient populations.[8] It is further supported by a published meta-analysis of TNF-alpha inhibitors which identified no differences in effect sizes between the rad- and nr-axSpA populations, and by an indirect comparison between IL-17 and TNF-alpha inhibitors in which it was concluded that "*although all these newer drugs were tested in AS, it can be assumed that efficacy results can also be extrapolated to nr-axSpA*".[24, 25] • Given the above, the Company consider that treatment outcomes with ixekizumab are likely to be generalisable between the rad- and nr-axSpA populations. **Biologic-naïve versus biologic experienced** • The Company **do** consider there to be a clinical rationale for why response to biologics such as ixekizumab would vary by prior biologic use and provide supportive evidence from the COAST trials that show prior biologic use is a treatment effect modifier.

- The COAST-V and COAST-W trials represent large populations of biologic-naïve and -experienced rad-axSpA patients, respectively. Despite the same underlying disease, these two trial populations differ in terms of their baseline characteristics. As presented in Section B.2.3.3 of Document B of the Company Submission, patients at baseline in the COAST-W trial (biologic-experienced) had mean ASDAS and BASDAI scores of approximately 4.2 and 7.4, respectively, as compared with approximately 3.8 and 6.8, respectively, in the COAST-V trial (biologic-naïve). Mean duration of symptoms since axSpA onset was longer in the COAST-W population as compared with COAST-V (16.5–19.9 years versus 15.6–16.6 years, respectively) and this is reflected in the older average age of patients (44.2–47.4 years in COAST-W as compared with 41.0–42.7 years in COAST-V). Together, these data indicate that the biologic-experienced patients in the COAST-W trial had more severe disease at baseline, and their increased age and longer duration of symptoms are treatment effect modifiers which clinically indicate a poorer response likelihood.[26, 27]
- These differences at baseline are suggestive of clinical heterogeneity between biologic-naïve and -experienced patients with the same disease subtype. This translates to evidence of varying efficacy at Weeks 16 and 52 across several key outcomes between the COAST-V and -W trials, as summarised in Table 1.

Table 1: Key efficacy outcome responses at Week 16 and 52 in the COAST-V and COAST-W populations

Outcome	COAST-V (biologic-naïve)		COAST-W (biologic-experienced)	
	PBO (N=87)	IXE Q4W (N=81)	PBO (N=104)	IXE Q4W (N=114)
Week 16				
ASAS40, n (%)	16 (18.4)	39 (48.1)	13 (12.5)	29 (25.4)
BASDAI50, n (%)	15 (17.2)	34 (41.9)	[redacted]	[redacted]
BASDAI, cfb LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
BASFI, cfb LSM (SE)	−1.16 (0.22)	−2.39 (0.22)	[redacted]	[redacted]
ASDAS <2.1	11 (12.6)	35 (43.2)	[redacted]	[redacted]
ASDAS<1.3	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
ASAS40	-	[redacted]	-	[redacted]
BASDAI50	-	[redacted]	-	[redacted]

BASDAI cfb	-	[redacted]	-	[redacted]
BASFI cfb	-	[redacted]	-	[redacted]
ASDAS <2.1	-	[redacted]	-	[redacted]
ASDAS<1.3	-	[redacted]	-	[redacted]

Abbreviations: ASAS: Assessment of SpondyloArthritis International Society; BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; IXE: ixekizumab; PBO: placebo; Q4W: every four weeks.

- In turn, this indicates that meta-analysis is unlikely to be meaningful between these two populations. In support of this, prior biologic use was shown to represent a treatment effect modifier upon attempting meta-analysis of the COAST- V and -W trials, (i.e. attempting meta-analysis between biologic-naïve and biologic-experienced patients). This analysis is discussed further in response to Part D of this question, where pooling between biologic-naïve and -experienced patients is concluded to be clinically and statistically inappropriate. This is in alignment with the recommendations of NICE Technical Support Document 1 (TSD1) where an assumption of equal efficacy across naïve and experienced populations is described as "*highly implausible*". In rheumatoid arthritis, an inflammatory disease similar to axSpA, TSD1 further concludes: "*one cannot assess the relative efficacy of biologics by combining trials of biologics in patients who have failed on standard therapies, with trials of patients who have failed on biologics. Summaries of effect sizes in these cases lack validity because… patients who are naïve to biologics and those who have failed on them represent different clinical populations and require different decisions, informed by different summaries of treatment effects*."[28]
- Therefore, the Company acknowledge the Technical Team's wish to minimise uncertainty associated with the presentation of subgroups by prior biologic-exposure, but considered that, based on this clinical rationale and statistical evidence, meta-analysing biologic naive and experience data would not offer greater decision-making certainty for the Committee.

Number of prior biologic treatments

- The Company consider there may be a clinical rationale for why response to biologics such as ixekizumab would vary by number of prior biologic treatments.
- As discussed above, disease duration is a prognostic indicator of response in axSpA patients, with increased time since symptom onset associated with a reduced probability of response. It is clinically plausible to extrapolate that

	patients with an increased disease duration, and thus a lower probability of response, are more likely to have had more previous biologics than those with short disease duration. **Type of prior biologic treatments** • With regards to a differential response by biologic type, as described in response to Part A, to optimise patient care, physicians may opt to switch classes to a treatment with a different mechanism of action following primary treatment failure based on the recommendation by the ACR and RMOC.[5, 13] However, the Company believe there is **no further** clinical rationale for why type of prior treatment would affect the efficacy of ixekizumab at later lines.
c) How many people would receive more than two biological therapies prior to ixekizumab in clinical practice?	• The Company provide evidence to suggest [redacted]% of axSpA patients in UK clinical practice would receive more than two bDMARDs prior to ixekizumab based on data collected from patients in current UK clinical practice who are receiving, or have previously received, secukinumab. As an alternative IL-17A inhibitor, secukinumab was selected as a proxy for this estimate. • As discussed further in response to Part A of this question, treatment guidelines suggest that selection of the appropriate biologic should be individualised based on several patient factors. This individualised treatment in UK clinical practice makes this question difficult to comment on, but as an illustrative example of where an IL-17 inhibitor might be used in clinical practice, the Company provide evidence derived from real-world evidence from patients in current UK clinical practice and collected as part of the Disease Specific Programmes of Adelphi Real World. These data, sourced from Adelphi DSP Plus 2019, with Patient Record Form Completion between April and August 2019, are presented in Table 8. • These data show that patients in UK clinical practice receive secukinumab following [redacted] prior biologics, with [redacted] receiving at least two prior biologics before secukinumab commencement. Assuming an equal market share between secukinumab and ixekizumab, these data suggest [redacted] of patients may receive ixekizumab after two or more prior biologics. This is in line with the unmet clinical need in biologic-experienced patients highlighted in response to Part A of this question.
d) What is the clinical effectiveness of ixekizumab versus placebo in the patients with rad-axSpA regardless of prior treatment exposure (i.e. the average effect across COAST-V and COAST-W)	• While the Company acknowledges the limitations raised by the technical team with regards to conducting NMAs within patient subgroups, they do not consider it statistically appropriate to synthesise treatment effect estimates for ixekizumab versus placebo regardless of prior treatment exposure by conducting a meta-analysis between the biologic-naïve rad-axSpA patients of COAST-V and the biologic-experienced rad-axSpA patients of COAST-W. This is due to heterogeneity in the populations with respect to their baseline characteristics and evidence of prior

	biologic use representing a treatment effect modifier. Such heterogeneity would introduce further uncertainty in the estimate of treatment effect for ixekizumab and render any results inappropriate for decision making. • As discussed further in response to Part B of this question, the COAST-V and COAST-W trial populations differ in terms of their baseline characteristics and these differences show that patients in COAST-W trial had more severe disease at baseline. The presence of significant clinical heterogeneity increases the risk of inconsistency and thus renders evidence synthesis inappropriate.[28, 29] • In order to determine whether prior biologic experience represents a treatment effect modifier, the Company attempted a meta-analysis of the ixekizumab versus placebo treatment effect from the COAST-V (rad-axSpA, biologic naïve) and COAST-W (rad-axSpA, biologic experienced) trials, utilizing the ITT populations and pooled loading doses (80 mg and 160 mg). Even though no heterogeneity was apparent when assessing the heterogeneity of the relative risks by means of the I^2 statistic for the endpoints ASAS40, BASDAI50, ASDAS<2.1 and ASDAS<1.3, and despite the known low power of the statistical test to detect heterogeneity, the meta-analysis identified substantial to considerable heterogeneity for these endpoints when comparing the risk difference between ixekizumab and placebo between the two studies (ASAS40 [I^2: [redacted], p[redacted]], BASDAI50 [I^2: [redacted], p[redacted]], ASDAS<2.1 [I^2: [redacted], p[redacted]], ASDAS<1.3 [I^2: [redacted], p[redacted]]. (It is noted that an I^2 value of >50% may be considered indicative that heterogeneity between studies can primarily be explained by systematic differences between studies (e.g. in terms of prognostic patient characteristics) rather than random sampling error within studies). This lends further strong support, beside the already presented clinical rationale, that a treatment effect in these patient populations is different, and advises against a pooling of these different patient populations. • Therefore, based on these findings, the Company conclude that significant heterogeneity in the study populations makes performance of a meta-analysis between biologic-naïve and biologic-experienced rad-axSpA patients inappropriate and that any estimates of treatment effect for ixekizumab obtained would be not meaningful, rendering them inappropriate for decision making. • In addition to being statistically inappropriate to perform, the Company further note that use of this meta-analysis to inform the comparison between ixekizumab and other comparator trials which contain mixed biologic-experienced and naïve data would produce misleading relative treatment effect estimates given the difference in treatment effect likely to be achieved by biologic-naïve and -experienced patients. This is due to the higher proportion of biologic-experienced patients in the combined COAST-V and -W trials ([redacted]%, with [redacted]% having received 2 prior TNF alpha inhibitors) as compared with the patient populations in the key clinical trials of secukinumab, MEASURE-2 and -4 (39% and 27–28%, respectively, none of whom had received more than one

	prior biologic) that include both biologic-naïve and -experienced patients, as shown in Table 9 below. Disease duration of patients in the MEASURE-2 and -4 trials has not been reported, but patients in the pooled COAST-V and -W trials had an average time since disease diagnosis of [redacted] years, as compared with 6.4–8.4 years in the MEASURE-2 and -4 trials (see Table 9). Overall, these data are suggestive of a harder-to-treat population in the COAST trials as compared with in the MEASURE trials, which would lead to misleading results.

ERG comment	1a. Position of ixekizumab in the treatment pathway The company states that ixekizumab will be used in patients with: • **rad-axSpA** who have responded inadequately to, or have not tolerated, NSAIDS, and at least **two** bDMARDs, or are contra-indicated or otherwise unsuitable for TNF-alpha inhibitor treatment and • **nr-axSpA** who have responded inadequately to, or have not tolerated, NSAIDS, and at least **one** bDMARD, or are contra-indicated or otherwise unsuitable for TNF-alpha inhibitor treatment The ERG highlights that there is no specific evidence to demonstrate the clinical effectiveness of ixekizumab when used to treat rad-axSpA or nr-axSpA patients who are contraindicated or otherwise unsuitable for treatment with NSAIDs or TNF-alpha inhibitors. Nor is there any evidence to support the clinical effectiveness of ixekizumab when used to treat biologic-experienced patients with rad-axSpA who have failed treatment with more than two biologics or any biologic-experienced patients with nr-axSpA (ERG Report p12, p25, p68). 1b. rad-axSpA versus nr-axSpA populations The BASDAI 50 response results for patients treated with ixekizumab (Q4W) at Week 16 differ between the COAST-V trial (biologic-naive rad-axSpA population) and the COAST-X trial (biologic-naive nr-AxSpA population) ([redacted] and [redacted] respectively). If this difference is due to underlying disease biology, then it is unreliable to use results from rad-axSpA trials as proxies for results from nr-axSpA trials (and vice versa). If the difference between the COAST-V and COAST-X trial results is solely due to different patient characteristics (patients with nr-axSpA are more likely to be younger and female than patients with rad-axSpA disease), then results from a rad-axSpA trial could only be used to inform effectiveness for patients with nr-axSpA disease (and vice versa) after appropriate adjustments had been made to account for differences in patient characteristics. 1d. Biologic-naïve vs biologic-experienced patients The ERG and the company consider that it is not appropriate to perform a meta-analysis using data from the COAST-V trial (biologic-naïve rad-axSpA population) and data from the COAST-W trial (biologic-experienced rad-axSpA population). Please see tables A and B for additional information.

Issue 2: Clinical effectiveness estimates for ixekizumab versus secukinumab	
a) Is the company able to provide any revised estimates of the clinical and cost effectiveness of ixekizumab compared with secukinumab?	• The Company provide estimates for the clinical efficacy of ixekizumab compared with secukinumab in nr-axSpA using data published since completion of the original submission documents and have identified no significant differences between these treatment options. • As suggested by the NICE Technical Team, the Company have included the PREVENT study, which reports the efficacy of secukinumab versus placebo in an nr-axSpA population, in the NMA.[30] The Company acknowledge that secukinumab is not a relevant comparator in the nr-axSpA population as per the final NICE scope. However, as discussed further in response to Issue 1, the Company considers the relative efficacy between ixekizumab and these results to be generalisable to a rad-axSpA population, given that these subtypes represent each end of a continuous spectrum of the same disease, and such an analysis may provide insight on a potential class effect amongst IL-17A inhibitors, and among biologic treatments more generally. • Therefore, the ITT population of this trial was incorporated into the networks for the ASAS40, BASDAI50, BASDAI change from baseline (cfb) and BASFI cfb to permit estimation of the relative efficacy of ixekizumab (pooled 80 mg and 160 mg loading doses) and secukinumab in the nr-axSpA population. The Company considered pooling of these loading doses to be suitable given that the COAST trials were designed and powered to detect a difference between the ixekizumab treatment arms (Q4W and Q2W) pooled by loading dose versus placebo, and efficacy loading dose analyses did not appear to have any meaningful impact on the treatment effect at week 16. In line with the original submission to NICE, the fixed effects model was selected as the random effects model did not converge. As discussed above, the Company acknowledge the limitations associated with the 'sensitivity analysis' NMAs, therefore results for the 'base case' NMA approach are presented, with sensitivity analysis results provided for completeness only as they provide results for a greater number of outcomes. • The results derived from the updated NMAs are presented in Table 10 and Table 11 (base case) and Table 12 and Table 13 (Sensitivity Analysis) below. The results found no statistically significant difference between ixekizumab and secukinumab for any of the outcomes assessed: ASAS40, BASDAI50, BASDAI cfb and BASFI cfb. Furthermore, an overlap between the credible intervals and posterior median outcomes of ixekizumab and secukinumab in their comparison versus placebo was observed, which was also the case for all of the biologic treatments for the outcomes assessed.

	• Based on these results, the Company consider a class effect between IL-17 inhibitors amongst rad- and nr-axSpA patients. The clinical and statistical justifications for assumption of class effects are discussed in more detail in response to Issue 3, alongside updated cost-effectiveness estimates in which these class effects are considered. • Due to a conclusion of a class effects amongst IL-17 inhibitors, a revised cost-effectiveness analysis between ixekizumab and secukinumab based on these NMA results has not be conducted. However, a cost-effectiveness analysis based on the assumption of class effects has been conducted (please see response to Issue 3, Part C for further details). **Secukinumab 300 mg dose** • As described in the Company Submission, an extension was made to the licence for secukinumab in ankylosing spondylitis (rad-axSpA) in October 2019, which states that "based on clinical response, the dose can be increased to 300 mg" following an initial dosing schedule with 150 mg. The cost-effectiveness of this dose in rad-axSpA patients has not been evaluated by NICE, however, real-world evidence demonstrates that there is substantial usage of this more expensive dose in UK clinical practice, as both a starting and maintenance treatment. • An analysis of the Adelphi AxSpA Plus Disease Specific Programme, a cross-sectional anonymised database, demonstrated that between April and August 2019 in the UK, [redacted]% of rad-axSpA patients in the database were currently receiving, or had been receiving prior to discontinuation, secukinumab at a dose of 300 mg either weekly ([redacted]%) or monthly ([redacted]%). It was further identified that a proportion of patients ([redacted]%) had been initiated on the 300 mg dose for the loading dose phase of treatment. • Given that a substantial proportion of patients are treated with the 300 mg dose of secukinumab in UK clinical practice, a scenario analysis was conducted to demonstrate the impact of the 300 mg secukinumab dose on the likely costs to the NHS (see Issue 3, Part C).

ERG comment	The company has updated the nr-axSpA population NMAs presented in the original CS. The ERG considers that the methods used to conduct the original and updated NMAs were appropriate. However, the ERG does not consider that the company's conclusion that "…the results found no statistically significant difference between ixekizumab and secukinumab for any of the outcomes assessed" is supported by the results from the updated NMAs. Relative treatment effects for ixekizumab versus secukinumab are not provided. It is possible to informally compare the absolute effect estimates for each treatment, and also to compare the relative effect estimates for ixekizumab versus placebo, and secukinumab versus placebo, but it is not possible to formally compare ixekizumab and secukinumab using the presented results. The ERG therefore does not consider that the assumption of a class effect between IL-17 inhibitors is well supported by the evidence provided. As stated in the ERG's response to Issue 1, assuming efficacy results from a trial recruiting nr-axSpA patients can be replicated in a rad-axSpA population without adjustment for patient characteristics is unreliable, and so results from any NMA where this assumption is made without appropriate adjustment is also unreliable.
Issue 3: Limitations in the network meta-analysis	
a) Is it reasonable to assume equal efficacy across all TNF-alpha inhibitors in rad-axSpa biologic naïve patients? If so, should the same assumption be applied in all other subgroups?	• The Company consider it reasonable to assume equal efficacy across all TNF-alpha inhibitors within the rad-axSpA biologic-naïve population given their same mechanism of action within the pathophysiology of axSpA, and further that this assumption may be applied within rad-axSpA biologic-experienced and nr-axSpA biologic-naive and -experienced subgroups. • Molecular and immunologic research has repeatedly supported the key role of cytokine dysregulation in the pathophysiology of axSpA. Studies show that patients with axSpA demonstrate overexpression of TNF-alpha in the sacroiliac joints and high levels of circulating soluble TNF receptors. This, combined with the significant improvements in axSpA symptoms following treatment with TNF-alpha inhibitors, implicates this cytokine as a key driver in the pathophysiology of the disease. Whilst minor differences in pharmacological properties between TNF-alpha inhibitors exist, which may influence the pharmacokinetics of each drug in the body, in clinical practice, selection of TNF-alpha inhibitor is not driven by differences in relief of axSpA symptoms, but rather the effects these differences have on comorbidities to axSpA, such as psoriasis, or factors including the patient's preferred mode of administration or desire to bear children.[31, 32] Accordingly, the common mechanism of these therapies, neutralisation of soluble TNF-alpha, may be considered to explain the class effect results observed statistically for key clinical outcomes in axSpA.

	• In addition to the clinical validity of a class effect across treatments with the same mechanism of action, no significant differences were identified between TNF-alpha inhibitors in either the NMAs presented in the original Company submission nor the updated NMA to include secukinumab as a comparator in the nr-axSpA population using data from the PREVENT trial (see response to Issue 2 and Table 10 and Table 11 below). • The Company are therefore aligned with the assertion made by the Technical Team (Technical Report, page 28) that combined with a biologic rationale, a lack of statistically significant difference between treatments provides reasonable grounds to assume a class effect among TNF-alpha inhibitors in the rad-axSpA biologic-naïve population. This is in line with the conclusion of the Committee in TA383 final appraisal determination (FAD) that "*given the lack of difference in effect between [the TNF-alpha inhibitors], they should be considered as a class with broadly similar, even if not completely identical, effects*."[8] The Company are of the view that this assumption can be generalised to the rad-axSpA biologic-experienced population; whilst the evidence presented in response to Issue 1 illustrates that prior biologic experience represents a treatment effect modifier, the Company deem it reasonable to assume that a reduction in treatment effect between naïve and experienced patients would apply in a similar manner across TNF-alpha inhibitors. As described in response to Part B of Issue 1, it was concluded by the Assessment Group in TA383 that a decrease in response rates over sequential lines of TNF-alpha inhibitor therapy as a class takes place in clinical practice, which is supported by evidence from a UK-based study in which mean drug survival was substantially shorter for the second TNF-alpha inhibitor as compared with the first.[4, 8] • For these reasons, the Company consider the assumption of a class effect amongst TNF-alpha inhibitors to be reasonable. However, as described further in response to Part C of this question, the Company consider it reasonable to extend this class effect assumption to all biologics. • Furthermore, as described in response to Issue 1, Part B, based on the underlying pathophysiology of each disease subtype, the Company consider it reasonable to assume that the assumption of class effects among TNF-alpha inhibitors may plausibly be applied *within* the other subpopulations of relevance to this appraisal.
b) Is it reasonable to assume equal efficacy across all IL-17-1A inhibitors in rad-axSpa biologic naïve patients? If so, should the same assumption be applied in all other subgroups?	• As above, the Company consider it reasonable to assume equal efficacy across IL-17A inhibitors in the rad-axSpA biologic-naïve population, given their same mechanism of action, and further that this assumption can be applied within the rad-axSpA biologic-experienced and nr-axSpA subgroups. • As described in response to Part A, cytokine dysregulation has been shown to be a major driver of pathophysiology in axSpA, and this extends to the IL-17 cytokine pathway.[33] In healthy individuals, the IL-17 superfamily of cytokines (IL-17A–IL-17F) functions in host defence against a range of bacterial and fungal pathogens. IL-17-A has been implicated in the pathophysiology of axSpA and other inflammatory diseases through *in vitro* and animal

	studies, with this role substantiated by high response rates to IL-17A inhibitors in clinical trials.[34] Whilst clinicians have not yet had the opportunity to prescribe both secukinumab and ixekizumab in routine clinical practice in axSpA, both treatments selectively neutralise IL-17A, and it is therefore reasonable to assume that they would result in similar relief of axSpA symptoms. Accordingly, it is deemed clinically reasonable that a class effect should exist in axSpA among IL-17A inhibitors. • The results of the NMA incorporating the PREVENT study (presented in response to Issue 2) identified no statistically significant differences between ixekizumab and secukinumab for any of the outcomes assessed (BASDAI50, BASDAI cfb, BASFI cfb and ASAS40). • As described in response to Issue 1, Part B, based on the underlying pathophysiology of each disease subtype, it is considered that class effects observed within the nr-axSpA population may be considered to similarly exist within the rad-axSpA (biologic-naive and -experienced) populations. • For these reasons, the Company consider the assumption of a class effect of IL-17A inhibitors to be reasonable. However, as described further in response to Part C of this question, the Company consider it reasonable to extend this class effect assumption to all biologics.
c) Is it reasonable to assume equal efficacy across all comparators and in all populations given the limited evidence to demonstrate that ixekizumab is more or less effective than other currently available treatments?	• The Company consider it reasonable to assume equal efficacy across all biologics in the rad-axSpA biologic-naïve population and further that this assumption can be applied within rad-axSpA biologic-experienced and nr-axSpA biologic-naive and -experienced subgroups. • As described in response to Parts A and B, evidence demonstrates that the pathophysiology of axSpA is strongly driven by dysregulation of inflammatory cytokines, in which TNF-alpha and IL-17 play key roles. • The results of the NMA incorporating the PREVENT study (presented in response to Issue 2) identified no evidence for differences between TNF-alpha inhibitors and IL-17A inhibitors for any of the outcomes assessed. This finding is in alignment with the conclusion of the NICE Committee in the appraisal of secukinumab (TA407) that "*secukinumab has a similar efficacy to the TNF-alpha inhibitors*".[6] • The Company note that the class effects analysis suggested by the NICE Technical Team comprising TNF-alpha inhibitors versus IL-17A inhibitors versus placebo, and any subsequent cost-effectiveness analyses, could not be performed in the rad- or nr-axSpA populations. This is due to the fact that to synthesise an input for the TNF-alpha inhibitor group in such an analysis for the populations of interest (biologic-experienced rad-axSpA and biologic-naïve nr-axSpA), data from trials including unclear or mixed populations (i.e. those originally informing the sensitivity analysis NMAs) would need to be utilised. Given the clinical and statistical implausibility of assuming

	generalisability of efficacy for biologics across biologic-naïve and biologic-experienced patient populations (as discussed further in response to Issue 1, Part B), it was deemed this approach was unsuitable. • Therefore, the Company present cost-effectiveness analysis in which a class effect across all biologics is assumed in the rad-axSpA biologic-experienced and nr-axSpA biologic-naïve populations only. The biologic-experienced population has been selected on the basis of the response to Issue 1, Part A, that ixekizumab would primarily be used after TNF-alpha inhibitors have been attempted, whilst the biologic-naïve nr-axSpA population has been selected in lieu of biologic-experienced data in this population (where ixekizumab is anticipated to be used), but with the assumption made that a class effects analysis would apply in a nr-axSpA biologic-experienced population (as discussed above). This analysis was implemented by assuming efficacy for all biologics is equal to the efficacy of ixekizumab in the COAST-W and -X trials for the rad-axSpA biologic-experienced and nr-axSpA biologic-naïve populations, respectively, for three efficacy inputs informing the model (BASDAI50, BASDAI cfb and BASFI cfb). Data from the COAST trials represent the most appropriate inputs for use, given that they are derived from well-powered, internally valid clinical trials and therefore remove the uncertainty associated with the NMA (see Issue 2 for further discussion). Economic analysis results produced following implementation of these relative efficacy estimates are presented for the rad-axSpA biologic-experienced and nr-axSpA biologic-naïve populations in Table 14 and Table 16, respectively. • The results of these analyses show that in the rad-axSpA population, over a lifetime horizon, ixekizumab is associated with either a comparable or less expensive total cost compared to five of the six biologic treatments recommended by NICE for these patients: certolizumab pegol, etanercept, secukinumab 150 mg (N.B. it was not possible to consider the confidential PAS in the analysis), golimumab and infliximab. These results support the positioning of ixekizumab after NSAIDs and at least two prior bDMARDs in rad-axSpA patients. Furthermore, a freedom of information request by the Company to determine the current biologic use in rad-axSpA patients in hospitals in the UK between June and August 2020 identified that a higher proportion of patients were receiving one of these five biologics that are comparable or more expensive than ixekizumab (combined 55.9%) than those who were receiving adalimumab (31.6%). This real world evidence reinforces that ixekizumab represents a cost-effective use of NHS resources in the rad-axSpA population. • An additional analysis is presented in Table 15 including the 300 mg dose of secukinumab (without confidential PAS), which, as noted in the response to Issue 2, is being prescribed frequently in clinical practice. The results show ixekizumab results in less expensive overall costs compared to secukinumab 300 mg.

	• In the nr-axSpA population, ixekizumab is associated with fewer total costs than three of the four relevant comparators, certolizumab pegol, etanercept and golimumab, which supports the positioning of ixekizumab after NSAIDs and at least one biologic in the nr-axSpA population.
ERG comment	3a. The company has not provided relative treatment effects for comparisons between TNF-alpha inhibitors either in the original CS or their technical response. It is, therefore, not possible for the ERG to comment on the validity of the following company statement: "No significant differences were identified between TNF-alpha inhibitors in either the NMAs presented in the original Company Submission nor the updated NMA to include secukinumab as a comparator in the nr-axSpA population using data from the PREVENT trial". 3b. The company has not provided relative treatment effects for comparisons between ixekizumab and secukinumab from the updated NMAs (incorporating the PREVENT study). It is, therefore, not possible for the ERG to comment on the validity of the following statement: "The results of the NMA incorporating the PREVENT study (presented in response to Issue 2) identified no statistically significant differences between ixekizumab and secukinumab for any of the outcomes assessed (BASDAI50, BASDAI cfb, BASFI cfb and ASAS40)." 3c. The company has not provided relative treatment effects for comparisons between IL-17 inhibitors and TNF-alpha inhibitors from the updated NMAs (incorporating the PREVENT study). It is, therefore, not possible for the ERG to comment on the validity of the following statement: "The results of the NMA incorporating the PREVENT study (presented in response to Issue 2) identified no evidence for differences between TNF-alpha inhibitors and IL-17A inhibitors for any of the outcomes assessed". It is possible to informally compare the absolute effect estimates for each comparator, and also to consider relative effect estimates for each comparator versus placebo, but it is not possible to formally compare the effectiveness of different TNF-alpha inhibitors or compare the effectiveness of different IL-17 inhibitors or compare the effectiveness of TNF-alpha inhibitors versus IL-17 inhibitors using the presented results. The ERG does not therefore consider that the assumption of a class effect between TNF-alpha inhibitors, or between IL-17 inhibitors, or across both TNF-alpha inhibitors and IL-17 inhibitors is well supported by the presented evidence.
Issue 4: Long-term effectiveness of ixekizumab	
a) Can the company supply the results of the COAST-Y study?	The COAST-Y study is an ongoing, multicentre, Phase 3, long-term extension study of 104 week to evaluate the maintenance of treatment effect of ixekizumab in patients with axial spondyloarthritis. COAST-Y provides patients with an opportunity to continue ixekizumab treatment for up to 2 additional years. COAST-Y includes patients who completed any of the originating studies of COAST-V, -X and -W.[35, 36]

At present, data are available for patients who have received treatment with ixekizumab Q4W from Week 0 of the originating studies through Week 64 of COAST-Y (totalling 116 weeks of continuous ixekizumab treatment). Results are provided below for ASAS40, BASDAI50 and change from baseline in BASDAI and BASFI. Overall, the results support that the treatment effect of ixekizumab observed at Week 16 is maintained or improved for at least 116 weeks.

ASAS40 response at Week 64 of COAST-Y

ASAS40 responses for patients treated with ixekizumab 80 mg Q4W at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y are presented in Table 2. With ixekizumab 80 mg Q4W treatment, ASAS40 responses were maintained or increased from Week 16 to Week 116 of continuous ixekizumab treatment.

Table 2: ASAS40 response (observed) at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y (Week 116 of ixekizumab 80 mg Q4W treatment)

Timepoint (duration of ixekizumab treatment)	N	n (%)
Week 16	157	64 (40.8)
Week 52	156	82 (52.6)
Week 116	[redacted]	[redacted]

BASDAI50 response at Week 64 of COAST-Y

BASDAI50 responses for patients treated with ixekizumab 80 mg Q4W at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y are presented in Table 3. With ixekizumab 80 mg Q4W treatment, BASDAI50 responses were maintained or increased from Week 16 to Week 116 of continuous ixekizumab treatment.

Table 3: BASDAI50 response (observed) at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y (Week 116 of ixekizumab 80 mg Q4W treatment)

Timepoint (duration of ixekizumab treatment)	N	n (%)
Week 16	157	58 (36.9)
Week 52	156	78 (50.0)
Week 116	[redacted]	[redacted]

BASDAI change from baseline at Week 64 of COAST-Y

Change from baseline in BASDAI score for patients treated with ixekizumab 80 mg Q4W at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y are presented in Table 4. With ixekizumab 80 mg Q4W treatment, changes from baseline were maintained or improved from Week 16 to Week 116 of continuous ixekizumab treatment.

Table 4: BASDAI change from baseline (observed) at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y (Week 116 of ixekizumab 80 mg Q4W treatment)

Timepoint (duration of ixekizumab treatment)	N	Mean (SD)
Week 16	157	–2.8 (2.1)
Week 52	156	–3.4 (2.2)
Week 116	[redacted]	[redacted]

BASFI change from baseline at Week 64 of COAST-Y

Change from baseline in BASFI score for patients treated with ixekizumab 80 mg Q4W at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y are presented in Table 5. With ixekizumab 80 mg Q4W treatment, changes from baseline were maintained or improved from Week 16 to Week 116 of continuous ixekizumab treatment.

Table 5: BASFI change from baseline (observed) at Weeks 16 and 52 of the originating studies, and Week 64 of COAST-Y (Week 116 of ixekizumab 80 mg Q4W treatment)

Timepoint (duration of ixekizumab treatment)	N	Mean (SD)
Week 16	157	–2.2 (2.2)
Week 52	156	–2.9 (2.3)
Week 116	[redacted]	–[redacted]

b) Can the company comment on the extent to which the currently available evidence supports the projected estimates of long-term treatment effects derived from the economic model?

As described in response to part a, the COAST-Y study includes patients derived from the three originating COAST studies, -V, -W and -X. Accordingly, since the COAST-Y data cover patients from across the spectrum of axSpA patients from these studies, and the cost-effectiveness models have been developed to focus on individual patient populations by disease subtype and prior biologic exposure, any conclusions drawn from a comparison between the COAST-Y data and the cost-effectiveness models must be interpreted with caution. Similarly, it should be considered that the model considers that only responders continue treatment, whereas

COAST-Y data is derived from responders and non-responders to ixekizumab treatment. It may nevertheless be useful to examine the general trend of the treatment effect estimates across the two sources, rather than precise numerical differences.

Long-term projections of BASDAI and BASFI may be extracted from the model in which BASFI scores change over time but responders to treatment are assumed to maintain their BASDAI score, which is based on the Week 16 data, over time. A comparison of long-term model outcomes in 16-week increments between Week 52 and 116 are presented in Table 6 and Table 7 in order to allow observation of the trend in results for BASDAI cfb and BASFI cfb, respectively.

The COAST-Y results show that the benefits to patients in terms of disease activity and function are consistently maintained up to Week 116. This maintenance of response aligns with the trend observed in the two sets of model predictions for biologic-experienced rad-axSpA patients and biologic-naïve nr-axSpA patients, although for the reasons discussed above, the values presented are illustrative only.

Table 6. BASDAI change from baseline (observed) in COAST-Y vs model predictions

Timepoint (duration of ixekizumab treatment)	COAST-Y Mean (SD)	Model prediction	
		Biologic-experienced rad-axSpA (IXE responders)	Biologic-naive nr-axSpA (IXE responders)
Week 52, cycle 12	–2.8 (2.1)	–4.89	–4.27
Week 68, cycle 17	[redacted]	–4.89	–4.27
Week 84, cycle 21	[redacted]	–4.89	–4.27
Week 100, cycle 25	[redacted]	–4.89	–4.27
Week 116, cycle 29	[redacted]	–4.89	–4.27

Abbreviations: BASDAI: Bath AS Disease Activity Index; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; rad-axSpA: radiographic axial spondyloarthritis; SD: standard deviation.

Table 7. BASFI change from baseline (observed) in COAST-Y vs model predictions

Timepoint (duration of ixekizumab treatment)	COAST-Y Mean (SD)	Model prediction	
		Biologic-experienced rad-axSpA (IXE responders)	Biologic-naive nr-axSpA (IXE responders)
Week 52, cycle 12	–2.9 (2.3)	–3.68	–3.84
Week 68, cycle 17	[redacted]	–3.67	–3.84
Week 84, cycle 21	[redacted]	–3.66	–3.83
Week 100, cycle 25	[redacted]	–3.64	–3.82
Week 116, cycle 29	[redacted]	–3.63	–3.82

Abbreviations: BASFI: Bath Ankylosing Spondylitis Functional Index; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; rad-axSpA: radiographic axial spondyloarthritis; SD: standard deviation.

ERG comment	The data presented by the company suggest that the efficacy of ixekizumab at Week 52 is maintained up to Week 116. However, this period is only approximately 5% of the model time horizon (40 years).
Issue 5: Modelling of BASFI scores after treatment discontinuation	
a) When treatment is discontinued, is it reasonable to assume that patients return to their baseline level of function?	• The Company are aligned with the technical team on this issue and consider it reasonable to assume that patients return to their baseline level of function, as measured by BASFI score, following treatment discontinuation. • As noted by the Technical Team, this is in alignment with clinical expert opinion provided during TA383 that following treatment discontinuation, patients would not be expected to deteriorate to a functional level more severe than that experienced prior to commencing biologic treatment. • An equivalent assumption was similarly adopted in the manufacturer's model in TA407, which evaluated secukinumab in ankylosing spondylitis (the assumption was not discussed by the Committee in this appraisal).[6]
ERG comment	No comment
Issue 6: Choice of utility regression equation	

a) What are the results of the utilities scenario analysis (company scenarios 3a-d) when tested in the new population/class scenario analyses requested by the technical team in issues 3?	• The Company explored the utilities scenario analyses (scenarios 3a–d in the original company submission) when the full biologics class effects analysis described in Issue 3 (Part C) is implemented. • For illustrative purposes, the results for one of these scenarios (scenario 3c in the original submission in which utility values are sourced from Wailoo *et al* [2015]), are presented for the rad-axSpA biologic experienced and nr-axSpA biologic naïve populations in Table 17 and Table 18, respectively. As shown, the results found the incremental QALYs to remain identical across all interventions when a class effect is assumed. • As described in Section B.3.4.5 of Document B of the original company submission, the health state utility of patients within the model is calculated using an algorithm which produces a relationship between disease activity and function, as measured by BASDAI and BAFSI scores change, and expected patient quality of life as an EQ-5D-3L score, incorporating a number of covariates including gender, race and disease duration. Due to these covariates, the relationship between efficacy and HRQoL (and therefore utility values implemented in the model) is not mathematically linear, but these scenario analyses show it to be close enough to linear as to be functionally a linear relationship. Therefore, an assumption of equal efficacy across all biologics results in the same expected quality of life for all patients within the model, and thus identical incremental QALYs. • Therefore, assumption of a class effect removes the relevance of these utility scenarios from further discussion.
ERG comment	No comment
Issue 7: Company's cost effectiveness scenario for patients with nr-axSpA that have had prior exposure to biologic treatments	
a) Can the company clarify how it calculated the modification factor used in its scenario analysis for the biologic-experienced nr-axSpA population?	• In the absence of data for the efficacy of ixekizumab in the biologic-experienced nr-axSpA population, a modification factor was derived in order to estimate this efficacy value from the available data from the biologic-naïve nr-axSpA population in the COAST-X trial. The use of a modification factor to estimate the efficacy of ixekizumab was based on the premise described in response to Issue 1: that prior biologic use has a significant impact on treatment efficacy, where disease subtype differences do not. • The BASDAI50 results at Week 16 for ixekizumab were compared between the biologic-naïve (COAST-V: 42.0%) and biologic-experienced (COAST-W: [redacted]) rad-axSpA patients to produce a modification factor associated with prior biologic use of [redacted]. This factor was applied to the BASDAI50 result at Week 16 for ixekizumab in the biologic-naïve nr-axSpA population (COAST-X: [redacted]) to produce an estimated efficacy of ixekizumab in the biologic-experienced nr-axSpA population of [redacted].

ERG comment	Thank you for the information. See ERG response to Issue 1.

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Appendix

Issue 1

Table 8: Number of prior biologics received by patients on any biologics and received by patients on secukinumab, derived from real-world evidence from patients in current UK clinical practice and collected as part of the Disease Specific Programmes of Adelphi Real World

Number of prior biologics	axSpA patients on any biologic, n (%) [N=[redacted]][b]	axSpA patients on secukinumab, n (%) [a] [N=[redacted]][c]
0 (first line)	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]

Data are derived from real-world evidence
[a] Includes patients who are currently receiving secukinumab and those who have previously received and discontinued from secukinumab. Number of prior biologics received at the time of secukinumab commencement is presented.
[b] Adelphi DSP IV: Patient Record Form, Completion July–December 2018
[c] Adelphi DSP Plus: Patient Record Form, Completion April–August 2019
Abbreviations: axSpA: axial spondyloarthritis.

Table 9: Proportion of patients in the key clinical trials of ixekizumab and its relevant comparators in the rad-axSpA population

Characteristic at baseline	COAST-V and COAST-W, pooled			MEASURE 2		MEASURE 4	
	IXE Q2W	IXE Q4W	PBO	SEC 150 mg	PBO	SEC 150 mg	PBO
Biologic-naïve, n (%)	[redacted]	[redacted]	[redacted]	44 (61)	45 (61)	85 (73)	83 (71)
Biologic experienced, n (%)	[redacted]	[redacted]	[redacted]	28 (39)	29 (39)	31 (27)	34 (29)
≥1 prior TNF-alpha inhibitor	[redacted]	[redacted]	[redacted]	28 (39)	29 (39)	31 (27)	34 (29)
≥2 prior TNF-alpha inhibitor	[redacted]	[redacted]	[redacted]	0 (0)	0 (0)	0 (0)	0 (0)
Time since diagnosis, years (SD)	[redacted]	[redacted]	[redacted]	7.0 + 8.2	6.4 + 8.9	8.4 + 10.84	7.1 + 9.23
Mean time since symptom onset, years (SD)	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR

Abbreviations: IXE: ixekizumab; NR: not reported; PBO: placebo; Q2W: every two weeks; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SD: standard deviation; SEC: secukinumab; TNF: tumour necrosis factor.

Table 10: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (binary endpoints) or MDs (continuous endpoints) (with 95% CrI) versus placebo at Week 12–18 in the nr-axSpA population following inclusion of the PREVENT trial in the NMAs, fixed-effect model (base case analysis)

Intervention	ASAS40			BASDAI50			BASDAI cfb			BASFI cfb		
	OR	95% CrI Lower limit	95% CrI Upper limit	OR	95% CrI Lower limit	95% CrI Upper limit	MD	95% CrI Lower limit	95% CrI Upper limit	MD	95% CrI Lower limit	95% CrI Upper limit
IXE (pooled LD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
ETN 50 mg QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
SEC 150 mg	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC	NC	NC	NC

Abbreviations: ADA: adalimumab; ASAS: Assessment of SpondyloArthritis International Society; BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; MD: median difference; NC: not calculable; NMA: network meta-analysis; nr-ax-SpA: non-radiographic axial spondyloarthritis; NRI: non-responder imputation; OR: odds ratio; Q4W: every four weeks; QW: weekly.

Table 11: Median posterior outcomes (with 95% CrI) at Week 12–18 in the nr-axSpA population following inclusion of the PREVENT trial in the NMAs, fixed-effect model (base case analysis)

Intervention	ASAS40			BASDAI50			BASDAI cfb			BASFI cfb		
	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
ETN 50 mg QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
SEC 150 mg	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC	NC	NC	NC

Table 12: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (binary endpoints) or MDs (continuous endpoints) (with 95% CrI) versus placebo at Week 12–18 in the nr-axSpA population following inclusion of the PREVENT trial in the NMAs, fixed-effect model (sensitivity analysis)

Intervention	ASAS40			BASDAI50			BASDAI cfb			BASFI cfb		
	OR	95% CrI Lower limit	95% CrI Upper limit	OR	95% CrI Lower limit	95% CrI Upper limit	MD	95% CrI Lower limit	95% CrI Upper limit	MD	95% CrI Lower limit	95% CrI Upper limit
IXE (pooled LD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
CZP pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 50 mg QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
SEC 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For completeness, these results are presented to supplement the base case NMA results in Table 10 to enable comparison for a greater number of outcomes. However, the Company acknowledge the SA is associated with limitations, as highlighted previously by the ERG.
Abbreviations: ADA: adalimumab; ASAS: Assessment of SpondyloArthritis International Society; BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; MD: median difference; NC: not calculable; NMA: network meta-analysis; nr-ax-SpA: non-radiographic axial spondyloarthritis; NRI: non-responder imputation; OR: odds ratio; Q4W: every four weeks; QW: weekly.

Table 13: Median posterior outcomes (with 95% CrI) at Week 12–18 in the nr-axSpA population following inclusion of the PREVENT trial in the NMAs, fixed-effect model (sensitivity analysis)

Intervention	ASAS40			BASDAI50			BASDAI cfb			BASFI cfb		
	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit	Median posterior outcome	95% CrI Lower limit	95% CrI Upper limit
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
CZP pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 50 mg QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NC	NC	NC	NC	NC	NC
SEC 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For completeness, these results are presented to supplement the base case NMA results in Table 11 to enable comparison for a greater number of outcomes. However, the Company acknowledge the SA is associated with limitations, as highlighted previously by the ERG.
Abbreviations: ADA: adalimumab; ASAS: Assessment of SpondyloArthritis International Society; BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CI: credible interval; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; MD: median difference; NC: not calculable; NMA: network meta-analysis; nr-ax-SpA: non-radiographic axial spondyloarthritis; NRI: non-responder imputation; OR: odds ratio; Q4W: every four weeks; QW: weekly.

Issue 3

Table 14: Economic analysis results with assumed class effects: biologic-experienced rad-axSpA (with ixekizumab PAS)

Technologies	Rad-axSpA biologic-experienced	
	Total costs (£)	Incremental costs (£)
Adalimumab	[redacted]	-
Conventional care	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]
Etanercept 25/50 mg	[redacted]	[redacted]
Ixekizumab Q4W	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]

Abbreviations: nr-axSpA: non-radiographic axial spondyloarthritis; PAS: patient access scheme; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.

Table 15: Economic analysis results with assumed class effects: biologic-experienced rad-axSpA (with ixekizumab PAS)

Technologies	Rad-axSpA biologic-experienced	
	Total costs (£)	Incremental costs (£)
Adalimumab	[redacted]	-
Conventional care	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]
Etanercept 25/50 mg	[redacted]	[redacted]

Technologies	Rad-axSpA biologic-experienced	
	Total costs (£)	Incremental costs (£)
Ixekizumab Q4W	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]

Abbreviations: nr-axSpA: non-radiographic axial spondyloarthritis; PAS: patient access scheme; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.

Table 16: Economic analysis results with assumed class effects: biologic-naive nr-axSpA (with ixekizumab PAS)

Technologies	Nr-axSpA biologic-naïve	
	Total costs (£)	Incremental costs (£)
Conventional care	[redacted]	-
Adalimumab	[redacted]	[redacted]
Ixekizumab Q4W	[redacted]	[redacted]
Etanercept 25/50 mg	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]

Abbreviations: nr-axSpA: non-radiographic axial spondyloarthritis; PAS: patient access scheme; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis.

Issue 6

Table 17: Scenario analyses in the biologic-experienced rad-axSpA population with utility values sourced from Wailoo *et al* (2015)[37] in the original company submission and updated to consider the results of the all-biologics class effect assumption presented in Technical Engagement Issue 3c

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Adalimumab	[redacted]	[redacted]	-	-	-
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab

Etanercept 25/50 mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Ixekizumab Q4W	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab

Pairwise comparisons for ixekizumab Q4W versus each comparator are presented. *Indicates ICERs in the south-west quadrant of the cost-effectiveness plane.
Abbreviations: ICER: incremental cost-effectiveness ratio; NC: not calculated; QALYs: quality-adjusted life years; rad-ax-SpA: radiographic axial spondyloarthritis.

Table 18: Scenario analyses in the biologic-naïve nr-axSpA population with utility values sourced from Wailoo *et al* (2015)[37] in the original company submission and updated to consider the results of the all-biologics class effect assumption presented in Technical Engagement Issue 3c

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional care	[redacted]	[redacted]	-	-	-
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£1,955
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Etanercept 25/50 mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by adalimumab

Pairwise comparisons for ixekizumab Q4W versus each comparator are presented. *Indicates ICERs in the south-west quadrant of the cost-effectiveness plane.
Abbreviations: ICER: incremental cost-effectiveness ratio; NC: not calculated; QALYs: quality-adjusted life years.