NICE National Institute for Health and Care Excellence

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Ixekizumab for treating axial spondyloarthritis after nonsteroidal anti-inflammatory drugs

Lead team presentation

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Key issues: clinical effectiveness

- All things being equal, would a TNF inhibitor usually be the first choice of biologic?
- Where might an IL-17A be used in preference to a TNF inhibitor?
- What is the committee's view on the available results from the COAST trials?
- Are treatment outcomes generalisable between the radiographic and non-radiographic axial spondyloarthritis populations, or could they be different based on differing diagnostic criteria?
- Is it reasonable to assume a class effect:
  - for the TNF inhibitors?
  - for the IL-17A-inhibitors ixekizumab and secukinumab?
  - across all biologic treatments i.e. do all TNF and IL-17A inhibitors have equivalent effectiveness?

Axial Spondyloarthritis (axSpA)

- Chronic rheumatic condition; inflammation of sacroiliac joint and spine which can lead to dysregulation of bone maintenance and structural/functional changes.
- AxSpA is an umbrella term which traditionally includes two distinct populations:
  - Radiographic (rad-axSpA) (also known as ankylosing spondylitis) where inflammatory changes in the sacroiliac joints or spine can be determined on X-ray
  - Non-radiographic (nr-axSpA) with absence of visible structural damage on X-ray, although inflammation may be observed on MRI although not required for diagnosis
- Recent clinical viewpoint may be moving towards classifying axSpA on a continuous disease spectrum with rad and nr sub types driven by the same underlying pathophysiology
- The tumor necrosis factor (TNF)-alpha and interleukin (IL)-17 cytokine families play a key role in symptom production and are important therapeutic targets
- Common symptoms include chronic back pain, stiffness, fatigue, sleep disturbance. Joint and tendon pain, stiffness, arthritis and swelling of the fingers are also common.
- Prevalence of axSpA is uncertain, but it is estimated around 62,650 people live with nr-axSpA and 100,815 with rad-axSpA in England
- No cure, treatment aims to relieve pain and stiffness, prevent joint and organ damage and preserve joint function and mobility

Ixekizumab (Taltz, Eli Lily)

- Humanised monoclonal antibody which selectively binds IL-17A and inhibits the release of pro-inflammatory cytokines, chemokines and prostaglandins responsible for the clinical symptoms of axSpA

Marketing authorisation	Treatment of adults with rad-axSpA who have responded inadequately to conventional therapy Treatment of adults with active nr-axSpA with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have not responded to nonsteroidal anti-inflammatory drugs (NSAIDs)
Administration and dosage	160mg by subcutaneous (SC) injection: (2 x 80mg) at week 0, followed by 80mg maintenance SC dose every 4 weeks Consider discontinuation for non responders after 16 to 20 weeks. Some partial responders may improve with treatment beyond 20 weeks
Price	Confidential PAS discount agreed with NHSE. List price: £1,125 per 80mg/ml pre-filled pen; per annum cost £16,875 (year 1), £14,625 (year 2)

Treatment pathway

NICE guideline 65 spondylarthritis in over 16s: diagnosis and management

Non–radiographic **axSpA**

Offer physical therapy

↓

Non steroidal anti-inflammatory drugs (NSAIDS)

↓

TNF-α inhibitors
adalimumab TA 383
certolizumab pegol TA383
etanercept TA383
golimumab TA497
Stopping rule at 12 weeks
Ixekizumab/Secukinumab?

↓

Repeat with another TNF-α inhibitor (if disease has not responded, stops responding or if first TNF-α inhibitor not tolerated (TA383))
Ixekizumab/Secukinumab?

Radiographic **axSpA**

Non-pharmacological interventions (exercise and physiotherapy)

↓

Inadequate response or intolerance to NSAIDs

↓

TNF-α inhibitors
adalimumab TA383
certolizumab pegol TA383
etanercept TA383
golimumab TA383
Infliximab (if treatment is started with least expensive infliximab product) TA383
Secukinumab TA407 Ixekizumab?

↓ Inadequate response or intolerance

Repeat with another TNF-α inhibitor (if disease has not responded, stops responding or if first TNF-α inhibitor not tolerated (TA383)
Secukinumab TA407 Ixekizumab?

Decision problem

	NICE scope
Population	People with axSpA for whom NSAIDs or TNF-alpha inhibitors have been inadequately effective or not tolerated, or are contraindicated
Comparators	**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
Outcomes	Disease activity, functional capacity; disease progression; pain; peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis); symptoms of extra-articular manifestations; adverse effects of treatment; health-related quality of life

Patient and carer perspectives

- AxSpA is a painful and debilitating condition, characterised by periods of fluctuating intensity, leading to slowly increasing spinal and peripheral joint damage
- Up to 25% of people with axSpA eventually develop complete fusion of the spine which leads to substantial disability and restriction
- Symptoms usually begin in adolescence or early adulthood, a critical period in terms of education, work and establishment of social frameworks and relationships. Can lead to social isolation at a young age if left untreated. Symptoms often present for 7-10 years before diagnosis is made
- Most people with axSpA live a normal lifespan but can be at increased risk of premature death from cardiovascular disease
- The disease burden of AxSpA is variable, many people live active and rewarding lives, others experience progressive spinal pain, immobility and functional impairment
- More than 50% of people have work instability. Consequences include loss of earnings and loss of self-esteem. Average age of diagnosis is 24, a prime time for establishing a career
- Many experience depression, fatigue and poor sleep during their lives, all of which exert a profound influence on quality of life

Patient and carer perspectives

- National Axial Spondyloarthritis Society conducted a survey in 2019 of people with axSpA and their carers, 330 responses received, showing a high unmet clinical need
- 55% believed that current treatments are not sufficient:
  - For some individuals, no medication developed so far has been effective
  - Some patients cannot tolerate current treatments due to underlying conditions
  - Efficacy of treatment can wear off over time
  - Worries about possible side effects
  - Concerns for patients with severe disease who do not meet criteria for biologic therapy
- Vast majority surveyed (88%) would like ixekizumab made available, particularly for nr-axSpA
- Currently the only biologic drugs available for nr-axSpA are TNFis. Patients with nr-axSpA who have not responded to TNFis could potentially benefit from ixekizumab
- Ixekizumab works differently to TNFis and could be hugely beneficial to new group of patients. Ixekizumab provides an additional IL17-a inhibitor for rad-axSpA.

Clinical outcomes

- The Assessment of Spondyloarthritis International Society (ASAS) response criteria is a clinical tool to assess and monitor axSpA, which contains 4 domains:
  - Disease activity (visual analogue scale)
  - Spinal pain (visual analogue scale)
  - Physical function (0-100) on Bath Ankylosing Spondylitis Functional Index (BASFI)
  - Inflammation using items 5 & 6 on Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- ASAS40 response (primary trial outcome) defined as improvement from baseline of ≥ 40% and absolute improvement from baseline of ≥ 2 units in at least 3 domains without worsening in remaining domains Primary trial outcome
- Efficacy outcomes used in the company's economic analysis are secondary trial outcomes:
  - BASDAI 50 response, classified as 50% improvement in BASDAI score across 10 items (8 items relating to functional anatomy, 2 items assessing patients' ability to cope) and BASDAI change from baseline
  - BASFI change from baseline

Primary clinical evidence: COAST trials

	COAST–V	COAST–W	COAST–X
Design	Double blind, Phase 3 RCT. Multicentre (North & South America, Europe, Asia)		
Population (all ITT)	• N=341 • **Rad-axSpA** • No response/ intolerance NSAIDs • **No prior TNF**	• N=316 • **Rad-axSpA** • No response/ intolerance to NSAIDs • **Prior TNF**	• N=303 • **Nr-axSpA** • No response/ intolerance NSAIDs • **No prior TNF***
Intervention	Ixekizumab[1]	Ixekizumab[1]	Ixekizumab[1]
Comparator	Placebo, Adalimumab	Placebo	Placebo
Outcomes	Primary: Proportion achieving ASAS40 response at week 16 Secondary: BASDAI50; BASDAI & BASFI change from baseline at week 16 COAST-V and COAST-W: comparator arms randomised to IXE after week-16, no longer term data Long term: ASAS40 response at week 52 (COAST-X only[3])		

1: Four treatment arms with alternative dose/regimens:

- Loading dose (LD) 80mg, then 80mg 2 weekly; LD 80mg, then 80mg 4 weekly; LD 160mg, then 80mg 2-weekly; **LD 160mg, then 80mg once every 4 weeks (licensed dose/regimen)**

***No trial data on second line use in Non-R**

NICE

COAST RCTs: ASAS40 response at week 16 compared with placebo

Intervention, dosing schedule	n	Response, n (%)	Difference int vs placebo (95% CI)	P-value vs placebo
COAST-V: Rad, no prior TNF				
Placebo	87	16 (18.4)	-	-
IXE, 80mg and 160mg LD*	**81**	**39 (48.1)**	**29.8 (16.2; 43.3)**	**<0.0001**
ADA every 2 weeks	90	32 (35.6)	17.2 (4.4; 30.0)	0.0053
COAST-W: Rad, prior TNF				
Placebo	104	13 (12.5)	-	-
IXE, 80mg and 160mg LD*	**114**	**29 (25.4)**	**12.9 (2.7; 23.2)**	**0.017**
COAST- X: non-Rad, no prior TNF				
Placebo	105	20 (19.0)	-	-
IXE, 80mg and 160mg LD*	**96**	**34 (35.4)**	[redacted]	**0.0094**

IXE= Ixekizumab; LD= loading dose; ADA= adalimumab; int= intervention; comp= comparator.
Table only reports results for dosing schedules where IXE is delivered every 4 weeks.
*Pooled 80mg and 160mg LD. No significant difference between 80mg and 160mg LD schedules.

COAST RCTs: BASDAI50 response week 16 compared with placebo

Intervention, dosing schedule	n	Response, n (%)	Difference int vs comp (95% CI)	P-value vs comp
COAST-V: Rad, no prior TNF				
Placebo	87	15 (17.2)	-	-
IXE, 80mg and 160mg LD	**81**	**34 (42.0)**	**24.7 (11.4; 38.1)**	**0.0003**
COAST-W: Rad, prior TNF				
Placebo	104	[redacted]	-	-
IXE, 80mg and 160mg LD	114	[redacted]	[redacted]	[redacted]
COAST- X: non-Rad, no prior TNF				
Placebo	105	[redacted]	-	-
IXE, 80mg and 160mg LD	96	[redacted]	[redacted]	[redacted]

IXE= Ixekizumab; LD= loading dose; ADA= adalimumab; int= intervention; comp= comparator.
Table only reports results for dosing schedules where Ixekizumab is delivered every 4 weeks.

COAST RCTs: BASFI change from baseline, week 16 compared with placebo

Intervention, dosing schedule	n	CFB, LSM (SE)	Difference int vs comp (95% CI)	P-value vs comp
COAST-V: Rad, no prior TNF				
Placebo	[redacted]	-1.16 (0.22)	-	-
IXE, 80mg and 160mg LD	[redacted]	**-2.39 (0.22)**	**-1.22 (-1.83; -0.62)**	**<0.0001**
COAST-W: Rad, prior TNF				
Placebo	[redacted]	[redacted]	-	-
IXE, 80mg and 160mg LD	[redacted]	[redacted]	[redacted]	[redacted]
COAST- X: non-Rad, no prior TNF				
Placebo	[redacted]	-1.34 (0.23)	-	-
IXE, 80mg and 160mg LD	[redacted]	**-2.01 (0.23)**	**-0.67 (-1.31; 0.03)**	**0.040**

CFB= change from baseline; LSM = least squares mean; IXE= Ixekizumab; LD= loading dose; ADA= adalimumab; int= intervention; comp= comparator.
Table only reports results for dosing schedules where Ixekizumab is delivered every 4 weeks.

Long term effectiveness (COAST-Y)

- COAST-Y RCT is an ongoing, multicentre, phase 3 long term extension study to evaluate the maintenance of treatment effect
- Includes extended treatments for people who completed any of the COAST V, W, and X.
- Inclusion to COAST-Y is not based on initial response. People excluded if they discontinued IXE during COAST V, W, or X.
- Company has provided results for IXE 80mg once every 4 weeks for total of 116 weeks (includes week 0 to 52 of original COAST RCTs and up to week 64 of COAST-Y).
- Evidence of long-term effectiveness for IXE across all outcomes

Timepoint (duration of IXE treatment)	N	ASAS40 response n (%)	BASDAI50 response n (%)	BASDAI50 cfb Mean (sd)	BASFI cfb Mean (sd)
Week 16	157	64 (40.8)	58 (36.9)	-2.8 (2.1)	-2.2 (2.2)
Week 52	156	82 (52.6)	78 (50.0)	-3.4 (2.2)	-2.9 (2.3)
Week 116	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IXE= Ixekizumab, 80mg administered once every 4 weeks. Cfb= change from baseline.
Week 16 and week 52 outcomes from COAST-V, COAST-W, or COAST-X.
Week 116 outcome from week 64 of ongoing COAST-Y RCT.

Treatment position of IXE

Company:

- Significant unmet need for effective treatments
- Acknowledges that TNFi will likely be used as first line treatment
- Response rates to first-line treatment estimated to be between 33–52%, and real-world studies consistently show lower effectiveness of sequential TNFi in rad-axSpA patients
- Therefore, IXE will be used primarily as follows in UK:
  - rad-axSpA: for adults who have responded inadequately to, or not tolerated NSAIDs and at least 2 biological DMARDs, or are contra-indicated or otherwise unsuitable for TNFi
  - nr-axSpA: for adults who have responded inadequately to, or not tolerated, NSAIDs and at least one TNFi, or are contra-indicated or otherwise unsuitable for TNFi
- COAST-W offers strong evidence for ixekizumab in biologic-experienced population

Clinical experts: IL-17i most needed in patients with primary non-response to TNFi or with tolerability issues or contraindications or those with secondary non-response to >2 TNFis

ERG: No evidence for effectiveness of ixekizumab when:

- patients are contra-indicated or otherwise unsuitable for NSAIDs or anti TNFs
- used to treat bio-experienced patients with rad-axSpA after more than 2 biologics or for any biologic-experienced patients with nr-axSpA

Where would ixekizumab be used in the treatment pathway?

Issue 1: treatment outcomes by disease subtype

- **Company**: treatment outcomes are generalisable between rad- and nr-axSpA populations
- Traditionally considered as 2 distinct disease entities but clinical practice has moved towards consideration of axSpA as a spectrum of disease, with the rad- and nr- subtypes representing either end of a continuous spectrum:
  - 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
  - patient and clinical experts in the NICE appraisal of TNFi (TA383) made clear that rad- and nr-axSpA are distinguishable conditions within a single disease spectrum
- **Professional group:** length of disease duration, inflammatory burden, degree of radiographic damage e.g. fusion in both rad- and nr-axSpA is likely to affect treatment outcome with IXE as these are heterogenous groups
- **ERG:** not appropriate to consider rad-axSpA and nr-axSpA as the same. BASDAI 50 results differ between COAST-V and COAST-X. If this is due to underlying disease biology, it is unreliable to use results from a rad-axSpA trial as proxy for results for nr-axSpA. If it is solely due to different patient characteristics, results from a rad-axSpA trial could be used to inform effectiveness for patients with nr-axSpA only after appropriate adjustment.

Are treatment outcomes generalisable between rad- and nr-axSpA populations?

COAST RCTs: ASAS40 response at week 16 versus placebo: reminder

Intervention, dosing schedule	n	Response, n (%)	Difference int vs placebo (95% CI)	P-value vs placebo
COAST-V: Rad-axSpA, no prior TNF (bio-naïve)				
Placebo	87	16 (18.4)	-	-
IXE, 80mg and 160mg LD	**81**	**39 (48.1)**	**29.8 (16.2; 43.3)**	**<0.0001**
COAST- X nr-axSpA, no prior TNF (bio-naïve)				
Placebo	105	20 (19.0)	-	-
IXE, 80mg and 160mg LD	**96**	**34 (35.4)**	[redacted]	**0.0094**

IXE= Ixekizumab; LD= loading dose; ADA= adalimumab; int= intervention; comp= comparator.
Table only reports results for dosing schedules where Ixekizumab is delivered every 4 weeks.

Issue 1: treatment outcomes by prior use of biologics

- **Company**: there is a clinical rationale for why response to biologics would vary by prior biologic use
- COAST-V and COAST-W represent large populations of biologic-naïve and -experienced rad-axSpA patients. The 2 trial populations differ in terms of baseline characteristics despite the same underlying disease:
  - patients at baseline in COAST-W (biologic-experienced) had mean ASAS and BASDAI scores of approx. 4.2 and 7.4 versus 3.8 and 6.8 in COAST-V (biologic-naïve)
  - mean duration of symptoms since axSpA onset was longer in COAST-W vs. COAST-V (16.5–19.9 years versus 15.6–16.6 years, respectively) and this is reflected in the older age of patients
- More severe disease at baseline in COAST-W, increased age and longer duration of symptoms are treatment effect modifiers which indicate a poorer response likelihood
- **ERG** agrees that prior biologic use is a treatment effect modifier, with efficacy declining with number of treatments

Key issues: clinical effectiveness

- All things being equal, would a TNF inhibitor usually be the first choice of biologic?
- Where might an IL-17A be used in preference to a TNF inhibitor?
- What is the committee's view on the available results from the COAST trials?
- Are treatment outcomes generalisable between the radiographic and non-radiographic axial spondyloarthritis populations, or could they be different based on differing diagnostic criteria?
- Is it reasonable to assume a class effect:
  - for the TNF inhibitors?
  - for the IL-17A-inhibitors ixekizumab and secukinumab?
  - across all biologic treatments i.e. do all TNF and IL-17A inhibitors have equivalent effectiveness?

Key issues: cost-effectiveness

- The ERG had concerns about the robustness of the network meta-analysis (NMA) results:
  - what is the committee's view of the results?
  - do the results support an assumption of class effects across all biologic treatments?
- After technical engagement the company updated its economic analysis to assume class effects across biologic treatments instead of using the NMA – is this analysis appropriate?

Network Meta-Analysis (NMA): background

- The original company submission included NMAs to facilitate comparison of IXE versus the comparator drugs using placebo as the common comparator
- Separate NMAs were conducted for 3 populations in line with COAST RCTs (Rad-axSpA biologically naïve; Rad-axSpA, biologically experienced; Nr-axSpA, biologically naïve).
- Two NMAs conducted for each subgroup - base case NMAs (of studies conducted in the relevant patient population) and sensitivity NMAs which informed the model (included additional studies with mixed populations and populations where prior treatment was unclear)
- Insufficient published data available to allow a full comparison of IXE versus secukinumab

ERG comments

- NMA methods were appropriate but some of the absolute effect estimates generated by the sensitivity NMAs differed substantially from the absolute effect estimates generated by the base case NMAs:
  - those generated by the base case NMAs likely to be more reliable as the risk of population heterogeneity is lower in the smaller network, but not used in model
- Some of the sensitivity NMAs for the rad-axSpA population were not considered suitable for decision making and cost effectiveness results that relied on these findings were **not robust**

NMA results before technical engagement: Rad-axSpA, bio naïve

- Relative effect: ixekizumab vs placebo / another intervention
- Sensitivity NMA results from fixed effects NMA (inform economic results)
- Due to available data: ixekizumab vs secukinumab not calculable for BASDAI50

Intervention	ASAS40 OR (95% CrI) vs IXE 80 mg Q4W	BASDAI50 OR (95% CrI) vs IXE 80 mg Q4W
Placebo	[redacted]	[redacted]
INX 5mg/kg	[redacted]	[redacted]
ADA 40mg	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]
ETN pooled	[redacted]	[redacted]
SEC 150 mg	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]

All interventions compared to ixekizumab 80mg Q4W with 160mg loading dose
Notes: * **Significant difference favouring ixekizumab**
Abbreviations: ADA: adalimumab; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: ixekizumab; SEC: secukinumab; Q4W: every 4 weeks; QW: weekly; NC: not calculable; OR: Odds ratio; cfb: change from baseline.

NMA results before technical engagement: Rad-axSpA, bio experienced

- Relative effect: ixekizumab vs placebo / another intervention
- Sensitivity NMA results from fixed effects NMA (inform economic results)
- Due to available data: Ixekizumab vs adalimumab or golimumab could not be estimated; ixekizumab vs secukinumab could not be estimated on BASDAI50

Intervention	ASAS40 OR (95% CrI) vs IXE 80 mg Q4W	BASDAI50 OR (95% CrI) vs IXE 80 mg Q4W
Placebo	[redacted]	[redacted]
INX 5mg/kg	[redacted]	[redacted]
SEC 150mg	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]
ETN 25mg	[redacted]	[redacted]

All interventions compared to ixekizumab 80mg Q4W with 160mg loading dose
Notes: * **significant difference favours IXE;** + ***significant difference favours comparator***
Abbreviations: CZP: certolizumab pegol; ETN: etanercept; INX: infliximab; IXE: ixekizumab; SEC: secukinumab; Q4W: every 4 weeks; NC: not calculable; OR: Odds ratio; cfb: change from baseline.

NMA results before technical engagement: Nr-axSpA, bio naïve

- Relative effect: ixekizumab vs placebo / another intervention
- Sensitivity NMA results from fixed effects NMA (inform economic results)

Intervention	ASAS40 OR (95% CrI) vs IXE 80 mg Q4W	BASDAI50 OR (95% CrI) vs IXE 80 mg Q4W
Placebo	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]
CZP pooled	[redacted]	[redacted]
ETN 50 mg QW	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]

All interventions compared to ixekizumab 80mg Q4W with 160mg loading dose
Notes: **+ *significant difference favours comparator***
Abbreviations: ADA: adalimumab; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; INX: infliximab; IXE: ixekizumab; SEC: secukinumab; Q4W: every 4 weeks; QW: weekly; NC: not calculable; OR: Odds ratio; cfb: change from baseline.

Issue 2: Comparison with secukinumab

Background: secukinumab approved for rad-axSpA, under appraisal for nr-axSpA

- **Company** updated the NMA at TE to provide efficacy estimates for IXE vs secukinumab using data published since original submission (PREVENT study of secukinumab vs. placebo in nr-axSpA). Results showed no significant differences between IXE and secukinumab for any outcomes
- Acknowledges that secukinumab is not a NICE comparator in this appraisal for nr-axSpA (currently being appraised) but considers the results to be generalisable to a rad-axSpA population (Issue 1) i.e. if equivalent in nr-axSpA, they will be equivalent in rad-axSpA
- Believes analysis supports a class effect among IL-17 inhibitors that can be generalised across rad- and nr-axSpA populations and assumed in the economic analysis

Clinical experts: IXE is comparable with biologic therapies currently available
Professional group: this is an area for further research and study
Other stakeholder: reasonable to assume equal efficacy across IL-17-1A inhibitors

ERG: Only possible to informally compare absolute effect estimates for each treatment, and compare the relative effect estimates for IXE vs placebo and secukinumab vs placebo. Assumption of a class effect for IL-17 inhibitors not well supported by evidence from NMA

Is it reasonable to assume a class effect for IL-17A-inhibitors?

Updated NMA results after technical engagement: Nr-axSpA, bio naïve

- Updated results include evidence for secukinumab vs placebo from the PREVENT RCT
- Sensitivity NMA results displayed only (inform economic results)
- Relative treatment effect of pairwise comparisons **vs placebo** at week 12-18

Intervention	ASAS40			BASDAI50		
	OR	Lower 95% CrI	Upper 95% CrI	OR	Lower 95% CrI	Upper 95% CrI
IXE (pooled LD)[1]	[redacted]					
ADA 40 mg						
CZP pooled						
ETN 50 mg QW						
GOL 50 mg						
SEC 150 mg						

1: Results pooled across 80mg and 160mg loading doses.
ADA: adalimumab; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; SEC: secukinumab; Q4W: every four weeks; QW: weekly. NC: not calculable.

Issue 3: Limitations in the NMA

Company:

- Given the uncertainties raised by ERG re the **robustness** of the NMA, company concluded at TE that it is reasonable to assume class effects amongst **all** biologics for the rad and nr-axSpA indications
  - in line with conclusion in TA383 that TNF inhibitors should be considered as a class with broadly similar effects
  - aligns with conclusion in TA407 that secukinumab has similar efficacy to TNFi in rad
  - studies demonstrate that axSpA is driven by cytokine dysregulation, with both the TNF-alpha and IL-17A cytokines playing key role
  - no evidence of difference between TNFi and IL-17i for any of the outcomes assessed in the NMAs in company's original submission or updated NMA to include secukinumab
  - **therefore after TE, the company updated its economic analysis to assume class effects across all biologics (NMA no longer used in updated economic analysis)**

Clinical experts: expectation is for IXE to be comparable with other biologic therapies
Professional group: this is an area for further research and study

ERG: company has not provided relative treatment effects for comparisons between treatments. Therefore not possible to comment on the validity of the company's statement that no significant differences were identified in the NMAs

Is it reasonable to assume class effects across all biologics?

Cost-effectiveness model

Model type	Markov model incorporating a 'trial period' which is represented by a set of tunnel states which are visited once in a fixed sequence for the maximum 5 treatment sequences
Health states	Trial periods, maintenance, conventional care (CC), death
Population	People with axSpA for whom NSAIDs or TNF-alpha inhibitors have been inadequately effective or not tolerated, or are contraindicated.
Intervention	Ixekizumab Q4W (once every four weeks)
Comparators	Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, conventional care (CC)
Time horizon	Lifetime
Model cycle	1 month
Discount rate	3.5% for both health and cost outcomes
Utility values	EQ-5D-5L data (COAST trials) Covariates for BASDAI & BASFI scores included age, sex, race and disease duration

Key model assumptions: class effects model

Company provide separate cost-effectiveness (class) analyses for:

1. Biologic-experienced rad-axSpA population
2. Biologic-naïve nr-axSpA population

The model's efficacy inputs are:

- BASDAI 50 response (clinical efficacy input)
- BASDAI and BASFI (to model symptom progression)

Efficacy input values

- Cost-effectiveness analysis applies class effect across IL-17A inhibitors and TNFis
- For the biologically-experienced rad-axSpA analysis, efficacy inputs *for all biologics* are equal to the efficacy of IXE in the COAST-W RCT
- For the biologically-naive nr-axSpA analysis, efficacy inputs *for all biologics* are equal to the efficacy of IXE in the COAST-X RCT
- Class effect means equivalent QALYs for all biologics (excludes conventional care). QALYs differ for biologics across analyses in biologic-experienced rad-axSpA and biologic-naïve nr-axSpA populations.

Additional modelling assumptions

Progression:

- BASDAI assumed constant over time, BASFI progressively worsens
- Treatment effect of IXE and comparators on disease progression applies from the end of the trial period (week 16) until the patient comes off-treatment
- Upon treatment discontinuation and transfer to conventional care:
  - Treatment response is lost (BASDAI)
  - Function declines, BASFI score returns to baseline. NICE technical team and ERG agree with company approach of 'rebound by initial gain' for BASFI (**issue 5 in TR – resolved**)

Adverse effects

- AEs included in the model were tuberculosis reactivation and severe infections with associated cost but no utility loss due to lack of data
- Different AEs costs applied for each biologic within class analysis

Costs

- Treatment costs for acquisition, administration, initiation, monitoring, long-term management
- ERG results using *confidential* PAS comparator costs will be used for decision making (part 2 presentation)
- Disease related costs were based on BASFI score using a regression equation from TA383

ERG critique of class effects model

- No ICER for IXE vs conventional care in the class effects model
- Rad axSpA
  - No results provided for TNFi contraindicated population. Can infer cost-effectiveness for IXE vs. all TNFis assuming: (i) bio-naïve and TNFi contraindicated population are equivalent, (ii) clinical effectiveness for bio-naïve nr-axSpA and rad-axSpA are equivalent
  - Clinical and cost effectiveness evidence for IXE relates to failure after 1 or 2 TNF However, company believes IXE will be used after 2 TNFis, or after 1 TNFi + secukinumab
  - Secukinumab is a relevant comparator for bio-naïve population, but is not included in CE analysis
- Nr- axSpA
  - No results presented for TNFi contraindicated population. Can infer results for IXE vs. all TNFis & CC if bio-naïve and TNFi contraindicated populations are equivalent
  - No results have been presented specifically for the nr-axSpA bio-experienced population
  - Under assumption that effectiveness in a bio-experienced rad-axSpA population is mirrored in a bio-experienced nr-axSpA population, then cost effectiveness results have been provided for IXE vs all TNFis and conventional care

Company's cost effectiveness results: class effects model, bio-experienced rad-axSpA

- Revised base case deterministic results after technical engagement (ixekizumab PAS)
- Assumes class effect across TNFi *and* IL17-A (excludes conventional care)
- Two separate analyses for secukinumab 150mg/ 300mg. Company suggest 300mg dose applicable to ~19% of rad-axSpA population (Adelphi AxSpA Plus cross sectional analysis).

Technologies	Total costs (£)	Incremental costs (£)
Adalimumab	[redacted]	-
Conventional care	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]
ETN 25/50 mg	[redacted]	[redacted]
Ixekizumab Q4W	[redacted]	[redacted]
SEC 150mg	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]

Technologies	Total costs (£)	Incremental costs (£)
Adalimumab	[redacted]	-
Conventional care	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]
ETN 25/50 mg	[redacted]	[redacted]
Ixekizumab Q4W	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
SEC 300 mg	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]

ETN: Etanercept; SEC: secukinumab; Q4W: every four weeks

Company's cost effectiveness results: class effects model, bio-naïve nr-axSpA

- Revised base case deterministic results after technical engagement (ixekizumab PAS)
- Assumes class effect across TNFi *and* IL17-A (excludes conventional care) resulting in equivalent QALYs for all biologics

Technologies	Total costs (£)	Incremental costs (£)
Conventional care	[redacted]	-
Adalimumab	[redacted]	[redacted]
Ixekizumab Q4W	[redacted]	[redacted]
Etanercept 25/50mg	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]

Q4W: every four weeks

Company's cost effectiveness results using original NMA: bio-naïve rad-axSpA

- **Deterministic** base case with ixekizumab PAS
- Efficacy inputs for golimumab BASDAI50 cfb and BASFI cfb estimated as unweighted average across all TNFis
- Secukinumab not included in company's base case analysis

Technologies	Mean costs (£)	Mean QALYs	ICER per QALY gained	
			Fully incremental	Pairwise vs. IXE
Conventional care	[redacted]	[redacted]	-	£39,851
Adalimumab	[redacted]	[redacted]	£4,387	Dominated
Etanercept	[redacted]	[redacted]	Dominated	£11,029
Ixekizumab	[redacted]	[redacted]	Dominated	-
Golimumab	[redacted]	[redacted]	Dominated	Dominant
Certolizumab pegol	[redacted]	[redacted]	Dominated	Dominant
Infliximab	[redacted]	[redacted]	Dominated	Dominant

ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life years; IXE: ixekizumab

Company's cost effectiveness results using original NMA: bio-experienced rad-axSpA

- **Deterministic** base case with ixekizumab PAS
- Efficacy inputs for adalimumab, golimumab (all inputs) and etanercept (BASDAI 50 cfb & BASFI cfb) estimated as unweighted average across all TNFis
- Secukinumab not included in company's base case analysis

Technologies	Mean costs (£)	Mean QALYs	ICER per QALY gained	
			Fully incremental	Pairwise vs. IXE
Conventional care	[redacted]	[redacted]	-	£1,603,221
Adalimumab	[redacted]	[redacted]	£56,119	Dominated
Ixekizumab	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	Dominated	£41,794*
Certolizumab pegol	[redacted]	[redacted]	Dominated	£954,573*
Golimumab	[redacted]	[redacted]	Dominated	£96,133*
Infliximab	[redacted]	[redacted]	£860,378	£287,583*

ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life years; IXE: ixekizumab.
*ICERs in south-west quadrant of CE plane (ICERs > £30,000 per QALY may be cost-effective).

Company's cost effectiveness results using original NMA: bio-naïve nr-axSpA

- **Deterministic** base case with ixekizumab PAS
- Efficacy inputs for adalimumab and golimumab (BASDAI 50 cfb & BASFI cfb) estimated as unweighted average across all TNFis

Technologies	Mean costs (£)	Mean QALYs	ICER per QALY gained	
			Fully incremental	Pairwise vs. IXE
Conventional care	[redacted]	[redacted]	-	£44,434
Adalimumab	[redacted]	[redacted]	£4,809	Dominated
Ixekizumab	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	Dominated	£14,372*
Golimumab	[redacted]	[redacted]	Extendedly dominated	£18,676*
Certolizumab pegol	[redacted]	[redacted]	£75,056	£15,163*

ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life years; IXE: ixekizumab.
*ICERs in south-west quadrant of CE plane (ICERs > £30,000 per QALY may be cost-effective).

ERG cost effectiveness results

- Decision making to be based on ERG results (to follow in part 2)
  - ERG results use confidential costs for IXE **and** comparators
  - ERG results provided for company's class analysis and company's original analysis
- ERG has not provided any additional preferred scenario analyses

Key issues: cost-effectiveness

- The ERG had concerns about the robustness of the NMA results:
  - what is the committee's view of the results?
  - do the results support an assumption of class effects across all biologic treatments?
- After technical engagement the company updated its economic analysis to assume class effects across biologic treatments instead of using the NMA – is this analysis appropriate?

Back up slides

Company's cost effectiveness results using original NMA: bio-naïve rad-axSpA

- **Probabilistic** base case with ixekizumab PAS
- Efficacy inputs for golimumab BASDAI50 cfb and BASFI cfb estimated as unweighted average across all TNFis
- Secukinumab not included in company's base case analysis.

Technologies	Mean costs (£)	Mean QALYs	ICER per QALY gained	
			Fully incremental	Pairwise vs. IXE
Conventional care	[redacted]	[redacted]	-	£36,031
Adalimumab	[redacted]	[redacted]	£861	Dominated
Etanercept	[redacted]	[redacted]	Dominated	£8,839
Ixekizumab	[redacted]	[redacted]	Dominated	-
Golimumab	[redacted]	[redacted]	Dominated	Dominant
Certolizumab pegol	[redacted]	[redacted]	Dominated	Dominant
Infliximab	[redacted]	[redacted]	Dominated	Dominant

ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life years; IXE: ixekizumab

Company's cost effectiveness results using original NMA: bio-experienced rad-axSpA

- **Probabilistic** base case with ixekizumab PAS
- Efficacy inputs for adalimumab, golimumab (all inputs) and etanercept (BASDAI 50 cfb & BASFI cfb) estimated as unweighted average across all TNFis
- Secukinumab not included in company's base case analysis.

Technologies	Mean costs (£)	Mean QALYs	ICER per QALY gained	
			Fully incremental	Pairwise vs. IXE
Conventional care	[redacted]	[redacted]	-	£1,635,912
Adalimumab	[redacted]	[redacted]	£44,867	Dominated
Ixekizumab	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	Dominated	£36,784*
Certolizumab pegol	[redacted]	[redacted]	Dominated	£1,117,054*
Golimumab	[redacted]	[redacted]	Extendedly dominated	£91,220*
Infliximab	[redacted]	[redacted]	£816,669	£272,720*

ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life years; IXE: ixekizumab.
*ICERs in south-west quadrant of CE plane (ICERs > £30,000 per QALY may be cost-effective).

Company's cost effectiveness results using original NMA: bio-naïve nr-axSpA

- **Probabilistic** base case with ixekizumab PAS
- Efficacy inputs for adalimumab and golimumab (BASDAI 50 cfb & BASFI cfb) estimated as unweighted average across all TNFis

Technologies	Mean costs (£)	Mean QALYs	ICER per QALY gained	
			Fully incremental	Pairwise vs. IXE
Conventional care	[redacted]	[redacted]	-	£42,705
Adalimumab	[redacted]	[redacted]	£2,285	Dominated
Ixekizumab	[redacted]	[redacted]	Dominated	-
Etanercept	[redacted]	[redacted]	Dominated	£10,580*
Golimumab	[redacted]	[redacted]	Dominated	£15,753*
Certolizumab pegol	[redacted]	[redacted]	£73,610	£12,652*

ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life years; IXE: ixekizumab.
*ICERs in south-west quadrant of CE plane (ICERs > £30,000 per QALY may be cost-effective).

Issue 4: Long-term effectiveness of ixekizumab

Background

- During maintenance treatment, responder patients are in each cycle at risk of dropping out of treatment due to severe AEs or loss of response
- There is a lack of randomised data for the comparison of ixekizumab to placebo past week 16 in the rad-axSpA population
- The results of the COAST-Y study provide useful evidence on the longer-term effectiveness of maintenance ixekizumab

Stakeholder comments

- ERG: The data presented by the company suggest that the efficacy of ixekizumab at Week 52 is maintained up to Week 116
- 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
- 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

Technical team: Company have provided data from the COAST-Y study to validate the relevant model assumptions during technical engagement

Issue 5: BASFI after treatment discontinuation

Background

- The company assumed that when treatment is discontinued, function (measured by BASFI scores) begins to decline (BASFI scores increase or 'rebound').
- The committee for TA383 considered the 'rebound by initial gain' approach appropriate
- 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

Stakeholder comments

- Clinical expert opinion provided during TA383 implies 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).

Technical team: The team agrees with the company's 'rebound by initial gain' approach

Issue 6: Choice of utility regression equation

Background

- 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 using the COAST-V, COAST-W or COAST-X data.
- The company tested the use of four alternative approaches in scenario analyses

Stakeholder comments

- The health state utilities are calculated using an algorithm which produces a relationship between disease activity and function (as measured by BASDAI and BAFSI scores change) and expected patient HRQoL (as an EQ-5D-3L score)
- Incorporated covariates result in mathematically non-linear relationship, but scenario analyses imply it is close enough to linear as to be functionally a linear relationship.
- An assumption of equal efficacy across all biologics results in the same expected HRQoL for all patients within the model

Technical team: Issue no longer relevant after technical engagement. The company's updated cost-effectiveness analysis is a class analysis where utility values are equivalent across all interventions.

Issue 7: Nr-axSpA biologic-experienced scenario

Background

- No clinical evidence for Ixekizumab in nr-axSpA biologic-experienced population.
- Original company submission included scenario with clinical effectiveness calculated using a 'modification factor' = 61.43%
- Modification factor calculated based on ratio of BASDAI50 response in COAST-V and COAST-W RCTS for biologic-naïve and biologic-experienced rad-axSpA populations

ERG comments

- Modification factor calculations used by company are not clear.
- No evidence to support same relationship between biologic-naïve and biologic-experienced in nr-axSpA and rad-axSpA populations.

Technical team

- Issue no longer relevant after TE. The company's updated submission (class analysis) does not require the 'modification factor' scenario analysis.