NICE National Institute for Health and Care Excellence

Ixekizumab for treating axial spondyloarthritis

2nd Appraisal Committee meeting

Chair presentation

Lead team: G J Melendez-Torres, Roger Whittaker, Richard Ballerand

ERG: University of Liverpool

Chair: Jane Adam

Technical team: Richard Mattock, Lukasz Grodzicki, Zoe Charles, Janet Robertson

Company: Eli Lilly

6th May 2021

Key issues

- Is the company's updated analysis which compares ixekizumab with conventional therapy using direct evidence from the COAST trials reliable?
- Does the committee consider ixekizumab to be cost-effective versus conventional therapy based on the company's updated analyses?
- Is the committee prepared to recommend ixekizumab for non-radiographic disease following inadequate or lost response to TNF-alpha inhibitors although direct trial evidence is lacking?

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 if blood inflammatory markers are raised
- 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, and arthritis
- No cure, treatment aims to relieve pain and stiffness, prevent joint and organ damage and preserve joint function and mobility

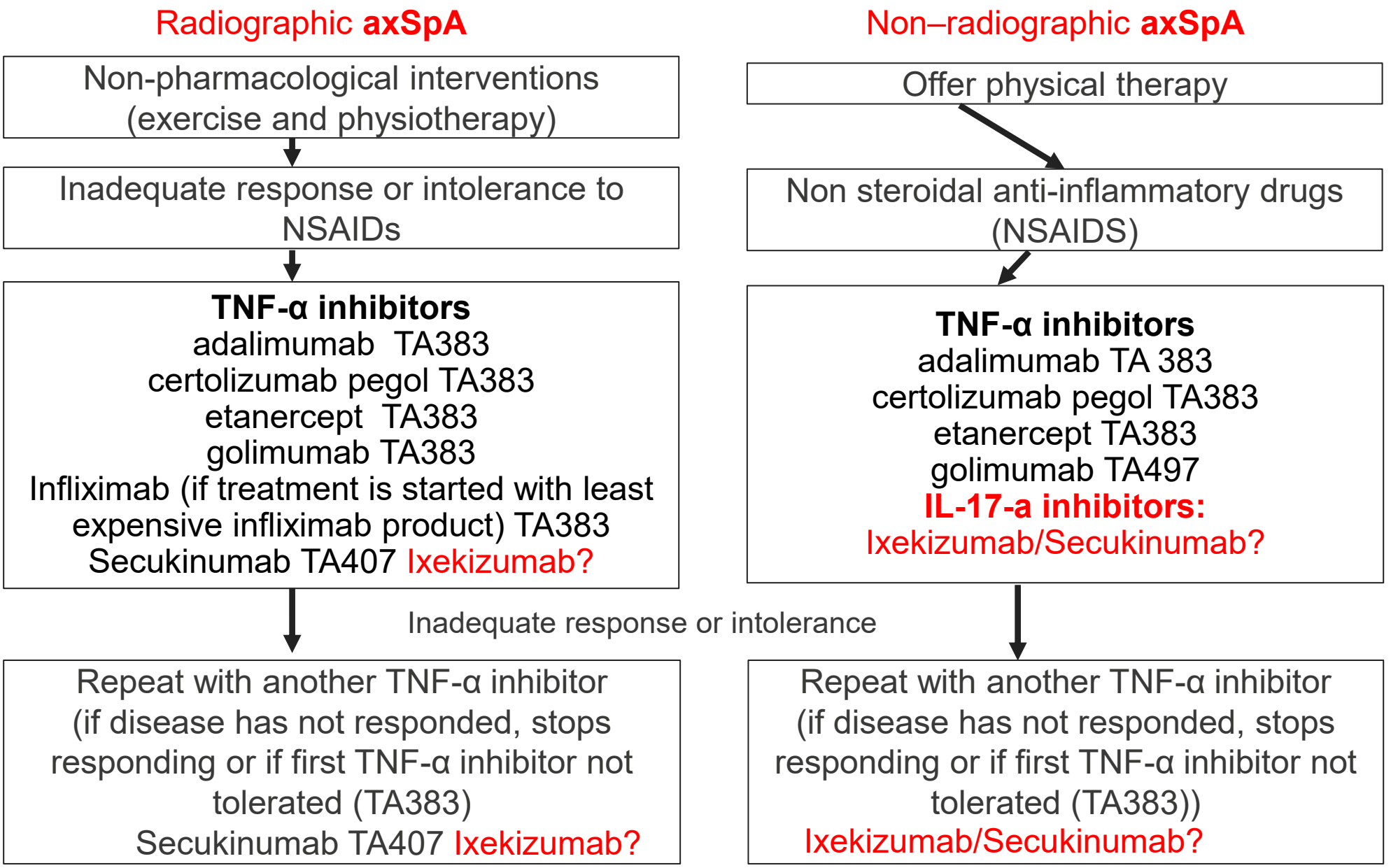
Ixekizumab (Taltz, Eli Lilly)

- 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 active **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



Committee conclusions at ACM1: clinical issues

- There is a clinical need for effective new treatments: ixekizumab is an IL17-a inhibitor with a different mechanism of action to TNF-alpha inhibitors
- Ixekizumab would be used when TNF-alpha inhibitors are contraindicated or otherwise not suitable first-line, or second line after primary non-response/poor response or loss of response to TNF-alpha therapy
  - IL-17-a inhibitors not expected to replace TNF-alpha inhibitors as standard first-line treatment - more expensive and less clinical experience with using them
  - Class effect across all biologics, or between IL-17s unproven
- Therefore, conventional therapy is the most reliable comparator for ixekizumab:
  - TNF-alpha inhibitors are not a relevant comparator because of how ixekizumab will be used in clinical practice
  - Secukinumab is a relevant comparator in rad-axSpA but there is insufficient clinical evidence to reliably compare it with ixekizumab,
- Treatment effects are not reliably generalisable across rad-axSpA and nr-axSpA
  - Degree of radiographic damage, inflammation, disease duration and treatment history are likely to differ in rad-axSpA and nr-axSpA, which may affect treatment outcomes
- Ixekizumab is clinically effective versus placebo, a proxy for conventional therapy

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 at week 16 vs placebo

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

NICE

COAST RCTs: BASDAI50 response week 16 compared with placebo

Intervention, dosing schedule	n	Response %	Difference int vs comp (95% CI)	P-value vs comp
COAST-V: Rad, no prior TNF				
Placebo	87	17.2	-	-
IXE, 80mg and 160mg LD	**81**	**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; 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; 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 ongoing, multicentre, phase 3 long term maintenance study
- 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 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 (%)	BASFI cfb Mean (sd)
Week 16	157	64 (40.8)	58 (36.9)	-2.2 (2.2)
Week 52	156	82 (52.6)	78 (50.0)	-2.9 (2.3)
Week 116	[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.

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

Committee conclusions at ACM1: cost effectiveness

- The structure of the company's economic model was appropriate
- The results of the network meta-analysis (NMA) used to inform efficacy estimates in the model were not robust, therefore the results of the model using the NMA were not reliable for decision making
  - results showed that ixekizumab was not cost-effective vs. conventional care
- An updated model submitted by the company at TE which assumed a class effect for all biologic treatments, was also not appropriate for decision making
  - a class effect for all TNF-alpha inhibitors and IL17-a inhibitors has not been established
  - no incremental cost-effectiveness ratio (ICER) was provided for ixekizumab versus conventional care
- Further analyses are needed to assess the cost effectiveness of ixekizumab:
  - the committee would like to see a comparison of ixekizumab with conventional therapy using direct evidence from the COAST trials

ACD: preliminary considerations

1.1 Ixekizumab is not recommended, within its marketing authorisation, for treating:

- active ankylosing spondylitis that has responded inadequately to conventional therapy in adults, or
- active non-radiographic axial spondyloarthritis with objective signs of inflammation (shown by elevated C-reactive protein or MRI, or both) that has responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs) in adults.

ACD consultation responses

Professional / patient organisations	None
Company (Eli Lilly)	Presents further economic analyses using data directly from the COAST clinical trials programme to compare ixekizumab with conventional care (CC), as requested by committee
Comparator company (Novartis)	Requests minor changes for improved clarity given the positive ACD draft recommendation for secukinumab (ID1419)
Public (web) comments	None

Company response (1)

- COAST trials provide direct evidence for the efficacy of ixekizumab versus placebo, which is a suitable proxy for conventional therapy
- Use of these direct data to estimate cost effectiveness removes the need for data from the NMA

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
COAST-V: Rad, no prior TNF					
CC	[redacted]		-	-	-
IXE Q4W	[redacted]	[redacted]	[redacted]	[redacted]	£18,775
COAST-W: Rad, prior TNF					
CC	[redacted]	[redacted]	-	-	-
IXE Q4W	[redacted]	[redacted]	[redacted]	[redacted]	£19,012
COAST- X: Non-Rad, no prior TNF					
CC	[redacted]	[redacted]	-	-	-
IXE Q4W	[redacted]	[redacted]	[redacted]	[redacted]	£24,772

- Results show that, compared with conventional care, ixekizumab represents a cost-effective use of NHS resources (ICERs under £30,000 per QALY in all populations)
- **ERG:** confirms that the new results can be reproduced by the model submitted after ACM1

Company Response (2)

- Company acknowledges the NICE Committee's rationale for deeming conventional care to be the most reliable comparator to ixekizumab
- Clinical expert opinion states that not all patients in whom TNF-alpha inhibition has worked insufficiently would be removed from biologic therapy and returned to conventional care
- Some patients may receive newer TNF-alpha inhibitor options recommended by NICE in axSpA: golimumab (GOL) or certolizumab pegol (CZP)
- Company provides the cost comparison results for ixekizumab, golimumab and certolizumab pegol, previously provided at the Technical Engagement step, as an alternative comparison

COAST-W: Rad, prior TNF	Total costs (£)	Incremental costs (£)
CZP	[redacted]	-
IXE Q4W	[redacted]	[redacted]
GOL	[redacted]	[redacted]

COAST-X: Non-rad, no prior TNF	Total costs (£)	Incremental costs (£)
IXE Q4W	[redacted]	-
CZP	[redacted]	[redacted]
GOL	[redacted]	[redacted]

- In both populations, over a lifetime horizon, ixekizumab has a comparable or lower total cost vs. two TNF-alpha inhibitors typically used later line following previous TNF-alpha inhibition failure
- **ERG:** assumption of a class effect across TNFi and IL-17i is not supported by the evidence

Key issues

- Is the company's updated analysis which compares ixekizumab with conventional therapy using direct evidence from the COAST trials reliable?
- Does the committee consider ixekizumab to be cost-effective versus conventional therapy based on the company's updated analyses?
- Is the committee prepared to recommend ixekizumab for non-radiographic disease following inadequate or lost response to TNF-alpha inhibitors although direct trial evidence is lacking?