National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ixekizumab for treating axial spondyloarthritis after NSAIDs

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Eli Lilly	Yes, this is an appropriate topic to refer to NICE for appraisal so appropriate advice can be given to the NHS in England and Wales regarding the use of ixekizumab within the anticipated licensed indication.	Comment noted.
	British Society for Rheumatology (BSR). Endorsed by Royal College of Physicians (RCP)	Few drugs are currently available for treatment of axial Spa. Addition of this drug will enable improved options and effective management of patient with diagnosis of axial spondyloartropathy.	Comment noted.
	National Ankylosing Spondylitis Society (NASS)	NASS believes that it is appropriate for this topic to be referred to NICE for appraisal.	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		It is estimated that 1 in 200 of the adult population in the UK have axial spondyloarthritis (axial SpA). Currently NSAIDs and exercise are the conventional treatment for axial SpA. If NSAIDs fail, under current NICE guidance, people with radiographic axial SpA, also known as ankylosing spondylitis (AS) can access TNF-alpha inhibitors adalimumab, certolizumab pegol, etanercept, golimumab and infliximab, followed by IL17a inhibitor secukinumab as treatment. People with non-radiographic axial SpA can access adalimumab, certolizumab pegol, etanercept, golimumab as treatment options. Evidence shows that the effectiveness of TNF-alpha inhibitors can wear off over time and under current NICE guidance (TA383) patients are able to switch to another TNF-alpha inhibitor or interleukin-17A (IL17-A) secukinumab (407). NASS welcomes an additional IL17-A inhibitor to further enhance treatment options.	
	AbbVie	No comment.	Response noted.
	Novartis	We consider the proposed appraisal appropriate.	Comment noted.
Wording	Eli Lilly	Yes.	Comment noted.
	BSR	Yes.	Comment noted.
	NASS	Yes. NASS welcomes use of the term axial spondyloarthritis.	Comment noted.
	AbbVie	No comment.	Response noted.
	Novartis	We consider the proposed wording appropriate.	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
Timing Issues	Eli Lilly	Advice to the NHS should be as close to marketing authorisation as is feasible within the NICE appraisal programme.	Comment noted.
	BSR	No immediate urgency as few drugs are already approved and available for clinician to use.	Comment noted.
	NASS	NASS believes that this topic should be treated as moderately urgent. Axial SpA usually begins in early adulthood, a critical period in terms of education, work and establishment of social relationships. Since biologic therapy was approved by NICE it has made a very significant difference to the lives of many with axial SpA. However, NSAIDs or anti TNF therapies are not tolerated, inadequately effective or where efficacy has waned over time in a significant amount of the population. An additional IL17-A as an alternative to other biologic therapies following failure using NSAIDs is welcomed.	Comment noted.
	AbbVie	No comment.	Response noted.
	Novartis	No comment.	Response noted.
Additional comments on the draft remit	Eli Lilly	No response.	Response noted.
	BSR	Can be positioned for Axial SpA patients who have failed NSAIDS. Ixekizumab should be used both first (biologic naïve) and second (biologic inadequate responders) line in non-radiographic and radiographic Axial SpA	Comment noted.
	NASS	No response.	Response noted.
	AbbVie	No response.	Response noted.
	Novartis	No response.	Response noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Eli Lilly	It should be noted in this section that certolizumab pegol and secukinumab are recommended only if the respective manufacturers provide the drugs to the NHS at confidential discounted prices under a patient access scheme (PAS).	Comment noted. The background section is intended to give a brief overview of current NICE guidance, therefore details of commercial arrangements are not included.
	BSR	This is clear	Comment noted.
	NASS	NASS welcomes the coverage of the full spectrum of disease in axial SpA.	Comment noted.
	AbbVie	No comment.	Response noted.
	Novartis	In the last sentence of the first paragraph a bracket should be added after "objective signs of inflammation" and before "elevated C-reactive protein". The final sentence of the last paragraph should be amended to refer to NSAIDs rather than conventional therapy since this more accurately reflects TA383 and TA497 i.e. TNF-alpha inhibitors are recommended "as treatment options in people whose disease does not respond adequately to or cannot tolerate non-steroidal anti-inflammatory drugs (NSAIDs)".	Comment noted. The text has been amended as suggested.
The technology/ intervention	Eli Lilly	The description of the technology is not accurate and should be amended as follows: "Ixekizumab is a humanised monoclonal antibody that binds with high affinity (< 3 pM) and specificity to interleukin 17A (both IL-17A and IL-17A/F)." In addition, the statement on clinical trials should be amended to "It has been studied in clinical trials compared with placebo in adults with spondyloarthritis (radiographic and non-radiographic) whose disease had responded inadequately to or who are intolerant to non-steroidal anti-inflammatory drugs.	Comment noted. The text has been amended to clarify that ixekizumab also binds to the IL-17A/F dimer.

Section	Consultee/ Commentator	Comments [sic]	Action
		Ixekizumab has also been studied in a clinical trial compared with placebo in adults with radiographic spondyloarthritis whose disease had responded inadequately to TNF alpha inhibitors."	The text has been amended to clarify that patients with non-radiographic spondyloarthritis in the clinical trials had not had TNF alpha inhibitors.
	BSR	It is accurate	Comment noted.
	NASS	Yes	Comment noted.
	AbbVie	Only biologic naïve patients were assessed in clinical trials for non-radiographic axSpA.	Comment noted. The text has been amended to clarify that patients with non-radiographic spondyloarthritis in the clinical trials had not had TNF alpha inhibitors.
	Novartis	No comment.	Response noted.
Population	Eli Lilly	The population is appropriately defined. Lilly agree that ixekizumab should be considered in the following groups of patients with axial spondyloarthritis for whom: - NSAIDs have been inadequately effective or not tolerated	Comment noted.

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		- TNF-alpha inhibitors have been inadequately effective - TNF-alpha inhibitors are contraindicated In addition, inflammation severity at baseline may be considered as a population subgroup.	
	BSR	Yes	Comment noted.
	NASS	People with axial spondyloarthritis, including non-radiographic.	Comment noted.
	AbbVie	No comment.	Response noted.
	Novartis	No comment.	Response noted.
Comparators	Eli Lilly	Lilly agree with the comparators listed in the scope. In the subgroups of patients for whom TNF-alpha inhibitors have been inadequately effective or are not tolerated, the following comparators should be considered: • **Radiographic axial spondyloarthritis:** Established non-biologic clinical management and secukinumab **Non-radiographic axial spondyloarthritis:** Established non-biologic clinical management	Comment noted. 'Established clinical management without biological treatments' has been added as a comparator in both groups.
	BSR	Yes	Comment noted.
	NASS	Yes	Comment noted.
	AbbVie	No comment.	Response noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	Novartis	Comparators seem appropriate. It is important that the comparator set differs for radiographic axial spondyloarthritis versus non-radiographic spondyloarthritis.	Comment noted.
Outcomes	Eli Lilly	The following outcomes will be considered in the submission to assess the clinical benefit of ixekizumab: • **Disease activity:** the primary endpoint in the clinical trials was ASAS40. BASDAI50 is the main outcome of interest for the economic analysis. • **Functional capacity** was assessed in the trials using the Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI). The impact of BASFI on cost and health-related quality of life will be captured in the economic analysis. • **Disease progression** will be captured in the economic analysis through modelling the link between BASFI and modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). • **Pain** is captured as a domain in the ASAS and BASDAI scores. • **Peripheral symptoms:** data on enthesitis (Maastricht Ankylosing Spondylitis Enthesitis Score [MASES], Spondyloarthritis Research Consortium of Canada [SPARCC] enthesitis score) and peripheral arthritis (tender joint count, swollen joint count) will be presented in the submission. Data on dactylitis outcomes were not collected in the COAST trial programme; the impact of ixekizumab on dactylitis has previously been documented in the NICE appraisal of ixekizumab in psoriatic arthritis (TA537). (1) • **Symptoms of extra-articular manifestations:** data on the proportion of patients with anterior uveitis or uveitis flares, inflammatory bowel disease and psoriasis will be presented in the submission. Ixekizumab	Comments noted.

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		has previously been assessed by NICE for the treatment of moderate-to-severe plaque psoriasis (TA442). (2) • **Adverse effects of treatment** will be reported for ixekizumab and comparators based on the results from the clinical studies. The cost impact of adverse effects will be modelled in accordance with the Technology Assessment Report for NICE TA383. (3) • **Health-related quality of life:** EQ-5D-5L data were collected in the COAST trial programme. Health utilities in the economic analysis will be estimated as a function of BASDAI and BASFI scores using an algorithm in accordance with the Technology Assessment Report for TA383. (3) In addition, as no biologic treatment for axial spondyloarthritis has demonstrated an effect on mortality outcomes in the context of a clinical trial, background mortality for the general UK population and standardised mortality ratios for axial spondyloarthritis will be captured in the model. References 1. https://www.nice.org.uk/guidance/ta537 2. https://www.nice.org.uk/guidance/ta442 https://www.nice.org.uk/guidance/ta383	
	BSR	Yes	Comment noted.
	NASS	Yes	Comment noted.
	AbbVie	No comment.	Response noted.
	Novartis	Specified outcomes are appropriate, however “Adverse effects of treatment” and “health-related quality of life” have been duplicated in the list.	Comment noted. The duplicated outcomes have been removed.

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Economic analysis	Eli Lilly	An economic analysis that addresses the requirements of the NICE reference case will be submitted. Cost-effectiveness results will be expressed as incremental cost per quality-adjusted life year, with a lifetime model horizon, considering costs from an NHS and PSS perspective. The cost of biosimilar adalimumab, biosimilar etanercept and biosimilar infliximab will be taken into consideration in the base case analysis. Results will be presented using the list price for treatments in the base case due to the confidentiality of the PAS for both ixekizumab and secukinumab. The PAS for certolizumab pegol will be taken into account.	Comments noted.
	BSR	Work productivity measures would be useful	Comment noted. The reference case stipulates that costs should be considered from an NHS and Personal Social Services perspective. Please see Guide to the methods of technology appraisal 2013.
	NASS	No comment.	Response noted.
	AbbVie	No comment.	Response noted.
	Novartis	We consider that it would be more appropriate to move the statement on biosimilars; “The availability and cost of biosimilar products should be taken into account”, which is currently included as an “other consideration”, to the “economic analysis” section.	Comment noted. No action required.
	Eli Lilly	No further comment.	Response noted.

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Equality and Diversity	BSR	Yes.	Response noted.
	NASS	No comment.	Response noted.
	AbbVie	No comment.	Response noted.
	Novartis	No comment.	Response noted.
Other considerations	Eli Lilly	An additional subgroup for consideration is inflammation severity at baseline. Where a biosimilar version of a comparator is available, the lowest cost will be used for the comparator in the economic analysis.	Comments noted. The committee will consider evidence presented for additional subgroups during the appraisal.
	BSR	None.	Comment noted.
	NASS	No comment.	Response noted.
	AbbVie	No comment.	Response noted.
	Novartis	We consider that it would be more appropriate to move the statement on biosimilars; “The availability and cost of biosimilar products should be taken into account”, which is currently included as an “other consideration”, to the “economic analysis” section.	Comment noted. No action required.
Innovation	Eli Lilly	Ixekizumab is the first monoclonal antibody to block both active forms of IL-17A (IL-17A is expressed in both homodimer and heterodimer forms). Furthermore, it has a high binding affinity to both forms of IL-17A.	Comment noted. The appraisal committee will consider the innovative nature of

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		Ixekizumab offers an alternative mechanism of action to TNF-alpha inhibitors, the first biologic therapy to do so in non-radiographic axial spondyloarthritis and the second IL-17 in radiographic axial spondyloarthritis. Furthermore, the COAST-W trial (NCT02696798) is the only trial to be conducted in an entirely TNF-inadequate responder population and has 316 patients randomised to ixekizumab or placebo.	ixekizumab during the appraisal.
	BSR	No.	Comment noted.
	NASS	NASS considers the technology to be innovative and could make a substantial impact on the lives of those who have not responded to or tolerated NSAIDs.	Comment noted. The appraisal committee will consider the innovative nature of ixekizumab during the appraisal.
	AbbVie	No comment.	Response noted.
	Novartis	No comment.	Response noted.
Questions for consultation	Eli Lilly	Our comments on comparators and outcomes have been captured above. NSAIDs and TNF inhibitors are established clinical practice in both radiographic and non-radiographic axial spondyloarthritis. Established clinical practice in radiographic axial spondyloarthritis also includes secukinumab as a treatment option. Ixekizumab is expected to receive marketing authorisation and be used in an adult population with [redacted].	Comments noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		Our comments on sub-groups for consideration have been captured above. Ixekizumab will likely fit into the treatment pathway where axial spondyloarthritis patients are currently being treated with TNF-inhibitors and secukinumab in the NHS, with the potential of also being available as an option for patients for whom TNF-alpha inhibitors have not been adequately effective or cannot be tolerated. Lilly believe that an appraisal of ixekizumab through the STA process is appropriate in order for NICE to be able to provide timely advice to the NHS.	
	BSR	None.	Comment noted.
	NASS	NASS considers ixekizumab will fit into the existing NICE pathway for spondyloarthritis after 'non-steroidal anti-inflammatory drugs' as part of 'choice of biological therapy for pain relief'.	Comment noted.
	AbbVie	"Is ixekizumab intended to be used in the same population that adalimumab, certolizumab pegol, etanercept and golimumab have a NICE recommendation (that is severe non‑radiographic axial spondyloarthritis)?" The comparators stated are also recommended for radiographic axial spondyloarthritis.	Comment noted.
	Novartis	Have all relevant comparators for ixekizumab been included in the scope? *Novartis: Comparators seem appropriate. It is important that the comparator set differs for radiographic axial spondyloarthritis versus non-radiographic spondyloarthritis.* Is ixekizumab intended to be used in the same population that adalimumab, certolizumab pegol, etanercept and golimumab have a NICE recommendation (that is severe non-radiographic axial spondyloarthritis)?	Comments noted.

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		Novartis: Trial inclusion criteria for COAST-X (NCT02757352), the study of ixekizumab in patients with nonradiographic axial spondyloarthritis, seem aligned to those for the anti-TNF trials such as RAPID-AxSpA. For example; disease fulfils ASAS criteria, history of back pain ≥ 3 months, active disease i.e. BASDAI ≥ 4, sacroiliitis on MRI and / or elevated CRP &, inadequate response to NSAIDs. Therefore we would anticipate that ixekizumab will be considered clinically appropriate for the same population as adalimumab, certolizumab pegol, etanercept and golimumab. Which treatments are considered to be established clinical practice in the NHS for: • radiographic axial spondyloarthritis • non-radiographic axial spondyloarthritis? *Novartis: For radiographic axial spondyloarthritis, MQT data to December 2018 indicates that Humira dominates, with [redacted]% patient share, followed by Benepali with [redacted]% share. Cosentyx, Cimzia, Enbrel and Erelzi and Simponi, all have smaller patient shares. For non-radiographic axial spondyloarthritis, MQT data to December 2018 indicates that Humira dominates, with [redacted]% patient share, followed by Benepali with [redacted]% share, and Cimzia with [redacted]% share. Enbrel and Simponi also have small shares.* Are the outcomes listed appropriate? *Novartis: See comments above on "Outcomes"* Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom ixekizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? *Novartis: No comment.*	

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		Where do you consider secukinumab will fit into the existing NICE pathway, 'spondyloarthritis'? *Novartis: We would expect ixekizumab to be positioned alongside the other biologics recommended by NICE for treating severe axial spondyloarthritis.* NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. *Novartis: No comment.* Do you consider ixekizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? *Novartis: An IL-17A inhibitor (secukinumab) is already licensed and NICE approved for the treatment of ankylosing spondylitis. As the second IL-17A inhibitor to market, we do not consider ixekizumab to represent an innovative treatment option.* Do you consider that the use of ixekizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? *Novartis: No comment.* Do you consider that there will be any barriers to adoption of this technology into practice? *Novartis: No comment.* NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process.	

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		Would it be appropriate to use the cost comparison methodology for this topic? *Novartis: No comment.* Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? *Novartis: No comment.* Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? *Novartis: The primary outcome of the COAST studies (NCT02757352, NCT02696785 and NCT02696798) is ASAS40. Previous models in axial spondyloarthritis have defined response based on BASDAI50 and have tracked both BASDAI and BASFI over time to determine anticipated health benefits. Whilst BASDAI and BASFI are still clinically relevant, both ASAS and ASDAS are increasingly clinically relevant. These outcomes could in future form the basis of alternative modelling approaches in axial spondyloarthritis.* Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? *Novartis: Publication of evidence on secukinumab in non-radiographic axial spondyloarthritis is anticipated in Q2 2020. 5 year data from MEASURE 1 for secukinumab in AS was published at ACR 2018.[1] Publication of 5 year data from MEASURE 2 is anticipated at EULAR 2019.* *1 X Baraliakos, J Braun, A Deodhar, D Poddubnyy, AJ Kivitz, H Tahir, F Van Den Bosch, EM Delicha, Z Talloczy, A Fierlinger on behalf of the MEASURE 1 study group. Long-term Evaluation of Secukinumab in Ankylosing Spondylitis: 5 Years Efficacy and Safety Results from a Phase 3 Trial. Poster presented at American College of Rheumatology (ACR) Annual Meeting, October 19 – 24, 2018, Chicago, United States.*	

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	Eli Lilly	None.	Comment noted.
	BSR	Useful to have another agent to increase treatment options in axial SpA	Comment noted.
	NASS	No response.	Response noted.
	AbbVie	No response.	Response noted.
	Novartis	None.	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope:

Amgen, Merck Sharp & Dohme, UCB.