NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Contents:

The following documents are made available to consultees and commentators:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Ixekizumab for treating axial spondyloarthritis

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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 number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1.	Company	Eli Lilly and Company Limited (Lilly)	Lilly would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for ixekizumab for treating axial spondyloarthritis (axSpA) [ID1532]. We are disappointed that the Appraisal Committee have made the preliminary decision not to recommend ixekizumab for this patient group as clinical and patient feedback throughout this appraisal has indicated a considerable unmet need for alternative treatment options in these patients. This need has been heightened by the ongoing COVID-19 pandemic, with nearly half of surveyed axSpA patients in the UK reporting that their symptoms had worsened during the pandemic.[1] We hope that the Committee will consider the additional evidence provided within this response document sufficient to make ixekizumab available for patients with axSpA. In alignment with the Committee's suggestion and to address the Committee's concerns regarding the most relevant comparator to ixekizumab in UK clinical practice, and the reliability of the indirect comparison results for decision-making, Lilly present further economic analyses using data directly from the COAST clinical trials programme to compare ixekizumab with conventional care (CC). These economic analyses are associated with an incremental cost-effectiveness ratio (ICER) below the willingness-to-pay (WTP) threshold of £30,000 in both the radiographic (rad-axSpA) and non-radiographic (nr-axSpA) populations, thus demonstrating ixekizumab to be a cost-effective use of NHS resources across the spectrum of axSpA. Lilly welcome the opportunity to present our response to this preliminary recommendation from NICE and, based on the results of these further analyses, hope that the Committee will revisit their	Thank you for your comments. The recommendations for ixekizumab have changed after consideration of the new analyses using direct data from the COAST trials in the cost effectiveness analyses.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			preliminary decision regarding the cost-effectiveness of ixekizumab and will recommend it as a treatment option for patients with axSpA.	
2.	Company	Eli Lilly and Company Limited (Lilly)	**Section 3.12, page 14:** The ACD states: "*The committee would like to see a comparison of ixekizumab with conventional therapy using direct evidence from the COAST trials*." As noted by the Committee, the COAST trials provide direct evidence for the efficacy of ixekizumab versus placebo, which is considered to be a suitable proxy for conventional therapy. In these trials, the use of NSAIDs, analgesics, cDMARDs and corticosteroids was permitted in both study arms as per the trial protocol. Therefore, the Company agree with the conclusion of the ERG that it is reasonable to consider placebo to be a proxy for established clinical management without biological treatments (Technical Report, Comparator(s) row of Decision Problem table, page 9), and thus performed cost-effectiveness analyses in which the data informing conventional care are sourced from the placebo arm of the appropriate COAST trial. The use of these direct data in the cost-effectiveness analyses removes the need for use of data derived from the NMA, respecting the Committee's conclusion that "*the results of the model using the NMA are not reliable for decision making*" (ACD, Section 3.10) and thus represents "*the most robust way of assessing the cost effectiveness of ixekizumab*" (Committee conclusion, ACD, Section 3.12). The results of these analyses in the biologic-naïve rad-axSpA population (COAST-V), biologic-experienced rad-axSpA population (COAST-W) and biologic-naïve nr-axSpA population (COAST-X) are presented in **Error! Reference source not found.**, **Error! Reference source not found.** and **Error! Reference source not found.** [removed from this document]. These results show that as compared with conventional care, ixekizumab represents a cost-effective use of NHS resources, with the ICERs in all three populations falling under the WTP threshold of £30,000 per QALY. Informed by clinical efficacy data derived from randomised controlled and appropriately powered clinical trials, these	The committee maintains its decision that the results of the model using the network meta-analysis are not reliable for decision making. The company's analyses comparing ixekizumab with conventional therapy using direct evidence from the COAST trials have been accepted and ixekizumab has been appraised as cost effective compared with conventional therapy (FAD 3.7, 3.10, 3.12, 3.13).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			results provide robust estimates for decision making. The Company understand the concerns raised by the Committee regarding the generalisability of efficacy results across rad-axSpA and nr-axSpA populations (ACD, Section 3.5). However, the above ICERs demonstrate ixekizumab to be a cost-effective treatment at the naïve and experienced positions of the treatment pathway across the full spectrum of axSpA. The Company hope the Committee will find these data sufficient to recommend ixekizumab as a treatment option for all patients across the axSpA spectrum who have not responded to, or are contraindicated to, TNF alpha inhibition.	
3.	Company	Eli Lilly and Company Limited (Lilly)	**Section 3.9, page 12:** The ACD states: "*The ERG said it could not comment on the validity of the company's class-effect assumption. This is because the company had not done an appropriate statistical analysis comparing relative treatment effects for TNF-alpha inhibitors and IL-17-a inhibitors […] The committee concluded that a class effect had not been established for all TNF-alpha inhibitors and IL17-a inhibitors.*" The Company acknowledge the concerns of the ERG and the Committee regarding the conclusion of a class effect based on the NMA data presented at Technical Engagement, which showed the relative treatment effect of biologics, including ixekizumab, versus placebo. In order to aid interpretation, the Company present these data expressed as the relative treatment effect of ixekizumab versus each bDMARD comparator (**Error! Reference source not found.** [removed from this document]). These results show that for the outcomes analysed (ASAS40, BASDAI50, BASDAI change from baseline [cfb] and BASFI cfb), there is no statistically significant difference between ixekizumab and the other biologics with the credible intervals and posterior median outcomes of the biologics assessed crossing 1 for every biologic comparator in every outcome. Based on these results, the Company hope that the Committee will re-consider the validity of an assumed class effect between biologics in rad- and nr-axSpA patients.	The committee considered that it is not reasonable to assume a class effect for all biologic treatments and concluded that the company's updated model assuming a class effect for biologic treatments is not appropriate (FAD 3.9 and 3.11).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			The results presented in **Error! Reference source not found.** [removed from this document] are informed by the base case NMA approach. For completeness, results informed by the sensitivity analysis approach of including studies with mixed or unclear patient populations are presented in **Error! Reference source not found.** [removed from this document], although as noted by the ERG (ACD, page 10), the sensitivity analysis approach is less reliable than the base case approach.	
4.	Company	Eli Lilly and Company Limited (Lilly)	**Page 2:** The ACD states: "*Ixekizumab would be offered when people cannot have tumour necrosis factor (TNF)-alpha inhibitors, or they have not worked well enough. The current treatment option in these situations is conventional therapy, which includes nonsteroidal anti-inflammatory drugs (NSAIDs) and physiotherapy*." The Company acknowledge the NICE Committee's rationale for deeming conventional care to be the most reliable comparator to ixekizumab. However, clinical expert opinion received over the course of this appraisal is that in UK clinical practice, not all patients in whom TNF-alpha inhibition has worked insufficiently, either due to primary or secondary non-response, would be removed from biologic therapy and returned to conventional care. Instead, some patients may receive newer TNF-alpha inhibitor options recommended by NICE in axSpA, for example, golimumab or certolizumab pegol, on the rationale that even a sub-optimal response to these therapies may be greater than the expected response to conventional care alone. Therefore, the Company provide the cost comparison results between ixekizumab, golimumab and certolizumab pegol previously provided at the Technical Engagement step as an alternative comparison in the post-TNF failure population for the Committee's consideration. These results in the biologic-experienced rad-axSpA population (COAST-W) and biologic-naïve nr-axSpA population (COAST-X) are presented in **Error! Reference source not found.** and **Error! Reference source not found.** [removed from this document]. These cost comparison analyses show that in both the biologic-	The committee noted the company's comment that not all patients in whom TNF-alpha inhibitors have worked insufficiently, either due to primary or secondary non-response, would be removed from biologic therapy and returned to conventional therapy. The committee accepted that some patients may receive newer TNF-alpha inhibitor options such as golimumab or certolizumab pegol. However, it concluded that conventional therapy was the most reliable comparator for ixekizumab based on available evidence (FAD 3.4).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			experienced rad-axSpA and biologic-naïve nr-axSpA populations, over a lifetime horizon, ixekizumab is associated with either a comparable or less expensive total cost as compared with two TNF-alpha inhibitors typically used at later line therapy following previous TNF-alpha inhibition failure.	
1.	Comparator company	Novartis Pharmaceuticals UK Ltd	Secukinumab is going through NICE appraisal currently for the treatment of non-radiographic axial spondyloarthritis (ID1419). Please could we request a small change for improved clarity in future ixekizumab documents given the positive Appraisal Consultation Document draft recommendation for secukinumab (ID1419); On page 6, section 3.2 please consider changing *"It would be particularly beneficial to patients with non-radiographic axial spondyloarthritis for whom the only biologics available are TNF-alpha inhibitors."* to *"It would be particularly beneficial to patients with non-radiographic axial spondyloarthritis for whom the only biologics currently available are TNF-alpha inhibitors."*	The editorial change suggested by the comparator company has been applied in the FAD (3.2).
2.	Comparator company	Novartis Pharmaceuticals UK Ltd	We disagree with the sentence on page 7, section 3.3. We consider it misleading as it currently reads.. *"IL-17-a inhibitors would not be expected to replace TNF-alpha inhibitors as the standard first-line treatment because they are more expensive and there is less clinical experience with using them."* Secukinumab is an IL-17 inhibitor and it is cheaper than at least two tumour necrosis factor-alp ha inhibitors.. Please could the sentence be corrected to read... *"IL-17-a inhibitors would not be expected to replace TNF-alpha inhibitors as the standard first-line treatment because they are more expensive than biosimilar TNF-alpha inhibitors and there is less clinical experience with using them."*	The editorial change suggested by the comparator company has been applied in the FAD (3.3).

NICE National Institute for Health and Care Excellence

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 20 April 2021 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eli Lilly and Company Limited (Lilly)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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NICE National Institute for Health and Care Excellence

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 20 April 2021 **email:** NICE DOCS

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Lilly would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for ixekizumab for treating axial spondyloarthritis (axSpA) [ID1532]. We are disappointed that the Appraisal Committee have made the preliminary decision not to recommend ixekizumab for this patient group as clinical and patient feedback throughout this appraisal has indicated a considerable unmet need for alternative treatment options in these patients. This need has been heightened by the ongoing COVID-19 pandemic, with nearly half of surveyed axSpA patients in the UK reporting that their symptoms had worsened during the pandemic.[1] We hope that the Committee will consider the additional evidence provided within this response document sufficient to make ixekizumab available for patients with axSpA. In alignment with the Committee's suggestion and to address the Committee's concerns regarding the most relevant comparator to ixekizumab in UK clinical practice, and the reliability of the indirect comparison results for decision-making, Lilly present further economic analyses using data directly from the COAST clinical trials programme to compare ixekizumab with conventional care (CC). These economic analyses are associated with an incremental cost-effectiveness ratio (ICER) below the willingness-to-pay (WTP) threshold of £30,000 in both the radiographic (rad-axSpA) and non-radiographic (nr-axSpA) populations, thus demonstrating ixekizumab to be a cost-effective use of NHS resources across the spectrum of axSpA. Lilly welcome the opportunity to present our response to this preliminary recommendation from NICE and, based on the results of these further analyses, hope that the Committee will revisit their preliminary decision regarding the cost-effectiveness of ixekizumab and will recommend it as a treatment option for patients with axSpA.
2	**Section 3.12, page 14:** The ACD states: "*The committee would like to see a comparison of ixekizumab with conventional therapy using direct evidence from the COAST trials*." As noted by the Committee, the COAST trials provide direct evidence for the efficacy of ixekizumab versus placebo, which is considered to be a suitable proxy for conventional therapy. In these trials, the use of NSAIDs, analgesics, cDMARDs and corticosteroids was permitted in both study arms as per the trial protocol. Therefore, the Company agree with the conclusion of the ERG that it is reasonable to consider placebo to be a proxy for established clinical management without biological treatments (Technical Report, Comparator(s) row of Decision Problem table, page 9), and thus performed cost-effectiveness analyses in which the data informing conventional care are sourced from the placebo arm of the appropriate COAST trial. The use of these direct data in the cost-effectiveness analyses removes the need for use of data derived from the NMA, respecting the Committee's conclusion that "*the results of the model using the NMA are not reliable for decision making*" (ACD, Section 3.10) and thus represents "*the most robust way of assessing the cost effectiveness of ixekizumab*" (Committee conclusion, ACD, Section 3.12). The results of these analyses in the biologic-naïve rad-axSpA population (COAST-V), biologic-experienced rad-axSpA population (COAST-W) and biologic-naïve nr-axSpA population (COAST-X) are presented in Table 1, Table 2 and Table 3, respectively. The input efficacy data used in these analyses are presented at the end of this document in Table 6 (COAST-V), Table 7 (COAST-W) and Table 8 (COAST-X).

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Table 1: Cost effectiveness results for ixekizumab versus conventional care in the biologic-naïve rad-axSpA population (COAST-V)

COAST-V	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CC	[redacted]	[redacted]	-	-	-
IXE Q4W	[redacted]	[redacted]	[redacted]	[redacted]	£18,775

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: CC: conventional care; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; Q4W: every four weeks; QALYs: quality-adjusted life years; rad-axSpA: radiographic axial spondyloarthritis.

Table 2: Cost effectiveness results for ixekizumab versus conventional care in the biologic-experienced rad-axSpA population (COAST-W)

COAST-W	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CC	[redacted]	[redacted]	-	-	-
IXE Q4W	[redacted]	[redacted]	[redacted]	[redacted]	£19,012

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: CC: conventional care; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; Q4W: every four weeks; QALYs: quality-adjusted life years; rad-axSpA: radiographic axial spondyloarthritis.

Table 3: Cost effectiveness results for ixekizumab versus conventional care in the biologic-naïve nr-axSpA population (COAST-X)

COAST-X	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CC	[redacted]	[redacted]	-	-	-
IXE Q4W	[redacted]	[redacted]	[redacted]	[redacted]	£24,772

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: CC: conventional care; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; Q4W: every four weeks; QALYs: quality-adjusted life years.

These results show that as compared with conventional care, ixekizumab represents a cost-effective use of NHS resources, with the ICERs in all three populations falling under the WTP threshold of £30,000 per QALY. Informed by clinical efficacy data derived from randomised controlled and appropriately powered clinical trials, these results provide robust estimates for decision making.

The Company understand the concerns raised by the Committee regarding the generalisability of efficacy results across rad-axSpA and nr-axSpA populations (ACD, Section 3.5). However, the above ICERs demonstrate ixekizumab to be a cost-effective treatment at the naïve and experienced positions of the treatment pathway across the full spectrum of axSpA. The Company hope the Committee will find these data sufficient to recommend ixekizumab as a treatment option for all patients across the axSpA spectrum who have not responded to, or are contraindicated to, TNF alpha inhibition.

3

Section 3.9, page 12: The ACD states: "*The ERG said it could not comment on the validity of the company's class-effect assumption. This is because the company had not done an appropriate statistical analysis comparing relative treatment effects for TNF-alpha inhibitors and IL-17-a inhibitors […] The committee concluded that a class effect had not been established for all TNF-alpha inhibitors and IL17-a inhibitors.*"

The Company acknowledge the concerns of the ERG and the Committee regarding the conclusion of a class effect based on the NMA data presented at Technical Engagement, which showed the relative treatment effect of biologics, including ixekizumab, versus placebo.

	In order to aid interpretation, the Company present these data expressed as the relative treatment effect of ixekizumab versus each bDMARD comparator (Table 9, found at the end of this document). These results show that for the outcomes analysed (ASAS40, BASDAI50, BASDAI change from baseline [cfb] and BASFI cfb), there is no statistically significant difference between ixekizumab and the other biologics with the credible intervals and posterior median outcomes of the biologics assessed crossing 1 for every biologic comparator in every outcome. Based on these results, the Company hope that the Committee will re-consider the validity of an assumed class effect between biologics in rad- and nr-axSpA patients. The results presented in Table 9 are informed by the base case NMA approach. For completeness, results informed by the sensitivity analysis approach of including studies with mixed or unclear patient populations are presented in Table 10, although as noted by the ERG (ACD, page 10), the sensitivity analysis approach is less reliable than the base case approach.
4	**Page 2:** The ACD states: "*Ixekizumab would be offered when people cannot have tumour necrosis factor (TNF)-alpha inhibitors or they have not worked well enough. The current treatment option in these situations is conventional therapy, which includes nonsteroidal anti-inflammatory drugs (NSAIDs) and physiotherapy*." The Company acknowledge the NICE Committee's rationale for deeming conventional care to be the most reliable comparator to ixekizumab. However, clinical expert opinion received over the course of this appraisal is that in UK clinical practice, not all patients in whom TNF-alpha inhibition has worked insufficiently, either due to primary or secondary non-response, would be removed from biologic therapy and returned to conventional care. Instead, some patients may receive newer TNF-alpha inhibitor options recommended by NICE in axSpA, for example, golimumab or certolizumab pegol, on the rationale that even a sub-optimal response to these therapies may be greater than the expected response to conventional care alone. Therefore, the Company provide the cost comparison results between ixekizumab, golimumab and certolizumab pegol previously provided at the Technical Engagement step as an alternative comparison in the post-TNF failure population for the Committee's consideration. These results in the biologic-experienced rad-axSpA population (COAST-W) and biologic-naïve nr-axSpA population (COAST-X) are presented in Table 4 and Table 5, respectively. **Table 4: Economic analysis results for IXE Q4W (with PAS) versus GOL and CZP with assumed class effects: biologic-experienced rad-axSpA (COAST-W)** **COAST-W** | **Total costs (£)** | **Incremental costs (£)** CZP | [redacted] | - IXE Q4W | [redacted] | [redacted] GOL | [redacted] | [redacted] The ixekizumab pooled 80 mg and 160 mg loading dose was considered. **Abbreviations:** CZP: certolizumab pegol; GOL: golimumab; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; LD: loading dose; Q4W: every four weeks; QALYs: quality-adjusted life years; rad-axSpA: radiographic axial spondyloarthritis. **Table 5: Economic analysis results for IXE Q4W (with PAS) versus GOL and CZP with assumed class effects: biologic-naïve nr-axSpA population (COAST-X)** **COAST-X** | **Total costs (£)** | **Incremental costs (£)** IXE Q4W | [redacted] | -

	CZP	[redacted]	[redacted]
	GOL	[redacted]	[redacted]

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: CZP: certolizumab pegol; GOL: golimumab; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; LD: loading dose; nr-axSpA: non-radiographic axial spondyloarthritis; Q4W: every four weeks; QALYs: quality-adjusted life years.

These cost comparison analyses show that in both the biologic-experienced rad-axSpA and biologic-naïve nr-axSpA populations, over a lifetime horizon, ixekizumab is associated with either a comparable or less expensive total cost as compared with two TNF-alpha inhibitors typically used at later line therapy following previous TNF-alpha inhibition failure.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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.

References

1. Marzo-Ortega H, Whalley S, Hamilton J, et al. COVID-19 in axial spondyloarthritis care provision: helping to straighten the long and winding road. The Lancet Rheumatology 2021;3:e11-e13.

Table 6: Efficacy inputs for the model for COAST-V (rad-axSpA, biologic-naïve)

Treatment	BASDAI50			BASDAI cfb				BASFI cfb			
	Proportion	Lower 95% CrI	Upper 95% CrI	LSM	SE	Lower 95% CrI	Upper 95% CrI	LSM	SE	Lower 95% CrI	Upper 95% CrI
Placebo	[redacted]										
IXE Q4W	[redacted]										

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; IXE: ixekizumab; LSM: least squares mean; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SE: standard error.

Table 7: Efficacy inputs for the model for COAST-W (rad-axSpA, biologic-experienced)

Treatment	BASDAI50			BASDAI cfb				BASFI cfb			
	Proportion	Lower 95% CrI	Upper 95% CrI	LSM	SE	Lower 95% CrI	Upper 95% CrI	LSM	SE	Lower 95% CrI	Upper 95% CrI
Placebo	[redacted]										
IXE Q4W	[redacted]										

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; IXE: ixekizumab; LSM: least squares mean; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SE: standard error.

Table 8: Efficacy inputs for the model for COAST-X (nr-axSpA, biologic-naïve)

Treatment	BASDAI50			BASDAI cfb				BASFI cfb			
	Proportion	Lower 95% CrI	Upper 95% CrI	LSM	SE	Lower 95% CrI	Upper 95% CrI	LSM	SE	Lower 95% CrI	Upper 95% CrI
Placebo	[redacted]										
IXE Q4W	[redacted]										

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; IXE: ixekizumab; LSM: least squares mean; nr-axSpA: non-radiographic axial spondyloarthritis; Q4W: every four weeks; SE: standard error.

Table 9: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (binary endpoints) or MDs (continuous endpoints) (with 95% CrI) versus ixekizumab 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	Lower 95% CrI	Upper 95% CrI	OR	Lower 95% CrI	Upper 95% CrI	MD	Lower 95% CrI	Upper 95% CrI	MD	Lower 95% CrI	Upper 95% CrI
Placebo	[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

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
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; CrI: 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 10: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (binary endpoints) or MDs (continuous endpoints) (with 95% CrI) versus ixekizumab 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	Lower 95% CrI	Upper 95% CrI	OR	Lower 95% CrI	Upper 95% CrI	MD	Lower 95% CrI	Upper 95% CrI	MD	Lower 95% CrI	Upper 95% CrI
Placebo	[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 9 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. The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
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; CrI: 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.

NICE National Institute for Health and Care Excellence

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 20 April 2021 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
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.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 20 April 2021 **email:** NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Secukinumab is going through NICE appraisal currently for the treatment of non-radiographic axial spondyloarthritis (ID1419). Please could we request a small change for improved clarity in future ixekizumab documents given the positive Appraisal Consultation Document draft recommendation for secukinumab (ID1419); On page 6, section 3.2 please consider changing *"It would be particularly beneficial to patients with non-radiographic axial spondyloarthritis for whom the only biologics available are TNF-alpha inhibitors."* to *"It would be particularly beneficial to patients with non-radiographic axial spondyloarthritis for whom the only biologics currently available are TNF-alpha inhibitors."*
2	We disagree with the sentence on page 7, section 3.3. We consider it misleading as it currently reads.. *"IL-17-a inhibitors would not be expected to replace TNF-alpha inhibitors as the standard first-line treatment because they are more expensive and there is less clinical experience with using them."* Secukinumab is an IL-17 inhibitor and it is cheaper than at least two tumour necrosis factor-alpha inhibitors.. Please could the sentence be corrected to read... *"IL-17-a inhibitors would not be expected to replace TNF-alpha inhibitors as the standard first-line treatment because they are more expensive than biosimilar TNF-alpha inhibitors and there is less clinical experience with using them."*

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

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NICE National Institute for Health and Care Excellence

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 20 April 2021 **email:** NICE DOCS

- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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.

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ERG critique of the company response to the ACD

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

ERG critique of the company response to the ACD

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number NIHR 17/156/08

Completed 26th April 2021

CONTAINS [redacted] AND [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

NICE National Institute for Health and Care Excellence

Ixekizumab for treating axial spondyloarthritis after NSAIDs [ID1532]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 20 April 2021 **email:** NICE DOCS

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Lilly would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for ixekizumab for treating axial spondyloarthritis (axSpA) [ID1532]. We are disappointed that the Appraisal Committee have made the preliminary decision not to recommend ixekizumab for this patient group as clinical and patient feedback throughout this appraisal has indicated a considerable unmet need for alternative treatment options in these patients. This need has been heightened by the ongoing COVID-19 pandemic, with nearly half of surveyed axSpA patients in the UK reporting that their symptoms had worsened during the pandemic.[1] We hope that the Committee will consider the additional evidence provided within this response document sufficient to make ixekizumab available for patients with axSpA. In alignment with the Committee's suggestion and to address the Committee's concerns regarding the most relevant comparator to ixekizumab in UK clinical practice, and the reliability of the indirect comparison results for decision-making, Lilly present further economic analyses using data directly from the COAST clinical trials programme to compare ixekizumab with conventional care (CC). These economic analyses are associated with an incremental cost-effectiveness ratio (ICER) below the willingness-to-pay (WTP) threshold of £30,000 in both the radiographic (rad-axSpA) and non-radiographic (nr-axSpA) populations, thus demonstrating ixekizumab to be a cost-effective use of NHS resources across the spectrum of axSpA. Lilly welcome the opportunity to present our response to this preliminary recommendation from NICE and, based on the results of these further analyses, hope that the Committee will revisit their preliminary decision regarding the cost-effectiveness of ixekizumab and will recommend it as a treatment option for patients with axSpA.
ERG comment	No comment
2	**Section 3.12, page 14:** The ACD states: "*The committee would like to see a comparison of ixekizumab with conventional therapy using direct evidence from the COAST trials*." As noted by the Committee, the COAST trials provide direct evidence for the efficacy of ixekizumab versus placebo, which is considered to be a suitable proxy for conventional therapy. In these trials, the use of NSAIDs, analgesics, cDMARDs and corticosteroids was permitted in both study arms as per the trial

protocol. Therefore, the Company agree with the conclusion of the ERG that it is reasonable to consider placebo to be a proxy for established clinical management without biological treatments (Technical Report, Comparator(s) row of Decision Problem table, page 9), and thus performed cost-effectiveness analyses in which the data informing conventional care are sourced from the placebo arm of the appropriate COAST trial.

The use of these direct data in the cost-effectiveness analyses removes the need for use of data derived from the NMA, respecting the Committee's conclusion that "*the results of the model using the NMA are not reliable for decision making*" (ACD, Section 3.10) and thus represents "*the most robust way of assessing the cost effectiveness of ixekizumab*" (Committee conclusion, ACD, Section 3.12).

The results of these analyses in the biologic-naïve rad-axSpA population (COAST-V), biologic-experienced rad-axSpA population (COAST-W) and biologic-naïve nr-axSpA population (COAST-X) are presented in Table 1, Table 2 and Table 3, respectively. The input efficacy data used in these analyses are presented at the end of this document in Table 6 (COAST-V), Table 7 (COAST-W) and Table 8 (COAST-X).

Table 1: Cost effectiveness results for ixekizumab versus conventional care in the biologic-naïve rad-axSpA population (COAST-V)

COAST-V	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CC	[redacted]	[redacted]	-	-	-
IXE Q4W	[redacted]	[redacted]	[redacted]	[redacted]	£18,775

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: CC: conventional care; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; Q4W: every four weeks; QALYs: quality-adjusted life years; rad-axSpA: radiographic axial spondyloarthritis.

Table 2: Cost effectiveness results for ixekizumab versus conventional care in the biologic-experienced rad-axSpA population (COAST-W)

COAST-W	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CC	[redacted]	[redacted]	-	-	-
IXE Q4W	[redacted]	[redacted]	[redacted]	[redacted]	£19,012

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: CC: conventional care; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; Q4W: every four weeks; QALYs: quality-adjusted life years; rad-axSpA: radiographic axial spondyloarthritis.

Table 3: Cost effectiveness results for ixekizumab versus conventional care in the biologic-naïve nr-axSpA population (COAST-X)

COAST-X	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CC	[redacted]	[redacted]	-	-	-
IXE Q4W	[redacted]	[redacted]	[redacted]	[redacted]	£24,772

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: CC: conventional care; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; nr-axSpA: non-radiographic axial spondyloarthritis; Q4W: every four weeks; QALYs: quality-adjusted life years.

These results show that as compared with conventional care, ixekizumab represents a cost-effective use of NHS resources, with the ICERs in all three populations falling under the WTP threshold of £30,000 per QALY. Informed by clinical efficacy data derived from randomised controlled and appropriately

	powered clinical trials, these results provide robust estimates for decision making. The Company understand the concerns raised by the Committee regarding the generalisability of efficacy results across rad-axSpA and nr-axSpA populations (ACD, Section 3.5). However, the above ICERs demonstrate ixekizumab to be a cost-effective treatment at the naïve and experienced positions of the treatment pathway across the full spectrum of axSpA. The Company hope the Committee will find these data sufficient to recommend ixekizumab as a treatment option for all patients across the axSpA spectrum who have not responded to, or are contraindicated to, TNF alpha inhibition.
ERG comment	The ERG can confirm that the cost effectiveness results presented by the company in this document can be reproduced by the model submitted after ACM1 Conventional care is only an appropriate comparator for the biologic-naïve TNF-alpha inhibitor contraindicated or the biologic-experienced nr-axSpA populations as secukinumab is not currently a treatment option for these populations
3	**Section 3.9, page 12:** The ACD states: "*The ERG said it could not comment on the validity of the company's class-effect assumption. This is because the company had not done an appropriate statistical analysis comparing relative treatment effects for TNF-alpha inhibitors and IL-17-a inhibitors […] The committee concluded that a class effect had not been established for all TNF-alpha inhibitors and IL17-a inhibitors.*" **The Company acknowledge the concerns of the ERG and the Committee regarding the conclusion of a class effect based on the NMA data presented at Technical Engagement, which showed the relative treatment effect of biologics, including ixekizumab, versus placebo. In order to aid interpretation, the Company present these data expressed as the relative treatment effect of ixekizumab versus each bDMARD comparator (** Table 9, found at the end of this document). These results show that for the outcomes analysed (ASAS40, BASDAI50, BASDAI change from baseline [cfb] and BASFI cfb), there is no statistically significant difference between ixekizumab and the other biologics with the credible intervals and posterior median outcomes of the biologics assessed crossing 1 for every biologic comparator in every outcome. Based on these results, the Company hope that the Committee will re-consider the validity of an assumed class effect between biologics in rad- and nr-axSpA patients. **The results presented in** Table 9 are informed by the base case NMA approach. For completeness, results informed by the sensitivity analysis approach of including studies with mixed or unclear patient populations are presented in Table 10, although as noted by the ERG (ACD, page 10), the sensitivity analysis approach is less reliable than the base case approach.

<table>
<tr><td>ERG response</td><td>The appropriate statistical tests of equivalence of biologic treatments have not been carried out. Overlapping confidence intervals provide insufficient evidence to demonstrate equivalence</td></tr>
<tr><td>4</td><td>
Page 2: The ACD states: “Ixekizumab would be offered when people cannot have tumour necrosis factor (TNF)-alpha inhibitors or they have not worked well enough. The current treatment option in these situations is conventional therapy, which includes nonsteroidal anti-inflammatory drugs (NSAIDs) and physiotherapy.”

The Company acknowledge the NICE Committee’s rationale for deeming conventional care to be the most reliable comparator to ixekizumab. However, clinical expert opinion received over the course of this appraisal is that in UK clinical practice, not all patients in whom TNF-alpha inhibition has worked insufficiently, either due to primary or secondary non-response, would be removed from biologic therapy and returned to conventional care. Instead, some patients may receive newer TNF-alpha inhibitor options recommended by NICE in axSpA, for example, golimumab or certolizumab pegol, on the rationale that even a sub-optimal response to these therapies may be greater than the expected response to conventional care alone.

Therefore, the Company provide the cost comparison results between ixekizumab, golimumab and certolizumab pegol previously provided at the Technical Engagement step as an alternative comparison in the post-TNF failure population for the Committee’s consideration. These results in the biologic-experienced rad-axSpA population (COAST-W) and biologic-naïve nr-axSpA population (COAST-X) are presented in Table 4 and Table 5, respectively.

Table 4: Economic analysis results for IXE Q4W (with PAS) versus GOL and CZP with assumed class effects: biologic-experienced rad-axSpA (COAST-W)
<table>
<tr><th>COAST-W</th><th>Total costs (£)</th><th>Incremental costs (£)</th></tr>
<tr><td>CZP</td><td>[redacted]</td><td>-</td></tr>
<tr><td>IXE Q4W</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>GOL</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: CZP: certolizumab pegol; GOL: golimumab; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; LD: loading dose; Q4W: every four weeks; QALYs: quality-adjusted life years; rad-axSpA: radiographic axial spondyloarthritis.

Table 5: Economic analysis results for IXE Q4W (with PAS) versus GOL and CZP with assumed class effects: biologic-naïve nr-axSpA population (COAST-X)
<table>
<tr><th>COAST-X</th><th>Total costs (£)</th><th>Incremental costs (£)</th></tr>
<tr><td>IXE Q4W</td><td>[redacted]</td><td>-</td></tr>
<tr><td>CZP</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>GOL</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: CZP: certolizumab pegol; GOL: golimumab; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; LD: loading dose; nr-axSpA: non-radiographic axial spondyloarthritis; Q4W: every four weeks; QALYs: quality-adjusted life years.

These cost comparison analyses show that in both the biologic-experienced rad-axSpA and biologic-naïve nr-axSpA populations, over a lifetime horizon, ixekizumab is associated with either a comparable or less expensive total cost as
</td></tr>
</table>

	compared with two TNF-alpha inhibitors typically used at later line therapy following previous TNF-alpha inhibition failure.
ERG comment	As previously stated in the ERG response to the company response to technical engagement, the ERG does not 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 evidence presented by the company. As such, the results presented in Table 4 and Table 5 remain unsuitable for decision making

1 REFERENCES

1. Marzo-Ortega H, Whalley S, Hamilton J, et al. COVID-19 in axial spondyloarthritis care provision: helping to straighten the long and winding road. The Lancet Rheumatology 2021;3:e11-e13.

Table 6: Efficacy inputs for the model for COAST-V (rad-axSpA, biologic-naïve)

Treatment	BASDAI50			BASDAI cfb				BASFI cfb			
	Proportion	Lower 95% CrI	Upper 95% CrI	LSM	SE	Lower 95% CrI	Upper 95% CrI	LSM	SE	Lower 95% CrI	Upper 95% CrI
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; IXE: ixekizumab; LSM: least squares mean; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SE: standard error.

Table 7: Efficacy inputs for the model for COAST-W (rad-axSpA, biologic-experienced)

Treatment	BASDAI50			BASDAI cfb				BASFI cfb			
	Proportion	Lower 95% CrI	Upper 95% CrI	LSM	SE	Lower 95% CrI	Upper 95% CrI	LSM	SE	Lower 95% CrI	Upper 95% CrI
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; IXE: ixekizumab; LSM: least squares mean; Q4W: every four weeks; rad-axSpA: radiographic axial spondyloarthritis; SE: standard error.

Table 8: Efficacy inputs for the model for COAST-X (nr-axSpA, biologic-naïve)

Treatment	BASDAI50			BASDAI cfb				BASFI cfb			
	Proportion	Lower 95% CrI	Upper 95% CrI	LSM	SE	Lower 95% CrI	Upper 95% CrI	LSM	SE	Lower 95% CrI	Upper 95% CrI
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
Abbreviations: BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; cfb: change from baseline; CrI: credible interval; IXE: ixekizumab; LSM: least squares mean; nr-axSpA: non-radiographic axial spondyloarthritis; Q4W: every four weeks; SE: standard error.

Table 9: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (binary endpoints) or MDs (continuous endpoints) (with 95% CrI) versus ixekizumab 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	Lower 95% CrI	Upper 95% CrI	OR	Lower 95% CrI	Upper 95% CrI	MD	Lower 95% CrI	Upper 95% CrI	MD	Lower 95% CrI	Upper 95% CrI
Placebo	[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

The ixekizumab pooled 80 mg and 160 mg loading dose was considered.
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; CrI: 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 10: Relative treatment effect of pairwise comparisons expressed as posterior median ORs (binary endpoints) or MDs (continuous endpoints) (with 95% CrI) versus ixekizumab 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	Lower 95% CrI	Upper 95% CrI	OR	Lower 95% CrI	Upper 95% CrI	MD	Lower 95% CrI	Upper 95% CrI	MD	Lower 95% CrI	Upper 95% CrI
Placebo	[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 9 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. The ixekizumab pooled 80 mg and 160 mg loading dose was considered.

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; CrI: 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.