NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Eli Lilly
   - Psoriasis Association
   - Psoriasis and Psoriatic Arthritis Alliance
   - British Association of Dermatologists
   - British Society for Rheumatology
   - Abbvie
   - Novartis

   The Department of Health stated that they had no comments

3. **Evidence Review Group addendum**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Ixekizumab for treating moderate to severe plaque psoriasis

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

Definitions:

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 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 determination (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, 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.

Comments received from consultees

Consultee	Comment [sic]	Response
Eli Lilly and Company	Thank you for the opportunity to respond to the Appraisal Consultation Document (ACD) on ixekizumab for treating moderate to severe plaque psoriasis [ID904]. Lilly welcome the Appraisal Committee's preliminary recommendation of ixekizumab as a treatment option for adults with plaque psoriasis based on the specific criteria stated in Section 1.1 of the ACD. Ixekizumab represents an important new biologic treatment option for patients living with psoriasis and Lilly are pleased to be able to work with NICE towards the goal of making ixekizumab available for clinicians and patients in England and Wales. Lilly would however like to raise a number of key issues which should be considered at the second Appraisal Committee meeting, in particular the stopping rules for ixekizumab and a suggested recommendation for use in TNF-inhibitor-refractory patients. These can be seen in Appendix 1: Issues for committee consideration.	Thank you for your response.
Eli Lilly and Company	Key point 1 **Section 1.2: Recommendations** The criterion for continuing treatment with ixekizumab in the draft ACD is a response criterion of a PASI 75 response assessed at 12 weeks. All other biologic therapies are recommended by NICE to be continued if a patient experiences either: • PASI 75 response; or, • PASI 50 response in combination with a five-point reduction in DLQI Lilly request that the committee consider amending the draft guidance so that the response criteria for continuing treatment at 12 weeks are consistent with previous (and forthcoming) guidance. These recommendations for the most appropriate criteria for the assessment of response to treatment originated from guidance provided in TA103 (etanercept and efalizumab for the treatment of adults with psoriasis). Based on criteria used by regulatory agencies and included in National guidelines, the committee concluded that the PASI 75 response assessed at 12 weeks was the most appropriate measure of response. However, the committee also heard from clinical expert testimony that a number of patients who, on the basis of improvements of quality of life, would derive significant benefit from treatment, but might fail to achieve a PASI 75 after 12 weeks of treatment. The additional criterion of a PASI 50 response in combination with a five-point reduction in DLQI after 12 weeks of treatment could	Thank you for your comments. Please see sections 1.2 and 4.26 of the final appraisal determination (FAD).

Consultee	Comment [sic]	Response
	also be used to determine whether or not patients had responded to treatment. It is not apparent that specific analyses from the assessment group were used to support the additional PASI 50 response in combination with a five-point reduction in DLQI criterion. Subsequent to the publication of TA103, both of these response criteria have been consistently included in guidance for all other biologic treatments for psoriasis recommended by NICE. When reviewing committee discussions for each piece of guidance, it appears that response criteria have been applied to be consistent with TA103 rather than on the basis of specific evidence submitted: • TA146 (Adalimumab for the treatment of adults with psoriasis; final appraisal determination) – 'In addition, the Committee agreed that the response criteria should be defined in a similar way to TA103 and should include an additional alternative criterion of a PASI 50 response and a five-point reduction in the DLQI from start of treatment.' • TA134 (Infliximab for the treatment of adults with psoriasis; final appraisal determination) – 'In addition the Committee were persuaded that for consistency the response criteria should be defined in a similar way to TA103 (including a 50% reduction in the PASI score and a five-point reduction in the DLQI) except that the assessment should made at 10 weeks after initiation of therapy.' • TA180 (Ustekinumab for the treatment of adults with moderate to severe psoriasis; final appraisal determination) – 'Furthermore, the clinical specialists indicated that the treatment continuation rules defined in section 1.2 of TA103 remain relevant to clinical practice.' • TA350 (Secukinumab for treating moderate to severe plaque psoriasis; final appraisal determination) – 'The Committee considered that, because secukinumab was likely to be given at the same point in the pathway as the other biologicals already recommended by NICE for treating psoriasis, any stopping rules should be consistent with previous appraisals.' • ID987 (Apremilast for treating moderate to severe plaque psoriasis rapid review currently at final appraisal determination stage) – 'The committee concluded that it was appropriate to include a stopping rule, and that this should be at 16 weeks and be defined in the same way as in NICE guidance for biological therapies in psoriasis.' Furthermore, we wish to highlight the following evidence to demonstrate that the inclusion of the PASI 50 response with at least a 5 point reduction in DLQI would be consistent with the clinical and cost effectiveness analyses supporting the current draft recommendation. A post-hoc analysis of patients in the UNCOVER studies who had a baseline DLQI of ≥10 and prior exposure to one or more systemic therapy/PUVA showed that [redacted] of patients had either a PASI 75 response or a PASI 50 response with at least a 5 point reduction in DLQI. This is consistent with the PASI 75 only response in the UNCOVER studies.	

Consultee	Comment [sic]	Response
	It should also be noted that patients who do not achieve PASI 75 at 12 weeks may subsequently achieve this with continued treatment as noted in the SmPC for ixekizumab. Cost-effectiveness data included in the Lilly submission is also supportive of the inclusion of the PASI 50 response in combination with a five-point reduction in DLQI after 12 weeks criterion in the final guidance for ixekizumab. A scenario analysis presented in the submission demonstrated that, as in the base case analysis, the ixekizumab sequence was the only sequence on the cost-effectiveness frontier with respect to the referent sequence when the continuation rule is a PASI 50 response (Table 1). Table 1: Scenario analysis: PASI 50 treatment continuation rule [*Table provided but not reproduced here*] Whilst it is acknowledged that the above does not explicitly account for change in DLQI, it should be noted that we are not aware of response rates for this criterion (i.e PASI 50 response and DLQI reduction of at least 5 points) being presented in any previous submission, likely driven by the fact that no clinical study appears to include a minimum DLQI at baseline within the inclusion criteria meaning that a 5 point reduction in DLQI cannot be achieved by patients with a baseline score of less than 5. In the light of this limitation, the analyses presented above should be taken into consideration. To conclude, Lilly therefore believe that both PASI 75 response and PASI 50 response in combination with a five-point reduction in DLQI stopping rules should be included in the final guidance for ixekizumab from the rationale of consistency (as used in previous appraisals) and the additional evidence presented here.	
Eli Lilly and Company	Key point 2 **Section 4.2 and 4.8: recommendation for treatment of TNF-alpha inhibitor-refractory patients** Lilly request that the committee consider recommending ixekizumab as a treatment option for patients who have failed, are contraindicated to, or are intolerant to one or more TNF alpha inhibitors, in addition to the recommendation in the draft guidance. Data presented in the Lilly submission demonstrates that ixekizumab is more effective than etanercept or placebo both for patients who had previously recevied biologic treatment (including TNF-alpha inhibitors) and for those who had not. Ixekizumab is able to achieve significant PASI 75, 90 and 100 response rates in patients with previous non-response to etanercept which are comparable to those achieved by the ITT population in the UNCOVER studies. In the UNCOVER-2 study, 358 patients were randomised to treatment with twice weekly etanercept. At week 12, 200 (56%) of these patients were classified as inadequate responders, with only 15.5% of these patients having achieved PASI 75. Following a 4-week washout period, etanercept inadequate-responders were treated with ixekizumab 80 mg Q4W. After 12 weeks of ixekizumab treatment (week 28) 83.5% of patients achieved PASI 75, 57.0% achieved PASI 90 and 22.0% achieved PASI 100.	Thank you for your comments. The committee considered that the recommendation wording includes ixekizumab as a treatment option for patients who have failed, are contraindicated to, or are intolerant to one or more TNF alpha inhibitors, and is consistent with the wording of

Consultee	Comment [sic]	Response
	These proportions increased to 88.0% for PASI 75, 66.0% for PASI 90 and 35.0% for PASI 100 following 20 weeks (week 36) of treatment with ixekizumab 80 mg Q4W (Figure 1). Following 44 weeks (week 60) of treatment with ixekizumab 82.5% of etanercept inadequate-responders achieved PASI 75, 68.5% achieved PASI 90 and 43.5% achieved PASI 100.1 It should be noted that these patients did not receive the ixekizumab 160 mg loading dose nor the 12 week Q2W induction regimen. The PASI responses observed in these patients were consistent with those observed in patients who received ixekizumab 80mg Q4W during the induction period of the UNCOVER studies. Figure 1: PASI response rates in etanercept inadequate-responders before starting (week 12), and after 12 weeks (week 28) and 20 weeks (week 36) of ixekizumab 80 mg Q4W treatment [*Figure provided but not reproduced here*] In addition, ixekizumab provides a high-level of efficacy regardless of previous treatment with biologic therapy. In the UNCOVER-2 study, a total of 288 patients had received prior biologic therapy and 936 patients were biologic-naive. For patients who had received prior biologic therapy and patients who were biologic-naive, PASI 75 response rates were significantly greater for ixekizumab 80 mg Q2W (92.9% and 88.8%, respectively) and ixekizumab 80 mg Q4W (74.1% and 78.6%, respectively) compared with those for placebo (0 and 3.2%, respectively [p<0.05]) and etanercept (30.3% and 44.3%, respectively [p<0.05]). Furthermore, the proportion of patients who achieved complete clearance of their symptoms (PASI 100) in the biologic experienced and biologic-naïve patient populations was significantly greater for ixekizumab 80 mg Q2W (48.8% and 37.8%, respectively) and ixekizumab Q4W (22.4% and 33.6%, respectively) compared with those for placebo (0 and 0.8%, respectively [p<0.05]) and etanercept (5.3% and 5.3%, respectively [p<0.05]). In addition, response rates were similar regardless of whether patients had received prior biologic therapy or not. Scenario analyses also demonstrate that ixekizumab is a cost-effective treatment option for patients who were contraindicated to or had inadequate response on a TNF-alpha inhibitor. Ixekizumab was compared to ustekinumab 45mg, ustekinumab 90mg and secukinumab as second-line therapy in a biologic treatment sequence following failure on adalimumab, and was estimated to be the dominant treatment strategy in this patient group (Table 2). Table 2: Scenario analysis: ixekizumab in patients with inadequate response to prior biologic therapy [*Table provided but not reproduced here*] <u>Given the evidence presented above, Lilly request that the committee consider recommending ixekizumab as a treatment option for patients who have failed, are contraindicated to, or are intolerant to one or more TNF-alpha inhibitors, in addition to the recommendation in the draft guidance.</u>	previous NICE appraisal recommendations for biological treatments in psoriasis. Please see section 1.1 of the final appraisal determination (FAD).
Eli Lilly and Company	<u>Other points for consideration</u> **Section 2: Clarification of the price of ixekiuzmab**	Thank you for your comments. Please see section 2 of the

Consultee	Comment [sic]	Response
	The table presented in Section 2 of the ACD outlines the ixekizumab price as 'the list price is £1,125 for 80 mg, and £2,250 for 160 mg.' Lilly would like to clarify that the 160 mg price outlined in the table actually represents 2 x 80 mg pens/syringes. Lilly suggest the following wording when describing the price of ixekizumab: • Ixekziumab 80mg solution for injection in prefilled pen or syringe x 1 = £1,125 • Ixekizumab 80 mg solution for injection in prefilled pen or syringe x 2 = £2,250	final appraisal determination (FAD).
Eli Lilly and Company	**Section 4.2: Clarification of wording in the ACD** Lilly would also like to clarify the point raised in section 4.2 of the ACD. The ACD states the following: 'The committee heard from the clinical experts that biological treatment is offered to patients whose disease has not responded to standard systemic therapies (such as ciclosporin and methotrexate) or when these treatments are contraindicated or not tolerated. It heard from the clinical experts that, because there are long-term data available for other biologicals and clinicians are familiar with using them, ixekizumab was likely to be offered to 2 groups: • patients who had already had a biological treatment to which their disease had not responded • patients for whom other biological agents were contraindicated'. Whilst Lilly recognise that for some clinicians who are not familiar with ixekizumab it may be used as a second-line biologic, there is no clinical or economic evidence for why ixekizumab cannot be used as a first-line biologic option and it is likely that over time ixekizumab will be the preferred treatment option over older, less efficacious biologics as a first-line biologic option.	Thank you for your comments. Please see section 4.2 of the final appraisal determination (FAD).
Eli Lilly and Company	**Section 4.9: Network meta-analysis results** In the draft guidance, ixekizumab is stated to be similarly effective compared with secukinumab and infliximab. Lilly would like to note that while PASI 75 response rates may be similar for the three treatments, the point estimates for PASI90 and PASI100 response rates were substantially higher in the network meta-analysis for ixekizumab than for secukinumab and infliximab (although it is noted that credible intervals overlap) (Table 3). These levels of response represent near-complete or complete skin clearance, respectively, and as such, a meaningful improvement in HRQoL for patients. Lilly would request that the committee consider updating the draft guidance to reflect these points regarding the efficacy of ixekizumab. Table 3: PASI base case NMA random-effects model – absolute probabilities of achieving ≥50%, ≥75%, ≥90% or 100% PASI symptom relief for each treatment. [*Table provided but not reproduced here*]	Thank you for your comments. The committee considered that its conclusions accurately represented the results of the network meta-analysis.
Eli Lilly and Company	**Section 4.18: Costs of adverse events** In the ACD it is stated that 'the committee concluded that the company should have included the costs of adverse events in its economic model'. Whilst adverse event costs were not modelled in the company's base case analysis as per previous technology appraisals of biologics in psoriasis, Lilly	Thank you for your comments. The committee were aware of the

Consultee	Comment [sic]	Response
	would like to re-iterate that these were incorporated in a sensitivity analysis (**Error! Reference source not found.**) presented in the original submission. Table 4: Scenario analysis: adverse events [*Table provided but not reproduced here*] Furthermore, inclusion of adverse events in the ERG base case did not alter the overall results of the cost-effectiveness analysis.	evidence in the company's submission and did not consider it necessary to make any changes to the wording of the final appraisal determination (FAD).
Eli Lilly and Company	**Section 4.20: Results of cost-effectiveness analysis** As noted by the ERG report for TA350 (secukinumab for treating moderate to severe plaque psoriasis) secukinumab annual dosing requires 13 administrations (52 weeks divided by 4 weeks) rather than 12 (once per month). As analyses accounting for the confidential patient access scheme cost for secukinumab were presented to the committee in the closed session, Lilly believe that this discrepancy needs to be taken into account as the clinical data for secukinumab is based on 13 administrations annually and only considering analyses based on 12 annual administrations may not present sufficient information for decision making.	Thank you for your comments. The committee concluded that the number of administrations of secukinumab used in the ERG's base case was appropriate. Please see section 4.20 in the final appraisal determination (FAD).
Eli Lilly and Company	**Section 4.23: Results of cost-effectiveness analysis** Lilly would like to draw attention to the statement in the second bullet point 'the sequence including ixekizumab had fewer total costs and QALYs than the sequence including secukinumab'. This statement ought to be amended to reiterate that these treatments are not compared in the same position, i.e. 'the sequence including ixekizumab as second-line had fewer total costs and QALYs than the sequence including secukinumab as first-line'. Lilly do not believe that a comparison of ixekizumab as second-line therapy versus secukinumab as first-line therapy is appropriate to make in this context. The ERG presented the second-line sequence of ixekizumab with the treatment sequence consisting of adalimumab-ixekizumab-infliximab to a secukinumab sequence comparing secukinumab ustekinumab 90mg-infliximab. Given the complications of a sequence model, making such a comparison is always going to result in lower QALYs for the	Thank you for your comments. Please see section 4.23 in the final appraisal determination (FAD).

Consultee	Comment [sic]	Response
	ixekizumab sequence as it contains a less efficacious treatment (adalimumab) whereas the secukinumab sequence contains a more efficacious treatment (ustekinumab). Therefore the QALY differences are not driven by secukinumab but the choice of treatments within the sequence. This context and detail should be made clear and amended in the draft guidance to avoid potentially misleading conclusions being drawn. A more relevant or, at the very least, equally valid comparison would be comparing both agents in the same position within a treatment sequence, as shown in Table 2. Whether compared with each other in first-line or in second-line, the ixekizumab sequence is associated with greater QALY gains over the secukinumab sequence, when the other components of the sequence are the same. Any analyses presented with the confidential patient access scheme price should take this issue regarding choice of treatments in the sequence into consideration.	
Eli Lilly and Company	**Section 4.23: Innovation** Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity (< 3pM) and specificity to both forms of interleukin 17A (IL-17A and IL-17A/F). The affinity of ixekizumab for both the homo and heterodimer significantly exceeds that of other IL-17 inhibitors. Furthermore, the ixekizumab autoinjector device has been designed through 13 separate qualitative and quantitative studies and three human factor studies (which included over 1,000 patients with various autoimmune conditions, as well as HCPs and caregivers), several design principles were identified as important for an autoinjector, including: • the device should be easy to use by patients with a range of physical abilities or comorbid conditions impacting dexterity • the device operation should be easy to understand • patients should feel confident that they are delivering the dose successfully and using the device appropriately • the device can be safely used and disposed of The autoinjector for ixekizumab is consistent with the principles outlined above and can be considered an innovative delivery method for patients who need to self-administer. In addition, a subcutaneous administration assessment questionnaire (SQAAQ) was used in the RHBL study to evaluate the ease of use and confidence in administering ixekizumab. This trial was an open-label 12 week phase 3 study of ixekizumab in moderate-to-severe psoriasis patients who were randomly assigned to an injection device (prefilled pen or prefilled syringe). The study found that, ixekizumab patients reported high levels of patient satisfaction across all parameters for both the prefilled pen and syringe, demonstrating convenience and ease of use of ixekizumab treatment.	Thank you for your comments. Please see section 4.27 in the final appraisal determination (FAD).

Comments received from clinical experts and patient experts

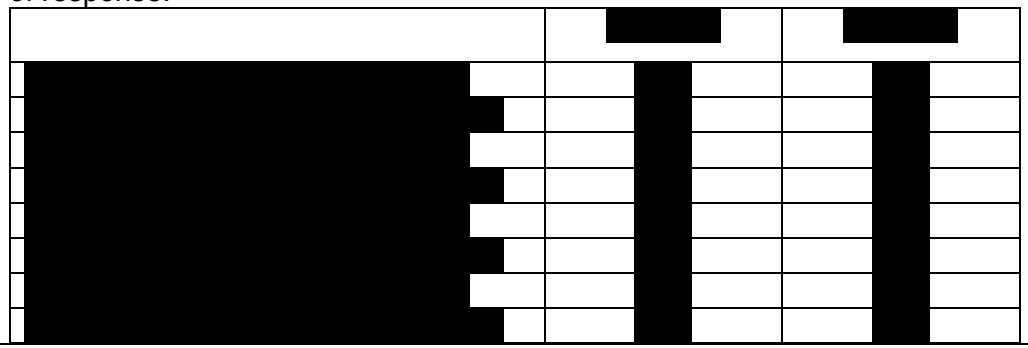
Nominating organisation	Comment [sic]	Response
British Society for Rheumatology	**Has all of the relevant evidence been taken into account?** We are not aware of additional evidence that should be taken in to account	Thank you for your response.
British Society for Rheumatology	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes, with no additional comments.	Thank you for your response.
British Society for Rheumatology	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** It is noted that the recommendation allows the use of Ixekizumab as a first biologic agent following systemic treatment, which is not aligned with the clinical expert opinion. The committee heard that from the clinical experts that, because there are long-term data available for other biologicals and clinicians are familiar with using them, Ixekizumab was likely to be offered to 2 groups: • patients who had already had a biological treatment to which their disease had not responded • patients for whom other biological agents were contraindicated The stopping rule: 4.26 In this draft Ixekizumab will be stopped if PASI 75% is not achieved at 12 weeks without the option to continue if a 50% reduction in the PASI score (PASI 50) and a 5 point reduction in DLQI from when treatment started. This is in contrast with STA 350 on secukinumab when either of the response measures can be used. Presumably the committee reached this decision because data were not presented to support this. Clearly the trial data support the effectiveness of Ixekizumab on DLQI- are there plans to perform such an analysis to be included in this STA?	Thank you for your comments. Please see sections 4.2, 1.2 and 4.26 in the final appraisal determination (FAD).
British Society for Rheumatology	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** The limitations of the DLQI (older people) and PASI (skin colour) are commented on and appropriate flexibility in 4.28.	Thank you for your comments.
Psoriasis Association	The Psoriasis Association welcomes the positive recommendation of ixekizumab as an option for people with severe plaque psoriasis. Psoriasis is a lifelong condition that is unique to each individual. People respond differently to different treatments and, as such, it is important to have the widest possible variety of therapies available to people with psoriasis. Although ixekizumab is similar to biologics that are currently available for psoriasis – particularly secukinumab – there are subtle differences in its mechanism which may mean the difference between ‘response’ and ‘no response’ for patients. Because of this, ixekizumab	Thank you for your comments.

Nominating organisation	Comment [sic]	Response
	represents a new option for people with severe psoriasis who have tried previous biologic therapy without lasting success, as well as those who are biologic naïve. The Psoriasis Association also welcomes the equality considerations around the use of the PASI and DLQI. I have read the Appraisal Consultation Document and have no further comment to add, aside from asserting our support once again for the positive recommendation of ixekizumab as an option for people with severe plaque psoriasis.	
The Psoriasis and Psoriatic Arthritis Alliance	Thank you for the opportunity to comment on the above review document. As an organisation that represents people affected by psoriasis and psoriatic arthritis, we support the opportunity for patients to get access to the latest therapies to alleviate their symptoms and limit disease progression. We also would like to see patients get better outcomes, fewer side effects and more convenient administration, therefore reducing the burden of being a patient, tied to frequent interventions, and dosage. We also acknowledge that the cost of treating each patient within the NHS has to be fair and equitable and any new treatment has to provide value for money and not have a detrimental effect on the service provided to others treated within the NHS. The decision to recommend ixekizumab as an option for treating plaque psoriasis will be welcomed by patients, as will allowing clinicians to decide when to prescribe in the biologic pathway, which we consider is a pragmatic and sensible option. The gathering of safety in our view is also important. We would like to suggest that a research recommendation is added to the Final Appraisal Document, where ixekizumab in the same way as other biologic agents, is included into a safety registry, such as the British Association of Dermatologists Biologic Interventions Register (BADBIR). This in our view will aid prescribing and reassure patients in the future, when deciding on the risk and benefit of ixekizumab for the treatment of their psoriasis.	Thank you for your comments. The committee heard from the company that ixekizumab has been included in the British Association of Dermatologists Biologic Interventions Register.
British Association of Dermatologists	On behalf of the British Association of Dermatologists, thank you for the opportunity to comment on the Appraisal Consultation Document. We wish to express our agreement with the recommendations.	Thank you for your comments.

Comments received from commentators

Commentator	Comment [sic]	Response
AbbVie	AbbVie welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for the single technology appraisal (STA) of Ixekizumab for treating moderate to severe plaque psoriasis [ID904]. AbbVie's	Thank you for your response.

Commentator	Comment [sic]	Response
	comments are set out under section headings containing the questions NICE asks stakeholders to comment on for the ACD.	
AbbVie	**Has all of the relevant evidence been taken into account?** AbbVie consider that the majority of relevant evidence has been taken into account by the Appraisal Committee in preparing the provisional recommendations detailed in the ACD. However, there are some considerations which AbbVie believes the Committee should also take into account before reaching a final decision and these are outlined below. 1.1 Pages 11-12, section 4.14: "[…] The committee concluded that the treatment sequences included by the company in its economic model reasonably represented current NHS practice". AbbVie notes that the manufacturer's submission assumed treatment response which did not vary with the specific position of ixekizumab in the treatment sequence. In particular, the manufacturer did not model the base case so to assume a decrease in the effectiveness of subsequent biologic treatment, which would have been the clinically most plausible approach. AbbVie believes that the issue of "effect modification" linked to a specific sequence of biologics needs to be addressed and adequately explored. In addition, AbbVie believes that it cannot be assumed that all possible sequences of biological treatments that can actually take place in clinical practice were captured in the manufacturer's model, and that the market share data presented, as stated in section 4.13, page 11 of the ACD (and upon which the sequences explored were based) are only an approximation of a very complex clinical practice.	Thank you for your comments. The committee took into account the issue of 'effect modification' and the treatment sequences included in the company's model as part of its decision-marking. Please see sections 4.8, 4.14 and 4.25 in the final appraisal determination (FAD).
AbbVie	**Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?** AbbVie consider the summaries of clinical and cost-effectiveness from the manufacturer and the ERG to be, on the whole, reasonable interpretations of the evidence. However, AbbVie concurs with the ERG and Committee's concerns relating to key model assumptions used by the manufacturer, and in particular those that unduly favour ixekizumab, namely: 2.1 Page 16, Section 4.25: Treatment pathway AbbVie agrees with the Appraisal Committee when it states that "The committee was aware that the company had not explored the full range of treatment sequences that might be offered in current NHS practice".	Thank you for your comments. Please see sections 4.2, 4.5 and 4.9 in the final appraisal determination (FAD).

Commentator	Comment [sic]	Response
	In addition, AbbVie believes that the guidance should be clear in stating that ixekizumab should be used in patients whose disease has not responded to a previous biological treatment and in patients for whom other biological agents are contraindicated 2.2 Page 6, Section 4.4: Generalisability of the trial populations "The committee was aware that the trials included patients with a PASI score of 12 or more and that in previous appraisals of technologies for treating psoriasis, a PASI score of 10 or more had been defined as severe disease" AbbVie notes that the definition of disease severity also reflects the DLQI value, which is assumed to be >10 for severe cases. AbbVie also notes that these discrepancies represent limitations in the generalisability of trial findings on ixekizumab to the UK population, and introduces inconsistencies with previous appraisals. 2.3 Pages 9-10, Section 4.9: Network meta-analysis results AbbVie believes that the uncertainty underpinning the network meta-analysis cannot lead the Committee to confidently state that "[..] ixekizumab was more clinically effective than adalimumab [..]" In particular, the network meta-analysis reported values for the relative risk for ixekizumab versus adalimumab are not clinically plausible. AbbVie is especially concerned with the values, reported at page 101 of the ERG report, in table 4.16 (PASI base-case NMA random-effects model - absolute probabilities of achieving ≥50%, ≥75%, ≥90% or 100% PASI symptom relief for each treatment - CS base-case and ERG calculation) for adalimumab. AbbVie wishes to note that data on file (supplied to the Committee in the table below) clearly show that the PASI scores for adalimumab are consistently higher than those reported in table 4.16 of the ERG report. The table below summarizes the rate of PASI response at the first visit in the British Association of Dermatologists Biologic Interventions Registry (BADBIR), 6 months after initiation, and how it is sustained over time as per the Last Observation Carried Forward LOCF analyses in each population and for each level of response. 	

Commentator	Comment [sic]	Response
	The table clearly shows that, for patients treated with adalimumab, the differences between populations are small in terms of achieving response and maintaining it. Patients with a baseline PASI≥10 and biologic-naive patients have similar efficacy profiles, performing a bit better than the entire cohort. The best efficacy is observed for biologic-naive patients with a baseline PASI≥10. 2.4 Page 12, Section 4.15: Modelling utility benefit AbbVie is particularly concerned that the manufacturer's model did not incorporate disutilities due to adverse events, and, as a consequence, did not investigate whether these disutilities appropriately reflected the specific biological treatments patients were receiving in the given treatment sequence considered. This introduces an important limitation in the interpretation of the findings from the cost-effectiveness analysis. 2.5 Page 14, Section 4.20: Results of the cost-effectiveness analysis": costs of adverse events AbbVie agrees with the committee when it concluded that the company should have included the costs of adverse events in its economic model. In particular, since a range of possible treatment sequences are included, the cost of adverse events should have reflected the management of the specific treatments that patients were receiving, as these may be different (in terms of frequency and duration) among the biologic treatments.	
AbbVie	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** 3.1. Page 3, Section 1.2: "Stop ixekizumab treatment at 12 weeks if the psoriasis has not responded adequately.[..]" AbbVie wishes to note that this statement on the relevant stopping rule for ixekizumab should be followed by the following sentence: "Further treatment cycles are not recommended in these patients", in line with a similar statement included in the NICE TA for secukinumab (TA350). This is to ensure consistency across existing NICE guidance. 3.2. Page 3, Section 1.3 "When using the PASI, health care professionals should take into account skin colour and how this could affect the PASI score, and make any adjustments they consider appropriate" AbbVie believes that this statement introduces unwarranted uncertainty around what could constitute as "any adjustment". In addition, no such similar statement was included in previous NICE appraisals for biological treatments in plaque. As a consequence, AbbVie would suggest that the statement is complemented with the wording "[..] and make any adjustments they consider appropriate for all biological treatments". 3.3. Pages 16-17, Section 4.26 "[...] It had not seen evidence for a 50% reduction in the PASI score and a 5-point reduction in DLQI and so it did not consider it appropriate to include these criteria" AbbVie regrets that this evidence was not available for the purpose of this appraisal, as it should have been ideally considered as criteria to advice on stopping rules.	Thank you for your comments. Please see sections 1.3, 4.28, 1.2 and 4.26 in the final appraisal determination (FAD). In line with more recent appraisals (TA146 and TA180) the committee agreed that a change to the wording of the stopping rule

Commentator	Comment [sic]	Response
		was not necessary.
AbbVie	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** None that AbbVie is aware of.	Thank you for your response.
AbbVie	**Additional comments** 5.1: There is inconsistency between the statements included at page 5, section 4.2 ("Treatment pathway") and the statement reported at page 20 ("What is the position of the treatment in the pathway of care for the condition?"). On page 20, the table states that "Ixekizumab is likely to be primarily offered to patients whose disease has not responded to a previous biological treatment and to patients who cannot have biological treatment". AbbVie wishes to highlight that the last part of the statement ([..] to patients who cannot have biological treatment") is not clinically acceptable, as ixekizumab itself is a biological treatment. AbbVie wishes to request that that this statement be amended in line with the wording included in section 4.2, page 5 ("ixekizumab was likely to be offered to 2 groups: patients who had already had a biological treatment to which their disease had not responded; patients for whom other biological agents were contraindicated.) 5.2: From page 20, the statement "Biological treatment is offered to patients whose disease has not responded to standard systemic therapies (such as ciclosporin and methotrexate) or when these treatments are contraindicated or not tolerated ", should also include PUVA (psoralen and longwave ultraviolet radiation), as on page 3 and 18 of the document.	Thank you for your comments. Please see pages 19 and 20 in the final appraisal determination (FAD).
Novartis	**Has all of the relevant evidence been taken into account?** Novartis considers that the relevant evidence has generally been taken into account by the Appraisal Committee in preparing the provisional recommendations detailed in the ACD. However, we are unclear why relevant published evidence on the efficacy of secukinumab in patients previously treated with biologic therapies, was not identified. The ixekizumab manufacturer states that literature searches were last updated in November 2015, eight months prior to submission in July 2016. Page 4 of the Company response to NICE's request for clarification (page 437 of the Committee papers) indicates that the November 2015 search update included reviewing conference proceedings from both the European Academy of Dermatology & Venereology Congress and the American Academy of Dermatology. Relevant data on secukinumab in biologic experienced patients was presented in poster format at both these congresses during 2014 / 2015. These data demonstrate that secukinumab 300mg achieved higher clinical response rates than both etanercept and placebo, in subjects both with and without previous biologic exposure.	Thank you for your comments. The committee considered that evidence for subgroups of patients receiving secukinumab would not have enabled the network meta-analysis to

Commentator	Comment [sic]	Response
	Had this data on secukinumab's efficacy in subgroups defined by prior treatments been identified by the ixekizumab manufacturer, it is possible that a different conclusion may have been drawn regarding the feasibility of a network meta-analysis in the subgroup of patients with previous use of biological therapy. In addition, we would like to draw the committee's attention to the different immunogenicity rates and clinical impact observed in the ixekizumab clinical studies and in the secukinumab clinical studies. Whilst the secukinumab Summary of Product Characteristics states that "less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. About half of the treatment-emergent anti-drug antibodies were neutralising, but this was not associated with loss of efficacy or pharmacokinetic abnormalities", the ixekizumab Summary of Product Characteristics states: "Approximately 9–17% of patients treated with Taltz at the recommended dosing regimen developed anti-drug antibodies... approximately 1% of patients treated with Taltz had confirmed neutralising antibodies associated with low drug concentrations and reduced clinical response. An association between immunogenicity and treatment emergent adverse events has not been clearly established." It is therefore possible that the simplifying modelling assumption that patients "maintain their level of response until discontinuation" (see page 216 of the Eli Lilly submission, page 307 of the Committee papers) may be inappropriate, since differentiation between secukinumab and ixekizumab response rates may be observed over the long-term. Novartis agrees with the committee's conclusion that "in clinical practice, ixekizumab would be offered at the same place in the treatment pathway as the existing biological treatments", including secukinumab. Furthermore, we agree with the conclusion the committee drew from the manufacturer's network meta-analysis that "ixekizumab was similarly effective compared with secukinumab and infliximab", and note "that the most plausible ICER was likely to be in line with the other biological treatments already recommended in previous NICE guidance".	address the subgroup of patients with previous use of biological therapy because this information was not available for all the comparator studies included in the analysis.
Novartis	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Novartis considers the summaries of clinical and cost-effectiveness in the ACD to be, on the whole, reasonable interpretations of the evidence. However, we are unclear regarding the statement on page 20 of the ACD "Ixekizumab is likely to be primarily offered …to patients who cannot have biological treatment". Since ixekizumab is itself a biological treatment, we query whether this statement was intended to read "who cannot have standard systemic therapies". Novartis agrees with the committee's interpretation of the evidence regarding the similar mechanisms of action of ixekizumab and secukinumab, i.e. "that ixekizumab did not differ substantially in its mechanism of action from secukinumab". However, we would like to correct a factual inaccuracy within the committee papers regarding differences in the mechanism of action between ixekizumab and secukinumab.	Thank you for your comments. Please see page 20 in the final appraisal determination (FAD). Please see section 4.27 in the final appraisal determination

Commentator	Comment [sic]	Response
	Page 79 of the pre-meeting briefing (page 81 of the committee papers) notes “a different mode of action and extended activity of ixekizumab compared with secukinumab because it binds to both IL-17 A and IL-17 F”, based on the submission from the British Association of Dermatologists. This is factually inaccurate since both ixekizumab and secukinumab inhibit IL-17 A and IL-17 A/F. Both drugs have the same mode of action and neither inhibits the homodimer IL-17 F.6 Statements made by the ixekizumab manufacturer regarding mode of action are accurate, since they do not mention IL-17 F, or claim any differentiation versus secukinumab. For instance; • “ixekizumab is an IgG4 monoclonal antibody that binds with high affinity and specificity to IL-17A” (page 44 of the manufacturer submission, page 135 of the committee papers) • “Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity (< 3pM) and specificity to interleukin 17A (both IL-17A and IL-17A/F)” (page 33 of the manufacturer submission, page 124 of the committee papers). We note a further factual inaccuracy within the submission from the British Association of Dermatologists. The statement on page 6 of their submission (page 482 of the committee papers), that “excluding ixekizumab means denying these individuals a possible therapy, since IL-17A blockade is not an otherwise available pharmacological intervention”, is untrue since IL-17A blockade via secukinumab is recommended by NICE in TA350.	(FAD), which sets out the committee’s conclusions about the mechanisms of action of ixekizumab and secukinumab.
Novartis	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Novartis has no comments.	Thank you for your response.
Novartis	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Novartis does not have any comments in relation to the above potential equality issues.	Thank you for your response.

The following consultees/commentators indicated that they had no comments on the appraisal consultation document:

Department of Health

21 November 2016

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RE: Lilly response to appraisal consultation document (ACD): Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

Dear Melinda,

Thank you for the opportunity to respond to the Appraisal Consultation Document (ACD) on ixekizumab for treating moderate to severe plaque psoriasis [ID904].

Lilly welcome the Appraisal Committee's preliminary recommendation of ixekizumab as a treatment option for adults with plaque psoriasis based on the specific criteria stated in Section 1.1 of the ACD.

Ixekizumab represents an important new biologic treatment option for patients living with psoriasis and Lilly are pleased to be able to work with NICE towards the goal of making ixekizumab available for clinicians and patients in England and Wales.

Lilly would however like to raise a number of key issues which should be considered at the second Appraisal Committee meeting, in particular the stopping rules for ixekizumab and a suggested recommendation for use in TNF-inhibitor-refractory patients. These can be seen in Appendix 1: Issues for committee consideration.

Please contact me if you have any further queries.

Yours sincerely,

James Parnham
Head of Health Outcomes & HTA

Appendix 1: Issues for committee consideration

Key point 1

Section 1.2: Recommendations

The criterion for continuing treatment with ixekizumab in the draft ACD is a response criterion of a PASI 75 response assessed at 12 weeks. All other biologic therapies are recommended by NICE to be continued if a patient experiences either:

- PASI 75 response; or,
- PASI 50 response in combination with a five-point reduction in DLQI

Lilly request that the committee consider amending the draft guidance so that the response criteria for continuing treatment at 12 weeks are consistent with previous (and forthcoming) guidance.

These recommendations for the most appropriate criteria for the assessment of response to treatment originated from guidance provided in TA103 (etanercept and efalizumab for the treatment of adults with psoriasis). Based on criteria used by regulatory agencies and included in National guidelines, the committee concluded that the PASI 75 response assessed at 12 weeks was the most appropriate measure of response. However, the committee also heard from clinical expert testimony that a number of patients who, on the basis of improvements of quality of life, would derive significant benefit from treatment, but might fail to achieve a PASI 75 after 12 weeks of treatment. The additional criterion of a PASI 50 response in combination with a five-point reduction in DLQI after 12 weeks of treatment could also be used to determine whether or not patients had responded to treatment. It is not apparent that specific analyses from the assessment group were used to support the additional PASI 50 response in combination with a five-point reduction in DLQI criterion. Subsequent to the publication of TA103, both of these response criteria have been consistently included in guidance for all other biologic treatments for psoriasis recommended by NICE. When reviewing committee discussions for each piece of guidance, it appears that response criteria have been applied to be consistent with TA103 rather than on the basis of specific evidence submitted:

- **TA146 (Adalimumab for the treatment of adults with psoriasis; final appraisal determination)** – 'In addition, the Committee agreed that the response criteria should be defined in a similar way to TA103 and should include an additional alternative criterion of a PASI 50 response and a five-point reduction in the DLQI from start of treatment.'
- **TA134 (Infliximab for the treatment of adults with psoriasis; final appraisal determination)** – 'In addition the Committee were persuaded that for consistency the response criteria should be defined in a similar way to TA103 (including a 50% reduction in the PASI score and a five-point reduction in the DLQI) except that the assessment should made at 10 weeks after initiation of therapy.'
- **TA180 (Ustekinumab for the treatment of adults with moderate to severe psoriasis; final appraisal determination)** – 'Furthermore, the clinical specialists indicated that the treatment continuation rules defined in section 1.2 of TA103 remain relevant to clinical practice.'
- **TA350 (Secukinumab for treating moderate to severe plaque psoriasis; final appraisal determination)** – 'The Committee considered that, because secukinumab was likely to be given at the same point in the pathway as the other biologicals already recommended by NICE for treating psoriasis, any stopping rules should be consistent with previous appraisals.'
- **ID987 (Apremilast for treating moderate to severe plaque psoriasis rapid review currently at final appraisal determination stage)** – 'The committee concluded that it was appropriate to include a stopping rule, and that this should be at 16 weeks and be defined in the same way as in NICE guidance for biological therapies in psoriasis.'

Furthermore, we wish to highlight the following evidence to demonstrate that the inclusion of the PASI 50 response with at least a 5 point reduction in DLQI would be consistent with the clinical and cost-effectiveness analyses supporting the current draft recommendation.

A post-hoc analysis of patients in the UNCOVER studies who had a baseline DLQI of ≥10 and prior exposure to one or more systemic therapy/PUVA showed that [redacted] of patients had either a PASI 75 response or a PASI 50 response with at least a 5 point reduction in DLQI. This is consistent with the PASI 75 only response in the UNCOVER studies.

It should also be noted that patients who do not achieve PASI 75 at 12 weeks may subsequently achieve this with continued treatment as noted in the SmPC for ixekizumab.

Cost-effectiveness data included in the Lilly submission is also supportive of the inclusion of the PASI 50 response in combination with a five-point reduction in DLQI after 12 weeks criterion in the final guidance for ixekizumab. A scenario analysis presented in the submission demonstrated that, as in the base case analysis, the ixekizumab sequence was the only sequence on the cost-effectiveness frontier with respect to the referent sequence when the continuation rule is a PASI 50 response (Table 1).

Table 1: Scenario analysis: PASI 50 treatment continuation rule

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
1C: ETN sequence	£150,659	1.36	Referent	Referent	Referent	£30,146
1B: ADA sequence	£154,534	1.41	£3,876	0.05	Extendedly dominated	£6,895
1F: UST45 mg sequence	£154,701	1.40	£4,043	0.04	Dominated	£4,928
1G: UST 90 mg sequence	£154,976	1.41	£4,318	0.05	Extendedly dominated	£2,855
1A: IXE sequence	£155,267	1.52	£4,608	0.15	£30,146	N/A
1D: INF sequence	£157,284	1.42	£6,626	0.06	Dominated	Dominated
1E: SEC sequence	£185,065	1.49	£34,406	0.13	Dominated	Dominated

ADA = adalimumab; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Whilst it is acknowledged that the above does not explicitly account for change in DLQI, it should be noted that we are not aware of response rates for this criterion (i.e PASI 50 response **and** DLQI reduction of at least 5 points) being presented in any previous submission, likely driven by the fact that no clinical study appears to include a minimum DLQI at baseline within the inclusion criteria meaning that a 5 point reduction in DLQI cannot be achieved by patients with a baseline score of less than 5. In the light of this limitation, the analyses presented above should be taken into consideration.

To conclude, Lilly therefore believe that both PASI 75 response and PASI 50 response in combination with a five-point reduction in DLQI stopping rules should be included in the final guidance for ixekizumab from the rationale of consistency (as used in previous appraisals) and the additional evidence presented here.

Key point 2

Section 4.2 and 4.8: recommendation for treatment of TNF-alpha inhibitor-refractory patients

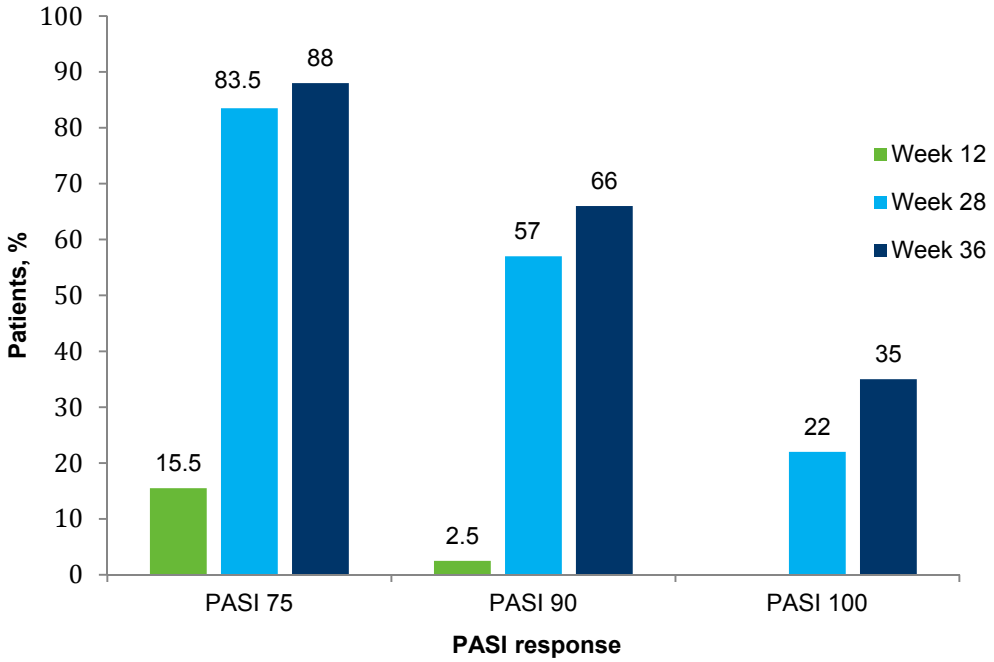
Lilly request that the committee consider recommending ixekizumab as a treatment option for patients who have failed, are contraindicated to, or are intolerant to one or more TNF-alpha inhibitors, in addition to the recommendation in the draft guidance.

Data presented in the Lilly submission demonstrates that ixekizumab is more effective than etanercept or placebo both for patients who had previously recevied biologic treatment (including TNF-alpha inhibitors) and for those who had not. Ixekizumab is able to achieve significant PASI 75, 90 and 100 response rates in patients with previous non-response to etanercept which are comparable to those achieved by the ITT population in the UNCOVER studies.

In the UNCOVER-2 study, 358 patients were randomised to treatment with twice weekly etanercept. At week 12, 200 (56%) of these patients were classified as inadequate responders, with only 15.5% of these patients having achieved PASI 75.[1] Following a 4-week washout period, etanercept inadequate-responders were treated with ixekizumab 80 mg Q4W. After 12 weeks of ixekizumab treatment (week 28) 83.5% of patients achieved PASI 75, 57.0% achieved PASI 90 and 22.0% achieved PASI 100.[1]

These proportions increased to 88.0% for PASI 75, 66.0% for PASI 90 and 35.0% for PASI 100 following 20 weeks (week 36) of treatment with ixekizumab 80 mg Q4W (Figure 1).[1] Following 44 weeks (week 60) of treatment with ixekizumab 82.5% of etanercept inadequate-responders achieved PASI 75, 68.5% achieved PASI 90 and 43.5% achieved PASI 100.[1] It should be noted that these patients did not receive the ixekizumab 160 mg loading dose nor the 12 week Q2W induction regimen. The PASI responses observed in these patients were consistent with those observed in patients who received ixekizumab 80mg Q4W during the induction period of the UNCOVER studies.[1]

Figure 1: PASI response rates in etanercept inadequate-responders before starting (week 12), and after 12 weeks (week 28) and 20 weeks (week 36) of ixekizumab 80 mg Q4W treatment[1]



Note: Etanercept inadequate-responders at week 12 had a 4 week washout period before receiving ixekizumab 80 mg Q4W from week 16. Therefore, week 12, week 28 and week 36 data presented above are the equivalent of 0, 12 and 20 weeks of ixekizumab treatment, respectively

In addition, ixekizumab provides a high-level of efficacy regardless of previous treatment with biologic therapy. In the UNCOVER-2 study, a total of 288 patients had received prior biologic therapy and 936 patients were biologic-naive.[2] For patients who had received prior biologic therapy and patients who were biologic-naive, PASI 75 response rates were significantly greater for ixekizumab 80 mg Q2W (92.9% and 88.8%, respectively) and ixekizumab 80 mg Q4W (74.1% and 78.6%, respectively) compared with those for placebo (0 and 3.2%, respectively [p<0.05]) and etanercept (30.3% and 44.3%, respectively [p<0.05]).[2] Furthermore, the proportion of patients who achieved complete clearance of their symptoms (PASI 100) in the biologic experienced and biologic-naïve patient populations was significantly greater for ixekizumab 80 mg Q2W (48.8% and 37.8%, respectively) and ixekizumab Q4W (22.4% and 33.6%, respectively) compared with those for placebo (0 and 0.8%, respectively [p<0.05]) and etanercept (5.3% and 5.3%, respectively [p<0.05]).[2] In addition, response rates were similar regardless of whether patients had received prior biologic therapy or not.

Scenario analyses also demonstrate that ixekizumab is a cost-effective treatment option for patients who were contraindicated to or had inadequate response on a TNF-alpha inhibitor. Ixekizumab was compared to ustekinumab 45mg, ustekinumab 90mg and secukinumab as second-line therapy in a biologic treatment sequence following failure on adalimumab, and was estimated to be the dominant treatment strategy in this patient group (Table 2).

Table 2: Scenario analysis: ixekizumab in patients with inadequate response to prior biologic therapy

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
2A: IXE sequence	£147,612	1.38	Referent	Referent	Referent	N/A
2C: UST 45 mg sequence	£147,842	1.30	£230	-0.08	Dominated	Dominated
2D: UST90 mg sequence	£148,350	1.32	£738	-0.06	Dominated	Dominated
2B: SEC sequence	£171,192	1.35	£23,580	-0.03	Dominated	Dominated

ADA = adalimumab; BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Given the evidence presented above, Lilly request that the committee consider recommending ixekizumab as a treatment option for patients who have failed, are contraindicated to, or are intolerant to one or more TNF-alpha inhibitors, in addition to the recommendation in the draft guidance.

Other points for consderation

Section 2: Clarification of the price of ixekiuzmab

The table presented in Section 2 of the ACD outlines the ixekizumab price as '*the list price is £1,125 for 80 mg, and £2,250 for 160 mg*.' Lilly would like to clarify that the 160 mg price outlined in the table actually represents 2 x 80 mg pens/syringes. Lilly suggest the following wording when describing the price of ixekizumab:

- Ixekziumab 80mg solution for injection in prefilled pen or syringe x 1 = £1,125
- Ixekizumab 80 mg solution for injection in prefilled pen or syringe x 2 = £2,250

Section 4.2: Clarification of wording in the ACD

Lilly would also like to clarify the point raised in section 4.2 of the ACD. The ACD states the following:

'The committee heard from the clinical experts that biological treatment is offered to patients whose disease has not responded to standard systemic therapies (such as ciclosporin and methotrexate) or when these treatments are contraindicated or not tolerated. It heard from the clinical experts that, because there are long-term data available for other biologicals and clinicians are familiar with using them, ixekizumab was likely to be offered to 2 groups:

- *patients who had already had a biological treatment to which their disease had not responded*
- *patients for whom other biological agents were contraindicated'.*

Whilst Lilly recognise that for some clinicians who are not familiar with ixekizumab it may be used as a second-line biologic, there is no clinical or economic evidence for why ixekizumab cannot be used as a first-line biologic option and it is likely that over time ixekizumab will be the preferred treatment option over older, less efficacious biologics as a first-line biologic option.

Section 4.9: Network meta-analysis results

In the draft guidance, ixekizumab is stated to be similarly effective compared with secukinumab and infliximab. Lilly would like to note that while PASI 75 response rates may be similar for the three treatments, the point estimates for PASI90 and PASI100 response rates were substantially higher in the network meta-analysis for ixekizumab than for secukinumab and infliximab (although it is noted that credible intervals overlap) (Table 3). These levels of response represent near-complete or complete skin clearance, respectively, and as such, a meaningful improvement in HRQoL for patients. Lilly would request that the committee consider updating the draft guidance to reflect these points regarding the efficacy of ixekizumab.

Table 3: PASI base case NMA random-effects model - absolute probabilities of achieving ≥50%, ≥75%, ≥90% or 100% PASI symptom relief for each treatment

	PASI 50			PASI 75			PASI 90			PASI 100		
	Probability	95% CrI		Probability	95% CrI		Probability	95% CrI		Probability	95% CrI	
Ixekizumab 80 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300mg	93.2%	89.5 %	96.1 %	81.8%	74.9 %	88.1%	59.6%	50.0 %	69.3%	28.6%	20.7%	37.9%
Infliximab 5 mg/kg	92.8%	88.1 %	96.1 %	81.1%	72.6 %	88.1%	58.7%	47.2 %	69.4%	27.8%	18.7%	38.0%
Ustekinumab 45 mg	87.1%	81.4 %	91.7 %	71.0%	62.2 %	78.8%	45.6%	36.0 %	55.2%	17.9%	12.0%	24.7%
Ustekinumab 90 mg	89.6%	84.2 %	93.7 %	75.1%	66.2 %	82.7%	50.6%	40.1 %	60.7%	21.4%	14.3%	29.5%
Ustekinumab 45 mg<100kg & 90 mg>100kg	82.8%	75.3 %	89.0 %	64.4%	54.0 %	73.9%	38.4%	28.4 %	48.8%	13.5%	8.3%	20.0%
Adalimumab 80 mg/40mg EOW	77.8%	68.9 %	85.5 %	57.5%	46.4 %	68.2%	31.7%	22.3 %	42.2%	10.0%	5.7%	15.6%
Etanercept	63.9%	52.8 %	74.3 %	41.3%	30.3 %	52.8%	18.9%	11.8 %	27.5%	4.6%	2.3%	7.9%
Placebo	13.7%	10.1 %	17.9 %	4.7%	3.1%	6.6%	1.0%	0.6%	1.5%	0.1%	0.0%	0.1%

CrI = credible intervals; EOW = every other week; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement in Psoriasis Area and Severity Index; PASI 75 = ≥75% improvement in Psoriasis Area and Severity Index; PASI 90 = ≥90% improvement in Psoriasis Area and Severity Index; PASI 100 = 100% improvement in Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks

Section 4.18: Costs of adverse events

In the ACD it is stated that '*the committee concluded that the company should have included the costs of adverse events in its economic model*'. Whilst adverse event costs were not modelled in the company's base case analysis as per previous technology appraisals of biologics in psoriasis, Lilly would like to re-iterate that these were incorporated in a sensitivity analysis (Table 4) presented in the original submission.

Table 4: Scenario analysis: adverse events

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
1C: ETN sequence	£145,588	1.27	Referent	Referent	Referent	£32,932
1F: UST45 mg sequence	£149,162	1.30	£3,573	0.04	Extendedly dominated	£17,174
1B: ADA sequence	£149,335	1.32	£3,746	0.05	Extendedly dominated	£17,670
1G: UST 90 mg sequence	£149,663	1.32	£4,075	0.06	Extendedly dominated	£15,506
1D: INF sequence	£151,331	1.33	£5,742	0.06	Extendedly dominated	£2,713
1A: IXE sequence	£151,671	1.45	£6,083	0.18	£32,932	N/A
1E: SEC sequence	£177,833	1.42	£32,245	0.15	Dominated	Dominated

ADA = adalimumab; BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Furthermore, inclusion of adverse events in the ERG base case did not alter the overall results of the cost-effectiveness analysis.

Section 4.20: Results of cost-effectiveness analysis

As noted by the ERG report for TA350 (secukinumab for treating moderate to severe plaque psoriasis) secukinumab annual dosing requires 13 administrations (52 weeks divided by 4 weeks) rather than 12 (once per month). As analyses accounting for the confidential patient access scheme cost for secukinumab were presented to the committee in the closed session, Lilly believe that this discrepancy needs to be taken into account as the clinical data for secukinumab is based on 13 administrations annually and only considering analyses based on 12 annual administrations may not present sufficient information for decision making.

Section 4.23: Results of cost-effectiveness analysis

Lilly would like to draw attention to the statement in the second bullet point '*the sequence including ixekizumab had fewer total costs and QALYs than the sequence including secukinumab'.* This statement ought to be amended to reiterate that these treatments are not compared in the same position, i.e. '*the sequence including ixekizumab as second-line had fewer total costs and QALYs than the sequence including secukinumab as first-line'*.

Lilly do not believe that a comparison of ixekizumab as second-line therapy versus secukinumab as first-line therapy is appropriate to make in this context. The ERG presented the second-line sequence of ixekizumab with the treatment sequence consisting of adalimumab-ixekizumab-infliximab to a secukinumab sequence comparing secukinumab-ustekinumab 90mg-infliximab. Given the complications of a sequence model, making such a comparison is always going to result in lower QALYs for the ixekizumab sequence as it contains a less efficacious treatment (adalimumab) whereas the secukinumab sequence contains a more efficacious treatment (ustekinumab). Therefore the QALY differences are not driven by secukinumab but the choice of treatments within the sequence. This context and detail should be made clear and amended in the draft guidance to avoid potentially misleading conclusions being drawn. A more relevant or, at the very least, equally valid comparison would be comparing both agents in the same position within a treatment sequence, as shown in Table 2. Whether compared with each other in first-line or in second-line, the ixekizumab sequence is associated with greater QALY gains over the secukinumab sequence, **when the other components of the sequence are the same**. Any analyses presented with the confidential patient access scheme price should take this issue regarding choice of treatments in the sequence into consideration.

Section 4.23: Innovation

Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity (< 3pM) and specificity to both forms of interleukin 17A (IL-17A and IL-17A/F). The affinity of ixekizumab for both the homo and heterodimer significantly exceeds that of other IL-17 inhibitors.

Furthermore, the ixekizumab autoinjector device has been designed through 13 separate qualitative and quantitative studies and three human factor studies (which included over 1,000 patients with various autoimmune conditions, as well as HCPs and caregivers), several design principles were identified as important for an autoinjector, including:[3]

- the device should be easy to use by patients with a range of physical abilities or comorbid conditions impacting dexterity
- the device operation should be easy to understand
- patients should feel confident that they are delivering the dose successfully and using the device appropriately
- the device can be safely used and disposed of

The autoinjector for ixekizumab is consistent with the principles outlined above and can be considered an innovative delivery method for patients who need to self-administer.[3]

In addition, a subcutaneous administration assessment questionnaire (SQAAQ) was used in the RHBL study to evaluate the ease of use and confidence in administering ixekizumab. This trial was an open-label 12 week phase 3 study of ixekizumab in moderate-to-severe psoriasis patients who were randomly assigned to an injection device (prefilled pen or prefilled syringe). The study found that, ixekizumab patients reported high levels of patient satisfaction across all parameters for both the prefilled pen and syringe, demonstrating convenience and ease of use of ixekizumab treatment.[4]

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17th November 2016

Ixekizumab for treating moderate to severe plaque psoriasis: Appraisal Consultation Document

To whom it may concern,

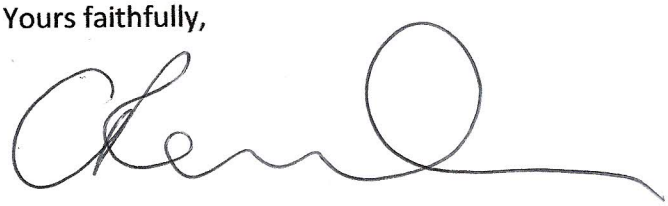
The Psoriasis Association welcomes the positive recommendation of ixekizumab as an option for people with severe plaque psoriasis.

Psoriasis is a lifelong condition that is unique to each individual. People respond differently to different treatments and, as such, it is important to have the widest possible variety of therapies available to people with psoriasis. Although ixekizumab is similar to biologics that are currently available for psoriasis – particularly secukinumab – there are subtle differences in its mechanism which may mean the difference between 'response' and 'no response' for patients. Because of this, ixekizumab represents a new option for people with severe psoriasis who have tried previous biologic therapy without lasting success, as well as those who are biologic naïve.

The Psoriasis Association also welcomes the equality considerations around the use of the PASI and DLQI.

I have read the Appraisal Consultation Document and have no further comment to add, aside from asserting our support once again for the positive recommendation of ixekizumab as an option for people with severe plaque psoriasis.

Yours faithfully,



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17 November 2016

Meindert Boysen
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Dear Meindert

Single Technology Appraisal (STA)
Ixekizumab for treating moderate to severe plaque psoriasis [ID904]
Appraisal consultation document

Thank you for the opportunity to comment on the above review document.

As an organisation that represents people affected by psoriasis and psoriatic arthritis, we support the opportunity for patients to get access to the latest therapies to alleviate their symptoms and limit disease progression. We also would like to see patients get better outcomes, fewer side effects and more convenient administration, therefore reducing the burden of being a patient, tied to frequent interventions, and dosage.

We also acknowledge that the cost of treating each patient within the NHS has to be fair and equitable and any new treatment has to provide value for money and not have a detrimental effect on the service provided to others treated within the NHS.

The decision to recommend ixekizumab as an option for treating plaque psoriasis will be welcomed by patients, as will allowing clinicians to decide when to prescribe in the biologic pathway, which we consider is a pragmatic and sensible option.

The gathering of safety in our view is also important. We would like to suggest that a research recommendation is added to the Final Appraisal Document, where ixekizumab in the same way as other biologic agents, is included into a safety registry, such as the British Association of Dermatologists Biologic Interventions Register (BADBIR). This in our view will aid prescribing and reassure patients in the future, when deciding on the risk and benefit of ixekizumab for the treatment of their psoriasis.

Yours sincerely

[redacted]

Comments on NICE Appraisal Consultation Document for the Single Technology Appraisal on Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

British Association of Dermatologists
Therapy & Guidelines sub-committee

On behalf of the British Association of Dermatologists, thank you for the opportunity to comment on the Appraisal Consultation Document.

We wish to express our agreement with the recommendations.

Therapy & Guidelines sub-committee

Single Technology Appraisal (STA)

Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

[redacted]

1. **Has all of the relevant evidence been taken into account?**

We are not aware of additional evidence that should be taken in to account

2. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

   Yes, with no additional comments.

3. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

   It is noted that the recommendation allows the use of Ixekizumab as a first biologic agent following systemic treatment, which is not aligned with the clinical expert opinion. The committee heard that from the clinical experts that, because there are long-term data available for other biologicals and clinicians are familiar with using them, Ixekizumab was likely to be offered to 2 groups:

   - patients who had already had a biological treatment to which their disease had not responded
   - patients for whom other biological agents were contraindicated

   The stopping rule: 4.26 In this draft Ixekizumab will be stopped if PASI 75% is not achieved at 12 weeks without the option to continue if a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started. This is in contrast with STA 350 on secukinumab when either of the response measures can be used. Presumably the committee reached this decision because data were not presented to support this. Clearly the trial data support the effectiveness of Ixekizumab on DLQI- are there plans to perform such an analysis to be included in this STA?

4. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

The limitations of the DLQI (older people) and PASI (skin colour) are commented on and appropriate flexibility in 4.28.

National Institute for Health and Care Excellence

Single Technology Appraisal

Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

AbbVie's Response to the Appraisal Consultation Document

Dear Meindert,

AbbVie welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for the single technology appraisal (STA) of Ixekizumab for treating moderate to severe plaque psoriasis [ID904]. AbbVie's comments are set out under section headings containing the questions NICE asks stakeholders to comment on for the ACD.

With kind regards

Antonia Morga
Senior HTA Manager, AbbVie UK Ltd.

1. Has all of the relevant evidence been taken into account?

AbbVie consider that the majority of relevant evidence has been taken into account by the Appraisal Committee in preparing the provisional recommendations detailed in the ACD. However, there are some considerations which AbbVie believes the Committee should also take into account before reaching a final decision and these are outlined below.

1.1 **Pages 11-12, section 4.14: "[…]** ***The committee concluded that the treatment sequences included by the company in its economic model reasonably represented current NHS practice***".

AbbVie notes that the manufacturer's submission assumed treatment response which did not vary with the specific position of ixekizumab in the treatment sequence. In particular, the manufacturer did not model the base case so to assume a decrease in the effectiveness of subsequent biologic treatment, which would have been the clinically most plausible approach.

AbbVie believes that the issue of "effect modification" linked to a specific sequence of biologics needs to be addressed and adequately explored.

In addition, AbbVie believes that it cannot be assumed that all possible sequences of biological treatments that can actually take place in clinical practice were captured in the manufacturer's model, and that the market share data presented, as stated in section 4.13, page 11 of the ACD (and upon which the sequences explored were based) are only an approximation of a very complex clinical practice.

2. Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

AbbVie consider the summaries of clinical and cost-effectiveness from the manufacturer and the ERG to be, on the whole, reasonable interpretations of the evidence. However, AbbVie concurs with the ERG and Committee's concerns relating to key model assumptions used by the manufacturer, and in particular those that unduly favour ixekizumab, namely:

2.1 Page 16, Section 4.25: Treatment pathway

AbbVie agrees with the Appraisal Committee when it states that “The committee was aware that the company had not explored the full range of treatment sequences that might be offered in current NHS practice”.

In addition, AbbVie believes that the guidance should be clear in stating that ixekizumab should be used in patients whose disease has not responded to a previous biological treatment and in patients for whom other biological agents are contraindicated

2.2 Page 6, Section 4.4: Generalisability of the trial populations

“The committee was aware that the trials included patients with a PASI score of 12 or more and that in previous appraisals of technologies for treating psoriasis, a PASI score of 10 or more had been defined as severe disease”

AbbVie notes that the definition of disease severity also reflects the DLQI value, which is assumed to be >10 for severe cases.

AbbVie also notes that these discrepancies represent limitations in the generalisability of trial findings on ixekizumab to the UK population, and introduces inconsistencies with previous appraisals.

2.3 Pages 9-10, Section 4.9: Network meta-analysis results

AbbVie believes that the uncertainty underpinning the network meta-analysis cannot lead the Committee to confidently state that “[..] ixekizumab was more clinically effective than adalimumab [..]”

In particular, the network meta-analysis reported values for the relative risk for ixekizumab versus adalimumab are not clinically plausible. AbbVie is especially concerned with the values, reported at page 101 of the ERG report, in table 4.16 (PASI base-case NMA random-effects model - absolute probabilities of achieving ≥50%, ≥75%, ≥90% or 100% PASI symptom relief for each treatment - CS base-case and ERG calculation) for adalimumab.

AbbVie wishes to note that data on file (supplied to the Committee in the table below) clearly show that the PASI scores for adalimumab are consistently higher than those reported in table 4.16 of the ERG report.

The table below summarizes the rate of PASI response at the first visit in the British Association of Dermatologists Biologic Interventions Registry (BADBIR), 6 months after initiation, and how it is sustained over time as per the Last Observation Carried Forward LOCF analyses in each population and for each level of response.

Population		PASI 75	PASI 90
All patients	***% achieving PASI after 6 months***	[redacted]	[redacted]
All patients	% of those sustaining it to 12 months	[redacted]	[redacted]
Patients with a baseline PASI >=10	***% achieving PASI after 6 months***	[redacted]	[redacted]
Patients with a baseline PASI >=10	% of those sustaining it to 12 months	[redacted]	[redacted]
Biologic-naive patients	***% achieving PASI after 6 months***	[redacted]	[redacted]
Biologic-naive patients	% of those sustaining it to 12 months	[redacted]	[redacted]
Biologic-naive patients with a baseline PASI >=10	***% achieving PASI after 6 months***	[redacted]	[redacted]
Biologic-naive patients with a baseline PASI >=10	% of those sustaining it to 12 months	[redacted]	[redacted]

The table clearly shows that, for patients treated with adalimumab, the differences between populations are small in terms of achieving response and maintaining it. Patients with a baseline PASI≥10 and biologic-naive patients have similar efficacy profiles, performing a bit better than the entire cohort. The best efficacy is observed for biologic-naive patients with a baseline PASI≥10.

2.4 Page 12, Section 4.15: Modelling utility benefit

AbbVie is particularly concerned that the manufacturer's model did not incorporate disutilities due to adverse events, and, as a consequence, did not investigate whether these disutilities appropriately reflected the specific biological treatments patients were receiving in the given treatment sequence considered. This introduces an important limitation in the interpretation of the findings from the cost-effectiveness analysis.

2.5 Page 14, Section 4.20: Results of the cost-effectiveness analysis": costs of adverse events

AbbVie agrees with the committee when it concluded that the company should have included the costs of adverse events in its economic model.

In particular, since a range of possible treatment sequences are included, the cost of adverse events should have reflected the management of the specific treatments that patients were receiving, as these may be different (in terms of frequency and duration) among the biologic treatments.

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

3.1. Page 3, Section 1.2: *"Stop ixekizumab treatment at 12 weeks if the psoriasis has not responded adequately.*[..]"

AbbVie wishes to note that this statement on the relevant stopping rule for ixekizumab should be followed by the following sentence: "Further treatment cycles are not recommended in these patients", in line with a similar statement included in the NICE TA for secukinumab (TA350). This is to ensure consistency across existing NICE guidance.

3.2. Page 3, Section 1.3 "*When using the PASI, health care professionals should take into account skin colour and how this could affect the PASI score, and make any adjustments they consider appropriate*"

AbbVie believes that this statement introduces unwarranted uncertainty around what could constitute as "any adjustment". In addition, no such similar statement was included in previous NICE appraisals for biological treatments in plaque. As a consequence, AbbVie would suggest that the statement is complemented with the wording "[..] and make any adjustments they consider appropriate *for all biological treatments*".

3.3. Pages 16-17, Section 4.26 "[...] *It had not seen evidence for a 50% reduction in the PASI score and a 5-point reduction in DLQI and so it did not consider it appropriate to include these criteria*"

AbbVie regrets that this evidence was not available for the purpose of this appraisal, as it should have been ideally considered as criteria to advice on stopping rules.

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

None that AbbVie is aware of.

5. Additional comments

5.1: There is inconsistency between the statements included at page 5, section 4.2 ("Treatment pathway") and the statement reported at page 20 ("What is the position of the treatment in the pathway of care for the condition?").

On page 20, the table states that “Ixekizumab is likely to be primarily offered to patients whose disease has not responded to a previous biological treatment and to patients who cannot have biological treatment”.

AbbVie wishes to highlight that the last part of the statement ([..] to patients who cannot have biological treatment”) is not clinically acceptable, as ixekizumab itself is a biological treatment. AbbVie wishes to request that that this statement be amended in line with the wording included in section 4.2, page 5 (“ixekizumab was likely to be offered to 2 groups: patients who had already had a biological treatment to which their disease had not responded; patients for whom other biological agents were contraindicated.)

5.2: From page 20, the statement “Biological treatment is offered to patients whose disease has not responded to standard systemic therapies (such as ciclosporin and methotrexate) or when these treatments are contraindicated or not tolerated “, should also include PUVA (psoralen and longwave ultraviolet radiation), as on page 3 and 18 of the document.

NOVARTIS

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Mr M Boysen
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
1st Floor 10 Spring Gardens
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22nd November 2016

Dear Mr Boysen,

Re: Ixekizumab for treating moderate to severe plaque psoriasis [ID904] – Appraisal Consultation Document

Thank you for your letter dated 25th October inviting comments on the Appraisal Consultation Document (ACD) for the above appraisal.

This document answers the four questions posed by NICE on page 1 of the ACD.

Has all of the relevant evidence been taken into account?

Novartis considers that the relevant evidence has generally been taken into account by the Appraisal Committee in preparing the provisional recommendations detailed in the ACD.

However, we are unclear why relevant published evidence on the efficacy of secukinumab in patients previously treated with biologic therapies, was not identified. The ixekizumab manufacturer states that literature searches were last updated in November 2015, eight months prior to submission in July 2016. Page 4 of the Company response to NICE's request for clarification (page 437 of the Committee papers) indicates that the November 2015 search update included reviewing conference proceedings from both the European Academy of Dermatology & Venereology Congress and the American Academy of Dermatology. Relevant data on secukinumab in biologic experienced patients was presented in poster format at both these congresses during 2014 / 2015.[1-3] These data demonstrate that secukinumab 300mg achieved higher clinical response rates than both etanercept and placebo, in subjects both with and without previous biologic exposure.

Had this data on secukinumab's efficacy in subgroups defined by prior treatments been identified by the ixekizumab manufacturer, it is possible that a different conclusion may have been drawn regarding the feasibility of a network meta-analysis in the subgroup of patients with previous use of biological therapy.

In addition, we would like to draw the committee's attention to the different immunogenicity rates and clinical impact observed in the ixekizumab clinical studies and in the secukinumab clinical studies. Whilst the secukinumab Summary of Product Characteristics states that "less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. About half of the treatment-emergent anti-drug antibodies were neutralising, but this was not associated with loss of efficacy or pharmacokinetic abnormalities",[4] the ixekizumab Summary of Product Characteristics states: "Approximately 9–17% of patients treated with Taltz at the recommended dosing regimen developed anti-drug antibodies... approximately 1% of patients treated with Taltz had confirmed neutralising antibodies associated with low drug concentrations and reduced clinical response. An association between immunogenicity and treatment emergent adverse events has not been clearly established."[5] It is therefore possible that the simplifying modelling assumption that patients "maintain their level of response until discontinuation" (see page 216 of the Eli Lilly submission, page 307 of the Committee papers) may be inappropriate, since differentiation between secukinumab and ixekizumab response rates may be observed over the long-term.

Novartis agrees with the committee's conclusion that "in clinical practice, ixekizumab would be offered at the same place in the treatment pathway as the existing biological treatments", including secukinumab. Furthermore, we agree with the conclusion the committee drew from the manufacturer's network meta-analysis that "ixekizumab was similarly effective compared with secukinumab and infliximab", and note "that the most plausible ICER was likely to be in line with the other biological treatments already recommended in previous NICE guidance".

<u>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</u>

Novartis considers the summaries of clinical and cost-effectiveness in the ACD to be, on the whole, reasonable interpretations of the evidence.

However, we are unclear regarding the statement on page 20 of the ACD "Ixekizumab is likely to be primarily offered …to patients who cannot have biological treatment". Since ixekizumab is itself a biological treatment, we query whether this statement was intended to read "who cannot have standard systemic therapies".

Novartis agrees with the committee's interpretation of the evidence regarding the similar mechanisms of action of ixekizumab and secukinumab, i.e. "that ixekizumab did not differ substantially in its mechanism of action from secukinumab".

However, we would like to correct a factual inaccuracy within the committee papers regarding differences in the mechanism of action between ixekizumab and secukinumab.

Page 79 of the pre-meeting briefing (page 81 of the committee papers) notes "a different mode of action and extended activity of ixekizumab compared with secukinumab because it binds to both IL-17 A and IL-17 F", based on the submission from the British Association of Dermatologists.

This is factually inaccurate since both ixekizumab and secukinumab inhibit IL-17 A and IL-17 A/F. Both drugs have the same mode of action and neither inhibits the homodimer IL-17 F.[6]

Statements made by the ixekizumab manufacturer regarding mode of action are accurate, since they do not mention IL-17 F, or claim any differentiation versus secukinumab. For instance;

- "ixekizumab is an IgG4 monoclonal antibody that binds with high affinity and specificity to IL-17A" (page 44 of the manufacturer submission, page 135 of the committee papers)
- "Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity (< 3pM) and specificity to interleukin 17A (both IL-17A and IL-17A/F)" (page 33 of the manufacturer submission, page 124 of the committee papers).

We note a further factual inaccuracy within the submission from the British Association of Dermatologists. The statement on page 6 of their submission (page 482 of the committee papers), that "excluding ixekizumab means denying these individuals a possible therapy, since IL-17A blockade is not an otherwise available pharmacological intervention", is untrue since IL-17A blockade via secukinumab is recommended by NICE in TA350.[7]

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Novartis has no comments.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Novartis does not have any comments in relation to the above potential equality issues.

I hope that our comments are of value. If you require clarification on any aspects of our response, please do not hesitate to contact me.

Yours sincerely,

[redacted]

Novartis Pharmaceuticals UK Ltd

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in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Ixekizumab for treating moderate to severe chronic plaque psoriasis

- Confidential addendum -

In an email of 19 December 2016, Jeremy Powell (NICE) asked the ERG to provide input on two points:

1. *"In their consultation response the company have referred to 2 of their scenario analyses to support their comments. We would be grateful if you could provide these, contingent on your own base case, with list price ICERs (containing ixekizumab and ustekinumab PASs), and separately in a confidential appendix, ICERs containing the comparator PAS. No supporting narrative is required. The scenarios are:*
    a. *Prior failure on or contraindication to TNF-a inhibitor (company submission, section 5.8.3, page 291 [Tables 99, 100])*
    b. *PASI 50 continuation rule (company submission, section 5.8.3, page 300 [Table 112])*
2. *AbbVie (a comparator company) has submitted a table of data as part of its consultation response (section 2.3 on pages 3-4 of AbbVie's response), containing PASI response rates for adalimumab to support their comment that they do not consider the results of the network meta-analysis (NMA) to be clinically plausible. The data is marked academic in confidence and is from a registry (British Association of Dermatologists Biologic Interventions Register), so it may not have been possible to include it in the NMA. However, we would be grateful for a brief comment from you on this, given the importance of the NMA in the decision-making."*

This document contains responses using the non-confidential comparator prices, the table including the confidential PAS was submitted alongside this document.

Re 1a) A table showing the "ERG base-case using intervention and comparators as second-line in treatment sequence" is presented below.

Re 1b) A table "ERG base-case using PASI50 as a definition of response (i.e. as continuation rule)" is presented in a table at the end of this document.

Re 2) As part of the consultation response (section 2.3), AbbVie presented a table containing PASI response rates. The table summarised the rate of PASI response at the first visit in the British Association of Dermatologists Biologic Interventions Registry (BADBIR), 6 months after initiation.

AbbVie emphasised that the rates are different from the ones presented in Table 4.16 (page 101) of the ERG report which was based on Table 52 of the company submission (CS).

According to the BADBIR data cited by AbbVie, [redacted] of patients treated with adalimumab achieve PASI75 after *6 months* while [redacted] achieve PASI90 after *6 months*. Slightly [redacted] rates are reported for three subgroups (patients with a baseline PASI≥10, biologic-naive patients, both groups combined). This compared to 57.5% (CS) or 57.9% (ERG report) of patients achieving PASI75 and 31.7% (CS) or 31.8% (ERG report) of patients achieving PASI90, *12 weeks* after treatment (Table 4.16 of the ERG report).

According to AbbVie, the values presented in the CS and reproduced in the ERG report are not "clinically plausible".

ERG comment: The ERG would like to highlight a few points in relation to the numbers cited by AbbVie.

1. According to the eligibility criteria of BABDIR, *"there is no PASI/DLQI minimum requirement, as it is assumed that the patient's psoriasis is of a reasonable severity as they are commencing a biologic therapy"* (http://www.badbir.org/Clinicians/Eligibility/, accessed 04 January 2017).
   In addition, it is unclear if inclusion and exclusion criteria used for the registry were comparable to the 32 randomised controlled trials (RCTs) included in the network meta-analyses (NMAs, Table 4.14 of the ERG report). The ERG suspects that stricter criteria were used for the RCTs.
   As the baseline characteristics of patients included in the database are not in the public domain and no comparative data were reported, it is unclear whether the patients and presented results are directly comparable to the NMA presented in the CS and the ERG report.
2. It should be noted that the time points of the results are different. One could reasonably speculate that the rates cited by AbbVie would be even higher after *12 weeks*.
3. The ERG notes that the results of the NMA presented in the CS (and reproduced in the ERG report) are in line with previous technology appraisals.
   For example, TA350 (Secukinumab for treating moderate to severe plaque psoriasis) included a NMA based on 30 studies. Table 12 presents the "Random effects multinomial NMA for PASI 75 response (reproduced from Table 56 from the company's submission)". The results are roughly in line with the results in Table 51 of the CS of the ixekizumab submission (Random effects multinomial NMA for PASI 75 response (RR at week 12)), e.g.:
   - IXE CS: Adalimumab 80mg/40mg EOW vs. placebo 12.56 (6.15, 21.05); SEC CS: adalimumab vs. placebo 15.18 (12.09, 18.76)
   - IXE CS: Adalimumab 80mg/40mg EOW vs. secukinumab 300 mg 0.74 (0.51, 0.91); SEC CS: adalimumab vs. secukinumab 0.68 (0.57, 0.79)

If the percentage achieving response for adalimumab was estimated based on a comparison with placebo then it might be that the value from the IXE CS is indeed an underestimate at least in comparison to the SEC CS. However, given that the results were reported in randomised controlled trials with peer-reviewed methods, the ERG considered the NMA results to be more accurate.

ERG base-case using intervention and comparators as second-line in treatment sequence

Sequence[a]	Total costs	Total QALYs gained	Incremental costs (versus 2A)	Incremental QALYs (versus 2A)	ICER (fully incremental)
2A: IXE sequence	£150,058	1.457			
2C: UST 45 mg sequence	£150,226	1.377	£168	-0.080	Dominance
2C: UST 90 mg sequence	£150,794	1.395	£736	-0.062	Dominance
2B: SEC sequence	£170,910	1.423	£20,852	-0.034	Dominance

[a]See CS Table 99 for more details regarding the treatment sequences.

ERG base-case using PASI50 as a definition of response (i.e. as continuation rule)

Sequence	Total costs	Total QALYs gained	Incremental costs (versus 1C)	Incremental QALYs (versus 1C)	ICER (fully incremental)	ICER (versus 1A)	ICER (versus 1H)
1C: ETN sequence	£153,416	1.434			-	£25,189	£21,467
1H:ADA-IXE sequence	£155,502	1.531	£2,086	0.097	£21,467	£30,848	-
1B: ADA sequence	£157,353	1.486	£3,937	0.052	Dominance	£1,098	Dominance
1F: UST45 sequence	£157,410	1.476	£3,993	0.042	Dominance	£530	Dominance
1A: IXE sequence	£157,473	1.595	£4,057	0.161	£30,848	-	£30,848
1G: UST90 sequence	£157,718	1.491	£4,302	0.056	Dominance	Dominance	Dominance
1D: INF sequence	£160,481	1.498	£7,065	0.064	Dominance	Dominance	Dominance
1E: SEC sequence	£184,150	1.568	£30,734	0.133	Dominance	Dominance	£789,767