in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs

ERRATUM

This document contains errata in the ERG report in response to the company's factual accuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page	Change
13	• Typographical errors corrected (etanercept, secukinumab, bDMARD) • The statement "fewer than five trials in most analyses" was replaced with "at most four trials in an analysis" • Changed sentence "These showed that for bDMARD-naïve patients [redacted] was the most effective treatment across all categories of ACR response but it was [redacted] to "These showed that for bDMARD-naïve patients with the exception of [redacted], the ACR response of ixekizumab q2w was [redacted] from other treatments and that with the exception of [redacted], ixekizumab q4w was [redacted] from other treatments".
16	• Amended sentence "The most influential parameters were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs associated with ixekizumab and secukinumab." to read "The most influential parameters in the company's sensitivity analyses (which were not exhaustive) were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs associated with ixekizumab and secukinumab.".
17	• The statement on the number and proportion of UK patients in the SPIRIT trials has been marked as academic in confidence
21	• "[sic!]" has been added to mark a typographical error in text quoted from the CS
31	• Typographical error corrected (clinicaltrials.gov)
41	• Mean disease duration (time since PsA diagnosis) for the SPIRIT trials corrected • Missing ")" has been added in the fifth bullet point • The number of rheumatologists and dermatologists in the Adelphi DSP has been marked as academic in confidence
59	• "456 patients" has been replaced with "454 patients"
71	• In Table 4.18, the row "Ustekinumab 90 mg q12w" has been deleted
73	• In Table 4.22, the duplicate rows "Placebo", "Adalimumab 40 mg q2w" and Apremilast 30 mg bid have been deleted
74	• The sentence "For PsARC responders, the changes from baseline in HAQ-DI for ixekizumab 80 mg q4w were [redacted] from the NMA and [redacted] in the trial data and for 80 mg q2w they were [redacted] from the NMA and [redacted] in the trial data." Was changed to read "For PsARC responders, the changes from baseline in HAQ-DI for ixekizumab 80 mg q4w were [redacted] from the NMA and [redacted] in the trial data and for 80 mg q2w they were [redacted] from the NMA and [redacted] in the trial data".
75	• The statement on the proportion of UK patients in the SPIRIT trials has been marked as academic in confidence • "456 patients" has been replaced with "454 patients"
76	• Typographical errors corrected (etanercept, secukinumab, bDMARD)

Page	Change
	• The statement "fewer than five trials in most analyses" was replaced with "at most four trials in an analysis" • Changed sentence "These showed that for bDMARD-naïve patients [redacted] was the most effective treatment across all categories of ACR response but it was [redacted]" to "These showed that for bDMARD-naïve patients with the exception of [redacted], the ACR response of ixekizumab q2w was [redacted] from other treatments and that with the exception of [redacted] from other treatments".
125	• Amended sentence "The cost effectiveness results were fairly robust to scenario and one-way sensitivity analyses conducted by the company, but the most influential parameters were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs associated with ixekizumab and secukinumab." to read "The cost effectiveness results were fairly robust to scenario and one-way sensitivity analyses conducted by the company, but the most influential parameters in the company's sensitivity analyses (which were not exhaustive) were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs associated with ixekizumab and secukinumab.".
148	• Typographical error corrected (etanercept, secukinumab, bDMARD)
150	• The statement on the number and proportion of UK patients in the SPIRIT trials has been marked as academic in confidence

groups than in the placebo group in both SPIRIT trials. Adverse events (AEs) across the two SPIRIT trials were mainly of mild or moderate severity and the proportion of patients who discontinued medication due to AEs was low across all treatment groups. There were no deaths across the two trials in the double-blind periods. Injection site reactions were statistically significantly more common with ixekizumab than placebo in both SPIRIT trials.

In the absence of trials directly comparing the active treatments specified in the NICE scope, the company conducted a Bayesian NMA of relevant trials for the outcomes of PsARC response, Psoriasis Area and Severity Index (PASI) 50/75/90/100 and change in HAQ-DI. Separate analyses were performed for bDMARD-naïve and bDMARD-experienced patients. The results for bDMARD-naïve patients showed that [redacted] had the best performance for PASI response but it was [redacted]. For PsARC response the most effective treatments were [redacted]. For both outcomes, PASI response and PsARC response, [redacted] to all other treatments. For change from baseline in HAQ-DI the NMA results showed that in PsARC responders all treatments were significantly better than placebo except for [redacted], [redacted] having the largest change from baseline. Changes in HAQ-DI score were smaller for PsARC non-responders and [redacted] were the most effective treatments.

There was less evidence for bDMARD-experienced patients (at most four trials in an analysis) and ixekizumab was [redacted] to ustekinumab for PsARC response. For PASI response, ustekinumab had the [redacted] response rate but it [redacted] to ixekizumab.

Additional NMA results for ACR 20/50/70 response and adverse events (AEs) were provided in the response to request for clarification. These showed that for bDMARD-naïve patients with the exception of [redacted], the ACR response of ixekizumab q2w was [redacted] from other treatments and that with the exception of [redacted] from other treatments. For bDMARD-experienced patients, both ixekizumab regimens had [redacted] ACR response compared to ustekinumab but the differences were [redacted]. Estimated conditional probabilities of treatment-emergent AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; serious AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; and discontinuations due to AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company conducted a systematic review of the evidence for ixekizumab and its potential comparators in adults with PsA as per the NICE scope. The submission and response to clarification provided sufficient details for the ERG to appraise the literature searches. A range of databases were searched, and additional searches of conference proceedings, trials registers and websites were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. However, the ERG has major concerns regarding the searches, as detailed in section 1.6.2.

The company presented two multicentre, randomised controlled trials of ixekizumab (SPIRIT-P1 and P2). Randomised trials represent the highest level of primary studies in medical research. This evidence base includes patients with experience of bDMARDs and those without and outcomes relevant to the NICE scope. Both trials are well-conducted. Both compare ixekizumab to placebo. The double-blind period of the SPIRIT trials is 24 weeks so long-term effectiveness results cannot be fully determined. The extension periods do, however, provide information on long-term safety. At week 16 in the trials, patients were permitted rescue therapy in case of inadequate response so results up to

the NHS Reference Costs. Furthermore, the company estimated the costs associated with HAQ-DI and PASI scores separately. HAQ-DI related costs were estimated using a linear regression informed by a study with sample size of 916 rheumatoid arthritis patients in the UK, dated 2002. PASI-related costs were sourced from the York model and justification was not provided for each cost item.

The company's deterministic base-case incremental cost effectiveness ratios (ICERs) of ixekizumab (with PAS) compared with other comparators showed that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per quality-adjusted life year QALY gained in the b/tsDMARD-experienced population when compared with BSC. It was [redacted] when compared with ustekinumab in that population in the no and mild-to-moderate psoriasis groups [redacted] in the moderate-to-severe group. The cost effectiveness results were fairly robust to scenario- and one-way sensitivity analyses conducted by the company. The most influential parameters in the company's sensitivity analyses (which were not exhaustive) were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs associated with ixekizumab and secukinumab. Scenario analyses indicated that assumptions with the greatest impact on the ICER for the ixekizumab sequences versus BSC relative to the base-case were HAQ-DI rebound to natural history in the BSC treatment state, alternative (i.e. the York model) utility model coefficients, an alternative (i.e. the Poole et al. 2010) algorithm for costs associated with HAQ-DI and combining PsARC and PASI rates as the treatment continuation rule. Furthermore, the inclusion of certolizumab pegol and secukinumab in the b/tsDMARD-experienced population led to certolizumab pegol being cost effective (at list prices for ixekizumab and secukinumab but with PAS schemes for certolizumab pegol and ustekinumab being accounted for).

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The cost effectiveness searches in the company submission and clarification response were reported in enough detail for the ERG to appraise them. Separate searches were conducted to identify cost effectiveness models and model input studies.

Reviewing the overall evidence, the ERG considers that the company's approach to use the revised York model as a basis for developing their model was appropriate. However, a limitation with this and the York model was that the allocation of patients to health states in the model was based on a relative measure of response (based on reductions in symptoms). This may lead to health states being composed of heterogeneous patient populations for which it is arguably difficult to assign costs and HRQoL estimates.

The economic model described in the CS is considered by the ERG to meet the NICE reference case, with the notable exceptions of a) the exclusion of comparators identified in the scope and b) a NMA (in the CS base-case) that did not consider all the relevant outcomes as identified in the scope, such as adverse events. Addressing a), the company justified the absence of secukinumab and certolizumab pegol from the b/tsDMARD-experienced patient population analysis by the unavailability of data in that population. However, it should be noted that studies on these two treatments were conducted in mixed populations, i.e. b/tsDMARD-naive and –experienced patients. Regarding b), the omission of adverse events from the NMA and economic model was considered a major limitation by the ERG, given that these differ per treatment and their inclusion would lead to potential differences in HRQoL, costs, and treatment discontinuation rates. Furthermore, the use of a limited network for the b/tsDMARD-experienced patient population, which omitted PASI 50 as an outcome, was considered by the ERG to result in potential bias in favour of treatments with a higher PsARC response (given PASI 50 response was presumably set to 0% in this case). This also resulted

in the exclusion of certolizumab pegol and secukinumab as comparators in this population, i.e. deviating from the scope, which again likely favoured ixekizumab in this population. Furthermore, treatment sequences used in the model for the b/tsDMARD-naive patient population exclude relevant treatments as, in addition to ustekinumab, certolizumab pegol and secukinumab could also be used in second line.

The ERG is concerned about the representativeness of the patient population in the SPIRIT trial programme and its impact on the relevance and validity of the NMA results for the UK context. BSC was not accurately described in the model and the ERG was unable to assess whether BSC was representative of the UK context and whether the effectiveness as well as the costs associated with BSC in the cost effectiveness model were valid.

The assumption of equal treatment discontinuation rates for all b/tsDMARD treatments was viewed as a major and influential limitation. Of further concern were the excess mortality which was considered potentially too high and the fact that the HAQ-DI reduction estimate for ixekizumab q4w responders and non-responders based on the NMA was inconsistent with the trial data. Furthermore, the ERG considers there to be large uncertainty about the resource use and cost estimates associated with HAQ-DI and PASI, with several limitations identified in both estimates.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Searches were carried out in line with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. The company's clarification response provided sufficient details for the ERG to appraise the searches. Additional searches were carried out for conference abstracts and clinical trials. The clinical evidence is based on two multinational RCTs covering a group of patients naïve to bDMARDs and those with prior experience of bDMARDs.

The cost effectiveness model is well built and transparent. The treatment effectiveness estimates from a network of studies are a strength as is the attempt to consider treatment sequences. The company performed many relevant sensitivity- and scenario analyses to reflect uncertainty about the cost effectiveness results. The model was relatively robust to these changes, with some notable exceptions as detailed in section 1.5 of this report.

1.6.2 Weaknesses and areas of uncertainty

The ERG was concerned about the overall quality of the searches for studies on clinical effectiveness as it identified numerous inconsistencies, omissions, inaccuracies and errors. This and the application of an English language restriction mean that it is possible that relevant evidence was missed.

The main trials in the submission included a small number of UK patients (approximately [redacted] across the two trials). Furthermore, NICE recommends that bDMARDs are given after two cDMARDs have been tried. However, in the SPIRIT trials patients have not all received two prior cDMARDs. The committee will need to decide, based on the factors highlighted by the ERG in this report whether it agrees with the company that the results of the SPIRIT trials are generalisable to UK practice. Another weakness of the submission is the lack of direct evidence available on ixekizumab in relation to the comparators in the scope.

Cost effectiveness searches of Medline and Embase contained extensive focussed MeSH and Emtree indexing which may have adversely impacted on search strategy recall. The ERG noted several typographical errors, incorrect truncation and syntax mistakes in several of the cost effectiveness

The CS states that *'switching to another anti-TNF is a well-established practice in the NHS'*.[1] The company also states that treatment may be less successful with these agents at second line, i.e. *'less than 50% of the patients who achieved an ACR 20, 50 and 70 response after treatment with a TNF-alpha inhibitor in first-line, achieved such a response after receiving treatment with a second-line TNF-alpha inhibitor*.[19]'The average persistence on anti-TNF-alpha therapies in relation to the chronic nature of PsA is highlighted. '*Average survival/persistence of patients with PsA on anti-TNFα therapy is in the range of 2 to 4 years for the first agent and shorter for subsequent anti-TNFα therapies'* based on a literature review.[20]

The company state the unmet need for ixekizumab as providing a new mechanism of action to obtain and sustain efficacy at a similar level to that of the anti-TNF-alpha therapies in both patients naïve to biologic DMARDs as well as those experienced with acceptable safety and minimal disturbance to lifestyle. The CS further state that '*treatments should be able to treat the core joint symptoms of PsA as well as the skin symptoms (psoriasis and nail psoriasis) and the extra-articular PsA symptoms (such as enthesitis and dactilytis [sic!])'*.[1]

The CS states that '*ixekizumab is the first monoclonal antibody to block both active forms of IL-17A (IL-17A is expressed in both homodimer and heterodimer forms) with high binding affinity.[REF CS 64] It is the second anti IL-17 (and third biologic therapy) to offer an alternative mechanism of action to TNF-α inhibitors'*.[1]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic review to identify randomised controlled trial (RCT) evidence of ixekizumab and potential relevant comparator treatments for psoriatic arthritis.

4.1.1 Searches

Initial searches were reported for Medline, Medline In-process & Other Non-Indexed Citations, Medline Daily Update, PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL). These were undertaken in August 2016 (1990-2016). Update searches were reported for May 2017 (2016-2017). The database host was not reported for the initial searches, Ovid was reported as the host for the update searches. The date the searches were conducted was provided.

Medline and Embase searches included unreferenced randomised controlled trials study design filters. The EBM Reviews CENTRAL search did not include an RCT filter. Medline, Embase and CENTRAL searches were all restricted to English language publications only. Searches of the following trials registers were reported in the appendices of the company submission (section 1.2.1) for 01/01/2016-09/05/2017: clinicaltrials.gov and World Health Organisation (WHO) ICTRP (International Clinical Trials Registry Platform).

Additional searches of the following conferences abstracts were reported: European League Against Rheumatism (EULAR, 2017 only), American College of Rheumatology/Association for Rheumatology Health Professionals (ACR/ARHP, 2016 only) and Asia Pacific Rheumatology Congress (APLAR, not included in the update). However, no details of the conference proceedings search terms, date of searches or results were provided.

The company submission noted that the initial review and update searches were conducted by different third-party vendors.[1] In Appendix D, the company acknowledgment significant mistakes in the Embase, Medline and CENTRAL searches (1990-2016).[28] The mistakes were corrected in the update searches (2016-2017). Unfortunately, the corrected searches were not repeated to cover the date span of the initial searches. The company reported checking whether the flawed initial review searches had missed studies.[28] The cross-checking process involved checking whether relevant included studies from previous systematic reviews (SRs) and network meta-analyses (NMAs) were picked up. The company was satisfied that *'it was deemed to be likely that the initial review captured all relevant studies over the period 1990-2016'*.[1, 28] The process for identifying candidate SRs and NMAs to check the initial review against was not reported in the CS nor appendices. In the clarification response,[25] the company reported selecting SRs and NMAs from the updated RCT search as well as from TA445;[13] independent searches specifically for SRs were not conducted by the company.

ERG comment:

- The main clinical effectiveness searches (1990-2016) contained consequential errors and flaws which will have impacted on retrieval of RCTs. Although the mistakes were corrected in the update searches (2016-2017), corrected searches were not re-run. Relevant studies could have been missed due to these mistakes.
- The company's approach to checking whether studies were missed or not was sub-optimal. Only RCT searches were conducted for the clinical effectiveness review. The company reported in the submission[28] and the clarification response[25] that earlier SRs and NMAs were used to cross-check for missed studies and as a method of validation for the review. As no SR searches were

The mean age of patients in SPIRIT-P1 was 49.5 and 51.9 years in SPIRIT-P2. Just under half were male (SPIRIT-P1: 46.0% and SPIRIT-P2: 46.6%). Most patients across the two trials were white (SPIRIT-P1: 94% and SPIRIT-P2: 91.5%). In total, 3.6% of the patients in SPIRIT-P1 and 5.8% in SPIRIT-P2 were Asian. The SPIRIT-P1 study was conducted with the majority of patients from Europe (73.4%) whereas in SPIRIT-P2 41% were from Europe.

Mean BMI in SPIRIT-P1 was 30.0 (SD 8.5) and 30.9 (SD 7.2) in SPIRIT-P2. The mean disease duration (time since PsA diagnosis) was 6.7 years in SPIRIT-P1 and 10.0 years in SPIRIT-P2. Current psoriasis occurred in 94.5% of patients in SPIRIT-P1 and in 93.4% of patients in SPIRIT-P2. Moderate to severe psoriasis was found in 13.8% of SPIRIT-P1 and 10.5% of SPIRIT-P2 patients. In SPIRIT-P1 58% had current enthesitis and 37.6% had current dactylitis. In SPIRIT-P2 the corresponding figures were 60.9% and 17.1%).[1]

ERG comment:

- Approximately 85% of the participants in SPIRIT-P1 had received a cDMARD which is normally given before a bDMARD in clinical practice so 15% of the patients in SPIRIT-P1 are not relevant to the population in the scope.
- Furthermore, NICE recommends that bDMARDs are given after two cDMARDs have been tried. However, in the SPIRIT trials patients have not all received two prior cDMARDs. A separate analysis of the NICE ITT population is provided in the CS based on [redacted] patients across the two trials.[1]
- Non-white participants are underrepresented across the two trials.
- Mean BMI in the SPIRIT trials is within the obese classification so patients in the trials may be more overweight than those seen in practice.
- The ERG asked the company to clarify whether patients included in those trials are representative of UK clinical practice. The company replied that they had sourced real world data to assess the representativeness of patients in the SPIRIT trials for UK practice.[25] In the Adelphi Psoriatic Arthritis Disease Specific Programme (DSP), a total of [redacted] patient record forms were completed by [redacted] rheumatologists and [redacted] UK dermatologists. Of these patients, [redacted] were bDMARD-naïve and [redacted] bDMARD experienced (based on the Adelphi Psoriatic Arthritis DSP; as cited in the Clarification response).[25] The company also compared the patients to a recently published UK study from The Health Improvement Network (THIN).[8]
- The company stated that patients in SPIRIT-P1 had higher baseline CRP and a greater number of tender and swollen joints than patients in the Adelphi study therefore '*at least the same level of ACR response rates would be expected to be achieved in UK practice as was demonstrated by SPIRIT-P1'*.[25]This is an assumption made by the company.
- The ERG noted that mean age and proportion of males was similar in the SPIRIT-P1 trial and the UK Adelphi study (biological-naïve) and THIN database studies. However, BMI did appear to be a little higher in SPIRIT-P1. The UK PsA patients in Adelphi DSP had slightly higher rates of prior conventional synthetic DMARD (csDMARD) use ([redacted] of UK PSA bio-naive patients).
- The ERG noted that mean age was similar in the SPIRIT-P2 trial and the UK Adelphi study (bio-experienced). The proportion of males was slightly higher ([redacted] in Adelphi vs. 46.6% in Spirit-P2). Again, BMI did appear to be a little higher in SPIRIT-P2. The company stated that '*The rate of prior csDMARD use is consistent in SPIRIT-P2 with the Adelphi DSP dataset. 77.5% of bio-experienced patients randomized to IXE80MGQ4W received prior csDMARD use compared to [redacted] of bio-experienced patients in the Adelphi DSP dataset.'*[25]
- Patients in SPIRIT-P2 generally had more severe disease at baseline than those bio-experienced patients treated in UK clinical practice as captured by Adelphi DSP. SPIRIT-P2 included a

ERG comment:

- In total, 454 patients have been exposed to ixekizumab across the two SPIRIT trials. This has revealed an increased but manageable set of adverse events when compared to placebo.
- Safety is evaluated in a double-blind manner for just 24 weeks. However, the long-term extension phases of the trials (up to two years available in SPIRIT-P1) add weight to the evidence of an acceptable safety profile in a population of patients with psoriatic arthritis.
- The increased incidence of infection with ixekizumab compared to placebo is noted. The Summary of Product Characteristics (SmPC) for ixekizumab notes that it '*should be used with caution in patients with clinically important chronic infection. If such an infection develops, monitor carefully and discontinue Taltz if the patient is not responding to standard therapy or the infection becomes serious. Taltz should not be resumed until the infection resolves. Taltz must not be given to patients with active tuberculosis (TB). Consider anti-TB therapy prior to initiation of Taltz in patients with latent TB*'.[34] Patients will need to be made aware of the increased risk of infections.
- Including both psoriatic arthritis trials and trials of plaque psoriasis, the SmPC notes that a total of 7,339 patients have been treated with ixekizumab representing 13,645.6 years of exposure. The SmPC notes that serious hypersensitivity reactions, including some cases of anaphylaxis, angioedema, urticaria and, rarely, late (10-14 days following injection) serious hypersensitivity reactions including widespread urticaria, dyspnea and high antibody titres have been reported. Cases of new or exacerbations of Crohn's disease and ulcerative colitis have also been reported. Caution is advised when prescribing ixekizumab to patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis, and that patients should be monitored closely. Furthermore, ixekizumab should not be used with live vaccines.[34] Regarding the SPIRIT trials, it was noted that injection site reactions were statistically significantly more common in ixekizumab groups in comparison to placebo.[34]
- The only direct safety comparisons, as for effectiveness comparisons, are between placebo and ixekizumab. However, SPIRIT-P1 has a reference adalimumab arm and it can be observed that occurrence of adverse events was similar in the adalimumab group to the ixekizumab groups although fewer of the adalimumab events appeared to be attributable to the drug. Additional safety comparisons between treatments are reported in the NMA results in section 4.3.

4.2.7 Ongoing trials

The CS mentioned two ongoing trials.[1] The first (SPIRIT-P3) has a dosage which is not in line with the licence, i.e. ixekizumab 80 mg q2w was given to all patients irrespective of psoriasis severity. Hence no further description of the trial was given in the CS. The second ongoing trial (SPIRIT-H2H) was described. SPIRIT-H2H was started in August 2017, is currently recruiting patients and is due to complete in April 2019. This randomised, open label trial will compare ixekizumab to adalimumab with 275 bDMARD naïve patients in each arm.[1]

ERG comment:

- Neither of the two ongoing trials at their current stage would have informed the submission. The ERG notes that SPIRIT-H2H will provide a direct comparison with adalimumab which is not available in the current submission.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As SPIRIT-P1 and SPIRIT-P2 were in different patient populations separate Bayesian network meta-analyses (NMAs) were performed for each population to compare ixekizumab with relevant

Table 4.1: PASI response for the biologic-experienced population

Treatment	PASI 75 (95% CrI)	PASI 90 (95% CrI)	PASI 100 (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q2w	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q4w	[redacted]	[redacted]	[redacted]
Ustekinumab 45 mg q12w	[redacted]	[redacted]	[redacted]

Source: Based on Table 26 of the CS[1]
Note: PASI 50 data were not included in the dataset as it was not reported by these studies.
CS = company submission; mg = milligram; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement from baseline in PASI score; PASI 75 = ≥75% improvement from baseline in PASI score; PASI 90 = ≥90% improvement from baseline in PASI score; PASI 100 = 100% improvement from baseline in PASI score; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

Table 4.2: PASI response for the biologic-experienced population including secukinumab and certolizumab pegol (pooled doses)

Treatment	PASI 50	PASI 75	PASI 90	PASI 100
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol pooled doses	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q2w	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 45 mg q12w	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 32 of the CS appendices[28]
bid = twice daily; CrI = credible interval; CS = company submission; mg = milligram; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement from baseline in PASI score; PASI 75 = ≥75% improvement from baseline in PASI score; PASI 90 = ≥90% improvement from baseline in PASI score; PASI 100 = 100% improvement from baseline in PASI score; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

The fixed effect NMA results for ACR response are shown in Table 4.19 These show that ixekizumab 80 mg q4w had the [redacted] of achieving an ACR 20 response [redacted], an ACR 50 response [redacted] and an ACR 70 response [redacted] which were [redacted] than the response with placebo but not ixekizumab 80 mg q2w or ustekinumab 45 mg.

Treatment	SAEs
Etanercept 25 mg biw/50 mg qiw	[redacted]
Golimumab 50 mg q4w	[redacted]
Infliximab 5 mg/kg q8w	[redacted]
Ixekizumab 80 mg q2w	[redacted]
Ixekizumab 80 mg q4w	[redacted]
Secukinumab 150 mg q4w	[redacted]
Secukinumab 300 mg q4w	[redacted]
Ustekinumab 45 mg q12w	[redacted]
Ustekinumab 90 mg q12w	[redacted]

Source: Based on Table 11 of the response to request for clarification[25]
bid = twice daily; biw = twice weekly; CS = company submission; kg = kilogram; mg = milligram; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks; q12w = once every 12 weeks; qiw = once weekly; SAE = serious adverse event

NMA results for DAE are shown in Table 4.22 and show that the estimated probabilities of discontinuing due to an AE were [redacted] for ixekizumab 80 mg q2w and [redacted] for ixekizumab 80 mg q4w. Certolizumab pegol (pooled doses) had the [redacted] and ustekinumab 45 mg [redacted]

Table 4.3: Conditional probabilities of experiencing a DAE

Treatment	DAEs
Placebo	[redacted]
Adalimumab 40 mg q2w	[redacted]
Apremilast 30 mg bid	[redacted]
Certolizumab pegol pooled doses	[redacted]
Golimumab 50 mg q4w	[redacted]
Infliximab 5 mg/kg q8w	[redacted]
Ixekizumab 80 mg q2w	[redacted]
Ixekizumab 80 mg q4w	[redacted]
Ustekinumab 45 mg q12w	[redacted]
Ustekinumab 90 mg q12w	[redacted]

Source: Based on Table 12 of the response to request for clarification[25]
bid = twice daily; biw = twice weekly; CS = company submission; DAE = discontinuation due to adverse event; kg = kilogram; mg = milligram; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks; q12w = once every 12 weeks; qiw = once weekly

4.4 Critique of the indirect comparison and/or multiple treatment comparison

- The NMA used standard Bayesian analysis methods as recommended in the NICE Decision Support Unit (DSU) Technical Support Documents 2.[35] The data and programs used for the PsARC, PASI and change in HAQ-DI were supplied by the company and checked by the ERG.

Due to the small size of most networks and the fact that many edges only contained a single trial, fixed effect models were used in the submission and economic model. Results from random effects models were also supplied in the clarification response and reviewed by the ERG. The ERG considers the NMA analysis methods and the presentation of fixed effect results to be appropriate, given the small size of many of the networks and little difference in fit between fixed and random effects models.

- Additional NMA results were provided in the clarification response for other outcomes including ACR response and adverse events (treatment-emergent, serious and discontinuation due to adverse events). However, the ERG did not have the associated data so these NMA results could not be verified.
- The ERG could verify the results for the PsARC and PASI outcomes. However, for change in HAQ-DI for PsARC responders and non-responders the results from the NMA for ixekizumab q2w and q4w produced by the ERG did not match those provided by the company. Results for other treatments from the same model could be reproduced but not those for ixekizumab. As there was only one study providing input data for ixekizumab in the dataset provided by the company the model estimates should have been similar to the study estimates. For PsARC responders, the changes from baseline in HAQ-DI for ixekizumab 80 mg q4w were [redacted] from the NMA and [redacted] in the trial data and for 80 mg q2w they were [redacted] from the NMA and [redacted] in the trial data. For PsARC non-responders, the changes from baseline in HAQ-DI for ixekizumab 80 mg q4w were [redacted] from the NMA and [redacted] in the trial data and for 80 mg q2w they were [redacted] from the NMA and [redacted] in the trial data.
- Potential limitations of the NMA analyses are:
  - The use of different timepoints, including 12, 14, 16, and 24 weeks although sensitivity analyses replacing ixekizumab week 12 data with week 16 data showed little impact on the results.
  - As stated in the CS, the networks may have contained undetectable heterogeneity and inconsistency which could not be evaluated in some of the smaller networks so the treatment effects from the fixed effects models may be too precise.
  - To include other key comparators (apremilast, secukinumab and certolizumab pegol), trial data were included for the full population (rather than only biologic-naïve or biologic-experienced). *"If prior biologic exposure is an effect modifier for these treatments, the NMA results will not be representative of the treatment effect in a pure biologic-naïve/experienced population"* (section 2.9.3 of the CS[1]).
  - As the NMA analyses are based on indirect comparisons they are a weaker source of evidence than direct treatment comparisons obtained within a RCT and need to be treated with caution given the potential for clinical and statistical heterogeneity.

4.5 Additional work on clinical effectiveness undertaken by the ERG

As described in section 4.1.1, the ERG did not consider the company's explanation of cross-checking recall of their flawed RCT searches adequate. The company checked recall of their searches against included studies in SRs, NMAs and health technology assessments (HTAs) also picked up in the RCT searches. Specific searches for SRs, NMAs and HTAs were not carried out nor were searches of SR or HTA databases conducted.

Therefore, the ERG conducted independent rapid appraisal searches to retrieve systematic reviews, meta-analyses and HTAs, searching the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), KSR Evidence, and Embase (Ovid). The ERG screened the rapid appraisal results and checked included

studies against the company submission. Full details of the independent rapid appraisal are presented in Appendix 1.

The ERG identified eight relevant publications, including SLRs, NMA and HTA reports.[52-59] These were checked for relevant primary studies potentially missed in the CS. Screening the results of the rapid appraisal searches, the ERG did not identify any study missed in the CS. However, the ERG identified one randomised study (Atteneo et al. 2010[60]) which has been excluded at the full paper review stage and was labelled as excluded for "Study design".[28] As detailed in section 4.1.1, the ERG believes that the appropriate response to address the substantial errors in the CS searches would have been to repeat the corrected searches to ensure the submission was based on a robust systematic review search. It should be noted that no full search was conducted by the ERG due to the limited time available for the assessment, i.e. not identifying relevant studies in the rapid appraisal should not be seen as evidence of absence of relevant studies missed in the CS.

4.6 Conclusions of the clinical effectiveness section

The CS included a systematic review of the evidence for ixekizumab and its comparators in patients with PsA as per the NICE scope. The company presented direct evidence from two RCTs, SPIRIT-P1 and SPIRIT-P2 that compared ixekizumab to placebo in adults with PsA. No direct evidence was presented for ixekizumab in relation to any of the other comparators in the NICE scope.

SPIRIT-P1 was conducted in biological DMARD naïve patients whilst SPIRIT-P2 was conducted in those with experience of biological DMARDs. SPIRIT-P1 included 417 patients and SPIRIT-P2 363 patients and both were well conducted, multinational trials. Across the two trials approximately [redacted] of patients were from the UK. Both trials demonstrated superiority of ixekizumab in relation to placebo on outcomes of importance to patients such as ACR criteria and PSARC measures during the double-blind phase of the trial up to 24 weeks. The company also provided more limited evidence on the efficacy of ixekizumab in relation to placebo for a population reflective of NICE current guidance on use of bDMARDs.

In total, 454 patients have been exposed to ixekizumab across the two SPIRIT trials. Data on adverse events are presented in the CS for the 24-week double blind period of the two SPIRIT trials and for the extension period (up to week 52). In the double-blind treatment phase patients experienced more adverse events in the ixekizumab groups than in the placebo group in both SPIRIT trials. Adverse events across the two SPIRIT trials were mainly of mild or moderate severity. There were no deaths across the two trials in the double-blind periods. The proportion of patients who discontinued medication due to AEs was low across all treatment groups with no statistically significant differences between ixekizumab and placebo groups. The most frequently reported AEs were infections which were comparable across groups. Injection site reactions were statistically significantly more common with ixekizumab than placebo in both SPIRIT trials. The only direct safety comparisons, as for effectiveness comparisons, are between placebo and ixekizumab. However, SPIRIT-P1 has a reference adalimumab arm and it can be observed that occurrence of adverse events was similar in the adalimumab group to the ixekizumab groups although fewer of the adalimumab events appeared to be attributable to the drug.

Ixekizumab represents an additional option for PsA alongside the existing biologic treatments after two or more non-biological approaches have been tried. The need for additional options has been highlighted by patient and professional organisations. However, in order to be added to the options or indeed to be used preferentially over another agent, the comparable or superior performance of ixekizumab needs to be investigated through comparison with all of the relevant biological agents. In

this submission, in the absence of trials directly comparing active treatments the company has conducted a Bayesian NMA of relevant trials for the outcomes of PsARC response, PASI 50/75/90/100 and change in HAQ-DI. Separate analyses were performed for bDMARD-naïve and bDMARD-experienced patients. The results for bDMARD-naïve patients showed that [redacted] had the best performance for PASI response but it was [redacted]. For PsARC response the most effective treatments were [redacted]. For both outcomes, [redacted] to all other treatments. For change from baseline in HAQ-DI the NMA results showed that in PsARC responders all treatments were significantly better than placebo except for [redacted] having the largest change from baseline. Changes in HAQ-DI score were smaller for PsARC non-responders and [redacted] were the most effect treatments.

There was less evidence for bDMARD-experienced patients (at most four trials in an analysis) and ixekizumab was [redacted] ustekinumab for PsARC response. For PASI response, ustekinumab had the [redacted] response rate but it was [redacted].

Additional NMA results for ACR 20/50/70 response and adverse events (AEs) were provided in the response to request for clarification. These showed that for bDMARD-naïve patients with the exception of [redacted], the ACR response of [redacted] from other treatments and that with the exception of [redacted] from other treatments. For bDMARD-experienced patients, both ixekizumab regimens had [redacted] ACR response compared to ustekinumab but [redacted]. Estimated conditional probabilities of treatment-emergent AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; serious AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; and discontinuations due to AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w.

way sensitivity analyses conducted by the company, but the most influential parameters in the company's sensitivity analyses (which were not exhaustive) were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs associated with ixekizumab and secukinumab. Scenario analyses indicated that assumptions with the greatest impact on the ICER for the ixekizumab sequences versus BSC relative to the base-case were HAQ-DI rebound to natural history in the BSC treatment state, the York utility model coefficients, the Poole et al. 2010 algorithm for costs associated with HAQ-DI,[72] and combining PsARC and PASI rates as the treatment continuation rule. Furthermore, the inclusion of certolizumab pegol and secukinumab in the b/tsDMARD-experienced population led to certolizumab pegol being cost effective (at list prices for ixekizumab and secukinumab but with PAS schemes for certolizumab pegol and ustekinumab.

The ERG incorporated various adjustments to the company's base-case. The ERG base-case shows that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per QALY gained in the b/tsDMARD-experienced population. In all psoriasis severity levels of the b/tsDMARD-experienced population, ixekizumab led to [redacted] compared to ustekinumab (the only other comparator for which an ICER was calculated in the fully incremental analyses).

The ERG identified major and minor issues and uncertainties that affected the cost effectiveness analysis. Major issues and uncertainties are listed in the following. One major limitation was the use of a limited network for the b/tsDMARD-experienced patient population, which omitted PASI 50 as an outcome, resulting in potential bias in favour of treatments with a higher PsARC response (given PASI 50 response was presumably set to 0% in this case). This also resulted in the exclusion of certolizumab pegol and secukinumab as comparators in this population, which deviated from the scope, again likely favouring ixekizumab in this population. This was partly addressed in the ERG base-case, although the data were not made available by the company to perform this analysis probabilistically. Furthermore, treatment sequences used in the model for the b/tsDMARD-naive patient population are excluding relevant treatments, as, in addition to ustekinumab, certolizumab pegol and secukinumab could also be used in second line. An alternative second-line treatment was explored in scenario analysis.

The ERG is concerned about the representativeness of the patient population in the SPIRIT trial programme and its impact on the relevance and validity of the NMA results in the UK context. The allocation of patients to health states in the model was based on a relative measure of response (based on reductions in symptoms), which leads to health states being composed of heterogeneous patient populations, for which it is arguably difficult to assign costs and HRQoL estimates. BSC was not accurately described in the CS and the ERG was unable to assess whether BSC was representative of the UK context, and whether the effectiveness and the costs associated with BSC in the cost effectiveness model were valid.

The assumption of equal treatment discontinuation rates for all b/tsDMARD treatments was viewed as a major and influential limitation. Of further concern were the excess mortality, which was considered high, and the fact that the HAQ-DI reduction estimate for ixekizumab q4w responders and non-responders based on the NMA did not reflect the trial data. The omission of adverse events from this submission is of particular concern, given that these differ per treatment and their inclusion would lead to potential differences in HRQoL, costs, and treatment discontinuation rates. Furthermore, the ERG considers there to be large uncertainty about the resource use and cost estimates associated with HAQ-DI and PASI, with several limitations identified in both estimates.

8. OVERALL CONCLUSIONS

8.1 Statement of principal findings

The company presented direct evidence from two RCTs, SPIRIT-P1 and SPIRIT-P2 that compared ixekizumab to placebo in adults with PsA. SPIRIT-P1 was conducted in biological DMARD-naïve patients whilst SPIRIT-P2 was conducted in those with experience of biological DMARDs. SPIRIT-P1 included 417 patients and SPIRIT-P2 363 patients and both were well conducted, multinational trials. Across the two trials approximately [redacted] of patients were from the UK.

In both SPIRIT trials, significantly more patients achieved an ACR 20 response at week 24 with ixekizumab compared to placebo (SPIRIT-P1: IXE 80 q4w 57.9%, IXE 80 q2w 62.1%, placebo 30.2%; SPIRIT-P2: IXE 80 q4w 53.3%, IXE 80 q2w 48.0%, placebo 19.5%; p<0.001 for all comparisons to placebo). In both SPIRIT trials, the percentage of patients who achieved a PsARC response at week 12 as well as week 24 were statistically significantly greater for both ixekizumab groups compared to placebo in all cases (Week 12 – SPIRIT-P1: IXE 80 q4w 55.1%, IXE 80 q2w 61.2%, placebo 34.0%; SPIRIT-P2: IXE 80 q4w 50.0%, IXE 80 q2w 52.0%, placebo 23.7%. Week 24 – SPIRIT-P1: IXE 80 q4w 57.9%, IXE 80 q2w 66.0%, placebo 32.1%; SPIRIT-P2: IXE 80 q4w 55.7%, IXE 80 q2w 47.2%, placebo 20.3%). In terms of quality of life, at week 12 patients in the two ixekizumab groups achieved significantly greater mean change from baseline in HAQ-DI total scores in both SPIRIT trials. As not all participants in the SPIRIT trials would have been eligible for biological therapy under current NICE criteria, the company conducted a subgroup analysis using an integrated set of patients from SPIRIT-P1 and P2 who met the NICE criteria. The total number of patients available for analysis was [redacted]. [redacted] patients who received ixekizumab 80 mg Q4W or Q2W achieved an ACR 20 response at week 24 compared to placebo [redacted] and [redacted] vs. [redacted] respectively). In the 24-week double-blind treatment phase patients experienced more adverse events in the ixekizumab groups than in the placebo group in both SPIRIT trials. Adverse events across the two SPIRIT trials were mainly of mild or moderate severity and the proportion of patients who discontinued medication due to AEs was low across all treatment groups. There were no deaths across the two trials in the double-blind periods. Injection site reactions were statistically significantly more common with ixekizumab than placebo in both SPIRIT trials.

In the absence of trials directly comparing the active treatments specified in the NICE scope, the company conducted a Bayesian NMA of relevant trials for the outcomes of PsARC response, PASI 50/75/90/100 and change in HAQ-DI. Separate analyses were performed for bDMARD-naïve and bDMARD-experienced patients. The results for bDMARD-naïve patients showed that [redacted] had the best performance for PASI response but it was [redacted]. For PsARC response the most effective treatments were [redacted]. For both outcomes, [redacted] to all other treatments. For change from baseline in HAQ-DI the NMA results showed that in PsARC responders all treatments were significantly better than placebo except for [redacted] having the largest change from baseline. Changes in HAQ-DI score were smaller for PsARC non-responders [redacted] were the most effect treatments.

There was less evidence for bDMARD-experienced patients (fewer than five trials in most analyses) and ixekizumab was [redacted] to ustekinumab for PsARC response. For PASI response, ustekinumab had the [redacted] response rate but it was [redacted] to ixekizumab.

Two randomised controlled trials comparing ixekizumab to placebo are presented in the CS, one in patients with experience of bDMARDs and one in patients naïve to bDMARDs. Both multinational trials included a small number of UK patients (approximately [redacted] across the two trials). Furthermore, NICE recommends that bDMARDs are given after two cDMARDs have been tried. However, in the SPIRIT trials patients have not all received two prior cDMARDs. A separate analysis of the NICE ITT population [redacted] in relation to placebo is provided in the CS based on [redacted] patients across the two trials. The committee will need to decide, based on the factors highlighted by the ERG in this report whether it agrees with the company that the results of the SPIRIT trials are generalisable to UK practice. Another weakness in the submission is the lack of direct evidence available on ixekizumab in relation to the comparators in the scope, i.e. the main results in the CS came from a NMA.

The cost effectiveness model is well built and transparent. The treatment effectiveness estimates from a network of studies are a strength, as is the attempt to consider treatment sequences. The company performed many relevant sensitivity and scenario analyses to reflect uncertainty about the cost effectiveness results. The model was relatively robust to these changes, with some notable exceptions as detailed in the previous sections.

Health states in the model are based on a relative measure of response (based on reductions in symptoms), which leads to health states being composed of heterogeneous patient populations, for which it is arguably difficult to assign costs and HRQoL estimates. Further limitations are the exclusion of comparators identified in the scope and the omission of adverse events from the NMA and economic model. For b/tsDMARD-experienced patient population, only a limited network was used, which omitted PASI 50 as an outcome. The ERG considers a weakness the assumption of equal treatment discontinuation rates for all b/tsDMARD treatments. The representativeness of the patient population in the SPIRIT trial programme, excess mortality in this population, resource use and cost estimates associated with HAQ-DI and PASI pose areas of uncertainty.

8.3 Suggested research priorities

Research is lacking directly comparing the active comparators in the scope to determine the best treatment available for patients with PsA. The ERG notes that there is an ongoing trial (SPIRIT-H2H) due to complete in April 2019 which compares ixekizumab to adalimumab in bDMARD naïve patients. It should also be noted that using direct evidence rather than NMA results would give more reliable estimates for both, clinical as well as cost effectiveness.