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Erasmus School of Health Policy & Management

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

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Xavier Pouwels, Willem Witlox and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter, Piet Portegijs and Elizabeth Matovinovic acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Kate Misso critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore critiqued the manufacturer's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ACR	American College of Rheumatology
ACR 20	At least 20% improvement in both tender and swollen joint counts
ACR 50	At least 50% improvement in both tender and swollen joint counts
ACR 70	At least 70% improvement in both tender and swollen joint counts
ADA	Adalimumab
ANA	Antinuclear antibody
APLAR	Asia Pacific Rheumatology Congress
APR	Apremilast
ARHP	Association for Rheumatology Health Professionals
AWMSG	All Wales Medicines Strategy Group
b/tsDMARD	Biologic/targeted synthetic disease-modifying anti-rheumatic drug
BC	Base-case
bDMARD	Biologic disease-modifying anti-rheumatic drug
bid	Twice daily
biw	Twice weekly
BMI	Body mass index
BSA	Body surface area
BSC	Best supportive care
BSR	British Society for Rheumatology
CADTH	Canadian Agency for Drugs and Technologies in Health
cDMARD	Conventional disease-modifying anti-rheumatic drug
CEA	Cost effectiveness analysis
CEM	Cost effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CODA	Convergence Diagnostic and Output Analysis
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CrI	Credible interval
CS	Company submission
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
CSR	Clinical study report
CZP	Certolizumab pegol
DAE	Discontinuation due to adverse events
DARE	Database of abstracts of reviews of effects
DAS28-CRP	Disease activity score 28 diarthrodial joint count based on c-reactive protein
DCE	Discrete choice experiment
DIC	Deviance information criteria
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
Ds	Double-stranded
DSA	Deterministic sensitivity analyses
DSP	Disease specific programme
DSU	Decision Support Unit
EBM	Evidenced-based medicine
EED	Economic Evaluation Database
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ESR	Erythrocyte sedimentation rate
ETA	Etanercept
ETN	Enbrel
EULAR	European League Against Rheumatism

EUR	Erasmus University Rotterdam
FBC	Full blood count
FE	Fixing errors
FV	Fixing violations
GOL	Golimumab
GP	General practitioner
HAQ-DI	Health Assessment Questionnaire-Disability Index
HCRU	Health Care Resource Utilisation
HEED	Health Economic Evaluations Database
HRQoL	Health-related quality of life
HTA	Health technology assessment
IA	Intra-articular
ICER	Incremental cost effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IL	Interleukin
INF	Infliximab
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IXE	Ixekizumab
kg	Kilogram
KSR	Kleijnen Systematic Reviews
LDI	Leeds Dactylitis Index
LDI-B	Leeds Dactylitis Index-Basic
LEI	Leeds Enthesitis Index
LFT	Liver Function Test
LOCF	Last observation carried forward
LSM	Least squares mean
mAb	monoclonal antibody
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
mBOCF	Modified baseline observation carried forward
MDA	Minimal Disease Activity
MeSH	Medical Subject Heading
mg	Milligram
MIMS	Monthly Index of Medical Specialities
MJ	Matters of judgement
MMRM	Mixed-effects model repeated measures
mTSS	Modified Total Sharp Score
NA	Not applicable
NAPSI	Nail Psoriasis Severity Index
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
NRI	Non-responder imputation
NSAID	Non-steroidal anti-inflammatory drug
PAS	Patient Access Scheme
PASI	Psoriasis Area and Severity Index
PBAC	Pharmaceutical Benefits Advisory Committee
PDE	Phosphodiesterase
PsA	Psoriatic arthritis
PSA	Probabilistic sensitivity analysis
PsARC	Psoriatic Arthritis Response Criteria
PSS	Personal Social Services

PSSRU	Personal Social Services Research Unit
q2w	Once every two weeks
q4w	Once every four weeks
q8w	Once every eight weeks
q12w	Once every 12 weeks
QALY	Quality-adjusted life year
qd	Once daily
qiw	Once weekly
RCT	Randomised controlled trial
RTF	Restriction to focus
SA	Scenario analysis
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEC	Secukinumab
SF	Short Form
SJC	Swollen joint count
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
SPARCC	Spondyloarthritis Research Consortium of Canada Enthesitis Index
sPGA	Static physician's global assessment
SR	Systematic review
TA	Technology appraisal
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
THIN	The Health Improvement Network
TJC	Tender joint count
TLV	Tandvårds- och läkemedelsförmånsverket (Swedish Dental and Pharmaceutical Benefits Board)
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitor
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drug
TTO	Time Trade-Off
U&E	Urea and electrolytes test
UK	United Kingdom
UMC	University Medical Center
URL	Uniform Resource Locator
UST	Ustekinumab
UVB	Ultraviolet B
VBA	Visual Basic for Applications
WHO	World Health Organisation

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population in the company submission (CS) is as defined in the National Institute for Health and Care Excellence (NICE) scope, i.e. adults with active psoriatic arthritis (PsA) whose disease has not responded adequately to previous disease-modifying anti-rheumatic drugs (DMARDs) or for whom DMARDs are not tolerated or contraindicated. However, ixekizumab is a biological DMARD (bDMARD) and under NICE guidance bDMARDs are normally given after failure of two or more conventional DMARDs (cDMARDs). Whilst the company aligns ixekizumab with NICE guidance, not all patients meet this criterion in the main trials of the submission (SPIRIT-P1 and P2). Furthermore, across the two trials, [redacted] patients were recruited to [redacted] centres in the UK which represents approximately [redacted] of the patients in the trials. The committee will need to decide, based on the factors highlighted by the Evidence Review Group (ERG) in this report whether it agrees with the company that the results of the SPIRIT trials are generalisable to clinical practice in the United Kingdom (UK).

However, the main weakness in the submission is the lack of direct evidence available on ixekizumab in relation to the comparators in the scope. The two main trials in the CS compare ixekizumab to placebo. The evidence in relation to the other DMARDs mentioned in the scope comes from indirect comparisons obtained through network meta-analyses (NMAs). The outcomes listed in the NICE scope are evaluated in the trials in the submission with the exception of mortality. The ERG recognises that short-term trials are unlikely to demonstrate any effect of treatment on mortality in PsA should one exist.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS 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. Both trials 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 once every four weeks (q4w) 57.9%, IXE 80 once every two weeks (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 percentages of patients who achieved a Psoriatic Arthritis Response Criteria (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 Health Assessment Questionnaire-Disability Index (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, respectively, 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 (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, ixekizumab was [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 effective treatments.

There was less evidence for bMARD-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.

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 [redacted] was the most effective treatment across all categories of ACR response but it was [redacted]. 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 16 weeks are

more reliable for the comparison between ixekizumab and placebo. Although the trials were multinational, across the two trials, just [redacted] patients were recruited by [redacted] centres in the UK. This represents approximately [redacted] of patients. Non-white participants are underrepresented across the two trials. Mean BMI in the SPIRIT trials is within the obese category so patients in the trials may be more overweight than those seen in practice in the UK. Patients in SPIRIT-P1 and SPIRIT-P2 may have more severe disease than seen in UK practice. Further information of comparisons made by the company to UK practice and the ERG's interpretation are given in this report.

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 company demonstrated efficacy of ixekizumab in relation to placebo for a population reflective of NICE current guidance on use of bDMARDs after failure of two cDMARDs. However, this analysis was based on [redacted] patients across both trials so percentages of responders should be treated with some caution.

No direct evidence is available on ixekizumab in relation to the other comparators in the scope. Comparisons between ixekizumab and other comparators were obtained from Bayesian NMA. Separate analyses were performed for bDMARD-naïve and bDMARD-experienced patients and although the analysis methods were appropriate and followed recommended guidance on performing NMA the results need to be treated with caution. This is because NMA results use indirect treatment comparisons across trials, in this case via placebo, and are less reliable than comparisons between different treatments within the same trial due to potential clinical and statistical heterogeneity between the trials.

1.4 Summary of cost effectiveness evidence submitted by the company

The company's systematic literature review (SLR) identified several cost effectiveness models in the present indication. The company developed a de novo cohort state transition model in Visual Basic for Applications (VBA) with a Microsoft Excel interface that was heavily based on the so-called "revised York model", a cost effectiveness model used in a previous technology appraisal (TA) 445 on secukinumab and certolizumab pegol for treating active psoriatic arthritis. In the base-case analysis, PsARC was used to determine treatment response while PASI (in the presence of concomitant psoriasis) and HAQ-DI scores were used to determine resource use and costs, and health state utility values. The model structure consisted of the following treatment states: the trial period, the continued treatment period, best supportive care (BSC), and death. The cycle length was one month and no half-cycle correction was applied, because the cycle length was considered to be sufficiently short.

The population in the CS was more narrowly defined than that for which ixekizumab was granted marketing authorisation by the European Medicines Agency (EMA). In the CS, the company considers patients who have responded inadequately to, or who are intolerant to, *at least two* cDMARD therapies. This represents the population which would be eligible for biological or targeted synthetic DMARD (b/tsDMARD) treatment according to NICE guidance while the EMA granted marketing access to patients who have responded inadequately to, or who are intolerant of *one or more* cDMARD therapies. Six subgroups were considered for this appraisal: b/tsDMARD-naive and b/tsDMARD-experienced patient populations, each stratified by psoriasis severity levels: no psoriasis, mild-to-moderate psoriasis and moderate-to-severe psoriasis.

The cost effectiveness of ixekizumab, q2w or q4w, was assessed against all b/tsDMARDs recommended by NICE for patients with PsA whose disease has not responded to two prior cDMARDs. A treatment sequencing approach was adopted by the company. Treatment sequences for b/tsDMARD-naïve patients were composed of two b/tsDMARD treatments, ustekinumab being the second-line treatment in all sequences, and then BSC, while treatment sequences for b/tsDMARD-experienced

patients included one b/tsDMARD treatment before BSC. All treatment sequences of the intervention began with ixekizumab while comparator treatment sequences began with another b/tsDMARD. These included adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, ustekinumab, and secukinumab. Dosing regimens and stopping rules (determining the length of the trial period) of each treatment were based on NICE guidance. The length of the trial period for ixekizumab was set to 12 weeks in the company's base-case analysis, while the summary of product characteristics (SmPC) for ixekizumab advises that treatment should be discontinued in patients who did not show response after 16 to 20 weeks of treatment.

The analysis took a National Health Service (NHS) and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The company adopted a lifetime time horizon.

Treatment effectiveness in the economic model was informed by PsARC, HAQ-DI and PASI, all sourced from the NMA. PsARC and PASI were estimated separately for patients with and without prior b/tsDMARD exposure while HAQ-DI was estimated for patients without prior b/tsDMARD exposure (due to lack of evidence). After the trial period, treatment was continued for patients classified as responders based on PsARC while treatment was discontinued for PsARC non-responders. An annual treatment discontinuation of 16.5% per year was applied (independent of both time and treatment) to the continued treatment state and represented treatment discontinuation due to any cause. It was assumed that 1) the change from baseline HAQ-DI and PASI occurred instantly after initiating treatment (in the trial period) and 2) patients maintained this improvement until treatment discontinuation. After active treatment discontinuation, patients received BSC, and both the HAQ-DI and PASI scores were assumed to immediately rebound to its baseline value. HAQ-DI then progressed at a rate equivalent to the natural history progression and plateaued at its maximum value. In contrast with HAQ-DI scores, the baseline PASI scores were assumed to be constant over time.

No adverse events were considered in the economic model. The company argued that adverse events were implicitly captured to the extent that they affected the initial response and the long-term treatment discontinuation rates.

To inform health-related quality of life (HRQoL), the company used the data from the SPIRIT trials in which the European Quality of Life-5 Dimensions (EQ-5D)-5L questionnaire was administered to patients at baseline and week 12. In line with NICE's position statement on EQ-5D-5L data, the obtained data were mapped to EQ-5D-3L using an indirect mapping approach. The company used the resulting EQ-5D-3L data to establish a relationship between patients' HAQ-DI and PASI scores and HRQoL using an ordinary least squares regression model, in accordance to how HRQoL was estimated in the York model.

Drug acquisition costs for b/tsDMARDs were sourced from the online version of the Monthly Index of Medical Specialities (MIMS). The list price of 80 mg ixekizumab is £1,125. Ixekizumab is provided with a confidential simple discount patient access scheme (PAS), lowering its price to [redacted] per 80 mg. Secukinumab and apremilast are also provided with a PAS but list prices were used for these two comparators in the CS model as these PAS prices were not publicly available. Certolizumab pegol and ustekinumab are recommended by NICE with complex PAS schemes in place, which were modelled in the CS. The cost of administration was obtained from the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2016 and the National Health Service (NHS) Reference Costs 2015-16. Costs for monitoring during treatment were obtained from 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 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 PubMed searches. Searches of the health technology assessment database (HTA) and the Health Economic Evaluations Database (HEED) contained unnecessary costs or HRQoL/Utilities search filters which were overly restrictive. Searching the NHS Economic Evaluation database would have been

beneficial. Due to these issues, it is possible that potentially relevant studies may have been missed, however the impact of this is difficult to assess without undertaking these reviews independently.

Health states in the cost effectiveness model are based on a relative measure of response (reductions in symptoms), which may lead 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 economic model. For the b/tsDMARD-experienced patient population, only a limited network was used, which omitted PASI 50 as an outcome. Moreover, the ERG considers the assumption of equal treatment discontinuation rates for all b/tsDMARD treatments as a weakness. 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.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The company's deterministic base-case ICERs of ixekizumab (with PAS) compared with other comparators showed that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population. In the b/tsDMARD-experienced population, ixekizumab (with PAS) had ICERs [redacted] per QALY gained when compared with BSC. It was [redacted] when compared with ustekinumab in no and mild-to moderate psoriasis and [redacted] in moderate-to severe psoriasis. The ERG incorporated various adjustments to the company base-case (probabilistic results for the b/tsDMARD-naïve population and deterministic results for the b/tsDMARD-experienced population). In the ERG base-case, ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per QALY gained versus BSC 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). Additionally, the ERG explored different scenarios based on the ERG base-case analysis. In those analyses, ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population except in the scenario in which both PASI 75 and PsARC responses were used simultaneously to determine treatment response. In that scenario, ixekizumab had an ICER of [redacted] per QALY gained versus BSC in the moderate-to-severe psoriasis subgroup. In the b/tsDMARD-experienced population, ixekizumab had ICERs below [redacted] per QALY gained versus BSC in all psoriasis severity levels in all scenarios, expect when both PASI 75 and PsARC responses were used simultaneously to determine treatment response. In this scenario, ixekizumab [redacted].

In conclusion, despite the ERG criticism and amendments to the company cost effectiveness analysis, ixekizumab remained [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population. Ixekizumab provided ICERs [redacted] per QALY gained versus BSC in the b/tsDMARD-experienced population. In this population, when compared to ustekinumab, ixekizumab [redacted] in all psoriasis severity levels. Using both PASI 75 and PsARC responses simultaneously to determine treatment response was the most influential scenario analysis performed by the ERG.

2. BACKGROUND

In this report the ERG provides a review of the evidence submitted by Eli Lilly in support of ixekizumab, trade name Taltz®, for the treatment of adult patients with active psoriatic arthritis (PsA) following inadequate response to previous disease-modifying anti-rheumatic drugs (DMARDs). In this section, we outline and critique the company's description of the underlying health problem and the overview of current service provision. The information is taken from Chapter 1 of Document B of the company's submission (CS) with sections referenced as appropriate.[1]

2.1 Critique of company's description of underlying health problem.

The underlying problem of this appraisal is psoriatic arthritis which is described in the CS as a '*chronic progressive, inflammatory arthropathy associated with psoriasis'*.[1]

The CS describes the burden to patients of '*pain, stiffness and swelling of joints, which can affect the whole body and, if untreated, cause permanent joint and tissue damage and ultimately disability'*.[1]

The company describes the heterogeneity of PsA and clarifies that joint and skin symptoms can range from mild to severe and do not always correlate with each other. The CS states that in around 70% of people, psoriasis precedes PsA with the onset of arthritis tending to occur from seven to 10 years after the onset of symptoms.[2] Importantly, the CS also notes that some patients present with no skin disease but have a family history of skin disease.[3]

The CS covers the main presenting symptoms and highlights the high frequency of dactylitis, enthesitis and nail psoriasis in PsA.[1] The CS states that more than half of patients have at least one comorbidity and provides a table of the incidence of PsA comorbidities reproduced from Husni 2015.[4]

The CS highlights the impact of the disease on a patient's health-related quality of life (HRQoL) including activities of daily living and notes that HRQoL is lower than the general population and compared to patients with other forms of inflammatory arthritis (based on a literature review by Lee et al.).[5] The CS cites a Canadian study based at the University of Toronto PsA Clinic between 1978 and 2004 which estimates a reduced life expectancy of approximately three years in patients with PsA compared to the general population.[6] A submission by the Psoriasis Association, a British patient organisation, provides examples of the challenges of living and working with PsA.[7]

The CS highlights that PsA affects men and women equally and that the age of onset tends to be between 30 and 50 years of age. Prevalence is cited to be 0.19% of the adult population in the UK based on a large cross-sectional study.[8] In a psoriasis population, the CS notes that prevalence of PsA will be higher (between one and two of every five people with psoriasis) particularly among those with severe psoriasis.[8]

ERG comment: The ERG checked the references cited by the company to support the statements made above and considered the company to have given overall an appropriate description of the underlying health problem relevant to this appraisal. However, the ERG would like to add the following:

- The prevalence of PsA is based on a UK study which is most relevant to the submission (variability between countries has been observed).[8] However even here, the prevalence of PsA should be treated with some caution as PsA may be underdiagnosed.[2, 9] The diagnosis of PsA in the UK study cited was based on a medical records diagnosis code recorded by general practitioners.
- Currently, there are no definitive guidelines for diagnosing psoriatic arthritis. Traditionally, the Moll and Wright (1973) criteria have been used.[10] The criteria are:
  - an inflammatory arthritis,
  - the presence of psoriasis,

- and a blood test negative for rheumatoid factor.

Although this criteria set is still used, it does not take account of the fact that psoriatic arthritis can occur without there being current psoriasis on the skin.

More recently the CASPAR criteria have been developed.[11] These consist of the presence of an inflammatory condition in a joint, the spine, or entheses plus at least three points from the following: Current psoriasis (two points); a personal or family history of psoriasis (in the absence of current psoriasis, one point); dactylitis (one point); nail dystrophy (one point); negative rheumatoid factor (one point); radiographic evidence of new bone formation (one point).[12]

- The impact of symptoms and the reduced quality of life in PsA is appropriately described. However, it should also be made clear that PsA can be variable and unpredictable including flares and remissions with possible associated variation in quality of life.[5]
- Not all of the studies cited in the CS found a reduced life expectancy with PsA. The estimate of a loss of three years was based on a Canadian study at the University of Toronto PsA Clinic between 1978 and 2004.[6] This study may not reflect a UK setting and the most up to date management of patients with PsA.

2.2 Critique of company's overview of current service provision

Figure 2.1 shows the current treatment pathway for PsA as described by the company in the submission.[1] The figure also shows the proposed place of ixekizumab in the treatment pathway with ixekizumab being listed as a first-line biological DMARD. Although ixekizumab is licenced for the treatment of active PsA in adult patients who have responded inadequately to, or who are intolerant to one or more non-biological DMARDs, the company aligns ixekizumab with guidance by the National Institute for Health and Care Excellence (NICE) that states that biological DMARDs should be given after failure of two or more conventional non-biological DMARDs. At this point in the pathway, ixekizumab is a competitor to secukinumab, also a IL-17 inhibitor, to the PDE4 drug apremilast and to the TNF-alpha inhibitor drugs, all of which have existing NICE guidance.[13-16]

Ixekizumab is also positioned as a second-line biological DMARD for patients who have not responded adequately or are intolerant to TNF-alpha inhibitor drugs. Ustekinumab, certolizumab and secukinumab are also available for these patients. Ixekizumab is further proposed for those in whom TNF-alpha inhibitor drugs are contraindicated (where ustekinumab and secukinumab are available).[1]

The company states that '*currently available systemic therapies (…) are associated with a number of limitations, such as lack of efficacy, inability to sustain efficacy, side-effects or poor tolerability, and inconvenience or lifestyle compromise. These limitations have led to widespread dissatisfaction with treatments*'.[1] To support these statements, the company cites a multinational survey of 391 dermatologists and 390 rheumatologists in which 30% of their PsA patients are described as using biological DMARDs.[17] The CS also cite a survey of 3,426 patients, 14% of whom are receiving biologic therapy, and 8% a combination of oral and biologic therapy.[18] In this survey, adalimumab and etanercept were the injectable biologics most commonly reported. The company stated that according to this survey 90% of patients with PsA felt there was a need for better therapies.

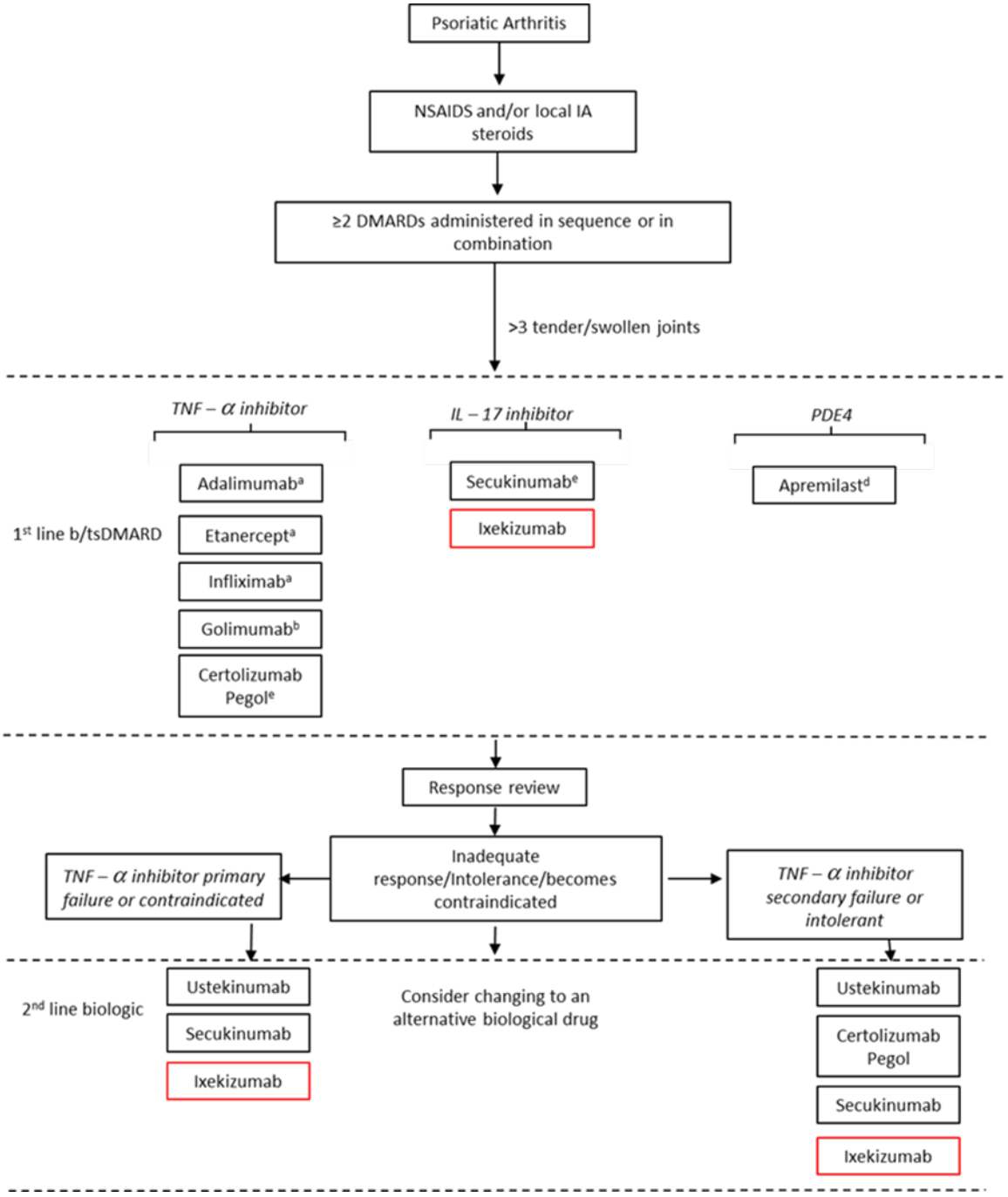
The CS outlines the limitations of the existing biologic therapies including anti-TNF-alpha therapies. A number of studies are cited to illustrate that, although effectiveness has been demonstrated in comparison to placebo, a proportion of patients do not respond adequately and extra-articular symptoms may be inadequately addressed.[1]

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)'*.[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]

Figure 2.1: Proposed position of ixekizumab within the treatment pathway for patients with PsA based on current NICE recommendations



Source: Section 1.3 of the CS[1]

a = NICE TA199[16]; b = NICE TA220[14]; c = NICE TA340[21]; d = NICE TA433[15]; e = NICE TA445[13]

bDMARD = biologic disease-modifying anti-rheumatic drug; CS = company submission; DMARD = disease-modifying anti-rheumatic drug; IA = intra-articular; IL = interleukin; NICE = National Institute for Health and Care Excellence; NSAID = non-steroidal anti-inflammatory drug; PDE = phosphodiesterase; PsA = psoriatic arthritis; tsDMARD = targeted synthetic disease-modifying anti-rheumatic drugs; TA = technology appraisal; TNF = tumour necrosis actor

ERG comment:

- 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 was highlighted by The British Society for Rheumatology who stated in their submission that '*it is most useful to patients and physicians to have access to more than one agent within the same class as well as different agents targeting different classes'*.[22] They also stated that *'there are now an increasing number of patients who have quite simply run out of options and are left with unremitting symptoms, a very poor quality of life and disease progression'*.[22] This was echoed by the Psoriasis Association who stated that *'as psoriatic arthritis often occurs in young adults, treatments need to be efficacious over a lifetime. It is well documented that treatments can lose efficacy, and so wide availability is vital. Some of the more traditional systemic treatments are limited in their use for younger people wishing to start a family which in turn restricts their treatment options'*.[7]
- In order to be added to the options, the comparable or superior performance of ixekizumab needs to be determined through comparison with all of the relevant biological agents.
- Based on the evidence in the submission and critiqued in this report, the committee will need to consider whether ixekizumab should be used in preference to any of the other agents at first or second line biological treatment.
- Any potential advantage of being the *'first monoclonal antibody to block both active forms of IL-17A'*[1] needs to be proven through a comparison of the two agents, ixekizumab and secukinumab. The committee will need to clarify whether the evidence is sufficient to recommend ixekizumab in place of secukinumab and/or for those who have failed on secukinumab.
- NICE guidance includes stopping rules for the biologic drugs in this pathway, e.g. by stating that etanercept, adalimumab and infliximab treatment should be discontinued in people whose psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks unless their Psoriasis Area and Severity Index (PASI) 75 response merits continuing treatment.[16] Similar criteria are in place for the other agents although at differing time points (e.g. ustekinumab for example is assessed at 24 weeks). An appropriate stopping rule will be needed for ixekizumab.
- Any comparisons of effectiveness between agents in this pathway should take account of the full range of symptoms that can be experienced in PsA including the core joint symptoms, the skin symptoms and the extra-articular symptoms such as enthesitis and dactilytis. Patient organisations have also highlighted the problem of fatigue.[23]

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3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with active psoriatic arthritis whose disease has not responded adequately to previous disease-modifying anti-rheumatic drug therapy.	Adults with active psoriatic arthritis whose disease has not responded adequately to previous DMARD therapy, or have not been able to tolerate or have a contraindication to previous DMARD therapy. Subgroups that should be considered separately are: • Patients whose disease has not responded adequately to at least two previous cDMARD therapies either alone or in combination • Patients whose disease has not responded adequately to one or more bMARD • Patients with concomitant moderate to severe psoriasis for whom the anticipated dosing schedule for ixekizumab would include a q2w induction dosing period and q4w maintenance dosing.	NA
Intervention	Ixekizumab (Taltz®)	Ixekizumab 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) every 4 weeks for patients without concomitant moderate-to-severe psoriasis and Ixekizumab 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at weeks 2, 4, 6, 8, 10,	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks for patients with concomitant moderate-to-severe psoriasis.	
Comparator(s)	For people who have only received one prior non-biological DMARD: • Non-biological DMARDs For people whose disease has not responded adequately to at least two non-biological DMARDs: • bDMARDs (with or without methotrexate, including etanercept, adalimumab, infliximab, golimumab, certolizumab pegol [subject to ongoing NICE appraisal], secukinumab [subject to ongoing NICE appraisal]) • Apremilast For people whose disease has not responded adequately to non-biological and biological DMARDs, or biological DMARDs are contraindicated: • Ustekinumab • Certolizumab pegol and secukinumab (subject to ongoing NICE appraisal) • Best supportive care.	For people who have failed on two or more prior standard DMARDs (biologic naïve): • TNF-alpha inhibitors (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol) • Secukinumab • Apremilast For people whose disease has not responded adequately to non-biological and biological DMARDs, or bDMARDs are contraindicated: • Ustekinumab • Certolizumab pegol • Secukinumab • Best supportive care.	The positioning of biologic therapy in patients with only one prior standard DMARD is not in line with current NICE pathways or BSR guidance (except in the case of adverse prognostic factors). As noted in the Final Appraisal Determination document for the multiple technology appraisal of secukinumab and certolizumab pegol, the committee questioned whether biologic therapy is established clinical practice in the NHS after failure on only one prior DMARD and which specific group of patients would use a biologic at this stage in the pathway.[13]
Outcomes	The outcome measures to be considered include: • Disease activity • Functional capacity • Disease progression	This submission includes a range of outcome measures to assess the clinical benefit of ixekizumab, including: • Disease activity (ACR 20/ 50/ 70, PsARC, MDA) • Functional capacity (HAQ-DI)	Skin involvement (e.g. PASI response) is a relevant outcome to include in the scope. The following outcomes will be modelled in the economic analysis: • Disease activity, assessed by the PsARC

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Periarticular disease (for example enthesitis, dactylitis) • Mortality • Adverse effects of treatment • Health-related quality of life	• Effect on concomitant skin condition (Psoriasis Area and Severity Index (PASI)) – including PASI 75/90/100 • Other complications of psoriatic arthritis including LEI- enthesitis, NAPSI- nail psoriasis (modified version), LDI- dactylitis, structural progression (mTSS) • Health related quality of life (EQ-5D) • Adverse events will be reported for ixekizumab and comparators based on the results from the clinical studies	• Functional capacity, measured by the HAQ-DI score • Health-related quality of life, measured by EQ-5D and mapped using PASI and HAQ-DI scores Data on the impact of ixekizumab on periarticular disease and disease progression, and the adverse effects of treatment are presented in the submission but not included in the economic analysis due to insufficient comparative data. No biologic treatment for psoriatic arthritis has demonstrated an effect on mortality outcomes in the context of a clinical trial, therefore mortality in the model has been modelled as the application of excess mortality risk associated with PsA to the mortality risk in the general population.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost effectiveness results are expressed as incremental cost per quality-adjusted life year, with a lifetime model horizon, considering costs from an NHS and PSS perspective. The cost of biosimilar etanercept and biosimilar infliximab are taken into consideration in the base-case analysis. Results are presented using the list price for treatments in the base-case due to the confidentiality of the patient access schemes (PAS) for apremilast and secukinumab. The PAS for certolizumab pegol is taken into account.	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. For the comparators the availability and cost of biosimilars should be taken into consideration.		
Subgroups to be considered	If evidence allows the following subgroups will be considered: • the reason for treatment failure (for example due to lack of efficacy, intolerance or adverse events) • Presence or severity of concomitant psoriasis (no psoriasis, mild to moderate psoriasis, moderate to severe psoriasis)	The subgroups of interest in the economic analysis are: • Comorbid psoriasis severity (no psoriasis, mild to moderate psoriasis, moderate to severe psoriasis) • Previous bDMARD experience (bDMARD-naïve, bDMARD-experienced).	
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	No equity or equality issues identified.	As per the reference case

Source: Based on Table 1 of the CS[1]

ACR = American College of Rheumatology; ACR 20/ 50/ 70 = at least 20%/ 50%/ 70% improvement in both tender and swollen joint counts; bDMARD = biological disease-modifying anti-rheumatic drug; BSR = British Society for Rheumatology; cDMARD = conventional disease-modifying anti-rheumatic drug; CS = company submission; DMARD = disease-modifying anti-rheumatic drug; EQ-5D = European Quality of Life-5 Dimensions; HAQ-DI = Health Assessment Questionnaire-Disability Index; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; MDA = minimal disease activity; mg = milligram; mTSS = modified Total Sharp Score; NA = not applicable; NAPSI = Nail Psoriasis Severity Index; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PAS = Patient Access Scheme; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks

3.1 Population

The population defined in the scope is adults with active psoriatic arthritis whose disease has not responded adequately to previous DMARD drug therapy or for whom DMARDs are not tolerated or contraindicated.[24] The population in the CS is in line with the scope. However, it is important to note that under NICE guidance bDMARDs are given after failure of two or more cDMARDs (see Figure 2.1). While the company aligns ixekizumab with NICE guidance, not all patients meet this criterion in the main trials of the submission (SPIRIT-P1 and P2). In section 2.7 of the CS, the company provides an integrated analysis of [redacted] patients across the two trials meeting NICE criteria. Efficacy of ixekizumab compared to placebo is [redacted] for the outcome of ACR 20.[1] Network meta-analyses (NMA) were performed separately for the bDMARD-naïve and bDMARD-experienced populations as the SPIRIT-P1 and SPIRIT-P2 trials were in different populations based on previous treatment with biologics.

The two main trials in the submission (SPIRIT-P1 and P2) were multinational trials. Across the two trials, [redacted] patients were recruited to [redacted] centres in the UK which represents approximately [redacted] of patients.[25] Comments submitted by the British Society for Rheumatology stated that the trials reflected current UK clinical practice.[22] The company was invited to further address applicability to the UK and their response along with ERG comments on applicability is detailed in sections 4.2.1 and 4.2.2 of this report. The committee will need to decide if it agrees with the company that the SPIRIT trials are sufficiently reflective of a UK patient population.

3.2 Intervention

The intervention (ixekizumab alone or in combination with conventional DMARD) is in line with the scope. In January 2018, it was approved in the EU for the treatment of patients with PsA: '*Ixekizumab, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic (DMARD) therapies'*.[1] Ixekizumab is also licenced and approved by NICE for the treatment of moderate to severe psoriasis (TA442).[24]

Ixekizumab is a biological DMARD, described as '*a recombinant humanised IgG4 monoclonal antibody (mAb) designed and engineered to selectively inhibit interleukin-17A (IL-17A), a pro-inflammatory cytokine'*.[1]However, it is not the first IL-17 agent available for this indication. Secukinumab is licenced and has associated NICE guidance.[26]

Ixekizumab is administered by subcutaneous injection and the dose is dependent on concomitant psoriasis severity. PsA patients without co-morbidity and moderate to severe psoriasis receive an initial dose of 160 mg by subcutaneous injection at week 0 followed by 80 mg every four weeks. Those with concomitant moderate to severe psoriasis receive the initial dose as above then 80 mg at weeks 2, 4, 6, 8, 10 and 12 then maintenance of 80 mg every four weeks. The company states that no additional tests or investigations are required.[1]

In SPIRIT-P1and P2, concomitant medications were permitted alongside ixekizumab. Any implications of this will be discussed in section 4 of this report.

3.3 Comparators

Ixekizumab is an addition to the range of existing DMARDs for PsA. The relevant comparators are presented in Figure 2.1 of this report. The NICE scope indicated the following comparators:

- For people whose disease has not responded adequately to one non-biological disease modifying anti-rheumatic drug
  - Non-biological DMARDs
- For people whose disease has not responded adequately to at least two non-biological DMARDs:
  - Biological DMARDs (with or without methotrexate, including etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, secukinumab)
  - Apremilast
- For people whose disease has not responded adequately to non-biological DMARDs and one or more TNF-alpha inhibitors:
  - Ustekinumab
  - Certolizumab pegol
  - Secukinumab
  - Best supportive care
- For people in whom TNF-alpha inhibitors are contraindicated:
  - Ustekinumab
  - Secukinumab
  - Best supportive care

The company does not present a comparison of ixekizumab with non-biological drugs for people who have not responded to one or more non-biological drugs as this does not reflect the NICE pathway and proposed positioning of ixekizumab. This appears appropriate to the ERG.

All the relevant comparators have been addressed in the submission. However, it is important to realise that the main two trials in the CS compare ixekizumab to placebo rather than to one or more of the active comparators in the scope. Although SPIRIT-P1 also included an active control (adalimumab), the study was not designed to test equivalence or non-inferiority of ixekizumab versus adalimumab.[1] Therefore, there is no direct evidence presented comparing ixekizumab with the comparators in the scope. The evidence in relation to the other DMARDs mentioned in the scope comes from network meta-analyses. This is less reliable than direct comparisons between ixekizumab and other comparators obtained from a direct comparison within one or more RCTs.

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- Disease activity
- Functional capacity
- Disease progression
- Periarticular disease (for example enthesitis, tendonitis, dactylitis)
- Mortality
- Adverse effects of treatment
- Health-related quality of life

These outcomes are evaluated in the trials in the submission with the exception of mortality. The company states that *'no biologic treatment for psoriatic arthritis has demonstrated an effect on mortality outcomes in the context of a clinical trial, therefore mortality in the model has been modelled as the application of excess mortality risk associated with PsA to the mortality risk in the general*

population'.[1] The ERG recognises that short-term trials are unlikely to demonstrate any effect of treatment on mortality, should one exist. Having said that, modelling of excess mortality associated with PsA appears reasonable. However the ERG had concerns on the source used to derive the excess mortality which was based on a Canadian study at the University of Toronto PsA Clinic between 1978 and 2004.[6] This study may not reflect a UK setting and the most up to date management of patients with PsA. The ERG considers that the modelled excess mortality was likely high, which would likely induce bias in favour of treatments with high response rates.

The company provided data on periarticular disease, disease progression and adverse events. However, these were not included in the economic analysis due to insufficient comparative data which leads to potential bias in the estimation of HRQoL and cost associated with all treatments.

In relation to disease activity, submissions from Rheumatology Pharmacists UK (RPUK) and the British Society for Rheumatology (BSR) emphasise that PsARC is a more relevant outcome to assess response in clinical practice than ACR measures.[22, 27] PsARC is assessed in the trials in the CS and is used to model disease activity in the economic model.

It should be noted that, as the two main trials in the CS compared ixekizumab to placebo, there is no direct evidence on these effectiveness outcomes of ixekizumab in relation to the other DMARDs. The evidence for comparisons of ixekizumab to other treatments for treatment-emergent adverse events, serious adverse events and discontinuation due to an adverse event was obtained from network meta-analysis provided in the response for request for clarification.[25]

Although not explicitly stated in the NICE scope, the company stated that skin involvement, e.g. PASI response, is a relevant outcome to include in the CS. The ERG believes this to be appropriate, particularly as NICE guidance for other DMARDs allows patients whose psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at the relevant timepoint to continue treatment if their PASI response merits this.[16]

In summary, relevant outcomes were measured in the trials in the CS which compared ixekizumab with placebo, but comparisons with other treatments are based on indirect treatment comparisons.

3.5 Other relevant factors

The company stated that they '*were unaware of any equality issues that could impact the appraisal of ixekizumab*'.[1]

A confidential patient access scheme (PAS) is provided for ixekizumab. The PAS is a [redacted] providing 80 mg solution for injection in prefilled pen x 2 at [redacted] and an 80 mg solution for injection in prefilled syringe at [redacted].

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: clnicaltrials.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 conducted and no SR databases were searched, their approach relied on relevant SRs and NMAs appearing in

- a search limited to randomised controlled trials. Therefore, the ERG did not consider this a robust approach for cross-checking or validation. The ERG believes a more appropriate response to address substantial errors would have been to repeat the corrected searches to ensure the submission was based on a robust systematic review search.
- The ERG was concerned about the language bias of restricting searches to English language only as this is not in line with current best practice.

4.1.2 Inclusion criteria

The eligibility criteria are presented in Table 4.1. All abstracts identified by the searches were reviewed independently by two reviewers and those considered relevant based on the eligibility criteria were then screened for full-text inclusion independently by the same two reviewers. Discrepancies between reviewers at each stage were resolved through discussion or with assistance from a third reviewer.

Table 4.1: Eligibility criteria

Criteria	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥ 18 years) with active psoriatic arthritis*	Studies not reporting data on adult patients with active PsA, including: • Studies reporting on psoriasis patients only • Studies reporting pooled data for PsA and other conditions • Studies not conducted in paediatric patients (< 18 years)
Interventions	Ixekizumab Biologics: • Adalimumab [Humira®] • Etanercept [Enbrel®] • Golimumab [Simponi®] • Infliximab [Remicade®] • Certolizumab pegol [Cimzia®] • Ustekinumab [Stelara®] • Secukinumab [Cosentyx®] Biosimilars: • Infliximab, etanercept and other biosimilars of the above listed branded biologics Target synthetic DMARDs: • Apremilast [Otezla®] Emerging therapies: • Brodalumab • Tildrakizumab • Abatacept • Tofacitinib • Guselkumab • Clazakizumab • Tocilizumab	Studies not reporting on any of the interventions specified in the inclusion criteria.

Criteria	Inclusion criteria	Exclusion criteria
Comparators	• Placebo (placebo-controlled studies) or best supportive care • Any of the above interventions of interest • Non-biologic approved treatments or cDMARDs as best supportive care or comparators of interventions of interest, including but not limited to: ciclosporin/cyclosporine, methotrexate, leflunomide, and sulfasalazine	Studies where the comparator is none of those specified in the inclusion criteria. Note: Single-arm (i.e. non-controlled) studies will be excluded under the 'Study design' criteria, rather than the 'Comparator' criteria.
Outcomes	Clinical and patient-reported outcomes including disease severity, disease response, and/or disability scores: • American College of Rheumatology 20/50/70 index (ACR20, ACR50, ACR70) • Psoriasis Area and Severity Index (PASI [absolute, % change], PASI 50/75/90/100) • Health Assessment Questionnaire-Disability Index (HAQ-DI) (absolute or mean change from baseline); proportion of patients achieving a change of >0.22 or 0.35) • Psoriatic Arthritis Response Criteria (PsARC) • Enthesitis/dactylitis (e.g. as measured by the Maastricht Ankylosing Spondylitis Enthesitis Score [MASES], or SPARCC or Leeds Enthesitis Index [LEI], Leeds Dactylitis Index-Basic [LDI-B]) • Structural joint outcomes (e.g. mTSS) • Minimal disease activity (Coates criteria for MDA) Drug safety measures: • Adverse events (AE) • Serious and severe adverse events (SAE) • Discontinuation (due to lack of efficacy or due to adverse events)	The study does not contain any of the outcomes of interest specified in the inclusion criteria.
Study designs	• Randomised clinical trials (RCTs) • Cross-over design RCTs[**] • Systematic literature reviews[***]	All other study types, for example, NMAs, non-systematic reviews, retrospective, non-randomised or non-controlled studies, publications that are commentary, editorial, errata, letter, note, or guideline.

Criteria	Inclusion criteria	Exclusion criteria
Language	English language Limit to publications from 1990 to present	• Publication in a language other than English • Publication prior to August 2016 Note: conference abstracts that report same data as a subsequent full-text publication will be marked as duplicates and also excluded.

Source: Based on Table 9 of the CS[1]

Footnote: * The following criteria were not included in the PICOS criteria as they may not be reported on by all studies of interest, and therefore were not used to exclude studies: definition of active PsA as patients having at least 3 tender and 3 swollen joints or at least 5 tender and 5 swollen joints; or as fulfilment of CASPAR criteria classification. ** The expectation was to use information prior to placebo cross-over phase. *** Previous SLRs were identified to validate this SLR, not as a source of data.

ACR = American College of Rheumatology; ACR 20 = at least 20% improvement in both tender and swollen joint counts; ACR 50 = at least 50% improvement in both tender and swollen joint counts; ACR 70 = at least 70% improvement in both tender and swollen joint counts; AE = adverse event; cDMARD = conventional disease-modifying anti-rheumatic drug; CS = company submission; DMARD = Disease-modifying anti-rheumatic drug; HAQ-DI = Health Assessment Questionnaire-Disability Index; LDI-B = Leeds Dactylitis Index-Basic; LEI = Leeds Enthesitis Index; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MDA = Minimum Disease Activity; mTSS = modified Total Sharp Score; NMA = network meta-analysis; 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; PsA = psoriatic arthritis; PsARC = Psoriasis Area and Severity Index; RCT = randomised controlled trial; SAE = serious adverse event; SLR = systematic literature review; SPARCC = Spondyloarthritis Research Consortium of Canada Enthesitis Index

4.1.3 Critique of data extraction

Data were extracted by two reviewers independently following methods recommended by the Cochrane Handbook for Systematic Reviews of Interventions.[29]

ERG comment: This approach follows recommendations by the Cochrane Handbook.[29]

4.1.4 Quality assessment

The risk of bias of additional studies included in the NMA was assessed using the risk of bias tool from the Cochrane Handbook for the Systematic Reviews of Interventions.[28, 29] Details of how many reviewers performed the assessment were not reported.

ERG comment: The risk of bias was assessed using an established tool. However, it is unclear how many reviewers were involved in the assessment of risk of bias.

4.1.5 Evidence synthesis

A meta-analysis of SPIRIT-P1 and SPIRIT-P2 was not performed as it was not considered appropriate to pool them due to major differences in the patient populations. SPIRIT-P1 was performed in biologic-naïve patients whereas SPIRIT-P2 was performed in biologic-experienced patients. *'As prior bDMARD exposure is a treatment effect modifier, a meta-analysis of the two trials would not have been appropriate'*.[1]

Separate NMA were performed for the biologic-naïve and biologic-experienced populations, further details are provided in section 4.3.

ERG comment: The ERG agrees that is would not have been appropriate to perform a meta-analysis of SPIRIT-P1 and SPIRIT-P2 due to the differences in population. However, it should be noted again that there is no direct evidence of ixekizumab in relation to the other DMARDs, i.e. that all results come from less robust network meta-analyses, as discussed in section 4.3.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Overview of the direct evidence in the submission

The evidence base for the clinical efficacy and safety of ixekizumab in the treatment of psoriatic arthritis following inadequate response to disease modifying ant-rheumatic drugs (DMARDs) consists of two randomised controlled trials (RCTs), as identified by a systematic literature review (SLR), discussed in section 4.1.1 of the ERG report: SPIRIT-P1 and SPIRIT-P2.[1]

The SPIRIT studies are phase III, multicentre, multinational randomised, double-blind, placebo-controlled, parallel group, adult outpatient trials comparing the efficacy and safety of ixekizumab to placebo in two sub-groups of patients: 1) biologic disease-modifying anti-rheumatic drug (bDMARD)-naïve patients (I1F-MC-RHAP, SPIRIT-P1) and 2) tumour necrosis factor (TNF) inhibitor-experienced patients (I1F-MC-RHBE, SPIRIT-P2). In addition, SPIRIT-P1 also included an active control arm (adalimumab). The main methodological features of the SPIRIT trials are summarised in Table 4.2 below.

No direct evidence of ixekizumab in relation to any of the comparators in the scope was presented.

Table 4.2: Overview of RCTs of ixekizumab in the submission

Trial name	SPIRIT-P1 (RHAP)	SPIRIT-P2 (RHBE)
Population	417 adult patients (≥18 years) with active PsA who were bDMARD-naïve	363 adult patients (≥ 18 years) with active PsA who were bDMARD-experienced
Intervention	Ixekizumab 80 mg q2w (n=103) Ixekizumab 80 mg q4w (n=107)	Ixekizumab 80 mg q2w (n=123) Ixekizumab 80 mg q4w (n=122)
Comparator	Placebo (n=106) Adalimumab 40 mg q2w (n=101, not an active comparator)	Placebo (n=118)
Outcomes	Primary outcome: ACR 20 at week 24 Other reported outcomes from the decision problem: • Disease activity (ACR 50/70, PsARC*, MDA) • Functional capacity (HAQ-DI*) • Effect on concomitant skin condition (PASI 75/90/100*) • Other complications of psoriatic arthritis (LEI-enthesitis, NAPSI-nail psoriasis [modified version], LDI-B dactylitis) • Health-related quality of life (EQ-5D*) • Adverse events • Mortality	
	Structural progression (mTSS)	
Trial design	Randomised, double-blind, placebo-controlled, active-controlled, parallel-group study.	Randomised, double-blind, placebo-controlled, parallel-group study.

Trial name	SPIRIT-P1 (RHAP)	SPIRIT-P2 (RHBE)
Duration of trial and trial phases	Double-Blind Treatment Period (week 0-24 – primary endpoint assessment)	
	• Extension Period (week 24-52) • Long-term Extension Period (week 52-156)	• Extension Period (week 24-156)
	Post-Treatment Follow-Up Period (from the last treatment period visit or ETV up to a minimum of 12 weeks after that visit)	
	Duration of trial (including long-term safety and efficacy follow up): 3 years	
Settings and locations where the data were collected	114 study sites in 15 countries: Belgium, Bulgaria, Canada, Czech Republic, Estonia, Japan, Spain, France, Great Britain, Mexico, Netherlands, Poland, Russia, Ukraine, United States	109 study sites in 10 countries: Australia, Czech Republic, France, Germany, Italy, Poland, Spain, Taiwan, United Kingdom, and United States

Source: Tables 5 and 8 of the CS[1]
Footnote: * included in economic model
ACR = American College of Rheumatology; ACR 20 = at least 20% improvement in both tender and swollen joint counts; ACR 50 = at least 50% improvement in both tender and swollen joint counts; ACR 70 = at least 70% improvement in both tender and swollen joint counts; bDMARD = biologic disease-modifying anti-rheumatic drugs; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; ETV = early termination visit; HAQ-DI = Health Assessment Questionnaire-Disability Index; LDI-B = Leeds Dactylitis Index-Basic; LEI = Leeds Enthesitis Index; MDA = Minimum Disease Activity; mg = milligram; mTSS = modified Total Sharp Score; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; 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; PsA = psoriatic arthritis; PsARC = Psoriasis Area and Severity Index; q2w = once every two weeks; q4w = once every four weeks

Although both trials last up to three years the double-blind period lasts for 24 weeks only. At week 16, patients were classified as responders or non-responders. Responders were those patients who achieved a ≥20% improvement in either tender joint count (TJC) and/or in swollen joint count (SJC) from baseline. All inadequate responders were administered rescue therapy (patient's background therapy) at week 16 which was maintained for the remainder of the treatment period. Patients receiving ixekizumab before week 16 were given rescue therapy while continuing with their same ixekizumab dose regimen. Those who were receiving adalimumab or placebo were re-randomised to receive either ixekizumab 80 mg q2w or q4w (following an eight week wash out period using placebo from weeks 16 to 24 for patients taking adalimumab). At week 24, any remaining patients on placebo or adalimumab were re-randomised to ixekizumab. Further description of the trial design is given in the CS.[1]

Patients receiving cDMARDs at the beginning of the studies were allowed to continue during the double-blind treatment period. However, alteration of the cDMARD dose and/or introduction of a new cDMARD was strongly discouraged unless for safety or used as rescue therapy for inadequate responders at week 16. The investigator could lower or stop the cDMARD if adverse effects could be attributed to it.[1]

ERG comment:

- The evidence is based on two randomised controlled trials which represent the highest level of evidence. However, both trials compare ixekizumab to placebo. No direct evidence is available on ixekizumab in relation to the other comparators in the scope.
- The evidence base includes both those with experience of bDMARDs and those without.
- Outcomes relevant to the scope are presented in the trials.

- The double-blind period is 24 weeks so long-term effectiveness results cannot be determined. The extension periods do, however, provide information on long-term safety.
- At week 16, patients were permitted rescue therapy in case of inadequate response so results up to 16 weeks are more reliable for the comparison between ixekizumab and placebo.
- Both trials were multinational but did include centres in the UK. Across the two trials, [redacted] patients were recruited by [redacted] centres in the UK.[25] This represents approximately [redacted] of patients. Despite the BSR submission[22] stating that the trials reflected current UK clinical practice, this aspect is drawn to the attention of the committee.

4.2.2 Participants in the SPIRIT trials

In both SPIRIT trials, in order to be included patients needed to have an established diagnosis of PsA (of at least six months and meeting the Classification Criteria for Psoriatic Arthritis). They needed to have active PsA defined as at least three of 68 tender and three of 66 swollen joints. Both trials specified that patients had to have active psoriatic skin lesions (plaques) or a documented history of plaque psoriasis. In SPIRIT-P1 and SPIRIT-P2 the main exclusion criteria were related to a history of malignant disease or recent history of infections.

Spirit-P1 required patients to have at least one disease-related joint erosion or a c-reactive protein (CRP) > 6 mg/l (approximately 90% had joint erosions).[1] Any history of biologic treatment for plaque psoriasis or PsA resulted in exclusion from the trial.[1] In SPIRIT P1, 15% of participants who entered the study were cDMARD naïve while 85% had received at least one cDMARD.[25]

Spirit P-2 required patients to have been previously treated with a TNF alpha inhibitor and to have had an inadequate response to one or two TNF alpha inhibitors or to be intolerant to them. In Spirit-P2 patients needed to have been previously treated with one or more cDMARDs (cf. Table 6 of the CS[1]).

Table 9 of the CS showing patient demographics had some errors which were brought to the company's attention and corrections were supplied in response to clarification.[25] The amended table is reproduced in Table 4.3.

Table 4.3: Participant demographics in the SPIRIT trial

Demographic parameter	SPIRIT-P1					SPIRIT-P2			
	Placebo	ADA40 q2w	IXE80 q4w	IXE80 q2w	Total	Placebo	IXE80 q4w	IXE80 q2w	Total
	n=106	n=101	n=107	n=103	n=417	n=118	n=122	n=123	n=363
Patient demographics									
Age, mean years (SD)	50.6 (12.3)	48.6 (12.4)	49.1 (10.1)	49.8 (12.6)	49.5 (11.9)	51.5 (10.4)	52.6 (13.6)	51.7 (11.9)	51.9 (12.0)
Male, n (%)	48 (45.3)	51 (50.5)	45 (42.1)	48 (46.6)	192 (46.0)	56 (47.5)	63 (51.6)	50 (40.7)	169 (46.6)
Race, n (%)									
White	99 (93.4)	95 (94.1)	102 (95.3)	96 (93.2)	392 (94.0)	108 (91.5)	111 (91.0)	113 (91.9)	332 (91.5)[**]
Asian	5 (4.7)	3 (3.0)	2 (1.9)	5 (4.9)	15 (3.6)	7 (5.9)	7 (5.7)	7 (5.7)	21 (5.8)[**]
Other	2 (1.9)[*]	3 (3.0)[*]	3 (2.8)[*]	2 (1.9)[*]	10 (2.6)[*]	3 (2.5)	4 (3.3)	2 (1.6)	9 (2.5)[**]
Number of patients by region, n (%)									
Europe	76 (71.7)	73 (72.3)	80 (74.8)	77 (74.8)	306 (73.4)	50 (42.4)	49 (40.2)	50 (40.7)	149 (41.0)
Rest of the world	30 (28.3)	28 (27.7)	27 (25.2)	26 (25.2)	111 (26.6)	68 (57.6)	73 (59.8)	73 (59.3)	214 (59.0)
United Kingdom	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight category, n (%)									
< 80 kg	44 (41.5)	33 (32.7)	43 (40.2)	54 (52.4)	174 (41.7)	38 (32.2)	45 (36.9)	55 (44.7)	138 (38.0)
≥ 80 to < 100 kg	45 (42.5)	36 (35.6)	43 (40.2)	34 (33.0)	158 (37.9)	47 (39.8)	41 (33.6)	43 (35.0)	131 (36.1)
≥ 100 kg	17 (16.0)	32 (31.7)	21 (19.6)	15 (14.6)	85 (20.4)	33 (28.0)	36 (29.5)	25 (20.3)	94 (25.9)
Mean BMI, kg/m^2 (SD)	29.2 (6.3)	32.1 (11.4)	30.2 (8.4)	28.6 (6.6)	30.0 (8.5)	31.6 (7.6)	30.9 (7.1)	30.1 (6.8)	30.9 (7.2)
Baseline characteristics									
Time since PsA diagnosis, mean years (SD)	6.3 (6.9)	6.9 (7.5)	6.2 (6.4)	7.2 (8.0)	6.7 (7.2)	9.2 (7.3)	11.0 (9.6)	9.9 (7.4)	10.0 (8.2)
Time since PsA onset, mean years (SD)	10.4 (8.8)	9.2 (7.3)	10.0 (9.5)	10.8 (10.8)	10.1 (9.3)	11.1 (8.5)	13.8 (10.6)	11.5 (7.5)	12.2 (9.0)

Demographic parameter	SPIRIT-P1					SPIRIT-P2			
	Placebo	ADA40 q2w	IXE80 q4w	IXE80 q2w	Total	Placebo	IXE80 q4w	IXE80 q2w	Total
	n=106	n=101	n=107	n=103	n=417	n=118	n=122	n=123	n=363
Previous non-biologic systemic agent, n (%)	67 (63.2)	64 (63.4)	63 (58.9)	72 (69.9)	266 (63.8)	90 (76.3)	95 (77.9)	103 (83.7)	288 (79.3)
Previous methotrexate	45 (42.5)	43 (42.6)	37 (34.6)	45 (43.7)	170 (40.8)	69 (58.5)	69 (56.6)	72 (58.5)	210 (57.9)
Previous sulfasalazine	20 (18.9)	26 (25.7)	19 (17.8)	30 (29.1)	95 (22.8)	31 (26.3)	38 (31.1)	29 (23.6)	98 (27.0)
Previous leflunomide	13 (12.3)	15 (14.9)	19 (17.8)	10 (9.7)	57 (13.7)	25 (21.2)	26 (21.3)	29 (23.6)	80 (22.0)
Previous apremilast	-	-	-	-	-	5 (4.2)	8 (6.6)	3 (2.4)	16 (4.4)
Current methotrexate use, n (%)	59 (55.7)	57 (56.4)	57 (53.3)	53 (51.5)	226 (54.2)	40 (33.9)	48 (39.3)	61 (49.6)	149 (41.0)
Past cDMARD use, n (%)	24 (22.6)	20 (19.8)	22 (20.6)	23 (22.3)	89 (21.3)	66 (55.9)	62 (50.8)	50 (40.7)	178 (49.0)
Current cDMARD use, n (%)	69 (65.1)	67 (66.3)	68 (63.6)	63 (61.2)	267 (64.0)	52 (44.1)	60 (49.2)	73 (59.3)	185 (51.0)
Previous biologic agent, n (%)	-	-	-	-	-	118 (100)	122 (100)	123 (100)	363 (100)
Prior TNFi experience, n (%)									
Inadequate responder to 1 TNFi	-	-	-	-	-	68 (57.6)	71 (58.2)	65 (52.8)	204 (56.2)
Inadequate responder to 2 TNFi	-	-	-	-	-	41 (34.7)	41 (33.6)	46 (37.4)	128 (35.3)
Intolerance to a TNFi	-	-	-	-	-	9 (7.6)	10 (8.2)	12 (9.8)	31 (8.5)
DAS28-CRP, mean (SD)	4.9 (1.0)	4.9 (1.0)	5.0 (1.0)	5.0 (1.1)	4.9 (1.0)	5.0 (1.1)	5.1 (1.1)	5.1 (1.1)	5.1 (1.1)
CRP (mg/l), mean (SD)	15.1 (23.6)	13.2 (19.1)	12.8 (16.4)	15.1 (25.9)	14.1 (21.5)	12.1 (19.6)	17.0 (27.5)	13.5 (26.1)	14.2 (24.7)
CRP category >6 mg/l, n (%)	65 (61.3)	62 (61.4)	69 (64.5)	54 (52.4)	250 (60)	57 (49.1)	60 (50.4)	53 (43.1)	170 (47.5)
Van der Heijde modified total Sharp score, mean (SD)[30]	17.6 (28.6)	15.9 (27.4)	19.2 (32.7)	15.2 (28.9)	17.0 (29.4)	-	-	-	-
SPARCC total score, mean (SD)	NR	NR	NR	NR	NR	5.7 (4.38)	5.6 (3.98)	6.1 (4.30)	5.8 (4.21)
Patients with erosions, n (%)	93 (98.9)	91 (95.8)	93 (93.0)	94 (95.9)	371 (95.9)	NR	NR	NR	NR
Tender joint count 68 joints, mean (SD)	19.2 (13.0)	19.3 (13.0)	20.5 (13.7)	21.5 (14.1)	20.1 (13.4)	23.0 (16.2)	22.0 (14.1)	25.0 (17.3)	23.4 (15.9)

Demographic parameter	SPIRIT-P1					SPIRIT-P2			
	Placebo	ADA40 q2w	IXE80 q4w	IXE80 q2w	Total	Placebo	IXE80 q4w	IXE80 q2w	Total
	n=106	n=101	n=107	n=103	n=417	n=118	n=122	n=123	n=363
Swollen joint count 66 joints, mean (SD)	10.6 (7.3)	9.9 (6.5)	11.4 (8.2)	12.1 (7.2)	11.0 (7.4)	10.3 (7.4)	13.1 (11.2)	13.5 (11.5)	12.3 (10.3)
HAQ-DI total score, mean (SD)	1.2 (0.6)	1.1 (0.6)	1.2 (0.5)	1.2 (0.6)	1.2 (0.6)	1.2 (0.7)	1.2 (0.6)	1.2 (0.6)	1.2 (0.6)
Current Psoriasis, n (%)	102 (96.2)	97 (96.0)	100 (93.5)	95 (92.2)	394 (94.5)	108 (91.5)	118 (96.7)	113 (91.9)	339 (93.4)
Percentage of BSA for patients who have baseline plaque psoriasis, mean (SD)	14.4 (20.2)	14.8 (19.2)	15.1 (16.3)	12.0 (15.6)	14.1 (17.9)	9.0 (12.7)	12.5 (17.4)	11.6 (18.6)	11.0 (16.4)
BSA ≥ 3%, n (%)	67 (67.7)	68 (72.3)	73 (73.0)	59 (64.8)	267 (69.5)	67 (62.6)	68 (61.8)	68 (63.0)	203 (62.5)
PASI score in patients ≥3% BSA, mean (SD)	6.2 (7.5)	5.5 (6.5)	6.9 (6.6)	6.0 (7.0)	6.1 (6.9)	7.1 (7.1)	9.3 (9.1)	8.8 (10.3)	8.4 (8.9)
Moderate to severe psoriasis as defined as PASI > 12, sPGA ≥ 3 and BSA ≥ 10, n (%)	16 (16.2)	8 (8.5)	17 (17.0)	12 (13.2)	53 (13.8)	11 (9.3)	15 (12.3)	12 (9.8)	38 (10.5)
Current enthesitis, n (%)	57 (53.8)	56 (55.4)	70 (65.4)	59 (57.3)	242 (58.0)	69 (58.5)[a]	68 (55.7)[a]	84 (68.3)[a]	221 (60.9)[a]
LEI score, mean (SD)	2.9 (1.7)	3.0 (1.6)	2.7 (1.6)	3.1 (1.8)	2.9 (1.7)	2.9 (1.7)	2.9 (1.4)	3.0 (1.7)	2.9 (1.6)
Current dactylitis, n (%)	39 (36.8)	23 (22.8)	54 (50.5)	41 (39.8)	157 (37.6)	14 (11.9)[b]	28 (23.0)[b]	20 (16.3)[b]	62 (17.1)[b]
LDI score, mean (SD)	46.2 (65.5)	93.9 (111.9)	58.1 (96.7)	40.6 (54.6)	55.8 (83.6)	37.3 (25.2)	31.5 (33.8)	53.9 (37.6)	40.1 (34.3)

Source: Based on Table 9 of the CS[1] and Table 6 of the response to request for clarification[25]

Footnotes: [a] Defined as LEI > 0; [b] Defined as LDI-B score > 0; [*] Derived from Mease et al, 2017[31]; [**] Derived from Nash et al, 2017[32]

ADA = adalimumab; BMI = body mass index; BSA = body surface area; cDMARD = conventional disease-modifying anti-rheumatic drug; CRP = c-reactive protein; DAS28-CRP = disease activity score 28 diarthrodial joint count based on c-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; IXE = ixekizumab; kg = kilogram; LEI = Leeds Enthesitis Index; PASI = Psoriasis Area and Severity Index; NR = not reported; PsA = psoriatic arthritis; q2w = once every two weeks; q4w = once every four weeks; SD = standard deviation, SPARCC = Spondyloarthritis Research Consortium of Canada Enthesitis Index; sPGA = static physician's global assessment; TNFi = tumour necrosis factor inhibitor

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 7.2 years in SPIRIT-P1 and 8.2 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

- population with higher baseline CRP scores, a greater proportion of patients with baseline CRP >6 mg/dl (47.5% vs [redacted]) and a greater number of tender joints at baseline (23.4 (SD 15.9) vs. [redacted] (SD [redacted])).
- In summary, the committee will need to decide, based on the factors highlighted by the ERG and the comparisons with the UK sample, whether it agrees with the company that the results of the SPIRIT trials are generalisable to UK practice.

4.2.3 Quality assessment of the SPIRIT trials

The quality of the SPIRIT trials was assessed by the company in the CS with further details of the rating of quality criteria in the CS appendices.[28] Elements assessed were randomisation, allocation concealment, comparability of groups, blinding of care providers, patients and outcome assessors and drop out, selective reporting of outcomes and use of intention to treat analysis and appropriate methods for dealing with missing data. Table 4.4 provides an overview of the quality assessment of the SPIRIT RCTs from the point of view of the company and the ERG.

Table 4.4: SPIRIT-P1 and P2 study quality

Quality dimension	SPIRIT-P1 CS	SPIRIT-P1 ERG	SPIRIT-P2 CS	SPIRIT-P2 ERG	ERG comment
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Patients were randomised using a computer-generated random sequence using an interactive voice response system (IVRS).
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	However, in SPIRIT-P2 greater proportions of patients in the ixekizumab 80 mg q2w group were using methotrexate at baseline, compared to patients in the placebo group (49.6% versus 33.9%). Methotrexate use was not different between the ixekizumab 80 mg q4w and placebo groups.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes	Patients and study site personnel were blinded to study treatment until after all patients had discontinued from treatment or completed week 24. Unblinding did not occur until the reporting database was locked for the week 24 statistical analysis.
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No	None identified
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes*	Yes*	No	No	The authors stated that the Itch Numeric Rating Scale was implemented to assess itching in SPIRIT-P1 but was not reported by Mease et al., 2017.[31] Results for this scale are going to be reported in a paper currently under development (and were in the CSR).
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes	Efficacy and health outcome analyses were conducted according to the treatment to which all randomised patients were assigned i.e. ITT population. NRI and mBOCF methods were used to account for missing data.

Quality dimension	SPIRIT-P1 CS	SPIRIT-P1 ERG	SPIRIT-P2 CS	SPIRIT-P2 ERG	ERG comment
Did the authors of the study publication declare any conflicts of interest?	Yes	Unclear	Yes	Unclear	Unclear which study publication is being referenced.

Source: Based on table 12 of the CS[1] and table 37 of the CS appendices[28]

Footnote: * Itch NRS was a gated secondary endpoint in SPIRIT-P1, however, statistical testing was not performed as the prior gated endpoint was not significant.

CS = company submission; CSR = clinical study report; ERG = evidence review group; ITT = intention-to-treat; IVRS = interactive voice response system; mBOCF = modified baseline observation carried forward; NRI = non-responder imputation; q2w = once every two weeks; q4w = once every four weeks

ERG comment:

- The ERG agrees with the company's assessment of the quality of the SPIRIT trials. Both are well conducted randomised, blinded trials.
- The quality comments refer only to the 24-week double blind period of the trial, not to the open label extension period.

4.2.4 Statistical analysis of the SPIRIT trials

Efficacy analyses of both SPIRIT trials were performed for the ITT population and patients were analysed according to the randomised treatment even if they did not take that treatment, did not receive the correct treatment or did not follow the protocol. Only data collected up to week 16 were included in the analyses for patients who were inadequate responders at week 16. A gatekeeping statistical testing strategy was used for the analysis of the primary and major secondary outcomes with testing being performed in a pre-defined order to minimise multiple comparisons.

The primary outcome in both trials was the proportion of patients achieving an ACR 20 response at week 24. This was compared between each ixekizumab arm and placebo using logistic regression analysis adjusting for geographic region and cDMARD experience (naïve, past or current use) at baseline in SPIRIT-P1 and for geographic region and TNFi experience (inadequate response to one, two, or intolerant) at baseline in SPIRIT-P2. Results were reported as odds ratios (OR) with 95% confidence intervals (CI) and p-values. Missing data were imputed using non-responder imputation with non-responders defined as patients not meeting the clinical response criteria, being eligible for rescue therapy at week 16, having missing clinical response data, discontinuing from the trial prior to week 24, or not having at least one post-baseline assessment. Other binary outcomes (PsARC at weeks 12 and 24; PASI 75, 90 and 100 at week 12; ACR 20 at week 12; and ACR 50 and 70 at weeks 12 and 24) were analysed using the same methods.

Continuous outcomes such as the change from baseline to weeks 12 and 24 in HAQ-DI and mTSS as well as the change from baseline to week 12 in LEI (for patients with enthesitis at baseline) and itch (for patients with baseline psoriatic lesions involving ≥ 3% BSA) were analysed using a mixed-effect repeated measures model (MMRM) which included treatment, geographic region, baseline score, the treatment-by-visit interaction and cDMARD use at baseline (for SPIRIT-P1) or TNFi use at baseline (for SPIRIT-P2). As this model accounted for data being missing at random, missing data were not imputed.

Subgroup analyses were performed using a logistic regression model containing treatment, the relevant subgroup and the treatment-by-subgroup interaction, the interaction was tested using a significance level of 0.10. Differences between treatments were analysed within each subgroup category using Fisher's exact test regardless of whether or not the interaction term was statistically significant. Subgroup analyses were performed for concomitant methotrexate use (as a post-hoc analysis), gender, age, concomitant cDMARD therapy at baseline, cDMARD experience at baseline, prior TNFi experience, baseline disease severity, previous therapy for PsA and duration of PsA (all pre-specified analyses), see section 4.2.5. A further subgroup analysis was used to evaluate the efficacy of ixekizumab in those patients who would be eligible for bDMARD treatment under current NICE criteria.

4.2.5 Efficacy results of the SPIRIT trials

The main results of the SPIRIT trials, as presented in the CS, are given in Table 4.5. Efficacy analyses were performed using the ITT population. The primary outcome in both SPIRIT trials was ACR 20

response rates at week 24. In both SPIRIT studies, significantly more patients achieved an ACR 20 response with ixekizumab compared with 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 the SPIRIT-P1 trial, patients treated with adalimumab had similar response rates to the ixekizumab arms. Ixekizumab was also found to be superior to placebo for ACR 20 at week 12 and for ACR 50 and 70 at 12 and 24 weeks, see Table 4.5.

In both SPIRIT-P1 and P2 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%), see Table 4.5.

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, see Table 4.5.

The company stated that '*statistically significant differences for the ixekizumab 80 mg Q4W and Q2W versus placebo were observed for all major secondary endpoints in SPIRIT-P1 with the exception of the change from baseline to week 12 in LEI ($p > .25$ for each comparison) and the change from baseline to week 12 in itch NRS*'.[1] A summary of further results relevant to the NICE scope is given below in Table 4.6.

Table 4.5: Main results of the SPIRIT trials

	SPIRIT-P1				SPIRIT-P2		
Endpoint	**Placebo n=106**	**ADA40 q2w n=101**	**IXE80 q4w n=107**	**IXE80 q2w n=103**	**Placebo n=118**	**IXE80 q4w n=122**	**IXE80 q2w n=123**
ACR 20 response rate at week 24							
ACR 20, n (%)	32 (30.2)	58 (57.4)	62 (57.9)	64 (62.1)	23 (19.5)	65 (53.3)	59 (48.0)
OR (95% CI) p-value	-	3.16 (1.78, 5.60) <0.001	3.24 (1.84, 5.72) <0.001	3.88 (2.18, 6.91) <0.001	-	4.74 (2.65, 8.48) <0.001	3.79 (2.12, 6.78) <0.001
PsARC response rate at week 12							
n (%)	36 (34.0%)	59 (58.4%)	59 (55.1%)	63 (61.2%)	28 (23.7%)	61 (50.0%)	64 (52.0%)
OR (95%CI) p-value	-	2.8 (1.59, 5.02) <0.001	2.5 (1.41, 4.34) 0.002	3.2 (1.81, 5.71) <0.001	-	3.26 (1.87, 5.69) <0.001	3.47 (1.99, 6.05) <0.001
PsARC response rate at week 24							
n (%)	34 (32.1%)	59 (58.4%)	62 (57.9%)	68 (66.0%)	24 (20.3%)	68 (55.7%)	58 (47.2%)
OR (95%CI) p-value	-	3.0 (1.70, 5.35) <0.001	3.0 (1.69, 5.22) <0.001	(2.36, 7.57) <0.001	-	5.0 (2.81, 8.90) <0.001	3.55 (1.99, 6.32) <0.001
Response rate at week 12							
PASI 75							
PASI 75, n (%)	5 (7.5)	23 (33.8)	55 (75.3)	41 (69.5)	7 (10.4)	39 (57.4)	42 (61.8)
OR (95%CI) p-value	-	6.3 (2.2, 17.95) <0.001	38.8 (13.36, 112.72) <0.001	29.1 (9.87, 85.53) <0.001	-	14.03 (5.28, 37.27) <0.001	16.67 (6.28, 44.24) <0.001
PASI 90							
PASI 90, n (%)	1 (1.5)	15 (22.1)	38 (52.1)	34 (57.6)	4 (6.0)	26 (38.2)	29 (42.6)
OR (95%CI) p-value	-	18.5 (2.36, 144.84) 0.006	71.6 (9.40, 545.52) <0.001	91.8 (11.86, 710.43) <0.001	-	10.52 (3.36, 32.95) NA	17.96 (5.32, 60.62) <0.001

PASI 100							
PASI 100, n (%)	1 (1.5)	10 (14.7)	23 (31.5)	24 (40.7)	4 (6.0)	13 (19.1)	16 (23.5)
OR (95%CI) p-value	-	10.9 (1.35, 88.49) 0.025	29.7 (3.86, 228.18) 0.001	46.1 (5.94, 357.57) <0.001	-	3.82 (1.16, 12.55) NA	5.87 (1.78, 19.32) 0.004
ACR response rates at week 12							
ACR 20							
ACR 20, n (%)	33 (31.1)	52 (51.5)	61 (57.0)	62 (60.2)	26 (22.0)	61 (50.0)	59 (48.0)
OR (95%CI) p-value	-	2.4 (1.34, 4.17) 0.003	2.9 (1.66, 5.14) <0.001	3.3 (1.88, 5.89) <0.001	-	3.56 (2.02, 6.26) <0.001	3.28 (1.85, 5.79) <0.001
ACR 50							
ACR 50, n (%)	5 (4.7)	30 (29.7)	36 (33.6)	41 (39.8)	4 (3.4)	38 (31.1)	41 (33.3)
OR (95%CI) p-value	-	8.6 (3.19, 23.35) <0.001	10.3 (3.83, 27.48) <0.001	13.4 (5.01, 35.77) <0.001	-	14.61 (4.82, 44.28) <0.001	14.58 (4.98, 42.68) <0.001
ACR 70							
ACR 70, n (%)	0	18 (17.8)	16 (15.0)	17 (16.5)	2 (1.7)	18 (14.8)	13 (10.6)
OR (95%CI) p-value	-	NA	NA	NA	-	11.9 (2.47, 57.41) 0.002	7.46 (1.63, 34.22) NA
ACR response rates at week 24							
ACR 50							
ACR 50, n (%)	16 (15.1)	39 (38.6)	43 (40.2)	48 (46.6)	6 (5.1)	43 (35.2)	41 (33.3)
OR (95%CI) p-value	-	3.6 (1.83, 6.94) <0.001	3.8 (1.97, 7.38) <0.001	5.0 (2.57, 9.64) <0.001	-	10.83 (4.31, 27.23) <0.001	9.31 (3.75, 23.13) <0.001
ACR 70							
ACR 70, n (%)	6 (5.7)	26 (25.7)	25 (23.4)	35 (34.0)	0 (0.0)	27 (22.1)	15 (12.2)
OR (95%CI) p-value	-	5.8 (2.27, 14.79) <0.001	5.1 (2.00, 13.09) <0.001	8.7 (3.46, 21.80) <0.001	-	NA	NA

HAQ-DI Change from baseline to week 12							
Patients in model	n=100	n=95	n=96	n=95	n=102	n=114	n=113
Endpoint (LSM) Change (SE)	-0.13 (0.05)	-0.35 (0.05)	-0.37 (0.05)	-0.47 (0.05)	-0.1 (0.06)	-0.4 (0.06)	-0.4 (0.06)
LSM Difference (95% CI)	-	-0.22 (-0.35, -0.09)	-0.24 (-0.36, -0.12)	-0.34 (-0.47, -0.21)	-	-0.3 (-0.5, -0.2)	-0.3 (-0.4, -0.1)
p-value	-	<0.001	<0.001	<0.001	-	<0.001	<0.001

Source: Based on Tables 13-18, of the CS[1]

Data are least squares mean (SE), n (%), or % (CI). Data were analysed with the Cochran-Mantel-Haenszel test with non-responder imputation for response rates and mixed-models repeated-measure analysis for least squares mean change from baseline HAQ-DI

ACR = American College of Rheumatology; ADA = adalimumab; CI = confidence interval; CS = company submission; HAQ-DI = Health Assessment Questionnaire-Disability Index; IXE = ixekizumab; LSM = least squares mean; NA = not available; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; SE = standard error; q2w = once every two weeks; q4w = once every four weeks

Table 4.6: Further results of the SPIRIT trials

	SPIRIT-P1				SPIRIT-P2		
Endpoint	**Placebo n=106**	**ADA40 q2w n=101**	**IXE80 q4w n=107**	**IXE80 q2w n=103**	**Placebo n=118**	**IXE80 q4w n=122**	**IXE80 q2w n=123**
mTSS from baseline to week 24 change (SE)	n = 61	n = 83	n = 82	n = 85	NA	NA	NA
	0.49 (0.09)	0.10 (0.09)	0.17 (0.08)	0.08 (0.08)	NA	NA	NA
Minimal disease activity at week 24	n = 106	n = 101	n = 107	n = 103	n = 118	n = 122	n = 123
	16 (15.1)	32 (31.7)	32 (29.9)	42 (40.8)	4 (3.4)	34 (27.9)	29 (23.6)
		OR = 2.61 (1.32 to 5.14)	OR = 2.42 (1.23 to 4.75)	OR = 3.93 (2.03 to 7.64)		OR = 11.58 (3.91 to 34.30)	OR = 8.89 (3.01 to 26.27)
Proportion of patients achieving complete dactylitis resolution at week 24	n = 28	n = 18	n = 39	n = 26	n = 14	n = 28	n = 20
	7 (25.0)	14 (77.8)	31 (79.5)	20 (76.9)	3 (21.4)	21 (75.0)	10 (50.0)
		OR = 10.3 (2.51 to 42.6)	OR = 12.3 (3.79 to 40.1)	OR = 10.0 (2.80 to 36.0)		OR = 16.59 (2.43 to 113.25)	OR = 6.20 (0.92 to 41.76)
Proportion of patients with complete enthesitis resolution at week 24	n = 57	n = 54	n = 68	n = 57	n = 69	n = 68	n = 84
	11 (19.3)	18 (33.3)	29 (42.6)	22 (38.6)	15 (21.7)	24 (35.3)	26 (31.0)
		OR = 2.23 (0.93 to 5.36)	OR = 3.23 (1.42 to 7.35)	OR = 2.66 (1.13 to 6.25)		OR = 2.01 (0.93 to 4.34)	OR = 1.57 (0.74 to 3.34)
Proportion of patients achieving psoriasis nail resolution at week 24	n = 74	n = 71	n = 70	n = 74	n = 73	n = 89	n = 74
	14 (18.9)	28 (39.4)	18 (25.7)	27 (36.5)	5 (6.8)	18 (20.2)	22 (29.7)
		OR = 2.8 (1.32 to 5.98)	OR = 1.50 (0.67 to 3.29)	OR = 2.5 (1.18 to 5.34)		OR = 3.67 (1.26 to 10.65)	OR = 7.33 (2.44 to 21.96)

Source: Based on Appendix P of the CS[28]

ADA = adalimumab; CS = company submission; IXE = ixekizumab; mTSS = modified Total Sharp Score; NA = not available; OR = odds ratio; SE = standard error; q2w = once every two weeks; q4w = once every four weeks

For both SPIRIT studies, subgroup analyses were conducted for the ACR 20 response rate at week 24 (ITT population). A range of subgroups were investigated including demographic characteristics such as gender and age, geographic regions, use of conventional DMARDs, prior TNFi use, baseline severity, duration of PsA and presence of bone erosion.[28] The company found that efficacy was shown '*regardless of age, race, baseline BMI, geographic region, baseline CRP, previous PsA therapy status, concomitant DMARD therapy (current use at baseline), cDMARD experience at baseline, duration since PsA onset, in both SPIRIT studies*'.[1]

The company noted a statistically significant interaction (p=0.01) between treatment and subgroup in the baseline weight subgroup in SPIRIT-P1 where there was a greater difference between ixekizumab and placebo for patients weighing between 80 and 100 kg compared to those weighing less than 80 kg, and there were no significant between treatment differences for patients weighing more than 100 kg. For SPIRIT-P2 there was a statistically significant interaction for the gender subgroup (p=0.008) although the size of the difference was not clinically significant. More males than females had an ACR 20 response at 24 weeks with ixekizumab.

The company conducted further post-hoc subgroup analysis based on concomitant methotrexate use. Treatment by subgroup interaction (concomitant methotrexate versus no concomitant methotrexate) was not significant for ACR 20 response (Table 4.7).[1]

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] of 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).[1]

Table 4.7: Subgroup results of the SPIRIT trials – ACR response rate at week 24

	SPIRIT-P1					SPIRIT-P2			
Endpoint	**p-value interaction[a]**	**Placebo n=106 n (%)**	**ADA40 q2w n=101 n (%)**	**IXE80 q4w n=107 n (%)**	**IXE80 q2w n=103 n (%)**	**p-value interaction[a]**	**Placebo n=118 n (%)**	**IXE80 q4w n=122 n (%)**	**IXE80 q2w n=123 n (%)**
Gender									
Male	0.436	16 (33.3)	36 (70.6)	28 (62.2)[b]	34 (70.8)[b]	0.008	7 (12.5%)	39 (61.9%)	31 (62.0%)
Female		16 (27.6)	22 (44.0)[c]	34 (54.8)[b]	30 (54.5)[c]		16 (25.8%)	26 (44.1%)	28 (38.4%)
Age									
< 65 years	0.883	30 (32.3)	54 (60.7)[c]	61 (60.4)[c]	58 (65.2)[c]	NA	18 (17.0%)	49 (52.1%)	51 (50.5%)
≥ 65 and < 75 years		2 (15.4)	4 (36.4)	1 (16.7)	5 (50.0)		5 (45.5%)	16 (59.3%)	7 (35.0%)
≥75 years		0	0	0	1 (33.3)		0 (0.0%)	0 (0.0%)	1 (50.0%)
Race									
American Indian or Alaska Native	0.992	1 (50.0)	2 (66.7)	1 (50.0)	2 (100.0)	NA		-	-
Asian		0	2 (66.7)	1 (50.0)	4 (80.0)		0 (0.0%)	4 (57.1%)	6 (85.7%)
Black or African American		0	0	0	0		0 (0.0%)	1 (100.0%)	0 (0.0%)
Native Hawaiian or other Pacific Islander		0	0	0	0		0 (0.0%)	0 (0.0%)	0 (0.0%)
White		31 (31.3)	54 (56.8)[c]	59 (57.8)[c]	58 (60.4)[c]		22 (20.4%)	59 (53.2%)	52 (46.0%)
Multiple		0	0	1 (100.0)	0		1 (50.0%)	1 (50.0%)	0 (0.0%)
Ethnicity									
Hispanic or Latino	NA	NA	NA	NA	NA	NA	2 (18.2%)	5 (45.5%)	4 (30.8%)

Not Hispanic or Latino		NA	NA	NA	NA		21 (19.8%)	59 (54.1%)	54 (49.5%)
Not Reported		NA	NA	NA	NA		0 (0.0%)	1 (50.0%)	1 (100.0%)
Baseline weight									
< 80 kg	0.010[b]	17 (38.6)	19 (57.6)	24 (55.8)	36 (66.7)[b]	0.431	9 (23.7%)	21 (46.7%)	21 (38.2%)
≥ 80 kg and < 100 kg		8 (17.8)	17 (47.2)[b]	30 (69.8)[c]	22 (64.7)[c]		8 (17.0%)	25 (61.0%)	26 (60.5%)
≥ 100 kg		7 (41.2)	22 (68.8)	8 (38.1)	6 (40.0)		6 (18.2%)	19 (52.8%)	12 (48.0%)
Baseline BMI									
Underweight	0.864	0	1 (100.0)	0	2 (100.0)	NA	0	0 (0.0%)	0
Normal		10 (43.5)	10 (62.5)	18 (66.7)	21 (63.6)		3 (17.6%)	12 (54.5%)	16 (51.6%)
Overweight		11 (24.4)	17 (53.1)[d]	18 (60.0)[b]	19 (65.5)[c]		8 (17.8%)	19 (51.4%)	19 (46.3%)
Obese		8 (25.8)	22 (56.4)	17 (51.5)[d]	20 (60.6)[b]		10 (23.3%)	30 (58.8%)	21 (48.8%)
Extreme obese		3 (50.0)	8 (61.5)	7 (53.8)	1 (20.0)		2 (15.4%)	4 (36.4%)	2 (33.3%)
Geographic region									
Europe	0.156	11 (36.7)	11 (39.3)	15 (55.6)	16 (61.5)	NA	10 (20.0%)	26 (53.1%)	22 (44.0%)
United States		NA	NA	NA	NA		13 (21.7%)	33 (50.8%)	29 (46.0%)
Rest of the world		21 (27.6)	47 (64.4)[c]	47 (58.8)[c]	48 (62.3)[c]		0 (0.0%)	6 (75.0%)	8 (80.0%)
Baseline CRP									
≤ 6 mg/l	0.274	14 (34.1)	21 (53.8)	18 (47.4)	26 (53.1)	0.083	15 (25.4%)	27 (45.8%)	35 (50.0%)
> 6 mg/l		18 (27.7)	37 (59.7)[c]	44 (63.8)[c]	38 (70.4)[c]		8 (14.0%)	36 (60.0%)	24 (45.3%)
Previous PsA therapy status									
Yes	0.949	22 (30.1)	38 (55.9)[b]	42 (59.2)[c]	48 (61.5)[c]				
No		10 (30.3)	20 (60.6)[d]	20 (55.6)	16 (64.0)[d]				
Concomitant DMARD therapy (current use at baseline)									
Yes	0.321	22 (31.9)	43 (64.2)[c]	38 (55.9)[b]	39 (61.9)[c]	0.511	12 (23.1%)	30 (50.0%)	34 (46.6%)

No		10 (27.0)	15 (44.1)	24 (61.5)[b]	25 (62.5)[b]		11 (16.7%)	35 (56.5%)	25 (50.0%)
Concomitant methotrexate (current use at baseline)[e]									
Yes	0.199	18 (30.5)	38 (66.7)[c]	31 (54.4)[d]	33 (62.3)[c]	NA	7 (17.5)	14 (50.0)[b]	31 (50.8)[c]
No		14 (29.8)	20 (45.5)	31 (62.0)[b]	31 (62.0)[b]		16 (20.5)	41 (55.4)[c]	28 (45.2)[b]
Conventional DMARD experience at baseline									
Current use at baseline	0.505	22 (31.9)	43 (64.2)[c]	38 (55.9)[b]	39 (61.9)[c]	NA	NA	NA	NA
Past use at baseline		7 (29.2)	10 (50.0)	16 (72.7)[b]	14 (60.9)[d]		NA	NA	NA
DMARD naïve		3 (23.1)	5 (35.7)	8 (47.1)	11 (64.7)[d]		NA	NA	NA
Prior TNFi experience									
Inadequate responder to 1 TNFi	NA	NA	NA	NA	NA	0.519	12 (17.6%)	39 (54.9%)	28 (43.1%)
Inadequate responder to 2 TNFi		NA	NA	NA	NA		7 (17.1%)	21 (51.2%)	24 (52.2%)
Intolerance to a TNFi		NA	NA	NA	NA		4 (44.4%)	5 (50.0%)	7 (58.3%)
Duration since PsA onset									
0 to < 2 years	0.415	5 (27.8)	8 (53.3)	8 (57.1)	7 (50.0)	NA	NA	NA	NA
≥ 2 to < 5 years		5 (38.5)	13 (59.1)	11 (45.8)	12 (44.4)	0.374	7 (26.9%)	15 (62.5%)	12 (42.9%)
≥ 5 years		22 (29.3)	37 (57.8)[c]	43 (62.3)[c]	45 (72.6)[c]		16 (17.4%)	50 (51.0%)	47 (49.5%)
Tobacco current use at baseline									
Yes	NA	NA	NA	NA	NA	0.987	6 (25.0%)	15 (60.0%)	14 (53.8%)
No		NA	NA	NA	NA		17 (18.1%)	50 (51.5%)	45 (46.4%)

Baseline percentage of BSA									
< 3%	NA	NA	NA	NA	NA	0.638	9 (18.0%)	25 (54.3%)	21 (42.0%)
≥ 3%		NA	NA	NA	NA		14 (20.9%)	34 (50.0%)	34 (50.0%)
Moderate to severe psoriasis									
Yes	NA	NA	NA	NA	NA	0.913	2 (18.2%)	9 (60.0%)	6 (50.0%)
No		NA	NA	NA	NA		21 (19.6%)	56 (52.3%)	53 (47.7%)
Current enthesitis									
Yes	NA	NA	NA	NA	NA	0.657	17 (20.0%)	46 (51.7%)	49 (49.5%)
No		NA	NA	NA	NA		6 (18.2%)	19 (57.6%)	10 (41.7%)
Baseline LDI									
Basic group: = 0	NA	NA	NA	NA	NA	0.889	21 (20.2%)	50 (53.2%)	50 (48.5%)
Basic group: > 0		NA	NA	NA	NA		2 (14.3%)	15 (53.6%)	9 (45.0%)

Source: Figures 5 and 6 of the CS[1]; Tables 38 and 39 of the CS appendix[28]

Footnote: [a] A logistic regression analysis with treatment, subgroup and the interaction of treatment by subgroup included as factors, and the treatment by subgroup interaction is tested at the 10% significance level. [b] $p<0.01$ versus placebo; [c] $p\leq0.001$ versus placebo; [d] $p<0.05$ versus placebo; [e] post-hoc analysis. NB: If no group within the subgroup is <10% of the total population, only summary statistics are provided for that subgroup (that is, no inferential testing and p-value is presented as NA). Footnotes b to d only reported for SPIRIT-P1 and post-hoc analysis of SPIRIT-P2.

ADA = adalimumab; BMI = body mass index; BSA = body surface area; CRP = c-reactive protein; CS = company submission; DMARD = disease-modifying anti-rheumatic drug; IXE = ixekizumab; kg = kilogram; LDI = Leeds Dactylitis Index; mg = milligram; NA = not available; PsA = psoriatic arthritis; q2w = once every two weeks; q4w = once every four weeks; TNFi = Tumour necrosis factor inhibitor

ERG comment:

- Both trials demonstrated superiority of ixekizumab in relation to placebo on outcomes of importance to patients. However, when interpreting 24 week results it should be noted that patients who were identified as inadequate responders at week 16 were required to modify their concomitant medication by adjusting the dose of existing medication(s) and/or introduction of new medication(s). The company stated that '*Modifications made at week 16 must have remained in place and unchanged throughout the remainder of the double-blind period of the study. The following medications were eligible for modification: NSAIDs and opiate analgesics, cDMARDs, and oral corticosteroids. Additionally, one intra-articular injection of a corticosteroid was permitted for Inadequate Responders*'.[1]However, only data of non-responders up to 16 weeks were included.
- The company demonstrated efficacy of ixekizumab in relation to placebo for a population reflective of NICE current guidance on use of bDMARDs after failure of two cDMARDs. However, this analysis was based on [redacted] patients across both trials so percentages of responders should be treated with some caution.

4.2.6 Safety results of the SPIRIT trials

Safety data were obtained from 416 patients (including 209 using ixekizumab) who took at least one dose of study drug in SPIRIT-P1 and by 363 patients (including 247 using ixekizumab) in SPIRIT-P2. Data on adverse events are presented in the CS for the 24-week double blind period of the two SPIRIT trials (see Table 4.8) and for the extension period (up to week 52). The company presented data on study drug discontinuation, adverse events, serious adverse events and discontinuations due to AEs. A serious adverse event (SAE) was defined as any AE '*that resulted in one of the following outcomes: death, initial or prolonged inpatient hospitalisation, a life-threatening experience (immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly/birth defect, or any other outcome considered significant by the investigator for any other reason*'.[1] Adverse events of special interest were also gathered and the main ones as presented by the company are listed in Table 4.8.

Patients experienced more adverse events in the ixekizumab groups than in the placebo group in both SPIRIT trials (SPIRIT-P1: IXE 80 q4w 66.4%, IXE 80 q2w 65.7%, adalimumab 64.4%, placebo 47.2%; SPIRIT-P2: IXE 80 q4w 68%, IXE 80 q2w 73.2%, placebo 64.4%). In SPIRIT-P1, the differences between both ixekizumab groups and placebo were statistically significant. Similarly, regarding AEs possibly related to the study drug, numbers were higher in both ixekizumab groups compared to placebo in both SPIRIT trials (SPIRIT-P1: IXE 80 q4w 29.9%, IXE 80 q2w 36.3%, adalimumab 20.8%, placebo 11.3%; SPIRIT-P2: IXE 80 q4w 28.7%, IXE 80 q2w 40.7%, placebo 24.6%). 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 appeared to be attributable to the drug, see Table 4.8.

The company commented that adverse events across the two SPIRIT trials were mainly of mild or moderate severity and it can be seen from Table 4.8 that SAEs were relatively uncommon (SPIRIT-P1: IXE 80 q4w 5.6%, IXE 80 q2w 2.9%, adalimumab 5.0%, placebo 1.9%; SPIRIT-P2: IXE 80 q4w 2.5%, IXE 80 q2w 6.5%, placebo 3.4%). 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 (25.7% of all patients in SPIRIT-P1 and 35.5% in SPIRIT-P2). Injection site reactions were statistically significantly

more common with ixekizumab than placebo in both, SPIRIT-P1 (IXE 80 q4w 12.1%, IXE 80 q2w 15.7%, adalimumab 2.0%, placebo 0%) and SPIRIT-P2 (IXE 80 q4w 11.5%, IXE 80 q2w 23.6%, placebo 4.2%).

A total of 381 patients in SPIRIT-P1 and 310 in SPIRIT-P2 entered the extension phase of the trials (up to week 52). As there is no placebo comparison at this stage, it is most useful to examine if the pattern of events seen in the double-blind phase continues in the extension phase. In SPIRIT-P1 in those receiving IXE 80 q4w throughout, the incidence of AEs was 55.7% and in those receiving IXE 80 q2w throughout the incidence of AEs was 56.3% compared to 66.4% and 65.7% up to week 24. In SPIRIT-P2 in those receiving IXE 80 q4w, the incidence of AEs was 71.2% and in those receiving IXE 80 q2w the incidence of AEs was 63.6% compared to 68% and 73.2% up to week 24. The company reported that most events continued to be mild or moderate.[1] Infections and injection site reactions continued to be the most frequently reported events. The company further commented that the safety profile of ixekizumab up to two years of treatment in SPIRIT-P1was similar to that obtained in the double-blind period. In SPIRIT-P2, one death caused by cardiorespiratory arrest was reported in the group randomised to placebo then to IXE 80 q2w. This event was reported in detail in the CSR supplied by the company and was not considered to be study-drug related.[33]

In response to the request for clarification, results for a network meta-analysis of adverse events were presented, see section 4.3 for details.[25]

Table 4.8: Overview of AEs in SPIRIT P1 and P2 – double blind period

	SPIRIT-P1				SPIRIT-P2		
Endpoint	**Placebo** (n=106), n (%)	**Adalimumab** (n=101), n (%)	**IXE80 q4w** (n=107), n (%)	**IXE80 q2w** (n=102), n (%)	**PBO** (n=118), n (%)	**IXE80 q4w** (n=122), n (%)	**IXE80 q2w** (n=123), n (%)
Patients with ≥1 TEAE	50 (47.2)	65 (64.4)	71 (66.4)	67 (65.7)	76 (64.4)	83 (68.0)	90 (73.2)
Discontinuations from study drug due to AE	2 (1.9)	2 (2.0)	2 (1.9)	4 (3.9)	6 (5.1)	5 (4.1)	8 (6.5)
Deaths	0	0	0	0	0	0	0
SAEs	2 (1.9)	5 (5.0)	6 (5.6)	3 (2.9)	4 (3.4)	3 (2.5)	8 (6.5)
TEAEs possibly related to study	12 (11.3)	21 (20.8)	32 (29.9)	37 (36.3)	29 (24.6)	35 (28.7)	50 (40.7)
Treatment-emergent AEs of Special Interest							
Cytopenias	6 (5.7)	4 (4.0)	1 (0.9)	4 (3.9)	0	0	0
Hepatic	7 (6.6)	13 (12.9)	5 (4.7)	9 (8.8)	2 (1.7)	2 (1.6)	5 (4.1)
Infection	27 (25.5)	26 (25.7)	30 (28.0)	24 (23.5)	35 (29.7)	47 (38.5)	47 (38.2)
Injection-site reactions	5 (4.7)	6 (5.9)	26 (24.3)	27 (26.5)	5 (4.2)	14 (11.5)	29 (23.6)
Allergic reactions / Hypersensitives	3 (2.8)	5 (5.0)	2 (1.9)	5 (4.9)	6 (5.1)	13 (10.7)	14 (11.4)
Cerebrocardiovascular events	0	3 (3.0)	0	0	2 (1.7)	0	0
Malignancies	1 (0.9)	1 (1.0)	0	0	0	2 (1.6)	0
Depression	0	1 (1.0)	0	0	3 (2.5)	2 (1.6)	2 (1.6)

Source: Tables 27 and 29 of the CS[1]

AE = adverse event; IXE = ixekizumab; q2w = once every two weeks; q4w = once every four weeks; SAE = serious adverse event; TEAE = treatment emergent adverse event

ERG comment:

- In total, 456 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 comparators. One analysis was performed for the biologic-naïve patient population and another for the

biologic-experienced patient population. Trials for the comparator treatments were identified through a systematic review as described in section 4.1 of this report.

The outcomes included in the NMA were:

- Joint response measured by the proportion of patients achieving PsARC response
- Functional capacity measured by the absolute change from baseline in HAQ-DI score conditional on achieving PsARC response
- Skin response measured by PASI 50/75/90/100

Additional NMA results were provided in the clarification response for ACR 20, 50 and 70 responses and adverse events.[25]

NMAs were performed using Bayesian methods following the guidance provided by the NICE Decision Support Unit Technical Support Document series.[35] Data for each treatment group were modelled using an arm-based likelihood. Bayesian models were performed in JAGS via R for the PsARC and PASI outcomes, and in a Lilly analysis tool based on R and OpenBUGs for change in HAQ-DI conditional on PsARC response.

PsARC response was modelled using a binomial likelihood model with a logit link and PASI 50/75/90/100 was modelled using multinomial probit model using conditional binomial likelihood. In the multinomial model, it is assumed that the treatment effect on the probit scale is the same for all four PASI outcomes so information can be borrowed from different PASI outcomes even if a particular study does not report one of the PASI outcomes. For both outcomes the primary analysis used 12-week results for ixekizumab, 16-week results were included in a sensitivity analysis. The Bayesian model used vague priors of normal (0, 10000) for trial baselines and treatment effects and uniform (0, 5) for binomial, multinomial and continuous standard deviations and multinomial categories. Three chains and a burn-in period of 30,000 runs were used with an additional 30,000 runs and a thinning parameter of 2 used to obtain parameter estimates.

Continuous outcomes such as the change from baseline in HAQ-DI were analysed using a normal model with an identity link. Three chains and a burn-in period of 10,000 runs were used with an additional 20,000 runs used to obtain parameter estimates.

Meta-regression controlling for baseline risk by including the response on placebo as a covariate were also performed for PsARC and PASI outcomes for the biologic-naïve analysis. There were insufficient studies available to perform these analyses for the biologic-experienced population.

For all analyses both fixed and random effects models were run and model fit was compared with the Deviance Information Criterion (DIC), the model with the lowest DIC was considered the best fit after accounting for the number of model parameters and good convergence with little autocorrelation. If the difference in DIC was less than five points, or the network was small or there were convergence difficulties then the fixed effect model was preferred. As many networks had edges consisting of only one study, it was difficult to accurately estimate between study heterogeneity in the random effects models. Fixed effect model results were presented and used in the economic model. Random effects model results were provided in the clarification response[25]

4.3.1 Biologic-naïve population

Details of the trials included in the NMA for the biologic-naïve population are provided in Table 4.9. The network diagram of trial evidence for the PsARC and PASI outcomes is shown in Figure 4.1 and the network diagram for the change from baseline in HAQ-DI is shown in Figure 4.2.

The fixed effect NMA results for PsARC response between 12 and 16 weeks are shown in Table 4.10. These show that the estimated probability of achieving a PsARC response was [redacted] for ixekizumab 80 mg q2w and [redacted] for ixekizumab 80 mg q4w compared to [redacted] for placebo, both ixekizumab results were significantly greater than placebo. However, the probability of a PsARC response with ixekizumab 80 mg was [redacted] than for all other treatments except [redacted]. [redacted] had the greatest probability of a PsARC response at [redacted] and [redacted] respectively. Results using 16-week ixekizumab results were similar with an estimated probability of a PsARC response of [redacted] (95% credible interval (CrI) [redacted]) for ixekizumab 80 mg q2w and [redacted] (95% CrI [redacted]) for ixekizumab 80 mg q4w.

Table 4.9: Trials included in NMA for the bDMARD-naïve population

Trial	First author, year	Treatment arm	Time (weeks)	PsARC	PASI 50	PASI 75	PASI 90	PASI 100	HAQ-DI
ADEPT	Mease 2005[36]	Adalimumab 40 mg q2w	12	Yes	Yes	Yes	Yes	No	Yes
ADEPT	Mease 2005[36]	Placebo	12	Yes	Yes	Yes	Yes	No	Yes
FUTURE 2*	Thom 2016[37]	Placebo	12	Yes	Yes	Yes	Yes	No	Yes
FUTURE 2*	Thom 2016[37]	Secukinumab 150 mg q4w	12	Yes	Yes	Yes	Yes	No	Yes
FUTURE 2*	Thom 2016[37]	Secukinumab 300 mg q4w	12	Yes	Yes	Yes	Yes	No	Yes
Genovese 2007	Genovese 2007[38]	Adalimumab 40 mg q2w	12	Yes	No	No	No	No	Yes
Genovese 2007	Genovese 2007[38]	Placebo	12	Yes	No	No	No	No	Yes
GO-REVEAL	Kavanaugh 2009[39]	Golimumab 50 mg q4w	14	Yes	Yes	Yes	Yes	No	Yes
GO-REVEAL	Kavanaugh 2009[39]	Placebo	14	Yes	Yes	Yes	Yes	No	Yes
IMPACT	Antoni 2005[40]	Infliximab 5 mg/kg q8w	16	Yes	Yes	Yes	Yes	No	Yes
IMPACT	Antoni 2005[40]	Placebo	16	Yes	Yes	Yes	Yes	No	Yes
IMPACT 2	Antoni 2005[41]	Infliximab 5 mg/kg q8w	14	Yes	Yes	Yes	Yes	No	Yes
IMPACT 2	Antoni 2005[41]	Placebo	14	Yes	Yes	Yes	Yes	No	Yes
Mease 2000	Mease 2000[42]	Etanercept 25 mg biw/50 mg qiw	12	Yes	Yes	Yes	No	No	Yes
Mease 2000	Mease 2000[42]	Placebo	12	Yes	Yes	Yes	No	No	Yes
Mease 2004	Mease 2004[43]	Etanercept 25 mg biw/50 mg qiw	12	Yes	No	No	No	No	Yes
Mease 2004	Mease 2004[43]	Placebo	12	Yes	No	No	No	No	Yes
OPAL-BROADEN	Mease 2016[44]	Adalimumab 40 mg q2w	12	No	No	Yes	No	No	Yes
OPAL-BROADEN	Mease 2016[44]	Placebo	12	No	No	Yes	No	No	Yes
PALACE 1*	Kavanaugh 2014[45]	Apremilast 30 mg bid	16	Yes	Yes	Yes	No	No	Yes
PALACE 1*	Kavanaugh 2014[45]	Placebo	16	Yes	Yes	Yes	No	No	Yes
PALACE 2*	Cutolo 2016[46]	Apremilast 30 mg bid	16	Yes	Yes	Yes	No	No	Yes

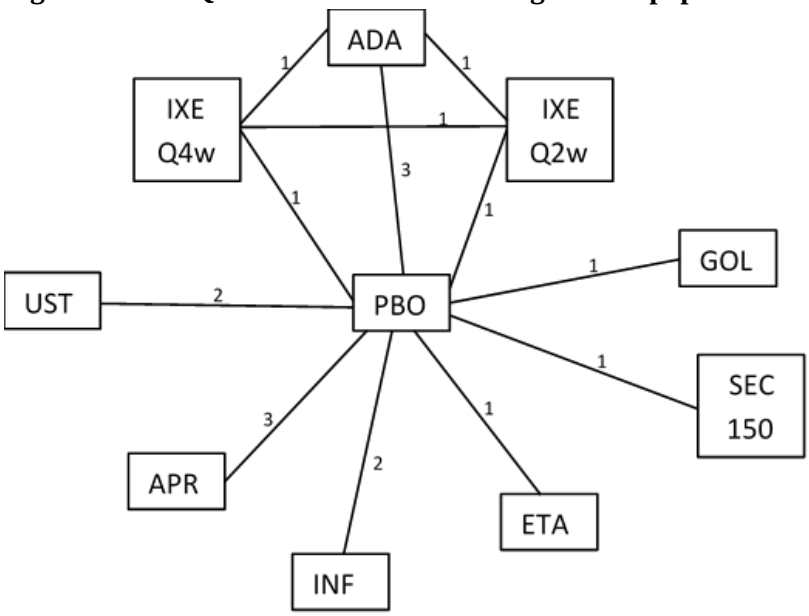
Trial	First author, year	Treatment arm	Time (weeks)	PsARC	PASI 50	PASI 75	PASI 90	PASI 100	HAQ-DI
PALACE 2*	Cutolo 2016[46]	Placebo	16	Yes	Yes	Yes	No	No	Yes
PALACE 3	Edwards 2016[47]	Apremilast 30 mg bid	16	No	Yes	Yes	No	No	Yes
PALACE 3	Edwards 2016[47]	Placebo	16	No	Yes	Yes	No	No	Yes
RAPID-PsA*	Mease 2014[48]	Certolizumab pegol pooled doses	12	Yes	Yes	Yes	Yes	No	No
RAPID-PsA*	Mease 2014[48]	Placebo	12	Yes	Yes	Yes	Yes	No	No
SPIRIT-P1	Eli Lilly and Company[49, 50]	Adalimumab 40 mg q2w	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Ixekizumab 80 mg q2w	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Ixekizumab 80 mg q4w	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Placebo	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Adalimumab 40 mg q2w	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Ixekizumab 80 mg q2w	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Ixekizumab 80 mg q4w	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Placebo	16	Yes	No	Yes	Yes	Yes	Yes

Source: Based on Table 20 of the CS[1]
Footnote: * Outcomes were not reported for bDMARD-naive subgroup at the response assessment time point specified in NICE guidance therefore overall population data are used
bDMARD = biologic disease-modifying anti-rheumatic drug; bid = twice daily; biw = twice weekly; CS = company submission; HAQ-DI = Health Assessment Questionnaire-Disability Index; kg = kilogram; mg = milligram; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; 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; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks; qiw = once weekly

Figure 4.1: PsARC and PASI network for the biologic-naïve population

Source: Based on Figure 7 of the CS[1]
bid = twice daily; CS = company submission; kg = kilogram; mg = milligram; PASI = Psoriasis Area and Severity Index; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks; qiw = once weekly
Circle size is proportional to the number of patients per treatment, line width is proportional to the number of studies per pairwise comparison of treatments.

Figure 4.2: HAQ-DI network for the biologic-naïve population



Source: Based on Figure 4 of the CS[1]
ADA = adalimumab; APR = apremilast; ETA = etanercept; GOL = golimumab; INF = infliximab; IXE = ixekizumab; PBO = placebo; q2w = once every two weeks; q4w = once every four weeks; SEC = secukinumab; UST = ustekinumab

Table 4.10: PsARC response for the biologic-naïve population

Treatment	PsARC (95% CrI)
Placebo	[redacted]
Adalimumab 40 mg q2w	[redacted]
Apremilast 30 mg bid	[redacted]
Certolizumab pegol pooled doses	[redacted]
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]

Source: Based on Table 21 of the of the CS[1]
bid = twice daily; biw = twice weekly; CrI = credible interval; CS = company submission; mg = milligram; PsARC = Psoriatic Arthritis Response Criteria; qiw = once weekly; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks

The fixed effect NMA results for PASI response are shown in Table 4.11. These show that for ixekizumab 80 mg q2w the estimated probability of achieving a PASI 50 response was [redacted], [redacted] for PASI 75, [redacted] for PASI 90 and [redacted] for PASI 100. For ixekizumab 80 mg q4w these results were [redacted] for PASI 50, [redacted] for PASI 75, [redacted] for PASI 90 and [redacted] for PASI 100. [redacted] had the highest overall probability of achieving each PASI response. Results using 16-week ixekizumab results were similar.

Table 4.11: PASI response for the biologic-naïve population

Treatment	PASI 50 (95% CrI)	PASI 75 (95% CrI)	PASI 90 (95% CrI)	PASI 100 (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg q2w	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast 30 mg bid	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol pooled doses	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 25 mg biw/ 50 mg qiw	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab 50 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg q8w	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q2w	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	PASI 50 (95% CrI)	PASI 75 (95% CrI)	PASI 90 (95% CrI)	PASI 100 (95% CrI)
Secukinumab 150 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 22 of the of the CS[1]
bid = twice daily; biw = twice weekly; CrI = credible interval; CS = company submission; mg = milligram; PASI = Psoriasis Area and Severity Index; qiw = once weekly; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks

The fixed effect NMA results for ACR response are shown in Table 4.12. These show that for ixekizumab 80 mg q2w the estimated probability of achieving an ACR 20 response was [redacted] an ACR 50 response was [redacted] and an ACR 70 response was [redacted]. For ixekizumab 80 mg q4w, the estimated probability of achieving an ACR 20 response was [redacted] an ACR 50 response was [redacted] and an ACR 70 response was [redacted]. [redacted] had the highest overall probability of achieving each ACR response.

Table 4.12: ACR response for the biologic-naïve population

Treatment	ACR20 (95% CrI)	ACR50 (95% CrI)	ACR70 (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg q2w	[redacted]	[redacted]	[redacted]
Apremilast 30 mg bid	[redacted]	[redacted]	[redacted]
Certolizumab pegol pooled doses	[redacted]	[redacted]	[redacted]
Etanercept 25 mg biw/ 50 mg qiw	[redacted]	[redacted]	[redacted]
Golimumab 50 mg q4w	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg q8w	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q2w	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q4w	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg q4w	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg q4w	[redacted]	[redacted]	[redacted]

Source: Based on Table 8 of the response to request for clarification[25]
ACR = American College of Rheumatology; ACR 20 = At least 20% improvement in both tender and swollen joint counts; ACR 50 = At least 50% improvement in both tender and swollen joint counts; ACR 70 = At least 70% improvement in both tender and swollen joint counts; bid = twice daily; biw = twice weekly; CrI = credible interval; mg = milligram; qiw = once weekly; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks

The fixed effect NMA results for the change from baseline in HAQ-DI score conditional on PsARC response are shown in Table 4.13. These show that in general patients who achieved a PsARC response had a greater reduction (improvement) in HAQ-DI compared to those patients who did not achieve a PsARC response. For PsARC responders, the mean change for ixekizumab 80 mg q2w was [redacted] and for ixekizumab 80 mg q4w it was [redacted] both of which were [redacted]. The most effective treatment was [redacted] with an estimated mean change from baseline in HAQ-DI of [redacted].

For PsARC non-responders, the treatments with the greatest improvement in HAQ-DI were [redacted] (mean change [redacted]) and [redacted] (mean change [redacted]) followed by [redacted] (mean change [redacted]). [redacted].

Table 4.13: Change from baseline in HAQ-DI

Treatment	Mean change from baseline – PsARC responders	95% CrI	Mean change from baseline – PsARC non-responders	95% CrI
Placebo	[redacted]	[redacted]	[redacted]	
Ixekizumab q4w	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab q2w	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 23 of the of the CS[1]
CrI = credible interval; CS = company submission; HAQ-DI = Health Assessment Questionnaire-Disability Index; PsARC = Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks

4.3.2 Biologic-experienced population

The trials used in the NMA for the biologic-experienced population are summarised in Table 4.14. The network diagram of trial evidence for PsARC and PASI outcomes is shown in Figure 4.3 and the network including additional evidence for secukinumab and certolizumab pegol (pooled doses) is shown in Figure 4.4. These networks were smaller than for the biologic-naïve population, i.e. mostly containing five or fewer studies.

Table 4.14: Trials included in NMA for the biologic-experienced population

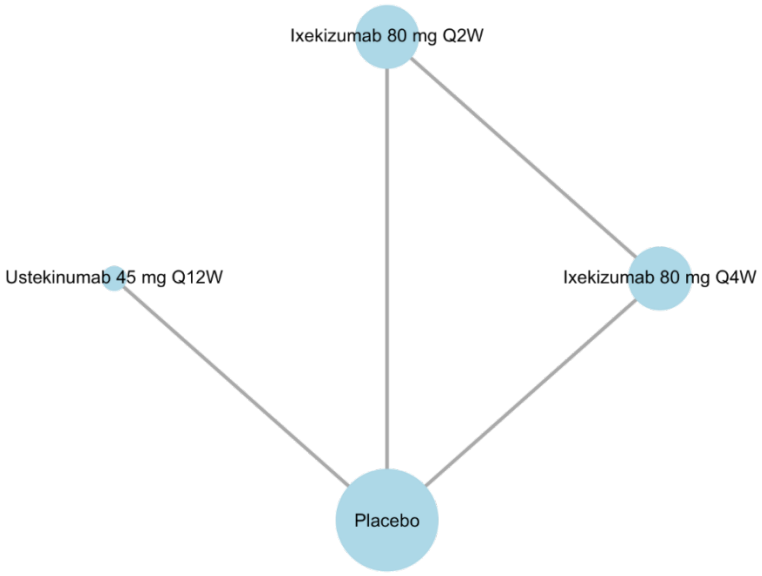
Trial	First author, year	Treatment arm	Timepoint (weeks)	PsARC	PASI 50	PASI 75	PASI 90	PASI 100	HAQ-DI
PSUMMIT 2	Ritchlin 2014[51]	Placebo	24	Yes	No	Yes	No	No	Yes
PSUMMIT 2	Ritchlin 2014[51]	Ustekinumab 45 mg q12w	24	Yes	No	Yes	No	No	Yes
SPIRIT-P2	Nash 2017[32]	Ixekizumab 80 mg q2w	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017[32]	Ixekizumab 80 mg q4w	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017[32]	Placebo	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017[32]	Ixekizumab 80 mg q2w	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017[32]	Ixekizumab 80 mg q4w	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017[32]	Placebo	16	Yes	No	Yes	Yes	Yes	Yes
FUTURE 2*	Thom 2016[37]	Placebo	12	Yes	Yes	Yes	Yes	No	Yes
FUTURE 2*	Thom 2016[37]	Secukinumab 300 mg q4w	12	Yes	Yes	Yes	Yes	No	Yes
RAPID-PsA	Mease 2014[48]	Certolizumab pegol pooled doses	12	Yes	Yes	Yes	Yes	No	No
RAPID-PsA	Mease 2014[48]	Placebo	12	Yes	Yes	Yes	Yes	No	No

Source: Based on Table 24 of the CS[1]

Footnote: * Outcomes were not reported for bDMARD-experienced subgroup at the response assessment time point specified in NICE guidance therefore overall population data are used

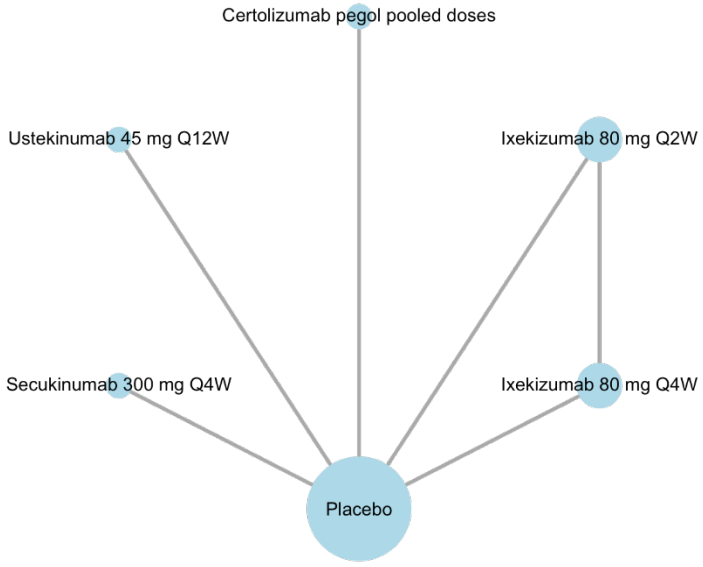
bid = twice daily; biw = twice weekly; CS = company submission; HAQ-DI = Health Assessment Questionnaire-Disability Index; kg = kilogram; mg = milligram; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement 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; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks; q12w = once every 12 weeks; qiw = once weekly

Figure 4.3: PsARC and PASI network for the biologic-experienced population



Source: Based on Figure 8 of the CS[1]
CS = company submission; mg = milligram; PASI = Psoriasis Area and Severity Index; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks
Circle size is proportional to the number of patients per treatment, line width is proportional to the number of studies per pairwise comparison of treatments.

Figure 4.4: PsARC and PASI network for the biologic-experienced population, sensitivity analysis including secukinumab and certolizumab pegol pooled doses



Source: Based on Figure 9 of the CS[1]
CS = company submission; mg = milligram; PASI = Psoriasis Area and Severity Index; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks
Circle size is proportional to the number of patients per treatment, line width is proportional to the number of studies per pairwise comparison of treatments.

The fixed effect NMA results for PsARC response are shown in Table 4.15 for the base-case analysis and Table 4.16 for the sensitivity analysis including overall population data for secukinumab and certolizumab pooled doses. These show that the estimated probabilities of achieving a PsARC response were [redacted] for ixekizumab 80 mg q2w [redacted] and ixekizumab 80 mg q4w [redacted] both of which were [redacted].

When overall population data (for both biologic-naïve and experienced patients) were included for secukinumab and certolizumab pooled doses the estimated proportions achieving a PsARC response were [redacted] for ixekizumab at [redacted] for ixekizumab 80 mg q2w and [redacted] for ixekizumab 80 mg q4w both of which were [redacted]. [redacted] had the greatest probability of PsARC response at [redacted]

Table 4.15: PsARC response for the biologic-experienced population

Treatment	PsARC (95% CrI)
Placebo	[redacted]
Ixekizumab 80 mg q2w	[redacted]
Ixekizumab 80 mg q4w	[redacted]
Ustekinumab 45 mg q12w	[redacted]

Source: Based on Table 25 of the CS[1]
CS = company submission; mg = milligram; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

Table 4.16: PsARC response for the biologic-experienced population including secukinumab and certolizumab pegol (pooled doses)

Treatment	PsARC (95% CrI)
Placebo	[redacted]
Certolizumab pegol pooled doses	[redacted]
Ixekizumab 80 mg q2w	[redacted]
Ixekizumab 80 mg q4w	[redacted]
Secukinumab 300 mg q4w	[redacted]
Ustekinumab 45 mg q12w	[redacted]

Source: Based on Table 29 of the CS appendices[28]
Note: Posterior median (95% credible interval). Mixed biologic naive and experienced population for the following treatments: Apremilast 30 mg bid, Certolizumab pegol pooled doses, Placebo, Secukinumab 150 mg q4w, Secukinumab 300 mg q4w
bid = twice daily; CrI = credible interval; CS = company submission; mg = milligram; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

The fixed effect NMA results for PASI response are shown in Table 4.17 for the base-case analysis and Table 4.18 for the sensitivity analysis including overall population data for secukinumab and certolizumab pooled doses. These show that the estimated probabilities of achieving each PASI response were [redacted] for ixekizumab 80 mg q2w than ixekizumab 80 mg q4w but overall [redacted] had the greatest estimated probability of each PASI response.

When overall population data (for both biologic-naïve and experienced patients) were included for secukinumab and certolizumab pooled doses, the treatment with the greatest probability of each PASI response was [redacted] followed by [redacted].

Table 4.17: 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 4.18: 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]
Ustekinumab 90 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 [redacted] but not [redacted] or [redacted]

Table 4.19: ACR response for the biologic-experienced population

Treatment	ACR 20	ACR 50	ACR 70
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 9 of the response to request for clarification[25]

ACR = American College of Rheumatology; ACR 20 = At least 20% improvement in both tender and swollen joint counts; ACR 50 = At least 50% improvement in both tender and swollen joint counts; ACR 70 = At least 70% improvement in both tender and swollen joint counts; CrI = credible interval; CS = company submission; mg = milligram; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

4.3.3 Adverse events

Additional NMAs of treatment-emergent adverse events (TEAE), serious adverse events (SAE) and discontinuation due to adverse events (DAE) were performed in response to the clarification letter and the results were provided in the clarification response [25].

NMA results for TEAE are shown in Table 4.20 and show that the estimated probabilities of a TEAE were [redacted] for ixekizumab 80 mg q2w and [redacted] for ixekizumab 80 mg q4w. Adalimumab 40 mg had the [redacted] of a TEAE at [redacted] and placebo the [redacted]

Table 4.20: Conditional probabilities of experiencing a TEAE

Treatment	TEAEs
Adalimumab 40 mg q2w	[redacted]
Certolizumab pegol pooled doses	[redacted]
Infliximab 5 mg/kg q8w	[redacted]
Ixekizumab 80 mg q2w	[redacted]
Ixekizumab 80 mg q4w	[redacted]
Placebo	[redacted]

Source: Based on Table 10 of the response to request for clarification[25]

CrI = credible interval; CS = company submission; mg = milligram; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks; TEAE = treatment-emergent adverse event

NMA results for SAE are shown in Table 4.21 and show that the estimated probability of a SAE was [redacted] for ixekizumab 80 mg q2w and [redacted] for ixekizumab 80 mg q4w. Secukinumab 300 mg had the [redacted] of a SAE at [redacted] and golimumab 50 mg the [redacted] but for most treatments the SAE rate was [redacted].

Table 4.21: Conditional probabilities of experiencing a SAE

Treatment	SAEs
Placebo	[redacted]
Adalimumab 40 mg q2w	[redacted]

Apremilast 30 mg bid	[redacted]
Certolizumab pegol pooled doses	[redacted]
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 4.22: 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]
Placebo	[redacted]
Adalimumab 40 mg q2w	[redacted]
Apremilast 30 mg bid	[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, 456 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, ixekizumab [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], with [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 bMARD-experienced patients (fewer than five trials in most analyses) and ixekizumab was [redacted] ustekinumab for PsARC response. For PASI response, ustekinumab [redacted] 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 [redacted] was the most effective treatment across all categories of ACR response [redacted]. For bDMARD-experienced patients, both ixekizumab regimens had [redacted] ACR response compared to ustekinumab [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.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

A literature review was conducted to identify relevant cost effectiveness studies and HTA appraisals in psoriatic arthritis. Two separate strands of searching were conducted to identify: cost effectiveness models, and model inputs. All searches were presented in Appendix G.[28]

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission. For both strands, initial searches were reported for PubMed, Embase, Health Technology Assessment Database (HTA via Centre for Reviews and Dissemination (CRD)) and the Health Economic Evaluations Database (HEED via Wiley), and were undertaken in November 2014 (2000-2014). Update searches were reported for June 2017 (2000-2017). Additional update searches for both strands were also undertaken in Medline via Ovid. The database hosts were reported for all initial searches. The date the searches were conducted was provided, though the date span of the databases searched was not given for all searches. Website searches of 11 key HTA agencies were also performed. For these searches, date of initial search and update search was reported, together with search terms and Uniform Resource Locators (URLs).

Searches for cost effectiveness analysis review

A SLR was conducted to identify cost effectiveness evaluations. Strategies were presented in the submission appendices,[28] and further information was provided in the clarification response.[25]

PubMed, Medline, Embase and HTA searches included unreferenced costs and economic evaluation study design filters. Although the company stated that the NHS Economic Evaluation Database (NHS EED) was searched, the search results clearly indicated the resource had not been searched.

Extensive restriction to focus (RTF) was applied to the indexing within the cost facet for the cost effectiveness model (CEM) Embase and Medline searches, where only Major subject indexing headings were retrieved. Extensive use of RTF may be overly restrictive and impair sensitivity of the searches. Current best practice recommendations[61, 62] caution against use of RTF in more than two concepts, which may have impaired performance of the CS CEM search strategies.

Searches for model inputs

A SLR was conducted to identify health-related quality of life studies. PubMed, Medline, Embase and HTA searches included unreferenced filters to identify quality of life and utilities. Although the company stated that the NHS EED was searched, the search results clearly indicated the resource had not been searched.[1, 28]

The initial model input searches focussed on quality of life and HRQoL studies. When the model input searches were updated and re-run in 2017, additional terms for health utilities were added. The company's clarification response reported that the results of the update search were deduplicated against the initial search results using Endnote reference management software.[25]

Unfortunately, the additional utilities terms in the update searches included incorrect truncation. The company attempted to use Ovid truncation commands through the PubMed search for all free-text terms. It was also noted that several Ovid MeSH commands were reproduced in this PubMed search, therefore the relevant PubMed MeSH terms were not searched for. These truncation and MeSH errors were not found in the initial PubMed search for model inputs. Consequently, the ERG did not think the

PubMed update search worked as intended and would have been much improved by applying the correct database syntax for PubMed, in PubMed.

The model inputs searches in Embase showed that extensive RTF was applied to the Quality of life/HRQoL, cost, and UK/Europe components. The Medline model inputs searches showed that extensive RTF was applied to the Quality of life/HRQoL, and cost components. Extensive use of RTF may be overly restrictive and impair sensitivity of the searches. As noted with the CEM searches above, use of extensive RTF in more than two concepts may have impaired performance of the CS model input search strategies.

The inclusion criteria presented in Table 40 (page 152 of the CS appendices[28]) stated that languages other than English, French, German, Italian and Spanish would be excluded. As current best practice states that *'whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication'*, the ERG was concerned about potential introduction of language bias.[63] The inclusion criteria for CEM studies published as abstracts was inconsistently applied between the initial review (2000-2014) and the update review (2014-2017). CEM abstracts were excluded from the initial review but were not excluded from the update review.

All the cost effectiveness searches were limited by date from 2000-2017/06. Potentially studies may have been missed due to the date restriction but the impact of this is difficult to assess.

Website searches of 11 key HTA agencies were also performed. For these searches, date of initial search and update search, search terms, number of records retrieved and URLs were all reported in the clarification response.[64]

ERG comment:

- The ERG noted the for both CEM and model inputs Medline and Embase searches used extensive focused MeSH and Emtree indexing terms which may have adversely affect recall of the search strategies. When RTF is applied to subject indexing terms, only Major subject indexing headings are retrieved. The ERG considered the extensive use of RTF overly restrictive and potentially impairing recall of possibly relevant references and did not consider the extensive implementation of RTF in the Embase and Medline searches adequately sensitive for this systematic review.
- The CEM and model inputs searches of the HTA database involved application of cost and HRQoL/utilities filters respectively. The ERG considered this inappropriate and unnecessary, as an HTA search for psoriatic arthritis retrieved only 36 records (date of search: 22.3.18). As the submission stated health technology assessments were of interest, it was not necessary to limit a database solely comprising of HTAs in this way.
- The CEM search of the HEED database included application of cost filter terms. As HEED was a database specifically of economic evaluations, it was inappropriate and unnecessary for the company to restrict the search with terms for costs and health economics. The HEED search for model inputs included only psoriatic arthritis and retrieved 42 records. Therefore, it would have preferable and quicker to use that population-only search for the CEM review as well.
- The ERG thought it was possible potentially relevant economic evaluations might have been overlooked by failing to conduct a search of NHS EED. An ERG test search of NHS EED retrieved 17 unique economic studies not retrieved by the company's HTA search (see Appendix 1). This omission was of particular concern in light of the strategy restrictions applied

to the HTA and HEED searches. It is possible that relevant evidence may have been missed as a consequence.

- The CEM PubMed search contained a typographical error in the MeSH indexing for Markov Chains, which impaired retrieval of references reporting use of Markov Chains analysis.
- Typographical errors, incorrect truncation and database syntax mistakes were noted in several of the cost effectiveness PubMed searches.

5.1.2 Inclusion/exclusion criteria used in the study selection

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 5.1.

Table 5.1: Eligibility criteria for the systematic literature reviews

PICOS	Inclusion criteria	Exclusion criteria
Patient population	Adult patients with PsA	Studies with paediatric-only populations were excluded.
Intervention	Conventional systemic DMARD (methotrexate, sulfasalazine, gold salts and leflunomide)† Novel targeted synthetic DMARDs (apremilast and tofacitinib) Biologic DMARD (adalimumab, etanercept, certolizumab pegol, golimumab, infliximab, brodalumab†, ustekinumab and secukinumab‡)	Treatments not listed in the inclusion criteria Updated review: treatments not listed and conventional systemic DMARDs
Comparator	Any comparator	None
Outcomes	QALY-based outcome measure	CEMs without outcome measures based on QALYs
Study design	CEMs, HTA appraisals of relevant CEMs. In the original review, only full publications for studies focusing on CEMs were included. The updated review did not exclude CEMs that were published as abstracts.	Languages other than English, French, German, Italian and Spanish were excluded. Studies published before January 1st 2000 were excluded

Source: Based on Table 40 of Appendix J of the CS appendices[28]
Footnote: † Conventional systemic DMARDs and brodalumab were not treatments of interest in the updated review. ‡ Secukinumab was added as a treatment of interest in the updated review.
CEM = cost effectiveness model; CS = company submission, DMARD = disease-modifying anti-rheumatic drug, HTA = health technology assessment; QALY = quality-adjusted life year

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. However, the ERG disagrees that searching for QALY-based outcomes only does fully capture the search for HRQoL and cost and resource use studies.

5.1.3 Included/excluded studies in the cost effectiveness review

The searches related to CEA resulted in six peer-reviewed CEM publications and two CEMs published in abstract form. Furthermore, seven HTA appraisals from the NICE website and another six submissions to other HTA agencies (All Wales Medicines Strategy Group (AWMSG), Canadian Agency for Drugs and Technologies in Health (CADTH), the Australian Pharmaceutical Benefits Advisory Committee (PBAC), Scottish Medicines Consortium (SMC), and the Swedish Dental and Pharmaceutical Benefits Board (TLV)) were identified.

In total, 37 studies reporting utility values for patients with PsA were identified in the initial review and 13 additional studies were identified in the updated review. Seven studies reported relevant EQ-5D utility values.[65-71]

The searches for costs and resource use studies resulted in two published studies in the initial review[8, 72] and three additional studies (all abstracts)[73-75] were identified in the updated review. Methodology, results and applicability of these studies are provided in appendix I of the CS.

ERG comment: The rationales for excluding CE studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria. The company conducted a *de novo* economic analysis and used the second revision of the York model as its foundation, in accordance with several of the identified CEMs.

5.1.4 Conclusions of the cost effectiveness review

The CS provides an overview of the included cost effectiveness studies but no specific conclusion was formulated. No specific conclusion has been formulated for the studies included in the resource use and costs review.

ERG comment: Eligibility criteria were suitable for the SLR on cost effectiveness studies. However, outcome criteria were considered not specific enough to capture all relevant HRQoL as well as cost and resource use studies. The company based their *de novo* analysis on the approach of the revised York model.

The cost effectiveness searches in the company's clarification response were all documented and reproducible. However, there were a number of inconsistencies and mistakes which impaired performance of the cost effectiveness and model input searches.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.2: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	Markov state-transition model using a treatment sequencing approach.	To assess the cost effectiveness of ixekizumab versus other recommended treatments in the treatment of PsA.	Chapter 3.2
States and events	Health states include: - Trial period - Continued treatment period - BSC - Death These health states are based on response assessed using the PsARC (transition from trial period health state to continued treatment health state), and utilities and costs are valued based on corresponding HAQ-DI and PASI scores.	The model structure is similar to that of the York model[13] which has been used in subsequent NICE submissions.	Chapter 3.2.2

	Approach	Source/Justification	Signpost (location in CS)
Comparators	B/tsDMARDs. B/tsDMARD-naïve patient population: - Adalimumab - Apremilast - Certolizumab pegol - Etanercept - Golimumab - Infliximab - Secukinumab B/tsDMARD-experienced patient population: - Ustekinumab - BSC	These comparators were recommended by NICE. Certolizumab pegol and secukinumab in the b/tsDMARD-experienced population were not considered in the company's base-case, which was justified based on the absence of studies on these treatments in that specific population.	Chapter 3.2.3
Population	Six subgroups are analysed separately. Patients are divided into three concomitant psoriasis severity levels and in each psoriasis severity level the following prior treatment experience is considered: - b/tsDMARD-naïve patients - b/tsDMARD-experienced patients	The licence wording of "one or more DMARD therapies" covers a broader patient population than the patient populations that have met NICE criteria for eligibility for b/tsDMARD therapy, i.e. patients who have not responded adequately to at least 2 cDMARDs.	Chapter 3.2.1
Treatment effectiveness	Based on PsARC response the proportion of responders to treatment (eligible for treatment continuation) is determined. Patients who do not achieve response enter the trial period for the next active treatment in the sequence or BSC (always last treatment in the sequence). Treatment discontinuation risk due to any cause is assumed to be treatment independent and constant over time. Upon discontinuation, patients revert to their baseline HAQ-DI and PASI scores. Change from baseline HAQ-DI is treatment specific and conditional on PsARC response.	In line with previous TAs.	Chapter 3.3
Adverse events	The impact of adverse events of treatments on HRQoL and costs are not explicitly incorporated in the model.	It was assumed that adverse events were captured only to the extent that they affect the initial response and the long-term withdrawal rates.	Chapter 3.4.4 and 3.5.3

	Approach	Source/Justification	Signpost (location in CS)
Health related QoL	Health utilities were assessed from patients in the SPIRIT trials using the EQ-5D-5L and were mapped to the EQ-5D-3L. The utility data subsequently informed a utility algorithm corresponding to HAQ-DI and PASI scores.	In line with previous TAs.	Chapter 3.4.5
Resource utilisation and costs	The following costs and resource use categories were considered in the company cost effectiveness model: - Acquisition costs of b/tsDMARDs - Treatment administration - Monitoring and tests - Disease management: HAQ-DI and PASI related costs	In line with recent NICE TAs of treatments in PsA. Costs were sourced from the NHS[76], MIMS[77], PSSRU[78] and published literature.	Chapter 3.5
Discount rates	Discount of 3.5% for utilities and costs	As per NICE reference case[79]	Chapter 3.2.2
Subgroups	The six subgroups considered in the economic analysis were stratified by prior treatment with b/tsDMARDs and the presence and extent of concomitant psoriasis. Severity thresholds for psoriasis were: - No psoriasis - Mild-to-moderate psoriasis: BSA≥3% and PASI≤10 - Moderate-to-severe psoriasis: BSA>3% and PASI>10	In line with NICE scope.	Chapter 3.9
Sensitivity analysis	Both DSA and PSA are performed, as well as scenario analyses.		Chapter 3.8

BSA = body surface area; BSC = best supportive care; CS = company submission; DMARD = disease-modifying anti-rheumatic drug; bDMARD = biologic disease-modifying anti-rheumatic drug; b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; cDMARD = conventional disease-modifying anti-rheumatic drug; DSA = deterministic sensitivity analysis; HAQ-DI = Health Assessment Questionnaire-Disability Index; MIMS = Monthly Index of Medical Specialities; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PSA = probabilistic sensitivity analysis; PsARC = Psoriatic Arthritis Response Criteria; PSSRU = Personal Social Services Research Unit; TA = technology appraisal

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Yes	
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	Partly	Not all possible treatment sequences were considered. Not all comparators were included in the base-case analyses for b/tsDMARD-experienced patients (excluded: certolizumab pegol, secukinumab). The costs of methotrexate as a concomitant treatment were not included in any of the analyses while it is stated in the scope.
Type of economic evaluation	Cost effectiveness analysis	Yes	
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	
Synthesis of evidence in outcomes	Systematic review	Partly	SLR and NMA, but not on all relevant outcomes as identified in the scope.
Measure of health effects	Quality adjusted life years (QALYs)	Yes	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Yes	
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	Yes	

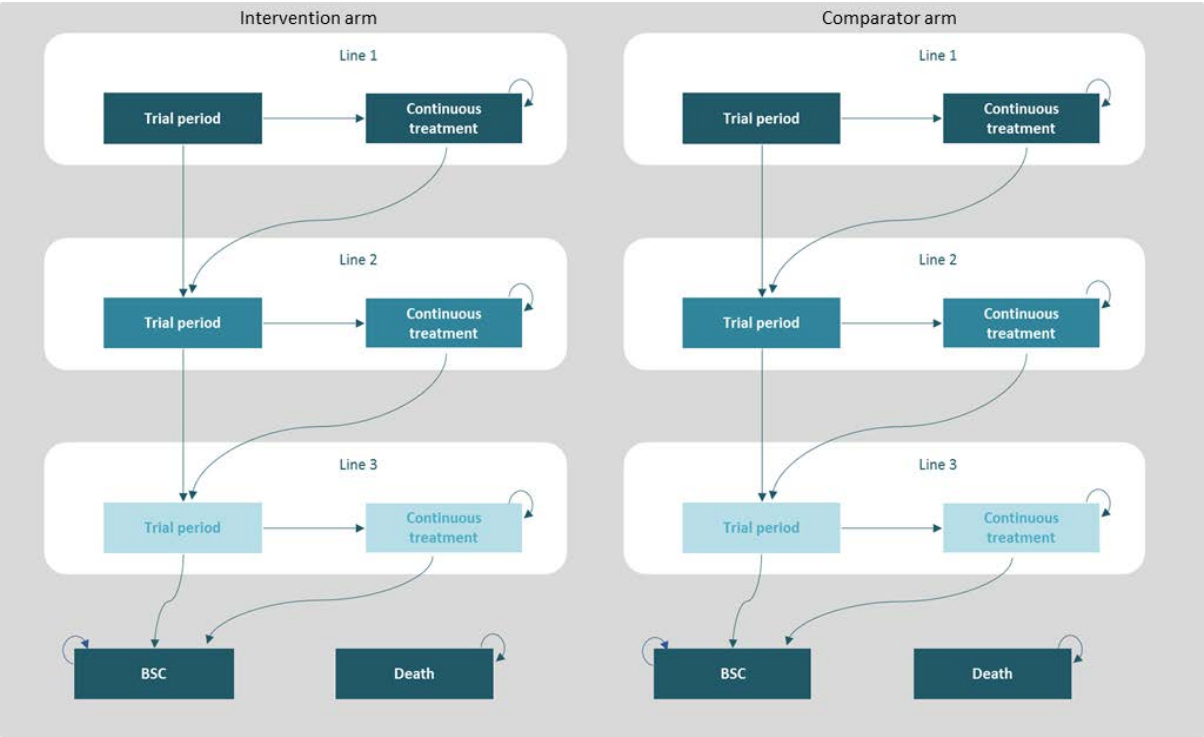
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic modelling	Yes	

b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; BSC = best supportive care; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PSS = Personal Social Services; QALY = quality-adjusted life year; SLR = systematic literature review

5.2.2 Model structure

The company developed a de novo Markov state-transition model in Visual Basic for Applications (VBA) with a Microsoft Excel interface. The model structure was mainly informed by the 2016 update of the York model (so-called "revised York model") and included treatment sequences, i.e. patients could receive multiple treatments in sequences (Figure 5.1).[26] The choice of this model structure was informed by expert opinions, as stated in the company submission. The original version of the York model (2011) was used for the TAs of ustekinumab[21] and golimumab[14] and the 2016 update of the York model was used for the multiple TA of secukinumab and certolizumab pegol.[26] Treatment effectiveness was determined by PsARC response, PASI score, and HAQ-DI score. PsARC was used to determine treatment response in the base-case analysis while PASI (in the presence of concomitant psoriasis) and HAQ-DI scores were used to determine resource use and costs, and health state utility values. In the current assessment, additional PASI response thresholds (PASI 50, PASI 90 and PASI 100) were added to the 2016 version of the York model. These alternative PASI response thresholds are used in sensitivity analyses in which alternative response criteria, based on a combination of PASI 50, PASI 90, or PASI 100 response and PsARC response, are used.

Figure 5.1: Model structure



Source: Based on Figure 10 of the CS[1]
Note: Arrows denote possible transitions. Transition to death is possible from all treatment states but not presented for simplicity.
BSC = best supportive care

The model structure consisted of the following treatment states: the trial period, the continued treatment period, BSC, and death. Patients entered the model in the first trial period. Trial periods were composed of tunnel states (i.e. 3-6 tunnel states) and lasted for 12-24 weeks, depending on the treatment received. From the start of the trial period, patients experienced a PASI and HAQ-DI score improvement based on PsARC response (theoretically assessed at the end of the trial period) and the treatment received. At the end of the trial period, PsARC response was assessed.

Patients responding to treatment, based on PsARC response, transited to the continued treatment period and maintained their abovementioned improvement in PASI and HAQ-DI scores. PASI and HAQ-DI scores remained constant during the continued treatment period until treatment discontinuation. Non-responders at the end of the trial period discontinued treatment. Upon treatment discontinuation, patients reverted to their baseline PASI and HAQ-DI scores and switched to the next active treatment in the sequence (i.e. next trial period) or BSC. BSC was the last treatment option after patients had been treated with all active treatments in the sequence. BSC was composed of a mix of cDMARDs and palliative care but no further detail on treatments composing BSC was provided. The effectiveness of BSC was assumed to be equal to the effectiveness of placebo.

Patients could die in all health states. Mortality rates based on the general UK population were adjusted using a standardised mortality ratio (SMR) of 1.36 to represent the excess mortality associated with PsA.[6] The cycle length was one month and no half-cycle correction was applied because the cycle length was considered to be sufficiently short. The cost effectiveness model does not include the HRQoL and economic consequences of adverse events.

ERG comment: The main concerns of the ERG related to the model structure are: a) the use of the PsARC response to determine the transition to the treatment continuation state, b) the instantaneous PASI and HAQ-DI improvement in the trial period states, c) the assumption that psoriasis does not progress over time, d) the non-inclusion of adverse events in the cost effectiveness model, e) the unclear definition of BSC, f) the cycle length of the model.

a) The main concern of the ERG concerning the model structure is the use of PsARC response to determine treatment effectiveness, for two reasons:
Firstly, the ERG acknowledges that this measure is commonly used to assess response in the PsA patient population. However, in health state transition models, the use of a relative measure to define health states may violate the assumption that patients in a health state are similar in terms of HRQoL and resource use consumption. In order to explore whether this assumption was violated in the current assessment, the ERG requested of the company to show that patients achieving (or not) PsARC response were homogeneous in terms of disease severity, utility gain, and resource use and costs.[80] The company provided an overview of baseline patient characteristics for PsARC responders and non-responders at 12 weeks but this did not allow for investigation of whether these patient populations are homogenous after (non-)response. Hence, the treatment continuation state may potentially be populated with a heterogeneous patient population.
Secondly, the use of PsARC response only to determine treatment continuation may not be representative of UK clinical practice. In peripheral spondyloarthritis, patients achieving PASI 75 response but no PsARC response may continue treatment based on dermatologist assessment. Consequently, the use of PsARC response only to determine treatment continuation does potentially underestimate the proportion of patients continuing treatment after the trial period.[81] The company incorporated a scenario in which treatment continuation was based on the probability of achieving both PsARC and PASI 75 response. This approach is also not representative of UK clinical practice and the estimated probabilities used in this scenario were not obtained from an NMA (rather calculation based on the correlation between PsARC and PASI).
Despite the abovementioned issues, the company approach of using the PsARC response only to determine treatment continuation is consistent with the 2016 York model. Moreover, both approaches (using PsARC response only or a combination of PsARC and PASI 75 responses) are likely not to be completely representative of UK clinical practice and there is probably no better alternative evidence to estimate the probabilities of continuing treatment. Therefore, the ERG used the same approach as the company in its base-case analysis, i.e. treatment continuation is based on PsARC response only.
b) The company incorporated an instantaneous PASI and HAQ-DI improvement at the beginning of the trial period (i.e. before PsARC response assessment) without justifying why this would be the most appropriate assumption.[1, 25, 28] This assumption potentially increases health benefits obtained with treatment with long trial periods, which are apremilast (16 weeks), ustekinumab (24 weeks) and secukinumab (16 weeks).
c) The company assumed no changes in baseline psoriasis over time. This assumption is in line with previous assessments in psoriasis and psoriatic arthritis.[15, 16, 26] However, the company acknowledges that psoriasis is a heterogeneous disease with an unpredictable natural history and that there is no evidence to support this assumption.[25] The company further explains that if psoriasis would progress over time, this would likely happen in the BSC state, which would potentially increase the cost effectiveness of treatments with high PsARC response rate. The ERG agrees with this claim.
d) The HRQoL and economic consequences of adverse events were not included in the cost effectiveness model which leads to biased estimates of HRQoL and economic consequences of

treatments for PsA in the current assessment. The ERG considers that adverse events should be incorporated in the cost effectiveness model since discontinuation rates due to adverse events differ between treatments. More details on this issue are provided in section 5.2.7.

e) Since BSC was not accurately described in the CS, the ERG requested the company to provide a definition of BSC. The company responded that BSC was composed of *"physiotherapy, NSAIDs, local glucocorticoid injections and cDMARDs"*, based on UK clinical expert opinion.[25] No details were provided on the expert opinion elicitation methods and results, and the company did not provide the proportion of patients who may receive each of the above-mentioned treatment as part of BSC. Hence, the ERG is not able to assess whether BSC is representative of the UK context, and whether the effectiveness and the costs associated with BSC in the cost effectiveness model are valid.

f) The company used a cycle length of one month while the trial periods of treatments vary between 12 and 24 weeks, which are modelled as tunnel states (three to six tunnel states). Hence, trial periods are modelled as periods of 3 to 6 months (13 to 26 weeks). Health benefits associated with the trial periods are thus potentially overestimated and resources used are distributed over a longer period of time than would be the case in clinical practice.

5.2.3 Population

Ixekizumab, with or without methotrexate, was granted marketing authorisation by the EMA for the treatment of active PsA in adults who have responded inadequately to, or who are intolerant to, one or more DMARD therapies.[34] This population is broader than the population of interest for the current decision problem, as defined by NICE guidance. According to the NICE guidance, only patients with an inadequate response to at least two cDMARDs become eligible for b/tsDMARDs in the UK.[13] However, the SPIRIT-P1 trial included patients who did not receive cDMARDs and SPIRIT-P2 included patients who were treated with one or more cDMARDs.

The cost effectiveness model discriminates between six subgroups based on the presence and severity of concomitant psoriasis and whether patients had been treated with another b/tsDMARD before ixekizumab. The severity of psoriasis was defined as follows: a) no psoriasis, b) mild-to-moderate psoriasis (BSA≥3% and PASI≤10), and c) moderate-to-severe psoriasis (BSA>3% and PASI>10). Table 5.4 presents the baseline PASI and HAQ-DI scores of each subgroup. The baseline age of the population was 51 years.

Table 5.4: Baseline PASI and HAQ-DI scores for each subgroup included in the cost effectiveness model

	b/tsDMARD-naive	b/tsDMARD-experienced
No psoriasis	Baseline PASI = 0 Baseline HAQ-DI = 1.17	Baseline PASI = 0 Baseline HAQ-DI =1.39
Mild-to-moderate psoriasis	Baseline PASI = 3.9 Baseline HAQ-DI = 1.17	Baseline PASI = 3.7 Baseline HAQ-DI = 1.2
Moderate-to-severe psoriasis	Baseline PASI = 20.4 Baseline HAQ-DI = 1.19	Baseline PASI = 23.4 Baseline HAQ-DI = 1.16

Source: Based on Table 36 in the CS[1], SPIRIT-P1 CSR[50] and SPIRIT-P2 CSR[33]
b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; CS = company submission; CSR = clinical study report, HAQ-DI = Health Assessment Questionnaire-Disability Index; PASI = Psoriasis Area and Severity Index

ERG comment: Issues concerning the patient population included in the current assessment are: a) the representativeness of the patient population from the SPIRIT trial programme for the current decision

problem, b) the choice of cut-off values to determine psoriasis severity, c) the different baseline PASI scores compared to the previous TA.

a) Concerns on the patient representativeness of the patient population from the SPIRIT trial programme and its impact on the relevance and validity of the NMA results to the UK context are expressed in section 4.2.2 of this report. Since the same patient characteristics and the NMA results have been used directly in the cost effectiveness model, these concerns also apply to the cost effectiveness analysis (and results) performed by the company.
b) The subgroups based on the presence and severity of psoriasis were only briefly described in the CS. The ERG requested more detail on the definitions of these subgroups in its clarification letter.[80] The company responded that the definitions used to derive these three subpopulations were based on the definitions used for the SPIRIT trials.[25] "No psoriasis" meant that "*the joint symptoms of these patients may be recognised as psoriatic arthritis due to family history or personal history of psoriasis or psoriatic nail symptoms.*" The ERG presumes that "no psoriasis" patients were the ones without psoriasis or with a BSA<10% and/or static physician's global assessment (sPGA) <3. Mild-to-moderate psoriasis was defined as PASI<12, sPGA≥3 and BSA≥10%, and moderate-to-severe psoriasis as PASI≥12 and sPGA≥3 and BSA≥10%. These definitions, based on the SPIRIT trials, do not align with the York model in which mild-to-moderate psoriasis is defined as a BSA≥3% and PASI score ≤10, and moderate-to-severe psoriasis as a BSA≥3% and PASI>10. Baseline PASI scores when using each definition are provided in Table 5.5. The York model definitions lead to a higher baseline PASI score in the mild-to-moderate psoriasis subgroup but to a lower baseline PASI score in the moderate-to-severe psoriasis subgroup.[25]

Table 5.5: Comparison of mean PASI scores (SD) at baseline in model subgroups

Source	b/tsDMARD-naive		b/tsDMARD-experienced	
	Mild-to-moderate psoriasis	Moderate-to-severe psoriasis	Mild-to-moderate psoriasis	Moderate-to-severe psoriasis
SPIRIT trial definition	3.9 (3.2)	20.4 (6.9)	3.7 (3.3)	20.4 (10.0)
York model definition	4.5 (2.6)	18.3 (7.1)	4.2 (2.5)	20.0 (10.0)

Source: Based on Table 45 of the response to the request for clarification[25]
b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; PASI = Psoriasis Area and Severity Index; SD = standard deviation

c) The ERG requested that the company explain the differences in baseline PASI scores between the current and previous appraisals because baseline PASI scores in the current assessment are noticeably higher in the moderate-to-severe psoriasis subgroup than in the 2016 York model.[26] As emphasised by the company, higher baseline PASI scores lead to higher absolute PASI reduction when achieving PASI 75 response.[25] The company did not provide an explanation for these discrepancies but stated that the influence of the baseline PASI score on the cost effectiveness results is expected to be minimal, without providing evidence to support this statement. The ERG used baseline PASI scores from the revised York model in a scenario analysis to assess the impact of this assumption on the results. Baseline PASI scores in that appraisal were 7.3 for the mild-to-moderate psoriasis subgroup and 12.5 for the moderate-to-severe psoriasis subgroup.[26]

5.2.4 Interventions and comparators

The cost effectiveness of ixekizumab, once every two weeks (q2w) or once every four weeks (q4w), is assessed against each b/tsDMARDs recommended by NICE for patients with PsA whose disease has not responded to two prior cDMARDs. All treatment sequences of the intervention began with ixekizumab while comparator treatment sequences began with another b/tsDMARDs. Dosing regimens and stopping rules (determining the length of the trial period) of each treatment are based on NICE guidance (Table 5.6). The length of the trial period for ixekizumab was set to 12 weeks in the company base-case analysis while the SmPC for ixekizumab advises that treatment should be discontinued in patients who did not show response after 16 to 20 weeks of treatment.[34] The company justified the use of the 12-week trial period stating that this was done to align with the stopping rules of other TNF-alpha inhibitors, however, the ERG is concerned that this may not be appropriate. The company provided results of a scenario analysis using a 16-week trial period for ixekizumab, which, in most cases, produced ICERs slightly less favourable for ixekizumab.

A treatment sequencing approach was adopted by the company. Hence, patients switched to a subsequent b/tsDMARD when they stopped responding to their first active treatment in the model. The company states that this approach is reflective of clinical practice in the UK and was adopted in the 2016 York model.[26] Tables 39 and 40 of the CS present the different treatment sequences included in the cost effectiveness model for the b/tsDMARD-naïve and b/tsDMARD-experienced subgroups, stratified by psoriasis severity.[1] Treatment sequences for b/tsDMARD-naïve patients were composed of two b/tsDMARD treatments, ustekinumab being the second-line treatment in all sequences, and then BSC while treatment sequences for b/tsDMARDs-experienced included one b/tsDMARD treatment before BSC. The CS does not describe how the treatment sequences have been selected.

Table 5.6: Treatments doses and length of trial period

Treatment	Dosing instructions	Stopping rule - NICE	Stopping rule - SmPC	Model trial period (weeks)	Trial period doses	Annual doses	Year 1 doses
Ixekizumab q2w	If patient has concomitant moderate-to-severe psoriasis, 80 mg every two weeks for 12 weeks, following a 160 mg starting dose in the trial period; thereafter 80 mg every 4 weeks	NA	Consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks	Base case: 12 Sensitivity analysis: 16	8	13	18
Ixekizumab q4w	80 mg every four weeks, following a 160 mg starting dose.	NA	Consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks.	Base case: 12 Sensitivity analysis: 16	5	13	15
Adalimumab	Injection, 40 mg administered every other week	Adalimumab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks[16]	Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period[82]	12	6	26	26
Apremilast	Oral tablet, 30 mg twice daily after an initial titration schedule: Day 1: 10 mg qd; Day 2: 10 mg bid; Day 3: 10 mg AM, 20 mg	Stop apremilast at 16 weeks if the psoriatic arthritis has not shown an adequate	If a patient shows no evidence of therapeutic benefit after 24 weeks, treatment should be reconsidered[83]	16	223	730	725

Treatment	Dosing instructions	Stopping rule - NICE	Stopping rule - SmPC	Model trial period (weeks)	Trial period doses	Annual doses	Year 1 doses
	PM; Day 4: 20 mg biw; Day 5: 20 mg AM, 30 mg PM	response using the PsARC[15]					
Certolizumab pegol 200 mg q2w	Injection, loading dose 40 mg at weeks 0,2 and 4; 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered	Certolizumab pegol should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks[13]	Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment[84]	12	10	26	29
Etanercept 50 mg qiw	Injection, 50mg once weekly	Etanercept should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks[16]	Treatment should be discontinued in patients who show no response after 12 weeks[85]	12	12	52	52
Golimumab 50mg	Injection, 50 mg once a month	Golimumab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks[14]	Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within 12 to 14 weeks of treatment (after 3-4 doses)[86]	12	3	12	12
Infliximab	By intravenous infusion, 5 mg/kg, repeated 2 weeks and 6 weeks after initial infusion, then every 8 weeks	Infliximab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks[16]	If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given[87]	12	3	6.5	8
Ustekinumab 45 mg	Injection, body-weight <100 kg, initially 45 mg, then 45 mg	Ustekinumab should be discontinued in people whose PsA has	Consideration should be given to discontinuing treatment in patients who have shown no	24	3	4.33	5

Treatment	Dosing instructions	Stopping rule - NICE	Stopping rule - SmPC	Model trial period (weeks)	Trial period doses	Annual doses	Year 1 doses
	4 weeks after initial dose, then 45 mg every 12 weeks	not shown an adequate response using the PsARC at 24 weeks[21]	response up to 28 weeks of treatment[85]				
Secukinumab 150 mg	Injection of 150mg at weeks 0, 1, 2 and 3 followed by monthly dosing from week 4 for b/tsDMARD-naïve patients without concomitant moderate-to-severe psoriasis	Secukinumab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 16 weeks[13]	Consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment[88]	16	7	13	16
Secukinumab 300 mg	Dose of 300mg (two 150 mg injections) at weeks 0, 1, 2 and 3 followed by monthly dosing from week 4 for TNF-naïve patients with concomitant moderate-to-severe psoriasis or patients with prior exposure to TNF-alpha inhibitors	Secukinumab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 16 weeks[13]	Consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment[88]	16	7	13	16

Source: Based on Table 38 of the CS[1]
biw = twice weekly; b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; CS = company submission; kg = kilogram; NA = not available; mg = milligram; NICE = National Institute for Health and Care Excellence; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; qd = once daily; qiw = once weekly; SmPC = Summary of Product Characteristics

ERG comment: The ERG is concerned about a) the selection of the treatment sequences included in the cost effectiveness model, and b) the non-inclusion of comparators included in the NICE scope.

a) The CS does not provide justification for the selection of the treatment sequences included in the cost effectiveness model, besides that these were included in the York model.[26] In its response to clarification question B8, the company states that the treatment sequences are informed by NICE recommendations and the license of treatments.[25] The company explains that, for b/tsDMARDs-naïve patients, all sequences consider ustekinumab as second-line treatment because it is recommended after TNF-alpha inhibitors failure in this population. The company acknowledges that secukinumab and certolizumab pegol are also recommended as second-line treatment but that only ustekinumab has been considered as second-line treatment to facilitate the comparison across all treatment sequences. In addition, the company states that the treatment sequences included in the current assessment are not exhaustive in the UK context.[25] The ERG explored alternative treatment sequences in its analyses, considering secukinumab and certolizumab pegol as second-line treatments.
   The CS does not explain why treatment sequences are restricted to a maximum of two b/tsDMARDs, i.e. two b/tsDMARDs followed by BSC in the b/tsDMARD-naïve subgroup and one b/tsDMARD followed by BSC in the b/tsDMARD-experienced subgroup. In its response to the clarification letter, the company states that this assumption was similar to the approach used in the 2016 York model and is supported by the Adelphi DSP real-world dataset in which only [redacted] of patients received three or more b/tsDMARD treatments. However, no details were provided on this dataset (years during which patients were included, patient characteristics, study design and analyses). The ERG was thus not able to judge the credibility of the argument that [redacted] use three or more DMARDs.
b) Certolizumab pegol and secukinumab are listed in the NICE final scope as comparators in the b/tsDMARD-experienced subgroup[89] but these treatments were not included in the company base-case analyses concerning this population. Additionally, the scope states that b/tsDMARDs may be administered with or without methotrexate. Hence, the ERG requested the company to include these comparators in its base-case analyses. The company did not include methotrexate, justified by stating that its acquisition costs were low and the clinical outcomes of studies included in the SLR were not reported separately for patients who did or did not receive concomitant methotrexate. The effectiveness of methotrexate is however indirectly included in the effectiveness estimates because a proportion of patients in SPIRIT and other trials included in the NMA received concomitant methotrexate.[31, 32, 36, 38, 40] The ERG agrees with the company that including the acquisition costs of methotrexate would not dramatically influence the cost effectiveness results.
   The company justified their decision to not include certolizumab pegol and secukinumab in the base-case analyses for the b/tsDMARD-experienced subgroup by stating that there was no study identified in the SLR which provided separate effectiveness estimates for b/tsDMARD-naïve and b/tsDMARD-experienced patients receiving these treatments. The identified studies provide effectiveness estimates for a mixed population of b/tsDMARD-naïve and b/tsDMARD-experienced patients treated with certolizumab pegol and secukinumab. These studies were used in the CS to estimate the effectiveness of these treatments in the b/tsDMARD-naïve subgroup. The company therefore assumed, in the b/tsDMARD-naïve subgroup, that the effectiveness of certolizumab pegol and secukinumab is equal in b/tsDMARD-experienced and b/tsDMARD-naïve patients. This contradicts its argument of not using the same evidence to estimate the effectiveness of certolizumab pegol and secukinumab in the b/tsDMARD-experienced subgroup because the studies do not provide estimates for b/tsDMARD-naïve and b/tsDMARD-experienced patients separately.

The ERG included both certolizumab pegol and secukinumab in its base-case analysis, by using the treatment effectiveness estimates obtained from the extended NMA for the b/tsDMARD-experienced subgroup. The extended NMA also has the advantage of providing the PASI 50 outcome which is needed for the calculation of change in PASI scores (see section 5.2.6 for more details on this issue).

5.2.5 Perspective, time horizon and discounting

The analysis takes a NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The company claim to have adopted a 40-year time horizon.[1]

ERG comment: In the CS, the company states a 40-year time horizon was used, however, the model continues until patients reach the age of 99 (less than 1% of patients are still alive). This was considered to represent a lifetime time horizon. The approach is in concordance with the NICE reference case.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness in the economic model is informed by PsARC, HAQ-DI and PASI, all sourced from the NMA described in section 4.3 of this report (section 2.9 of the CS).[1] PsARC and PASI are estimated separately for patients with and without prior b/tsDMARD exposure while HAQ-DI is estimated in patients without prior b/tsDMARD exposure (due to lack of evidence).

PsARC

The PsARC is a PsA-specific composite responder index and based on four items related to joint tenderness, joint swelling, patient global assessment and physician global assessment. Response is achieved if improvements in two out of four items is obtained, of which at least one is related to the joint tenderness or swelling score (≥30% improvement), and no item has worsened.[90]

In the economic model, after the trial period, treatment is continued for patients classified as responders based on PsARC while treatment is discontinued for PsARC non-responders. The company argues that this is consistent with current UK practice (by referring to the NICE Pathway for musculoskeletal conditions[91]) and with cost effectiveness studies identified in the SLR. Patients who continue treatment (i.e. PsARC responders) are assumed to maintain their improvement(s) in joint and/or skin outcomes until treatment discontinuation.

Treatment discontinuation

A constant annual treatment discontinuation of 16.5%[92] (i.e. 1.49% per model cycle of one month) is applied to the continued treatment state and represents treatment discontinuation due to any cause. The company argued that in absence of alternative data, the same treatment discontinuation rate is applied for all treatments and treatment lines.[1]

HAQ-DI

The HAQ-DI (range 0-3) considers the amount of difficulty patients have in performing the following activities[93]:

1. dressing and grooming
2. arising
3. eating
4. walking
5. hygiene
6. reach

7. grip
8. common daily activities

The baseline HAQ-DI scores used in the model are reported in Table 5.4. The change from baseline HAQ-DI is assumed to be dependent on treatment and PsARC response and used to estimate utility and costs. Moreover, it is assumed that the change from baseline HAQ-DI occurs instantly after initiating treatment (in the trial period) and that patients maintain this improvement until treatment discontinuation. After active treatment discontinuation, patients receive BSC and the HAQ-DI score is assumed to immediately rebound to its baseline value. HAQ-DI then progresses at a rate equivalent to the natural history progression (annual deterioration of 0.072[14]) until it plateaus at the maximum value of the HAQ-DI scale (i.e. 3).

PASI

The PASI provides a quantitative assessment of psoriasis lesion burden. This is calculated based on the amount of BSA involved and degree of severity of erythema, induration, and scale, weighted by body part. [90]

The baseline PASI scores used in the model are reported in Table 5.4. Similar to the changes in HAQ-DI, the change from baseline PASI is assumed to be dependent on treatment and PsARC response and used to estimate utility and costs. Moreover, it is assumed that the change from baseline PASI occurs instantly after initiating treatment (in the trial period) and that patients maintain this improvement until treatment discontinuation. After active treatment discontinuation, patients receive BSC and the PASI score is assumed to immediately rebound to its baseline value. In contrast with HAQ-DI scores (for which natural history progression is incorporated), the baseline PASI scores were assumed to be constant over time. The company stated that this assumption was made in the absence of data to model otherwise.

For PsARC responders, the reduction in PASI (i.e. improvement) compared with baseline PASI was assumed to be 75% (i.e. assuming all PsARC responders would have PASI 75). The PsARC non-responders were assumed to have either PASI 50 (i.e. reduction in baseline PASI by 50%) or no reduction in baseline PASI (see CS Table 42 for the calculation details).[1]

Mortality

Mortality was independent of health states patients were in. It was calculated based on background mortality increased by a standardised mortality ratio (SMR) of 1.36[6] to reflect disease-related mortality.

ERG comment: The ERG's concerns relate to a) the lack of information provided on treatment effectiveness parameters used in the economic model (in CS section 3.3[1]); b) the calculation of change in PASI depending on PsARC response; c) assumptions regarding natural progression of HAQ-DI after active treatment discontinuation; d) the SMR of 1.36 applied to reflect disease-related mortality; e) the assumption of no treatment response for BSC (after active treatment discontinuation); f) assuming treatment discontinuation to be equal for all b/tsDMARD treatments (and independent of treatment line) and g) the estimated HAQ-DI for ixekizumab q4w.

a) The "Clinical parameters and variables" section of the CS (Section 3.3) does not provide an overview of the parameters and variables used in the model. However, in response to clarification question B12, the company provided a transition matrix to illustrate the transitions probabilities used in the model, see Table 5.7.[25] In addition to the transition matrix, the ERG retrieved an overview of PsARC and PASI response per treatment (different for the b/tsDMARD-naïve and experienced populations) and an overview of HAQ-DI reduction per treatment (identical for the

b/tsDMARD-naïve and experienced populations) from the economic model submitted by the company (provided in Tables Table 5.8 and Table 5.9).

b) The ERG identified an inconsistency between the calculation of change in PASI depending on PsARC response in the economic model and the calculation methods reported in Table 42 of the CS.[1] Although the formulae reported in CS Table 42 lack justification (e.g. that all PsARC responders would have PASI 75), the ERG adjusted the calculation of change in PASI in the model to be consistent with CS Table 42. Related to this, the ERG noted that the NMA used in the CS base-case for the b/tsDMARD-experienced population did not provide estimates for PASI 50 (see Table 5.8). Therefore, the ERG preferred to use the NMA including secukinumab and certolizumab pegol for the b/tsDMARD-experienced population as these did have estimates for PASI 50 needed to estimate the calculation of change in PASI (Table 5.8). See ERG comments in section 5.2.4 for further details regarding the ERG's preference of the NMA including secukinumab and certolizumab pegol. In case PASI 50 estimates were missing, the company presumably assumed 0% PASI 50, likely benefiting treatments with higher PsARC response.

c) After active treatment discontinuation, patients receive BSC and their HAQ-DI score immediately rebounds to its baseline value and subsequently progresses using an annual deterioration of 0.072 until the maximum value of the HAQ-DI scale (i.e. 3). Although the ERG requested more detail regarding this calculation (clarification question B6d), it remains unclear to the ERG whether this linear deterioration is plausible, or whether a multiplicative progression factor would have been more plausible, for instance.[25, 80] This assumption of linear deterioration is consistent with the York model.[13] It should however be noted that if, in fact, the annual deterioration were non-linear and decreased over time, the assumption made by the company is likely benefiting treatments with a higher PsARC.

d) The SMR of 1.36[6] used by to company to increase background mortality and reflect disease related mortality seems an overestimation of the actual mortality in this population as this SMR was derived from the period between 1978 and 2004. If only the subset analysis with a follow-up period between 1996-2004 was to be considered, the SMR would be 1.05 (95% CI 0.79 to 1.41).[6] The ERG prefers to adopt the SMR of 1.05 in its base-case given it is based on more recent data (and the SMR seems to have declined over time).[6]

e) Once patients transit to BSC, positioned after discontinuation of active treatment in the model, the PASI and HAQ-DI immediately rebound to its baseline value. This implicitly assumes no treatment effect of BSC (regarding PASI and HAQ-DI). In response to clarification question B9, the company indicates that for BSC *"a combination of physiotherapy, NSAIDs, local glucocorticoid injections and cDMARDs may be used"*.[25]Although the assumption of no treatment effect can be questioned, it does not seem unreasonable to assume that the treatment response to BSC in that setting, i.e. after failure on two b/tsDMARD therapies, will be modest. Moreover, the ERG acknowledges that the evidence on BSC after failing two lines of b/tsDMARD treatment is likely scarce.

f) Treatment discontinuation was assumed to be equal for all b/tsDMARD treatments (independent of treatment line). This assumption (although consistent with the York model) is questionable, given that all-cause treatment discontinuation might differ substantially between treatments (see clarification response Table 50).[25]

g) As discussed in section 4.4 of this report, the reduction in HAQ-DI scores (retrieved from the NMA) for ixekizumab q4w (both responders and non-responders) seems inconsistent with the trial data. Therefore, the ERG preferred to use the reduction in HAQ-DI scores from the trial for ixekizumab q4w, this would be [redacted] and [redacted] for responders and non-responders respectively.

Table 5.7: Overview of transition probabilities in sequencing approach

	Treatment 1 trial period month 1	**Treatment 1 trial period month 2**	**Treatment 1 trial period month 3/4**	**Treatment 1 continued treatment period**	**Treatment 2 trial period month 1**	**Treatment 2 trial period month 2**	**Treatment 2 trial period month 3/4**	**Treatment 1 continued treatment period**	**BSC**	**Death**
Treatment 1 trial period month 1	NA	1-(mortality risk)	NA	NA	NA	NA	NA	NA	NA	Mortality risk
Treatment 1 trial period month 2	NA	NA	1-(mortality risk)	NA	NA	NA	NA	NA	NA	Mortality risk
Treatment 1 trial period month 3/4	NA	NA	NA	PsARC response rate	1-PsARC response-(mortality risk)	NA	NA	NA	NA	Mortality risk
Treatment 1 continued treatment period	NA	NA	NA	1-(mortality risk)- 1.49%	1.49%	NA	NA	NA	NA	Mortality risk
Treatment 2 trial period month 1	NA	NA	NA	NA	NA	1-(mortality risk)	NA	NA	NA	Mortality risk
Treatment 2 trial period month 2	NA	NA	NA	NA	NA	NA	1-(mortality rate)	NA	NA	Mortality risk
Treatment 2 trial	NA	NA	NA	NA	NA	NA	NA	PsARC response rate	1-PsARC response-	Mortality risk

	Treatment 1 trial period month 1	Treatment 1 trial period month 2	Treatment 1 trial period month 3/4	Treatment 1 continued treatment period	Treatment 2 trial period month 1	Treatment 2 trial period month 2	Treatment 2 trial period month 3/4	Treatment 1 continued treatment period	BSC	Death
period month 3/4									(mortality risk)	
Treatment 2 continued treatment period	NA	NA	NA	NA	NA	NA	NA	1-(mortality risk)-1.49%	1.49%	Mortality risk
BSC	NA	NA	NA	NA	NA	NA	NA	NA	1-(mortality risk)	Mortality risk
Death	NA	NA	NA	NA	NA	NA	NA	NA	NA	1

Source: Based on Table 49 of the response to the request for clarification[25]
BSC = best supportive care; NA = not available; PsARC = Psoriatic Arthritis Response Criteria

Table 5.8: PsARC and PASI response

Name	PsARC	PASI 50	PASI 75	PASI 90	PASI 100	Absolute PASI score[a]			
						Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
						Responders	Non-responders	Responders	Non-responders
b/tsDMARD-naive population									
Ixekizumab q2w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biosimilar etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biosimilar infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b/tsDMARD-experienced population									
Ixekizumab q2w	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[c]	[redacted]	[c]
Ixekizumab q4w	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[c]	[redacted]	[c]
Ustekinumab	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[c]	[redacted]	[c]
BSC	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[c]	[redacted]	[c]

Name	PsARC	PASI 50	PASI 75	PASI 90	PASI 100	Absolute PASI score[a]			
						Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
						Responders	Non-responders	Responders	Non-responders
b/tsDMARD-experienced population (including secukinumab and certolizumab pegol)									
Ixekizumab q2w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Retrieved from the economic model[94]

Notes: [a] These values are calculated by the ERG based on the formulae provided in CS Table 42.[1] The absolute PsARC and PASI response for BSC represents the response for BSC as comparator (i.e. not BSC as treatment state after discontinuation of active treatment, here the baseline PASI is assumed). [b] Ustekinumab data for the b/tsDMARD-naïve population was retrieved from the b/tsDMARD-experienced population. This was presumably assumed given Ustekinumab was only provided as the second treatment sequence. [c] It is unclear how this is calculated in the model given PASI50 is missing.

b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; BSC = best supporting care; mg = milligram; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks

Table 5.9: HAQ-DI reduction compared with baseline (retrieved from the economic model)

Name	HAQ-DI reduction	
	Responders	Non-responders
Adalimumab	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Biosimilar etanercept	[redacted]	[redacted]
Biosimilar infliximab	[redacted]	[redacted]
BSC	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Ixekizumab q2w	[redacted]	[redacted]
Ixekizumab q4w	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]

Source: Retrieved from the economic model[94]
BSC = best supporting care; HAQ-DI = Health Assessment Questionnaire-Disability Index; mg = milligram; q2w = once every two weeks; q4w = once every four weeks

5.2.7 Adverse events

No adverse events are considered in the economic model. The company argued that adverse events are implicitly captured to the extent that they affect the initial response and the long-term treatment discontinuation rates.

ERG comment: The ERG believes the justification provided by the company stating that adverse events are implicitly captured by the long-term withdrawal rates is flawed, given that these withdrawal rates are assumed to be identical for all treatments. Furthermore, the scope identified adverse events as relevant outcomes for this appraisal. The ERG believes that not incorporating adverse events is a substantial weakness of the economic model, particularly given that treatment discontinuation due to adverse events might differ between treatments, as was shown in response to clarification question A8 (see section 4.3.3, Table 4.22).[25]

5.2.8 Health-related quality of life

According to the CS, the SLR identified seven studies reporting UK relevant utility values. Out of these, the company considered only one study to be consistent with the NICE reference case and to be appropriate for the CEA model (Saad et al, 2010[71]). However, according to the company, this study, and the others, were not used in the health economic model because *"the studies identified in the HRQoL review reported only health state utility values"*.[1]

Instead, the company used the data from the SPIRIT trials in which the EQ-5D-5L questionnaire was administered to patients at baseline and week 12. The data collected from these studies were then analysed separately, to reflect the differences in terms of functional disability and skin involvement between the two populations of b/tsDMARD-naïve (utility derived from SPIRIT-P1) and b/tsDMARD-experienced (utility derived from SPIRIT-P2) patients. Consistent with the NICE reference case, health state utility values were obtained from the responses to the EQ-5D-5L using a hybrid of time-trade-off (TTO) and discrete choice experiments (DCE) on a representative sample from England. The

company did not impute missing values and justified this stating that the proportions of patients with missing EQ-5D score were small (20/417 in SPIRIT-P1 and 32/331 in SPIRIT-P2). In the CS, no further information was provided as to how these EQ-5D data were used.

In line with NICE's position statement on EQ-5D-5L data, the obtained data were mapped to EQ-5D-3L using the indirect mapping approach according to van Hout et al. 2012.[95] The EQ-5D-5L utility values were used in a scenario analysis.

The company used these EQ-5D-3L (5L in scenario analysis) data to establish a relationship between patients' HAQ-DI and PASI scores and HRQoL using an ordinary least squares regression model that had previously been used in the York models and was considered by the company to provide a better goodness-of-fit than alternative specifications of the model, e.g. including an interaction term between HAQ-DI and PASI and including adjustments for age and gender. Thus, the model specification only includes an intercept and coefficients for HAQ-DI and PASI scores, as shown in equation 1, with coefficients reported in Table 5.10:

Equation 1 – Utility regression model

$$Utility = \beta_0 - \beta_{HAQ} * HAQ - \beta_{PASI} * PASI$$

Table 5.10: Coefficients of linear regression of utility versus HAQ-DI and PASI

	Intercept		HAQ-DI		PASI	
Source	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
b/tsDMARD-naïve: SPIRIT-P1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b/tsDMARD-experienced: SPIRIT-P2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 43 of the CS[1]
b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; HAQ-DI = Health Assessment Questionnaire-Disability Index; PASI = Psoriasis Area and Severity Index; SE = standard error

The company did not incorporate the HRQoL associated with adverse events in their health economic model. The company justified this by stating that the HRQoL impact of AEs was also not modelled in other economic models submitted to HTA agencies. The company stated that the impact of AEs was captured only to the extent that they affect the initial response and the long-term withdrawal rates.

A summary of all utility values used in the cost effectiveness analysis is provided in Table 5.11.

Table 5.11: Summary of utility values used for CEA

State	Utility value (PsARC responders)	Utility value (PsARC non-responders)	Reference in company submission	Justification
b/tsDMARD-naïve, no psoriasis				
Trial period	0.624		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE q4w	0.744	0.624	Table 21, Table 22, Table 23,	Derived from treatment-specific response rates in the
ADA	0.717	0.647		

State	Utility value (PsARC responders)	Utility value (PsARC non-responders)	Reference in company submission	Justification
APR	0.693	0.641	Table 36, Equation 2	biologic-naïve NMA and from baseline HAQ-DI score
CZP	0.702	0.637		
ETA	0.750	0.662		
GOL	0.702	0.637		
INF	0.756	0.661		
SEC 150	0.735	0.652		
b/tsDMARD-naïve, mild-moderate psoriasis				
Trial period	0.605		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE q4w	0.739	0.613	Table 21, Table 22, Table 23, Table 36, Equation 2	Derived from treatment-specific response rates in the biologic-naïve NMA and from baseline PASI and HAQ-DI scores
ADA	0.709	0.629		
APR	0.683	0.622		
CZP	0.692	0.618		
ETA	0.736	0.642		
GOL	0.694	0.619		
INF	0.750	0.649		
SEC 150	0.729	0.639		
b/tsDMARD -naïve, moderate-severe psoriasis				
Trial period	0.518		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE q2w	0.716	0.600	Table 21, Table 22, Table 23, Table 36, Equation 2	Derived from treatment-specific response rates in the biologic-naïve NMA and from baseline PASI and HAQ-DI scores
ADA	0.669	0.550		
APR	0.638	0.539		
CZP	0.642	0.533		
ETA	0.675	0.556		
GOL	0.657	0.539		
INF	0.723	0.596		
SEC 300	0.701	0.590		
b/tsDMARD -experienced, no psoriasis				
Trial period	0.589		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE q4w	0.763	0.634	Table 23, Table 25, Equation 2	Derived from treatment-specific response rates in the biologic-experienced NMA and from baseline HAQ-DI score
UST	0.737	0.675		

State	Utility value (PsARC responders)	Utility value (PsARC non-responders)	Reference in company submission	Justification
b/tsDMARD -experienced, mild-moderate psoriasis				
Trial period	0.577		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE q4w	0.711	0.586	Table 23, Table 25, Table 26, Equation 2	Derived from treatment-specific response rates in the biologic-experienced NMA and from baseline PASI scores, which determines the severity of psoriasis.
UST	0.683	0.637		
b/tsDMARD -experienced, moderate-severe psoriasis				
Trial period	0.310		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE q2w+q4w	0.497	0.422	Table 23, Table 25, Table 26, Equation 2	Derived from treatment-specific response rates in the biologic-experienced NMA and from baseline PASI scores, which determines the severity of psoriasis.
UST	0.453	0.493		
BSC	Point estimate NA	NA	NA	HAQ-DI progresses each cycle according to natural history in BSC
Death	0	NA	NA	No utility assigned in death state

Source: Based on Table 44 of the CS[1]

ADA = adalimumab; APR = apremilast; b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; BSC = best supportive care; CEA = cost effectiveness analysis, CS = company submission; CZP = certolizumab pegol; ETA = etanercept; GOL = golimumab; HAQ-DI = Health Assessment Questionnaire-Disability Index; INF = infliximab; IXE = ixekizumab; NA = not available; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; SEC = secukinumab; UST = ustekinumab

ERG comment: The ERG's concerns related to a) the omission of alternative utility values from the literature without clear justification, b) the methods used for analysing the SPIRIT HRQoL observations, c) the use of utility values unadjusted to the general population age-related utilities, and d) the fact that the HRQoL impact of AEs is not incorporated.

a) The company identified seven studies reporting UK utility values. None of these were used in the base-case CEA or scenarios and the justification provided by the company was that *"the studies identified in the HRQoL review reported only health state utility values"*.[1] The company furthermore stated that *"the model followed the approach of the 2016 York model by modelling utility as a function of HAQ and PASI"*.[1] The ERG was concerned that important studies to inform HRQoL might have been excluded and checked the company's Appendix H[28] to verify that the company's decision not to use the identified HRQoL studies was appropriate. Apart from Saad et

al. 2010,[71] the other six studies were deemed irrelevant because they did not report utility values according to disease severity or functional status. The ERG agrees with the company on this. Utilities reported in Saad et al. 2010 were SF-6D scores based on the SF-36 questionnaire which was administered every six months in a cohort of 596 PsA patients starting to receive anti-TNF therapies in the UK setting. The baseline HAQ-DI score in this population was higher than in the population considered in this appraisal (1.88 instead of 1.18 in the b/tsDMARD-naive group, i.e. the SPIRIT-P1 population). SF-6D scores and HAQ-DI scores were reported for baseline, six months, 12 months and 18 months follow-up. SF-6D scores were also available for different treatments (etanercept, infliximab and adalimumab) but differences between these groups were very small. PASI scores were not reported. Given that, in the CS, utility values were modelled in relationship with HAQ-DI and PASI, the use of this study was indeed limited. The company's approach of using HRQoL data from their pivotal trials was therefore deemed reasonable.

b) The ERG had two concerns with regards to the analysis of HRQoL data from the SPIRIT trial programme. Firstly, no imputation method was applied in case of missing information on EQ-5D, thereby assuming that HRQoL data were missing completely at random. In their response to clarification question B16.a), the company justified this by having examined the data for, and not found, a pattern in the potential association between missing information and study- and patient-related characteristics.[25] No further information on this exercise was provided and the ERG therefore considers the non-imputation of missing data as a limitation. In a scenario, the company used the "Last observation carried forward" (LOCF) approach to impute missing data. This approach would address missing values only for those patients that had filled in the EQ-5D questionnaire at baseline and therefore might not address all missing information. Furthermore, the LOCF method is rarely appropriate and usually creates biased results.[96] The differences in the resulting regressions are shown in the equations below. Since the number of missing values was small in the SPIRIT trials and the LOCF method for imputation is generally not recommended, the ERG did not pursue this scenario further.

   Secondly, utility values were obtained using only the week 12 measurements, thus excluding baseline observations. The use of a mixed model for repeated measures could have facilitated accounting for baseline EQ-5D values and other factors but this was not explored by the company. In response to clarification question B16.b), the company stated that a mixed effects model for repeated measures would not have been appropriate because it would reduce the variability around EQ-5D.[25] The ERG considers that it may have been better to use all available data, potentially by estimating 12-week EQ-5D with baseline EQ-5D as a covariate. However, the ERG did not consider this a major issue.

c) In the CS model, utilities were not adjusted for general population utilities. This was addressed in response to clarification question B17.[25] The results of this scenario show that this adjustment has only a minor impact on cost effectiveness analysis results. The ERG prefers this and uses this adjustment in its base-case.

d) The HRQoL impact of AEs was not incorporated in the company's analysis. Due to the differing AE profiles of the different treatments (see section 5.2.7), which could have a significant impact on HRQoL, this is considered a major limitation.

5.2.9 Resources and costs

In Appendix I, the company stated that five studies reporting cost and resource use in the population of interest were identified through the SLR and its update.[28] One of these was deemed clearly not applicable to clinical practice in England and the applicability to clinical practice in England was considered unclear in the four other studies. Of these four studies only the study by Poole et al. (2010)[72]

was used to inform a scenario analysis. Other than this, the company used sources that were also used in the revised York model used in the previous TA by Corbett et al. 2017.[26]

Drug acquisition costs

Drug acquisition costs for b/tsDMARDs were sourced from the online version of the Monthly Index of Medical Specialities (MIMS)[77] and are shown in Table 5.12. Ixekizumab is provided with a confidential simple discount patient access scheme (PAS). Secukinumab and apremilast are also provided with a PAS, but list prices were used for these two comparators in the CS model as these PAS prices were not publicly available. Certolizumab pegol and ustekinumab are recommended by NICE with complex PAS schemes in place, which require the manufacturer of certolizumab pegol to provide the first 12 weeks of treatment free of cost; and the high dose of ustekinumab (90 mg) needed for people who weigh more than 100 kg is provided at the same total cost as the low dose (45 mg). Both of these schemes are incorporated in the present CEA. The cost of infliximab was calculated based on the weight-based dosing, and the weight for this was obtained from the SPIRIT trial programme. For infliximab and etanercept, biosimilar prices are used in the base-case model and branded prices are used in a sensitivity analysis.

Table 5.12: Drug acquisition costs

Items	Pack size	Dose strength	Pack cost	Cost per dose	Total cost (trial period)	Total annual cost (continued treatment)	Source
IXE q2w	1	80 mg	£1,125	£1,125	£9,000	£14,625	List price: MIMS 2017[77]
IXE q4w	1	80 mg	£1,125	£1,125	£5,625	£14,625	List price: MIMS 2017[77]
IXE q2w	1	80 mg	[redacted]	[redacted]	[redacted]	[redacted]	PAS price
IXE q4w	1	80 mg	[redacted]	[redacted]	[redacted]	[redacted]	PAS price
ADA	2	40 mg/ 0.8 ml	£704.28	£352.14	£2,112.84	£9,155.64	MIMS 2017[77]
APR*	56	30 mg	£550.00	£9.82	£2,190.18	£7,150.00	MIMS 2017[77]
CZP†	2	200 mg	£715.00	£357.50	£0†	£9,295.00	MIMS 2017 [77]; NICE FAD TA445 [13]
ETA (Enbrel)	4	50 mg	£715.00	£178.75	£2,145.00	£9,295.00	MIMS 2017[77]
ETA biosimilar (Benepali)	4	50 mg	£656.00	£164.00	£1,968.00	£8,528.00	MIMS 2017[77]
GOL	1	50 mg	£762.97	£762.97	£2,288.91	£9,155.64	MIMS 2017[77]
INF (Remicade)‡	1	100 mg	£419.62	£2,056.40	£6,169.21	£13,366.63	MIMS 2017[77]
INF biosimilar (Remsima) ‡	1	100 mg	£377.00	£1,847.54	£5,542.62	£12,009.01	MIMS 2017[77]
SEC 150 mg*	2	150 mg	£1218.78	£609.39	£4,265.73	£7,922.07	MIMS 2017[77]

Items	Pack size	Dose strength	Pack cost	Cost per dose	Total cost (trial period)	Total annual cost (continued treatment)	Source
SEC 300 mg*	2	150 mg	£1218.78	£1,218.78	£8,531.46	£15,844.14	MIMS 2017[77]
UST 45	1	45 mg	£2,147.00	£2,147.00	£4,294.00	£9,303.67	MIMS 2017[77]

Source: Based on Table 45 of the CS[1]
Footnote: * List price used in model due to confidential discount PAS; † CZP is associated with a PAS that provides the first 12 weeks of treatment free; ‡Infliximab dose based on a baseline weight of 87.02 kg
ADA = adalimumab; APR = apremilast; CZP = certolizumab pegol; ETA = etanercept; GOL = golimumab; INF = infliximab; IXE = ixekizumab; mg = milligram; ml = millilitre; MIMS = Monthly Index of Medical Specialities; q2w = once every two weeks; q4w = once every four weeks; SEC = secukinumab; UST = ustekinumab

Drug administration costs

All therapies of interest are administered as a subcutaneous (SC) injection with the exception of oral apremilast, and infliximab, which is administered via intravenous (IV) infusion. Patients who received SC injections incurred administration costs only for one hour nurse training for self-administration in the trial period and no further administration costs in the continued treatment period. Patients who received infliximab incurred an IV infusion cost three times in the trial period and an average of 6.5 times each year they remained on treatment. No administration costs were applied to oral administration of apremilast.

The cost of administration was obtained from the PSSRU Unit Costs of Health and Social Care 2016[78] and the NHS Reference Costs 2015-16[76] and is shown in Table 5.13.

Table 5.13: Drug administration costs

Administration method	Admin cost	Admin: trial period	Annual admin	Total cost: trial period	Total annual cost	Source
SC self-injection: a hour-long nurse training sessions	£43.00	1	0	£108.00	£0.00	PSSRU, Unit Costs of Health and Social Care 2016, section 10, cost per hour of Nurse in GP practice[78]
IV infusion, outpatient procedure	£236.19	3	6.5	£291.24	£631.02	NHS Reference Cost 2015-2016, Deliver Simple Parenteral Chemotherapy at First Attendance, code SB12Z[76]
Oral administration	£0.00	N/A	N/A	£0.00	£0.00	Assumption

Source: Based on Table 46 of the CS[1]
CS = company submission; GP = general practitioner; IV = intravenous; NHS = National Health Service; PSSRU = Personal Social Services Research Unit; SC = subcutaneous

Monitoring

Costs for monitoring during treatment have been obtained from the NHS Reference Costs[76] and are shown in Table 5.14. Resource use estimates were mainly taken from Corbett et al. 2017,[26] were deemed in line with the guidelines from the British Society for Rheumatology (BSR) for the use of biologics, and were stratified by method of administration (Table 5.14).[97]

Table 5.14: Resource use and costs for administration and monitoring of treatment in the trial and continued treatment periods

Resource	Time period	SC	Oral	IV	Price	Reference	Cost year
Rheumatologist visit	Trial period	2	2	2	£142.74	NHS Reference Cost 2015-2016, code DAPS05[76]	2016
	Continued treatment period	0	1	0			
Full blood count	Trial period	2	2	2	£3.00	NHS Reference Cost 2015-2016, code DAPS05[76]	2016
	Continued treatment period	2	0	2			
Liver function test	Trial period	2	2	2	£1.00	NHS Reference Cost 2015-2016, code DAPS04[76]	2016
	Continued treatment period	2	0	2			
Urea and electrolytes	Trial period	2	2	2	£1.00	NHS Reference Cost 2015-2016, code DAPS04[76]	2016
	Continued treatment period	2	0	2			
ESR	Trial period	2	2	2	£3.00	NHS Reference Cost 2015-2016, code DAPS05[76]	2016
	Continued treatment period	2	0	2			
Chest X-Ray	Trial period	1	1	1	£30.00	NHS Reference Cost 2015-2016, code DAPF [76]	2016
	Continued treatment period	0	0	0			
TB Heaf test	Trial period	1	1	1	£8.91	Rodgers et al. 2011[92]	2016
	Continued treatment period	0	0	0			
ANA test	Trial period	1	1	1	£3.00	NHS Reference Cost 2015-2016, , code DAPS05 [76]	2016
	Continued treatment period	0	0	0			
ds DNA test	Trial period	1	1	1	£3.00	NHS Reference Cost 2015-2016, , code DAPS05 [76]	2016
	Continued treatment period	0	0	0			

Source: Based on Tables 47 and 48 of the CS[1]
ANA = Antinuclear antibody; CS = company submission; DNA = deoxyribonucleic acid; ds = double-stranded; ESR = Erythrocyte sedimentation rate; IV = intravenous; NHS = National Health Service; SC = subcutaneous; TB = Tuberculosis

Disease-related costs and resource use

Disease-related costs are included in the model through estimating costs related to HAQ-DI (see equation 2) and costs related to PASI (see Table 5.15). The CS states that this method is assumed to capture the cost of BSC.[1]

The linear regression to inform HAQ-DI related costs was taken from Kobelt et al. 2002,[50] a study with sample size of 916 patients for the UK cohort. This study was based on rheumatoid arthritis patients. The company updated the costs to 2017 GBP. The company stated that Kobelt et al. 2002 estimated that costs for cDMARDs would account for 15% of the direct cost. To avoid double-counting with drug acquisition costs applied elsewhere in the current model, the company modelled patients on biologic treatment to incur 85% of the HAQ-DI related costs. For BSC, the full HAQ-DI related costs were assumed (i.e. without the 15% reduction). An alternative costing approach by Poole et al. 2010[72] was used in a scenario analysis.

Equation 2 – Health state costs associated with HAQ-DI

$$Annual\ direct\ costs = £565.64\ x\ HAQ + £1{,}867.56$$

Costs related to the treatment of controlled psoriasis were informed by the York model (Rodgers et al. (2011)[92]) and are presented in Table 5.15. Controlled psoriasis is defined as achieving a PASI 75 response. The company assumed that patients with mild-to-moderate and moderate-to-severe concomitant psoriasis incur the same costs, due to lack of data that would allow differential costing. For patients without concomitant psoriasis, it is assumed that no additional psoriasis-related costs occur.

Costs for treating patients with mild-to-moderate concomitant psoriasis who are not treated with or have not responded to active therapy (i.e. uncontrolled psoriasis) are based on UK unit costs for phototherapy and other treatment costs, including drug costs and physician visits estimated from a UK RCT on 232 psoriasis patients randomised to receive calcipotriol or dithranol published in 1999.[98] For patients with uncontrolled moderate-to-severe concomitant psoriasis, costs are based on a Dutch RCT comparing psoriasis treatment with dithranol with ultraviolet B (UVB) phototherapy[99] and adjusted to UK price levels.

Table 5.15: Annual costs for controlled and uncontrolled psoriasis

Description	No psoriasis	Mild to moderate	Moderate to severe
Costs for uncontrolled psoriasis	£0	£892	£2,552
Costs for controlled psoriasis (PASI 75 response)	£0	£72	£72

Source: Based on Table 49 of the CS[1]
CS = company submission; PASI = Psoriasis Area and Severity Index

An overview of all health states and associated costs is shown in Table 5.16. The company did not take into account cost and resource use associated with adverse events.

Table 5.16: List of health states and associated costs in the economic model

Health states	Item	Value	Reference
PsARC response and non-response	**Treatment costs**		
	Ixekizumab	£1,125 per dose	MIMS, January 2017[77]
	Adalimumab	£352.14 per dose	MIMS, January 2017[77]
	Apremilast	£9.82 per dose	MIMS, January 2017[77]

Health states	Item	Value	Reference
	Certolizumab pegol	£357.50 per dose	MIMS, January 2017[77]
	Etanercept (biosimilar)	£164 per dose	MIMS, January 2017[77]
	Golimumab	£762.97 per dose	MIMS, January 2017[77]
	Infliximab (biosimilar)	£1,847.54 per dose	MIMS, January 2017[77]
	Secukinumab 150 mg	£609.39 per dose	MIMS, January 2017[77]
	Secukinumab 300 mg	£1,218.78 per dose	MIMS, January 2017[77]
	Ustekinumab	£2,147.00 per dose	MIMS, January 2017[77]
	BSC	£0	Captured in HCRU due to skin and joint symptoms
	Administration costs		
	Nurse training for SC administration	£43.00 per hour of nurse time	PSSRU, Unit Costs of Health and Social Care 2015, Nurse (GP practice), wage cost per hour[78]
	IV infusion	£236.19 per administration	NHS Reference Cost 2015-2016, Deliver Simple Parenteral Chemotherapy at First Attendance, code SB12Z[76]
	Monitoring costs		
	Rheumatologist visit costs	£142.74 per visit	NHS Reference Cost 2015-2016[76]
	FBC	£3.00 per test	NHS Reference Cost 2015-2016[76]
	LFT	£1.00 per test	NHS Reference Cost 2015-2016[76]
	U&E	£1.00 per test	NHS Reference Cost 2015-2016[76]
	ESR	£3.00	NHS Reference Cost 2015-2016[76]
	Chest X-Ray	£30.00	NHS Reference Cost 2015-2016[76]
	TB Heaf test	£8.91	NHS Reference Cost 2015-2016[76]
	ANA test	£3.00	NHS Reference Cost 2015-2016[76]
	ds DNA test	£3.00	NHS Reference Cost 2015-2016[76]
HCRU due to skin and joint symptoms			
Joint symptoms	HAQ-DI	£565.64 per unit change + £1,867.56	Kobelt et al. 2002[100]
No psoriasis		£0	Annualised cost from Corbett et al. 2016[26]
Mild-to-moderate psoriasis	PASI≥75	£72.00	Annualised cost from Corbett et al. 2016[26]
	PASI<75	£892	Annualised cost from Corbett et al. 2016[26]
Moderate-to-severe psoriasis	PASI≥75	£72.00	Annualised cost from Corbett et al. 2016[26]

Health states	Item	Value	Reference
	PASI<75	£2,552	Annualised cost from Corbett et al. 2016[26]

Source: Based on Table 50 of the CS[1]
ANA = Antinuclear antibody; BSC = best supportive care; CS = company submission; DNA = deoxyribonucleic acid; ds = double-stranded; ESR = Erythrocyte sedimentation rate; FBC = full blood count; GP = General practitioner; HAQ-DI = Health Assessment Questionnaire-Disability Index; HCRU = Health Care Resource Utilisation; IV = intravenous; LFT = liver function test; mg = milligram; MIMS = Monthly Index of Medical Specialities; NHS = National Health Service; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; PSSRU = Personal Social Services Research Unit; SC = subcutaneous; TB = Tuberculosis; U&E = urea and electrolytes test

ERG comment: The ERG's concerns relate to a) whether HAQ-DI associated resource use and costs used in the model were appropriate, b) whether PASI-related costs used in the model were appropriate, c) whether there may be double-counting of resource use and costs when psoriasis and arthritis-related costs are added after being estimated separately, d) whether the cost of BSC is appropriately reflected and, e) the exclusion of costs related to adverse events.

a) The ERG had two major concerns regarding the estimation of HAQ-DI related costs:
Firstly, the ERG was concerned that neither the Kobelt et al. 2002[100] nor the Poole et al. 2010[72] studies were considered appropriate for estimating healthcare resource utilisation associated with the HAQ-DI score. This was because Kobelt et al. is a study in a different patient population (rheumatoid arthritis patients), the study is dated and might not be representative of resource use and costs of patients today while the Poole et al. study was associated with limitations in the calculation of the estimates such as that it did not cover the full range of the HAQ-DI score. When used to predict the costs for the full range of the HAQ-DI score, there could be errors especially for more severe disease. The company's justification provided in response to clarification question B20.a) was that Kobelt et al. and Poole et al. were also used in the revised York model.[25] The company furthermore claimed[25] that neither the SPIRIT trials nor the studies included in D'Angiolella et al. 2018,[101] a review of cost effectiveness studies in PsA, would have been appropriate to inform UK healthcare resource use estimates in the cost effectiveness model because none of these studies reflected UK clinical treatment practice appropriately. The ERG notes that the use of Kobelt et al. 2002 is a limitation and source of uncertainty but acknowledges that there may not have been more appropriate data and therefore also uses the Kobelt et al. 2002 algorithm in its base-case and Poole et al. 2010 in a scenario.
Secondly, the ERG questions the appropriateness of subtracting 15% of the HAQ-DI related costs when patients are treated with active treatment. These 15% were estimated in a study from 1996 (McIntosh, 1996)[102] and likely do not reflect the proportion of active treatment costs within the overall HAQ-DI related costs. However, to the knowledge of the ERG, there are no better estimates available.

b) The resource use and costs related to psoriasis were based on the York 2016 model. The ERG was concerned that the data used to inform uncontrolled mild-to-moderate psoriasis were potentially dated as they were sourced from Poyner et al. 1999.[98] Furthermore, the costs for uncontrolled moderate-to-severe costs were sourced from a Dutch RCT and may therefore not be generalisable to the UK setting.[99] The costs associated with no psoriasis were assumed to be £0 but no evidence was cited to inform this. Lastly, although the costs for controlled mild-to-moderate and moderate-to-severe psoriasis were sourced from the York model,[92] it was not clear where these costs came from. Therefore, the ERG notes that there is substantial uncertainty about the costs of non-active treatment costs of treating psoriasis in patients with psoriatic arthritis.

c) The uncertainty in both HAQ-DI and PASI related costs translates further into uncertainty whether there may be double-counting of costs when arthritis and psoriasis-related costs are added after being estimated independently. While it may be reassuring that the York model made the same assumptions, the ERG considers this another area of uncertainty.
d) The ERG noted a lack of clarity regarding the composition of BSC. It is therefore also unclear whether, as stated by the company, the addition of HAQ-DI and PASI-related costs fully captures the true cost of BSC.
e) The impact of AEs on resource use and costs was not incorporated in the company's analysis. Due to the differing AE profiles of the different treatments (see section 5.2.7) which could have an impact on resource use and costs, this is considered a major limitation.

5.2.10 Cost effectiveness results

The company's deterministic fully incremental base-case results using the PAS price of ixekizumab are presented for the biologic-naïve subpopulation for all psoriasis severity subgroups in Table 5.17and for the biologic-experienced subpopulation for all psoriasis severity subgroups in Table 5.18. It should be noted that these results do not take the PAS prices for secukinumab and apremilast into account.

The company pointed out that when the PAS price of ixekizumab is used (but not using the PAS price for secukinumab and apremilast), ixekizumab is associated with [redacted] in the b/tsDMARD-naïve subgroup with no psoriasis and mild-to-moderate psoriasis and is associated with [redacted] than ustekinumab in the b/tsDMARD-experienced subgroups.1 The ixekizumab q4w sequence was associated with an ICER [redacted] versus BSC in the no psoriasis and mild-to-moderate psoriasis subgroups in both the b/tsDMARD-naïve and b/tsDMARD-experienced populations and the ixekizumab q2w sequence had an ICER [redacted] versus BSC in the moderate-to-severe psoriasis subgroups. In the b/tsDMARD-experienced subgroup, ixekizumab q2w [redacted] ustekinumab.

The company further highlighted that the QALY difference between the b/tsDMARDs with the most and least QALYs in each subgroup is less than one QALY over a lifetime time horizon. In contrast, the range in costs between the least and most expensive treatments, due to the confidential price discounts for apremilast and secukinumab, is likely to be wider than predicted by the model. While these results may not reflect the true cost to the NHS of apremilast and secukinumab, they are more representative of the cost effectiveness of the ixekizumab sequences relative to the other b/tsDMARDs that have been recommended by NICE without a confidential price discount.

Table 5.17: Company's base-case results for b/tsDMARD-naïve subpopulation; PAS price

Treatment sequence	Second-line	Third-line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs comparator
No psoriasis								
BSC			£54,046	8.09	Referent	Referent	Referent	[redacted]
Apremilast	Ustekinumab	BSC	£93,347	9.49	[redacted]	1.39	Extendedly dominated	[redacted]
Ixekizumab q4w	Ustekinumab	BSC	[redacted]	9.69	[redacted]	1.60	[redacted]	Referent
Certolizumab pegol	Ustekinumab	BSC	£99,866	9.67	[redacted]	1.57	Dominated	[redacted]
Secukinumab 150 mg	Ustekinumab	BSC	£100,241	9.78	[redacted]	1.68	Extendedly dominated	[redacted]
Adalimumab	Ustekinumab	BSC	£101,322	9.71	[redacted]	1.61	Dominated	[redacted]
Biosimilar etanercept	Ustekinumab	BSC	£103,692	10.02	[redacted]	1.92	£25,810	[redacted]
Golimumab	Ustekinumab	BSC	£108,195	9.90	[redacted]	1.80	Dominated	[redacted]
Biosimilar infliximab	Ustekinumab	BSC	£127,297	10.12	[redacted]	2.02	£236,122	[redacted]
Mild-to-moderate psoriasis								
BSC			£70,006	7.74	Referent	Referent	Referent	[redacted]
Apremilast	Ustekinumab	BSC	£105,446	9.16	[redacted]	1.41	Extendedly dominated	[redacted]
Ixekizumab q4w	Ustekinumab	BSC	[redacted]	9.38	[redacted]	1.64	[redacted]	Referent
Certolizumab pegol	Ustekinumab	BSC	£111,375	9.34	[redacted]	1.60	Dominated	[redacted]
Secukinumab 150 mg	Ustekinumab	BSC	£111,743	9.47	[redacted]	1.72	Extendedly dominated	[redacted]
Adalimumab	Ustekinumab	BSC	£112,849	9.39	[redacted]	1.64	Dominated	[redacted]

Treatment sequence	Second-line	Third-line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs comparator
Biosimilar etanercept	Ustekinumab	BSC	£114,657	9.69	[redacted]	1.95	£22,948	[redacted]
Golimumab	Ustekinumab	BSC	£118,987	9.59	[redacted]	1.85	Dominated	[redacted]
Biosimilar infliximab	Ustekinumab	BSC	£138,072	9.82	[redacted]	2.08	£175,823	[redacted]
Moderate-to-severe psoriasis								
BSC			£99,884	6.21	Referent	Referent	Referent	[redacted]
Apremilast	Ustekinumab	BSC	£127,576	7.70	[redacted]	1.49	Extendedly dominated	[redacted]
Certolizumab pegol	Ustekinumab	BSC	£132,373	7.90	[redacted]	1.69	Extendedly dominated	[redacted]
Adalimumab	Ustekinumab	BSC	£133,882	7.97	[redacted]	1.77	Extendedly dominated	[redacted]
Ixekizumab q2w	Ustekinumab	BSC	[redacted]	8.11	[redacted]	1.91	[redacted]	Referent
Biosimilar etanercept	Ustekinumab	BSC	£134,567	8.24	[redacted]	2.03	£17,055	[redacted]
Golimumab	Ustekinumab	BSC	£138,550	8.23	[redacted]	2.02	Dominated	[redacted]
Secukinumab 300 mg	Ustekinumab	BSC	£155,532	7.97	[redacted]	1.77	Dominated	[redacted]
Biosimilar infliximab	Ustekinumab	BSC	£157,603	8.51	[redacted]	2.31	£84,228	[redacted]

Source: Based on Table 54 of the CS[1]

b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; BSC = best supportive care; CS = company submission; ICER = incremental cost effectiveness ratio; IXE = ixekizumab; mg = milligram; PAS = patient access scheme; q4w = once every four weeks; QALY = quality-adjusted life year

Table 5.18: Company's base-case results for b/tsDMARD-experienced subpopulation; PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs comparator
No psoriasis						
BSC	£55,942	7.38	Referent	Referent	Referent	[redacted]
Ixekizumab q4w	[redacted]	8.21	[redacted]	0.83	[redacted]	Referent
Ustekinumab	£82,143	8.24	[redacted]	0.86	[redacted]	[redacted]
Mild-to-moderate psoriasis						
BSC	£70,271	7.06	Referent	Referent	Referent	[redacted]
Ixekizumab q4w	[redacted]	7.93	[redacted]	0.87	[redacted]	Referent
Ustekinumab	£94,133	7.97	[redacted]	0.91	[redacted]	[redacted]
Moderate-to-severe psoriasis						
BSC	£99,618	2.26	Referent	Referent	Referent	[redacted]
Ixekizumab q2w	[redacted]	3.24	[redacted]	0.98	[redacted]	Referent
Ustekinumab	£118,915	3.21	[redacted]	0.95	[redacted]	[redacted]

Source: Based on Table 55 of the CS[1]

b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; BSC = best supportive care; ICER = incremental cost effectiveness ratio; IXE = ixekizumab; mg = milligram; PAS = patient access scheme; q4w = once every four weeks; QALY = quality-adjusted life year

ERG comment: The ERG wishes to highlight that a) there is a difference in absolute costs and QALYs accrued by comparators in this model compared with the York model, and b) that the b/tsDMARD-experienced analyses do not contain all appropriate comparators.

a) The ERG noticed that compared with the updated York model, total costs of comparators were generally lower in the current model for b/tsDMARD-naive and higher for b/tsDMARD-experienced patients. Total QALYs of comparators were generally higher in the current model for b/tsDMARD-naive and lower for b/tsDMARD-experienced patients. More detail on this can be found in section 5.2.12.
b) The ERG considers that the results presented for the b/tsDMARD-experienced subgroups are incomplete because relevant comparators as identified in the scope are missing (secukinumab and certolizumab pegol), see section 5.2.4 for more details.

5.2.11 Sensitivity analyses

The company performed and presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analyses (DSA) in order to quantify the uncertainty surrounding the base-case results. The PSA contained 2,000 model simulations and PSA results were only shown using the list price for ixekizumab. The PSA showed similar incremental costs and QALYs compared with the deterministic results. Results can be found in Table 57 of the CS[1] and are not reproduced here because they do not take the PAS price into account. At list price, ixekizumab was 0% cost effective at a threshold of £30,000 per QALY gained in all six subgroups.

The company conducted a one-way DSA to study the impact of varying individual parameter values on ICERs of ixekizumab versus secukinumab in the b/tsDMARD-naive and ustekinumab in the b/tsDMARD-experienced population. The three parameters that affected the ICERs most were the PsARC response rates for secukinumab and ixekizumab and the annual discontinuation rate for the b/tsDMARD-naive population, no and mild-to-moderate psoriasis severity. For the moderate-to-severe psoriasis severity level, the three most impactful parameters were the PsARC response for ixekizumab and the treatment costs of ixekizumab and secukinumab, followed by fourth the PsARC response rates for secukinumab and fifth the annual discontinuation rate. In the b/tsDMARD-experienced population, the three most influential parameters were the annual discontinuation rate followed by PsARC response rates for ustekinumab and ixekizumab.

The following scenario analyses were performed by the company (using list prices for all, including ixekizumab):

- Single-treatment comparators in the b/tsDMARD naive population
- Single-treatment comparators in the b/tsDMARD naive population with placebo-adjusted response rates
- Ixekizumab response assessment at 16 weeks instead of at 12 weeks
- Inclusion of secukinumab and certolizumab pegol in b/tsDMARD-experienced patient population
- Alternative excess mortality
- Alternative HAQ-DI related costs (Poole et al. 2010[72])
- HAQ-DI rebound to natural history in BSC
- HAQ-DI rebound to 50% of initial gain
- York model utility coefficients
- 5-level EQ-5D utilities
- PSARC in combination with PASI 75/90/100 as alternative response assessments

These scenarios do have an impact on absolute costs and QALYs but do not change the cost effectiveness conclusions based on list prices, as the ixekizumab sequence was either extendedly dominated or dominated in all scenario analyses which were based on the list price of ixekizumab. Assumptions that had 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 being accounted for).

ERG comment: The ERG considers the deterministic sensitivity analyses to be sufficient. The PSA does not include all relevant parameters for all scenarios, e.g. the Convergence Diagnostic and Output Analysis (CODA) for the extended network for the b/tsDMARD experienced population is not available in the model file. PSA results were not provided for the analyses with ixekizumab PAS price.

5.2.12 Model validation and face validity check

Face validity
Face validity of the conceptual model was assessed in an advisory board with clinical and health economic experts.

Internal validity
The model was developed by an external consultancy company and internal validation was undertaken by another external consultancy company. The programming of the model was checked to identify errors or omissions. A cell-by-cell technical validation was carried out and the VBA code was checked.

Cross validity
The company stated that cross validation by replicating comparisons from previous submissions was difficult because PAS prices for secukinumab and apremilast are confidential.

External validity
The company stated that external validity was difficult to assess, because long term observational studies have not been carried out for ixekizumab.

Predictive validity
A head-to-head study comparing ixekizumab and adalimumab is currently underway and could later be used to assess the predictive validity of the cost effectiveness model.

ERG comment: The ERG has concerns related to the lack of detailed cross validity. The company did provide a cross validation exercise in response to clarification question B21.[25] TA445[13] and TA433[15] were the most relevant studies for cross-validity, as these were also based on the York model and were the most recent TAs. Compared with TA445 (the revised York model):

- Total costs of comparators were generally lower in the current model for b/tsDMARD-naive- and higher for b/tsDMARD-experienced patients.
- Total QALYs of comparators were generally higher in the current model for b/tsDMARD-naive and lower for b/tsDMARD-experienced patients.
- Discrepant results compared with the current model could be explained by
  a. differences in PsARC response probabilities (generally lower in current model),

b. different changes in HAQ-DI for PsARC responders and non-responders (generally larger reduction in current model for PsARC responders),
c. differences in PASI response probabilities as well as PASI baseline scores.

In conclusion, it is unclear why the discrepancies between the current assessment and TA445 exist.

The comparison with TA433 was hampered by the fact that this model did not split the model population into psoriasis and b/tsDMARD-naïve and -experienced subgroups.[15] It was therefore difficult to compare costs and QALYs with the current model. Compared with TA433, total costs of apremilast (the main comparator in TA433) were generally lower in the current model for no- and mild-to-moderate psoriasis subgroups but higher in the moderate-to-severe psoriasis subgroup. Also compared with TA433, total QALYs of apremilast were higher in the current model for no- and mild-to-moderate psoriasis subgroups but lower in the moderate-to-severe psoriasis subgroup.

Details of the cross-validity check provided by the company are shown in Table 5.19 below.

Table 5.19: Cross-validity check

		Current assessment		TA 445		TA433	
Subgroup	**Intervention**	**Total costs**	**Total QALY**	**Total costs**	**Total QALY**	**Total costs**	**Total QALY**
Biologic-naïve, no psoriasis	Certolizumab pegol	£99,866	9.67	£122,832	9.074	-	-
	Secukinumab	£100,241	9.78	£120,303	9.067	-	-
	Apremilast	£93,347	9.49	-	-	£116,199*	8.01*
	BSC	£54,046	8.09	£51,436	6.188	-	-
Biologic-naïve, mild-to-moderate psoriasis	Certolizumab pegol	£111,375	9.34	£135,946	8.667	-	-
	Secukinumab	£111,743	9.47	£132,500	8.685	-	-
	Apremilast	£105,446	9.16	-	-	£116,199*	8.01*
	BSC	£70,00	7.74	£67,000	5.676	-	-
Biologic-naïve moderate-to-severe psoriasis	Certolizumab pegol	£132,373	7.90	£159,951	8.377	-	-
	Secukinumab	£155,532	7.97	£179,692	8.524	-	-
	Apremilast	£127,576	7.70	-	-	£116,199*	8.01*
	BSC	£99,884	6.21	£95,965	5.312	-	-
Biologic-experienced, no psoriasis	Ustekinumab	£82,143	7.38	£76,712	7.132	-	-
	BSC	£55,2	8.24	£51,436	6.188	-	-
Biologic-experienced, mild-to-moderate psoriasis	Ustekinumab	£94,133	7.97	£91,246	6.666	-	-
	BSC	£70,271	7.06	£67,000	5.676	-	-
Biologic-experienced,	Ustekinumab	£118,915	3.21	£118,127	6.334	-	-

		Current assessment		TA 445		TA433	
Subgroup	**Intervention**	**Total costs**	**Total QALY**	**Total costs**	**Total QALY**	**Total costs**	**Total QALY**
moderate-to-severe psoriasis	BSC	£99,618	2.26	£95,965	5.312	-	-

Source: Response to request for clarification[25]
Footnote: * Population in TA433 was not split into subgroups. Therefore costs and QALYs for the total population in TA433 are shown.
BSC = best supportive care; QALY = quality-adjusted life year; TA = technology appraisal

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Table 5.20 summarises the main issues highlighted by the ERG in section 5.2, indicates the expected direction of bias introduced by these issues and whether these are examined in any analyses/incorporated in the ERG base-case.

Table 5.20: Main ERG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
Model structure (section 5.2.2)			
Use of relative effectiveness measure (PsARC response)	+/-	None	Not addressed
Assumption of instantaneous PASI and HAQ-DI improvements	+	None	Not addressed
No modelling of AEs	+	None	Not addressed
Population, interventions and comparators, perspective and time horizon (sections 5.2.3-5.2.5)			
Questionable representativeness of patient population	+/-	None	Not addressed
Baseline PASI scores different from in previous TA	+/-	SA	Not addressed
Selection of treatment sequences unclear	+/-	None	Addressed in SA
Exclusion of comparators in the scope	+	BC (FV)	Partly addressed in SA
Treatment effectiveness and extrapolation (section 5.2.6)			
Calculation of PASI change	+/-	BC (MJ)	Not addressed
Assumption of linear HAQ-DI progression	+	None	Not addressed
Use of a high SMR	+	BC (MJ)	Explored in SA
Assumption of equal treatment discontinuation for all treatments	+	None	Not addressed
Use of NMA results not in line with trial data	+/-	BC (FE)	Not addressed
Health-related quality of life (section 5.2.8)			
Non-adjustment for general population utility values	+/-	BC (MJ)	Addressed in SA
Impacts of AEs on HRQoL not reflected	+	None	Not addressed
Resources and costs (section 5.2.9)			
Modelled HAQ-DI related costs potentially inappropriate	+/-	SA	Addressed in SA
Psoriasis-related costs likely inappropriate	+/-	None	Not addressed

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
Impact of AEs on costs not reflected	+	None	Not addressed
Cost effectiveness analyses (sections 5.2.10 and 5.2.11)			
Comparator costs and QALYs deviate from previous TA445	+/-	None	Not addressed
Validation (section 5.2.12)			
Complete cross validation with previous TAs not performed	NA	None	Partly addressed

Footnotes: [a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator.
AE = adverse event; BC = base-case; ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; HAQ-DI = Health Assessment Questionnaire-Disability Index; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; MJ = matters of judgement; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; SA = scenario analysis; SMR = standardized mortality ratio; TA = technology appraisal

Based on all considerations in section 5.2 (summarised in Table 5.20), the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[103])

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Additionally, exploratory sensitivity analyses were performed by the ERG to examine the potential impact of alternative assumptions on the cost effectiveness estimates.

The ERG's base-case:

Fixing errors

1. NMA results for the reduction in HAQ-DI scores for ixekizumab q4w that are inconsistent with trial data.
   The ERG used the trial data instead of the NMA results.

Fixing violations

2. Use of the limited NMA results for the b/tsDMARD-experienced population, which does not consider PASI50.
   The ERG used the extended NMA for the b/tsDMARD experienced population, which considers PASI50.
3. Exclusion of secukinumab and certolizumab pegol as comparators in b/tsDMARD-experienced patients.
   The ERG included these by using the extended NMA, as per scope.
4. Utilities were not adjusted to general population utility values.
   The ERG adjusted utilities.

Matters of judgment

5. The use of a potentially dated and high SMR.
   The ERG used a SMR derived from more recent data.
6. The use of calculations for PASI change in the model that are inconsistent with the CS report.
   The ERG used the calculations detailed in the CS report (Table 42).

5.3.1 ERG base-case results

The ERG base-case was performed probabilistically for b/tsDMARD-naïve patients and deterministically for b/tsDMARD-experienced patients because there were no probabilistic estimates provided for secukinumab and certolizumab pegol when using the extended NMA (due to CODA not provided for this network). All ERG base-case analyses are conditional on the PAS price of ixekizumab. Additionally, the ERG used secukinumab 300 mg for all psoriasis severity levels in the b/tsDMARD-experienced population because no results were provided for secukinumab 150 mg in the extended NMA. For all analyses including biosimilar etanercept as a comparator, a correlation coefficient of 0.26, instead of 0.4, was used to derive the distribution of PASI 75 responders amongst patients who achieve a PsARC response.

Ixekizumab was [redacted] in all b/tsDMARD-naïve subgroups while it resulted in ICERs of respectively [redacted], [redacted], and [redacted] per QALY gained versus BSC in the no psoriasis, mild-to-moderate psoriasis and moderate-to-severe psoriasis subgroups of 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).

5.3.2 Additional exploratory analyses performed based on the ERG base-case

Additional sensitivity analyses were performed to examine the potential impact of the following alternative assumptions on the cost effectiveness estimates. These were all performed using the ERG base-case. Results are presented in Table 6.2 in section 6. The ERG used secukinumab 300 mg for all psoriasis severity levels in the b/tsDMARD-experienced population because no results were provided for secukinumab 150 mg in the extended NMA.

Exploratory analyses using the ERG base-case:

1. The use of the company's preferred network for the b/tsDMARD-experienced population, excluding secukinumab and certolizumab pegol from the analysis.
2. Use of Poole et al for HAQ-DI related costs instead of Kobelt et al.
3. Use of the York model baseline PASI scores.
4. Alternative second line treatment in b/tsDMARD-naive patients.
5. Use of PASI 75 and PsARC instead of only PsARC.

5.3.3 Subgroup analyses performed based on the ERG base-case

No subgroup analyses were performed.

5.4 Conclusions of the cost effectiveness section

The ERG considers that the company's approach to use the revised York model as a basis for developing their model was appropriate.

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 network meta-analysis that did not consider all the relevant outcomes as identified in the scope.

a) The absence of secukinumab and certolizumab pegol from the b/tsDMARD-experienced patient population analysis was justified by the unavailability of data in that population, however, it should be noted that studies on these two treatments were conducted in mixed (b/tsDMARD-naive and -experienced) populations.
b) The omission of adverse events from the economic model was considered a major limitation by the ERG. The ERG considers that treatment-specific adverse events could have an impact on treatment discontinuation, HRQoL and cost and resource use, and that not reflecting this in the model could lead to biased outcomes. The direction of this bias is difficult to determine.

The company's deterministic base-case 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 QALY gained in the b/tsDMARD-experienced population when compared with BSC but [redacted] when compared with ustekinumab in that population. 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. 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.

In exploratory analysis the ERG found that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population, except in the scenario in which both PASI 75 and PsARC responses were used simultaneously to determine treatment response. In that scenario, ixekizumab resulted in an ICER of [redacted] per QALY gained versus BSC in the moderate-to-severe psoriasis subgroup. In the b/tsDMARD-experienced population, ixekizumab resulted in ICERs below [redacted] per QALY gained versus BSC in all psoriasis severity levels in all scenarios, except when both PASI 75 and PsARC responses were used simultaneously to determine treatment response. In this scenario, ixekizumab [redacted]. 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), except in Scenario 1 in moderate-to severe psoriasis when ustekinumab [redacted].

In conclusion, despite the ERG criticism and amendments to the company's cost effectiveness analysis, ixekizumab remained [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population. Ixekizumab had ICERs [redacted] per QALY gained versus BSC in the b/tsDMARD-experienced population. Using both PASI 75 and PsARC responses simultaneously to determine treatment response was the most influential scenario analysis performed by the ERG.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Analyses undertaken by the ERG

In section 5.3, the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.1 shows both the probabilistic company and ERG base-case analyses. The analyses numbers in Table 6.1 correspond to the analyses numbers reported in Section 5.3. Moreover, the exploratory sensitivity analyses, conditional on the ERG base-case, are presented in Table 6.2. Appendix 2 and the economic model sent by the ERG contain the technical details on the analyses performed by the ERG.

Table 6.1: Probabilistic ERG base-case; PAS price

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
Company base-case (probabilistic, performed by the ERG)						
bDMARD-naïve; no psoriasis						
BSC	£54,046	8.09	-	-	-	[redacted]
APR-UST-BSC	£93,347	9.49	[redacted]	1.39	[redacted]	[redacted]
IXE q4w-UST-BSC	[redacted]	9.69	[redacted]	1.60	[redacted]	Referent
CZP-UST-BSC	£99,866	9.67	[redacted]	1.57	[redacted]	[redacted]
SEC150-UST-BSC	£100,241	9.78	[redacted]	1.68	[redacted]	[redacted]
ADA-UST-BSC	£101,322	9.71	[redacted]	1.61	[redacted]	[redacted]
ETA-UST-BSC	£103,692	10.02	[redacted]	1.92	[redacted]	[redacted]
GOL-UST-BSC	£108,195	9.90	[redacted]	-0.12	[redacted]	[redacted]
INF-UST-BSC	£127,297	10.12	[redacted]	0.10	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£70,006	7.74	-	-	-	[redacted]
APR-UST-BSC	£105,446	9.16	[redacted]	1.41	[redacted]	[redacted]
IXE q4w-UST-BSC	[redacted]	9.38	[redacted]	1.64	[redacted]	Referent
CZP-UST-BSC	£111,375	9.34	[redacted]	1.60	[redacted]	[redacted]
SEC150-UST-BSC	£111,743	9.47	[redacted]	1.72	[redacted]	[redacted]
ADA-UST-BSC	£112,849	9.39	[redacted]	1.64	[redacted]	[redacted]
ETA-UST-BSC	£114,657	9.69	[redacted]	1.95	[redacted]	[redacted]
GOL-UST-BSC	£118,987	9.59	[redacted]	-0.10	[redacted]	[redacted]
INF-UST-BSC	£138,072	9.82	[redacted]	0.13	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£99,884	6.21	-	-	-	[redacted]
APR-UST-BSC	£127,576	7.70	[redacted]	1.49	[redacted]	[redacted]
CZP-UST-BSC	£132,373	7.90	[redacted]	1.69	[redacted]	[redacted]
ADA-UST-BSC	£133,882	7.97	[redacted]	1.77	[redacted]	[redacted]
IXE q2w-UST-BSC	[redacted]	8.11	[redacted]	1.91	[redacted]	Referent
ETA-UST-BSC	£134,567	8.24	[redacted]	2.03	[redacted]	[redacted]
GOL-UST-BSC	£138,550	8.23	[redacted]	-0.01	[redacted]	[redacted]
SEC300-UST-BSC	£155,532	7.97	[redacted]	-0.27	[redacted]	[redacted]
INF-UST-BSC	£157,603	8.51	[redacted]	0.27	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£55,942	7.38	-	-	-	[redacted]
IXE q4w-BSC	[redacted]	8.21	[redacted]	0.83	[redacted]	Referent
UST-BSC	£82,143	8.24	[redacted]	0.03	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£70,271	7.06	-	-	-	[redacted]
IXE q4w-BSC	[redacted]	7.93	[redacted]	0.87	[redacted]	Referent
UST-BSC	£94,133	7.97	[redacted]	0.03	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£99,618	2.26	-	-	-	[redacted]
IXE q2w-BSC	[redacted]	3.24	[redacted]	0.98	[redacted]	Referent
UST-BSC	£118,915	3.21	[redacted]	-0.03	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
ERG base-case						
bDMARD-naïve; no psoriasis (probabilistic)						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-UST-BSC	£99,754	9.89	[redacted]	1.54	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	10.04	[redacted]	1.69	[redacted]	Referent
CZP-UST-BSC	£106,247	10.08	[redacted]	1.73	[redacted]	[redacted]
SEC150-UST-BSC	£106,591	10.15	[redacted]	1.80	[redacted]	[redacted]
ADA-UST-BSC	£107,703	10.12	[redacted]	1.77	[redacted]	[redacted]
ETA-UST-BSC	£109,998	10.34	[redacted]	1.99	[redacted]	[redacted]
GOL-UST-BSC	£114,501	10.31	[redacted]	-0.02	[redacted]	[redacted]
INF-UST-BSC	£133,706	10.41	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis (probabilistic)						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-UST-BSC	£112,192	9.61	[redacted]	1.62	[redacted]	[redacted]
IXE q4w-UST-BSC	[redacted]	9.76	[redacted]	1.78	[redacted]	Referent
CZP-UST-BSC	£118,101	9.80	[redacted]	1.82	[redacted]	[redacted]
SEC150-UST-BSC	£118,438	9.89	[redacted]	1.91	[redacted]	[redacted]
ADA-UST-BSC	£119,574	9.84	[redacted]	1.85	[redacted]	[redacted]
ETA-UST-BSC	£121,313	10.09	[redacted]	2.10	[redacted]	[redacted]
GOL-UST-BSC	£125,644	10.05	[redacted]	-0.04	[redacted]	[redacted]
INF-UST-BSC	£144,833	10.17	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis (probabilistic)						
BSC	£104,874	6.38	-	-	-	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
APR-UST-BSC	£134,903	8.33	[redacted]	1.95	[redacted]	[redacted]
CZP-UST-BSC	£139,690	8.56	[redacted]	2.18	[redacted]	[redacted]
ADA-UST-BSC	£141,198	8.59	[redacted]	2.22	[redacted]	[redacted]
IXE q2w-UST-BSC	[redacted]	8.68	[redacted]	2.30	[redacted]	Referent
ETA-UST-BSC	£141,826	8.96	[redacted]	2.58	[redacted]	[redacted]
GOL-UST-BSC	£145,815	8.85	[redacted]	-0.11	[redacted]	[redacted]
SEC300-UST-BSC	£162,971	8.55	[redacted]	-0.41	[redacted]	[redacted]
INF-UST-BSC	£164,972	9.07	[redacted]	0.11	[redacted]	[redacted]
bDMARD-experienced; no psoriasis (deterministic)						
BSC	£58,838	7.61	-	-	-	[redacted]
IXE q4w -BSC	[redacted]	8.54	[redacted]	0.93	[redacted]	Referent
CZP -BSC	£83,355	8.53	[redacted]	-0.02	[redacted]	[redacted]
UST-BSC	£88,828	8.64	[redacted]	0.09	[redacted]	[redacted]
SEC300-BSC	£106,747	8.54	[redacted]	-0.10	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis (deterministic)						
BSC	£73,880	7.26	-	-	-	[redacted]
IXE q4w-BSC	[redacted]	8.36	[redacted]	1.09	[redacted]	Referent
CZP-BSC	£95,702	8.35	[redacted]	-0.01	[redacted]	[redacted]
UST-BSC	£101,087	8.46	[redacted]	0.11	[redacted]	[redacted]
SEC300-BSC	£119,384	8.31	[redacted]	-0.15	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis (deterministic)						
BSC	£104,602	2.23	-	-	-	[redacted]
CZP-BSC	£121,172	3.98	£16,570	1.75	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
IXE q2w-BSC	[redacted]	4.11	[redacted]	0.13	[redacted]	Referent
UST-BSC	£126,390	4.13	[redacted]	0.02	[redacted]	[redacted]
SEC300-BSC	£145,424	3.91	[redacted]	-0.22	[redacted]	[redacted]

ADA = adalimumab; APR = apremilast; bDMARD = biologic disease-modifying anti-rheumatic drug; BSC = best supportive care; CZP = certolizumab pegol; ERG = Evidence Review Group; ETA = etanercept; GOL = golimumab; ICER = Incremental cost effectiveness ratio; INF = infliximab; IXE = ixekizumab; PAS = patient access scheme; q2w = once every two weeks; q4w = once every four weeks; QALY = quality-adjusted life year; SEC = secukinumab; UST = ustekinumab

Table 6.2: Deterministic scenario analyses conditional on ERG base-case, PAS price

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
ERG base-case (deterministic)						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-UST-BSC	£99,754	9.89	[redacted]	1.54	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	10.04	[redacted]	1.69	[redacted]	Referent
CZP-UST-BSC	£106,247	10.08	[redacted]	1.73	[redacted]	[redacted]
SEC150-UST-BSC	£106,591	10.15	[redacted]	1.80	[redacted]	[redacted]
ADA-UST-BSC	£107,703	10.12	[redacted]	1.77	[redacted]	[redacted]
ETA-UST-BSC	£109,998	10.34	[redacted]	1.99	[redacted]	[redacted]
GOL-UST-BSC	£114,501	10.31	[redacted]	-0.02	[redacted]	[redacted]
INF-UST-BSC	£133,706	10.41	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-UST-BSC	£112,192	9.61	[redacted]	1.62	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.76	[redacted]	1.78	[redacted]	Referent
CZP-UST-BSC	£118,101	9.80	[redacted]	1.82	[redacted]	[redacted]
SEC150-UST-BSC	£118,438	9.89	[redacted]	1.91	[redacted]	[redacted]
ADA-UST-BSC	£119,574	9.84	[redacted]	1.85	[redacted]	[redacted]
ETA-UST-BSC	£121,313	10.09	[redacted]	2.10	[redacted]	[redacted]
GOL-UST-BSC	£125,644	10.05	[redacted]	-0.04	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
INF-UST-BSC	£144,833	10.17	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	£0	[redacted]
APR-UST-BSC	£134,903	8.33	[redacted]	1.95	[redacted]	[redacted]
CZP-UST-BSC	£139,690	8.56	[redacted]	2.18	[redacted]	[redacted]
ADA-UST-BSC	£141,198	8.59	[redacted]	2.22	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	8.68	[redacted]	2.30	[redacted]	Referent
ETA -UST-BSC	£141,826	8.96	[redacted]	2.58	[redacted]	[redacted]
GOL-UST-BSC	£145,815	8.85	[redacted]	-0.11	[redacted]	[redacted]
SEC300-UST-BSC	£162,971	8.55	[redacted]	-0.41	[redacted]	[redacted]
INF-UST-BSC	£164,972	9.07	[redacted]	0.11	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£58,838	7.61	-	-	-	[redacted]
IXEq4w -BSC	[redacted]	8.54	[redacted]	0.93	[redacted]	Referent
CZP-BSC	£83,355	8.53	[redacted]	-0.02	[redacted]	[redacted]
UST-BSC	£88,828	8.64	[redacted]	0.09	[redacted]	[redacted]
SEC300-BSC	£106,747	8.54	[redacted]	-0.10	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£73,880	7.26	-	-	£0	[redacted]
IXEq4w-BSC	[redacted]	8.36	[redacted]	1.09	[redacted]	Referent
CZP-BSC	£95,702	8.35	[redacted]	-0.01	[redacted]	[redacted]
UST-BSC	£101,087	8.46	[redacted]	0.11	[redacted]	[redacted]
SEC300-BSC	£119,384	8.31	[redacted]	-0.15	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£104,602	2.23	-	-	£0	[redacted]
CZP-BSC	£121,172	3.98	[redacted]	1.75	[redacted]	[redacted]
IXEq2w-BSC	[redacted]	4.11	[redacted]	0.13	[redacted]	Referent
UST-BSC	£126,390	4.13	[redacted]	0.02	[redacted]	[redacted]
SEC300-BSC	£145,424	3.91	[redacted]	-0.22	[redacted]	[redacted]
Scenario 1: The use of the company's preferred network for the bDMARD-experienced population, excluding secukinumab and certolizumab pegol from the analysis.						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-UST-BSC	£96,450	9.77	[redacted]	1.42	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.92	[redacted]	1.57	[redacted]	Referent
CZP-UST-BSC	£103,043	9.96	[redacted]	1.61	[redacted]	[redacted]
SEC 150-UST-BSC	£103,393	10.03	[redacted]	1.68	[redacted]	[redacted]
ADA-UST-BSC	£104,495	10.00	[redacted]	1.65	[redacted]	[redacted]
ETA 150-UST-BSC	£106,901	10.22	[redacted]	1.87	[redacted]	[redacted]
GOL-UST-BSC	£111,437	10.20	[redacted]	-0.02	[redacted]	[redacted]
INF-UST-BSC	£130,648	10.30	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-UST-BSC	£109,258	9.48	[redacted]	1.49	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.63	[redacted]	1.65	[redacted]	Referent

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-UST-BSC	£115,255	9.67	[redacted]	1.69	[redacted]	[redacted]
SEC150-UST-BSC	£115,598	9.76	[redacted]	1.78	[redacted]	[redacted]
ADA-UST-BSC	£116,725	9.71	[redacted]	1.73	[redacted]	[redacted]
ETA-UST-BSC	£118,563	9.96	[redacted]	1.98	[redacted]	[redacted]
GOL-UST-BSC	£122,924	9.93	[redacted]	-0.04	[redacted]	[redacted]
INF-UST-BSC	£142,118	10.04	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	£0	[redacted]
APR-UST-BSC	£132,710	8.14	[redacted]	1.76	[redacted]	[redacted]
CZP-UST-BSC	£137,563	8.38	[redacted]	2.00	[redacted]	[redacted]
ADA-UST-BSC	£139,069	8.42	[redacted]	2.04	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	8.50	[redacted]	2.12	[redacted]	Referent
ETA-UST-BSC	£139,770	8.79	[redacted]	2.41	[redacted]	[redacted]
GOL-UST-BSC	£143,781	8.68	[redacted]	-0.10	[redacted]	[redacted]
SEC300-UST-BSC	£160,813	8.36	[redacted]	-0.42	[redacted]	[redacted]
INF-UST-BSC	£162,942	8.90	[redacted]	0.11	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£58,838	7.61	-	-	-	[redacted]
IXEq4w-BSC	[redacted]	8.40	[redacted]	0.79	[redacted]	Referent
UST-BSC	£85,151	8.49	[redacted]	0.10	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£73,880	7.26	-	-	-	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
IXEq4w -BSC	[redacted]	8.18	[redacted]	0.92	[redacted]	Referent
UST-BSC	£97,830	8.28	[redacted]	0.10	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£104,602	2.23	-	-	-	[redacted]
IXEq2w -BSC	[redacted]	3.80	[redacted]	1.57	[redacted]	Referent
UST-BSC	£123,956	3.77	[redacted]	-0.03	[redacted]	[redacted]
Scenario 2: Use of Poole et al.[72] for HAQ-DI related costs instead of Kobelt et al.[100]						
bDMARD-naïve; no psoriasis						
BSC	£36,728	8.35	-	-	-	[redacted]
APR-UST-BSC	£72,980	9.89	[redacted]	1.54	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	10.04	[redacted]	1.69	[redacted]	Referent
CZP-UST-BSC	£79,793	10.08	[redacted]	1.73	[redacted]	[redacted]
SEC150-UST-BSC	£80,172	10.15	[redacted]	1.80	[redacted]	[redacted]
ADA-UST-BSC	£81,297	10.12	[redacted]	1.77	[redacted]	[redacted]
ETA-UST-BSC	£83,130	10.34	[redacted]	1.99	[redacted]	[redacted]
GOL-UST-BSC	£87,305	10.31	[redacted]	-0.02	[redacted]	[redacted]
INF-UST-BSC	£106,666	10.41	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£36,728	7.99	-	-	-	[redacted]
APR-UST-BSC	£72,980	9.61	[redacted]	1.62	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.76	[redacted]	1.78	[redacted]	Referent

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-UST-BSC	£79,793	9.80	[redacted]	1.82	[redacted]	[redacted]
SEC150-UST-BSC	£80,172	9.89	[redacted]	1.91	[redacted]	[redacted]
ADA-UST-BSC	£81,297	9.84	[redacted]	1.85	[redacted]	[redacted]
ETA-UST-BSC	£83,130	10.09	[redacted]	2.10	[redacted]	[redacted]
GOL-UST-BSC	£87,305	10.05	[redacted]	-0.04	[redacted]	[redacted]
INF-UST-BSC	£106,666	10.17	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£37,361	6.38	-	-	£0	[redacted]
APR-UST-BSC	£73,474	8.33	[redacted]	1.95	[redacted]	[redacted]
CZP-UST-BSC	£80,270	8.56	[redacted]	2.18	[redacted]	[redacted]
ADA-UST-BSC	£81,772	8.59	[redacted]	2.22	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	8.68	[redacted]	2.30	[redacted]	Referent
ETA-UST-BSC	£83,580	8.96	[redacted]	2.58	[redacted]	[redacted]
GOL-UST-BSC	£87,757	8.85	[redacted]	-0.11	[redacted]	[redacted]
SEC300-UST-BSC	£103,068	8.55	[redacted]	-0.41	[redacted]	[redacted]
INF-UST-BSC	£107,108	9.07	[redacted]	0.11	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£44,052	7.61	-	-	£0	[redacted]
IXEq4w -BSC	[redacted]	8.54	[redacted]	0.93	[redacted]	Referent
CZP-BSC	£63,939	8.53	[redacted]	-0.02	[redacted]	[redacted]
UST-BSC	£69,163	8.64	[redacted]	0.09	[redacted]	[redacted]
SEC300-BSC	£87,760	8.54	[redacted]	-0.10	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£37,680	7.26	-	-	£0	[redacted]
IXEq4w -BSC	[redacted]	8.36	[redacted]	1.09	[redacted]	Referent
CZP -BSC	£58,297	8.35	[redacted]	-0.01	[redacted]	[redacted]
UST-BSC	£63,602	8.46	[redacted]	0.11	[redacted]	[redacted]
SEC300-BSC	£82,091	8.31	[redacted]	-0.15	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£36,414	2.23	-	-	-	[redacted]
CZP -BSC	£57,191	3.98	[redacted]	1.75	[redacted]	[redacted]
IXEq2w -BSC	[redacted]	4.11	[redacted]	1.88	[redacted]	Referent
UST-BSC	£62,512	4.13	[redacted]	0.02	[redacted]	[redacted]
SEC300 -BSC	£80,978	3.91	[redacted]	-0.22	[redacted]	[redacted]
Scenario 3: Use of the York model baseline PASI scores.						
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.67	-	-	-	[redacted]
APR-UST-BSC	£112,192	9.36	[redacted]	1.69	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.52	[redacted]	1.85	[redacted]	Referent
CZP-UST-BSC	£118,101	9.56	[redacted]	1.89	[redacted]	[redacted]
SEC150-UST-BSC	£118,438	9.66	[redacted]	1.99	[redacted]	[redacted]
ADA-UST-BSC	£119,574	9.60	[redacted]	1.93	[redacted]	[redacted]
ETA-UST-BSC	£121,313	9.87	[redacted]	2.20	[redacted]	[redacted]
GOL-UST-BSC	£125,644	9.82	[redacted]	-0.05	[redacted]	[redacted]
INF-UST-BSC	£144,833	9.95	[redacted]	0.08	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	7.12	-	-	-	[redacted]
APR-UST-BSC	£134,903	8.91	[redacted]	1.79	[redacted]	[redacted]
CZP-UST-BSC	£139,690	9.12	[redacted]	2.00	[redacted]	[redacted]
ADA-UST-BSC	£141,198	9.16	[redacted]	2.04	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	9.23	[redacted]	2.11	[redacted]	Referent
ETA-UST-BSC	£141,826	9.48	[redacted]	2.36	[redacted]	[redacted]
GOL-UST-BSC	£145,815	9.39	[redacted]	-0.09	[redacted]	[redacted]
SEC300-UST-BSC	£162,971	9.12	[redacted]	-0.36	[redacted]	[redacted]
INF-UST-BSC	£164,972	9.57	[redacted]	0.09	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£73,880	6.32	-	-	-	[redacted]
IXEq4w -BSC	[redacted]	7.53	[redacted]	1.21	[redacted]	Referent
CZP-BSC	£95,702	7.52	[redacted]	0.00	[redacted]	[redacted]
UST-BSC	£101,087	7.65	[redacted]	0.12	[redacted]	[redacted]
SEC300-BSC	£119,384	7.51	[redacted]	-0.14	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£104,602	5.09	-	-	-	[redacted]
CZP-BSC	£121,172	6.48	[redacted]	1.39	[redacted]	[redacted]
IXEq2w-BSC	[redacted]	6.60	[redacted]	1.51	[redacted]	Referent
UST-BSC	£126,390	6.61	[redacted]	0.01	[redacted]	[redacted]
SEC300-BSC	£145,424	6.44	[redacted]	-0.17	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
Scenario 4: Alternative second line treatment in bDMARD-naive patients.						
Second-line certolizumab pegol						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-CZP-BSC	£94,747	9.80	[redacted]	1.45	[redacted]	[redacted]
IXEq4w-CZP-BSC	[redacted]	9.95	[redacted]	1.60	[redacted]	Referent
SEC150-CZP-BSC	£101,737	10.07	[redacted]	1.71	[redacted]	[redacted]
ADA-CZP-BSC	£102,840	10.03	[redacted]	1.68	[redacted]	[redacted]
ETA-CZP-BSC	£105,293	10.25	[redacted]	1.90	[redacted]	[redacted]
GOL-CZP-BSC	£109,844	10.23	[redacted]	-0.02	[redacted]	[redacted]
INF-CZP-BSC	£129,054	10.33	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-CZP-BSC	£107,261	9.51	[redacted]	1.53	[redacted]	[redacted]
IXEq4w-CZP-BSC	[redacted]	9.67	[redacted]	1.68	[redacted]	Referent
SEC150-CZP-BSC	£113,658	9.80	[redacted]	1.81	[redacted]	[redacted]
ADA-CZP-BSC	£114,785	9.75	[redacted]	1.76	[redacted]	[redacted]
ETA-CZP-BSC	£116,679	10.00	[redacted]	2.02	[redacted]	[redacted]
GOL-CZP-BSC	£121,058	9.96	[redacted]	-0.04	[redacted]	[redacted]
INF-CZP-BSC	£140,252	10.08	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	£0	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
APR-CZP-BSC	£130,123	8.22	[redacted]	1.84	[redacted]	[redacted]
ADA-CZP-BSC	£136,556	8.49	[redacted]	2.12	[redacted]	[redacted]
IXEq2w-CZP-BSC	[redacted]	8.58	[redacted]	2.20	[redacted]	Referent
ETA-CZP-BSC	£137,333	8.86	[redacted]	2.49	[redacted]	[redacted]
GOL-CZP-BSC	£141,368	8.76	[redacted]	-0.10	[redacted]	[redacted]
SEC300-CZP-BSC	£158,263	8.44	[redacted]	-0.42	[redacted]	[redacted]
INF-CZP-BSC	£160,531	8.97	[redacted]	0.11	[redacted]	[redacted]
Second-line secukinumab						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-		[redacted]
APR-SEC-BSC	£115,979	9.77	[redacted]	1.42	[redacted]	[redacted]
IXEq4w-SEC-BSC	[redacted]	9.93	[redacted]	1.58	[redacted]	Referent
CZP-SEC-BSC	£121,980	9.96	[redacted]	1.61	[redacted]	[redacted]
ADA-SEC-BSC	£123,452	10.00	[redacted]	1.65	[redacted]	[redacted]
ETA-SEC-BSC	£125,210	10.23	[redacted]	1.88	[redacted]	[redacted]
GOL-SEC-BSC	£129,547	10.21	[redacted]	-0.02	[redacted]	[redacted]
INF-SEC-BSC	£148,725	10.30	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	£0	[redacted]
APR-SEC-BSC	£128,749	9.49	[redacted]	1.51	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
IXEq4w-SEC-BSC	[redacted]	9.65	[redacted]	1.66	[redacted]	Referent
CZP-SEC-BSC	£134,155	9.69	[redacted]	1.71	[redacted]	[redacted]
ADA-SEC-BSC	£135,646	9.73	[redacted]	1.74	[redacted]	[redacted]
ETA-SEC-BSC	£136,836	9.98	[redacted]	2.00	[redacted]	[redacted]
GOL-SEC-BSC	£140,998	9.95	[redacted]	-0.04	[redacted]	[redacted]
INF-SEC-BSC	£160,160	10.06	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	£0	[redacted]
APR-SEC-BSC	£152,123	8.20	[redacted]	1.83	[redacted]	[redacted]
CZP-SEC-BSC	£156,388	8.44	[redacted]	2.06	[redacted]	[redacted]
ADA-SEC-BSC	£157,914	8.48	[redacted]	2.10	[redacted]	[redacted]
ETA-SEC-BSC	£157,970	8.85	[redacted]	2.47	[redacted]	[redacted]
IXEq2w-SEC-BSC	[redacted]	8.56	[redacted]	-0.29	[redacted]	Referent
GOL-SEC-BSC	£161,783	8.74	[redacted]	-0.10	[redacted]	[redacted]
INF-SEC-BSC	£180,913	8.96	[redacted]	0.11	[redacted]	[redacted]
Scenario 5: Use of PASI 75 & PsARC instead of only PsARC						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-UST-BSC	£88,297	9.41	[redacted]	1.06	[redacted]	[redacted]
ETA-UST-BSC	£89,270	9.45	[redacted]	1.10	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-UST-BSC	£89,445	9.47	[redacted]	1.12	[redacted]	[redacted]
ADA-UST-BSC	£93,971	9.59	[redacted]	1.24	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.79	[redacted]	1.44	[redacted]	Referent
SEC-UST-BSC	£98,711	9.82	[redacted]	1.46	[redacted]	[redacted]
GOL-UST-BSC	£100,301	9.79	[redacted]	-0.03	[redacted]	[redacted]
INF-UST-BSC	£124,354	10.13	[redacted]	0.32	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-UST-BSC	£102,249	9.10	[redacted]	1.12	[redacted]	[redacted]
ETA-UST-BSC	£103,121	9.14	[redacted]	1.16	[redacted]	[redacted]
CZP-UST-BSC	£103,147	9.16	[redacted]	1.18	[redacted]	[redacted]
ADA-UST-BSC	£107,381	9.29	[redacted]	1.30	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.50	[redacted]	1.51	[redacted]	Referent
SEC-UST-BSC	£111,545	9.53	[redacted]	1.55	[redacted]	[redacted]
GOL-UST-BSC	£113,031	9.50	[redacted]	-0.04	[redacted]	[redacted]
INF-UST-BSC	£136,306	9.87	[redacted]	0.34	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	-	[redacted]
APR-UST-BSC	£128,012	7.71	[redacted]	1.33	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-UST-BSC	£128,430	7.79	[redacted]	1.41	[redacted]	[redacted]
ETA-UST-BSC	£128,704	7.77	[redacted]	1.40	[redacted]	[redacted]
ADA-UST-BSC	£132,082	7.93	[redacted]	1.55	[redacted]	[redacted]
GOL-UST-BSC	£136,374	8.19	[redacted]	1.81	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	8.34	[redacted]	1.96	[redacted]	Referent
SEC300-UST-BSC	£155,462	8.19	[redacted]	-0.15	[redacted]	[redacted]
INF-UST-BSC	£158,093	8.70	[redacted]	0.36	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£58,838	7.61	-	-	-	[redacted]
SEC300-BSC	£63,744	7.70	[redacted]	0.08	[redacted]	[redacted]
IXEq4w-BSC	[redacted]	8.13	[redacted]	0.52	[redacted]	Referent
CZP-BSC	£73,787	8.18	[redacted]	0.57	[redacted]	[redacted]
UST-BSC	£84,054	8.45	[redacted]	0.27	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£73,880	7.26	-	-	£0	[redacted]
SEC300-BSC	£78,735	7.35	[redacted]	0.09	[redacted]	[redacted]
IXEq4w-BSC	[redacted]	7.87	[redacted]	0.61	[redacted]	Referent
CZP-BSC	£87,175	7.94	[redacted]	0.68	[redacted]	[redacted]
UST-BSC	£96,859	8.24	[redacted]	0.30	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£104,602	2.23	-	-	-	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-BSC	£114,685	3.32	[redacted]	1.09	[redacted]	[redacted]
IXEq2w-BSC	[redacted]	3.34	[redacted]	0.02	[redacted]	Referent
UST-BSC	£123,230	3.78	[redacted]	0.46	[redacted]	[redacted]
SEC300-BSC	£139,794	3.63	[redacted]	-0.15	[redacted]	[redacted]

Note: Small discrepancies between full incremental and pairwise ICERs are caused by rounding. Full incremental ICERs are correct.
ADA = adalimumab; APR = apremilast; bDMARD = biologic disease-modifying anti-rheumatic drug; BSC = best supportive care; CZP = certolizumab pegol; ERG = Evidence Review Group; ETA = etanercept; GOL = golimumab; ICER = Incremental cost effectiveness ratio; INF = infliximab; IXE = ixekizumab; PAS = patient access scheme; q2w = once every two weeks; q4w = once every four weeks; QALY = quality-adjusted life year; SEC = secukinumab; UST = ustekinumab

7. END OF LIFE

Not relevant for this submission.

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, ixekizumab was [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], with [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 bMARD-experienced patients (fewer than five trials in most analyses) and ixekizumab [redacted] ustekinumab for PsARC response. For PASI response, ustekinumab had the [redacted] response rate [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 [redacted] was the most effective treatment across all categories of ACR response but it was [redacted]. 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.

Economic evaluation

The company's deterministic base-case 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 QALY gained in the b/tsDMARD-experienced population when compared with BSC but [redacted] when compared with ustekinumab in that population at all severity levels. The ERG has incorporated various adjustments to the company base-case (probabilistic results for the b/tsDMARD-naïve population and deterministic results for the b/tsDMARD-experienced population). In the ERG base-case, ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per QALY gained versus BSC 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). Additionally, the ERG explored different scenarios based on the ERG base-case analysis. In those analyses, ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population, except in the scenario in which both PASI 75 and PsARC responses were used simultaneously to determine treatment response. In that scenario, ixekizumab had an ICER of [redacted] per QALY gained versus BSC in the moderate-to-severe psoriasis subgroup. In the b/tsDMARD-experienced population, ixekizumab had ICERs below [redacted] per QALY gained versus BSC in all psoriasis severity levels in all scenarios, except when both PASI 75 and PsARC responses were used simultaneously to determine treatment response. In this scenario, ixekizumab [redacted].

In conclusion, despite the ERG criticism and amendments to company cost effectiveness analysis, ixekizumab remained [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population. Ixekizumab provided ICERs [redacted] per QALY gained versus BSC in the b/tsDMARD-experienced population. Using both PASI 75 and PsARC responses simultaneously to determine treatment response was the most influential scenario analysis performed by the ERG.

8.2 Strengths and limitations of the assessment

Following clarification, the company submission searches were well presented and reproducible. Searches were carried out on a range of databases and supplementary resources. However, the ERG was concerned about the overall quality of the searches conducted, as there were numerous inconsistencies, inaccuracies, errors and redundancy throughout. The extensive use of restrict to focus, date limit (2000-2017), omission of the NHS EED database and application of language limits were all considered overly restrictive. It is possible that relevant evidence may have been missed as a consequence.

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.

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Appendix 1: ERG search strategies

Detailed critique of clinical effectiveness searches:

- The database searches were clearly structured (population and study design), using a combination of subject heading indexing and free text terms, with synonyms, adjacency operators and truncation.
- During the clarification process, the ERG asked why the clinical effectiveness searches were restricted to English language.[80] The company responded that '*Most key clinical publications are typically published in the English languages and all publications identified as relevant in previous appraisals in PsA were in the English language'*.[64] The ERG did not accept this explanation as adequate reassurance that language bias had not been introduced during the search process. Current best practice states that *'Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication'*.[63]
- In the Medline, Embase and CENTRAL search for the initial review, line #2 was an orphan line and omitted from the final results. Interleukin was incorrect spelled, and IL was incorrectly included in the term "Interluekin IL-17a".
- In the Medline and CENTRAL searches for the initial review, Emtree subject indexing terms were used incorrectly instead of MeSH terms. Throughout both strategies, the Emtree terms retrieved 0 hits in the population and intervention/comparator facets.
- The Updated Medline search is incorrectly reported as having a date limit of *'August 2018 to May 2017'*.
- The PICO criteria presented in Table 9 (page 18)[28], list *'systematic literature reviews'* as an inclusion criteria for study design. Searches were restricted to randomised controlled trials. A systematic review study design filter was not used and specific systematic review databases, such as CDSR or DARE, were not searched. Therefore, attempts to identify SLRs were sub-optimal.
- No attempts were made to tailor the search to find non-randomised or adverse events literature.

Detailed critique of cost effectiveness searches:

- The NHS Economic Evaluation Database (NHS EED) was not searched and would have been a useful addition to the company's searches. In the clarification response B3, the company stated that "*The Centre for Reviews and Dissemination was searched for relevant cost effectiveness data. The CRD search included the NHS EED, DARE and HTA databases*".[25] The ERG's test search of DARE, NHS EED and HTA databases via the Cochrane Library demonstrated that the searches presented in the company submission were only carried out on the HTA database. NHS EED and DARE were not searched. The company searches reported in Tables 37 and 41 of the clarification response document searches restricted only to the HTA database. It is important to note that the ERG's test search below demonstrated that there were 17 references unique to NHS EED that were not retrieved from the HTA database. These references were potentially relevant economic studies.

ERG search of DARE, NHS EED and HTA via the Cochrane Library (Wiley)

Searched 9.4.18

#1 psoriatic arthritis in Other Reviews, Technology Assessments and Economic Evaluations 85

#2 psoriatic arthritis in Technology Assessments 36

#3 psoriatic arthritis in Economic Evaluations 17

#4 #3 not #2 17 [unique references in NHS EED, not contained in HTA database]

Company searches presented in the clarification response[25]

Table 37 Search string for CEM studies in CRD-HTA

Search	Query - models	Items found*
1	(psoriatic arthritis) IN HTA	33

Table 41 Search string for model input studies in CRD-HTA

Search	Query	Items found*
1	(psoriatic arthritis) IN HTA	33

- The PubMed strategy presented in Table 34 of the clarification response[25] contained a spelling error in the MeSH terms for "Markov Chain" in line #13. "Markov Chaines" [MESH] is not a valid MESH term and retrieved 0 hits. The ERG conducted a test search to explore the potential impact for this spelling error. The correct MeSH term (line #6) retrieves 12250 PubMed records (line #8) not picked up by the free text equivalent (line #7). This consequential typographical error would impair recall of references reporting use of this analytical method.

ERG test search for Markov Chains in PubMed (Internet)

Searched 9.4.18

Search	Add to builder	Query	Items found	Time
#8	Add	Search **(#6 NOT #7)**	12250	10:23:15
#7	Add	Search **"markov chains"[Title/Abstract]**	629	10:21:48
#6	Add	Search **"Markov Chains"[Mesh:NoExp]**	12570	10:21:20

- Medline and Embase searches for both CEM and model inputs presented in Tables 26, 30, 35, 36, 39 and 40 of the clarification response, all show extensive use of Restrict to Focus in the MeSH and Emtree subject indexing.[25] The ERG noted the for both CEM and model inputs Medline and Embase searches used extensive focused MeSH and Emtree indexing terms which may have adversely affect recall of the search strategies. When restriction to focus (RTF) is applied to subject indexing terms, only Major subject indexing headings are retrieved. The ERG considered the extensive use of RTF overly restrictive and potentially impairing recall of possibly relevant references and did not consider the extensive implementation of RFT in the Embase and Medline searches adequately sensitive for this systematic review. Extensive RTF was applied to the indexing within the cost facet for the CEM Embase and Medline searches, where only Major subject indexing headings were retrieved. The model inputs searches in Embase showed that extensive RTF was applied to the Quality of life/HRQOL, cost, and UK/Europe components. The Medline model inputs searches showed that extensive RTF was applied to the Quality of life/HRQOL, and cost components. Recent investigations have been conducted into the impact of using RTF in Emtree on overall search sensitivity and recall.[61, 62] Current recommendations for best practice advocate caution when considering introduction of RTF in the population facet of an Embase search. Furthermore, prudence is also recommended when considering Emtree RTF in more than two concepts,[61, 62] as the ERG noted in the CS CEM and model input searches. The ERG considered the extensive use of RTF overly restrictive and potentially impairing recall of possibly relevant references and did not consider the extensive implementation of RTF in the Embase and Medline searches adequately sensitive for this systematic review.

- When the ERG requested further details and hits per line for CEM Embase search strategy, the company responded that the actual Embase update strategy was not available *"due to technical issues"* and provided a copy of the search protocol instead *"as an approximation"*.[64] The ERG was concerned at the lack of accuracy in the documentation and reporting of the CEM search methods, and did not consider the protocol search an accurate report or adequate proxy for the CEM updated Embase search.
- The PubMed update search for model inputs contained incorrect use of Ovid truncation and indexing through the Quality of Life/HRQoL and cost facets. Ovid commands do not work in PubMed, therefore the following search lines reported in Table 38 would have failed to perform adequately: lines #4, #16 and #18. These errors would have impacted on how well that model inputs search performed overall and may have resulted in potentially relevant studies being missed.
- The Ovid Medline search for model inputs (Table 40) contained syntax errors in line #4.[64] This affected successful inclusion of "index of well-being" in the search strategy. As the word "of" is a stop word, line #4 was not searched as the company intend. Stop words are frequently occurring words (such as and, the, of) that are ignored by Ovid to improve search processing time. In order to force Ovid to search for a phrase containing a stop word, the phrase must be contained within quotation marks, e.g. "index of well being". Effectively the company searched for "index" appearing anywhere in the .tw. fields, and "well being" variants appearing anywhere in the .tw. fields. In the ERG test search below, the CS search logic is reproduced in line #1. Correct application of quotation marks could have increase specificity to search for the phrase properly, as demonstrated in lines #2-4. The company's approach will have resulted in a high number of incorrect results being retrieved by this term.

ERG test search for "index of well being" in Medline (Ovid)

# ▲	Searches	Results
1	(index of and (wellbeing or well being or well-being)).tw.	4127
2	"index of well-being".tw.	80
3	"index of well being".tw.	80
4	"index of wellbeing".tw.	4

ERG Rapid appraisal search to identify systematic reviews, protocols, meta-analyses and health technology assessments

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 3/March 2018: all years
Database of Abstracts of Reviews of Effects (DARE) (Wiley): Issue April/2015: all years
Health Technology Assessment Database (HTA) (Wiley): Issue 4/Oct 2016 : all years
Searched 20.3.18

#1 MeSH descriptor: [Arthritis, Psoriatic] explode all trees 258
#2 (Psoria* near/4 (Arthrit* or Arthropath* or polyarthrit* or poly-arthrit* or rheumat*)):ti,ab,kw 1097
#3 ("Arthritis mutilans" or Spondyloarthrit* or Spondylo-arthrit*):ti,ab,kw 428
#4 "alibert bazin disease":ti,ab,kw 0
#5 #1 or #2 or #3 or #4 in Cochrane Reviews (Reviews and Protocols) 14
#6 #1 or #2 or #3 or #4 in Other Reviews 20
#7 #1 or #2 or #3 or #4 in Technology Assessments 39

CDSR search retrieved 14 records.
DARE search retrieved 20 records.
HTA search retrieved 39 records.

KSR Evidence: 2015-2018/03/20
Searched 20.3.18
https://ksrevidence.com/
Searched across any field

Any field		**Results**
psoriatic		64
Psoria	AND Arthrit	63
Psoria	AND Arthropath	5
Psoria	AND polyarthrit	0
Psoria	AND rheumat	53
Arthritis mutilans OR Spondyloarthritis		37
alibert bazin disease		0
Total retrieved		**222**
After deduplication		**106**

Duplicate records were removed in Endnote.

Embase (Ovid): 2017-2018/03/19
Searched 20.3.18
1 exp meta-analysis/ (140210)
2 "systematic review"/ (161171)
3 "meta analysis (topic)"/ (36687)
4 "systematic review"/ (161171)
5 "systematic review (topic)"/ (21856)
6 biomedical technology assessment/ (12722)
7 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kw. (10040)
8 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kw. (161694)
9 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kw. (28004)
10 (data synthes* or data extraction* or data abstraction*).ti,ab,kw. (25292)
11 (handsearch* or hand search*).ti,ab,kw. (9635)
12 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kw. (27231)
13 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kw. (11857)
14 (meta regression* or metaregression*).ti,ab,kw. (7480)
15 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. (358792)
16 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. (214243)
17 (cochrane or (health adj2 technology assessment) or evidence report).jw. (26059)
18 (comparative adj3 (efficacy or effectiveness)).ti,ab,kw. (15642)
19 (outcomes research or relative effectiveness).ti,ab,kw. (11360)
20 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kw. (3146)
21 or/1-20 (523243)
22 animal/ (1838304)

23 animal experiment/ (2172333)
24 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6659144)
25 or/22-24 (6659146)
26 exp human/ (19344078)
27 human experiment/ (399545)
28 or/26-27 (19345606)
29 25 not (25 and 28) (5188401)
30 21 not 29 (510953)
31 psoriatic arthritis/ (17324)
32 (Psoria$ adj4 (Arthrit$ or Arthropath$ or polyarthrit$ or poly-arthrit$ or rheumat$)).ti,ab,ot,hw. (20893)
33 (Arthritis mutilans or Spondyloarthrit$ or Spondylo-arthrit$).ti,ab,ot,hw. (6110)
34 "alibert bazin disease".ti,ab,ot,hw. (1)
35 or/31-34 (25587)
36 35 and 30 (1513)
37 limit 36 to yr="2017 -Current" (273)

SR filter adapted from:
Canadian Agency for Drugs and Technologies in Health. Systematic Reviews/Meta-Analysis/Health Technology Assessment – OVID Medline, Embase, PsycINFO [Internet]. Ottawa: CADTH, (April 2016) [accessed 9.11.17]. Available from: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters

Appendix 2: ERG updates, overview of modified cells and VBA code

1. NMA results for Ixekizumab q4w that are not in line with trial data.

Modified cells:

- 'Input Data Default'!L172:M172
- 'Input Data Default'!L198:M198
- 'Input Data Default'!L224:M224
- 'Input Data Default'!L250:M250
- 'Input Data Default'!L276:M276
- 'Input Data Default'!L302:M302

2. Use of limited network for the b/tsDMARD-experienced population, which does not consider PASI50.

The network 3B has been used for treatment administered to b/tsDMARD-experienced patients. Hence:

- POP 6: (Line 1) Bio-naive UK 1A // (Line 2) Bio-exp 3B (incl secu, cert) has been used for all analyses concerning b/tsDMARD-naive patients
- POP 15: (All lines) Bio-exp 3B (incl secu, cert) has been used for all analyses concerning b/tsDMARD-experienced patients

Modified VBA in 'ResetGlobalInputs ()'-sub:

Ln27, Col 10:

```
If Worksheets("ERG").Range("ERG_2") = 1 Then

    .Range("UITreatmentHistory") = 6 'Patient subpopulation / NMA network

    ElseIf Worksheets("ERG").Range("ERG_2") = 2 Then

    .Range("UITreatmentHistory") = 15 'Patient subpopulation / NMA network

    Else: .Range("UITreatmentHistory") = 1 'Patient subpopulation / NMA network

    End If
```

3. Exclusion of secukinumab and certolizumab pegol as comparators in b/tsDMARD-experienced patients.

The network 3B has been used for treatment administered to b/tsDMARD-experienced patients. Hence:

- POP 6: (Line 1) Bio-naive UK 1A // (Line 2) Bio-exp 3B (incl secu, cert) has been used for all analyses concerning b/tsDMARD-naive patients
- POP 15: (All lines) Bio-exp 3B (incl secu, cert) has been used for all analyses concerning b/tsDMARD-experienced patients

Modified VBA in 'ResetGlobalInputs ()'-sub:

Ln27, Col 10:

```
If Worksheets("ERG").Range("ERG_2") = 1 Then
```

```
.Range("UITreatmentHistory") = 6 'Patient subpopulation / NMA network
ElseIf Worksheets("ERG").Range("ERG_2") = 2 Then
.Range("UITreatmentHistory") = 15 'Patient subpopulation / NMA network
Else: .Range("UITreatmentHistory") = 1 'Patient subpopulation / NMA network
End If
```

4. Utilities were not adjusted to general population utility values.

Modified VBA in 'ResetUtilityCalc()'-sub:

Ln 46, Col 9:

```
If Worksheets("ERG").Range("ERG_4") = 1 Then
.Range("UIUtilityCap") = "Yes"
ElseIf Worksheets("ERG").Range("ERG_4") = 0 Then
.Range("UIUtilityCap") = "No"
End If
```

5. The use of a potentially dated and high SMR.

Modified VBA code in 'InputReadMain()'-sub:

Ln 288, Col 5:

```
If Worksheets("ERG").Range("ERG_5") = 1 Then
  inputMortalityRatesPsA = 1.05

  Else
  inputMortalityRatesPsA = Worksheets("Mortality").Range("IDataMortalityPsAHR")
  inputMortalityRatePsAMaleWang =
Worksheets("Mortality").Range("IDataMortalityPsAMaleHR")
  inputMortalityRatePsAFemaleWang =
Worksheets("Mortality").Range("IDataMortalityPsAFemaleHR")

  End If
```

6. The use of calculations for PASI change in the model that are inconsistent with the CS report.

Modified VBA-code PASIRedRespFunction:

Ln 507, Col 17:

```
If tPsARC <> 0 Then

        If Worksheets("ERG").Range("ERG_6") = 1 Then

        PASIRedRespFunction = inputBaselinePASI - inputBaselinePASI * 0.25

        Else: PASIRedRespFunction = inputBaselinePASI - inputBaselinePASI * (0.25 * pPsARCPASI75 + 0.5 * (pPsARCNonPASI75 - pPsARCNonPASI50) + 1 * pPsARCNonPASI50) / tPsARC

        End If

    End If
```

Additional remarks concerning the ERG analyses:

- In order to be able to include biosimilar etanercept in all analyses (i.e. b/tsDMARD-naive patients, mild-to-moderate and moderate-to-severe psoriasis), the correlation coefficient of 0.255977942567321 between PsARC and PASI (Cell L19 of the Main-worksheet)
- There were no NMA estimates for Secukinumab 150mg when using the extended NMA, therefore Secukinumab 300mg has been used in all analyses involving this network.