# Secukinumab for treating moderate to severe plaque psoriasis

**Produced by** Aberdeen HTA Group

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**Rider on responsibility for report**

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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**Contribution of authors**

Ewen Cummins acted as health economist, critiqued and reviewed the cost-effectiveness evidence presented in the submission, checked and rebuilt the economic model, and carried out further sensitivity analyses. Neil Scott acted as statistician, critiqued the statistical methods presented in the submission, checked the numerical results, tables, and figures related to the review of the clinical effectiveness evidence. Moira Cruickshank acted as systematic reviewer, critiqued the clinical effectiveness methods. Cynthia Fraser acted as information scientist, critiqued the methods used for identifying relevant studies in the literature and conducted additional searches. Anthony Ormerod acted as clinical expert, provided clinical advice and general guidance. Miriam Brazzelli acted as project lead for this appraisal, critiqued and reviewed the clinical effectiveness methods, and supervised the work throughout the project. All authors contributed to the writing of the report and approved its final version.

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## List of abbreviations

| | |
|---|---|
| **A&E** | Accident and Emergency |
| **BMI** | Body mass index |
| **BNF** | British National Formulary |
| **CEAC** | Cost effectiveness acceptability curve |
| **CEAF** | Cost effectiveness acceptability frontier |
| **CG** | Clinical Guidance |
| **CHMP** | Committee for medicinal products for human use |
| **CI** | Confidence interval |
| **CMU EMIT** | Commercial Medicines Unit - Drugs and pharmaceutical electronic Market Information |
| **CSR** | Clinical study report |
| **CRD** | Centre for reviews and dissemination |
| **DLQI** | Dermatology life quality index |
| **EQ-5D** | EuroQol-5 dimension |
| **ERG** | Evidence review group |
| **FCE** | Finished consultant episode |
| **FDA** | (United States) Food and Drug Administration |
| **GP** | General practitioner |
| **HES** | Hospital Episode Statistics |
| **HRQoL** | Health-related quality of life |
| **IP** | Inpatient |
| **IGA** | Investigator's global assessment |
| **IL** | Interleukin |
| **LoS** | Length of stay |
| **MIMS** | Medical Information Management System |
| **NHS** | National Health Service |
| **NICE** | National Institute for Health and Care Excellence |
| **NMA** | Network meta-analysis |
| **NMSC** | Non-melanoma skin cancer |
| **PASI** | Psoriasis area severity index |
| **PGA** | Physician's global assessment |
| **PSS** | Personal social services |
| **PUVA** | Psoralen and ultraviolet A |

| | |
|---|---|
| **QALY** | Quality Adjusted Life Year |
| **QoL** | Quality of life |
| **RCT** | Randomised controlled trial |
| **SAE** | Serious adverse events |
| **SmPC** | Summary of product characteristics |
| **SoC** | Standard of care |
| **TA** | Technology Assessment |
| **TNF** | Tumour necrosis factor |

# 1 SUMMARY

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

The NICE scope encompassed the clinical and cost-effectiveness of secukinumab (brand name Cosentyx®) within its licensed indication for the treatment of moderate to severe plaque psoriasis in adults for whom other systemic therapies have been inadequately effective, not tolerated or contraindicated. In January 2015 secukinumab has gained United States FDA approval and marketing authorisation in the UK for the *treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy*.

In line with the NICE final scope for this appraisal, the comparators considered in the company's submission were biologic therapies (including etanercept, infliximab, adalimumab and ustekinumab).

Efficacy was assessed using the Psoriasis Area and Severity Index (PASI) and the Investigator's Global Assessment (IGA) responses. Health-related quality of life was assessed using the EuroQol 5-Dimension (EQ-5D) and Dermatology Life Quality Index (DLQI).

## *1.2 Outcomes*

The outcomes specified in the NICE final scope are: severity of psoriasis, remission rate, relapse rate, adverse effects of treatment, and health-related quality of life. The company's submission addressed the severity of psoriasis by means of the Psoriasis Area and Severity Index (PASI), including PASI 50/75/90/100, with the primary focus on PASI 75. The company also assessed the efficacy of secukinumab in terms of the Investigator's Global Assessment (IGA) for proriasis

## *1.3 Summary of clinical effectiveness evidence submitted by the company*

The clinical effectiveness evidence submitted by the company consists primarily of four phase III double-blind RCTs, FIXTURE (1,306 participants), ERASURE (738 participants), JUNCTURE (182 participants) and FEATURE (177 participants), which compared secukinumab with placebo. In addition, the company included a dose-response trial ,the SCULPTURE, which was deemed relevant to the decision problem. Efficacy was measured using the PASI and the IGA mod 2011 for clear to almost clear skin in all identified trials.

There was strong evidence from the main four trials that participants receiving secukinumab 300mg achieved a statistically significant skin improvements at 12 weeks compared with those receiving placebo ($p<0.0001$ in all cases). The proportion of patients achieving clear or almost clear skin were higher with secukinumab 300mg than with placebo in all four trials.

One trial, FIXTURE, included also a head-to-head comparison between secukinumab 300mg and etanercept. No other head-to-head trials comparing secukinumab with other relevant biologic therapies were identified. Secukinumab 300mg achieved a significantly superior PASI 75 and IGA mod 2011 0/1 responses compared with etanercept at week 12 and at subsequent timepoints. The incidence of adverse events was similar for secukinumab 300mg and etanercept up to week 52.

In SCULPTURE, non-inferiority of a secukinumab 'treatment on relapse' regimen compared with a fixed treatment regimen for maintaining week 12 PASI response up to week 52 could not be achieved.

Three network meta-analyses (NMA) were conducted to compare the relative efficacy of secukinumab 300mg against a network of other relevant biologic comparators. The proportions of participants across four mutually exclusive PASI categories (0-49, 50-74, 75-89, and 90-100) were assessed at the primary trial endpoint specific to each comparator. The NMA used the standard methods recommended by NICE for an ordinal outcome reported at different cut-points. The main analysis included data at 10, 12 or 16 weeks depending on the comparator (26 studies). A second NMA examined only data at 12 weeks and the third was similar to the first but included secukinumab data at 16 weeks.

Results were presented as risk ratios for PASI 50, PASI 75 and PASI 90. There was evidence that secukinumab 300mg had favourable PASI outcomes compared with placebo, secukinumab 150mg, etanercept 50mg, ustekinumab 45mg and adalimumab. There was no clear evidence of a difference between the efficacy of secukinumab 300mg and ustekinumab 90mg, and between secukinumab 300mg and infliximab.

The safety of secukinumab was assessed in five trials, FIXTURE, ERASURE, JUNCTURE, FEATURE, and SCULPTURE. The majority of adverse events were mild, with the most common being upper respiratory tract infections. Serious infections were very rare.

### *1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted*

The company's submission appears to be complete in that it included the four main trials, FIXTURE, ERASURE, JUNCTURE, and FEATURE, comparing secukinumab with placebo. Apart from etanercept (FIXTURE trial) no head-to-head trials were available for the comparison between secukinumab and other relevant biologic therapies. The company conducted a NMA in order to assess the relative efficacy of secukinumab versus the biologic treatments included in the NICE final scope.

Though the criteria for inclusion of comparators and doses in the NMA were not completely transparent, the ERG considered the review of clinical effectiveness evidence generally well-conducted and the quality of the evidence robust.

### *1.5 Summary of cost effectiveness submitted evidence by the company*

The company presents a de-novo model, the structure of which is broadly in line with many of the previous NICE assessments, including the TA103 of etanercept and efalizumab. The model time horizon is ten years, with a patient perspective for benefits and an NHS/PSS perspective for costs. Benefits and costs are discounted at 3.5%.

Patients are treated with one of the following comparators:

- Standard of care without biologics (SoC);
- Secukinumab 300mg;
- Etanercept 25mg;
- Adalimumab;
- Ustekinumab 45mg;
- Ustekinumab 90mg; or,
- Infliximab 5mg/kg.

After an induction period of 12 weeks, or 16 weeks in the case of adalimumab, patients are assessed for their response. Four response categories are considered:

- PASI <50;
- PASI 50-74;
- PASI 75-89; and,
- PASI 90.

The rates of these for each comparator are taken from the company network meta-analysis. Those with a PASI <50 response or a PASI 50-74 response are assumed to cease treatment, to go on to SoC and to revert to a PASI <50 response. Those with a PASI 75-89 response or a PASI 90 response are assumed to continue with their existing treatment, but for the remainder of the first year there is an 11.7% discontinuation rate as drawn from the FIXTURE and ERASURE trials. There is an annual discontinuation rate of 20% thereafter, based upon expert opinion. Those discontinuing go on to SoC and revert to a PASI<50 response.

Serious adverse events (SAEs) are associated with the biologics. Increases in the number of phototherapy sessions, day case admissions and inpatient days are associated with those on SoC with a PASI <50 response.

Quality of life values are estimated using the pooled EQ-5D data across the company trial programme, using a complete case analysis approach. The model chosen by the company estimates the change in quality of life from baseline at each EQ-5D data collection time point as a function of a patient's contemporaneous PASI response, the difference between the patient's baseline DLQI and the pooled mean baseline DLQI and the product of these.

Dosing is drawn from the biologics' SmPCs, with this being costed using the BNF and MIMS. Subcutaneous biologics require one hour of nurse training for self-administration, with it being assumed that all patients will manage to self-administer. Infliximab administrations are costed at £92.39, based upon NHS reference costs. SoC is associated with direct drug costs of £807 for the first two years, with this then falling to £13.

The SAEs for the biologics are assumed to require one inpatient admission, with the mean annual cost per patient ranging from £38 for ustekinumab to £491 for infliximab. Those on SoC with a PASI <50 response experience an annual increase of:

- around 3 phototherapy sessions at a cost of £349
- 5 day centre admissions at a cost of £2,300
- 10.7 inpatient days at a cost of £5,337

The company base case estimates the following:

**Company base case results**

| | Tx | Medical | SAE | Total | QALYs | Δ Cost | Δ QALY | ICER |
|---|---|---|---|---|---|---|---|---|
| SoC | £1,857 | £26,500 | £45,253 | £73,610 | 6.440 | | | |
| Etaner. | £14,785 | £22,471 | £38,533 | £75,788 | 6.596 | £2,178 | 0.156 | £13,948 |
| Secukin. | [redacted] | [redacted] | [redacted] | £76,361 | 6.829 | £573 | 0.233 | £2,464 |
| Adalim. | £20,712 | £21,036 | £35,233 | £76,981 | 6.688 | £620 | -0.140 | Dominated |
| Ust. 45mg | £27,723 | £19,611 | £32,210 | £79,544 | 6.770 | £3,182 | -0.059 | Dominated |
| Ust. 90mg | £29,276 | £19,180 | £31,275 | £79,732 | 6.798 | £3,371 | -0.031 | Dominated |
| Infliximab | £41,523 | £20,653 | £31,363 | £93,539 | 6.824 | £17,177 | -0.004 | Dominated |

Secukinumab extendedly dominates etanercept, and has a cost effectiveness estimate compared to SoC of £7,076 per QALY.

The cost effectiveness estimates of the company sensitivity analyses are sensitive to:

- The costs of SoC including;
  - Hospitalisation costs;
  - Day care costs; and
  - And to a lesser extent the costs of phototherapy.
- The drug cost of the biologics.
- The effectiveness estimates, in terms of the medians of the NMA.
- Discount rates.

A range of scenario analyses are presented for different cuts of the network meta-analysis. The cost effectiveness estimates of these are similar to those of the company base case.

### *1.6 Summary of the ERG's critique of cost effectiveness evidence submitted*

The ERG has rebuilt the company model and the results of the rebuild cross check with those of the company model. With the exception of a few minor, the submitted company model reflects the stated assumptions.

The model assumes that patients try one biologic and when this fails revert to SoC. This may have been a reasonable assumption to make during the technology assessment of etanercept and efalizumab (TA103), with the original FAD recommending sequencing efalizumab after etanercept until efalizumab was withdrawn on safety grounds. ERG expert opinion suggests that patients failing on one biologic now go on to try another, leading to a sequence of

treatments. In the light of this, the most relevant cost effectiveness estimate of the submitted model among patients who would be given a current sequence of biologics, if secukinumab will displace one of these biologics from the sequence, may be the cost effectiveness estimate of secukinumab compared to the biologic that is likely to be displaced. If secukinumab will be additional to the sequence of current biologics, the most relevant cost effectiveness estimate of the submitted model may be the cost effectiveness estimate of secukinumab compared to SoC. But these cost effectiveness estimates are obviously imperfect reflections of those that would results from a modelling of treatment sequences.

The clinical effectiveness estimates of the company base case correspond with those of the network meta-analysis of the company's submission.

The rates and costs of the SAEs may be questionable and may bias the model slightly against the biologics, but these have only a limited impact upon the outcomes of the model.

The analysis of the EQ-5D quality of life data appears to be sound, though there is no exploration of a possible treatment effect. The company reasons for preferring the quality of life model of the base case are weak, but the results of the cost effectiveness model are not sensitive to which model is chosen.

The company preference for the costing template of the CG 153 and company expert opinion for the costs associated with those on SoC with a PASI <50 is not obviously justified. The company summary of Fonia et al (2010), a resource use study of 76 UK patients in the twelve months before and the twelve months after starting a biologic, should in the opinion of the ERG have presented further details on the mean numbers of day case admissions and inpatient days before and after starting a biologic. The data of Fonia et al (2010) suggest no increase in the number of day case admissions and only perhaps around an additional 5 days as an inpatient pre biologic compared to post biologic. The estimates for these inputs have to be quite a lot larger than these to generate sufficient cost offsets to justify the drug cost of secukinumab. The assumption that all patients can self-administer their subcutaneous biologic therapy can be regarded as optimistic, even though the ERG clinical advisor indicates that the vast majority of patients can. If only a relatively small percentage of patients were unable to self-administer, this could add a reasonable amount to the costs of the subcutaneous biologics.

The main areas of disagreement between the ERG and the submitted model structure are whether:

- The resource use for those on and reverting to SoC with a PASI <50 should be sourced from Fonia et al (2010) or from the costing template of CG 153 and company expert opinion;
- Secukinumab annual dosing requires 13 administrations or 12 administrations.
- Ustekinumab first year post induction dosing requires 3 administrations or 4 administrations;
- First year hospitalisation costs for those with a PASI 50 response should or should not be conditioned by the duration of the post induction period;
- Hospitalisation costs should or should not be removed from PASI 75 responders in the SoC arm.

## *1.7 ERG commentary on the robustness of evidence submitted by the company*

### 1.7.1 Strengths

The report was written in a clear manner and included relevant studies to address the objectives of this assessment.

In general the clinical effectiveness methods were appropriate. The methodology used in the network meta-analyses appeared to be correct and followed NICE guidelines.

With regard to the economic evaluation included in the submission, points of strength are:

- A good identification of the previous STAs and cost effectiveness estimates previously undertaken, and of the literature about resource use and quality of life;
- A clear and comprehensive summary of the economic model structure and its inputs within the written submission which, save for a few discrepancies, corresponds with the submitted electronic model;
- A well-constructed electronic model that is transparently presented and simple to parse;

- A de novo model, which reflects much of the structure of those of previous assessments, including the TA103;
- The analysis of the trials' EQ-5D data;
- A good set of one-way sensitivity analyses and scenario analyses.

### 1.7.2 Weaknesses and areas of uncertainty

Main weaknesses of the submission are:

- Lack of direct head-to-head comparisons with other biologic treatments apart from etanercep;
- Meta-analysis was only conducted for one outcome (PASI);
- Lack of transparency/consistency over inclusion of drugs and doses in each NMA;
- Some coyness in the summary of the identified literature, particularly of the UK resource use study of Fonia et al (2010);
- A model that assumes that patients try only one biologic and if they fail on this they revert to SoC. ERG expert opinion suggests that patients failing on one biologic go on to try another, with patients often working through a sequence of biologics;
- An apparent lack of correspondence between the patients in the HES resource use data the company relies upon for length of stay data and the company budget impact analysis.

## *1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG*

The ERG has made a number of revisions to the economic model, and for the ERG SoC resource use scenario based upon Fonia et al (2010) this significantly worsens the cost effectiveness estimate for secukinumab compared to SoC from £7,076 per QALY to £52,760 per QALY. For the company SoC resource use scenario, the ERG revisions to the company model still worsen the cost effectiveness estimate for secukinumab compared to SoC from £7,076 per QALY to £14,902 per QALY.

If among SoC patients with a PASI<50 response the mean annual numbers of day case admissions and the days as an inpatient total around 11, the cost effectiveness estimate for secukinumab compared to SoC is around £30,000 per QALY. If the total number of days is around 14 the cost effectiveness estimate for secukinumab compared to SoC is around £20,000 per QALY. For the ERG SoC resource use scenario the pairwise cost effectiveness

estimates of secukinumab compared to etanercept, adalimumab, ustekinumab 45mg and ustekinumab 90mg are £42,368, £38,684, £26,321 and £17,717 per QALY, respectively. It is estimated to dominate infliximab.

For the company SoC resource use scenario the pairwise cost effectiveness estimates of secukinumab compared to etanercept and adalimumab are £8,899 and £6,979 per QALY respectively. It is estimated to dominate ustekinumab 45mg, ustekinumab 90mg and infliximab.

Intermittent etanercept dosing would, if clinical effectiveness were maintained, significantly worsen the cost effectiveness of secukinumab compared to etanercept. While perhaps an extreme value, the ERG inferred 1.33 doses for intermittent use etanercept compared to the 2.00 doses for continuous use etanercept worsens the cost effectiveness estimate for the ERG SoC resource use scenario from £42,368 per QALY to £59,268 per QALY, and for the company SoC resource use scenario from £8,899 per QALY to £25,800 per QALY.

The application of the quality of life values from the other NICE assessments in the area also tends to improve the cost effectiveness estimates. This applies particularly to the quality of life values from the TA180 ustekinumab and the TA134 infliximab.

Results are not particularly sensitive to the other variables explored by the ERG, though varying the clinical effectiveness inputs and the direct drug costs of the biologics would obviously have an impact.

Issues that cannot be quantified within the submitted model at present are:

- The impact of modelling treatment sequences;
- The extent to which the model may strip some of the placebo effect from SoC but retain it for the biologics;
- Whether there is a treatment effect within the EQ-5D data. It seems possible that within the PASI <50 response category the distribution of response may have differed between arms and, while speculation by the ERG, could have been worse in the SoC arm;

- Whether a significant proportion of those with a week 12 PASI 75-89 response further improve to a week 52 PASI 90 response;
- Whether a significant proportion of those with a week 12 PASI 50 response further improve to a week 52 PASI 75 response which might justify a partial responder analysis, though perhaps not of the form submitted within the company model.

## 2 BACKGROUND

Psoriasis is a common, chronic, relapsing, inflammatory skin disease that is characterised by an accelerated rate of turnover of the upper layer of the skin.[1-3] Psoriasis is considered to be immune mediated, with intralesional T lymphocytes and their proinflammatory signals activating rapid proliferation of primed basal layer keratinocytes.[4] Psoriasis is considered to be a complex and multifactorial disease with a recognised genetic predisposition[4-10] even though the exact aetiology of the disease remains unknown.[5,9,11,12] People with psoriasis have been reported to have a greater risk of significant co-morbidities including obesity, diabetes, and cardiovascular disease,[8,13,14] Potential triggers for psoriasis exacerbations include infectious disease, trauma, smoking, alcohol, psychological stress, and depression.[4,7,15]

There are a number of different clinical subtypes of psoriasis,[15] with classification based upon morphology, distribution and pattern of disease.[4,7]The most common type is psoriasis vulgaris, or plaque psoriasis, which accounts for around 80-90% of all cases[2,2,7,7,16,16,17,17] and is characterised by well-demarcated, raised, erythematous plaques covered with white or silvery scales.[2,16,18] The most common areas of the body affected are the elbows, knees, lower back, buttocks and scalp but any cutaneous surface can be involved and there is wide variation in the severity and extent of the disease[7,17] Psoriasis can have a significant impact upon health-related quality of life, regardless of the amount of body surface affected[19-23] Psoriasis is believed to have a bimodal pattern of onset: early onset (at 20 to 30 years of age, with a tendency of genetic basis) and late onset (at 50 to 60 years).[8,24] Although psoriasis is a chronic disease, its course is unpredictable, with flares and remissions. It may be progressive with age and vary in severity over time.[15]

Psoriasis is generally graded as mild, moderate or severe. Assessment of severity is commonly based upon the proportion of body surface affected, disease activity (degree of plaque redness, thickness and scaling), response to previous treatment and impact of the disease upon the person.[9] Measures commonly used for assessing the severity of the disease include the Psoriasis Area Severity Index (PASI) and the Physician's Global Assessment (PGA), sometimes referred to as the psoriasis global assessment or Investigator's Global Assessment (IGA).[9,25] The PASI grades area, erythema, elevation and scaling in the head and neck, upper limbs, trunk and lower limbs, weights each region of the body for the proportion

of the skin it represents to derive a composite score, theoretically ranging 0-72, while the IGA/PGA provides a subjective evaluation of the overall severity of psoriasis ranging from "clear" to "severe". Different versions of the IGA/PGA tool have been used in clinical trials. The recent 5-point IGA/PGA modified version is considered to be a more robust measure capable of providing a stronger association with clearance compared with broader versions used previously.[25]

The Dermatology Life Quality Index (DLQI)[26] is a validated measure for assessing quality of life in people with dermatologic conditions, where scores range from 0 to 30, with higher scores indicating poorer quality of life.

Psoriasis occurs worldwide but prevalence varies among different populations.[6,9] Accurate rates for the prevalence of the disease are difficult to ascertain due to the lack of validated diagnostic criteria and, therefore, to the inconsistent identification of cases.[3,16] Nonetheless, the prevalence of psoriasis is estimated to lie between 1.3% and 4% of the general population in western countries, with men and women equally affected.[1,16,27] Published UK-based studies have reported consistent results with rates of 1.48% [28] and 1.5% [1] A recent systematic review of epidemiological studies assessing the worldwide prevalence of psoriasis has showed high variability within and between countries. In Europe, the UK had the lowest and most consistent estimates for the prevalence of the disease in adults: from 1.3% (95%CI 1.21-1.39)[29] to 2.6% (95%CI 2.47-2.78). Around the world, prevalence rates ranged from 0.91% in the USA to 8.5% in Norway.[3]

There is no definite cure for psoriasis but there are a wide range of topical and systemic treatments, which help to keep the condition under control. The choice of treatment depends on a number of factors including the severity of the condition and the extent of body surface area affected. The aim of treatments is to gain rapid control of the disease process, reduce the amount of body surface affected, decrease plaque lesions, achieve long-term remission, minimise adverse events and improve quality of life.[30] Treatments are generally based on a stepwise approach, starting with the safest alternative and progressing to more aggressive methods, as required.[31] In general treatments fall in three main categories: i) topical treatments -creams and ointments that are applied directly to the affected skin; ii) phototherapy, which involves the use of ultraviolet light; and iii) systemic treatments - oral

and injected medications that work throughout the entire body. Treatment regimens can be combination, rotational, or sequential.[30]

Mild psoriasis can safely and effectively be managed with topical treatments[4] such as emollients and occlusive dressing, topical corticosteroids, vitamin D analogues, calcineurin inhibitors, keratolytic agents, coal tar, dithranol, and retinoic acid.[4,9] Moderate to severe disease often requires more aggressive systemic treatments[32] including phototherapy with or without psoralen, oral non-biologic medications such as methotrexate, ciclosporin (cyclosporine), acitretin, and biologic treatments.[32,33] Oral non-biologic therapies can be given alone or in combination with topical treatments.[34] Use of the traditional oral therapies has continued over the years but due to their serious side effects and toxicity require adequate monitoring and supervision.[34]

Biological treatments or "biologic response modifiers"[32,33,35] are a more recent drug development and represent a more targeted approach to the treatment of psoriasis; Cameron, ch1, [4,9,33,34,36]

Biologic treatments are therapeutic agents bio-engineered from living organisms. In psoriasis they aim to reduce inflammation by targeting specific molecular targets in the immune system.[37] The TNF inhibitors, etanercept, adalimumab, and infliximab, and the IL-12/23 compound, ustekinumab, have revolutionised the treatment of psoriasis[4] and are commonly used in clinical practice. Secukinumab, a human antibody to IL-17A, is a more recently available biologic option for the treatment of psoriasis.[31] These biologic treatments are usually considered when other treatments are not suitable or have been unsuccessful.

Secukinumab (Cosentyx, Novartis Pharma AG, Basel, Switzerland) is a fully human IgG1κ monoclonal antibody that selectively binds and neutralises IL-17A.[4,38,39] Secukinumab gained positive CHMP opinion in November 2014, with European full licence approval granted on 19th January 2015 and United States FDA approval granted on 21st January 2015. The current approved indication is: "for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy". The recommended dose is 300mg.[40]

### *2.1 Critique of company's description of underlying health problem*

The company's description of moderate to severe plaque psoriasis is accurate and appropriate to the decision problem.

### *2.2 Critique of company's overview of current service provision*

The company adequately refer to the NICE clinical guideline CG153[41] for the assessment and management of psoriasis and the NICE quality standard no. 40 for psoriasis.[42] In general terms, NICE CG153[41] recommends topical therapy as first line treatment, followed by phototherapy for people whose psoriasis cannot be controlled with topical treatments alone. Systemic non-biological therapy is recommended for psoriasis that cannot be controlled by topical therapy and has a significant impact on physical, psychological and social wellbeing. Systemic biological therapy is recommended for the treatment of severe psoriasis that has not successfully responded to standard systemic therapies.

Figure 1 presents the clinical pathway for the management of psoriasis as described in the NICE CG153 and adapted to include the likely position of secukinumab. [41]

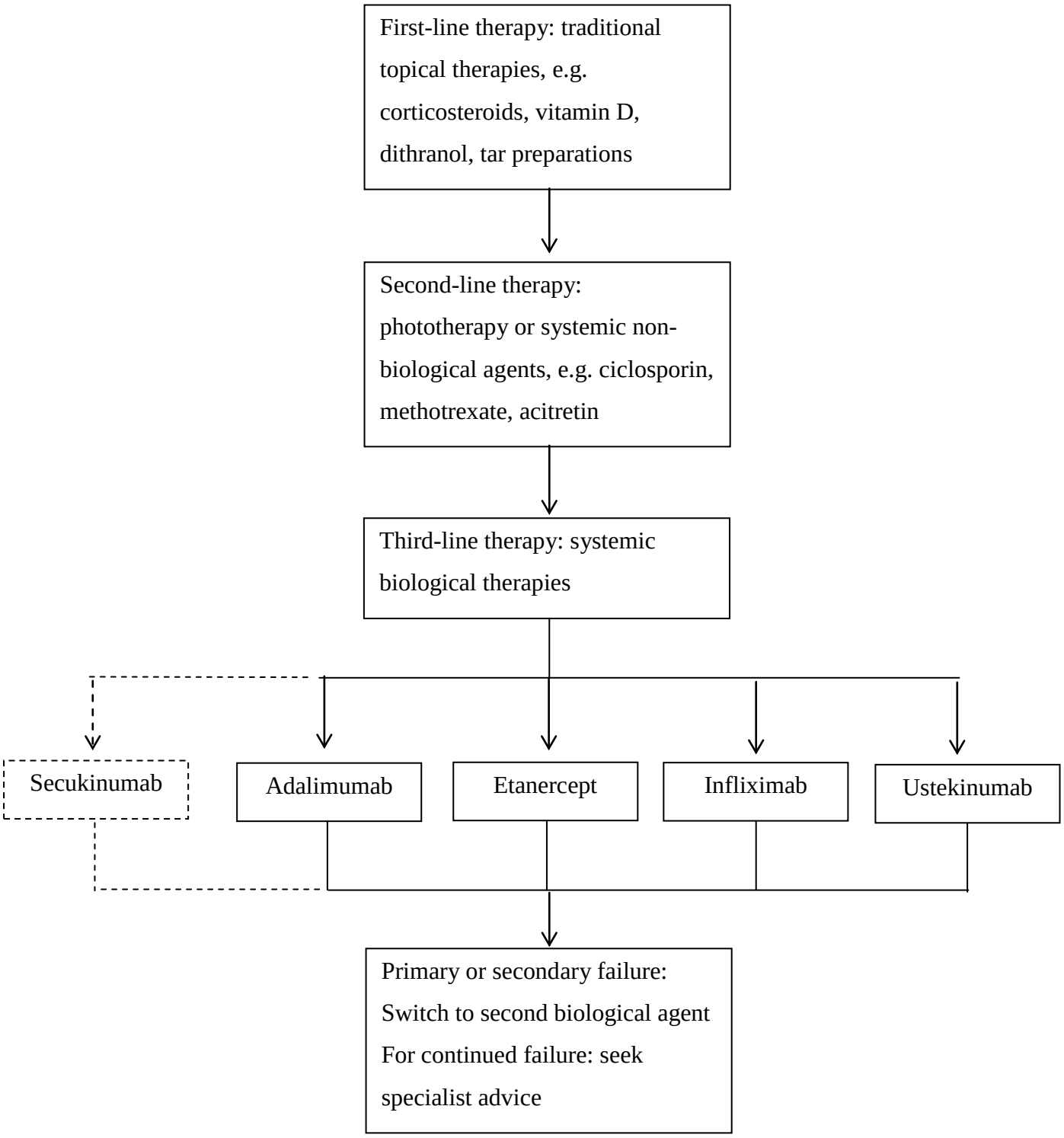



**Figure 1 NICE CG153 clinical pathway, adapted to include likely position of secukinumab**

There are four sets of NICE guidelines related to the use of biologic therapies for the treatment of psoriasis:

**TA103** Etanercept and efalizumab (the later subsequently withdrawn from the market) for the treatment of adults with psoriasis, published July 2006. Etanercept (Wyeth Pharmaceuticals) is a recombinant human tumour necrosis factor (TNF) receptor fusion protein that inhibits the activity of TNF. TNF is a cytokine that is released from T lymphocytes; it mediates inflammation and modulates the cellular immune response.[43]

**TA146** Adalimumab for the treatment of adults with psoriasis, published June 2008. Adalimumab (Humira, Abbott Laboratories) is a recombinant human monoclonal antibody that binds specifically to tumour necrosis factor alpha (TNF-α), blocking interaction with its cell-surface receptors and thereby limiting the promotion of inflammatory pathways.[44]

**TA180** Ustekinumab for the treatment of adults with moderate to severe psoriasis, published September 2009. Ustekinumab (Stelara, Janssen-Cilag) is a fully human monoclonal antibody that targets interleukin-12 (IL-12) and IL-23. It binds to the p40 subunit, common to both IL-12 and IL-23, which prevents these cytokines from binding to the cell surface of T cells, thereby disrupting the inflammatory cascade implicated in psoriasis.[45]

The above three biologics therapies are recommended, within their licensed indications, for the treatment of adults with plaque psoriasis only when the following criteria are met:

- The disease is severe as defined by a total Psoriasis Area Severity Index [PASI] of ten or more **and** a Dermatology Life Quality Index [DLQI] of more than ten.
- The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments.

Etanercept is administered by subcutaneous injection at a dose of 25 mg twice weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly. The recommended dosage for adalimumab is an initial 80mg dose administered by subcutaneous injection, followed by 40mg given subcutaneously every other week starting 1 week after the initial dose. The recommended

dose of ustekinumab is 45mg, administered by subcutaneous injection, for people who weigh 100Kg or less and 90mg (two 45 mg vials) for people who weigh more than 100kg. Etanercept and ustekinumab should be stopped if standard assessment show that a person's psoriasis has not clearly improved after 12 weeks or after 16 weeks, respectively. Adalimumab should be continued beyond 16 weeks only if the psoriasis has clearly improved within this time.

**TA134** Infliximab for the treatment of adults with psoriasis, published January 2008. Infliximab (Remicade, Schering-Plough) is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology.[46] It is recommended, within its licensed indications, as a treatment option for adults with plaque psoriasis only when the following criteria are met:

- The disease is very severe as defined by a total Psoriasis Area Severity Index (PASI) of 20 or more **and** a Dermatology Life Quality Index (DLQI) of more than 18.
- The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate **or** PUVA (psoralen and long-wave ultraviolet radiation), **or** the person is intolerant to or has a contraindication to these treatments.

The recommended dosage for infliximab is 5mg/kg as intravenous infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after first infusion, then every 8 weeks thereafter. Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment.

The company's submission states that *people with more severe or uncontrolled psoriasis are the biggest psoriasis users of healthcare resources, through lengthy hospital stays, frequent clinical visits for specialist topical treatments, phototherapy and monitoring associated with systemic therapies*.

The submission indicates also that *the proportion of adults with psoriasis in England and Wales is estimated to be approximately 800,000 or 1.75% of the total adult population. Of these, an estimated 20,000 people (2.55%) are thought to be eligible to receive biologic therapies.*

The UK Hospital Episode Statistics data for the year April 2012-March 2013, show that there were 1,023 finished consultant episodes for psoriasis vulgaris (code L40.0) in England. Of these, 679 were male and 344 were female with a mean age of 48 years. There were 952 admissions, including 120 emergency admissions, with an average length of stay of 10.7 days, and 605 day cases.[47]

In conclusion, the company does appear to illustrate adequately the current state of service provision for moderate to severe psoriasis in the UK

# 3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

## *3.1 Population*

Both the NICE final scope and the company's submission specify as the relevant population for this appraisal "*people with moderate to severe plaque psoriasis for whom other systemic therapies including ciclosporin, methotrexate and phototherapy with or without psoralen have been inadequately effective, or are not tolerated or contraindicated*". This choice reflect the current NICE recommendations for the use of biologic therapies for the treatment of moderate to severe psoriasis[41,43-46] Secukinumab received a positive opinion from the CHMP in November 2014[40] and full European and FDA approval in January 2015. The current secukinumab license indication is for *the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy*.

## *3.2 Intervention*

Secukinumab is a fully human IgG1κ monoclonal antibody that selectively binds and neutralizes the pro-inflammatory cytokine interleukin IL-17A [38,48] Secukinumab blocks the action of IL-17A.[39]

Secukinumab is formulated as a solution for injection in either a pre-filled syringe or pre-filled pen, each pre-filled syringe/pen containing 150mg secukinumab in 1ml. The recommended dose is 300mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2 and 3 followed by monthly dosing from week 4. Each 300mg injection is administered as two injections of 150mg. If no response is shown at 16 weeks of treatment, consideration should be given to discontinuing treatment. Some people may show an initial partial response but improve with continued treatment beyond 16 weeks.[48]

Secukinumab received a positive opinion from the CHMP on 20th November 2014 for treating moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Full licence approval was granted on 19th January 2015.

The final scope issued by NICE for this appraisal specified the intervention as secukinumab. The decision problem addressed by the company was specified as secukinumab 300mg.

### *3.3 Comparators*

The comparators addressed in the decision problem in the company's submission were biologic therapies (including etanercept, infliximab, adalimumab and ustekinumab) and best supportive care (for people in whom biologic therapies are not tolerated or contraindicated). These comparators are in line with the final scope issued by NICE for this appraisal.

### *3.4 Outcomes*

The outcomes specified in the NICE final scope are: severity of psoriasis, remission rate, relapse rate, adverse effects of treatment, and health-related quality of life. The company's submission addressed the severity of psoriasis by means of the Psoriasis Area and Severity Index (PASI), including PASI 50/75/90/100, with the primary focus on PASI 75. The company also assessed the efficacy of secukinumab in terms of the Investigator's Global Assessment (IGA) for proriasis. The company considered PASI 100 (i.e. totally clear skin) as an indicator of remission and based their assessment of relapse on sustainability of response at 52 weeks. Health-related quality of life (HRQoL) was assessed using the EuroQol 5-Dimension (EQ-5D) and Dermatology Life Quality Index (DLQI). Although all outcomes specified in the NICE final scope were considered, the company did not perform network meta-analyses for relapse rate or HRQoL.

### *3.5 Other relevant factors*

Table 1 illustrates the differences between the NICE final scope and the decision problem addressed by the company.

**Table 1 Comparison of NICE final scope and decision problem addressed by company**

| | Final scope issued by NICE | Decision problem addressed in the submission |
|---|---|---|
| **Population** | • People with moderate to severe plaque psoriasis for whom other systemic therapies including ciclosporin, methotrexate and phototherapy with or without psoralen have been inadequately effective, or are not tolerated or contraindicated | • People with moderate to severe plaque psoriasis for whom other systemic therapies including ciclosporin, methotrexate and phototherapy with or without psoralen have been inadequately effective, or are not tolerated or contraindicated |
| **Intervention** | • Secukinumab | • **Secukinumab 300mg** |
| **Comparator(s)** | • Biologic therapies (including etanercept, infliximab, adalimumab and ustekinumab)<br>• Best supportive care (for people in whom biologic therapies are not tolerated or contraindicated) | • Biologic therapies (including etanercept, infliximab, adalimumab and ustekinumab)<br>• Best supportive care (for people in whom biologic therapies are not tolerated or contraindicated) |
| **Outcomes** | The outcome measures to be considered included:<br>• Severity of psoriasis<br>• Remission rate<br>• Relapse rate<br>• Adverse effects of treatment<br>• Health-related quality of life | • Psoriasis Area and Severity Index (PASI), including PASI 50/75/90/100 but with the prime focus on PASI 75<br>• Investigator's Global Assessment (IGA) for psoriasis (for secukinumab efficacy)<br>• PASI 100 as an indicator of remission<br>• Sustainability of response at 52 weeks (as assessment of relapse prevention) |

| | Final scope issued by NICE | Decision problem addressed in the submission |
|---|---|---|
| | | • Adverse events (based on results from the clinical trial programme)<br>• Health-related quality of life (EQ5D, DLQI) |
| **Economic analysis** | • Incremental cost per quality-adjusted life year<br>• Time horizon should be sufficiently long to reflect differences in costs or outcomes between technologies being compared<br>• Costs will be considered from an NHS and Personal Social Services perspective<br>• Availability of any patient access schemes for the intervention or comparator technologies should be taken into account | • Incremental cost per quality-adjusted life year<br>• 10 year time horizon<br>• Costs considered from an NHS and PSS perspective |

# 4 CLINICAL EFFECTIVENESS

## *4.1 Critique of methods of the review*

### 4.1.1 Description of company's search strategies and critique

The company's submission states that literature searches were initially undertaken in June 2013 and subsequently updated in October 2014. An appropriate range of databases were searched: MEDLINE, MEDLINE in Process (via PUBMED for the main search and Ovid for the update); EMBASE (vis Embase.com for the main search and Ovid for the update); and CENTRAL, Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Effects - DARE (via The Cochrane Library for the main search and Ovid for the update). In addition, the World Congress of Dermatology conference proceedings for the last five years were screened and reference lists of identified studies were searched for further reports of secukinumab and the comparator drugs. Unpublished studies, however, were sought only for secukinumab from Novartis Clinical Study Reports and Clinical Trials.gov. Full details of the search strategies are reported in Appendix 10.2 of the company's submission and are reproducible.

The searches were designed to identify all trials of secukinumab or the comparator drugs for psoriasis using a range of controlled vocabulary and text word terms. The PUBMED search did not used the Cochrane RCT search filter but instead used a wider range of terms that covered most of the search terms in the filter. However, the text word term 'placebo' and the subheading 'drug therapy' were omitted. The Cochrane Library searches also included a trials facet, which was unnecessary since CENTRAL consists mostly of trials and the inclusion risked compromising the sensitivity of the search. The updated search used a common search in OVID across MEDLINE, EMBASE and the Cochrane databases that included appropriate controlled vocabulary terms for all the databases searched. Thus, while some terms were inappropriate for one database, they were appropriate for another. Once again, the use of terms relating to trials in the Cochrane Library is questionable.

The company explains in the submission that additional adverse events searches were not undertaken because the identified secukinumab trials reported already adverse events.

In conclusion, while some deficiencies were identified in some of the searches, the overall effect is likely to have had minimal impact on the sensitivity of identifying published trials. For the comparator drugs, the company did not report searching Clinical Trials.gov where results for completed studies may have been reported.

### 4.1.2 Inclusion criteria

The inclusion criteria applied in the company's systematic review of effectiveness are presented in Table 2.

**Table 2 Inclusion criteria used in systematic review of clinical effectiveness**

| | |
|---|---|
| **Population** | • Adults (≥ 18 years) with moderate to severe chronic plaque-type psoriasis<br>• Adults with severe progressive or uncontrolled psoriasis |
| **Intervention** | • Secukinumab (studies had to include a 300 mg dose treatment arm to be included) |
| **Comparators** | • Etanercept<br>• Adalimumab<br>• Infliximab<br>• Ustekinumab<br>• Placebo |
| **Outcomes** | **Efficacy measurements (all reported time points, e.g., 4, 8, 12, 16, 24, and 52 weeks, will be extracted for each of these outcomes, in addition to the primary endpoint):**<br>• PASI 50<br>• PASI 75<br>• PASI 90<br>• PASI 100<br>• Investigator's Global Assessment or Physician's Global Assessment (including definition, if reported)<br>• Time to response<br>• Primary non-responders to biologics<br>• Treatment failures due to non-response<br>**Safety outcomes (all reported time points, e.g., 4, 8, 12, 16, 24, and 52 weeks, will be extracted for each of these outcomes, in addition to the primary endpoint):** |

| | |
|---|---|
| | • Occurrence of Grade 3 and Grade 4 haematological adverse events<br>• Serious infections resulting in hospitalisation (e.g. tuberculosis)<br>• Malignancies<br>• Overall non-serious infections (e.g. Candida)<br>• Discontinuation rates due to treatment<br>• Other treatment-related adverse events (e.g. systemic lupus erythematosus)<br>• Mortality due to major adverse cardiac and cerebrovascular events<br><br>**HRQoL assessments:**<br>• Dermatology related quality of life (DLQI)<br>• EuroQol 5-DimensionHealth Status Questionnaie (EQ-5D)<br>• Family and carer HRQoL (Family Dermatology Life Quality Index) |
| **Study design** | • Phase 2/3 Randomised Controlled, Prospective Clinical Trials<br>• Systematic reviews (including meta-analyses) (for identification of relevant primary studies) |
| **Language restrictions** | • None |
| **Dates** | • All dates |

The company indicate in the footnotes of Table 3, page 40, of the submission that Phase I and Phase II studies were excluded at full-text screening. However, they further state that Phase II studies were included in the NMA. The procedure for the inclusion/exclusion of Phase II studies is, therefore, not entirely clear to the ERG.

### 4.1.3 Identified studies

The company's submission identified five RCTs assessing the effects of secukinumab: FIXTURE,[25] ERASURE ,[25] JUNCTURE,[49] FEATURE[50] and SCULPTURE.[51] All trials involved the comparison of secukinumab (150mg and 300mg) versus placebo, with the exception of FIXTURE, which also included a comparison with etanercept. The study design was identical for FIXTURE, ERASURE, JUNCTURE and FEATURE. The SCULPTURE trial was essentially a dose-response study, comparing a fixed dose of secukinumab versus a re-treatment at start of relapse regimen (dosing as required in the event of relapse). The company considered SCULPTURE relevant to the decision problem as it provides supporting evidence for secukinumab. All five trials were sponsored by Novartis Pharmaceuticals, Basel, Switzerland.

The company identified also another trial, STATURE, which is a sub-group follow-on study of SCULPTURE partial responders (i.e. intravenous secukinumab (10mg/kg) versus subcutaneous secukinumab (300mg) in SCULPTURE partial responders). STATURE was not further assessed in the submission due to the lack of placebo control and because the comparator dosing regimen used within this trial was not in line with the secukinumab SmPC. Similarly, two further Phase II secukinumab trials[38,52] were excluded because their dosing regimens were not considered relevant to the scope of the appraisal.

### 4.1.4 Characteristics of included RCTs

FIXTURE, ERASURE, JUNCTURE, FEATURE and SCULPTURE were all Phase 3, double masked RCTs. All were placebo controlled and included 150mg and 300mg secukinumab arms. In addition, FIXTURE included an etanercept arm. All were worldwide, multi-centre trials and involved a 12-week induction period followed by a 40-week maintenance period. While in ERASURE, JUNCTURE and FEATURE participants were randomised 1:1:1 to receive secukinumab 300mg, secukinumab 150mg or placebo, in FIXTURE, randomisation was 1:1:1:1 to secukinumab 300mg, secukinumab 150mg, etanercept or placebo. Participants randomised to secukinumab received either two 150mg injections (300mg arm) or one 150mg injection plus one placebo injection (150mg arm). Both injections were administered at baseline, then weekly until week 4 and then every 4 weeks until week 48. In JUNCTURE, injections

were self-administered by an autoinjection device. In FEATURE, injections were self-administered by a pre-filled syringe. In FIXTURE, participants randomised to etanercept received 50mg subcutaneously twice weekly from baseline to week 12 then once weekly to week 51. In all studies, participants randomised to placebo who did not show a reduction of at least 75% in the baseline PASI score (i.e. PASI 75) at week 12 were re-randomised to receive either secukinumab 300mg or secukinumab 150mg. These participants are not included in any efficacy analyses reported here. In the SCULPTURE trial, participants were randomised to receive either secukinumab 300mg or secukinumab 150mg at baseline and then weekly until week 4. Dosing was then at weeks 8 and 12, at which point, participants fulfilling the criteria for PASI 75 were re-randomised to either secukinumab 300mg or 150mg re-treatment-as-needed or fixed-interval treatment (every 4 weeks). In the re-treatment-as-needed arm, secukinumab was administered for disease relapse, otherwise participants received a placebo injection. Table 3 presents the study characteristics of the five RCTs.

## Table 3 Characteristics of the five included RCTs

| | FIXTURE | ERASURE | JUNCTURE | FEATURE | SCULPTURE |
|---|---|---|---|---|---|
| **Study duration (Overall/induction period/maintenance period)(weeks)** | 52/12/40 | 52/12/40 | 52/12/40 | 52/12/40 | 52/12/40 |
| **No participants randomised** | 1306 | 738 | 182 | 177 | 966 |
| **Country** | [a]Argentina, Australia, Belgium, Guatemala, Iceland, Hungary, India, Canada, Colombia, Egypt, Finland, France, Italy, Philippines, Poland, Germany, Romania, Singapore, South Korea, Spain, Sweden, UK, USA | Argentina, Canada, Colombia, Estonia, Mexico, Taiwan, USA, Iceland, Israel, Japan, Latvia, Lithuania, | [b]USA, Germany, France, Estonia, Canada | Canada, Estonia, France, Germany, USA | Austria, Bulgaria, Canada, Czech Republic, France, Germany, India, Italy, Japan, Poland, Singapore, Slovakia, Switzerland, UK, USA, Vietnam |
| **Intervention & comparator(s)** | Secukinumab 300mg versus secukinumab 150mg versus etanercept versus placebo | Secukinumab 300mg versus secukinumab 150mg versus placebo | Secukinumab 300mg versus secukinumab 150mg versus placebo | Secukinumab 300mg versus secukinumab 150mg versus placebo | Secukinumab 300mg versus secukinumab 150mg |
| **Inclusion criteria** | • 18 years of age or older<br>• Moderate-to-severe plaque psoriasis, diagnosed at least 6 months before randomisation<br>• Poorly controlled with topical treatments, phototherapy, systemic therapy or a combination of these<br>• PASI score of at least 12<br>• Modified IGA score of 3 or 4<br>• Involvement of at least 10% of body-surface area | • 18 years of age or older<br>• Moderate-to-severe plaque psoriasis, diagnosed at least 6 months before randomisation<br>• Poorly controlled with topical treatments, phototherapy, systemic therapy or a combination of these<br>• PASI score of at least 12<br>• Modified IGA score of 3 or 4<br>Involvement of at least 10% of body-surface area | • 18 years of age or older<br>• Moderate-to-severe plaque psoriasis, diagnosed at least 6 months before randomisation<br>• Poorly controlled with topical treatments, phototherapy, systemic therapy or a combination of these<br>• PASI score of at least 12<br>• Modified IGA score of 3 or 4<br>Involvement of at least 10% of body-surface area | • 18 years of age or older<br>• Moderate-to-severe plaque psoriasis, diagnosed at least 6 months before randomisation<br>• Poorly controlled with topical treatments, phototherapy, systemic therapy or a combination of these<br>• PASI score of at least 12<br>• Modified IGA score of 3 or 4<br>Involvement of at least 10% of body-surface area | • 18 years of age or older<br>• Moderate-to-severe plaque psoriasis, diagnosed at least 6 months before randomisation<br>• Poorly controlled with topical treatments, phototherapy, systemic therapy or a combination of these<br>• PASI score of at least 12<br>• Modified IGA score of 3 or 4<br>Involvement of at least 10% of body-surface area |
| **Main exclusion criteria** | • Forms of psoriasis other than chronic plaque-type | • Forms of psoriasis other than chronic plaque-type | • Forms of psoriasis other than chronic plaque-type | • Forms of psoriasis other than chronic plaque-type<br>• Drug-induced psoriasis | • Forms of psoriasis other than chronic plaque-type<br>• Drug-induced psoriasis |

| | FIXTURE | ERASURE | JUNCTURE | FEATURE | SCULPTURE |
|---|---|---|---|---|---|
| | • Drug-induced psoriasis<br>• People who had used etanercept at any time<br>• Use of medications that might confound efficacy | • Drug-induced psoriasis<br>• Use of medications that might confound efficacy | • Drug-induced psoriasis<br>• Use of medications that might confound efficacy<br>• Inability or unwillingness to undergo repeated venepuncture or self-injection with the autoinjector device[c] | • Use of medications that might confound efficacy<br>• Inability or unwillingness to undergo repeated venepuncture or self-injection with a pre-filled syringe[c] | • People who had used etanercept at any time<br>• Use of medications that might confound efficacy |
| **Primary outcome** | PASI 75 and modified IGA score of 0 or 1 (both at 12 weeks) | PASI 75 and modified IGA score of 0 or 1 (both at 12 weeks) | PASI 75 and modified IGA score of 0 or 1 (both at 12 weeks) | PASI 75 and modified IGA score of 0 or 1 (both at 12 weeks) | Non-inferiority of retreatment-as-needed versus fixed interval for maintenance of PASI 75 response |
| **Other key outcomes** | Week 12: PASI 50, 90, 100; patient-reported psoriasis-related itching, pain and scaling on the Psoriasis symptom diary;<br>Until Week 52: PASI 50, 75, 90, 100; response of 0 or 1 on modified IGA score; DLQI score of 0 or 1 | Week 12: PASI 50, 90, 100; patient-reported psoriasis-related itching, pain and scaling on the Psoriasis symptom diary;<br>Until Week 52: PASI 50, 75, 90, 100; response of 0 or 1 on modified IGA score; DLQI score of 0 or 1 | Usability of the autoinjector; PASI and modified IGA scores over time | Usability of the pre-filled syringe; PASI and modified IGA scores over time | PASI 75/90/100 and IGA mod 2011 0/1 responses over time to Week 52; time to start of relapse; safety and immunogenicity |

[a]The company's submission report that FIXTURE was conducted in 26 countries, including Brazil, the Russian Federation and Turkey. These countries were not evident in the list of participating sites in the FIXTURE/ERASURE supplementary appendix[25]

[b]The JUNCTURE supplementary appendix lists 40 participating sites[49] while the CS indicates that 38 sites were involved.

[c]These exclusion criteria were reported in the company's submission but not in the relevant publications[49,50]

Table 4 present the baseline demographics and disease characteristics of participants enrolled in FIXTURE and ERASURE while Table 5 those of participants enrolled in JUNCTURE, FEATURE and SCULPTURE.

The submission states (page 53) that compared to the other RCTs, the FEATURE study enrolled a lower proportion of Asian participants (1.7-3.4%) and a higher proportion of Caucasian participants (86.4-96.6%). The information related to the Asian participants seems, however, to be missed in Table 15 *Characteristics of participants in FEATURE across randomised groups* and is not reported in the relevant published paper (i.e. Blauvelt, 2014). As the FEATURE CSR was not included in the company's submission, the ERG was unable to check the data on Asian participants.

ERASURE had a slightly higher proportion of participants who had failed to respond to previous TNF inhibitor than FIXTURE while FEATURE had a substantial proportion of participants who failed prior systemic biologic. This information was not reported for JUNCTURE. [redacted] Mean weight of participants in JUNCTURE and FEATURE was higher than those in the other trials. Participants in FIXTURE, ERASURE [redacted] had a shorter mean time since psoriasis diagnosis than participants in JUNCTURE and FEATURE.

## Table 4 Baseline demographics and disease characteristics: FIXTURE and ERASURE trials

| Characteristic | FIXTURE (n=1306) | | | | ERASURE (n=738) | | |
|---|---|---|---|---|---|---|---|
| | **Secukinumab 300mg (n=327)** | **Secukinumab 150mg (n=327)** | **Etanercept (n=326)** | **Placebo (n=326)** | **Secukinumab 300mg (n=245)** | **Secukinumab 150mg (n=245)** | **Placebo (n=248)** |
| Mean (SD) age, years | 44.5 (13.2) | 45.4 (12.9) | 43.8 (13.0) | 44.1 (12.6) | 44.9 (13.5) | 44.9 (13.3) | 45.4 (12.6) |
| Sex, n (%) | | | | | | | |
| Male | 224 (68.5) | 236 (72.2) | 232 (71.2) | 237 (72.7) | 169 (69.0) | 168 (68.6) | 172 (69.4) |
| Female | 103 (31.5) | 91 (27.8) | 94 (28.8) | 89 (23.3) | 76 (31.0) | 77 (31.4) | 76 (30.6) |
| Race, n (%) | | | | | | | |
| White | 224 (68.5) | 219 (67.0) | 219 (67.2) | 218 (66.9) | 171 (69.8) | 171 (69.8) | 176 (71.0) |
| Asian | 73 (22.3) | 72 (22.0) | 74 (22.7) | 72 (22.1) | 52 (21.2) | 54 (22.0) | 46 (18.5) |
| Other/unknown | 30 (9.2) | 36 (11.0) | 33 (10.1) | 36 (11.0) | 22 (9.0) | 20 (8.2) | 26 (10.5) |
| Mean (SD) weight, kg | 83.0 (21.6) | 83.6 (20.8) | 84.6 (20.5) | 82.0 (20.4) | 88.8 (24.0) | 87.1 (22.3) | 89.7 (25.0) |
| Mean (SD) BMI | 28.4 (6.4) | 28.4 (5.9) | 28.7 (5.9) | 27.9 (6.1) | 30.3 (7.2) | 29.8 (6.8) | 30.3 (7.8) |
| Mean (SD) time since psoriasis diagnosis, years | 15.8 (12.3) | 17.3 (12.2) | 16.4 (12.0) | 16.6 (11.6) | 17.4 (11.1) | 17.5 (12.0) | 17.3 (12.4) |
| Mean (SD) PASI score | 23.9 (9.9) | 23.7 (10.5) | 23.2 (9.8) | 24.1 (10.5) | 22.5 (9.2) | 22.3 (9.8) | 21.4 (9.1) |
| Modified IGA score, n (%) | | | | | | | |
| 3 | 203 (62.1) | 206 (63.0) | 195 (59.8) | 202 (62.0) | 154 (62.9) | 161 (65.7) | 151 (60.9) |
| 4 | 124 (37.9) | 121 (37.0) | 131 (40.2) | 124 (38.0) | 91 (37.1) | 84 (34.3) | 97 (39.1) |
| Psoriatic arthritis, n (%) | 50 (15.3) | 49 (15.0) | 44 (13.5) | 49 (15.0) | 57 (23.3) | 46 (18.8) | 68 (27.4) |
| Previous systemic treatment, n (%) | | | | | | | |
| Any | 206 (63.0) | 212 (64.8) | 214 (65.6) | 204 (62.6) | 163 (66.5) | 156 (63.7) | 146 (58.9) |
| Conventional agent | 195 (59.6) | 198 (60.6) | 204 (62.6) | 199 (61.0) | 128 (52.2) | 125 (51.0) | 108 (43.5) |
| Biologic agent: | 38 (11.6) | 45 (13.8) | 45 (13.8) | 35 (10.7) | 70 (28.6) | 73 (29.8) | 73 (29.4) |
| TNF inhibitor | 12 (3.7) | 15 (4.6) | 21 (6.4) | 12 (3.7) | 48 (19.6) | 44 (18.0) | 51 (20.6) |
| Anti-IL-12 & anti-IL-23 agent | 23 (7.0) | 23 (7.0) | 22 (6.7) | 21 (6.4) | 32 (13.1) | 37 (15.1) | 31 (12.5) |
| No response to previous TNF inhibitor, n (%) | 10 (3.1) | 9 (2.8) | 10 (3.1) | 3 (0.9) | 17 (6.9) | 18 (7.3) | 21 (8.5) |

**Table 5 Baseline demographics and disease characteristics: JUNCTURE, FEATURE and SCULPTURE trials**

| Characteristic | JUNCTURE (n=182) | | | FEATURE (n=177) | | | SCULPTURE (n=966) | |
|---|---|---|---|---|---|---|---|---|
| | **Secukinumab 300mg (n=60)** | **Secukinumab 150mg (n=61)** | **Placebo (n=61)** | **Secukinumab 300mg (n=59)** | **Secukinumab 150mg (n=59)** | **Placebo (n=59)** | **Secukinumab 300mg (n=[redacted])** | **Secukinumab 150mg (n=[redacted])** |
| Mean (SD) age, years | 46.6 (14.2) | 43.9 (14.4) | 43.7 (12.7) | 45.1 (12.6) | 46.0 (15.1) | 46.5 (14.1) | [redacted] | [redacted] |
| Sex, n (%) | | | | | | | | |
| Male | 46 (76.7) | 41 (67.2) | 38 (62.3) | 38 (64.4) | 40 (67.8) | 39 (66.1) | [redacted] | [redacted] |
| Female | 14 (23.3) | 20 (32.8) | 23 (37.7) | 21 (35.6) | 19 (32.2) | 20 (33.9) | | |
| Race, n (%) | | | | | | | | |
| White | 56 (93.3) | 58 (95.1) | 59 (96.7) | 54 (91.5) | 51 (86.4) | 57 (96.6) | [redacted] | [redacted] |
| Asian | NR | NR | NR | NR | NR | NR | | |
| Black | NR | NR | NR | 3 (5.1) | 3 (5.1) | 1 (1.7) | | |
| Other/unknown | NR | NR | NR | NR | NR | NR | | |
| Mean (SD) weight, kg | 91.0 (23.1) | 93.7 (31.7) | 90.2 (21.2) | 92.6 (25.9) | 93.7 (25.6) | 88.4 (21.6) | | |
| Mean (SD) BMI | 30.0 (6.9) | 30.6 (9.5) | 30.0 (6.8) | NR | NR | NR | | |
| Mean (SD) time since psoriasis diagnosis, years | 21.0 (13.5) | 20.6 (14.5) | 19.9 (12.2) | 18.0 (11.9) | 20.4 (13.0) | 20.2 (14.2) | | |
| Mean (SD) PASI score | 18.9 (6.4) | 22.0 (8.9) | 19.4 (6.7) | 20.7 (8.0) | 20.5 (8.3) | 21.1 (8.5) | [redacted] | [redacted] |
| Modified IGA score, n (%) | | | | | | | | |
| 3 | | | | | | | | |
| 4 | 39 (65.0) | 35 (57.4) | 38 (62.3) | 40 (67.8) | 37 (62.7) | 34 (57.6) | [redacted] | [redacted] |
| | 21 (35.0) | 26 (42.6) | 23 (37.7) | 19 (32.2) | 22 (37.3) | 25 (42.4) | | |
| Psoriatic arthritis, n (%) | 14 (23.3) | 16 (26.2) | 12 (19.7) | 50 (15.3)[a] | 49 (15.0)[a] | 49 (15.0)[a] | [redacted][b] | [redacted][b] |
| Previous systemic treatment, n (%) | | | | | | | | |
| Any | 34 (56.7) | 34 (55.7) | 33 (54.1) | 35 (59.3) | 45 (76.3) | 39 (66.1) | [redacted] | [redacted][b] |
| Conventional agent | 30 (50.0) | 31 (50.8) | 29 (47.5) | 20 (33.9) | 39 (66.1) | 29 (49.2) | | |
| Biologic agent: | | | | | | | | |
| TNF inhibitor | 15 (25.0) | 15 (24.6) | 13 (21.3) | 23 (39.0) | 28 (47.5) | 26 (44.1) | [redacted] | [redacted] |
| Anti-IL-12 & anti- | NR | NR | NR | NR | NR | NR | | |
| IL-23 agent | NR | NR | NR | NR | NR | NR | | |
| Prior failure | | | | | | | | |
| Systemic biologic | NR | NR | NR | 9/23 (39.1) | 18/28 (64.3) | 14/26 (53.8) | [redacted] | [redacted] |
| Systemic therapy | NR | NR | NR | NR | NR | NR | | |
| Biologic therapy | NR | NR | NR | NR | NR | NR | | |
| Non-biologic therapy | NR | NR | NR | NR | NR | NR | | |

[a]As reported in the company's submission. The ERG note that the percentages appear incorrect. This information is not reported in Blauvelt 2015.[50]

[b]Data derived from the SCULPURE CSR.

### 4.1.5 Critique of data extraction

The company did not specify whether they based the methods of their systematic review of clinical evidence on published guidance. Title/abstract screening and full-text screening were carried out by two researchers with a third researcher acting as arbitrator, where necessary. The level of independence of these two researchers was not reported. The company used a specifically designed data extraction form to collect information from the identified studies but did not specify the number of researchers performing data extraction. Quality assessment of included studies was conducted at the time of data extraction but, again, the number of researchers involved is not specified.

### 4.1.6 Quality assessment

The company adopted the criteria recommended by the CRD for assessing the risk of bias in the included RCTs. The criteria, which involve assessment of selection bias, performance bias, detection bias, attrition bias and reporting bias, are considered appropriate by the ERG. Methods of randomisation and allocation were considered appropriate by the ERG and baseline demographics and disease characteristics were, in general, balanced across intervention groups. Study personnel and participants were masked throughout the trials. An intention-to-treat approach was adopted in all included studies.

With regard to unexpected imbalances in drop-outs between intervention groups, it is worth noting that in FIXTURE 11% participants in the secukinumab 300mg group dropped out compared with 16% in the secukinumab 150mg group, 19% in the etanercept group, and 17% in the placebo group. Figure 8 in the company's submission shows that lack of efficacy was the main reason for discontinuation of treatment in both the secukinumab 150mg group and the etanercept group. This pattern of drop-outs was similar to that observed in the ERASURE trial, where 12% of participants discontinued maintenance in the secukinumab 300mg group, 18% in the secukinumab 150mg group, and 17% in the placebo group. For JUNCTURE and FEATURE only discontinuations in the induction phase were reported and numbers were balanced across groups.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the CRD criteria. Results are presented in Table 6.

**Table 6 Quality assessment of the company's systematic review of evidence**

| CRD quality item | Score |
|---|---|
| 1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question? | Yes |
| 2. Is there evidence of a substantial effort to search for all of the relevant research? | Yes |
| 3. Is the validity of included studies adequately assessed? | Yes |
| 4. Are sufficient details of the individual studies presented? | Yes |
| 5. Are the primary studies summarised appropriately? | Yes |

Overall, the systematic review conducted by the company was of good quality with no major concerns in any of the specified quality areas.

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

The company presents the results of the FIXTURE, ERASURE, JUNCTURE, and FEATURE trials, which assessed secukinumab administered subcutaneously versus placebo in patients with moderate to severe chronic plaque psoriasis. ERASURE, JUNCTURE, and FEATURE included two secukinumab arms (i.e. 150mg and 300mg) and a placebo arm; FIXTURE also included an etanercept arm. In each study a secondary randomisation stage took place at week 12, when some patients in the placebo arm were randomised to receive an active treatment. Another randomised trial, SCULPTURE, compared patients receiving secukinumab 300mg with those receiving secukinumab 150mg.

A limitation of the evidence base is the lack of direct head-to-head evidence versus active comparators other than etanercept.

The ERG did not identify any further secukinumab RCTs.

In FIXTURE, ERASURE, JUNCTURE, and FEATURE the primary efficacy outcome was to demonstrate the superiority of secukinumab with respect to both PASI 75 and IGA 0 to 1 response at week 12 compared to placebo. In SCULPTURE the primary outcome was to demonstrate the non-inferiority of 150mg and 300mg secukinumab administered at the start of relapse versus fixed interval regimens of 150mg and 300mg of secukinumab respectively, in patients who were PASI 75 responders at week 12.

The company pre-specified a number of subgroup analyses within the identified RCTs including: gender, age, race, weight, geographical location, age at diagnosis, disease duration, baseline measurements and previous treatments for psoriasis. In addition the company examined *post hoc* whether there were differences in PASI 75 response at 12 weeks for patients with DLQI >10 versus those with DLQI $\leq$10 at baseline. The complete list of subgroup analyses and their rationale is presented in Table 20 of the submission.

*Results of the identified studies*

At 12 weeks, higher proportions of participants receiving secukinumab 300mg had achieved PASI 50, 75, 90 and 100 responses compared with participants randomised to placebo. For example, over three-quarters of the participants in FIXTURE, ERASURE, JUNCTURE and FEATURE randomised to secukinumab 300mg (75.9% to 86.7% of participants) achieved at least a PASI 75 response, whereas fewer than 5% of participants randomised to the corresponding placebo arms achieved this level of response ($p<0.0001$ in all cases). Similar results in favour of secukinumab 300mg over placebo were found for participants achieving “clear” or “almost clear” results at the IGA mod 2011outcome measure. DLQI reductions and EQ-5D improvements were also consistently higher for secukinumab 300 mg than placebo in FIXTURE, ERASURE, JUNCTURE and FEATURE.

In FIXTURE, ERASURE, JUNCTURE, FEATURE and SCULPTURE, better rates of PASI response were found for the secukinumab 300mg groups compared with the secukinumab 150mg groups

In FIXTURE and ERASURE PASI 75, PASI 90, PASI 100 and IGA mod 2011 0/1 response rates continued to increase from week 12 to week 16.

At week 12 the FIXTURE trial found that statistically significantly higher PASI 75 and IGA mod 2011 0/1 responses were achieved with secukinumab 300mg compared with etanercept given at the highest licensed dose (77.1% versus 44% and 62.5% versus 27.2% respectively; $p<0.0001$ in all cases). A $\geq$50% mean decrease from baseline in PASI score was achieved as early as week 3 with secukinumab 300mg compared with week 7 with etanercept. A more pronounced decrease in DLQI was also observed in the secukinumab 300mg group than in the etanercept group.

In SCULPTURE the efficacy of secukinumab was similar to that observed in the other four trials. However, non-inferiority of a secukinumab 'treatment on relapse' regimen compared with a fixed treatment regimen for maintaining week 12 PASI response up to week 52 could not be achieved.

Table 7 (reproduced from Table 22 of the company's submission) summarises the results of FIXTURE, ERASURE, JUNCTURE, FEATURE and SCULPTURE for the main efficacy outcomes (PASI and IGA mod 2011 'clear' or 'almost clear' response). Results are given for the secukinumab 300mg, secukinumab 150mg, etanercept (FIXTURE trial only) and placebo groups at week 12 and, where available, at week 16 and week 52. No results are presented for the placebo groups at week 16 and week 52 as placebo participants underwent conditional re-randomisation at week 12.

*Subgroup analyses*

In FIXTURE, ERASURE, JUNCTURE, and FEATURE results of pre-specified subgroup analyses by body weight and previous treatments for psoriasis were consistent with the overall study results. [redacted]

## Table 7 Summary of results for key efficacy endpoints by study (reproduced from Table 22 of the company's submission)

| | Week 12 | | | | Week 16 | | | Week 52 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **300 mg** | **150 mg** | **Placebo** | **Etanercept** | **300 mg** | **150 mg** | **Etanercept** | **300 mg** | **150 mg** | **Etanercept** | **300 mg SoR** | **150 mg SoR** |
| **FIXTURE** | | | | | | | | | | | | |
| Number of patients | 323 | 327 | 324 | 323 | 323 | 327 | 323 | 323 | 327 | 323 | N/A | N/A |
| PASI 50 response: n (%) | 296 (91.6%) | 266 (81.3%) | 49 (15.1%) | 226 (70.0%) | 302 (93.5%) | 290 (88.7%) | 257 (79.6%) | 274 (84.8%) | 249 (76.1%) | 234 (72.4%) | N/A | N/A |
| PASI 75 response: n (%) | 249 (77.1%)** | 219 (67.0%)** | 16 (4.9%) | 142 (44.0%) | 280 (86.7%) | 247 (75.5%) | 189 (58.5%) | 254 (78.6%) | 215 (65.7%) | 179 (55.4%) | N/A | N/A |
| PASI 90 response: n (%) | 175 (54.2%) | 137 (41.9%) | 5 (1.5%) | 67 (20.7%) | 234 (72.4%) | 176 (53.8%) | 101 (31.3%) | 210 (65.0%) | 147 (45.0%) | 108 (33.4%) | N/A | N/A |
| PASI 100 response: n (%) | 78 (24.1%) | 47 (14.4%) | 0 (0%) | 14 (4.3%) | 119 (36.8%) | 84 (25.7%) | 24 (7.4%) | 117 (36.2%) | 65 (19.9%) | 32 (9.9%) | N/A | N/A |
| IGA mod 2011 "clear" or "almost clear" response n (%) | 202 (62.5%)** | 167 (51.1%)** | 9 (2.8%) | 88 (27.2%) | 244 (75.5%) | 200 (61.2%) | 127 (39.3%) | 219 (67.8%) | 168 (51.4%) | 120 (37.2%) | N/A | N/A |
| **ERASURE** | | | | | | | | | | | | |
| Number of patients | 245 | 244 | 246 | N/A | 245 | 244 | N/A | 245 | 244 | N/A | N/A | N/A |
| PASI 50 response: n (%) | 222 (90.6%) | 203 (83.5%) | 22 (8.9%) | N/A | 224 (91.4%) | 212 (87.2%) | N/A | 207 (84.5%) | 187 (77%) | N/A | N/A | N/A |
| PASI 75 response: n (%) | 200 (81.6%)** | 174 (71.6%)** | 11 (4.5%) | N/A | 211 (86.1%) | 188 (77.4%) | N/A | 182 (74.3%) | 146 (60.1%) | N/A | N/A | N/A |
| PASI 90 response: n (%) | 145 (59.2%)** | 95 (39.1%)** | 3 (1.2%) | N/A | 171 (69.8%) | 130 (53.5%) | N/A | 147 (60.0%) | 88 (36.2%) | N/A | N/A | N/A |
| PASI 100 response: n (%) | 70 (28.6%) | 31 (12.8%) | 2 (0.8%) | N/A | 102 (41.6%) | 51 (21.0%) | N/A | 96 (39.2%) | 49 (20.2%) | N/A | N/A | N/A |
| IGA mod 2011 "clear" or "almost clear" response n (%) | 160 (65.3%)** | 125 (51.2%)** | 6 (2.40%) | N/A | 180 (73.5%) | 142 (58.2%) | N/A | 148 (60.4%) | 101 (41.4%) | N/A | N/A | N/A |
| **JUNCTURE** | | | | | | | | | | | | |
| Number of patients | 60 | 60 | 61 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| PASI 50 response: n (%) | 58 (96.7%) | 48 (80.0%) | 5 (8.2%) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| PASI 75 response: n (%) | 52 | 43 | 2 (3.3%) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |

| | Week 12 | | | | Week 16 | | | Week 52 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **300 mg** | **150 mg** | **Placebo** | **Etanercept** | **300 mg** | **150 mg** | **Etanercept** | **300 mg** | **150 mg** | **Etanercept** | **300 mg SoR** | **150 mg SoR** |
| | (86.7%)** | (71.7%)** | | | | | | | | | | |
| PASI 90 response: n (%) | 33 (55.0%) | 24 (40.0%) | 0 (0.0%) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| PASI 100 response: n(%) | 16 (26.7%) | 10 (16.7%) | 0 (0.0%) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| IGA mod 2011 “clear” or “almost clear” response n (%) | 44 (73.3%)** | 32 (53.3%)** | 0 (0.0%) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| **FEATURE** | | | | | | | | | | | | |
| Number of patients | 58 | 59 | 59 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| PASI 50 response: n (%) | 51 (87.9%) | 51 (86.4%) | 3 (5.1%) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| PASI 75 response: n (%) | 44 (75.9%)** | 41 (69.5%)** | 0 (0.0%) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| PASI 90 response: n (%) | 35 (60.3%) | 27 (45.8%) | 0 (0.0%) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| PASI 100 response: n (%) | 25 (43.1%) | 5 (8.5%) | 0 (0.0%) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| IGA mod 2011 “clear” or “almost clear” response n (%) | 40 (69.0%)** | 31 (52.5%)** | 0 (0.0%) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| **SCULPTURE** | | | | | | | | | | | | |
| Number of patients | 483 | 481 | N/A | N/A | 216 | 203 | N/A | 216 | 203 | N/A | 217 | 206 |
| PASI 50 response: n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75 response: n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 90 response: n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 100 response: n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| IGA mod 2011 “clear” or “almost clear” response n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Abbreviations**: start of relapse, SoR; ,PASI; ,IGA: not available,N/A The IGA mod 2011 is a 5-category scale including “0 = clear”, “1 = almost clear”, “2 = mild”, “3 = moderate” or “4 = severe”, indicating the physician’s overall assessment of

| | Week 12 | | | | Week 16 | | | Week 52 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **300 mg** | **150 mg** | **Placebo** | **Etanercept** | **300 mg** | **150 mg** | **Etanercept** | **300 mg** | **150 mg** | **Etanercept** | **300 mg SoR** | **150 mg SoR** |
| the psoriasis severity focusing on induration, erythema and scaling. Treatment success of “clear” or “almost clear” consisted of no signs of psoriasis or normal to pink colouration of lesions, no thickening of the plaque and none to minimal focal scaling. ** p values versus placebo and adjusted for multiplicity: p<0.0001. | | | | | | | | | | | | |

*Adverse events*

The company's submission provides detailed information on adverse events for the FIXTURE, ERASURE, JUNCTURE, FEATURE and SCULPTURE trials. Most adverse events were minor with upper respiratory tract infections being the most commonly reported. Table 8 (reproduced from Table 63 of the company's submission) presents a summary of adverse events after combining the results from the four placebo-controlled trials. Overall, infections were reported in 28.7% of patients with secukinumab compared with 18.9% of patients treated with placebo. Serious infections occurred in 0.14% of participants treated with secukinumab and in 0.3% of participants treated with placebo (the relevant numerators and denominators were not given in the company's submission). In FIXTURE the proportion of participants who experienced adverse events throughout the 52-week duration of the trial (Table 58 of the company's submission) was similar in the secukinumab 300mg and etanercept groups (376/467, 80% and 253/323, 78%, respectively).

**Table 8 Summary of Adverse Events in Clinical Studies (reproduced from Table 63 of the company's submission)**

| System organ Class | | Secukinumab 300 mg (n =690) n (%) | Secukinumab 150 mg (n = 692) n (%) | Placebo (n = 694) n (%) |
|---|---|---|---|---|
| **Infections and infestations** | | | | |
| Very Common | Upper Respiratory tract infections | 117 (17.0) | 129 (18.6) | 72 (10.4) |
| Common | Oral herpes | 9 (1.3) | 1 (0.1) | 2 (0.3) |
| Uncommon | Oral candidiasis | 4 (0.6) | 1 (0.1) | 1 (0.1) |
| Uncommon | Tinea pedis | 5 (0.7) | 5 (0.7) | 0 (0) |
| **Blood and lymphatic system disorders** | | | | |
| Uncommon | Neutropenia | | | |
| **Eye disorders** | | | | |
| Uncommon | Conjunctivitis | | | |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Common | Rhinorrhoea | 8 (1.2) | 2 (0.3) | 1 (0.1) |
| **Gastrointestinal disorders** | | | | |
| Common | Diarrhoea | 28 (4.1) | 18 (2.6) | 10 (1.4) |
| **Skin and subcutaneous tissue disorders** | | | | |
| Common | Urticaria | 4 (0.6) | 8 (1.2) | 1 (0.1) |
| Placebo-controlled clinical studies (phase III) in plaque psoriasis patients exposed to secukinumab 300 mg, 150 mg or placebo up to 12 weeks treatment duration | | | | |

*Meta-analyses*

For the secukinumab versus placebo comparison, results of the FIXTURE, ERASURE, JUNCTURE, FEATURE and SCULPTURE trials could have been combined in formal meta-analyses. However, these meta-analyses may have been of little benefit as the results would have been similar to those of the network meta-analyses (NMA) presented in Section 6.7 of the submission. Meta-analysis could also have been conducted for quality of life measures (i.e. EQ-5D and DLQI). There were no other possible head-to-head comparisons with secukinumab 300mg that involved more than one trial.

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

*Inclusion of trials in the network meta-analyses (NMA)*

The company identified 45 potential suitable studies in the literature, of which 30 studies were deemed suitable for inclusion in the NMA.

The company conducted quality assessment of the studies included in the NMA, based upon randomisation, allocation concealment, baseline characteristics, blinding, incomplete outcome data, selective reporting and whether an intention-to-treat approach was used. The company's assessment shows that the included studies were, on the whole, of good quality, with the main outstanding questions relating to unreported data regarding methods of randomisation and/or allocation concealment.

Table 9 presents a summary of the main characteristics of the RCTs included in the NMA, by treatment. Appendix 1 presents the baseline participant characteristics of all RCTs included in the NMA.

## Table 9 Summary of main characteristics of RCTs included in NMA, by treatment

| Treatment | No of participants (total no of studies) | Age, years | Male, % | Weight, kg | Psoriasis duration, years | Treatment biologic naïve, no:yes | Prior biologic exposure, % | Prior topical agent, % | Prior photo-therapy, % | Prior systemic therapy, % | PASI | DLQI | PGA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Secukinumab | | | | | | | | | | | | | |
| 150mg | 234.4 (59-481) (5 studies) | 45.1 (43.9-46) | 67.8 (63.3-72.2) | 88.7 (83.6-93.7) | 18.2 (17.2-20.6)[d] | 4:0[d] | 28.9 (24.6-47.5)[d] | NR | NR | NR | 22.5 (20.5-23.7) | 13.4 (13.4-13.4)[b] | NR |
| 300mg | 234.6 (58-483) (5 studies) | 45.6 (44.9-46.7) | 64.5 (63.8-76.7) | 88.1 (83-92.6) | 17.9 (15.8-21)[d] | 4:0[d] | 26.1 (11.6-39)[d] | NR | NR | NR | 21.9 (18.9-23.9) | 13.4 (13.4-13.4)[b] | NR |
| All | 234.5 (58.5-482) (5 studies) | 45.4 (44.9-46) | 68.2 (63.6-72) | 88.4 (83.3-93.2) | 18.1 (16.6-20.8)[d] | 4:0[d] | 27.5 (12.7-43.3)[d] | NR | NR | NR | 22.2 (20.5-23.8) | 13.6 (13.4-13.7)[b] | NR |
| Adalimumab | 266.3 (20-814) (4 studies) | 47.1 (42.9-56.1) | 75 (67.1-85) | 84.7 (69.7-95.1) | 16.4 (13.3-18.1)[c] | 2:1[c] | 26.5 (11.9-41)[b] | 56.9 (17-96.7)[b] | 18.3 (17-19.5)[b] | 33.6 (23.1-44.1)[b] | 19.7 (11.6-28) | 8.6[a] | 3.9[a] |
| Etanercept | 208.2 (96-347) (9 studies) | 45.3 (43.1-48.2) | 66.7 (61.5-71.2) | 90.2 (83.4-95.8)[f] | 18.9 (16.4-23) | 4:3[g] | 15 (11.8-20.1)[d] | 94.5 (92.2-96.8)[b] | 38.5 (23.4-64.6)[c] | 41.8 (26.2-57.3)[c] | 20.4 (17.8-26.2)[f] | 12.5 (12.2-13.4)[c] | 2.8[a] |
| Infliximab | 140 (11-298) (6 studies) | 43.4 (39.4-46.9) | 68.2 (62.9-72.2) | 80.1 (68.2-92.1)[d] | 17.2 (14.2-19.1)[d] | 3:2[e] | 49.3 (15-100)[c] | 94.5 (88.9-100)[b] | 65.3 (62.9-67.7)[b] | 90 (85.7-94.3)[b] | 22.2 (11.5-31.9)[e] | 12.9 (11.5-14.4)[e] | NR |
| Ustekinumab | | | | | | | | | | | | | |
| 45mg | 170.3 (61-409) (7 studies) | 43.7 (40.1-45.1) | 72.2 (61-82) | 83.3 (69.9-92.8) | 17.1 (14.6-19.8) | 5:2 | 23 (1.6-52.5)[d] | 96.4 (94-100)[d] | 63 (37.5-80.3) | 61 (39.4-73.4) | 22.5 (18.9-30.1) | 12.9 (11.1-16.1)[d] | 3.5[a] |
| 90mg | 227.8 (62-411) (5 studies) | 45.1 (44-46.6) | 71.7 (66.7-81) | 87.9 (71.1-93.8) | 18.6 (17.3-20.3) | 3:2 | 24.4 (0-50.8)[d] | 95.1 (92-100) | 69.9 (66-82.3)[d] | 60.2 (52.4-83.9) | 21.5 (19-28.7)[d] | 11.4 (10.5-12.6) | 3.5[a] |

Mean of means (range) reported unless otherwise stated

[a]1 study; [b]2 studies; [c]3 studies; [d]4 studies; [e]5 studies; [f]6 studies; [g]7 studies

Table 10, which reproduces Table 50 of the company's submission, illustrates the relevant interventions (secukinumab, etanercept, infliximab, adalimumab and ustekinumab) and the doses that were considered for the NMA.

**Table 10 Interventions and doses of interest, network meta-analysis (reproduced from Table 50 from the company's submission)**

| Drug | Induction Phase | Maintenance dose |
|---|---|---|
| secukinumab | 150[a] or 300 mg week 0,1,2,3,4 | 150[a] or 300 mg every month |
| etanercept | 25mg BD for 12 weeks | 25 mg twice weekly or 50 mg weekly |
| infliximab | 5 mg/kg week 1,2,6 | 5 mg/kg every 8 weeks |
| adalimumab | 80 mg week 1 | 40 mg every 2 weeks |
| ustekinumab | 45 or 90 mg week 1,4 | 45 or 90 mg every 12 weeks |

[a] 150 mg dose included in NMA but is not recommended dose. Phase 2 studies that did not include a 300 mg secukinumab arm were excluded from the NMA.

For most of the interventions only recommended (licensed) doses were included. Secukinumab 150mg, however, is not the current recommended dose for the treatment of moderate to severe psoriasis in the UK. On clarification the company explained that they included this regimen for completeness and transparency and because all five relevant secukinumab phase III trials assessed both 150mg and 300mg regimens. The ERG agree that inclusion of the secukinumab 150mg arms may have strengthened the network of available evidence, but note that inclusion of doses has not been handled consistently for secukinumab and the other relevant comparators and no sensitivity analyses excluding the secukinumab 150mg groups were presented.

The STATURE trial (which compared secukinumab 300mg with an intravenous dose of 10 mg/kg) was excluded from the analyses due to the lack of a placebo control group, the fact that the comparator dosing regimen was not in line with the secukinumab draft guidelines and because the trial was not statistically powered to meet the co-primary endpoints. On the other hand, the SCULPTURE trial, which compared secukinumab 300 mg with secukinumab 150mg, was included despite the lack of a placebo control group or a comparator with a recommended dose and despite the indication that studies should not be excluded on the basis of their sample size.[53] Even though the ERG agree that it was reasonable to exclude STATURE from the analyses due to other reasons (e.g. because participants had already

received secukinumab), find the rationale for inclusion/exclusion of treatments and doses not completely transparent.

The ERG also noted that etanercept 100mg, the highest licensed dose, was included in only one of the three NMAs to allow a connected network (see below).

*Time points included in the network meta-analyses (NMA)*

Three network meta-analyses (NMA) were reported in the company's submission:

- Base case (NICE 12-week endpoint)
- 12-week analysis
- NICE 16-week endpoint

The NICE 12-week endpoint was considered the primary analysis while the 12-week analysis and the NICE 16-week endpoint were described as "scenario analyses".

Figures 2, 3 and 4 (reproduced from Figures 19, 24 and 25 of the company's submission) show the diagrams for the three network analyses.

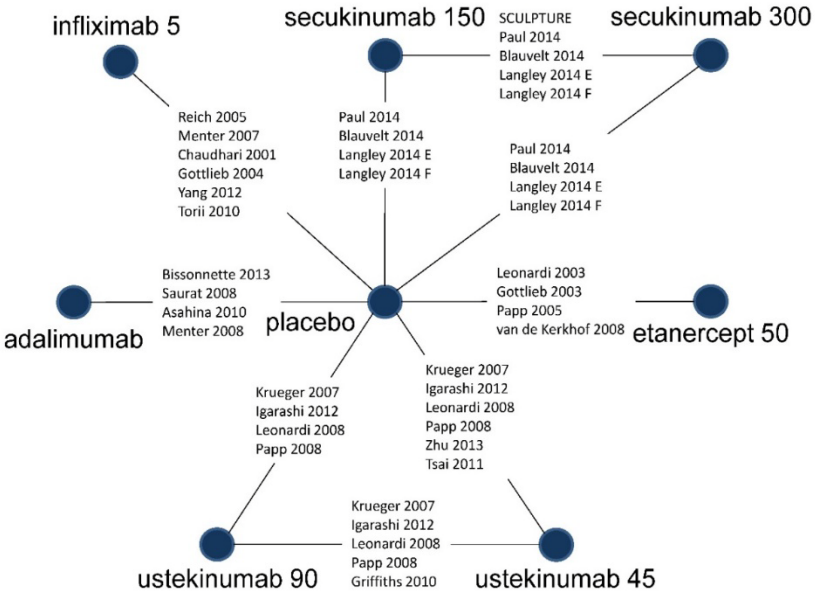



**Figure 2 Network of trials for the comparison of secukinumab versus other biologics for PASI response (NICE 12 week endpoint, base-case) (reproduced from Figure 19 of the company's submission)**

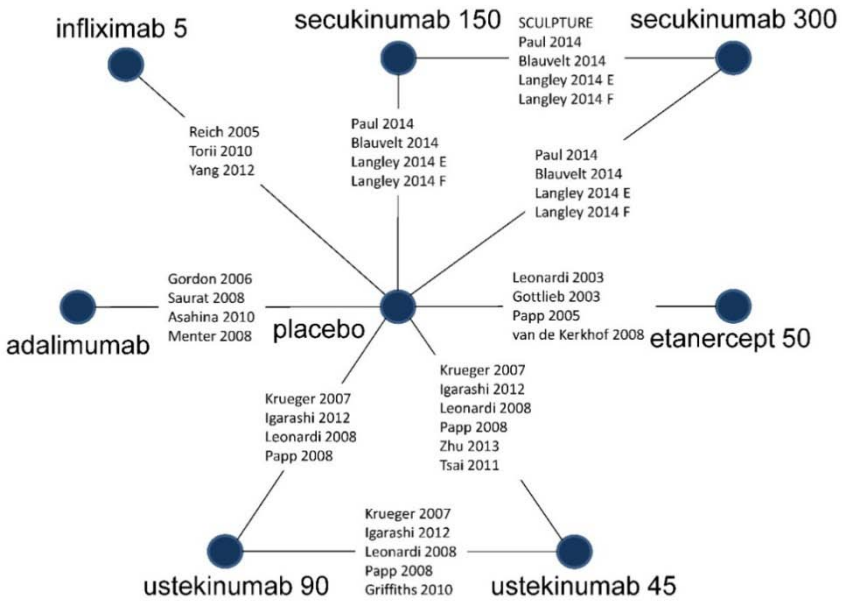



**Figure 3 Network of trials for the comparison of secukinumab versus other biologics for PASI response (12 week analysis, scenario analysis) (reproduced from Figure 24 of the company's submission)**

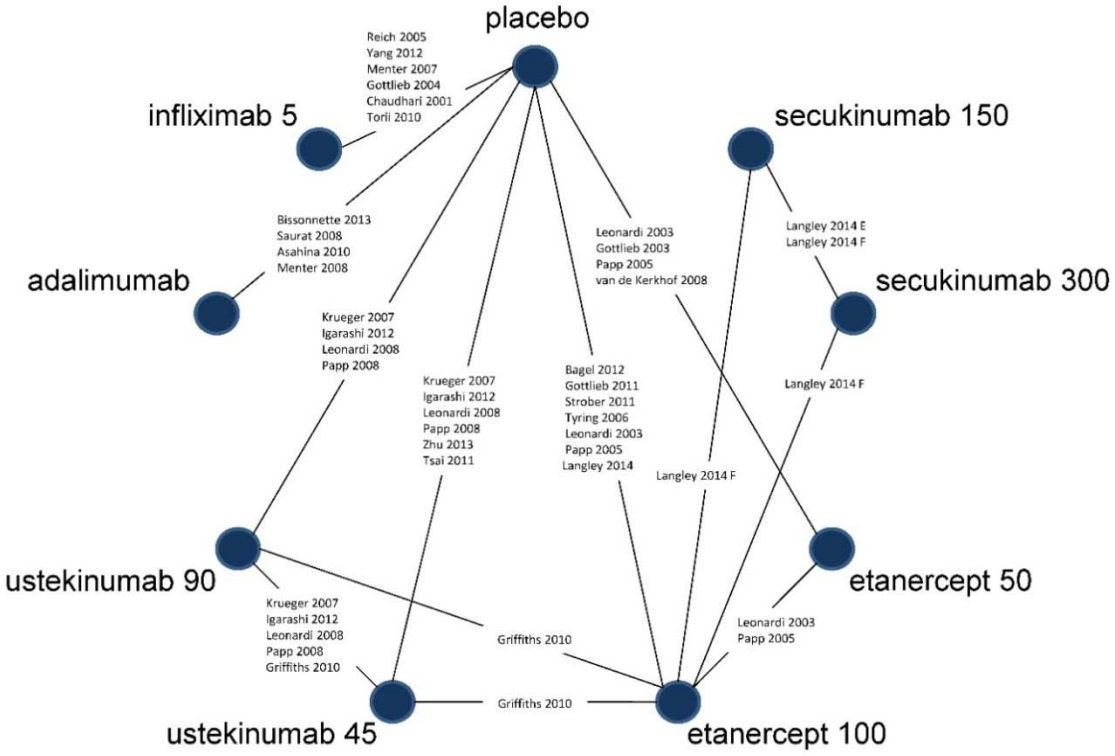



**Figure 4 Network of trials for the NICE 16 week endpoint analysis (secukinumab 16 week data) (reproduced from Figure 25 from the company's submission)**

The time point for the primary base case analysis varied according to different comparators and was based on the primary endpoints used in individual trials: 10 weeks for infliximab, 12 weeks for secukinumab, ustekinumab and etanercept and 16 weeks for adalimumab. These align with the NICE CG153[41] and the BAD guidelines[54] with the exception of ustekinumab for which both sets of guidelines recommend 16 weeks as the time point for decision to continue treatment. The proportions of patients across four mutually exclusive PASI categories (0-49, 50-74, 75-89, 90-100) were assessed at each trial's primary endpoint.

The 12-week scenario analysis used only data at 12 weeks, when available. There were some discrepancies between the information provided on page 108 of the submission, the network diagram shown in Figure 24 of the submission (Figure 3 above) and Table 13 provided by the company at clarification. The network diagram includes 23 unique studies agreeing with the number given in the text, but five studies (Reich 2005, Torii 2010, Yang 2012, Langley 2014 – ERASURE, and Menter 2008) are omitted from the 12 week column in Table 13. As no data were given in the NMA programs submitted by the company, the ERG had assumed that the revised Table 13 represented the definitive data used in the analyses. However, these discrepancies suggest a certain degree of uncertainty over which studies were included in the 12 week scenario analysis.

The NICE 16-week endpoint analysis was similar to the base case analysis except that 16-week secukinumab data were used instead of the 12-week secukinumab data. Data from other comparators came from 10, 12 or 16 weeks as in the base case.

The ERG understand that the rationale for the NICE 16 week endpoint analysis comes from a 16-week stopping rule recommended in the draft SmPC. Participants in the placebo group were re-randomised at 12 weeks and it was therefore not possible to include any direct comparison of secukinumab with placebo in the NMA for later time points. The ERG agree that inclusion of an intention-to-treat "placebo plus" comparator would not have been adequate. The company had to include etanercept 100mg as a comparator in order to form a connected network and allow secukinumab to be compared with placebo and other comparators, even though this is not a typical dose and was not considered to be a relevant comparator for the other analyses – its inclusion could be considered arbitrary but it seems that this is the only available comparator that would have formed a connected network.

Because of these issues, the ERG suggest that lower emphasis should be placed on the results of the NICE 16-week scenario analysis.

*Outcome measures included in the network meta-analyses (NMA)*

The final scope issued by NICE (page 32 of the company's submission) include five main outcome measures: severity, remission, relapse rate, adverse events, and quality of life. Although these outcomes are reported for individual trials, a formal meta-analysis was only conducted for the PASI ordinal outcome. At clarification, the company clarified that it was not possible to include these measures in the NMA due to the lack of data reported across trials or the differences in reporting of outcomes across trials. across trials. The ERG noted that quality of life data (EQ-5D and DLQI) had been collected in more than one secukinumab study

*Data included in the network meta-analyses (NMA)*

The data used in the NMA were originally provided in Table 53 of the company's submission. The ERG noted some discrepancies when comparing the included studies with the studies listed in the network diagrams. At clarification the company produced a corrected version of the tables used in the NMA (Table 13, clarification document) along with an updated list of included and excluded studies (Tables 11-12, clarification document). The ERG have not identified any further randomised studies that could have been included.

As the analysis programs supplied did not include the actual data used, the ERG have therefore assumed that the corrected Table 13 provided at clarification is what was used in the NMA and conducted a check of the PASI data presented in this table against the original study publications. The results of this cross check showed a certain number of discrepancies. The vast majority of these were minor and seemed to relate to rounding when counts in each PASI category had to be calculated from percentages reported in a study publication. There were some ambiguous situations where two or more counts might yield the same percentages, but even allowing for this, the ERG noticed an apparent systematic pattern with numbers rounded down rather than to the nearest whole number.

*Results of the network meta-analyses (NMA)*

The results of the indirect comparison analyses are given in Tables 11, 12 and 13 for the NICE 12-week analysis (26 studies in total). These tables show the risk ratios for each pair of

treatments in the network, along with 95% credible intervals to two decimal places. The methodology used in the NMA is discussed in the following section.

The results of the NMA indicate that secukinumab 300mg performed favourably to placebo at all three PASI thresholds with risk ratios (95% CrI) of 0.13 (0.11, 0.14), 0.04 (0.04, 0.05) and 0.01 (0.01, 0.01) for PASI 50, PASI 75 and PASI 90, respectively. Compared with the other treatments in the network secukinumab 300mg had the highest estimated rates of PASI 50, 75 and 90 response. There was also evidence that secukinumab 300mg performed favourably when compared with four of the other comparators in the network: secukinumab 150mg, etanercept 50mg, ustekinumab 45mg and adalimumab. There was no clear evidence of differences between secukinumab 300mg and ustekinumab 90mg and between secukinumab 300mg and infliximab 5mg.

Results for the other two NMAs (12-week analysis and NICE 16-week analysis) showed similar results.

**Table 11 Random effects multinomial NMA for PASI 50 response (reproduced from Table 55 from the company's submission)**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **placebo** | **0.13 (0.12, 0.15)** | **0.13 (0.11, 0.14)** | **0.19 (0.16, 0.23)** | **0.13 (0.12, 0.15)** | **0.13 (0.11, 0.15)** | **0.15 (0.13, 0.18)** | **0.13 (0.11, 0.14)** |
| **7.41 (6.53, 8.44)** | **secukinumab 150** | **0.93 (0.90, 0.96)** | **1.41 (1.24, 1.63)** | 0.99 (0.93, 1.05) | 0.96 (0.90, 1.01) | **1.12 (1.03, 1.25)** | **0.93 (0.88, 0.99)** |
| **7.99 (7.05, 9.11)** | **1.08 (1.05, 1.12)** | **secukinumab 300** | **1.52 (1.35, 1.75)** | **1.07 (1.02, 1.12)** | 1.03 (0.99, 1.08) | **1.21 (1.12, 1.34)** | 1.00 (0.96, 1.05) |
| **5.24 (4.42, 6.22)** | **0.71 (0.61, 0.80)** | **0.66 (0.57, 0.74)** | **etanercept 50** | **0.70 (0.61, 0.79)** | **0.68 (0.59, 0.77)** | **0.80 (0.68, 0.93)** | **0.66 (0.57, 0.75)** |
| **7.49 (6.62, 8.53)** | 1.01 (0.95, 1.07) | **0.94 (0.89, 0.98)** | **1.43 (1.26, 1.64)** | **ustekinumab 45** | **0.97 (0.94, 1.00)** | **1.14 (1.04, 1.26)** | **0.94 (0.89, 1.00)** |
| **7.74 (6.84, 8.82)** | 1.05 (0.99, 1.11) | 0.97 (0.93, 1.01) | **1.48 (1.30, 1.70)** | **1.03 (1.00, 1.07)** | **ustekinumab 90** | **1.17 (1.08, 1.30)** | 0.97 (0.93, 1.02) |
| **6.59 (5.68, 7.63)** | **0.89 (0.80, 0.97)** | **0.83 (0.75, 0.89)** | **1.26 (1.07, 1.47)** | **0.88 (0.79, 0.96)** | **0.85 (0.77, 0.92)** | **adalimumab** | **0.83 (0.75, 0.90)** |
| **7.95 (6.93, 9.16)** | **1.07 (1.01, 1.14)** | 1.00 (0.95, 1.04) | **1.51 (1.33, 1.75)** | **1.06 (1.01, 1.12)** | 1.03 (0.98, 1.08) | **1.21 (1.11, 1.34)** | **infliximab 5** |

**Table 12 Random effects multinomial NMA for PASI 75 response (reproduced from Table 56 from the company's submission)**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| placebo | 0.05 (0.04, 0.06) | 0.04 (0.04, 0.05) | 0.10 (0.08, 0.12) | 0.05 (0.04, 0.06) | 0.05 (0.04, 0.06) | 0.07 (0.05, 0.08) | 0.05 (0.04, 0.06) |
| 18.94 (15.82, 22.78) | secukinumab 150 | 0.85 (0.80, 0.91) | 1.83 (1.48, 2.33) | 0.98 (0.87, 1.11) | 0.91 (0.81, 1.03) | 1.25 (1.06, 1.52) | 0.86 (0.76, 0.98) |
| 22.25 (18.70, 26.62) | 1.17 (1.10, 1.26) | secukinumab 300 | 2.15 (1.76, 2.71) | 1.15 (1.05, 1.28) | 1.07 (0.98, 1.19) | 1.46 (1.26, 1.76) | 1.01 (0.92, 1.13) |
| 10.29 (8.01, 13.26) | 0.55 (0.43, 0.68) | 0.46 (0.37, 0.57) | etanercept 50 | 0.53 (0.42, 0.66) | 0.50 (0.40, 0.61) | 0.68 (0.53, 0.89) | 0.47 (0.37, 0.58) |
| 19.36 (16.31, 23.12) | 1.03 (0.90, 1.15) | 0.87 (0.78, 0.96) | 1.88 (1.52, 2.37) | ustekinumab 45 | 0.93 (0.88, 0.99) | 1.28 (1.09, 1.53) | 0.88 (0.78, 0.99) |
| 20.74 (17.47, 24.72) | 1.10 (0.97, 1.23) | 0.93 (0.84, 1.02) | 2.01 (1.63, 2.52) | 1.07 (1.01, 1.14) | ustekinumab 90 | 1.37 (1.17, 1.63) | 0.94 (0.85, 1.05) |
| 15.18 (12.09, 18.76) | 0.80 (0.66, 0.94) | 0.68 (0.57, 0.79) | 1.47 (1.13, 1.90) | 0.78 (0.65, 0.92) | 0.73 (0.61, 0.85) | adalimumab | 0.69 (0.57, 0.81) |
| 22.01 (18.00, 26.97) | 1.16 (1.02, 1.31) | 0.99 (0.89, 1.09) | 2.13 (1.71, 2.70) | 1.14 (1.01, 1.28) | 1.06 (0.95, 1.18) | 1.45 (1.23, 1.75) | infliximab 5 |

**Table 13 Random effects multinomial network meta-analysis for PASI 90 response (reproduced from Table 57 from the company's submission)**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| placebo | 0.01 (0.01, 0.02) | 0.01 (0.01, 0.01) | 0.04 (0.03, 0.06) | 0.01 (0.01, 0.02) | 0.01 (0.01, 0.02) | 0.02 (0.02, 0.03) | 0.01 (0.01, 0.01) |
| 67.85 (52.36, 88.50) | secukinumab 150 | 0.73 (0.65, 0.82) | 2.72 (1.93, 3.96) | 0.96 (0.78, 1.22) | 0.84 (0.68, 1.06) | 1.47 (1.11, 2.06) | 0.75 (0.60, 0.96) |
| 92.53 (71.67, 119.30) | 1.36 (1.22, 1.54) | secukinumab 300 | 3.71 (2.69, 5.33) | 1.30 (1.09, 1.61) | 1.15 (0.96, 1.40) | 2.00 (1.54, 2.76) | 1.02 (0.84, 1.28) |
| 24.76 (17.26, 35.77) | 0.37 (0.25, 0.52) | 0.27 (0.19, 0.37) | etanercept 50 | 0.35 (0.25, 0.50) | 0.31 (0.22, 0.44) | 0.54 (0.36, 0.82) | 0.28 (0.19, 0.39) |
| 70.57 (55.22, 90.47) | 1.05 (0.82, 1.29) | 0.77 (0.62, 0.91) | 2.85 (2.02, 4.06) | ustekinumab 45 | 0.88 (0.78, 0.99) | 1.53 (1.16, 2.09) | 0.78 (0.63, 0.98) |
| 80.42 (62.82, 103.30) | 1.19 (0.94, 1.46) | 0.87 (0.71, 1.04) | 3.24 (2.30, 4.62) | 1.14 (1.02, 1.28) | ustekinumab 90 | 1.74 (1.33, 2.36) | 0.89 (0.72, 1.11) |
| 46.10 (32.98, 63.19) | 0.68 (0.48, 0.90) | 0.50 (0.36, 0.65) | 1.86 (1.21, 2.77) | 0.65 (0.48, 0.86) | 0.57 (0.42, 0.75) | adalimumab | 0.51 (0.37, 0.69) |
| 90.38 (66.96, 122.40) | 1.33 (1.04, 1.68) | 0.98 (0.78, 1.19) | 3.63 (2.54, 5.29) | 1.28 (1.02, 1.60) | 1.13 (0.90, 1.39) | 1.96 (1.46, 2.70) | infliximab 5 |

Several subgroup and sensitivity analyses were also conducted. These agreed with those specified in the company's submission and an additional sensitivity analysis involving excluding Asian studies was also performed. The results were generally consistent with the overall results.

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

Although the outline of the NMA methodology was clear from the company's submission, not all aspects were fully explained. At clarification the company supplied two standalone reports prepared by Redwood Outcomes, one providing details of the two 12-week analyses and one of the 16-week analysis. The reports were dated January 2015 and may have been recently updated. The ERG noted that the "pure" 12-week analysis was denoted the primary analysis in the first Redwood report, rather than the NICE 12-week endpoint, which was reported as the primary analysis in the main company's submission.

The ERG consider the methodology used to conduct the NMA for the PASI outcomes appropriate. PASI is an ordinal outcome and different studies reported the numbers of participants reaching different PASI thresholds. The Redwood Outcomes reports include the recommended WinBUGS/OPENBUGS program reported in the NICE DSU TSD2 for ordinal outcomes.[55] This methodology uses a conditional binomial likelihood and a probit link function and allows for the fact that different studies may report different PASI thresholds. The primary analyses used random effects models as their assumptions were deemed more plausible than those of fixed effect models. A series of non-informative priors were used.

The consistency between direct and indirect evidence was evaluated by the edge-splitting method. The ERG consider the approach used adequate.

There are several ways in which the results of the NMA could have been reported. Unlike in Section 6 of the NICE DSU TSD2 document,[55] the actual model parameters for each treatment versus placebo have not been presented. Although for some models this does seem to be available, i.e. in Appendices K1 to K3 of the main Redwood Outcomes report and in the cost-effectiveness section of the main submission, the ERG did not find this very easy to follow. Instead risk ratios and their 95% credible intervals have been presented for each combination of treatments at three separate PASI thresholds. The ERG could not find a clear explanation of how the risk ratios were calculated in the text of the report, other than from the programs reported in Appendix 8 where it is clear that they were calculated from the predicted probabilities of reaching given PASI thresholds. Even though it is easier to interpret the risk ratios, an additional clearer presentation of the treatment effects versus placebo on the probit scale would have been useful.

In brief, the ERG consider the methodology used for the indirect comparisons adequate, although some information and results could have been presented more clearly.

### *4.5 Conclusions of the clinical effectiveness section*

Although there were some issues with the transparency of including certain treatment doses in the network meta-analyses, the ERG was generally happy with the methodology used in the company's submission.

There was strong evidence from head-to-head randomised controlled trials for the superiority of secukinumab 300mg compared with placebo with respect to the PASI and IGA efficacy outcomes at week 12.

There is evidence from the NMA that secukinumab at a dose of 300mg has favourable PASI outcomes when compared with etanercept 50mg, ustekinumab 45mg and adalimumab and performs similarly to ustekinumab 90mg and infliximab as shown by the similar proportions of patients in the 50-74 (PASI 50), 75-89 (PASI 75) and 90-100 (PASI 90) categories.

# 5 COST EFFECTIVENESS

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

### 5.1.1 State objective of cost effectiveness review. Provide description of companys search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

The company states that literature searches were undertaken in December 2013and updated in October 2014. An appropriate range of databases were searched: MEDLINE, MEDLINE in Process, EMBASE, EconLIT and NHS EED. In addition the NICE website was searched for relevant appraisals. The searches were restricted to reports published from 1998 onwards and to the English language. This seems consistent with the introduction of the drugs of interest on the market and a preference to identify literature relating to a UK setting.

Full details of the search strategies are included in Appendix 10.11 of the submission and are reproducible.

The searches were designed to identify relevant economic evaluations as well as costs and resource use for psoriasis and used a comprehensive list of both controlled vocabulary and text word terms.

Separate HRQOL literature searches were undertaken by the comapny in December 2013 and updated in October 2014. An appropriate range of databases were searched: MEDLINE, MEDLINE in Process, EMBASE, EconLIT and NHS EED. Full details of the search strategies are included in Appendix 10.13 of the submission and are reproducible. The searches combined a comprehensive range of controlled vocabulary and text word terms relating to HRQOL and psoriasis.

In conclusion the searches for economic evaluations and HRQOL data were very sensitive and are likely to have retrieved the relevant evidence.

### 5.1.2 State the inclusion/exclusion criteria used in the <u>study selection</u> and comment on whether they were appropriate.

The eligibility criteria used in the search strategies were in line with the NICE final scope. Table 64 (page 143) of the submission details these criteria. The population of interest was

defined as *adults with moderate to severe chronic plaque-type psoriasis (CPP) including those in whom CPP is poorly controlled by topical treatment and/or phototherapy and /or previous systemic therapy.* Children, patients with mild psoriasis, patients with other types of psoriasis, and patients with ongoing inflammatory diseases were excluded. The interventions were systemic biologic therapies in use in the UK. Non-biological treatments, phototherapy and photochemiotherapy were not considered suitable for inclusion.

### 5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the <u>most important</u> cost effectiveness studies.

The main cost effectiveness studies are reported as:

- Woolacott et al 2006[56] based upon the work undertaken for the TA103, evaluating the cost effectiveness of etanercept; and efalizumab;
- Lloyd et al 2009,[57] which models the cost effectiveness of etanercept compared to SoC;
- Fonia et al 2010,[58] identified as a relevant UK resource use study.

It appears, however, that the reporting of results is actually from Woolacott et al 2005[59]: the assessment report for the TA103.[43] This is not identified within the company's submission, but within the company reference pack. These studies differ in that Woolacott et al 2005[59] include intermittent etanercept dosing while Woolacott et al 2006[56] do not.

### 5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

An element that is not particularly stressed within the company review of Woolacott et al 2005[59] is that the base case for this study does not assume an annual hospitalisation of 21 days on average for patients with a PASI<50 response. This is introduced as a scenario analysis.

The company summary of the cost effectiveness literature fails to highlight that the cost effectiveness estimates for etanercept of Woolacott et al 2005[59] included estimates of the cost effectiveness of both continuous use etanercept and intermittent use etanercept. It appears that it was only the intermittent use etanercept that was estimated to be cost effective

at conventional thresholds. The company summary of Woolacott et al 2005[59] only quotes the cost effectiveness estimates for intermittent use etanercept, while those for continuous use etanercept are somewhat higher. For instance, the £66,703 per QALY for etanercept 25mg compared to SoC quoted by the company relates to intermittent use etanercept 25mg, while that for continuous use etanercept 25mg was reported as £88,258 per QALY. The annual direct drug costs are very different in 2004/05 prices: £6,934 for intermittent use etanercept 25mg compared to £9,327 for continuous use etanercept 25mg.

It is unclear in Woolacott et al 2005[59] whether the annual treatment period and cost for intermittent dosing includes the 12 week induction period. The ERG assumption is that it does - with this implying, for intermittent dosing, a mean weekly post induction administration of 1.33 doses. However, if it does not include the induction period, the mean weekly dose post induction administration rises to 1.49 doses.

The SmPC for etanercept states:

> *The recommended dose of Enbrel is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients (see section 5.1). Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Enbrel is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly.*

TA103 approved etanercept for use "*within its licensed indications, administered at a dose not exceeding 25 mg twice weekly*" with treatment being ceased at 12 weeks if there is not a sufficient response: either a PASI 75, or a PASI 50 and a 5-point DLQI reduction.

The ERG clinical advisor maintains that due to its shorter half-life, etanercept is less likely to result in the development of drug antibodies and therefore more suitable for intermittent use. However, many patients once started on a biologic may, if doing well, continue with it. Patients receiving Adalimumab may have their dosing reduced to three weekly, partly to reduce cost but mainly to reduce toxicity.

The company review of Lloyd et al[57] omits to mention that the paper was sponsored by Wyeth, the company of etanercept. The company summary of Lloyd et al[57] is fair, and highlights the assumptions around intermittent use of etanercept. This is explicitly built into the model structure of Lloyd et al.[57] Those with a PASI 75 response at 12 weeks cease treatment and only resume it when response is lost. Partial responders with a PASI 50-74 response at 12 weeks are treated for a further 12 weeks: if a PASI 75 responder at 24 weeks they follow the PASI 75 responder path but if not they cease treatment and are not retreated. The frequency of treatment with etanercept 25mg is given as 21.9 per 12 week cycle, or 1.82 per week, based upon pooled trial results apparently.

In the opinion of the ERG, the review of the Fonia et al 2010[58] resource use study, presented in section 7.5.3 of the company's submission, is partial. Key variables within the economics of the submission, as identified by the sensitivity analyses of the company, are the number of day case admissions and the number of days patients are hospitalised before and after receiving a biologic, or while on SoC and while on a biologic. This information is available in the study by Fonia et al, but it is not presented in the submission.[58] Section 5.3.2 below provides further details on this.

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

### 5.2.1 NICE reference case checklist

| **Attribute** | **Reference case and TA Methods guidance** | **Does the *de novo* economic evaluation match the reference case** |
|---|---|---|
| **Comparator(s)** | Therapies routinely used in the NHS, including technologies regarded as current best practice | Yes. The comparators are as per the scope, with the additional consideration of secukinumab. |
| **Patient group** | As per NICE scope. "*People with moderate to severe plaque psoriasis for whom other systemic therapies … have been inadequately effective, or are not tolerated or contraindicated*" | The patient group is based upon the inclusion criteria of the secukinumab trials, which is as per the scope with the possible exception of requiring a PASI score of at least 12 coupled with an affected body surface area of at least 10%. |
| **Perspective costs** | NHS & Personal Social Services | Yes. |
| **Perspective benefits** | All health effects on individuals | Yes. |
| **Form of economic evaluation** | Cost-effectiveness analysis | Yes. Cost utility analysis. |
| **Time horizon** | Sufficient to capture differences in costs and outcomes | 10 years. |
| **Synthesis of evidence on outcomes** | Systematic review | Yes. |
| **Outcome measure** | Quality adjusted life years | Yes. |
| **Health states for QALY** | Described using a standardised and validated instrument | Yes. EQ-5D. |
| **Benefit valuation** | Time-trade off or standard gamble | It appears likely to be time-trade off through the use of the UK social tariff though the submission is not explicit about this. |

| | | |
|---|---|---|
| **Source of preference data for valuation of changes in HRQL** | Representative sample of the public | Yes. |
| **Discount rate** | An annual rate of 3.5% on both costs and health effects | Yes. |
| **Equity** | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Yes. |
| **Probabilistic modelling** | Probabilistic modelling | Yes. |
| **Sensitivity analysis** | | A range of univariate sensitivity analyses are presented. |

### 5.2.2 Model structure

Each comparator is associated with an induction period during which the patient group is split into four response categories:

- PASI <50;
- PASI 50-74;
- PASI 75-89;
- PASI 90.

Patients in the PASI <50 and PASI 50-74 response categories are assumed to cease treatment, go onto SoC and revert to a PASI <50 response. In addition to the SoC drug costs, this is associated with an increase in day case admissions and phototherapy treatments. SoC is also a mean annual hospital admission per patient of 10.7 days at a cost of £5,337 per admission.

Patients in the PASI 75-89 and PASI 90 response categories are assumed to continue on treatment and remain in their response category. Those remaining on treatment with a biologic have adverse event rates associated with them. Those remaining on a biologic during the first year after induction have a discontinuation rate of 11.7% based upon the ERASURE and FIXTURE trials data, and after the first year a discontinuation rate of 20% based upon expert opinion. Patients that discontinue go onto SoC and revert to a PASI<50 response.

### 5.2.3 Population

The scope specifies patients with moderate to severe plaque psoriasis for whom other systemic therapies including ciclosporin, methotrexate and phototherapy with or without psoralen have been inadequately effective, or are not tolerated or contraindicated. The patient population is as per the trial entry criteria. For the secukinumab trials the entry criteria corresponded with the scope, with the possible exception of requiring a PASI score of at least 12 coupled with an affected body surface area of at least 10%.

### 5.2.4 Interventions and comparators

Secukinumab 300mg is compared with:

- Standard of care without biologics (SoC);
- Etanercept 25mg;
- Adalimumab;
- Ustekinumab 45mg;
- Ustekinumab 90mg; and,
- Infliximab 5mg/kg.

### 5.2.5 Perspective, time horizon and discounting

The perspective is that of the patient for benefits and that of the NHS/PSS for costs.

The time horizon is 10 years. Benefits and costs are both discounted at 3.5%.

### 5.2.6 Treatment effectiveness and extrapolation

*Treatment effectiveness*

The rates of PASI responses are drawn from the network meta-analysis. For the base case the time point for the assessment of response is assumed to be 12 weeks for all the comparators with the exception of adalimumab for which it is 16 weeks. This is described as the NICE time endpoints analysis. An alternative scenario, which assumes that adalimumab is assessed at 12 weeks, is also presented.

Table 14 shows the distribution between PASI response states.

**Table 14 Deterministic PASI response rates: base case: NICE time endpoints analysis**

| | SoC | Secukin. | Adalim. | Etanercept | Ust. 45mg | Ust. 90mg | Infliximab |
|---|---|---|---|---|---|---|---|
| PASI < 50 | 88% | 7% | 23% | 39% | 13% | 10% | 8% |
| PASI 50-74 | 8% | 12% | 22% | 24% | 17% | 15% | 13% |
| PASI 75-89 | 3% | 25% | 27% | 22% | 28% | 27% | 25% |
| PASI 90-100 | 1% | 55% | 28% | 15% | 42% | 48% | 54% |
| PASI 75 | 4% | 80% | 55% | 37% | 70% | 75% | 80% |

Secukinumab is estimated to have a higher point estimate PASI 75 response rate and a higher PASI 90 response rate at 12 weeks than all its comparators with the exception of infliximab. Secukinumab and infliximab have almost identical PASI 75 and PASI 90 response rates. Infliximab has a slightly lower PASI <50 response rate and a slightly higher PASI 50-74 response rate than secukinumab.

For the probabilistic analysis a lookup table of 40,000 CODA output iterations is randomly accessed. These 40,000 rows of outputs imply the following mean PASI response rates. The proportion of rows for which each treatment has the highest PASI 75 response rate is also reported.

**Table 15 Probabilistic mean PASI response rates: base case: NICE time endpoints analysis**

| | SoC | Secukin. | Adalim. | Etanercept | Ust. 45mg | Ust. 90mg | Infliximab |
|---|---|---|---|---|---|---|---|
| PASI < 50 | 88% | 7% | 24% | 39% | 13% | 10% | 8% |
| PASI 50-74 | 8% | 12% | 22% | 24% | 17% | 15% | 13% |
| PASI 75-89 | 3% | 25% | 27% | 22% | 27% | 27% | 25% |
| PASI 90-100 | 1% | 56% | 28% | 15% | 42% | 48% | 54% |
| PASI 75 | 4% | 81% | 55% | 37% | 69% | 75% | 79% |
| P max PASI75 | 0% | 56% | 0% | 0% | 0% | 3% | 41% |

The probabilistic modelling suggests that secukinumab has the highest probability of having the maximum PASI 75 response rate across the comparators at 56% (Table 15). This is followed by infliximab at 41%, with there being a small 3% probability of ustekinumab having the highest probability of having the maximum PASI 75 response rate across the comparators.

It is assumed that those with a PASI 75+ response continue on treatment and retain their response. Those without a PASI 75+ response are assumed to come off treatment and to revert to a PASI 0-49 response.

A scenario analysis of a 12 week time point for the assessment of response is also included (Table 16).

**Table 16 PASI response rates: 12 week assessment**

| | SoC | Secukin. | Adalim. | Etanercept | Ust. 45mg | Ust. 90mg | Infliximab |
|---|---|---|---|---|---|---|---|
| PASI < 50 | 89% | 8% | 23% | 41% | 14% | 11% | 11% |
| PASI 50-74 | 7% | 13% | 22% | 24% | 18% | 16% | 16% |
| PASI 75-89 | 3% | 25% | 27% | 21% | 28% | 27% | 27% |
| PASI 90-100 | 1% | 54% | 28% | 14% | 41% | 47% | 46% |
| PASI 75 | 3% | 79% | 55% | 35% | 68% | 73% | 73% |

A further scenario analysis is based upon the NICE time endpoints but with a 16 week assessment for secukinumab (Table 17).

**Table 17 PASI response rates: NICE time endpoints scenario analysis: Secukinumab 16 weeks**

| | SoC | Secukin. | Adalim. | Etanercept | Ust. 45mg | Ust. 90mg | Infliximab |
|---|---|---|---|---|---|---|---|
| PASI < 50 | 89% | 6% | 24% | 41% | 15% | 12% | 8% |
| PASI 50-74 | 8% | 12% | 24% | 25% | 20% | 18% | 15% |
| PASI 75-89 | 2% | 22% | 25% | 20% | 26% | 25% | 24% |
| PASI 90-100 | 1% | 60% | 27% | 14% | 40% | 45% | 54% |
| PASI 75 | 3% | 82% | 52% | 34% | 65% | 70% | 77% |

And a final scenario analysis restricts itself to the FIXTURE trial data (Table 18).

**Table 18 PASI response rates: FIXTURE trial data**

| | SoC | Secukin. | Etanercept |
|---|---|---|---|
| PASI < 50 | 85% | 8% | 30% |
| PASI 50-74 | 10% | 15% | 26% |
| PASI 75-89 | 3% | 23% | 23% |
| PASI 90-100 | 2% | 54% | 21% |
| PASI 75 | 5% | 77% | 44% |

In short, in all of the scenarios considered secukinumab is estimated to be superior to all its comparators in terms of the PASI 75 and PASI 90 response rates. Only for the scenario of the differing NICE assessment time points does infliximab have similar PASI 75 and PASI 90 response rates compared to secukinumab, with the infliximab PASI <50 being slightly less than that of secukinumab and the infliximab PASI 50-74 being slightly more than that of secukinumab.

For the probabilistic modelling it appears that secukinumab has the greatest probability of having the highest PASI 75 response rate across the comparators, with that of infliximab being slightly below this. The probabilities of the other comparators having the greatest probability of having the highest PASI 75 response rate are to all intents and purposes zero.

*Serious adverse events: rates*

Adverse event rates were taken directly from trial data, SmPCs and Dixon et al 2006,[45,60] rather from any network meta-analysis of these data. It was assumed that SoC was not associated with any of the SAEs.

**Table 19 SAE rates**

| | SoC | Secu. | Etan. | US 45 | US 90 | Infl. | Adal. |
|---|---|---|---|---|---|---|---|
| NMSC | 0.00000 | [redacted] | 0.03540 | 0.00650 | 0.00650 | 0.00400 | 0.00970 |
| non NMSC | 0.00000 | [redacted] | 0.00043 | 0.00160 | 0.00160 | 0.07670 | 0.00600 |
| Severe infection | 0.00000 | [redacted] | 0.05130 | 0.01000 | 0.01000 | 0.05520 | 0.05190 |

*Extrapolation*

Extrapolation assumes that 20% of those on active treatment discontinue each year, reverting to SoC and a PASI<50 response.

### 5.2.7 Health related quality of life

*Quality of life: by PASI response status*

The EQ-5D data across all time points and five trials was pooled in a complete case analysis. A number of functional forms were explored. The ERG assumption is that this was valued using the UK social tariff, though this does not appear to be explicitly stated in the company's submission or the company commissioned utility report. The company chose the

model of EQ-5D QoL changes from baseline at a given time point being a function of the patient's:

- PASI response at that time point;
- Baseline DLQI difference from the pooled mean baseline DLQI;
- The above two bullets multiplied together.

This resulted in the following estimates for the quality of life changes from baseline by PASI response category. These changes can be added to the pooled average baseline quality of life to give quality of life values. The quality of life values of the last column are ERG constructs, are used solely for ease of presenting the final outcomes of the model in what may be a more intuitive manner, and have no effect upon the cost effectiveness estimates.

**Table 20 Quality of life values by PASI response state**

| | Baseline | QoL impact | QoL |
|---|---|---|---|
| PASI < 50 | 0.642 | 0.109 | 0.751 |
| PASI 50-74 | | 0.193 | 0.835 |
| PASI 75-89 | | 0.226 | 0.868 |
| PASI 90-100 | | 0.264 | 0.906 |

*Quality of life: serious adverse events*

The company's submission states that the quality of life impacts of adverse events have been captured through the use of the EQ-5D data.

### 5.2.8 Resources and costs

*Direct drug costs: main drug treatments*

The base case assumes a 12 week induction period for all treatments with the exception of adalimumab which has a 16 week induction period. The scenario analysis of the 12 week NMA revises the induction period of adalimumab to 12 weeks. The doses required during the induction period, the remaining doses for the first year and for subsequent years are shown in Table 21.

**Table 21 Dosing frequency**

| | Secukin. | Etanercept | Ust 45mg | Ust 90mg | Infliximab | Adalimumab | |
|---|---|---|---|---|---|---|---|
| Ind. Length | 12 wks | 12 wks | 12 wks | 12 wks | 12 wks | 12 wks | 16 wks |
| Induction | 6 | 24 | 2 | 2 | 3 | 8 | 9 |
| Post induction | 10 | 80 | 4 | 4 | 5 | 20 | 19 |
| Subs. Annual | 12 | 104 | 4.33 | 4.33 | 6.5 | 26 | 26 |

The dosing for infliximab is 5mg/kg, with it being available in 20mg vials. The number of vials required per dose was based upon an average patient weight of 86.6kg with a standard deviation of 19.8kg (according to the electronic copy of the model, this was derived from Reich et al 2006).[61] While these data may be skewed, an assumption of normality resulted in 9% being under 60kg, 28% being between 60kg and 80kg, 38% being between 80kg and 100kg and 25% being above 100kg. This would imply 3, 4, 5 and 6 vials, respectively with an average estimate of 4.8 vials of infliximab per dose.

Unit costs were drawn from BNF 64 and MIMS, resulting in the direct drug costs presented in Table 22.

**Table 22 Direct drug costs**

| | Secukin. | Etanercept | Ust 45mg | Ust 90mg | Infliximab | Adalimumab | |
|---|---|---|---|---|---|---|---|
| Ind. Length | 12 wks | 12 wks | 12 wks | 12 wks | 12 wks | 12 wks | 16 wks |
| Unit cost | [redacted] | £89.38 | £2,147.00 | £2,147.00 | £419.62 | £352.14 | |
| Induction | [redacted] | £2,145 | £4,294 | £4,294 | £6,030 | £2,817 | £3,169 |
| Post induction | [redacted] | £7,150 | £8,588 | £8,588 | £10,050 | £7,043 | £6,691 |
| 1st year | [redacted] | £9,296 | £12,882 | £12,882 | £16,081 | £9,860 | |
| Subs. Annual | [redacted] | £9,296 | £9,297 | £9,297 | £13,066 | £9,156 | |

[redacted]

[redacted]

*Drug administration costs: biologics*

The subcutaneous formulations are assumed to require a one off training costs of £39, based upon one hour of nurse time, with this enabling all administrations to be self-administered by the patient. Infliximab administrations are assumed to cost £92.39, based upon the dermatology NHS reference WF01A: non-admitted face to face follow-up, averaged across consultant led and non-consultant led appointments. This results in administration costs for infliximab of £277 during induction and £462 for the remainder of the first year, hence £739 in the first year, and an annual £601 thereafter.

*Direct drug costs: SoC*

Those on SoC are assumed to receive either methotrexate, ciclosporin or nothing. During years one and two:

- 45% are assumed to require 15mg of oral methotrexate each week;
- 45% are assumed to require 300mg of oral ciclosporin each day;
- 10% are assumed to require no medication.

From year three those on ciclosporin are assumed to cease. Table 23 illustrates the direct drug costs in the SoC arm.

**Table 23 Direct drug costs: SoC**

| | SoC |
|---|---|
| Ind. Length | 12 wks |
| Induction | £186 |
| Post induction | £621 |
| Year 1&2 | £807 |
| Subs. Annual | £13 |

*Other treatment costs: SoC*

SoC is also assumed to require the rates of day centre care and UVB phototherapy showed in Table 24.

**Table 24 Rates of day centre care and phototherapy: SoC**

| | Day Centre | Phototherapy |
|---|---|---|
| Induction | 1.54 | 1.18 |
| Post ind. Year 1 | 3.46 | 2.66 |
| Annual thereafter | 5.00 | 3.84 |

Given unit costs of £460 for day centre care and £91 for UVB phototherapy these result in the costs presented in Table 25.

**Table 25 Costs of day centre care and NBUVB phototherapy: SoC**

| | Day Centre | NBUVB | Total |
|---|---|---|---|
| Induction | £708 | £108 | £815 |
| Post ind. Year 1 | £1,592 | £242 | £1,834 |
| Annual thereafter | £2,300 | £349 | £2,649 |

*Monitoring costs*

Various tests are assumed to occur at each specialist outpatient visit: complete blood count, urea, creatinine and electrolytes, liver function tests and total protein tests. The total cost of these tests of £6.76 is added to the £98.00 per specialist outpatient visit to arrive at a total monitoring visit cost of £104.76[a]. The number of specialist outpatient visits during induction is 4 for all treatments, with the exception of adalimumab for which it is 5. Note that for

[a] This is very slightly incorrect for the post induction period during the first year, but this has no practical impact upon results. Infliximab is also assumed to require six sets of tests annually after the first year which is broadly in line with the number of administrations assumed, rather than the number of specialist outpatient visits.

infliximab these specialist outpatient visits are in addition to the IV administration costs. During the post induction period of the first year the number of specialist outpatient visits is 3 for all treatments, and is assumed to be 4 annually thereafter. This results in the monitoring costs shown in Table 26.

**Table 26 Monitoring costs**

| | SoC | Secu. | Etan. | US 45 | US 90 | Infl. | Adal. |
|---|---|---|---|---|---|---|---|
| Induction | £432 | £424 | £424 | £424 | £424 | £424 | £530 |
| Post ind. Year 1 | £322 | £319 | £319 | £319 | £319 | £319 | £322 |
| Annual thereafter | £222 | £424 | £424 | £424 | £424 | £440 | £424 |

*SAEs and hospitalisation costs*

The costs of SAEs and hospitalisations are based upon NHS reference costs, with all being assumed to require one episode of inpatient care.

The average cost of non-melanoma skin cancer is calculated as £1,460. Malignancies other than non-melanoma skin cancer are costed based upon the average of £8,178 for lymphoma and £1,460 for melanoma resulting in an average cost of £4,819. Severe infections are based upon an average of the costs of £2,102 for sepsis, £2,403 for tuberculosis, £1,852 for pneumonia, £1,383 for soft tissue infection, £3,087 for bone and joint infections and £1,754 for urinary tract infection, resulting in an average cost of £2,097.

The cost per hospitalisation while on SoC is based upon an average daily inpatient cost of £499 coupled with a mean length of stay of 10.7 days as drawn from HES data, resulting in an average cost of £5,337 (Table 27).

These costs are coupled with the annual rates of the model to yield the mean SAE and hospitalisation costs for patients receiving a given treatment as below. Note that the SoC costs apply to all in the SoC arm and to those in the other arms who have discontinued treatment.

**Table 27 Annual SAE and hospitalisation costs**

| | SoC | Secu. | Etan. | US 45 | US 90 | Infl. | Adal. |
|---|---|---|---|---|---|---|---|
| NMSC | | £6 | £52 | £9 | £9 | £6 | £14 |
| Non-NMSC malig. | | £29 | £2 | £8 | £8 | £370 | £29 |
| Severe infections | | £50 | £108 | £21 | £21 | £116 | £109 |
| Hospitalisation | £5,337 | | | | | | |
| Total | £5,337 | £85 | £161 | £38 | £38 | £491 | £152 |

It appears that the SAE costs for the main drug treatment are not applied in the first year. All those who discontinue from the main active treatments and go on to SoC in the first year, whether due to a lack of a PASI 75 response or due to other discontinuations have the annual hospitalisation cost applied to them.

Within the SoC arm, in the first year those without a PASI 75 response have the annual hospitalisation cost applied to them. Thereafter, all patients remaining alive in the SoC arm have the annual hospitalisation cost applied to them, regardless of response status.

*Resource use summary*

Resource use information based upon a 12-week induction period, with the exception of adalimumab for which the induction period is 16 weeks, is summarised in Tables 28. Resource use information for the post-induction period during the first year, for patients remaining on treatment throughout year 1, and for patients after the first year of treatment is presented in Tables 29, 30 and 31.

**Table 28 Resource use: induction period**

| | SoC | Secu. | Etan. | US 45 | US 90 | Infl. | Adal. |
|---|---|---|---|---|---|---|---|
| Drug Tx | £186 | [redacted] | £2,145 | £4,294 | £4,294 | £6,030 | £3,169 |
| Other Tx | £815 | | | | | | |
| Administration | | £39 | £39 | £39 | £39 | £277 | £39 |
| Monitoring | £432 | £424 | £424 | £424 | £424 | £424 | £530 |
| Subtotal | £1,433 | [redacted] | £2,608 | £4,757 | £4,757 | £6,731 | £3,738 |
| Hosp if not PASI75 | £1,232 | £1,232 | £1,232 | £1,232 | £1,232 | £1,232 | £1,642 |

**Table 29 Resource use: post induction period year 1**

| | SoC | Secu. | Etan. | US 45 | US 90 | Infl. | Adal. |
|---|---|---|---|---|---|---|---|
| Drug Tx | £621 | [redacted] | £7,150 | £8,588 | £8,588 | £10,050 | £6,691 |
| Other Tx | £1,834 | | | | | | |
| Administration | | | | | | £462 | |
| Monitoring | £322 | £319 | £319 | £319 | £319 | £319 | £322 |
| Subtotal | £2,777 | [redacted] | £7,469 | £8,907 | £8,907 | £10,831 | £7,013 |
| Hosp if not PASI75 | £4,105 | £4,105 | £4,105 | £4,105 | £4,105 | £4,105 | £3,695 |

**Table 30 Resource use: for those remaining on treatment throughout year 1**

| | SoC | Secu. | Etan. | US 45 | US 90 | Infl. | Adal. |
|---|---|---|---|---|---|---|---|
| Drug Tx | £807 | [redacted] | £9,295 | £12,882 | £12,882 | £16,080 | £9,860 |
| Other Tx | £2,649 | | | | | | |
| Administration | | £39 | £39 | £39 | £39 | £739 | £39 |
| Monitoring | £754 | £743 | £743 | £743 | £743 | £743 | £852 |
| Subtotal | £4,210 | [redacted] | £10,077 | £13,664 | £13,664 | £17,562 | £10,751 |
| Hosp if not PASI75 | £5,337 | £5,337 | £5,337 | £5,337 | £5,337 | £5,337 | £5,337 |

**Table 31 Resource use: annual thereafter**

| | SoC | Secu. | Etan. | US 45 | US 90 | Infl. | Adal. |
|---|---|---|---|---|---|---|---|
| Drug Tx | £807[b] | [redacted] | £9,296 | £9,297 | £9,297 | £13,066 | £9,156 |
| Other Tx | £2,649 | | | | | | |
| Administration | | | | | | £601 | |
| Monitoring | £222 | £424 | £424 | £424 | £424 | £440 | £424 |
| SAEs | | £85 | £161 | £38 | £38 | £491 | £152 |
| Subtotal | £3,678 | [redacted] | £9,881 | £9,759 | £9,759 | £14,598 | £9,732 |
| Hosp if PASI75 | £5,337 | | | | | | |
| Hosp if not PASI75 | £5,337 | £5,337 | £5,337 | £5,337 | £5,337 | £5,337 | £5,337 |

### 5.2.9 Cost effectiveness results

The deterministic base case results are shown in Table 32. Tx, include only the direct drug costs for the main drug treatments and those drug treatment that apply when the patient is on SoC. Medical costs include:

- all monitoring costs;
- the training costs for subcutaneous injections;
- the administration costs for infliximab;

[b] Only £13 for year 3 and thereafter.

- the day care costs for SoC; and,
- the UVB treatment costs for SoC.

**Table 32 Base case results: deterministic costs effectiveness**

| | Tx | Medical | SAE | Total | QALYs[c] | Δ Cost | Δ QALY | ICER |
|---|---|---|---|---|---|---|---|---|
| SoC | £1,857 | £26,500 | £45,253 | £73,610 | 6.440 | | | |
| Etaner. | £14,785 | £22,471 | £38,533 | £75,788 | 6.596 | £2,178 | 0.156 | £13,948 |
| Secukin. | [redacted] | [redacted] | [redacted] | £76,361 | 6.829 | £573 | 0.233 | £2,464 |
| Adalim. | £20,712 | £21,036 | £35,233 | £76,981 | 6.688 | £620 | -0.140 | Dominated |
| Ust. 45mg | £27,723 | £19,611 | £32,210 | £79,544 | 6.770 | £3,182 | -0.059 | Dominated |
| Ust. 90mg | £29,276 | £19,180 | £31,275 | £79,732 | 6.798 | £3,371 | -0.031 | Dominated |
| Infliximab | £41,523 | £20,653 | £31,363 | £93,539 | 6.824 | £17,177 | -0.004 | Dominated |

The SAE costs include the SAE costs when on the main drug treatments and the hospitalisation costs when on SoC.

While the treatment costs of secukinumab are [redacted] more expensive than etanercept, medical costs are [redacted] lower and SAE costs are [redacted] lower resulting in a net cost of only £573. Due to this and the net gain of [redacted] QALYs, secukinumab extendedly dominates etanercept. Compared to SoC, treatment costs for secukinumab are [redacted] more expensive but there are [redacted] medical cost savings and [redacted] SAE cost savings resulting in an overall net cost of £2,752. Given the estimated gain of 0.389 QALYs this results in a cost effectiveness estimate for secukinumab compared to SoC of £7,076 per QALY.

The central estimates and the probabilities of the individual therapies being the most cost effective are presented in Table 33. These are based upon the model being run over 5,000 iterations.

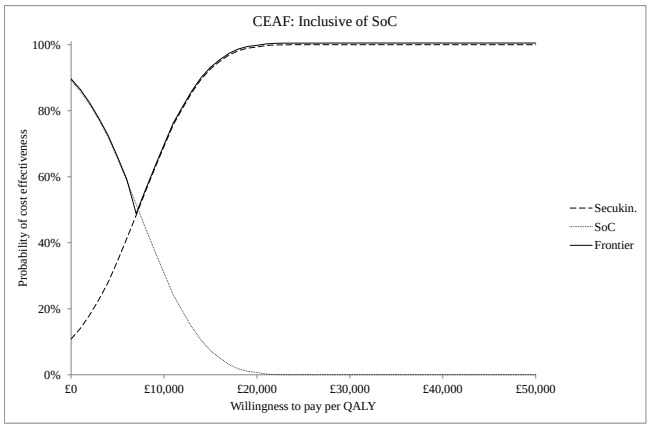
[c] Note that the total QALYs differ from those reported in the company's submission, these having had the baseline mean QoL of 0.642 added to the increments by the ERG within the model. This is implemented by adding 0.642 to cells G11:G15 of the Utility_Calculations worksheet. Note also that this baseline QoL of 0.642 has not been implemented probabilistically, but since it nets out between the comparators in the net QALYs calculation this has no impact upon results. This revision is purely for presentational purposes and does not affect any results.

**Table 33 Base case results: probabilistic vs deterministic**

| | Deterministic | | Probabilistic | | | | |
|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Δ Cost | Δ QALY | ICER |
| SoC | £73,610 | 6.440 | £73,517 | 6.451 | | | |
| Etaner. | £75,788 | 6.596 | £75,868 | 6.622 | £2,350 | 0.171 | £13,735 |
| Secukin. | £76,361 | 6.829 | £76,377 | 6.873 | £510 | 0.252 | £2,025 |
| Adalim. | £76,981 | 6.688 | £77,120 | 6.721 | £742 | -0.153 | Dominated |
| Ust. 45mg | £79,544 | 6.770 | £79,752 | 6.809 | £3,375 | -0.064 | Dominated |
| Ust. 90mg | £79,732 | 6.798 | £79,962 | 6.840 | £3,585 | -0.034 | Dominated |
| Infliximab | £93,539 | 6.824 | £94,811 | 6.868 | £18,433 | -0.006 | Dominated |

The central estimates of the probabilistic modelling suggest similar net costs and net QALYs, with similar cost effectiveness estimates resulting. As for the deterministic modelling, at the central estimates etanercept is extendedly dominated by secukinumab. Secukinumab has a cost effectiveness estimate compared to SoC of £6,763 per QALY.

As there is no probability for any of the comparator active treatments to be the most cost effective, regardless of the willingness to pay, the CEAF only considers SoC and secukinumab[d]. Note that for ease of illustration the CEAF has had an arbitrary 0.5% added to it in order to separate it visually from the other curves (Figure 5).



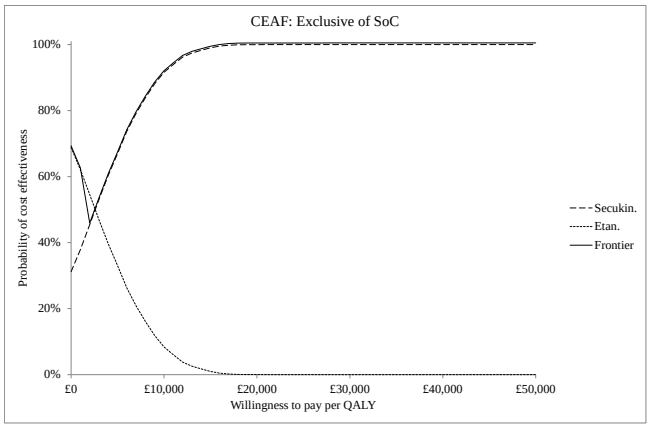

| WTP | Secukin. | SoC | Frontier |
|---|---|---|---|
| £0 | 11% | 89% | 89% |
| £10,000 | 69% | 31% | 69% |
| £20,000 | 99% | 1% | 99% |
| £30,000 | 100% | 0% | 100% |
| £40,000 | 100% | 0% | 100% |
| £50,000 | 100% | 0% | 100% |

**Figure 5 Base case results: probabilistic including SoC CEAF**

If SoC is excluded from the list of comparators, there is no probability for any of the active treatments other than etanercept to be cost effective, regardless of the willingness to pay. For

[d] These are as calculated by the ERG. The company calculations only present the CEACs, and it appears that these do not make any allowance for which quadrant the cost effectiveness point estimate of each iteration falls in. However, the ERG pairwise CEACs are very similar with those of the company.

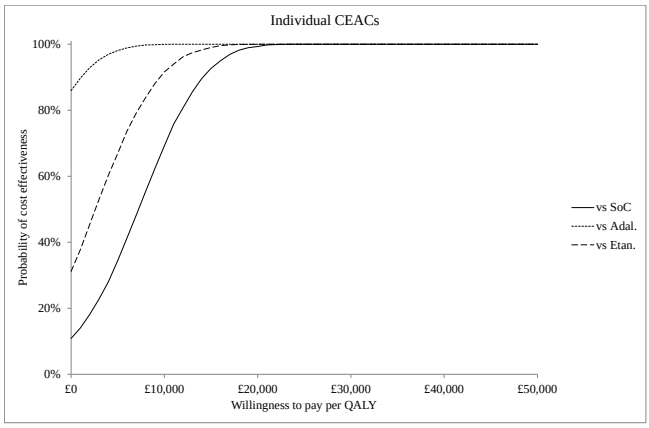
this reason, the CEAF that excludes SoC only considers etanercept and secukinumab (Figure 6).




| WTP | Secukin. | Etan. | Frontier |
|---|---|---|---|
| £0 | 31% | 69% | 69% |
| £10,000 | 92% | 8% | 92% |
| £20,000 | 100% | 0% | 100% |
| £30,000 | 100% | 0% | 100% |
| £40,000 | 100% | 0% | 100% |
| £50,000 | 100% | 0% | 100% |

**Figure 6 Base case results: probabilistic excluding SoC CEAF**

The company presents the individual pairwise CEACs for secukinumab against the various comparators. Due to there being no probability of ustekinumab 45mg, ustekinumab 90mg or infliximab being cost effective within these pairwise comparisons, regardless of the willingness to pay, these have not been presented below.




| WTP | vs SoC | vs Adal. | vs Etan. |
|---|---|---|---|
| £0 | 11% | 86% | 31% |
| £10,000 | 69% | 100% | 92% |
| £20,000 | 99% | 100% | 100% |
| £30,000 | 100% | 100% | 100% |
| £40,000 | 100% | 100% | 100% |
| £50,000 | 100% | 100% | 100% |

**Figure 7 Base case results: pairwise CEACs**

### 5.2.10 Sensitivity analyses

One-way sensitivity analyses around the base case were conducted across a large range of parameters and values, as outlined in Table 107 on page 206 of the company's submission. The impacts upon the pairwise comparisons were reported for the fourteen most influential variables. The tornado diagrams underlying these are presented in Figures 31, 32, 33, 34 , 35

and 36 on pages 222 to 225 of the submission. The values underlying these are presented in Tables 34, 35, 36, 37, 38 and 39, below.

The cost effectiveness estimates of the company sensitivity analyses are sensitive to:

- The costs of SoC including;
  - Hospitalisation costs;
  - Day care costs; and
  - And to a lesser extent the costs of phototherapy.
- The drug cost of the biologics.
- The effectiveness estimates, in terms of the medians of the NMA.
- Discount rates.

**Table 34 Company OWSA secukinumab versus SoC**

| | Base | Low value | | | | High value | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Input | Input | Costs | QALYs | ICER | Input | Costs | QALYs | ICER |
| Secuk. cost | [redacted] | [redacted] | £2,752 | 0.389 | £7,076 | [redacted] | £9,211 | 0.389 | £23,688 |
| SoC IP rate | 1.00 | 0.80 | £5,766 | 0.389 | £14,828 | 1.20 | -£263 | 0.389 | Dom. |
| Psoriasis IP cost | £5,337 | £4,270 | £5,766 | 0.389 | £14,828 | £6,405 | -£263 | 0.389 | Dom. |
| Mean psoriasis LoS | 10.70 | 8.56 | £5,766 | 0.389 | £14,828 | 12.84 | -£263 | 0.389 | Dom. |
| Disc rate yr2-10 | 0.20 | 0.05 | £3,363 | 0.693 | £4,856 | 0.43 | £2,454 | 0.204 | £12,006 |
| SoC Day Care days | 5.00 | 4.00 | £3,741 | 0.389 | £9,622 | 6.00 | £1,762 | 0.389 | £4,531 |
| SoC Day Care rate | 1.00 | 0.80 | £3,119 | 0.389 | £8,021 | 1.20 | £2,384 | 0.389 | £6,132 |
| Ciclosporin cost | £48 | £39 | £3,003 | 0.389 | £7,722 | £58 | £2,500 | 0.389 | £6,431 |
| Tx effect SEC | -2.65 | -2.85 | £2,730 | 0.420 | £6,501 | -2.48 | £2,773 | 0.359 | £7,717 |
| DR benefits | 0.04 | 0.00 | £2,752 | 0.422 | £6,519 | 0.05 | £2,752 | 0.376 | £7,309 |
| UVB cost | £91 | £73 | £2,958 | 0.389 | £7,607 | £109 | £2,545 | 0.389 | £6,546 |
| SoC UVB admins | 0.16 | 0.13 | £2,958 | 0.389 | £7,607 | 0.19 | £2,545 | 0.389 | £6,546 |
| Dropout yr1 | 0.12 | 0.09 | £2,742 | 0.398 | £6,897 | 0.14 | £2,762 | 0.379 | £7,284 |
| PASI 50 cut point | 1.20 | 1.12 | £2,744 | 0.393 | £6,975 | 1.27 | £2,760 | 0.383 | £7,216 |

**Table 35 Company OWSA secukinumab versus etanercept**

| | Base | Low value | | | | High value | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Input | Input | Costs | QALYs | ICER | Input | Costs | QALYs | ICER |
| Secuk. cost | [redacted] | [redacted] | £573 | 0.233 | £2,464 | [redacted] | £7,033 | 0.233 | £30,226 |
| Etan. cost | £89 | £72 | £3,326 | 0.233 | £14,293 | £107 | -£2,179 | 0.233 | Dom. |
| Mean psoriasis LoS | 10.70 | 8.56 | £2,211 | 0.233 | £9,504 | 12.84 | -£1,065 | 0.233 | Dom. |
| SoC IP rate | 1.00 | 0.80 | £2,211 | 0.233 | £9,504 | 1.20 | -£1,065 | 0.233 | Dom. |
| Psoriasis IP cost | £5,337 | £4,270 | £2,211 | 0.233 | £9,504 | £6,405 | -£1,065 | 0.233 | Dom. |
| Disc rate yr2-10 | 0.20 | 0.05 | -£209 | 0.407 | Dom. | 0.43 | £1,088 | 0.127 | £8,564 |
| SoC Day Care days | 5.00 | 4.00 | £1,104 | 0.233 | £4,747 | 6.00 | £42 | 0.233 | £182 |
| Tx Effect ETAN | -1.47 | -1.68 | £339 | 0.190 | £1,786 | -1.27 | £780 | 0.270 | £2,888 |
| SoC Day Care rate | 1.00 | 0.80 | £694 | 0.233 | £2,985 | 1.20 | £452 | 0.233 | £1,944 |
| Tx effect SEC | -2.65 | -2.85 | £551 | 0.264 | £2,091 | -2.48 | £595 | 0.203 | £2,928 |
| DR Costs | 0.04 | 0.00 | £470 | 0.233 | £2,019 | 0.05 | £612 | 0.233 | £2,631 |
| UVB cost | £91 | £73 | £672 | 0.233 | £2,890 | £109 | £474 | 0.233 | £2,039 |
| SoC UVB admins | 0.16 | 0.13 | £672 | 0.233 | £2,890 | 0.19 | £474 | 0.233 | £2,039 |
| Ciclosporin cost | £48 | £39 | £662 | 0.233 | £2,844 | £58 | £485 | 0.233 | £2,085 |

**Table 36 Company OWSA secukinumab versus udalimumab**

| | Base | Low value | | | | High value | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Input | Input | Costs | QALYs | ICER | Input | Costs | QALYs | ICER |
| Secuk. cost | [redacted] | [redacted] | -£620 | 0.140 | Dom. | [redacted] | £5,839 | 0.140 | £41,607 |
| Adal. cost | £704 | £563 | £3,355 | 0.140 | £23,909 | £845 | -£4,595 | 0.140 | Dom. |
| Mean psoriasis LoS | 10.70 | 8.56 | £345 | 0.140 | £2,462 | 12.84 | -£1,586 | 0.140 | Dom. |
| SoC IP rate | 1.00 | 0.80 | £345 | 0.140 | £2,462 | 1.20 | -£1,586 | 0.140 | Dom. |
| Psoriasis IP cost | £5,337 | £4,270 | £345 | 0.140 | £2,462 | £6,405 | -£1,586 | 0.140 | Dom. |
| Disc rate yr2-10 | 0.20 | 0.05 | -£1,849 | 0.247 | Dom. | 0.43 | £149 | 0.076 | £1,973 |
| Tx effect ADAL | -1.92 | -2.13 | -£785 | 0.097 | Dom. | -1.70 | -£443 | 0.186 | Dom. |
| SoC Day Care days | 5.00 | 4.00 | -£307 | 0.140 | Dom. | 6.00 | -£933 | 0.140 | Dom. |
| DR Costs | 0.04 | 0.00 | -£781 | 0.140 | Dom. | 0.05 | -£560 | 0.140 | Dom. |
| Tx effect SEC | -2.65 | -2.85 | -£642 | 0.171 | Dom. | -2.48 | -£598 | 0.111 | Dom. |
| PASI 50 cut point | 1.20 | 1.12 | -£691 | 0.136 | Dom. | 1.27 | -£546 | 0.144 | Dom. |
| SoC Day Care rate | 1.00 | 0.80 | -£549 | 0.140 | Dom. | 1.20 | -£691 | 0.140 | Dom. |
| UVB cost | £91 | £73 | -£562 | 0.140 | Dom. | £109 | -£679 | 0.140 | Dom. |
| SoC UVB admins | 0.16 | 0.13 | -£562 | 0.140 | Dom. | 0.19 | -£679 | 0.140 | Dom. |

**Table 37 Company OWSA secukinumab versus ustekinumab 45mg**

| | Base | Low value | | | | High value | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Input | Input | Costs | QALYs | ICER | Input | Costs | QALYs | ICER |
| Secuk. cost | [redacted] | [redacted] | -£3,182 | 0.059 | Dom. | [redacted] | £3,277 | 0.059 | £55,889 |
| Ust 45 cost | £2,147 | £1,718 | £2,227 | 0.059 | £37,991 | £2,576 | -£8,592 | 0.059 | Dom. |
| Tx effect Ust 45 | -2.32 | -2.48 | -£3,378 | 0.030 | Dom. | -2.17 | -£2,970 | 0.089 | Dom. |
| Tx effect SEC | -2.65 | -2.85 | -£3,204 | 0.090 | Dom. | -2.48 | -£3,161 | 0.029 | Dom. |
| Disc rate yr2-10 | 0.20 | 0.05 | -£4,981 | 0.104 | Dom. | 0.43 | -£2,081 | 0.031 | Dom. |
| Mean psoriasis LoS | 10.70 | 8.56 | -£2,791 | 0.059 | Dom. | 12.84 | -£3,574 | 0.059 | Dom. |
| SoC IP rate | 1.00 | 0.80 | -£2,791 | 0.059 | Dom. | 1.20 | -£3,574 | 0.059 | Dom. |
| Psoriasis IP cost | £5,337 | £4,270 | -£2,791 | 0.059 | Dom. | £6,405 | -£3,574 | 0.059 | Dom. |
| DR benefits | 0.04 | 0.00 | -£3,182 | 0.064 | Dom. | 0.05 | -£3,182 | 0.056 | Dom. |
| PASI50 cut point | 1.20 | 1.12 | -£3,291 | 0.056 | Dom. | 1.27 | -£3,066 | 0.061 | Dom. |
| DR Costs | 0.04 | 0.00 | -£3,416 | 0.059 | Dom. | 0.05 | -£3,096 | 0.059 | Dom. |
| SoC Day Care days | 5.00 | 4.00 | -£3,056 | 0.059 | Dom. | 6.00 | -£3,309 | 0.059 | Dom. |
| PASI 75 cut point | 0.60 | 0.57 | -£3,223 | 0.058 | Dom. | 0.63 | -£3,139 | 0.059 | Dom. |
| SoC Day Care rate | 1.00 | 0.80 | -£3,153 | 0.059 | Dom. | 1.20 | -£3,211 | 0.059 | Dom. |

**Table 38 Company OWSA secukinumab versus ustekinumab 90mg**

| | Base | Low value | | | | High value | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Input | Input | Costs | QALYs | ICER | Input | Costs | QALYs | ICER |
| Tx effect SEC | -2.65 | -2.85 | -£3,393 | 0.062 | Dom. | -2.48 | -£3,349 | 0.001 | Dom. |
| Tx effect Ust 90 | -2.47 | -2.63 | -£3,558 | 0.002 | Dom. | -2.30 | -£3,157 | 0.062 | Dom. |
| Secuk. cost | [redacted] | [redacted] | -£3,371 | 0.031 | Dom. | [redacted] | £3,089 | 0.031 | £99,990 |
| Ust 90 cost | £2,147 | £1,718 | £2,360 | 0.031 | £76,418 | £2,576 | -£9,102 | 0.031 | Dom. |
| Disc rate yr2-10 | 0.20 | 0.05 | -£5,340 | 0.055 | Dom. | 0.43 | -£2,170 | 0.016 | Dom. |
| DR benefits | 0.04 | 0.00 | -£3,371 | 0.034 | Dom. | 0.05 | -£3,371 | 0.030 | Dom. |
| PASI 50 cut point | 1.20 | 1.12 | -£3,471 | 0.029 | Dom. | 1.27 | -£3,263 | 0.032 | Dom. |
| DR Costs | 0.04 | 0.00 | -£3,626 | 0.031 | Dom. | 0.05 | -£3,276 | 0.031 | Dom. |
| Mean psoriasis LoS | 10.70 | 8.56 | -£3,167 | 0.031 | Dom. | 12.84 | -£3,574 | 0.031 | Dom. |
| SoC IP rate | 1.00 | 0.80 | -£3,167 | 0.031 | Dom. | 1.20 | -£3,574 | 0.031 | Dom. |
| Psoriasis IP cost | £5,337 | £4,270 | -£3,167 | 0.031 | Dom. | £6,405 | -£3,574 | 0.031 | Dom. |
| PASI 75 cut point | 0.60 | 0.57 | -£3,408 | 0.030 | Dom. | 0.63 | -£3,331 | 0.031 | Dom. |
| SoC Day Care days | 5.00 | 4.00 | -£3,305 | 0.031 | Dom. | 6.00 | -£3,437 | 0.031 | Dom. |
| SEC SAE infect. | 2.77 | 0.02 | -£3,392 | 0.031 | Dom. | 0.03 | -£3,349 | 0.031 | Dom. |

**Table 39 Company OWSA secukinumab versus infliximab**

| | Base | Low value | | | | High value | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Input | Input | Costs | QALYs | ICER | Input | Costs | QALYs | ICER |
| Tx effect SEC | -2.65 | -2.85 | -£17,199 | 0.035 | Dom. | -2.48 | -£17,156 | -0.025 | £678k* |
| Tx effect INFL | -2.62 | -2.84 | -£18,207 | -0.029 | £623k* | -2.39 | -£15,862 | 0.045 | Dom. |
| Infl. cost | £420 | £336 | -£8,987 | 0.004 | Dom. | £504 | -£25,368 | 0.004 | Dom. |
| Secuk. cost | [redacted] | [redacted] | -£17,177 | 0.004 | Dom. | [redacted] | -£10,718 | 0.004 | Dom. |
| Patient kg | 86.60 | 69.28 | -£10,719 | 0.004 | Dom. | 103.92 | -£22,832 | 0.004 | Dom. |
| DR Costs | 0.04 | 0.00 | -£18,769 | 0.004 | Dom. | 0.05 | -£16,588 | 0.004 | Dom. |
| DR benefits | 0.04 | 0.00 | -£17,177 | 0.005 | Dom. | 0.05 | -£17,177 | 0.004 | Dom. |
| PASI 50 cut point | 1.20 | 1.12 | -£17,577 | 0.004 | Dom. | 1.27 | -£16,740 | 0.004 | Dom. |
| Disc rate yr2-10 | 0.20 | 0.05 | -£29,468 | 0.007 | Dom. | 0.43 | -£9,713 | 0.002 | Dom. |
| PASI 75 cut point | 0.60 | 0.57 | -£17,329 | 0.004 | Dom. | 0.63 | -£17,017 | 0.004 | Dom. |
| Infl SAE malig. | 0.08 | 0.06 | -£17,020 | 0.004 | Dom. | 0.09 | -£17,335 | 0.004 | Dom. |
| Lymphoma cost | £8,178 | £6,543 | -£17,054 | 0.004 | Dom. | £9,814 | -£17,301 | 0.004 | Dom. |
| Dropout yr1 | 0.12 | 0.09 | -£17,604 | 0.004 | Dom. | 0.14 | -£16,708 | 0.004 | Dom. |
| PASI 90 cut point | 1.32 | 1.28 | -£17,177 | 0.004 | Dom. | 1.36 | -£17,177 | 0.004 | Dom. |

* SW quadrant, hence the values depict the cost effectiveness of infliximab compared to secukinumab.

### 5.2.11 Scenario analyses

The company presents a range of scenario analyses:

- Those with a partial response of PASI 50-74 continuing on treatment, in effect treating a patient with a PASI 50-74 response as a responder;
- Basing the PASI response estimates upon the 12 week endpoints for all comparators, rather than upon the primary trial endpoints;
- Basing the PASI response estimates upon the 16 week assessment point for secukinumab and the primary trial endpoints for the other comparators;
- Applying the quality of life values used in the STA of adalimumab for plaque psoriasis, TA146;
- For a comparison of SoC, secukinumab and etanercept using the head to head data of the FIXTURE trial to derive the 12 week PASI response estimates.

**Table 40 Scenario analysis: inclusion of partial responders**

| | Tx | Medical | SAE | Total | QALYs | Δ Cost | Δ QALY | ICER |
|---|---|---|---|---|---|---|---|---|
| SoC | £2,209 | £26,228 | £44,826 | £73,262 | 1.004 | | | |
| Etaner. | £19,988 | £20,240 | £34,128 | £74,356 | 1.138 | £1,094 | 0.134 | £8,170 |
| Secukin. | [redacted] | [redacted] | [redacted] | £75,014 | 1.367 | £658 | 0.228 | £2,879 |
| Adalim. | £25,205 | £18,970 | £31,189 | £75,365 | 1.230 | £351 | -0.137 | Dominated |
| Ust. 45mg | £31,146 | £18,007 | £28,985 | £78,138 | 1.310 | £3,124 | -0.057 | Dominated |
| Ust. 90mg | £32,285 | £17,770 | £28,441 | £78,496 | 1.337 | £3,482 | -0.030 | Dominated |
| Infliximab | £45,190 | £19,632 | £29,096 | £93,918 | 1.363 | £18,904 | -0.004 | Dominated |

Secukinumab extendedly dominates etanercept, having a cost effectiveness compared to SoC of £4,834 per QALY. Note that within the submitted model structure adding the baseline quality of life value of 0.642 to all the PASI response category quality of life values[e] changes the cost effectiveness estimates to those below.

**Table 41 Scenario analysis: inclusion of partial responders: 0.642 baseline QoL**

| | Tx | Medical | SAE | Total | QALYs | Δ Cost | Δ QALY | ICER |
|---|---|---|---|---|---|---|---|---|
| SoC | £2,209 | £26,228 | £44,826 | £73,262 | 6.407 | | | |
| Etaner. | £19,988 | £20,240 | £34,128 | £74,356 | 6.457 | £1,094 | 0.050 | £21,792 |
| Secukin. | [redacted] | [redacted] | [redacted] | £75,014 | 6.755 | £658 | 0.299 | £2,202 |
| Adalim. | £25,205 | £18,970 | £31,189 | £75,365 | 6.561 | £351 | -0.195 | Dominated |
| Ust. 45mg | £31,146 | £18,007 | £28,985 | £78,138 | 6.670 | £3,124 | -0.086 | Dominated |
| Ust. 90mg | £32,285 | £17,770 | £28,441 | £78,496 | 6.710 | £3,482 | -0.046 | Dominated |
| Infliximab | £45,190 | £19,632 | £29,096 | £93,918 | 6.749 | £18,904 | -0.006 | Dominated |

The ERG has not managed to parse why this happens within the scenario analysis of partial responders. Due to this and other concerns around the modelling of partial responders as outlined in the sections that follow, the ERG has not undertaken any further formal analysis of the partial responders scenario.

The cost effectiveness estimates of the other scenario analyses not affected by adding the baseline quality of life value of 0.642 to all the PASI response category quality of life values.

[e] Implemented within the *Utility_Calculations* worksheet by adding 0.642 to cells G11:G15; e.g. G11= CHOOSE(Utility_ctrl,I11,J11) + 0.642

**Table 42 Scenario analysis: 12 week NMA**

| | Tx | Medical | SAE | Total | QALYs | Δ Cost | Δ QALY | ICER |
|---|---|---|---|---|---|---|---|---|
| SoC | £1,838 | £26,391 | £45,272 | £73,501 | 6.436 | | | |
| Etaner. | £14,281 | £22,767 | £38,869 | £75,917 | 6.587 | £2,416 | 0.151 | £15,976 |
| Secukin. | [redacted] | [redacted] | [redacted] | £76,768 | 6.821 | £851 | 0.234 | £3,632 |
| Adalim. | £20,594 | £21,023 | £35,213 | £76,830 | 6.689 | £62 | -0.132 | Dominated |
| Ust. 45mg | £27,201 | £19,843 | £32,538 | £79,582 | 6.761 | £2,813 | -0.061 | Dominated |
| Ust. 90mg | £28,817 | £19,385 | £31,565 | £79,766 | 6.789 | £2,998 | -0.032 | Dominated |
| Infliximab | £38,632 | £21,178 | £32,567 | £92,377 | 6.786 | £15,608 | -0.035 | Dominated |

Secukinumab extendedly dominates etanercept, having a cost effectiveness compared to SoC of £8,473 per QALY.

**Table 43 Scenario analysis: NICE 16 week NMA**

| | Tx | Medical | SAE | Total | QALYs | Δ Cost | Δ QALY | ICER |
|---|---|---|---|---|---|---|---|---|
| SoC | £1,827 | £26,500 | £45,283 | £73,610 | 6.434 | | | |
| Etaner. | £13,728 | £22,777 | £39,184 | £75,688 | 6.581 | £2,077 | 0.147 | £14,133 |
| Secukin. | [redacted] | [redacted] | [redacted] | £76,656 | 6.840 | £968 | 0.259 | £3,732 |
| Adalim. | £19,927 | £21,269 | £35,730 | £76,927 | 6.678 | £271 | -0.162 | Dominated |
| Ust. 45mg | £26,275 | £20,013 | £33,080 | £79,368 | 6.748 | £2,713 | -0.092 | Dominated |
| Ust. 90mg | £27,841 | £19,579 | £32,139 | £79,558 | 6.776 | £2,902 | -0.064 | Dominated |
| Infliximab | £40,580 | £20,799 | £31,753 | £93,132 | 6.815 | £16,477 | -0.025 | Dominated |

Secukinumab extendedly dominates etanercept, having a cost effectiveness compared to SoC of £7,495 per QALY.

**Table 44 Scenario analysis: TA146 utilities**

| | Tx | Medical | SAE | Total | QALYs | Δ Cost | Δ QALY | ICER |
|---|---|---|---|---|---|---|---|---|
| SoC | £1,857 | £26,500 | £45,253 | £73,610 | 5.964 | | | |
| Etaner. | £14,785 | £22,471 | £38,533 | £75,788 | 6.108 | £2,178 | 0.144 | £15,118 |
| Secukin. | [redacted] | [redacted] | [redacted] | £76,361 | 6.352 | £573 | 0.244 | £2,345 |
| Adalim. | £20,712 | £21,036 | £35,233 | £76,981 | 6.199 | £620 | -0.153 | Dominated |
| Ust. 45mg | £27,723 | £19,611 | £32,210 | £79,544 | 6.286 | £3,182 | -0.066 | Dominated |
| Ust. 90mg | £29,276 | £19,180 | £31,275 | £79,732 | 6.317 | £3,371 | -0.035 | Dominated |
| Infliximab | £41,523 | £20,653 | £31,363 | £93,539 | 6.347 | £17,177 | -0.005 | Dominated |

Secukinumab extendedly dominates etanercept, having a cost effectiveness compared to SoC of £7,082 per QALY.

**Table 45 Scenario analysis: FIXTURE study data**

| | Tx | Medical | SAE | Total | QALYs | Δ Cost | Δ QALY | ICER |
|---|---|---|---|---|---|---|---|---|
| SoC | £1,926 | £26,391 | £45,182 | £73,499 | 6.458 | | | |
| Etaner. | £16,868 | £22,002 | £37,272 | £76,142 | 6.635 | £2,643 | 0.177 | £14,903 |
| Secukin. | [redacted] | [redacted] | [redacted] | £76,773 | 6.815 | £631 | 0.180 | £3,508 |

Secukinumab extendedly dominates etanercept, having a cost effectiveness compared to SoC of £9,166 per QALY.

### 5.2.12 Model validation and face validity check

The ERG has rebuilt the deterministic base case with the results of the rebuild cross checking with those of the company's submission.

The only other immediately obvious additional face validity check that can be undertaken is to compare the estimated cost effectiveness of etanercept 25mg compared to SoC with that estimated during TA103 for continuous use etanercept 25mg compared to SoC for the scenario of an annual hospitalisation among non-responders.[43]

**Table 46 Continuous use etanercept cost effectiveness compared to TA103 estimate**

| | Current submission | | | TA103[f] |
|---|---|---|---|---|
| | Etanercept | SoC | net | net |
| Costs | £75,788 | £73,610 | £2,178 | £5,337 |
| QALYs | 1.129 | 0.973 | 0.156 | 0.116 |
| ICER | | | £13,948 | £45,975 |

Both the current submission and TA103 modelled a 10 year time horizon.[43] PASI response rates were quite similar between the two submissions, though the quality of life steps for the difference PASI response categories were smaller under TA103.Unfortunatley, the discount rates differed markedly, TA103 still using the old NICE discount rates of 6.0% for costs and 1.5% for benefits, which makes a direct read across between the results of the two modelling exercises difficult.

For the comparison with SoC a concern may be the large cost offsets due in part to SoC treatment costs, but more due to day care, phototherapy and hospitalisation costs for those on

[f] Taken from Table 6.3.7 of Woolacott et al (2005)

SoC. Patients receiving SoC, whether due to being in the SoC arm or having discontinued a biologic, are assumed to be on average hospitalised 10.7 days more than those on a biologic at an annual cost of £5,337. Excluding just the SoC hospitalisation costs[g] worsens the cost effectiveness of secukinumab compared to SoC from £7,076 per QALY to £45,836 per QALY.

## *5.3 ERG cross check and critique*

### 5.3.1 Base case results

The base case results of the model cross check with those presented in the company's submission.

### 5.3.2 Data inputs: correspondence between written submission and sources cited

*PASI response rates*

The PASI response rates of the base case cross check with those implied by Figures 20, 21 and 22 of the company's submission, with the exception of a very small discrepancy of probably less than 1% for the PASI 50-74 response rate for secukinumab.

*Serious adverse event rates*

The clinical effectiveness Section 6.9 of the submission only reports non-fatal serious adverse event rates and infection rates, with the latter presumably being any infection rather than necessarily being an SAE. There is no ready read across between these and the SAE rates used in the model.

**Table 47 FIXTURE AE rates versus those used in the model**

| | SoC | Secu. |
|---|---|---|
| FIXTURE: Submission Table 58 | | |
| Non-fatal SAEs | 0.042 | 0.072 |
| Infection | 0.715 | 0.387 |
| Model | | |
| NMSC | 0.000 | [redacted] |
| non NMSC | 0.000 | [redacted] |
| Severe infection | 0.000 | [redacted] |

[g] Implemented within the *Inputs* worksheet by setting cell G133=0

The ERG has not cross checked the rates of adverse events for the other active treatments as these currently have little impact upon the modelled outcomes.

*Quality of life: by PASI response status*

The TA103 etanercept and efalizumab,[43] the TA146 adalimumab,[44] and the TA134 infliximab,[46] also derived quality of life values from EQ-5D data. The company reports that the TA180 ustekinumab, resorted to a mapping exercise. Table 48 shows the quality of life increments for the various NICE assessments (derived from Table 84 of the submission).

**Table 48 Quality of life values of NICE HTAs**

| Assessment | TA103 | TA146 | TA134 | TA180 | Current |
|---|---|---|---|---|---|
| PASI < 50 | 0.050 | 0.054 | 0.120 | 0.040 | 0.109 |
| PASI 50-74 | 0.170 | 0.140 | 0.290 | 0.170 | 0.193 |
| PASI 75-89 | 0.190 | | 0.380 | 0.220 | 0.226 |
| PASI 90 | 0.210 | 0.219 | 0.410 | 0.250 | 0.264 |

The company's submission also presents the results of a number of other EQ-5D studies assessing quality of life among patients with psoriasis using the various PASI response categories. These are mostly reported as the changes in EQ-5D QoL, though Knight et al 2012[62] give absolute EQ-5D QoL values. Pan et al 2011[63] present two sets of values, the first based upon the PHOENIX trial and the second apparently based upon calculations from an adalimumab HTA.

**Table 49 EQ-5D quality of life values: values from published papers**

| Paper | Sizto | Shikiar | Anis | Pan | | Knight |
|---|---|---|---|---|---|---|
| PASI <50 | 0.06 | 0.04 | 0.04 | 0.04 | 0.063 | 0.660 |
| PASI 50-74 | 0.18 | 0.20 | 0.12 | 0.17 | 0.178 | 0.861 |
| PASI 75-89 | | 0.25 | | 0.22 | | 0.892 |
| PASI 90 | 0.31 | | 0.21 | 0.25 | 0.308 | |

The values cross check with the cited sources.

*Etanercept: continuous treatment versus intermittent treatment*

Woolacott et al 2005[59] explored the impact of both continuous use of etanercept and intermittent use of etanercept. This appears to have assumed the same effectiveness for

etanercept intermittent use as for etanercept continuous use. The annual direct drug costs were, however, very different: for etanercept 25mg £9,327 for continuous compared to £6,933 for intermittent use.

This led to the cost effectiveness estimates differing considerable. Etanercept 25mg, both continuous and intermittent, was estimated to result in an additional 0.116 QALYs compared to SoC. Nevertheless, for the base case, which did not include hospitalisation costs for non-responders, the total net costs compared to SoC in 2004/05 prices were £7,743 for intermittent use and £9,665 for continuous use. These resulted in cost effectiveness estimates of £66,703 per QALY for intermittent use and £83,258 per QALY for continuous use.

For the scenario analysis that included an annual 21 days hospitalisation for non-responders at a total cost of £5,208, the net total cost of etanercept over SoC was £3,415 for intermittent use and £5,337 for continuous use. This resulted in cost effectiveness estimates of £29,420 per QALY for intermittent use and £45,975 per QALY for continuous use. Thus, the approval of etanercept may have been based in part upon an assumption of intermittent use.

*Hospitalisations and costs of SoC*

Woolacott et al 2005[59] assumed that SoC would require two outpatient appointments annually. No other treatment costs appear to have been applied for the base case.

A scenario analysis that applied an average annual 21 days inpatient visit per non-responder at an average daily cost of £248 in 2004/05 prices resulted in a annual hospitalisation cost of £5,208 per non-responder.

As already noted, the cost effectiveness estimates of the TA103[43] base case of no additional hospitalisations for non-responders and the scenario analysis of an annual 21 day inpatient stay differed considerably. Those for intermittent use etanercept 25mg fell from £66,703 per QALY to £29,420 per QALY when hospitalisations were included, while those for continuous use etanercept 25mg fell from £83,258 per QALY to £45,975 per QALY.

The conclusions of the assessment committee for TA103 were:

> *In considering the economic modelling the Committee recognised that there was considerable uncertainty in the estimates of cost effectiveness that had been produced.*

*This uncertainty related principally to estimates of the efficacy of the alternative interventions and treatment regimens and the evidence on long-term outcomes… Noting this uncertainty in the economic modelling, the Committee concluded it was unlikely that these interventions would be cost effective except in people who had very poor quality of life and who would be likely to require hospital admission for treatment. Testimony from the clinical experts and consultees suggested that these people would be those with severe disease as defined by a PASI of 10 or more and DLQI of more than 10, who had not responded to standard systemic therapies.*

It also noting:

*Research on the rate of inpatient hospitalisation in people with moderate to severe psoriasis is warranted, and the effect of treatment on this rate.*

*Hospitalisation unit costs and rates for psoriatic patients*

In response to clarification, the company has supplied the 2012-13 HES data presented in Table 50. The number of inpatient admissions has been inferred by the ERG by subtracting the number of day cases from the number of admissions.

**Table 50 2012-13 HES data for psoriasis admissions**

| Primary diagnosis | FCEs | Admiss. | Day case | *IP* | Bed days | Mean LoS |
|---|---|---|---|---|---|---|
| Psoriasis vulgaris | 1,023 | 952 | 605 | *347* | 3,761 | 10.7 |
| Generalized pustular psoriasis | 202 | 151 | 64 | *87* | 1,074 | 11.8 |
| Acrodermatitis continua | 2 | 2 | 1 | *1* | 8 | 8 |
| Pustulosis palmaris et plantaris | 75 | 58 | 40 | *18* | 225 | 9.8 |
| Guttate psoriasis | 38 | 31 | 4 | *27* | 199 | 5.7 |
| Arthropathic psoriasis | 5,722 | 5,606 | 5,024 | *582* | 3,243 | 5.6 |
| Other psoriasis | 306 | 200 | 59 | *141* | 1,573 | 11.1 |
| Psoriasis, unspecified | 5,947 | 5,735 | 4,152 | *1,583* | 5,933 | 8.5 |

The column of FCE bed days states that for psoriasis vulgaris (L40.0) there were a total of 3,761 bed days. Day cases are in-patients who have been admitted but who by definition, as summarised in the field descriptors worksheet of the data supplied by the company, have a zero length of stay. This suggests that of the 952 admissions for psoriasis vulgaris only 347 involved bed days, which given a mean length of stay of 10.7 days would suggest a total of 3,713 bed days. This is reasonably close to the actual total of 3,761 FCE bed days, with any

discrepancies possibly being due to uncompleted episodes during the year. This suggests a balance between day cases and admissions requiring an overnight stay being 64:36, with the average length of stay of 10.7 days applying to the 36% of patients requiring an overnight stay.

The number of admissions can be compared with the estimated patient numbers that are eligible for secukinumab within the company budget impact analysis (the ERG has not critically reviewed these estimates). This indicates that 20,269 patients are eligible for treatment with a biologic with [redacted] of these patients currently receiving therapy with a biologic. This suggests that [redacted], ([redacted]) patients, are currently receiving some form of SoC.

If the ERG calculation of the number of inpatient admissions is correct, it is very difficult to align the number of inpatient admissions implied by the 2012-13 HES data with the suggested eligible population. For psoriasis vulgaris which is the company preferred category the inpatient admissions are a fraction of the [redacted] eligible patients of the budget impact analysis. The grand total across all psoriasis categories appears to be 2,786. Even if it is assumed that all these inpatient admissions are among moderate to severe patients on SoC, it still falls well short of the [redacted] suggested by the budget impact analysis. There appears to be a major discrepancy between the data underlying the 10.7 average length of inpatient stay, the budget impact section, and the assumption that all those currently on SoC experience an average of one inpatient admission every year.

*Hospitalisations and the cost of SoC*

Woods et al (2007), in a review 183 psoriasis patients' information from four UK specialist centres provide data on the mean lengths of stay split by PASI on admission. The vast majority of patients, 86%, had plaque psoriasis. The two tertiary referral centres, Manchester and London, had similar overall mean lengths of stay - 22.3 days and 23.4 days, respectively. The regional university dermatology department of Newcastle had a mean length of stay of 18.1 days, while the regional referral centre had a mean length of stay of 13.1 days. The overall average length of stay was 19.7 days across the four centres, but this may not be reflective of the balance between tertiary referral centres and regional referral centres in the NHS. Patients were split into those with a PASI of less than 10, between 10 and 20, and more than 20 at admission, with the mean lengths of stay among these groups being 19 days, 21

days, and 24 days, respectively. This association was statistically significant, with a p value of 0.02.

Conway and Currie 2008[64] in a study sponsored by Wyeth, the company of etanercept, identified 1,935 admissions with a primary diagnosis of psoriasis over a 15-year period in an urban area of South Wales with a population of 435,000. Taking into account mortality, this indicated a crude prevalence rate of people hospitalised with psoriasis of 0.23% of the general population over the 15-year period. Between 65% and 77% of those admitted had only one admission for psoriasis, with the median time between first and second admission among the remainder being 1.4 years. The mean length of stay was 16.8 days. It seems likely that this study encompassed all the coding variants for psoriasis.

Fonia et al 2010[58] in a study sponsored by Janssen Cilag, the company of ustekinumab, used case notes of a sequential patient cohort of patients who were referred to a London tertiary severe psoriasis service. Data on hospital resource use and drug usage was collected 12 months prior to and at least 6 months and up to 12 months subsequent to starting a biologic, with the primary analysis being based upon the 76 patients with 12 months follow-up data after initiation of a biologic. The mean patient age was 47 with 54% being male, and the mean duration of disease was 22 years prior to the initiation of a biologic. Among the 76 patients with 12-month data pre and post initiation of a biologic, 8% received adalimumab, 12% received efalizumab, 71% received etanercept and 32% received infliximab during the year after initiation of a biologic (these proportions sum up to more than 100% due to some patients receiving more than one biologic). The mean hospital resource use per patient measured during the 12 months prior to and the 12 months post initiation of a biologic is shown in Table 51.

**Table 51 Fonia et al (2010): UK hospital resource use pre and post starting a biologic[58]**

| | | Pre-biologic | | Post-biologic | |
|---|---|---|---|---|---|
| | Unit cost | Units | Mean cost | Units | Mean cost |
| IP admission (days) | £291 | 6.49 | £1,888 | 1.55 | £452 |
| A&E visit | £86 | 0.03 | £2 | 0.04 | £3 |
| Outpatient visit | £72 | 3.22 | £232 | 3.25 | £234 |
| Day case | £441 | 0.14 | £64 | 1.16 | £511 |
| Phototherapy | £282 | 2.73 | £771 | 0.26 | £75 |
| Total mean cost | | | £2,957 | | £1,274 |

There was a significant reduction in the total cost of hospital care among those referred. But the net impact upon inpatient admissions is lower than that suggested in the company's submission. While not all patients will have responded to a biologic therapy, and Fonia et al[58] appear to suggest a mean response of around a PASI 50, the above appears to suggest an average reduction of around 5 inpatient days. The above provides some support for the assumption that SoC is associated with an increase in phototherapy costs, though again the net impact of between 2 and 3 phototherapy sessions, which is a little less than the 3.84 of the company's submission. The above does not appear to support the company's assumption that SoC is associated with an additional 5 day case visits.

Driessen et al 2010[65] analysed the data of 140 high need psoriasis patients in the Netherlands who had failed to respond or were contraindicated to phototherapy, methotrexate or ciclosporin and had a PASI of more than 10. Patients were only included if they had data for 12 months prior to and 12 months after initiation of a biologic. Among 67 patients, who were included in the analyses, the mean PASI at the start of the biologic treatment was 19.7.

Driessen et al 2010[65] presented also the data for the subset of 12 (18%) patients, who were admitted for more than 30 days per year, on average. For these patients the mean hospitalisation was 53 days per person per year in the pre-biologic period and 22 days per person per year in the post biologic period. These figures, however, may be skewed by a single patient requiring 65 days in the pre-biologic period and 159 days in the post-biologic period (medians were 53 days pre-biologic and 5.3 days post-biologic). Across all 67 patients Driessen et al found that the average day care use fell from 5.1 days to 0.3 days, and the average hospitalisation fell from 14.9 days to 5.4 days. Even though, it is not entirely clear

whether these averages are means or medians, the reporting does mention that the mean costs are calculated from these values. These values are more in line with those of the company's submission.

The data reported above need to be considered together with the apparent general thrust to reduce the inpatient admissions among psoriasis patients, with fewer beds being available over time. The study by Woods et al[66] and that by Conway and Currie[64] may be slightly dated, with the study by Fonia et al[58] providing, probably, more relevant information, albeit from a relative small sample that cannot guarantee to be representative of the general UK practice. The relevance of the study by Driessen et al,[65] conducted in the Netherlands, is questionable, given that the study by Fonia et al[58] is available as a UK source with a slightly larger sample size.

To the ERG the Fonia et al[58] estimates appear the more attractive, having been collected in a patient population of interest in the UK setting. As a scenario analysis it seems reasonable to assume that SoC is associated with an additional 5 inpatient visits and an additional 3 phototherapy sessions each year, but with no increase in the rate of day cases. Even this may be an overestimate if hospitalisation rates have tended to continue to fall since the Fonia et al[58] data were collected, with the paper referring to some data being as old as 2006. The findings of the expert survey presented in the submission indicate that "*inpatient stays for psoriasis are very rare and have diminished in the last 5 years*".

The company's submission also identified the Fonia et al study,[58] but chose not to use it on the grounds that "*more up to date inputs from NICE CG153 and expert opinion*" were available. The ERG can confirm that the costing of SoC outlined in Table 87 of the company's submission corresponds with the 2012 CG153 costing report. Note that within CG153 the cost per hospitalisation for the high need patients is given as £5,876, which is similar to the £5,337 estimated by the company.

*Direct drug costs and administration schedules*

The unit drug costs for the biologics given in the company's submission and in the electronic model, cross check with those of MIMS February 2015. There are no entries for the biologics within either the NHS drug tariff or the CMU EMIT database. The CMU EMIT database

indicates a cost of £46.15 for 30 100mg ciclosporin tablets compared to the £48.49 of the company's submission, but this has no practical impact upon results.

The dosing schedule given in the *Advisory Drugs Committee Secukinumab* document provided by the company cross checks with that used in the model for the first year. The ERG interprets the monthly dosing to be four weekly dosing, which suggest 13 doses per year thereafter rather than the 12 of the company base case.

The dosing schedules of the SmPCs of the other biologics cross check with the dosing of the company base case with the exception of that for ustekinumab during the first year. The SmPC specifies "*an initial dose of 45mg administered subcutaneously, followed by a 45mg dose 4 weeks later, and then every 12 weeks thereafter*", which to the ERG suggests a first year dosing schedule of the starts of weeks 1, 5, 17, 29 and 41 with the last dose being sufficient to the end of the year. This, in turn, suggests 2 doses during induction and 3 doses post induction, while the company base case assumes 2 doses during induction and 4 doses post induction.

*Infliximab average dose per administration*

The electronic model of the company bases the number of vials per administration upon patient weights drawn from Reich et al 2006.[61] This reference is not included in the submission and does not appear to have been supplied by the company in the reference pack. The mean weight of 86.6kg (standard deviation 19.8kg) of the electronic model is similar to that reported in the FIXTURE trial (83.3kg).

*Infliximab administration resource use*

The unit cost per administration of £92.39 cross checks with a weighted average of the NHS reference cost of an outpatient dermatology appointment: WF01A. This is slightly higher than the £65 outpatient cost used in the TA134 infliximab for psoriasis. The ERG report for TA134 did query the £65, suggesting that the true cost might be higher, though it did not provide an alternative estimate. Revising the administration cost to an inflation adjusted value drawn from TA134 is unlikely to have any real impact upon results.

*NHS reference costs*

The average costs of £499 per inpatient day, which when coupled with an assumption of an average stay of 10.7 days leads to the £5,337 inpatient cost for SoC and £461 per day case, cross check with the NHS reference costs cited.

Note that the £461 per day is based upon a dermatology weighted average of day cases that may or may not involve an intervention. The weighted average across those not requiring an intervention only falls to £452.

### 5.3.3 Data inputs: correspondence between written submission and electronic model

The company's submission and the electronic model correspond, with the exception of minor elements that are outlined below. Where there are ambiguities, the ERG summary of what has been submitted relies upon the implementation within the electronic model.

*Secukinumab administration costs*

Within the electronic model the administration and monitoring costs for secukinumab have also included, inadvertently, the costs of five intravenous infusions.

*Serious adverse events: first year resource use*

It appears that the first year of treatment has not had the SAE costs applied, but subsequent years have[h]. It is relatively simple to add these into the model. It may also raise the question around SoC hospitalisations and whether the £5,337 should be added to all SoC patients during the first year.

### 5.3.4 ERG commentary on model structure, assumptions and data inputs

*Model structure: general comments*

The model, in common with those of previous assessments in the area, assumes that patients try one biologic and if the response to treatment is less than a PASI 75 they revert to SoC with some day care treatment and PUVA treatment. According to the ERG clinical advisor this does not mirror clinical practice. Patients who fail to respond to the initial treatment would either be switched to another treatment, or have additional agents such as methotrexate or PUVA treatment added to their therapy strategy.

[h] For instance, within the *Markov_* worksheets there appear to be no dependents to cell F$23 or to cell H$23 within rows 61:86, but cells AK101:AK104 are dependents of cell F$23.

In the light of this, it appears that a more complicated sequencing of treatments might be the most appropriate model structure. This would require some assumptions to be made about the effectiveness of 2nd line and subsequent treatments, which in the absence of data would probably have to be assumed to be a proportion of their 1st line effectiveness. Sensitivity analyses would also be required around these assumptions. This might provide, however, a better estimate of the cost effectiveness of the active treatments compared to SoC. An exploration of this would have been possible with the number of possible treatments before reversion to SoC being a variable within the modelling, with the base case still being able to retain an assumption of only one possible treatment before reversion to SoC. This would also have helped address the protocol: "*If the evidence allows, the place of secukinumab in a sequence of biologics will be considered*" although it remains debateable if the evidence truly allows this to be explored. Some indication of the possible impact of this within the current modelling is the sensitivity of the cost effectiveness estimate of secukinumab compared with SoC from a reduction in the annual drop-out rate.

Exploring the optimal sequencing of treatments does not imply, necessarily, that trialling the least costly treatment first is likely to be the most cost effective treatment. For instance, the company NMA suggests that etanercept has a PASI 75 response rate of 37% compared to a rate of 80% for secukinumab. The company PAS is confidential, but suppose that etanercept is cheaper. It would be possible to have an initial 12-week trial of etanercept and maintain the 37% of PASI 75 responders at the lower cost of etanercept, before trialling the more expensive secukinumab in the remaining 63% of patients. However, within the company NMA etanercept is also associated with a lower PASI 90 response rate of 15% compared to the 55% of secukinumab. Maintaining 37% of patients on etanercept with a PASI 75 response might mean to deprive some of these patients of a PASI 90 response had they been trialled on secukinumab first. This might only become apparent once the initial efficacy of etanercept had worn off, with these patients moving on to secukinumab.

*The treatment of the placebo effect within the modelling*

It appears that the modelling approach may remove the placebo effect from patients who do not achieve a PASI 75 response but retain it for those achieving a PASI 75 response. For instance, suppose that a given patient receiving SoC achieved a PASI 50 response while the same patient receiving a biologic would have achieved a PASI 75 response. It could be argued that the PASI 75 response of the biologic is on the back of the PASI 50 response of

SoC. The modelling assumes that the PASI 50 response of SoC falls back to a PASI <50 response, while the full PASI 75 response of the biologic is retained. This seems likely to bias the analysis in favour of the more effective treatment.

The degree of bias will be dependent upon the size of the placebo response. The estimated response rates for SoC are relatively poor: PASI <50 of 88%, PASI 50-74 of 8%, PASI 75 of 3% and PASI 90 of 1%. There is no information about where the weight of the PASI <50 responses lies, whether towards the lower end or the upper end.

*Model structure: first year QALY calculations*

It appears that during the first year it is assumed that the patient remains in their week 12 PASI response category within the QALY calculation. For patients with a PASI 50-75 response it would seem more appropriate to apply the quality of life associated with the PASI 50-75 response category for the duration of induction and the quality of life associated with the PASI <50 response category for the remaining period of the first year.

*Model structure: SoC arm discontinuations*

Within the SoC arm at 12 weeks there are percentages of patients in the PASI 50-74, PASI 75-89 and PASI 90 response categories of 8%, 3% and 1%, respectively. It is not straightforward why the patients in the PASI 50-74 response category should be assumed to revert to the PASI <50 response category at the end of 12 weeks. This may bias the analysis against SoC.

*First year discontinuation rate*

Considering that non-responders are assumed to discontinue during the first year, it is not obvious that the 11.7% first year discontinuation rate should be applied. This argues for a sensitivity analysis excluding setting this to zero.

*Discontinuation rates among responders*

ERG expert opinion suggests that a rate of 15% to 20% for annual discontinuations after an initial response is reasonable. ERG expert opinion suggests that there may be a longer duration of effect among responders from ustekinumab compared to some other biologics in current use. This argues for sensitivity analyses around the discontinuation rate, and around the discontinuation rate specific to secukinumab.

*Mortality risk associated with psoriasis*

Although the company note an increased mortality risk from psoriasis through a number of routes, they only apply the general all-cause mortality rates of the UK life tables with no mortality multiplier associated with psoriasis. This seems an evident omission, and it is unclear why they have not undertaken a literature review to explore this issue and what values might be applied within the modelling. There are at least two considerations that may arise:

- A general mortality multiplier associated with moderate to severe plaque psoriasis. If there are values available within the literature, the inclusion of a general mortality multiplier may worsen the cost effectiveness estimates through curtailing the net benefits of the more effective treatment;
- Mortality multipliers associated with PASI categories among those with moderate to severe plaque psoriasis. These might result in a model that yields a survival advantage to the more effective treatment and so improves the cost effectiveness estimates. However, in order to apply these within any modelling, there would need to be a clear link or assumption that improving the PASI score of an individual has the same impact upon their psoriasis mortality multiplier as the difference between the mortality multiplier of those with the higher PASI score compared with those with the lower PASI score. In other words, addressing the PASI element of psoriasis by treatment with a biologic has an impact upon the cardiovascular risk and other mortality risks associated with psoriasis as outlined in Section 2.3 of the company's submission.

*Mortality within the cohort flow*

It appears that there are errors in the cohort flow in terms of mortality. There is no mortality applied in the first year, but this is likely to have only a small impact upon the model outputs. Of greater concern is that those discontinuing are assumed not to have the mortality rate applied[i]. While the proportion of patients across the health states still sums to the overall cohort, this tends to result in a rate of attrition too high among patients remaining on treatment from year 2 onwards, which is to the detriment of the more effective treatment.

[i] For instance, within the *Markov_Trace_SEC_300 worksheet* cell K101 is the sum of those previously in PASI < 50 in cell K100 plus those discontinuing from cells L100:N100 minus those previously in PASI < 50 who die. But those discontinuing from cells L100 to N100 are not conditioned by death.

*Partial responders: PASI response evolution over time among week 12 PASI 50-74 patients*
With regard to the scenario analysis of partial responders with a PASI 50-74 at week 12 who remain on treatment, the assumption is that these patients maintain a PASI 50-74 response at week 52 and for as long thereafter as they remain on treatment. Data supplied by the company at clarification suggest that among the FIXTURE trial some patients fall back to a PASI <50 response at week 52, while others improve further into PASI 75-89 and PASI 90 responses.

**Table 52 PASI responses at week 52 among week 12 PASI50-74 patients**

| | SoC (n=[redacted]) | | Secukinumab (n=[redacted]) | | Etanercept (n=[redacted]) | |
|---|---|---|---|---|---|---|
| PASI < 50 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 50-74 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75-90 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 90 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 100 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

[redacted] [redacted]

**Figure 8 PASI response categories over time among week 12 PASI50-74 patients**

Therefore, the partial responder analysis may not fully account for the proportion of partial responders who would fall back into a PASI <50 response at week 52 given the first year discontinuation rate of 11.7%. But it may also fail to reflect some ongoing improvement among these patients within the biologic arms.

While the percentages for secukinumab appear superior to those of etanercept, there is no obvious means to differentiate this between the biologics in general and the company cautions against reading too much into the subgroup data due to the relatively small patient numbers. Any attempt to take this into account would be limited to the FIXTURE data scenario analysis.

*Responders: PASI response evolution over time among week 12 responders*
The company supplied data on the evolution of response among week 12 responders, as shown in Figures 9 and 10. The data underlying these Figures is presented in Appendix 2.

[redacted]

**Figure 9  PASI response categories over time among week 12 PASI 74-90 patients**

[redacted]

**Figure 10  PASI response categories over time among week 12 PASI 90 patients**

These data suggest that by week 52 quite a substantial proportion of patients in the secukinumab arm who achieve a week 12 PASI 75-89 response go on to improve further and move into the PASI 90 response category. The corresponding proportion of patients in the etanercept arm appears to be slightly lower. There is, however, quite a substantial proportion of patients who worsen by week 52 and fall back into the PASI <75 category.

The week 12 PASI 90 response appears to be maintained by the large majority of patients in the secukinumab arm.
The overall proportions falling back into a PASI <75 can be contrasted with the 11.7% discontinuation rate applied within the first year and the 20% discontinuation rate assumed thereafter. There may be some suggestion that a lower discontinuation rate may apply for secukinumab, in particular given the higher proportion of patients achieving a PASI 90 response.

*Serious adverse event rates*
Non-melanoma skin cancer (NMSC), melanoma and lymphoma are potentially serious adverse events. It is questionable how sensibly the rates of these diseases can be differentiated between the biologics, and between the biologics and SoC. The ERG clinical advisor explained that a clinical register has been established to explore this issue, but relevant data are not yet available.

ERG expert opinion also noted that since the biologics are immunosuppressive there is concern that cancer rates might be increased. There is also some evidence that rheumatoid arthritis may increase the risk of melanoma, albeit to a small degree. This has not yet been demonstrated in psoriasis. There is no evidence for lymphoma, and any effect is currently entirely theoretical. Phototherapy can also increase the risk of both NMSC and melanoma, and prolonged ciclosporin treatment has been associated with lymphoma.

*Quality of life and costs among partial responders*

It appears to be hard coded into the model to exclude both the utility gains and the costs of treatment of patients with a partial response who continue on treatment during the post induction period of the first year[j]. The base case assumes that these patients do not continue on treatment and so is unaffected by this.

*Quality of life: by PASI response status*

The submission references a utility report from IMS Health commissioned by the company. This report contains eight models, four being based upon EQ-5D QoL levels and four being based upon changes in EQ-5D QoL from baseline. The explanatory variables are variously:

- Which of the PASI response categories PASI <50, PASI 50-74, PASI 75-89 and PASI 90+ patients fall into;
- The difference between the baseline DLQI measurement and the mean baseline DLQI of the sample;
- Interaction terms of the PASI response categories multiplied by the difference between the baseline DLQI and the mean baseline DLQI;
- Whether the patients had psoriatic arthritis at baseline.

Note that within the utility analysis the PASI response categories were contemporaneous with the EQ-5D QoL measurement. The EQ-5D QoL was not modelled as a function of the PASI response categories at week 12.

The data collection timepoints were generally at 4, 8, 12, 24, 36 and 52 weeks, though the SCULPTURE trial provided additional measurements at 16, 20, 28, 32, 40, 44 and 48 weeks, and some additional values at follow-up. A complete case analysis was undertaken but the rationale for this remains unclear. Table 53 illustrates the parameter estimates and the goodness of fit statistics.

[j] For instance, within the *Markov_* worksheets cell W72 explicitly omits cell W80 from its sum with this being a very clear choice on the part of the modeller, with the corollary of this also applying in X72:AJ72. Given the obvious choice around this sum, it may be that the ERG misunderstands the reason for excluding W80 and the like from within these sums.

**Table 53 Parameter estimates of the original company EQ-5D model**

| Model | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| PASI 50-74 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75-89 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 90+ | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| DLQI | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| DLQI.(PASI 50-74) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| DLQI.(PASI 75-89) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| DLQI.(PASI 90+) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BPSA | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Constant | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| $R^2$ overall | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Wald $X^2$ | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

For the representative patient the difference between the baseline DLQI measurement and the mean baseline DLQI of the sample collapses to zero. Therefore, when calculating the quality of life values for the representative patient the DLQI and the DLQI*PASI interaction terms effectively disappear and the quality of life values shown in Table 54 result[k].

**Table 54 Quality of life values of the original company EQ-5D model**

| | EQ-5D QoL | | | | Δ EQ-5D QoL from baseline | | | |
|---|---|---|---|---|---|---|---|---|
| **Model** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| PASI < 50 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 50-74 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75-89 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 90+ | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

During the clarification process, the company acknowledged that "*689 observations on 10 patients*" had been incorrectly excluded from the analysis due to the way baseline DLQI had been recorded. Including these observations resulted in a second version of the utility report and the parameter estimates presented in Table 55. The second version of the utility report did not include any goodness of fit parameters.

[k] For model 4 and model 8 the parameter relating to whether a patient had psoriatic arthritis at baseline has been multiplied by the ERG by the weighted average proportion with psoriatic arthritis at baseline of [redacted]. Note that this estimate is quite heavily skewed by the inclusion of the FEATURE and the SCULPTURE trial, excluding them causing the weighted average to fall to [redacted].

**Table 55 Parameter estimates of the second company EQ-5D model**

| Model | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| PASI 50-74 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75-89 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 90+ | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| DLQI | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| DLQI.(PASI 50-74) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| DLQI.(PASI 75-89) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| DLQI.(PASI 90+) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BPSA | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Constant | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

The parameter estimates of the second utility report result in the quality of life estimates shown in Table 56.

**Table 56 Quality of life values of the second company EQ-5D model**

| | EQ-5D QoL | | | | Δ EQ-5D QoL from baseline | | | |
|---|---|---|---|---|---|---|---|---|
| **Model** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| PASI < 50 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 50-74 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75-89 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 90+ | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

A further two models were presented in the second utility report. These models explored the impact of applying a study effect. Adding these to the EQ-5D QoL levels model 3 resulted in FIXTURE, JUNCTURE and SCULPTURE being found to have statistically significant parameters associated with them. Adding the trial interaction effects to the EQ-5D QoL changes from baseline model 7 still resulted in SCULPTURE being found to have a statistically significant parameter, but not FIXTURE or JUNCTURE. The company state that a chi-squared test on the trial coefficients gave a p value of [redacted].

Adding the trial effects to model, the parameter estimates for the other explanatory variables were virtually identical between the model with and without the trial effects. The ERG can confirm that the estimates for the EQ-5D QoL changes from baseline are virtually the same as those of model 7.

The company argue that a complete case analysis is justified as this only excluded 125 patients out of a total of 3,366 (i.e. less than 5% of the total). However, the ERG struggle to understand the rationale for adopting a complete case analysis. The more natural approach would seem to be that even if a patient had some missing data at, say, week 24 to still include that patient's week 36 data if the week 36 data were complete. The company's justification is that this would have little impact upon results. It is unclear whether the company has conducted this analysis and its impact upon results.

Due to the EQ-5D QoL being modelled as a function of the contemporaneous PASI response rather than the PASI response at week 12 the resulting quality of life values are most relevant to those maintaining a given PASI response. They may be less relevant to those, for example, who achieve a PASI 75 response at week 12 but gradually lose this response over time.

It is unclear why there has been no exploration of a possible treatment effect; (e.g. active versus placebo) in addition to the impacts of PASI, DLQI etc. A treatment effect might arise from a number of sources. For instance, within the week 12 PASI <50 response subgroup the mean PASI response in the active treatment group might be larger than that in the placebo group. Side effects of active treatments might also have an impact. However, there are relatively few patients in the SoC arm with a PASI 75 response so differentiating quality of life values between the arms for this category might prove infeasible. The model also assumes that patients who discontinue treatment go on to SoC and receive the PASI <50 quality of life. The main impact of any exploration of a treatment effect might be to lower the SoC PASI <50 quality of life value applied.

The company justify the choice of the model 7 estimates for the base case on grounds of consistency with the company's submission for the TA146 adalimumab, rather than on any statistical grounds. Unfortunately, the $R^2$ and $X^2$ statistics that are provided within the utility report are not sufficient to discriminate between the models, and the report does not supply the log likelihoods.

*Serious adverse events: quality of life*

The company's submission states that the quality of life impacts of adverse events have been captured through the use of the EQ-5D data. This seems unlikely due to the fact that the EQ-5D data have been stratified by PASI response category but not by treatment arm. There is no obvious means by which the apparently lower rates of SAEs within the SoC arm compared with the active treatment arms would be reflected in the EQ-5D values for a given PASI response.

If the active treatments did give rise to higher rates of malignancies than those in the SoC arm, it would also be anticipated that the some of the quality of life impacts would be more prolonged than the duration of therapy. This would apply with particular force if there was a survival impact, even if the survival impact was small.

*Injection training resource use for the subcutaneous biologics*

TA103 etanercept assumed three one hourly sessions for training for self-injection, and the ERG clinical advisor agrees with this. This has only a small impact upon results.

*Proportion that can self-administer the subcutaneous biologics*

The assumption that all patients can self-administer their subcutaneous biologic therapy can be regarded as optimistic, even though the ERG clinical advisor indicates that the vast majority of patients can. If only a relatively small percentage of patients were unable to self-administer, this could add a reasonable amount to the costs of the subcutaneous biologics.

*Intermittent etanercept resource use*

The acceptability of the cost effectiveness of etanercept compared to SoC within TA103 may have rested upon an assumption of intermittent dosing. It should be noted, however, that while the EAG report for TA103 included intermittent etanercept dosing, it was excluded from the subsequent HTA monograph. ERG expert opinion suggests that in the UK it is likely that a biologic therapy will be used continuously if a patient is responding well to it.

The impact of intermittent etanercept dosing as per Lloyd et al (2009) cannot be explored within the company model, even though this appear to be a more appropriate model structure. The only scenario analysis that can be undertaken using the company model is to vary the dosing and cost of etanercept post induction. TA103[43] notes a cost per dose of £89.38 and annual costs of £9.327.44 and £6,933.67 for continuous and intermittent dosing respectively. Assuming that the intermittent dosing cost includes the 12-week induction period with 2 doses per week, this suggests an average of 1.33 doses per week thereafter.

*Application of SoC costs among those discontinuing treatment*

During the first year, the costs of day care, phototherapy, monitoring and tests within the SoC arm are £3,294. During subsequent years these costs fall to £3,073. During the first two years of treatment the direct drug cost for SoC is £807. This fall to £13 in subsequent years. Ignoring hospitalisation costs, which are flat over time, this suggests a cost difference between the first year and the second year of £221, between the first year and the third and subsequent years of £1,015 and between the second year and subsequent years of £794.

These costs are applied in the first, second and third and subsequent years of the model. They are not applied in the first, second and third and subsequent years that patients spend receiving SoC. Within the cohort flows of the biologics most patients typically cease biologic treatment and start SoC after the first or the second year, due to the annual 20% of initial responders assumed to cease treatment. Consequently, patients who start SoC in the second, third and subsequent years avoid the initially higher costs of SoC treatment[l]. This will bias the analysis against SoC.

The correction of the cost calculations within the cohort flow to take this into account would be considerably time consuming. The simpler method employed by the ERG to explore the possible impact of this was to set the first year and second year costs of SoC to be equal to those of the third and subsequent years.

*Serious adverse events: resource use*

The company's submission costs malignancies as incurring a single inpatient stay, with the costs of these being derived from NHS reference costs. In the opinion of the ERG this seems likely to have missed a number of cost elements which may be quite significant, such as ongoing drug costs. It is also unclear whether all patients would only require a single inpatient stay: some may have none, others may have multiple stays. It is beyond the scope of the ERG report to perform a costing analysis of the identified malignancies (e.g. melanoma, lymphoma and non-melanoma skin cancer). It seems probable that the costs of these have been underestimated.

### *5.4 Exploratory and sensitivity analyses undertaken by the ERG*

The ERG has revised the company base case to:

- Correct the mortality calculations within the cohort flow[m];
- Revise the QALY calculations for those with a PASI 50-74 response during the first year to apply the PASI <50 quality of life value for the post induction period[n];

[l] This is most easily seen by tracing the dependents of e.g. cell F33 within one of the biologic cohort flow worksheets. There are only dependent cells in the second year; i.e. row 101, and as a consequence any patients discontinuing biologic treatment after the second year do not have these costs applied.

[m] Implemented within the cohort flow calculations by setting cell K101=(K100+(SUM(L100:N100)*H101))*(1-G101), cell L101=(L100-(L100*$H101))*(1-$G101), cell M101=(M100-(M100*$H101))*(1-$G101) and cell N101=(N100-(N100*$H101))*(1-$G101) and cutting and pasting these formulae into cells K102:N114.

[n] Implemented within the *Markov_* worksheets by setting cell L79= IF(Clin_Data_Source=5,16, IF(Clin_Data_Source=1,12,12)) with the exception of adalimumab where L79= IF(Clin_Data_Source=5,16,

- Include the costs and quality of life benefits from those continuing treatment between induction and the end of the first year for the sensitivity analysis that applied this[o];
- Remove the IV infusion costs from secukinumab[p];
- Include the SAE costs for those on biologics for the first year[q];
- Remove the hospitalisation cost for those remaining on drug therapy in the SoC arm with a PASI 75 response[r];
- Condition the costs of hospitalisation in the first year among those with a PASI 50 response by the length of the maintenance period;
- Revise the quality of life values to reflect those supplied at clarification[s];
- Revise the number of nurse hours for self-administration of subcutaneous biologics from one to three[t];
- Revise the mean patient weight to be the 83.3kg of the FIXTURE trial[u];
- Revise the annual number of secukinumab administrations from 12 to 13[v];
- Revise the first year post induction ustekinumab administrations from 4 to 3[w].

Due to the uncertainties about resource use in the SoC arm two scenarios are presented.

- The ERG preferred base case that relies upon the UK estimates of Fonia et al,[58] which suggests that SoC is associated with an average increase of 5 inpatient days, an average increase of 3 phototherapy sessions and no increase in the average number of day case attendances[x];

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IF(Clin_Data_Source=1,12,16)) and infliximab where L79= IF(Clin_Data_Source=5,16, IF(Clin_Data_Source=1,12,10)), and M79=52-L79,

[o] Implemented within the *Marko_* worksheets sums of W72: AJ72 by making them the sum of e.g. W76:W86.

[p] Implemented within the *Monitoring_cost_calculations* worksheet by setting cell H31= CHOOSE(Induction_period,U31,AV31)

[q] Implemented within the *Markov_Trace_* worksheets, with the exception of the *Markov_Trace_SoC* worksheet, by revising cell F56=SUM($AJ$72,$AJ$96:$AK$96)+F23

[r] Implemented within the *Markov_Trace_SoC* worksheet by setting cell F23=0

[s] Implemented within the Utility_calculations worksheet by setting cells ?? equal to the parameter values supplied at clarification. Note that this retain the old choleski decomposition matrix and so is not entirely correct for any probabilistic modelling, though the it seems likely to the ERG any biases introduced to the probabilistic modelling are likely to be slight.

[t] Implemented in the *Monitoring_costs_calculation* worskeet by setting cells G16, G17, G18, G20 and G21 equal to 3

[u] Implemented in the *Inputs* worksheet by setting cell I177=83.3.

[v] Implemented in the *Inputs* worksheet by setting cell I166=13.

[w] Implemented in the *Inputs* worksheet by setting cell G180=3 and G184=3.

[x] Implemented in the *Inputs* worksheet by setting cell I201 and I290 equal to the required value and if this is zero also setting cell T290 to zero, setting cell I265=3 and conditioning cell I202 by ¾, and setting I143 to the required value.

- An analysis based upon the company base case assumptions of an average increase of 10.7 inpatient days, an average increase of 3.84 phototherapy sessions and an average increase of 5 day case attendances.

**Table 57 Base case analysis: ERG SoC resource use scenario**

| | Tx | Medical | SAE | Total | QALYs | Δ Cost | Δ QALY | ICER |
|---|---|---|---|---|---|---|---|---|
| SoC | £1,857 | £6,172 | £20,424 | £28,453 | 6.479 | | | |
| Etan. | £14,804 | £5,878 | £18,087 | £38,768 | 6.629 | £10,315 | 0.150 | £68,730 |
| Adal. | £20,740 | £5,832 | £16,512 | £43,084 | 6.719 | £4,316 | 0.090 | £48,165 |
| Ust 45 | £26,433 | £5,594 | £14,973 | £46,999 | 6.801 | £3,916 | 0.083 | £47,453 |
| Ust 90 | £27,895 | £5,551 | £14,547 | £47,993 | 6.829 | £994 | 0.028 | £35,919 |
| Secukin. | [redacted] | [redacted] | [redacted] | £48,540 | 6.860 | £547 | 0.031 | £17,717 |
| Infl. | £40,346 | £7,313 | £15,569 | £63,227 | 6.856 | £14,688 | -0.004 | Dominated |

Secukinumab extendedly dominates the other biologics and has a cost effectiveness estimate compared to SoC of £52,760 per QALY. The cost effectiveness estimates of secukinumab compared to etanercept, adalimumab, ustekinumab 45mg and ustekinumab 90mg are £42,367, £38,684, £26,321 and £17,717 per QALY respectively.

The ERG scenario analysis that reduces the costs of SoC to be in line with what appears to be implied by Fonia et al[58] greatly worsens the cost effectiveness estimate of secukinumab compared to both SoC and the other subcutaneous biologics. The worsening in the cost effectiveness estimate against SoC seems reasonable given the assumptions feeding into the model.

The worsening in the cost effectiveness estimate for the comparison with the other biologics may be in part a function of the model structure, which assumes that those failing on one biologic go onto SoC rather than trialling another biologic. Due to the inferior response rates for the other biologics, these have a higher proportion of patients on SoC than does the secukinumab arm. Some of the worsening of the cost effectiveness of secukinumab when compared to the other biologics is perhaps more a function of its poor cost effectiveness relative to SoC than to the other biologics per se. What a model, which considered sequences of treatments, would consider as the most cost effective biologic to try first if the biologics are in general not cost effective against SoC, it is questionable.

**Table 58 Base case analysis: company SoC resource use scenario**

| | Tx | Medical | SAE | Total | QALYs | Δ Cost | Δ QALY | ICER |
|---|---|---|---|---|---|---|---|---|
| SoC | £1,857 | £26,500 | £43,707 | £72,064 | 6.479 | | | |
| Etan. | £14,804 | £22,543 | £38,338 | £75,685 | 6.629 | £3,621 | 0.150 | £24,126 |
| Adal. | £20,740 | £21,106 | £34,907 | £76,753 | 6.719 | £1,068 | 0.090 | £11,921 |
| Secukin. | [redacted] | [redacted] | [redacted] | £77,737 | 6.860 | £984 | 0.141 | £6,979 |
| Ust 45 | £26,433 | £19,679 | £31,916 | £78,028 | 6.801 | £291 | -0.059 | Dominated |
| Ust 90 | £27,895 | £19,247 | £30,999 | £78,141 | 6.829 | £404 | -0.031 | Dominated |
| Infl. | £40,346 | £20,644 | £31,560 | £92,550 | 6.856 | £14,813 | -0.004 | Dominated |

Secukinumab extendedly dominates etanercept and adalimumab, and is estimated to have a cost effectiveness compared to SoC of £14,902 per QALY. The cost effectiveness estimates of secukinumab compared to etanercept and adalimumab are £8,899 and £6,979 per QALY respectively.

Results are sensitive to the SoC resource use assumptions. Since the ERG scenario and the company scenario phototherapy sessions are broadly in line, these can be ignored. A cross tabulation of the cost effectiveness of secukinumab compared with SoC can then be presented for differing annual numbers of day care admissions and inpatient days for those on SoC with a PASI <50 response. The cost effectiveness estimates of the approximate ERG and company SoC resource use assumptions are highlighted, as are the values corresponding to approximate willingness to pay values of £30,000 per QALY and £20,000 per QALY.

**Table 59 ICERs vs SoC for different annual SoC day cases and inpatient days**

| | | SoC mean annual inpatient LoS | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| SoC day cases | 0 | **£52,760** | £49,368 | £45,976 | £42,584 | £39,192 | £35,800 | **£32,408** |
| | 1 | £49,191 | £45,799 | £42,407 | £39,015 | £35,623 | **£32,231** | £28,839 |
| | 2 | £45,622 | £42,230 | £38,838 | £35,446 | **£32,054** | £28,662 | £25,270 |
| | 3 | £42,053 | £38,661 | £35,269 | **£31,877** | £28,485 | £25,093 | **£21,701** |
| | 4 | £38,484 | £35,092 | **£31,699** | £28,307 | £24,915 | **£21,523** | £18,131 |
| | 5 | £34,914 | **£31,522** | £28,130 | £24,738 | **£21,346** | £17,954 | **£14,562** |
| | 6 | **£31,345** | £27,953 | £24,561 | **£21,169** | £17,777 | £14,385 | £10,993 |

Due to the similar day case unit cost and cost per inpatient day, the cost effectiveness estimates along each diagonal are roughly equal. If the mean annual numbers of day case admissions and days as an inpatient together total around 11 the cost effectiveness estimate

for secukinumab compared to SoC is around £30,000 per QALY. If the mean annual numbers of day case admissions and days as an inpatient together total around 14 the cost effectiveness estimate for secukinumab compared to SoC is around £20,000 per QALY.

Sensitivity analyses explore the impact of:

- Etanercept requiring only 1.33 administrations rather than 2.00 administrations after induction[y], as inferred by the ERG from TA103.[43] Note that this is perhaps an extreme value, and it might be more reasonable to use the 1.82 of Lloyd et al 2009;[57]
- Reducing the secukinumab discontinuation rate subsequent to the first year to 15%[z];
- Varying the discontinuation rate subsequent to the first year to 15% and 25%[aa];
- Setting the first year discontinuation rate to zero[bb];
- An arbitrary increase in mortality risk of 20% associated with psoriasis[cc];
- Flattening the SoC costs so that costs in years one and two of the model are the same as in subsequent years[dd];
- Arbitrarily doubling the SAE costs of the biologics[ee];
- Revising the quality of life impacts to be from the various NICE assessments or EQ-5D models submitted by the company[ff];

[y] Implemented within the *Tx_cost_calculations* by conditioning cells F180 and E189 by 1.33/2.
[z] Implemented within the *Markov_trace_SEC_300* worksheet by setting cell F19=0.15.
[aa] Implemented within the *Drop_out_calculations* worksheet by setting cell H30 equal to the appropriate value.
[bb] Implemented within the *Drop_out_calculations* worksheet by setting cell H23=0.
[cc] Implemented within the *Mortality_Inputs* worksheet by multiplying the values within cells N9:N89 by 1.2.
[dd] Implemented within the Monitoring_costs_calculations worksheet by setting cells Q22=12/52*P50 and P31=(52-12)/52*P50, and within the Tx_cost_calculation worksheet by setting cells E238=12/52*H238, F238=(52-12)/52*h238 and G238=H238.
[ee] Implemented within the *Adverse_event_calculations* worksheet by doubling the values in cells G30:G32.
[ff] Implemented within the *Utility_calculations* worksheet by setting cells G11:G15 to the relevant values.

**Table 60a ERG SoC costs scenario: sensitivity analyses**

| | versus SoC | | | versus etanarcept | | | versus adalimumab | | |
|---|---|---|---|---|---|---|---|---|---|
| | Δ £ | Δ Q | ICER | Δ £ | Δ Q | ICER | Δ £ | Δ Q | ICER |
| Base case | £20,087 | 0.381 | £52,760 | £9,771 | 0.231 | £42,368 | £5,456 | 0.141 | £38,685 |
| Etan. Dose | | | | £13,669 | 0.231 | £59,268 | | | |
| Sec. disc 15% | £23,311 | 0.454 | £51,376 | £12,996 | 0.304 | £42,798 | £8,680 | 0.214 | £40,552 |
| All disc 15% | £23,311 | 0.454 | £51,376 | £11,394 | 0.272 | £41,819 | £6,371 | 0.167 | £38,233 |
| All disc 25% | £17,569 | 0.324 | £54,298 | £8,504 | 0.198 | £42,975 | £4,741 | 0.121 | £39,188 |
| No 1st yr disc. | £22,211 | 0.421 | £52,778 | £10,840 | 0.254 | £42,742 | £6,069 | 0.155 | £39,130 |
| Mort mult 1.2 | £20,063 | 0.380 | £52,758 | £9,760 | 0.230 | £42,372 | £5,449 | 0.141 | £38,688 |
| Flat SoC cost | £20,424 | 0.381 | £53,645 | £9,762 | 0.231 | £42,327 | £5,450 | 0.141 | £38,646 |
| SAE cost | £20,355 | 0.381 | £53,466 | £9,717 | 0.231 | £42,134 | £5,348 | 0.141 | £37,924 |
| QoL | | | | | | | | | |
| TA103 | £20,087 | 0.415 | £48,391 | £9,771 | 0.242 | £40,423 | £5,456 | 0.145 | £37,654 |
| TA146 | £20,087 | 0.388 | £51,731 | £9,771 | 0.247 | £39,546 | £5,456 | 0.157 | £34,859 |
| TA134 | £20,087 | 0.755 | £26,610 | £9,771 | 0.443 | £22,066 | £5,456 | 0.265 | £20,613 |
| TA180 | £20,087 | 0.541 | £37,102 | £9,771 | 0.319 | £30,603 | £5,456 | 0.192 | £28,416 |
| EQ_5D | | | | | | | | | |
| Model 3 | £20,087 | 0.391 | £51,402 | £9,771 | 0.237 | £41,299 | £5,456 | 0.145 | £37,709 |
| Model 5 | £20,087 | 0.375 | £53,511 | £9,771 | 0.228 | £42,940 | £5,456 | 0.139 | £39,187 |
| Model 6 | £20,087 | 0.375 | £53,510 | £9,771 | 0.228 | £42,943 | £5,456 | 0.139 | £39,190 |
| Model 7 | £20,087 | 0.381 | £52,760 | £9,771 | 0.231 | £42,368 | £5,456 | 0.141 | £38,685 |
| Model 8 | £20,087 | 0.381 | £52,760 | £9,771 | 0.231 | £42,368 | £5,456 | 0.141 | £38,685 |
| Original | £20,087 | 0.389 | £51,689 | £9,771 | 0.235 | £41,542 | £5,456 | 0.144 | £37,949 |

**Table 60b ERG SoC costs scenario: sensitivity analyses**

| | versus ustekinumab 45mg | | | versus ustekinumab 90mg | | | versus infliximab | | |
|---|---|---|---|---|---|---|---|---|---|
| | Δ £ | Δ Q | ICER | Δ £ | Δ Q | ICER | Δ £ | Δ Q | ICER |
| Base case | £1,540 | 0.059 | £26,321 | £547 | 0.031 | £17,717 | -£14,688 | 0.004 | Dom. |
| Sec. disc 15% | £4,765 | 0.132 | £36,223 | £3,771 | 0.104 | £36,304 | -£11,463 | 0.077 | Dom. |
| All disc 15% | £1,805 | 0.069 | £26,031 | £602 | 0.037 | £16,465 | -£17,119 | 0.004 | Dom. |
| All disc 25% | £1,334 | 0.050 | £26,651 | £504 | 0.026 | £19,090 | -£12,784 | 0.003 | Dom. |
| No 1st yr disc. | £1,766 | 0.064 | £27,394 | £638 | 0.034 | £18,771 | -£16,332 | 0.004 | Dom. |
| Mort mult 1.2 | £1,538 | 0.058 | £26,324 | £546 | 0.031 | £17,727 | -£14,671 | 0.004 | Dom. |
| Flat SoC cost | £1,538 | 0.059 | £26,283 | £546 | 0.031 | £17,679 | -£14,688 | 0.004 | Dom. |
| SAE cost | £1,699 | 0.059 | £29,031 | £700 | 0.031 | £22,693 | -£15,960 | 0.004 | Dom. |
| QoL | | | | | | | | | |
| TA103 | £1,540 | 0.058 | £26,366 | £547 | 0.031 | £17,915 | -£14,688 | 0.003 | Dom. |
| TA146 | £1,540 | 0.067 | £22,857 | £547 | 0.036 | £15,173 | -£14,688 | 0.004 | Dom. |
| TA134 | £1,540 | 0.107 | £14,404 | £547 | 0.056 | £9,794 | -£14,688 | 0.007 | Dom. |
| TA180 | £1,540 | 0.078 | £19,743 | £547 | 0.041 | £13,389 | -£14,688 | 0.005 | Dom. |
| EQ_5D | | | | | | | | | |
| Model 3 | £1,540 | 0.060 | £25,664 | £547 | 0.032 | £17,275 | -£14,688 | 0.004 | Dom. |
| Model 5 | £1,540 | 0.058 | £26,647 | £547 | 0.030 | £17,933 | -£14,688 | 0.004 | Dom. |
| Model 6 | £1,540 | 0.058 | £26,651 | £547 | 0.030 | £17,935 | -£14,688 | 0.004 | Dom. |
| Model 7 | £1,540 | 0.059 | £26,321 | £547 | 0.031 | £17,717 | -£14,688 | 0.004 | Dom. |
| Model 8 | £1,540 | 0.059 | £26,321 | £547 | 0.031 | £17,717 | -£14,688 | 0.004 | Dom. |
| Original | £1,540 | 0.060 | £25,836 | £547 | 0.031 | £17,394 | -£14,688 | 0.004 | Dom. |

**Table 61a Company SoC costs scenario: sensitivity analyses**

| | versus SoC | | | versus etanarcept | | | versus adalimumab | | |
|---|---|---|---|---|---|---|---|---|---|
| | Δ £ | Δ Q | ICER | Δ £ | Δ Q | ICER | Δ £ | Δ Q | ICER |
| Base case | £5,673 | 0.381 | £14,902 | £2,052 | 0.231 | £8,899 | £984 | 0.141 | £6,979 |
| Etan. Dose | | | | £5,950 | 0.231 | £25,800 | | | |
| Sec. disc 15% | £6,174 | 0.454 | £13,608 | £2,554 | 0.304 | £8,409 | £1,485 | 0.214 | £6,939 |
| All disc 15% | £6,174 | 0.454 | £13,608 | £2,214 | 0.272 | £8,127 | £1,038 | 0.167 | £6,231 |
| All disc 25% | £5,287 | 0.324 | £16,341 | £1,929 | 0.198 | £9,748 | £944 | 0.121 | £7,802 |
| No 1st yr disc. | £5,940 | 0.421 | £14,116 | £2,125 | 0.254 | £8,378 | £996 | 0.155 | £6,423 |
| Mort mult 1.2 | £5,667 | 0.380 | £14,901 | £2,051 | 0.230 | £8,906 | £984 | 0.141 | £6,986 |
| Flat SoC cost | £6,064 | 0.381 | £15,928 | £1,973 | 0.231 | £8,556 | £938 | 0.141 | £6,649 |
| SAE cost | £5,942 | 0.381 | £15,607 | £1,998 | 0.231 | £8,665 | £877 | 0.141 | £6,219 |
| QoL | | | | | | | | | |
| TA103 | £5,673 | 0.415 | £13,668 | £2,052 | 0.242 | £8,491 | £984 | 0.145 | £6,793 |
| TA146 | £5,673 | 0.388 | £14,611 | £2,052 | 0.247 | £8,307 | £984 | 0.157 | £6,289 |
| TA134 | £5,673 | 0.755 | £7,516 | £2,052 | 0.443 | £4,635 | £984 | 0.265 | £3,719 |
| TA180 | £5,673 | 0.541 | £10,479 | £2,052 | 0.319 | £6,428 | £984 | 0.192 | £5,127 |
| EQ_5D | | | | | | | | | |
| Model 3 | £5,673 | 0.391 | £14,518 | £2,052 | 0.237 | £8,675 | £984 | 0.145 | £6,803 |
| Model 5 | £5,673 | 0.375 | £15,114 | £2,052 | 0.228 | £9,020 | £984 | 0.139 | £7,070 |
| Model 6 | £5,673 | 0.375 | £15,114 | £2,052 | 0.228 | £9,020 | £984 | 0.139 | £7,071 |
| Model 7 | £5,673 | 0.381 | £14,902 | £2,052 | 0.231 | £8,899 | £984 | 0.141 | £6,979 |
| Model 8 | £5,673 | 0.381 | £14,902 | £2,052 | 0.231 | £8,899 | £984 | 0.141 | £6,979 |
| Original | £5,673 | 0.389 | £14,599 | £2,052 | 0.235 | £8,726 | £984 | 0.144 | £6,847 |

**Table 61b Company SoC costs scenario: sensitivity analyses**

| | versus ustekinumab 45mg | | | versus ustekinumab 90mg | | | versus infliximab | | |
|---|---|---|---|---|---|---|---|---|---|
| | Δ £ | Δ Q | ICER | Δ £ | Δ Q | ICER | Δ £ | Δ Q | ICER |
| Base case | -£291 | 0.059 | Dom. | -£404 | 0.031 | Dom. | -£14,813 | 0.004 | Dom. |
| Sec. disc 15% | £210 | 0.132 | £1,597 | £97 | 0.104 | £932 | -£14,312 | 0.077 | Dom. |
| All disc 15% | -£376 | 0.069 | Dom. | -£530 | 0.037 | Dom. | -£17,268 | 0.004 | Dom. |
| All disc 25% | -£224 | 0.050 | Dom. | -£305 | 0.026 | Dom. | -£12,890 | 0.003 | Dom. |
| No 1st yr disc. | -£303 | 0.064 | Dom. | -£437 | 0.034 | Dom. | -£16,473 | 0.004 | Dom. |
| Mort mult 1.2 | -£290 | 0.058 | Dom. | -£403 | 0.031 | Dom. | -£14,796 | 0.004 | Dom. |
| Flat SoC cost | -£310 | 0.059 | Dom. | -£414 | 0.031 | Dom. | -£14,814 | 0.004 | Dom. |
| SAE cost | -£132 | 0.059 | Dom. | -£251 | 0.031 | Dom. | -£16,085 | 0.004 | Dom. |
| QoL | | | | | | | | | |
| TA103 | -£291 | 0.058 | Dom. | -£404 | 0.031 | Dom. | -£14,813 | 0.003 | Dom. |
| TA146 | -£291 | 0.067 | Dom. | -£404 | 0.036 | Dom. | -£14,813 | 0.004 | Dom. |
| TA134 | -£291 | 0.107 | Dom. | -£404 | 0.056 | Dom. | -£14,813 | 0.007 | Dom. |
| TA180 | -£291 | 0.078 | Dom. | -£404 | 0.041 | Dom. | -£14,813 | 0.005 | Dom. |
| EQ_5D | | | | | | | | | |
| Model 3 | -£291 | 0.060 | Dom. | -£404 | 0.032 | Dom. | -£14,813 | 0.004 | Dom. |
| Model 5 | -£291 | 0.058 | Dom. | -£404 | 0.030 | Dom. | -£14,813 | 0.004 | Dom. |
| Model 6 | -£291 | 0.058 | Dom. | -£404 | 0.030 | Dom. | -£14,813 | 0.004 | Dom. |
| Model 7 | -£291 | 0.059 | Dom. | -£404 | 0.031 | Dom. | -£14,813 | 0.004 | Dom. |
| Model 8 | -£291 | 0.059 | Dom. | -£404 | 0.031 | Dom. | -£14,813 | 0.004 | Dom. |
| Original | -£291 | 0.060 | Dom. | -£404 | 0.031 | Dom. | -£14,813 | 0.004 | Dom. |

As would be anticipated, revising the etanercept dosing to be in line with that inferred from TA103 for intermittent dosing greatly worsens the costs effectiveness of secukinumab compared to etanercept. The estimate rises from £42,368 per QALY to £59,268 per QALY within the ERG SoC costs scenario, and from £8,899 per QALY to £25,800 per QALY within the company SoC cost scenario.

The cost effectiveness of secukinumab compared to SoC is not particularly sensitive to the rate of discontinuations subsequent to induction, which the ERG finds slightly surprising. If secukinumab has a lower discontinuation rate than the other biologics this tends to worsen the cost effectiveness of secukinumab, particularly compared to ustekinumab.

Results are not sensitivity to an arbitrary 1.2 mortality multiplier for psoriasis being introduced. They are also not sensitive to the cost of SoC in the first two years being flattened out, this being introduced to explore an apparent bias in the model structure.

The different EQ-5D models of quality of life estimated by the company from its trial data have little impact upon results. A larger impact occurs when the quality of life values used in previous NICE assessments are applied. The values of the TA103 etanercept and efalizumab,[43] have some impact and improve the cost effectiveness estimates, though these are typically not large and depend upon the comparator being considered. It is a similar scenario with the values of the TA146 adalimumab,[44] although in this case the impacts are slightly larger. Much more dramatic are the values from the TA134 infliximab,[46] and the TA180 ustekinumab,[45] with these significantly improving the cost effectiveness estimates, particularly those of TA134.[46]

### *5.5 Conclusions of the cost effectiveness section*

The company conducted what appears to be a good literature review of the cost effectiveness, resource use and quality of life literature in the area. The reporting of this literature review within the company's submission has two main deficiencies:

- The summary of Woolacott et al 2005[59] fails to mention that the cost effectiveness estimates for etanercept relate to intermittent dosing. If intermittent etanercept dosing still occurs, this will significantly worsen the cost effectiveness of secukinumab compared to etanercept. It also needs to be acknowledged that Woolacott et al 2006[56] do not apply intermittent etanercept dosing.
- The summary of Fonia et al 2010[58] fails to mention the estimates for pre and post introduction of biologic mean day case admissions and mean inpatient days.

The key variables within the economic analysis are:

- The clinical effectiveness estimates;
- The direct drug costs of the biologics;
- The mean annual increase in day case admissions for those on SoC with a PASI <50 response compared to those with a PASI 75 response;
- The mean annual increase in inpatient days for those on SoC with a PASI <50 response compared to those with a PASI 75 response.

The ERG revisions of the company model tend to worsen the cost effectiveness estimates compared with those presented in the company's submission. When the ERG preferred resource use estimates for SoC - as drawn from Fonia et al 2010[58] - are applied, the cost effectiveness estimates are above the usual NICE thresholds. When the company preferred resource use estimates for SoC are applied, the cost effectiveness estimates remain within the usual NICE thresholds.

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

The ERG has made a number of revisions to the economic model, and for the ERG SoC resource use scenario based upon Fonia et al 2010[58] this significantly worsens the cost effectiveness estimate for secukinumab compared to SoC to £52,760 per QALY. For the company SoC resource use scenario, the ERG revisions to the company model still worsen the cost effectiveness estimate for secukinumab compared to SoC from £7,076 per QALY to £14,902 per QALY.

If among SoC patients with a PASI <50 response the mean annual numbers of day case admissions and the days as an inpatient total around 1, the cost effectiveness estimate for secukinumab compared to SoC is around £30,000 per QALY. If this total is around 14 days, the cost effectiveness estimate for secukinumab compared to SoC is around £20,000 per QALY.

For the ERG SoC resource use scenario the pairwise cost effectiveness estimates of secukinumab compared to etanercept, adalimumab, ustekinumab 45mg and ustekinumab 90mg are £42,367, £38,684, £26,321 and £17,717 per QALY respectively. Secukinumab is estimated to dominate infliximab.

For the company SoC resource use scenario the pairwise cost effectiveness estimates of secukinumab compared to etanercept and adalimumab are £8,899 and £6,979 per QALY respectively. Secukinumab is estimated to dominate ustekinumab 45mg, ustekinumab 90mg and infliximab.

The application of the quality of life values from the other NICE assessments in the area also tends to improve the cost effectiveness estimates. This applies particularly to the quality of life values from the TA180 ustekinumab,[45] and the TA134 infliximab.[46]

Results are not particularly sensitive to the other variables explored by the ERG, though varying the clinical effectiveness inputs and the direct drug costs of the biologics would obviously have an impact.

There are a number of issues that cannot be quantified within the current modelling:

- The model structure assumes that only one biologic is tried and when this fails the patient reverts to SoC. ERG expert opinion suggests that patients failing on one biologic tend to be treated with another one. Modelling a sequence of treatments with biologics would explore whether the treatment sequences are cost effective compared to SoC, whether adding an additional biologic within the treatment sequences is cost effective and what the most cost effective sequencing of biologics was. While speculation on the part of the ERG:
    - If the individual biologics are not cost effective compared to SoC, it is difficult to imagine that a treatment sequence of these biologics will be cost effective compared to SoC.
    - If secukinumab is not individually cost effective compared to SoC and treatment sequences of current biologics are not cost effective compared to SoC, it is difficult to imagine that adding secukinumab to a treatment sequence of current biologics will be cost effective compared to SoC.
    - If secukinumab is cost effective compared to the other biologics but is not cost effective compared to SoC, it is not difficult to imagine that if secukinumab displaces an existing biologic that the cost effectiveness of that treatment sequence compared to SoC will improve. However, if it is an addition to the treatment sequence, it is more difficult to imagine that this will improve the cost effectiveness of the treatment sequence.
    - If secukinumab is cost effective compared to SoC, it is not difficult to imagine that adding secukinumab to a treatment sequence will improve the cost effectiveness of that treatment sequence compared to SoC.
- The model may strip some of the placebo effect from SoC while retaining it for more effective treatments. If a patient receiving SoC has a PASI 50-75 response but would have had a PASI 75 response on a biologic, it could be argued that the biologic PASI 75 response is in some sense on the back of the placebo PASI 50-75 response. Those with a PASI 50-75 response are assumed to fall back to a PASI <50 response while those with a PASI 75 response are assumed to maintain it. If this is a concern, it seems likely to have biased the ICER(s) in favour of secukinumab.
- The analysis of the EQ-5D data does not explore a treatment effect. It is possible that the distribution among week 12 PASI <50 patients in the SoC arm is worse than that

in the biologic arms, given the other response categories' data. This might suggest a lower EQ-5D QoL value in the PASI <50 SoC arm patients than in the PASI <50 biologic arms patients, though whether this could be demonstrated statistically is a moot point. If this occurred and was applied within the modelling it could increase the patient benefits from the biologics compared to SoC. However, there would be problems in terms of taking the two biologics into consideration. The possible existence of such an effect is pure speculation by the ERG. If this is a concern, it seems likely to have biased the ICER(s) against secukinumab.

- The model does not take into account possible changes in PASI response categories among week 12 PASI 75-89 responders between week 12 and week 52. Given the discontinuation rate of the model which could be assumed to apply to those with a worsening PASI response, there is a suggestion that this might tend to increase the patient benefits from secukinumab and etanercept over SoC as some of these patients may move into the PASI 90 response category. If this is a concern, it seems likely to have biased the ICER(s) in favour of SoC.
- The ERG has not parsed the partial responder analysis of the company. But this apparently assumes that those with a PASI 50-74 response continue on treatment, in effect lowering the bar for a response to a PASI 50. It may have been appropriate to have considered the evolution of PASI responses within this category. The model structure might then have had two response evaluations: one at 12 weeks when week 12 PASI <50 response patients have treatment withdrawn, and one at 52 weeks when week 52 PASI <75 response patients have treatment withdrawn. This might be the more logical partial PASI response model structure. This analysis would only be possible for the FIXTURE trial comparators. This might increase the patient benefits from secukinumab over both etanercept and SoC. But as the company points out, patient numbers within the week 12 PASI 50-74 category are not large and some caution would be required. If this is a concern, it seems likely to have biased the ICER(s) in favour of SoC

# 7 OVERALL CONCLUSIONS

The clinical evidence base for secukinumab 300mg for the treatment of moderate to severe psoriasis consists of five phase III RCTs - FIXTURE, ERASURE, JUNCTURE, FEATURE and SCULPTURE. Compared with placebo, the four main trials, FIXTURE, ERASURE, JUNCTURE, and FEATURE, showed consistent levels of secukinumab 300mg efficacy with regard to PASI and IGA responses.

The FIXTURE trial included also a head-to-head comparison with etanercept. Efficacy outcomes were significantly better in patients treated with secukinumab compared with those treated with etanercept.

A network meta-analysis of the PASI outcome including data from 27 RCTs from 10 to16 weeks provided evidence that secukinumab 300 mg performed favourably when compared with other comparators including placebo, etanercept 50 mg, adalimumab and ustekinumab 45 mg. It also showed that secukinumab 300 mg performed similarly to infliximab.

With regard to the economic model, the main differences between ERG and the company, which affect the size of the ICERs, are whether, in order of importance:

- The resource use for those on and reverting to SoC with a PASI<50 should be sourced from Fonia et al 2010[58] or from the costing template of CG 15341 and company expert opinion.
- Secukinumab annual dosing requires 13 administrations or 12 administrations.
- Ustekinumab first year post induction dosing is 3 administrations or 4 administrations.
- First year hospitalisation costs for those with a PASI 50 response should or should not be conditioned by the duration of the post induction period.
- Hospitalisation costs should or should not be removed from PASI 75 responders in the SoC arm.

Strengths of the submission are:

- Inclusion of relevant studies to address the objectives of this assessment;
- Appropriate methods to assess the clinical evidence base including the recommended methods for the conduct of network meta-analysis for an ordinal outcome;

- A good identification of the previous STAs and cost effectiveness estimates previously undertaken, and of the literature about resource use and quality of life;
- A clear and comprehensive summary of the economic model structure and its inputs within the written submission which, save for a few discrepancies, corresponds with the submitted electronic model;
- A well-constructed electronic model that is transparently presented and simple to parse;
- A de novo model which reflects much of the structure of those of previous assessments, including the TA103;[43]
- The analysis of the trials' EQ-5D data;
- A good set of one way sensitivity analyses and scenario analyses.

Weaknesses of the submission are:

- The lack of head-to-head comparisons versus active biologic treatments, apart from etanercept;
- Some issues of transparency/consistency over which comparators and doses were eligible for the NMA;
- Some uncertainty on which studies' data were used in the 12 week scenario NMA;
- Some coyness in the summary of the identified economic literature, particularly of the UK resource use study of Fonia et al 2010;[58]
- A model which assumes that patients try only one biologic and if they fail on this they revert to SoC. ERG expert opinion suggests that patients failing on one biologic go on to try another, with patients often working through a sequence of biologics;
- An apparent lack of correspondence between the patients in the HES resource use data the company relies upon for length of stay data and the company budget impact analysis;

There are some uncertainties about whether:

- Intermittent use etanercept should be considered. ERG expert opinion suggests that while possible this is not typical;
- The model strips some of the placebo effect from the SoC arm while retaining it for the biologics;

- The analysis of the EQ-5D data should have explored a treatment effect, and what impact this could have had upon the modelling;
- Not exploring the assumption that all patients can self-administer the subcutaneous biologics. It would not require a large percentage of patients to not be able to do so to add a reasonable amount to the costs of the subcutaneous biologics;
- A significant proportion of those with a week 12 PASI 75-89 response on the biologics continue to improve thereafter and achieve a week 52 PASI 90 response;
- A significant proportion of those with a week 12 PASI 50-74 response on the biologics continue to improve thereafter and achieve a week 52 PASI 75 response, and whether this could justify a partial responder analysis;
- The partial responder analysis of the company is reliable. Even though time constraints have prevented the ERG from parsing this aspect of the model in details, some concerns have arisen around it.

### *7.1 Implications for research*

A head-head comparison of secukinumab and ustekinumab would be clinically relevant.

If Fonia et al 2010[58] is not a convincing UK reference, further research into the resource use by PASI response category and pre and post initiation of a biologic may still be warranted.

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# 9 APPENDICES

## Appendix 1 Baseline participant characteristics of RCTs included in NMA (reproduced from Table 52 of company's submission)

| Trial | Treatment | N | Age | Male (%) | Weight (kg) | Psoriasis duration (years) | Treatment biologic-naïve | Prior biologic exposure (%) | Prior topical agent (%) | Prior photo-therapy (%) | Prior systemic therapy (%) | PASI | DLQI | PGA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ACCEPT (Griffiths 2010) | etanercept 100 | 347 | 45.7 | 70.9 | 90.8 | 18.8 | No | 11.8 | 96.8 | 64.6 | 57.3 | 18.6 | | |
| ACCEPT (Griffiths 2010) | ustekinumab 45 | 209 | 45.1 | 63.6 | 90.4 | 18.9 | No | 12.4 | 96.7 | 66 | 61.7 | 20.5 | | |
| ACCEPT (Griffiths 2010) | ustekinumab 90 | 347 | 44.8 | 67.4 | 91 | 18.7 | No | 10.4 | 96.8 | 66.3 | 52.4 | 19.9 | | |
| Bissonnette 2013 | adalimumab | 20 | 56.1 | 85 | 95.1 | | | | | | | 11.6 | | |
| Bissonnette 2013 | Placebo | 10 | 57.4 | 60 | 94.8 | | | | | | | 13.1 | | |
| ERASURE (Langley 2014) | secukinumab 150 | 245 | 44.9 | 68.6 | 87.1 | 17.5 | No | 29.8 | | | | 22.3 | 13.4 | |
| ERASURE (Langley 2014) | secukinumab 300 | 245 | 44.9 | 69 | 88.8 | 17.4 | No | 28.6 | | | | 22.5 | 13.9 | |
| ERASURE (Langley 2014) | Placebo | 248 | 45.4 | 69.4 | 89.7 | 17.3 | No | 29.4 | | | | 21.4 | 12 | |
| FIXTURE (Langley 2014) | etanercept 100 | 326 | 43.8 | 71.2 | 84.6 | 16.4 | No | 13.8 | | | | 23.2 | 13.4 | |
| FIXTURE (Langley 2014) | secukinumab 300 | 327 | 44.5 | 68.5 | 83 | 15.8 | No | 11.6 | | | | 23.9 | 13.3 | |
| FIXTURE (Langley 2014) | secukinumab 150 | 327 | 45.4 | 72.2 | 83.6 | 17.3 | No | 13.8 | | | | 23.7 | 13.4 | |
| FIXTURE (Langley 2014) | Placebo | 324 | 44.1 | 72.7 | 82 | 16.6 | No | 10.7 | | | | 24.1 | 13.4 | |
| SCULPTURE | secukinumab 150 | 481 | 45.3 | 63.3 | 85.2 | 17.2 | | | | | | 24 | | |
| SCULPTURE | secukinumab 300 | 483 | 46.7 | 63.8 | 85.1 | 17.4 | | | | | | 23.3 | | |
| FEATURE (Blauvelt 2014) | secukinumab 150 | 59 | 46 | 67.8 | 93.7 | | No | 47.5 | | | | 20.5 | | |
| FEATURE (Blauvelt 2014) | secukinumab 300 | 58 | 45.1 | 64.4 | 92.6 | | No | 39 | | | | 20.7 | | |
| FEATURE (Blauvelt 2014) | Placebo | 59 | 46.5 | 66.1 | 88.4 | | No | 44.1 | | | | 21.1 | | |
| JUNCTURE (Paul 2014) | secukinumab 150 | 60 | 43.9 | 67.2 | 93.7 | 20.6 | No | 24.6 | | | | 22 | | |
| JUNCTURE (Paul 2014) | secukinumab 300 | 60 | 46.6 | 76.7 | 91 | 21 | No | 25 | | | | 18.9 | | |
| JUNCTURE (Paul 2014) | Placebo | 61 | 43.7 | 62.3 | 90.2 | 19.9 | No | 21.3 | | | | 19.4 | | |
| CHAMPION (Saurat 2008) | adalimumab | 108 | 42.9 | 64.8 | 81.7 | 17.9 | Yes | | | | | 20.2 | | |
| CHAMPION (Saurat 2008) | Placebo | 53 | 40.7 | 66 | 82.6 | 18.8 | Yes | | | | | 19.2 | | |
| Krueger 2007 | ustekinumab 45 | 64 | 45 | 61 | 92.8 | 19.8 | Yes | | 94 | | 72 | 18.9 | 12.6 | |
| Krueger 2007 | ustekinumab 45 x 1 | 63 | 46 | 59 | 94.3 | 19.1 | Yes | | 98 | | 61 | 19 | 11.9 | |
| Krueger 2007 | ustekinumab 90 | 64 | 44 | 81 | 91.9 | 17.3 | Yes | | 92 | | 55 | 19 | 10.5 | |
| Krueger 2007 | ustekinumab 90 x 1 | 63 | 46 | 73 | 92.9 | 17.9 | Yes | | 98 | | 58 | 18.8 | 13.4 | |

| Trial | Treatment | N | Age | Male (%) | Weight (kg) | Psoriasis duration (years) | Treatment biologic-naïve | Prior biologic exposure (%) | Prior topical agent (%) | Prior photo-therapy (%) | Prior systemic therapy (%) | PASI | DLQI | PGA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Krueger 2007 | Placebo | 64 | 44 | 72 | 92.8 | 16.9 | Yes | | 95 | | 61 | 19.9 | 12 | |
| EXPRESS (Reich 2006) | infliximab 5 | 298 | 42.6 | 69 | | 19.1 | Yes | | | | | 22.9 | 12.7 | |
| EXPRESS (Reich 2006) | Placebo | 76 | 43.8 | 79 | | 17.3 | Yes | | | | | 22.8 | 11.8 | |
| EXPRESS II (Menter 2007) | infliximab 3 | 313 | 43.4 | 65.8 | 92 | 18.1 | No | 15.7 | | | | 20.1 | 12.8 | |
| EXPRESS II (Menter 2007) | infliximab 5 | 314 | 44.5 | 65 | 92.2 | 19.1 | No | 14.3 | | | | 20.4 | 13.1 | |
| EXPRESS II (Menter 2007) | Placebo | 208 | 44.4 | 69.2 | 91.1 | 17.8 | No | 13 | | | | 19.8 | 13.4 | |
| Leonardi 2003 | etanercept 100 | 164 | 44.8 | 65 | | 18.6 | Yes | | | | | 18.4 | 11.3 | |
| Leonardi 2003 | etanercept 25 | 160 | 44.4 | 74 | | 19.3 | Yes | | | | | 18.2 | 12.2 | |
| Leonardi 2003 | etanercept 50 | 162 | 45.4 | 67 | | 18.5 | Yes | | | | | 18.5 | 12.7 | |
| Leonardi 2003 | Placebo | 166 | 45.6 | 63 | | 18.4 | Yes | | | | | 18.3 | 12.8 | |
| Gottlieb 2003 | etanercept 50 | 57 | 48.2 | 58 | 91.8 | 23 | | | | | | 17.8 | | 2.8 |
| Gottlieb 2003 | Placebo | 55 | 46.5 | 67 | 90.7 | 20 | | | | | | 19.5 | | 2.9 |
| Chaudari 2001 | infliximab 10 | 11 | 35 | 72.7 | 96 | | Yes | | | | | 26.6 | | |
| Chaudari 2001 | infliximab 5 | 11 | 51 | 63.6 | 87 | | Yes | | | | | 22.1 | | |
| Chaudari 2001 | Placebo | 11 | 45 | 72.7 | 85 | | Yes | | | | | 20.3 | | |
| Chaudari 2001 | etanercept 100 | 239 | 45.2 | 69.9 | 95.8 | 16.9 | No | 20.1 | | 27.6 | 41.8 | 18.3 | | |
| Chaudari 2001 | etanercept 100 + methotrexate | 239 | 43 | 64 | 93.6 | 17.9 | No | 17.6 | | 35.1 | 45.2 | 18.2 | | |
| Igarashi 2012 | ustekinumab 45 | 64 | 45 | 82.8 | 73.2 | 15.8 | Yes | 1.6 | 100 | 56.3 | 73.4 | 30.1 | 11.4 | 3.5 |
| Igarashi 2012 | ustekinumab 90 | 62 | 44 | 75.8 | 71.1 | 17.3 | Yes | 0 | 100 | 82.3 | 83.9 | 28.7 | 10.7 | 3.5 |
| Igarashi 2012 | Placebo | 32 | 49 | 83.9 | 71.2 | 16 | Yes | 0 | 100 | 62.5 | 65.6 | 30.3 | 10.5 | 3.4 |
| LOTUS (Zhu 2013) | ustekinumab 45 | 160 | 40.1 | 78.1 | 69.9 | 14.6 | No | 11.9 | 95 | 37.5 | 39.4 | 23.2 | 13.7 | |
| LOTUS (Zhu 2013) | Placebo | 161 | 39.2 | 75.9 | 70 | 14.2 | No | 6.8 | 96.9 | 37 | 42.6 | 22.7 | 13.1 | |
| Asahina 2010 | adalimumab 80 x 0 | 38 | 47.8 | 84.2 | 69.7 | 14.2 | No | 38 | 94.7 | 18.4 | 47.4 | 25.4 | 8.4 | 3.8 |
| Asahina 2010 | adalimumab | 43 | 44.2 | 81.4 | 67.4 | 14 | No | 43 | 95.3 | 23.3 | 41.9 | 30.2 | 8.5 | 4.1 |
| Asahina 2010 | adalimumab 80 x 3+ | 42 | 43.5 | 83.3 | 72 | 11.6 | No | 42 | 100 | 16.7 | 42.9 | 28.3 | 8.8 | 3.8 |

| Trial | Treatment | N | Age | Male (%) | Weight (kg) | Psoriasis duration (years) | Treatment biologic-naïve | Prior biologic exposure (%) | Prior topical agent (%) | Prior photo-therapy (%) | Prior systemic therapy (%) | PASI | DLQI | PGA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Asahina 2010 | Placebo | 46 | 43.9 | 89.1 | 71.3 | 15.5 | No | 46 | 95.7 | 41.3 | 37 | 29.1 | 8.4 | 3.9 |
| PEARL (Tsai 2011) | ustekinumab 45 | 61 | 40.9 | 82 | 73.1 | 11.9 | No | 21.3 | 96.7 | 80.3 | 70.5 | 25.2 | 16.1 | |
| PEARL (Tsai 2011) | Placebo | 60 | 40.4 | 88.3 | 74.6 | 13.9 | No | 15 | 98.3 | 86.7 | 71.7 | 22.9 | 15.2 | |
| PHOENIX 1 (Leonardi 2008) | ustekinumab 45 | 225 | 44.8 | 68.6 | 93.7 | 19.7 | No | 52.5 | 96.1 | 67.8 | 55.3 | 20.5 | 11.1 | |
| PHOENIX 1 (Leonardi 2008) | ustekinumab 90 | 255 | 46.2 | 67.6 | 93.8 | 19.6 | No | 50.8 | 93.4 | 66 | 55.1 | 19.7 | 11.6 | |
| PHOENIX 1 (Leonardi 2008) | Placebo | 255 | 44.8 | 71.8 | 94.2 | 20.4 | No | 50.2 | 94.9 | 58.8 | 55.7 | 20.4 | 11.8 | |
| PHOENIX 2 (Papp 2008) | ustekinumab 45 | 409 | 45.1 | 69.2 | 90.3 | 19.3 | No | 38.4 | 96.1 | 69.9 | 54.5 | 19.4 | 12.2 | |
| PHOENIX 2 (Papp 2008) | ustekinumab 90 | 411 | 46.6 | 66.7 | 91.5 | 20.3 | No | 36.5 | 93.4 | 65 | 54.5 | 20.1 | 12.6 | |
| PHOENIX 2 (Papp 2008) | Placebo | 410 | 47 | 69 | 91.1 | 20.8 | No | 38.8 | 96.6 | 67.3 | 58.8 | 19.4 | 12.3 | |
| Papp 2005 | etanercept 100 | 194 | 44.5 | 67 | | 18.1 | Yes | | | | | 16.1 | | |
| Papp 2005 | etanercept 50 | 196 | 46 | 65 | | 21.5 | Yes | | | | | 16.9 | | |
| Papp 2005 | Placebo | 193 | 44 | 64 | | 17.5 | Yes | | | | | 16 | | |
| REVEAL (Menter 2008) | adalimumab | 814 | 44.1 | 67.1 | 92.3 | 18.1 | No | 11.9 | 75 | 17 | 23.1 | 19 | | |
| REVEAL (Menter 2008) | Placebo | 398 | 45.4 | 64.6 | 94.1 | 18.4 | No | 13.3 | 72.9 | 14.8 | 22.1 | 18.8 | | |
| SPIRIT (Gottlieb 2004) | infliximab 3 | 98 | 45 | 70.7 | | 18 | No | 32.3 | 85.9 | 66.7 | 82.4 | 11 | 11 | |
| SPIRIT (Gottlieb 2004) | infliximab 5 | 99 | 44 | 73.7 | | 16 | No | 33.3 | 91.9 | 68.7 | 88.9 | 12 | 12 | |
| SPIRIT (Gottlieb 2004) | Placebo | 51 | 45 | 60.8 | | 16 | No | 31.4 | 98 | 66.7 | 82.4 | 14 | 14 | |
| Yang 2012 | infliximab 5 | 84 | 39.4 | 71.4 | 68.2 | 16 | No | | | | | | 14.4 | |
| Yang 2012 | Placebo | 45 | 40.1 | 77.8 | 67.4 | 16 | No | | | | | | 14.4 | |
| van de Kerkhof 2008 | etanercept 50 | 96 | 45.9 | 61.5 | 83.4 | 19.3 | | | | | | 21.4 | | |
| van de Kerkhof 2008 | Placebo | 46 | 43.6 | 54.4 | 79.1 | 17.3 | | | | | | 21 | | |
| Tyring 2006 | etanercept 100 | 311 | 45.8 | 65 | | 20.1 | Yes | | | | | 18.3 | 12.1 | |
| Tyring 2006 | placebo | 307 | 45.6 | 70 | | 19.7 | Yes | | | | | 18.1 | 12.5 | |
| Torii 2011 | infliximab 5 | 35 | 46.9 | 62.9 | 68.5 | 14.2 | | | 100 | 62.9 | 94.3 | 31.9 | 12.7 | |
| Torii 2011 | placebo | 19 | 43.3 | 73.7 | 69.7 | 11.1 | | | 100 | 73 | 94.7 | 33.1 | 10.5 | |
| M10-114 (Gottlieb 2011) | etanercept 100 | 141 | 43.1 | 69.5 | 94.5 | 17 | No | 14.2 | 92.2 | 23.4 | 26.2 | 19.4 | | |
| M10-114 (Gottlieb 2011) | etanercept 100 | 141 | 43.1 | 69.5 | 94.5 | 17 | No | 14.2 | 92.2 | 23.4 | 26.2 | 19.4 | | |

## Appendix 2 Evolution of PASI response by PASI response at week 12 subgroup

The company supplied the following FIXTURE trial data at clarification.

**Table 1 PASI response evolution among those with PASI<50 at week 12**

| | PASI<75 | | | | PASI75-90 | | | | PASI90 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Secukinumab | | Etanercept | | Secukinumab | | Etanercept | | Secukinumab | | Etanercept | |
| Week | n | % | n | % | n | % | n | % | n | % | n | % |
| 12 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 13 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 14 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 15 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 16 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 20 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 24 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 28 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 32 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 36 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 40 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 44 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 48 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 52 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Table 2 PASI response evolution among those with PASI50-74 at week 12**

| | PASI<75 | | | | PASI75-90 | | | | PASI90 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Secukinumab | | Etanercept | | Secukinumab | | Etanercept | | Secukinumab | | Etanercept | |
| Week | n | % | n | % | n | % | n | % | n | % | n | % |
| 12 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 13 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 14 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 15 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 16 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 20 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 24 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 28 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 32 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 36 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 40 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 44 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 48 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 52 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Table 3 PASI response evolution among those with PASI75-89 at week 12**

| | PASI<75 | | | | PASI75-90 | | | | PASI90 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Secukinumab | | Etanercept | | Secukinumab | | Etanercept | | Secukinumab | | Etanercept | |
| Week | n | % | n | % | n | % | n | % | n | % | n | % |
| 12 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 13 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 14 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 15 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 16 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 20 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 24 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 28 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 32 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 36 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 40 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 44 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 48 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 52 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Table 4 PASI response evolution among those with PASI90 at week 12**

| | PASI<75 | | | | PASI75-90 | | | | PASI90 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Secukinumab | | Etanercept | | Secukinumab | | Etanercept | | Secukinumab | | Etanercept | |
| Week | n | % | n | % | n | % | n | % | n | % | n | % |
| 12 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 13 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 14 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 15 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 16 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 20 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 24 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 28 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 32 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 36 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 40 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 44 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 48 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 52 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |