# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Premeeting briefing

# Secukinumab for the treatment of moderate to severe plaque psoriasis

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

## Key issues for consideration

### *Clinical effectiveness*

- The population in the marketing authorisation is broader than the population in the decision problem. Does it reflect the patients in England to whom secukinumab would be offered?
- Is best supportive care an appropriate comparator?
- Is etanercept given continuously or intermittently in clinical practice?
- The only direct head to head comparison available for comparators is with etanercept.
- Are the outcomes collected in the clinical trials used in clinical practice? Specifically, are PASI 75 and IGA mod 2011 0 or 1 the most clinically appropriate definitions of response?
- The network meta-analyses were only conducted for one outcome (PASI).

  - Is it important to also have network meta-analyses on other outcomes (relapse rate and health related quality of life?)
  - Should the analyses have excluded unlicensed doses of secukinumab?
  - Is it sufficiently clear how the company calculated relative risks?

### *Cost effectiveness*

- The model assumes that once one biological treatment has failed, patients move directly to best supportive care.
  - Should the model take into account treatment sequencing with biologics?
- Is the most appropriate comparator another biological treatment or best supportive care?
- Cost-effectiveness is highly sensitive to company's assumptions about the costs of best supportive care:
  - The company assumes in its base case that each patient on best supportive care requires 1 inpatient admission per year because of psoriasis, with an average length of stay of 10.7 days – is this realistic?
  - For resources used in standard care, which is the most appropriate source – NICE clinical guideline 153 (psoriasis) or Fonia et al. (2010)?
  - Data used by the company to inform length of stay in the model does not correspond with implementation data it used in its submission – has the company accounted for length of stay adequately?
- The company assumes that from week 12 to 1 year, patients remain in the same health state defined by their improvement in their PASI scores. Patients accrue costs and benefits of that health state for the duration of their treatment. Is this appropriate? Clinical data from FIXTURE suggests that patients move between PASI health states from week 12 to 52.
- It is not clear why the company had applied a discontinuation rate at the end of year 1, because the model already assumed that non-responders discontinue treatment.
- Is EQ5D utility data from the trials (used in the company model) or utility data from previous technology appraisals more appropriate?

- Although the model assumes that etanercept is given continuously, is intermittent dosing of etanercept (which was the basis of the positive recommendation of etanercept in TA103) more appropriate?
- Is a time horizon of 10 years appropriate given the chronic nature of psoriasis?

# 1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of secukinumab within its licensed indication for moderate to severe plaque psoriasis in people for whom other systemic therapies have been inadequately effective, not tolerated or contraindicated.

**Table 1 Decision problem**

| | Final scope issued by NICE | Decision problem addressed in the submission | Comments from the company | Comments from the ERG |
|---|---|---|---|---|
| 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. | | The marketing authorisation population (candidates for systemic therapy) is broader than the population addressed in the decision problem. However, it is expected that secukinumab will be used similarly to existing biologic treatments within the current clinical pathway; in patients who have failed at least two standard systemic therapies. | The population reflects the current NICE recommendations for the use of biologic therapies for the treatment of moderate to severe psoriasis. |
| Intervention | Secukinumab | | As per reference case (300 mg is the licenced dose). | 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 |
| Comparators | • Biologic therapies (including etanercept, infliximab, adalimumab and ustekinumab)<br>• Best supportive care (for people in whom biologic therapies are not tolerated or contraindicated). | | As per reference case. | These comparators are in line with the final scope issued by NICE for this appraisal. |

| | | | | |
|---|---|---|---|---|
| Outcomes | The outcome measures to be considered include:<br>• severity of psoriasis<br>• remission rate<br>• relapse rate<br>• adverse effects of treatment<br>• health-related quality of life. | As per reference case:<br>• Psoriasis Area and Severity Index (PASI) 50/75/90/100.<br>• Investigator's Global Assessment for psoriasis<br>• Relapse prevention<br>• Adverse events<br>• Health-related quality of life | The primary focus will be PASI 75 as this was the primary outcome measure in the clinical trials and is the current measure of response used by NICE.<br>PASI 90 is recommended by the EMA the best evidence of efficacy.<br>PASI 100 has been used as an indicator of remission<br>Relapse prevention will be assessed based on sustainability of response at 52 weeks.<br>Adverse events are taken from clinical trial results.<br>Health-related quality of life is measured by EuroQol 5-Dimension (EQ5D) 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 health related quality of life. |
| Other considerations | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be | Cost-effectiveness expressed as incremental cost per quality-adjusted life year, with 10 year time horizon, considering costs from an NHS and PSS perspective. | As per reference case. | |

| | | | | |
|---|---|---|---|---|
| | sufficiently long to reflect any differences in costs or outcomes between the technologies being compared<br><br>If the evidence allows, subgroup analyses according to severity of psoriasis and previous use of biologics will be considered.<br>If the evidence allows, the place of secukinumab in a sequence of biologics will be considered. | Subgroup analyses have been carried out according to severity of psoriasis as measured by DLQI and previous use of biologic therapies. These subgroups are in accordance with the marketing authorisation. | | |

# 2 The technology and the treatment pathway

2.1 Psoriasis is an inflammatory skin disease characterised by an accelerated rate of turnover of the upper layer of the skin (epidermis). Plaque-type psoriasis, characterised by red, scaly plaques of varying size, is the most common form of the disease, occurring in >80% of cases. Psoriasis is generally graded as mild, moderate or severe, using indices such as the Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI). The PASI score considers severity, location and extent of involvement of disease. Absolute PASI scores range from 0 (no disease) to 72 (worst possible disease). Percentage reduction in absolute PASI score is used to measure the effectiveness of treatments, for example, "PASI 75" demonstrates a ≥75% reduction in the disease. DLQI measures health related quality of life in adults with skin disease on a scale of 0-30, and has 10 questions with 4 levels each (not at all/not relevant=0, a little=1, a lot=2 and very much=3.) Higher total scores indicate worse quality of life.

2.2 NICE clinical guideline 153 on assessing and managing psoriasis incorporates recommendations from several technology appraisals for people with psoriasis. Etanercept (NICE technology appraisal 103), adalimumab (NICE technology appraisal 146) and ustekinumab (NICE technology appraisal 180) are recommended as treatment options for people with severe psoriasis (as defined by both a total PASI score ≥10 and DLQI score of >10). Infliximab (NICE technology appraisal 134) is recommended for people with very severe psoriasis (PASI score ≥20 and DLQI score of >18). All recommendations apply to people for whom other systemic therapies (including ciclosporin, methotrexate and phototherapy with or without psoralen) have been inadequately effective, not tolerated or contraindicated.

2.3 The population defined in the marketing authorisation for secukinumab is broader than the population addressed in the decision problem. Specifically, the marketing authorisation is "treatment of moderate to

severe plaque psoriasis in adults who are candidates for systemic therapy", whereas the population in the decision problem is for "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". However the company stated that it expected secukinumab would be used similarly to existing biologic treatments for adults with plaque psoriasis with a PASI ≥10 and a DLQI >10 (Figure 1).

**Figure 1: Psoriasis clinical pathway of care and proposed position of secukinumab**

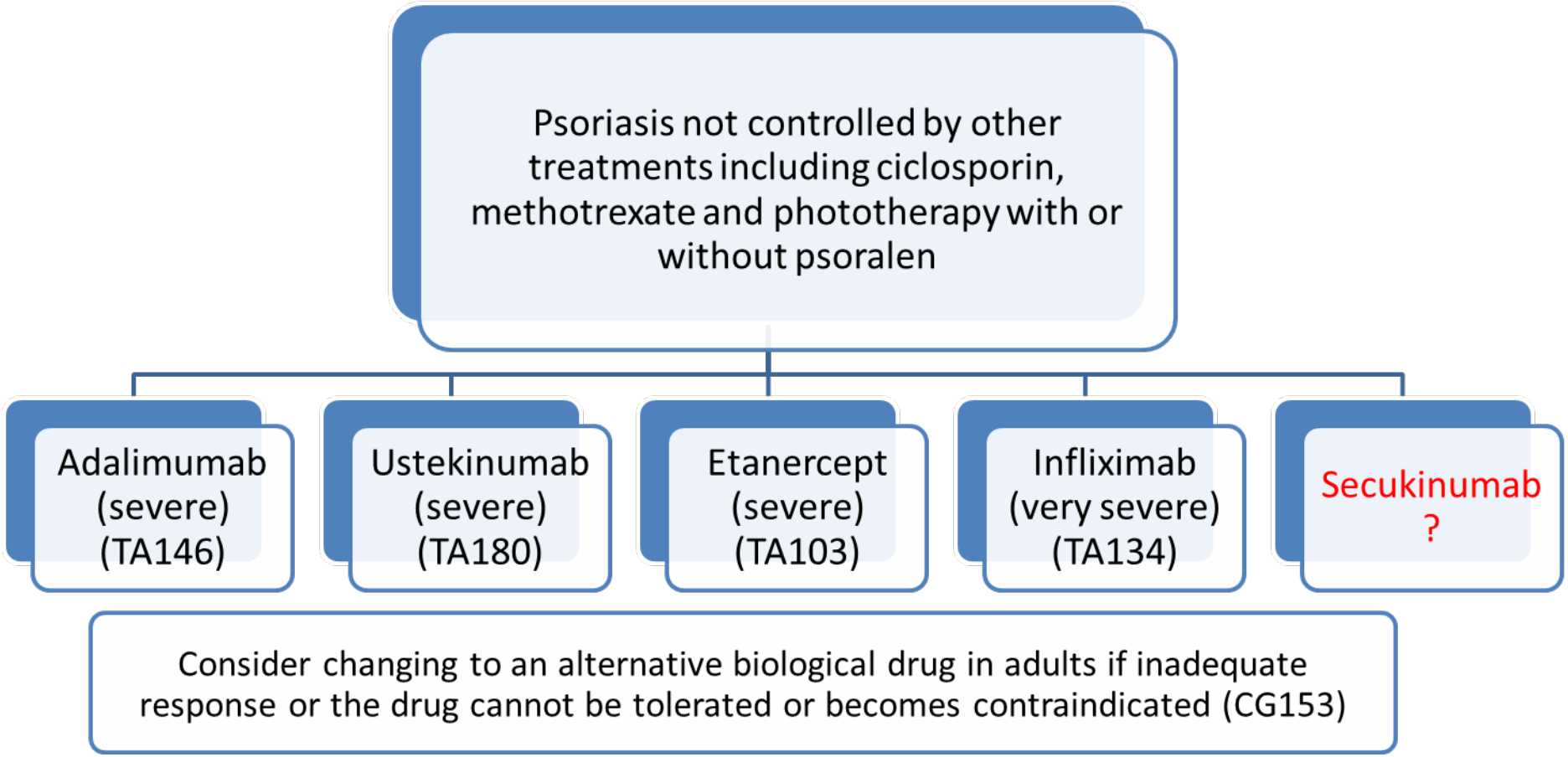


**Table 2 Technology and costs**

| | Secukinumab | Etanercept | Infliximab | Adalimumab | Ustekinumab |
|---|---|---|---|---|---|
| Marketing authorisation | Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy<br><br>Note: Secukinumab has a broader population than the population in the scope. | Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or **who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA)** | | | |
| Administration method | Subcutaneous | Subcutaneous | Intravenous | Subcutaneous | Subcutaneous |
| Acquisition cost | 2 x 150 mg prefilled pen or syringe: List price £1,218.78, patient access scheme price [redacted],<br>Company submission | 25-mg vial (with solvent) = £89.38.<br>25-mg prefilled syringe = £89.38; 50-mg prefilled pen or prefilled syringe = £178.75.<br>BNF Jan 2015 | 100-mg vial = £419.62.<br>BNF Jan 2015 | 40-mg prefilled pen or prefilled syringe = £352.14;<br>40 mg/0.8-mL vial = £352.14.<br>BNF Jan 2015 | 90 mg/mL, net price 0.5-mL (45-mg) prefilled syringe = £2147.00.<br>BNF Jan 2015 |
| Number of doses | 300 mg of secukinumab at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. | 25 mg twice weekly or 50 mg once weekly. Alternatively, 50 mg twice weekly may be used for up to 12 weeks followed, if | 5 mg/kg, repeated 2 weeks and 6 weeks after initial infusion, then every 8 weeks; Continued therapy beyond 16 weeks | Initially 80 mg, then 40 mg on alternate weeks starting 1 week after initial dose; consider discontinuing treatment if no response within 16 | Body-weight under 100 kg, initially 45 mg, then 45 mg 4 weeks after initial dose, then 45 mg every 12 weeks<br>Body-weight over 100 |

| | | | | | |
|---|---|---|---|---|---|
| | Consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 16 weeks.<br><br>Source: SPC | necessary, by 25 mg twice weekly or 50 mg once weekly. Treatment should continue until remission, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate. Discontinue treatment if no response within 12 weeks.<br>Source: SPC | should be carefully reconsidered in a patient not responding within this time period<br>Source: SPC | weeks<br>Source: SPC | kg, initially 45–90 mg, then 45–90 mg 4 weeks after initial dose, then 45–90 mg every 12 weeks.<br>Consider discontinuing if no response within 28 weeks.<br>Source: SPC |

See summary of product characteristics for details on adverse reactions and contraindications.

# 3 Comments from consultees

3.1 The patient and professional groups described the treatment pathway for psoriasis. They stated that people with psoriasis are initially treated with phototherapy and conventional systemic therapies such as methotrexate and ciclosporin. These treatments may take a long time, cause adverse effects (for example, skin cancer, impacts on fertility), and typically cannot be used long term. For those whose disease does not respond adequately to conventional systemic therapies, clinicians offer biologic treatments including anti-TNF therapies or IL-12/23 blockade. The patient and professional groups stated that secukinumab would provide an alternative when other biologic treatments have failed. The professional group stated that secukinumab use would be restricted to use in the secondary or tertiary care setting in departments that treat severe psoriasis with biological therapies. The professional group stated that the resources required to deliver secukinumab from secondary/tertiary care settings are already in place, and staff would not need additional training. Patient groups stated that many patients would also already know how to self-administer subcutaneous therapies and store treatments such as secukinumab.

3.2 Patient and professional groups noted that practice varied with respect to treating people with psoriasis. They stated that often patients feel they are being denied treatment, for example, not being referred to secondary care, or denied access to biologics even if recommended by NICE. The professional group stated that there is a major unmet need for systemic therapies for psoriasis in patients with moderate disease that is too widespread for topical treatments, yet not severe enough to warrant biologics. One patient group said more information in sequencing existing biologic therapies would be useful.

3.3 The patient groups described living with the condition. They outlined that people with moderate to severe disease have psoriasis that is visible, unsightly, itchy, painful and scaly (which in some instances cause issues

with employment and work colleagues). In addition, the patient groups emphasised the psychological impact; because psoriasis is visible, it can be an isolating and lonely disease, and people may avoid social situations or intimate relationships. One patient organisation reported the results of 2 surveys, from 2009 (1564 people) and 2012 (173 people). The 2012 survey reported that most people wanted to achieve a normal everyday life (31.3%), achieve long term clearance (25%) and total clearance now (18.8%) particularly in visible areas.

3.4 The patient and professional groups considered the advantages of secukinumab. The professional group stated that the number of people who achieved complete remission (PASI 100 –meaning 100% of disease gone) was significantly higher with secukinumab than other treatments. The patient group stated that those who conduct trials should make achieving a PASI 100 a higher priority in psoriasis trials, because while PASI 75 was substantial, it did not reflect completely clearing the disease, and even low levels of psoriasis impact on a patient's quality of life.

# 4 Clinical-effectiveness evidence

## *Overview of the clinical trials*

4.1 The company conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of secukinumab for treating people with moderate to severe chronic plaque psoriasis. It identified 5 relevant international, multicentre, phase 3, double-blind, randomised controlled trials: 3 compared secukinumab with placebo (ERASURE; JUNCTURE; FEATURE); 1 compared secukinumab with both placebo and etanercept (FIXTURE); and 1 compared 2 different doses of secukinumab (150mg or 300mg) at 2 different dosing regimens (a regular dose regimen of secukinumab compared with re-treatment with secukinumab administered only at relapse) (SCULPTURE). The company found no further head to head studies, so it undertook a network meta-analysis to compare secukinumab with all 5 comparators identified in the

scope (best supportive care, etanercept, ustekinumab, adalimumab and infliximab). The company identified no relevant non-randomised controlled or observational studies.

4.2 The company considered FIXTURE (n=1306, based in 26 countries including the UK) and ERASURE (n=738, based in 12 countries including Canada and Japan) to be 'pivotal' trials, and JUNCTURE (n=182) and FEATURE (n=177) (both based in 5 countries including France and Germany) to be 'core' trials. SCULPTURE (n=966, based in 16 countries including the UK) was designed to assess the non-inferiority of secukinumab when administered only at relapse, compared with a regular dose regimen; the company noted that retreatment following relapse was outside of the marketing authorisation, however it included the trial as it contained data related to safety and efficacy.

4.3 The 4 placebo-controlled trials (FIXTURE, ERASURE, JUNCTURE and FEATURE) had similar designs. Patients were stratified by either body weight alone (≥90kg or <90kg), or geographical location and body weight, and randomised to receive secukinumab 300mg or 150mg or placebo. Secukinumab was given at weeks 0, 1, 2, and 3, and then 4 weekly. The FIXTURE trial also included an etanercept comparator arm (50 mg twice a week initially, then 50mg once per week). At week 12, people in the placebo arms who did not achieve the primary outcome (PASI 75) were 're-randomised' to receive either 150mg or 300mg secukinumab (at weeks 12, 13, 14 and 15, followed by the same dose every month from week 16). All trials had a placebo-controlled period lasting 12 week followed by a 40 week maintenance period, however JUNCTURE and FEATURE allowed an extension of a further 156 weeks (still ongoing – only 12 week data has been presented in the company submission). SCULPTURE randomised patients to initially receive a fixed dose regimen of secukinumab (150mg or 300mg) before people who achieved PASI 75 at week 8 were 're-randomised' to receive the same dose either as a regular dose regimen, or as a retreatment administered only following relapse regimen.

4.4 Patients were eligible for inclusion in the trials if they had moderate to severe chronic plaque psoriasis that was not adequately controlled by topical treatment, phototherapy or previous systemic therapy. Severity was determined by: the percentage body surface area affected by psoriasis; PASI score, and; IGA mod 2011 score (investigator global assessment, modified in 2011, hereafter referred to as IGA. IGA is a 5 point scale for measuring psoriasis severity ranging from 0 [clear] to 4 [severe disease]). To be eligible for inclusion patients required a ≥10% body surface area affected by psoriasis, a score of PASI ≥12, or an IGA score ≥3. Patient characteristics were generally similar across the trials (please see Tables 12 to 16 in the company submission for full details). Patients in the trials differed by:

- Ethnicity: Most trial populations were primarily white (around 70%) and Asian (around 25%), however FEATURE included a lower proportion of people who were Asian (1.7% to 3.4%) and a higher proportion of people who were white (86.4% to 96.7%).
- Prior treatment: FIXTURE and ERASURE had a lower proportion of people who received prior biological treatments (10.7% to 29.4%) than JUNCTURE and FEATURE (21.3% to 47.5%).
- Prior failure of treatment: FEATURE and ERASURE had a higher proportion of patients for whom a prior biologic had failed. Characteristics for prior failure of treatment included:
  - FIXTURE: No response to previous TNF inhibitor: 2.8 to 3.1%
  - ERASURE: No response to previous TNF inhibitor 6.9 to 8.5%
  - JUNCTURE: not presented
  - FEATURE: prior failure of systemic biologic: 39.1 to 64.3%
  - SCULPURE: prior failure of:
    - ◊ systemic: 50%
    - ◊ biologic: 13.3% to 15.3%
    - ◊ non-biologic 43.4 to 44.6%

**ERG comments**

4.5 Overall the ERG stated that the systematic review conducted by the company was of good quality, and appeared complete as it included the 4 main clinical trials (FIXTURE, ERASURE, JUNCTURE, and FEATURE). The ERG further noted that the quality of the clinical trial evidence was robust.

## *Clinical trial results*

4.6 The company presented clinical trial results for both the 150mg and 300mg secukinumab arms. This pre-meeting briefing only presents the results for the licenced dose (300mg). An intention-to-treat population was used to analyse the efficacy outcomes.

4.7 The primary outcomes in the FIXTURE, ERASURE, JUNCTURE and FEATURE trials were designed to assess the superiority of secukinumab compared with placebo (or active comparator in the FIXTURE trial). The primary outcome of SCULPTURE was to demonstrate the non-inferiority of secukinumab when administered only at relapse compared with a regular dosing regimen.

4.8 The co-primary outcome measures in all 4 placebo-controlled trials were measured at week 12 and include PASI 75 (that is, a 75% reduction from baseline in PASI score) and IGA 0 or 1 response (that is, an IGA of either 0 [clear] or 1 [almost clear]). In all 4 placebo-controlled trials, secukinumab 300mg (hereafter referred to as secukinumab) demonstrated statistically significant improvements in the co-primary outcomes compared with placebo. Across trials at week 12, 75.9% to 86.7% of patients randomised to secukinumab achieved a 75% reduction in their baseline PASI scores, compared with a 0% to 4.9% ($p<0.0001$ all trials) of patients randomised to placebo. For the outcome related to achieve IGA 0 or 1 at week 12, secukinumab response ranged from 62.5% to 73.3%, compared with a placebo response from 0% to 2.8% ($p<0.0001$ all trials). For the FIXTURE trial only, secukinumab also demonstrated statistically significant improvements compared with

etanercept. PASI 75 response was 77.1% with secukinumab compared with 44% for etanercept, and IGA 0 or 1 response was 62.5% and 27.2% respectively (p<0.0001 in all cases). The company also noted that response to secukinumab 300 mg for these endpoints continued to increase between weeks 12 and weeks 16. Therefore, although not reflecting the primary endpoint of the trials, the Committee for Medicinal Products for Human Use (CHMP) have recommended that 16 weeks is the appropriate time point for evaluating response to secukinumab.

4.9 The company noted that efficacy results for SCULPTURE were similar to the other trials; however the non-inferiority of a treatment following relapse compared with a fixed dose regimen was not demonstrated.

4.10 Secondary outcomes in the trials included assessing health-related quality of life, different PASI and IGA responses, for example week 12 PASI 50/90/100 responses, and maintenance of PASI 75 or IGA 0 or 1 response at week 16 and 52 (only for FIXTURE and ERASURE). Secukinumab demonstrated statistically significant improvements for several secondary outcomes compared with placebo across the 4 placebo-controlled trials. Pease see section 6.5 of the company submission for full results. Secondary outcomes included response over time analyses as follows (FIXTURE and ERASURE only):

- Week 52
  - ◊ PASI 75: in the ERASURE trial 74.3% of people in the secukinumab arm achieved PASI 75. In the FIXTURE trial, 78.6% of people in the secukinumab arm achieved PASI 75, which was higher than etanercept (55.4%) (no statistical analyses presented)
  - ◊ PASI 100: in the ERASURE trial, 39.2% of people in the secukinumab arm achieved PASI 100. In the FIXTURE trial, 36.2% of people achieved PASI 100, which was higher than etanercept (9.9%) (statistical analyses not performed).

**Table 3 Clinical trial primary and selected secondary outcomes at 12 weeks, all trials**

| | 300mg | Placebo | Etanercept | 300 mg | Placebo | 300 mg | Placebo | 300 mg | Placebo | 300mg* |
|---|---|---|---|---|---|---|---|---|---|---|
| | FIXTURE | | | ERASURE | | JUNCTURE | | FEATURE | | SCULPTURE |
| **N.** | 323 | 324 | 323 | 245 | 246 | 60 | 61 | 58 | 59 | [redacted] |
| **PASI 75** | 77.1% | 4.9% | 44.0% | 81.6% | 4.5% | 86.7% | 3.3% | 75.9% | 0.0% | [redacted] |
| **IGA 0 or 1** | 62.5% | 2.8% | 27.2% | 65.3% | 2.40% | 73.3% | 0.0% | 69.0% | 0.0% | [redacted] |
| **PASI 50** | 91.6% | 15.1% | 70.0% | 90.6% | 8.9% | 96.7% | 8.2% | 87.9% | 5.1% | [redacted] |
| **PASI 90** | 54.2% | 1.5% | 20.7% | 59.2% | 1.2% | 55.0% | 0.0% | 60.3% | 0.0% | [redacted] |
| **PASI 100** | 24.1% | 0% | 4.3% | 28.6% | 0.8% | 26.7% | 0.0% | 43.1% | 0.0% | [redacted] |

"300 mg" = secukinumab 300 mg arm. Secukinumab 150mg arm results not presented. Please see company submission Table 22 for full results.

Week 12 PASI 75 and IGA are co-primary outcomes; p<0.0001 compared with placebo in all trials.

*SCULPTURE 300mg arm includes patients randomised to both the secukinumab arm administered only at relapse, and a regular dosing regimen. Please see section 4.3 for further details.

4.11 All trials undertook **pre-specified subgroup analyses**, including based on gender, age, weight, geographic location, age at diagnosis, disease duration, quality of life, and previous experience of other treatments (biological and non-biological). The company provided the results for primary and secondary endpoints as academic in confidence and these were consistent with the main results. In order to reflect the population with moderate to severe disease used in existing NICE guidance, the company also undertook a **post-hoc subgroup analysis** comparing efficacy for those with a DLQI > or ≤ 10 at baseline in the FIXTURE and ERASURE trials. The results for both trials showed that although response was generally higher for secukinumab in those with a DLQI ≤10 when compared with DLQI>10, there was no statistically significant difference in efficacy between those with a DLQI >10 compared with the overall study population. Full results of subgroup analyses can be seen in the manufacturer submission in Tables 29-31, 38-40, 44-45, and 48-49.

**Health related quality of life**

4.12 **DLQI:** In all 4 placebo-controlled trials, secukinumab improved (reduced) DLQI score at week 12 from baseline of between 5 to 11.6 points, which was higher than placebo (1.1 to 1.9 points; p<0.001 all trials other than FIXTURE, no p value presented). For the FIXTURE trial, secukinumab improved DLQI from baseline to week 12 by 10.4 points compared with etanercept (7.9 points). The company stated that these improvements were maintained at week 52 for the FIXTURE and ERASURE trials. The number of people with a week 12 DLQI response of 0 or 1 (showing no impact on daily living) was statistically significantly higher for secukinumab in all trials compared with placebo (p<0.001) and etanercept (p<0.001).

4.13 **EQ5D**: Absolute changes from baseline in EQ5D score, using a visual analogue scale assessing the health status from 0 (worst possible health state) to 100 (best possible health state), were statistically significantly higher with secukinumab than comparators in all 4 placebo-controlled trials. For example, in the FIXTURE trial absolute change from baseline

with secukinumab reached a mean score of 22.3 out of 100 compared with 2.2 for placebo (p<0.0001 from week 4 onwards) and 14.4 for etanercept (p=0.0008 from week 8 onwards). The FIXTURE trial reported that the proportion of patients feeling no pain or discomfort increased from 23.6% at baseline to 71.8% at week 12 in the secukinumab arm compared with 24.3% to 65.1% in the etanercept arm, and 21.5% to 34.4% in the placebo arm (no statistical analyses presented). The percentage of people not feeling anxious or depressed increased from 43.1% at baseline to 78% at week 12 in the secukinumab arm, 46.7% to 71.3% in the etanercept arm, and 43.3% to 49.7% in the placebo arm (no statistical analyses presented).

**ERG comments**

4.14 The ERG stated that there was strong evidence that secukinumab 300mg is superior to placebo for PASI and IGA efficacy outcomes at week 12. Overall the ERG stated that the review of clinical evidence was generally well-conducted, with an appropriate assessment of bias. The ERG stated that patients in the clinical trials were appropriately randomised and allocated to treatment, and baseline demographics and disease characteristics balanced across intervention groups. The ERG noted that the FIXTURE trial demonstrated that secukinumab decreased patients' baseline PASI by ≥50% at an earlier time point (3 weeks) than did etanercept (7 weeks).

## *Meta-analyses/indirect comparison/MTC*

4.15 The company conducted network meta-analyses for the 4 categories reflecting the degree to which PASI reduces from baseline (<50%, 50-74%, 75-90%, 90%+) to compare secukinumab with all the comparators identified in the final scope. The company identified 30 relevant trials for the network meta-analyses from its systematic literature review, including the 5 relevant secukinumab trials (as described above) and 25 comparator trials (Figure 2). However, the company did not include all the trials in all its analyses. The company assessed the appropriateness of

combining the trials (for example considering patient characteristics that may affect outcomes), and it also evaluated the consistency between the estimates generated by the direct and indirect evidence. The company excluded studies it deemed to increase the risk of effect modification, which did not affect the results. Doses included in the base care are described in Table 5 below. The company excluded studies or arms reporting irrelevant doses or comparators, however it included a 150mg dose arm for secukinumab and a 100mg arm for etanercept (16 week scenario only) in order to allow connections in the network. See Table 51 in company submission.

**Figure 2: Network of trials included in the network meta-analysis (base case)**

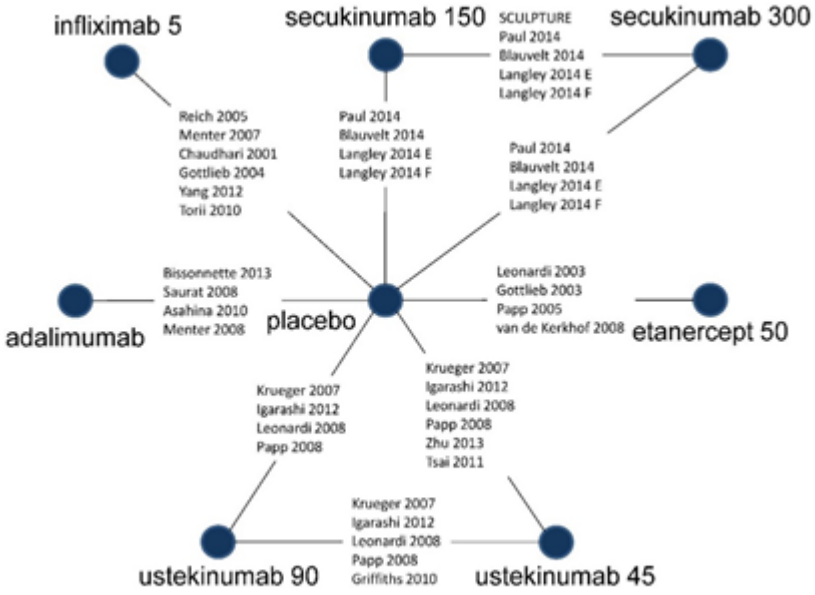



**Table 4: Interventions and doses of interest used in base case**

| Drug | Induction Phase | Maintenance dose |
|---|---|---|
| Secukinumab | 150 or 300mg week 0,1,2,3,4 | 150 or 300mg every month |
| Etanercept | 25mg twice weekly for 12 weeks | 25mg twice weekly or 50mg weekly |
| Infliximab | 5mg/kg week 1,2,6 | 5mg/kg every 8 weeks |
| Adalimumab | 80mg week 1 | 40mg every 2 weeks |
| Ustekinumab | 45 or 90mg week 1,4 | 45 or 90mg every 12 weeks |

4.16 For each outcome based on PASI, the company based its base case network meta-analyses (including 26 trials) on each trial's primary endpoint (hereafter referred to as 'NICE 12 week endpoint analysis', even though they may not reflect the 12 week point in all trials): 12 weeks (secukinumab, etanercept and ustekinumab), 10 weeks (infliximab) or 16 weeks (adalimumab). The company also presented 2 scenario analyses: the results of all trials reporting data at 12 weeks (including 23 trials, hereafter referred to as 'actual 12 week analysis'), and a repeat of the base case but using 16 week secukinumab data (including 27 trials, hereafter referred to as '16 week NICE endpoint analysis'). The company used a random effects model, stating that although the goodness of fit analysis suggested the fixed effects model was more appropriate, it considered the random effects model to be more plausible.

***Results***

4.17 For each outcome, the company used the median of the posterior distributions of the network meta-analysis as its estimated treatment effect (shown as a relative risk), together with 95% credible intervals. The company used a mathematical function (a probit link function) in the network meta-analysis to determine the probabilities of people reaching the various PASI health states, and then the relative risks of achieving a PASI health state for secukinumab 300mg compared with each of the comparator treatments.

4.18 In the base case (NICE 12 week endpoint analysis) for the reduction in PASI by 50%, 75% and 90%, the network meta-analysis showed that secukinumab 300mg was statistically significantly more effective than placebo, secukinumab 150mg, etanercept and adalimumab, and there were no statistically significant differences when compared with ustekinumab or infliximab. Table 6 presents results for the base case. Results for the scenario analyses ('actual12 week analysis' and '16 week NICE endpoint analysis') were consistent with the base case. The company stated that it demonstrated similar results with sensitivity

analyses including: DLQI>10 (other than adalimumab where comparisons were not possible), duration of psoriasis, baseline PASI score, and prior exposure to biological drugs. The company also reported that it demonstrated similar results with a meta-regression adjusting for prior biologic exposure. Please see section 6.7.6 of the company submission for full results.

**Table 5: Base case network meta-analyses (NICE 12 week analysis): Treatment effect (relative risk) and credible intervals; secukinumab 300mg compared with all treatments.**

| | PASI 75 | PASI 50 | PASI 90 |
|---|---|---|---|
| **Placebo** | 22.25 (18.7 to 26.62) | 7.99 (7.05 to 9.11) | 92.53 (71.67 to 119.3) |
| **Secukinumab 150mg** | 1.17 (1.10 to 1.26) | 1.08 (1.05 to 1.12) | 1.36 (1.22 to 1.54) |
| **Etanercept** | 2.15 (1.76 to 2.71) | 1.52 (1.35 to 1.75) | 3.71 (2.69 to 5.33) |
| **Ustekinumab 45mg** | 1.15 (1.05 to 1.28) | 1.07 (1.02 to 1.12) | 1.3 (1.09 to 1.61) |
| **Ustekinumab 90mg** | 1.07 (0.98 to 1.19) | 1.03 (0.99 to 1.08) | 1.15 (0.96 to 1.4) |
| **Adalimumab** | 1.46 (1.26 to 1.76) | 1.21 (1.12 to 1.34) | 2.0 (1.54 to 2.76) |
| **Infliximab** | 1.01 (0.92 to 1.13) | 1.0 (0.96 to 1.05) | 1.02 (0.84 to 1.28) |

**ERG comments**

4.19 The ERG stated that the description of the network meta-analysis, the method used to conduct the network meta-analysis, and the method used to evaluate consistency between direct and indirect evidence, were all generally appropriate. However, the ERG noted several issues:

- The company had inconsistently included non-licensed doses for secukinumab when compared with other relevant comparators, and had not conducted sensitivity analyses that excluded the 150mg dose.
- When the ERG cross-checked data used in the network meta-analysis with the original study source publications, the company appeared to

have systematically rounded numbers down rather than to the nearest whole numbers.

- The company had stated that it had conducted network meta-analyses for PASI outcomes only because data were not available for other outcomes. However, for at least 1 outcome in the scope (quality of life) data were available.
- The company had not fully explained the details of the network meta-analysis, for example how it had calculated relative risks.
- For the 16 week scenario network meta-analysis, the ERG noted that, because non-responders in the secukinumab trials had been re-randomised at week 12, it was not possible to include any direct evidence compared with placebo after week 12. In addition, the company had included a 100mg dose of etanercept in the network meta-analysis even though this dose is not typically given. The ERG therefore stated that one should place less emphasis on this analysis.

### *Adverse effects of secukinumab*

4.20 All trials captured adverse effects of treatment. The most commonly reported adverse effects for secukinumab were nasopharyngitis, headache, diarrhoea, upper respiratory tract infection, pruritus and pyrexia. In FIXTURE, ERASURE, FEATURE (50.8% to 55.5%) and JUNCTURE (70%) the proportion of participants who developed any adverse event with 300 mg secukinumab was higher than with placebo (47% to 49.8%). The FIXTURE study showed similar rates of any adverse events at week 52 for secukinumab and etanercept (252 and 243.4 cases per 100 patient-years respectively). The company stated that in all 5 studies the risk of serious adverse events was low. The secukinumab 300mg arm showed no increase in safety related events compared with the 150 mg arm.

#### ERG comments

4.21 ERG expert clinical opinion had noted that, since the biological treatments are immunosuppressive, this may increase rates of cancer. The ERG

clinical expert also stated that there is no evidence for an increase in lymphoma for people with psoriasis, that phototherapy can increase the risk of both melanoma and non-melanoma skin cancer, and that prolonged ciclosporin treatment has been associated with lymphoma.

4.22 The ERG noted that the company reported non-fatal serious adverse events and infection rates, and that the infection rate included any, rather than only serious, infections. The ERG was concerned that it was not clear whether the company had used the same rates of adverse events given in the clinical section of its submission and in its model.

# 5 Cost-effectiveness evidence

5.1 The company did not identify and relevant cost effectiveness analyses for secukinumab in its systematic review. For the comparators, it identified 2 studies (Woolacott et al. [2006]), and Lloyd et al. [2008]) for the comparator etanercept. It further identified the previous NICE technology appraisals for psoriasis, 1 NICE clinical guideline (CG153, 'assessment and management of psoriasis' [2012]), and 1 clinical guideline by the British Association of Dermatologists ('guidelines for use of biological interventions in psoriasis' [2005]). As the company found no studies evaluating the cost-effectiveness of secukinumab for people with psoriasis, it developed an independent economic model.

## *Cost effectiveness studies*

5.2 Woolacott et al. (2006) conducted a cost-utility study comparing etanercept (25mg or 50mg) with efalizumab and best supportive care for people with moderate to severe psoriasis. The study used an initial treatment period of between 10-16 weeks, before responders (defined as PASI 75) moved into a 10-year Markov model and non-responders discontinued treatment. Compared with best supportive care, the base case incremental cost-effectiveness ratio (ICER) ranged from £66,703 per quality adjusted life year (QALY) gained (etanercept 25 mg) to £120,855 per QALY gained (etanercept 50 mg).

5.3 The company used relevant technology appraisals and clinical guidelines (including the costing template for NICE clinical guideline CG153) for the treatment of psoriasis identified in the systematic review to validate the approaches used in its cost effectiveness analysis, including assumptions about the treatment pathway, and cost and utility figures.

**ERG comments**

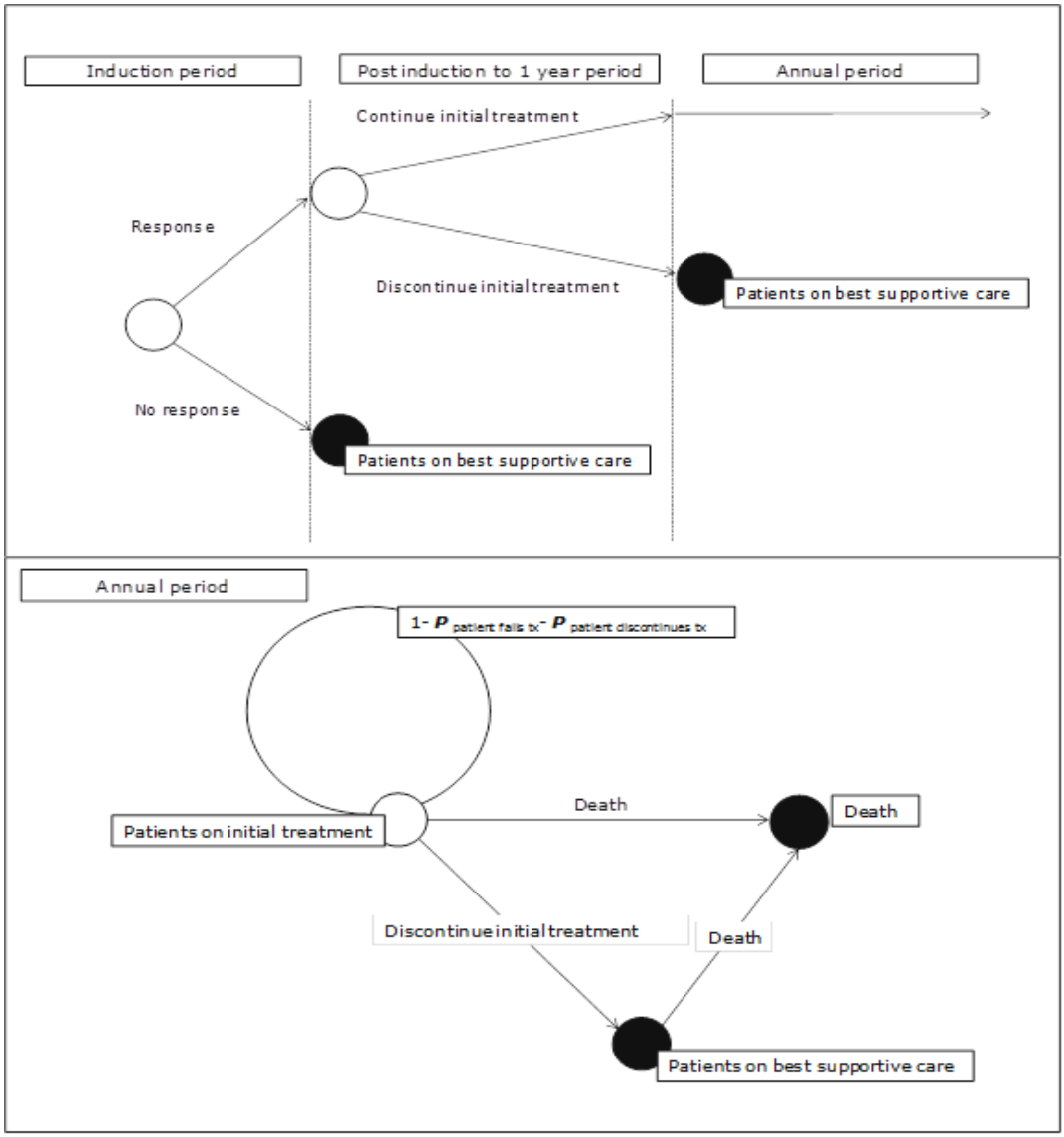
5.4 The ERG stated that the company likely retrieved the relevant evidence for economic evaluations and data on health related quality of life. However it stated that the company's review of Woolacott et al. (2005; the company incorrectly described the paper as 2006 but reported results of a 2005 paper) was incomplete. This was because the company had provided cost effectiveness results based only on intermittent use of etanercept, whereas Woolacott et al. had also included results for continuous use etanercept. Intermittent use was found to be more cost-effective than continuous in the study. The ERG's expert stated that although patients can take etanercept intermittently, in clinical practice, any effective biologic drug was likely to be used continuously. In order to compare continuous and intermittent dosing in the company model, the ERG used Woolacott et al. (see section 5.2) to derive an intermittent dosing frequency of 1.33 doses per week, and used this value in a scenario analysis (compared with 2.0 doses per week used in the base case which assumed continuous dosing)..

## *Model structure*

5.5 The company developed a new economic model that combined a decision tree with a Markov state-transition model to compare secukinumab 300 mg with etanercept, ustekinumab (45mg and 90mg), adalimumab, infliximab and best supportive care, for treating adults with moderate to severe plaque psoriasis (defined as absolute values of PASI ≥10 and DLQI >10) who had an inadequately responded to at least 2 standard systemic therapies. The model had a 10 year time horizon (1 year decision tree followed by 9 year Markov model) with 3 key time periods:

an induction phase (12-16 weeks depending on comparator); a post-induction to 1 year phase; and an annual phase (9 years). Within each phase patients could be in 1 of 4 health states based on the PASI response of patients receiving treatment (improving baseline PASI by <50%, 51-74%, 75-90%, >90%), plus a state reflecting death. The company assigned resource use, costs and quality adjusted life years (QALYs) associated with each of these health states to patients in that health state at that time. The company conducted the analysis from the perspective of the NHS and Personal Social Services (PSS), and discounted costs and health effects at an annual rate of 3.5%.

**Figure 3: Health economic model**



5.6 Patients entered the decision tree when they started treatment with the induction period, the duration of which was determined by which drug they were taking, and the primary endpoint of the trial generating the evidence (that is, 12 weeks for secukinumab, ustekinumab and etanercept; and 10 and 16 weeks respectively for infliximab and adalimumab). All patients remained on treatment for the whole induction period. If during the induction period patients did not respond (that is, they did not achieve PASI 75, an improvement of >75% in their absolute PASI score) then the biologic treatment was stopped and patients moved on to best supportive care (to the PASI <50 health state, where it was assumed there was an improvement of <50% in their absolute PASI score). In the best supportive care state, treatments included systemic therapies (90% received either methotrexate or ciclosporin), phototherapy (16%) and day centre care (psoriasis day case admission), based on assumptions from the costing template for CG153 (see section 5.3). Patients who responded to treatment during the induction phase (that is, who had a PASI 75 or above) continued on treatment for 1 year. At 1 year, the company assumed that 11.7% (based on the FIXTURE and ERASURE trials) of these patients stopped treatments with biological drugs and moved to the PASI<50 state to receive best supportive care. All other patients who had been on biological treatment for 1 year progressed into the annual Markov model, with a 20% annual all-cause discontinuation rate (based on expert opinion) applied beyond 1 year. The company assumed that after the induction period, patients do not change PASI health states: patients either remained in their PASI health state and accrued the costs and benefits of that health state, or transitioned to best supportive care (PASI <50 health state) or death. The company noted that, although people with severe psoriasis have a reduced life expectancy because of an increased risk of cardiovascular disease, lymphoma and non-melanoma skin cancer; it did not model disease specific mortality rates but instead used age-specific all-cause mortality for the general population. The company did not model a survival benefit from treating psoriasis with biological agents.

**ERG comments**

5.7 The ERG validated the model, noting it was similar to models used in previous NICE appraisals for psoriasis. It noted that this and previous models assumed that people use a single biologic, and if this fails, proceed immediately to standard of care. However, the ERG clinical adviser stated that this was not a realistic assumption, because in clinical practice, people whose disease does not respond to initial treatment would switch to another biologic treatment, or add treatments (for example methotrexate or phototherapy). The ERG stated that a more appropriate model would take into account treatment sequencing. It suggested that one approach could be to retain the current model structure, but to include a variable related to the number of possible treatments people would receive before progressing to standard of care. However, the ERG stated that it was debateable whether data were available to explore treatment sequencing appropriately.

5.8 The ERG considered the discontinuation rates that the company had applied in its model. For the discontinuation rate at the end of year 1, the ERG was not clear why the company had applied a discontinuation rate, because the model already assumed that non-responders discontinue treatment. For the annual discontinuation rate beyond the first year, the ERG clinical expert stated that a rate of 15% to 20% per year was reasonable. However, the clinical expert stated that secukinumab may have a longer duration of effect compared with other biological treatments, and the FIXTURE trial showed that the effectiveness of secukinumab compared with etanercept increased over time; this suggested that secukinumab should have a lower rate of discontinuation than the default rate applied to all treatments. Therefore, the ERG conducted sensitivity analyses varying the discontinuation rates, including the rate specific to secukinumab.

5.9 The ERG noted that the company had not undertaken a literature review to estimate the increased risk of mortality for people with psoriasis in the

modelling. Further, the ERG noted that patients discontinuing treatment do not die within the time horizon of the model. This would mean that the rate at which people left the model was too high for patients remaining on treatment compared with those discontinuing treatment, which may have biased the model against the more effective treatments.

## *Company model details*

### Effectiveness

5.10 To estimate the effectiveness of each treatment, the company populated the model with data of pooled clinical efficacy taken from its network meta-analysis, which estimated the probabilities of people reaching the various PASI health states, and the relative risks between treatments. The company chose a population cohort aged 45 years based on FIXTURE and ERASURE data. The company used pooled data for the primary outcome, PASI 75 at weeks 12-16, to determine the proportions of people reaching the various heath states in the model for all of the treatments. The PASI response distributions following induction for each comparator are shown in Table 7 and are maintained for the remainder of the model.

**Table 6: Percentage of patients achieving a given PASI response state at the end of the induction period**

| **Treatment** | PASI improving by <50% | PASI improving by 50-74% | PASI improving by 75-89% | PASI improving by 90%+ |
|---|---|---|---|---|
| Standard of care | 88.4% | 8.0% | 3.0% | 0.6% |
| Secukinumab | 7.3% | 12.5% | 24.8% | 55.4% |
| Adalimumab | 23.4% | 21.7% | 27.2% | 27.7% |
| Infliximab 5 | 7.7% | 12.8% | 25.1% | 54.4% |
| Ustekinumab 45 mg | 13.0% | 17.0% | 27.5% | 42.4% |
| Ustekinumab 90 mg | 10.1% | 15.0% | 26.6% | 48.3% |
| Etanercept | 39.1% | 23.7% | 22.3% | 14.9% |

### *ERG comments*

5.11 The ERG noted the company's assumptions that people remain in a given health state from the end of the induction period for the duration of the

model. However, during communications with the ERG and NICE, the company supplied data from the FIXTURE trial that showed that of patients with a PASI 50-74, the majority either improved or worsened over time; that is, they did not stay stable (Table 8). The company also gave figures showing change over time for people who achieved a PASI >75 at week 12. For people who at week 12 with a PASI 75-90, a substantial proportion moved into to PASI 90 or PASI 50-74 response categories. For people who by week 12 had a PASI 90, the ERG noted that patients in the secukinumab arm maintained response. Please see Table 52, Figures 8-10, and Appendix 2 of ERG report for more details.

**Table 7: PASI response at week 52 for those who had achieved PASI 50-74 at week 12, FIXTURE trial**

| % reduction in baseline PASI score | **Standard of care (n=[redacted])** | | **Secukinumab (n=[redacted])** | | **Etanercept (n=[redacted])** | |
|---|---|---|---|---|---|---|
| < 50 | [redacted] | [redacted] | [redacted] | < 50 | [redacted] | [redacted] |
| 50-74 | [redacted] | [redacted] | [redacted] | 50-74 | [redacted] | [redacted] |
| 75-90 | [redacted] | [redacted] | [redacted] | 75-90 | [redacted] | [redacted] |
| 90 | [redacted] | [redacted] | [redacted] | 90 | [redacted] | [redacted] |
| 100 | [redacted] | [redacted] | [redacted] | 100 | [redacted] | [redacted] |

5.12 The ERG noted that the company assumed in the model that patients who were partial responders at week 12 (PASI 50-74) moved to the PASI <50 health state, whereas those who achieved week 12 PASI 75 maintained the full response. The ERG stated that partial responders moving to a lower health state could deduct any placebo effect which may have arisen from biological treatments, while retaining the full effect (including any potential placebo effect) of active treatment. The ERG further stated that the justification for this was not clear, and that this may bias the model in favour of more effective treatments.

**Utility values**

5.13 For the health related quality of life data used in the model, the company converted EQ5D data from the 5 secukinumab trials into utility increments

for each PASI health state. In order to consider the generalisibility of the utility values used, it extracted and presented utility values from previous NICE technology appraisals and from a systematic review of the literature for people with psoriasis (summarised in Tables 76 to 83 in the company submission). As the company had collected EQ5D directly in the secukinumab trials, it considered the trials to be the most robust source of data, and stated that the utility values used in the model were between the range of estimates identified in the literature and in prior NICE technology appraisals. Utility values from TA146 (adalimumab) were used in a sensitivity analysis. The company stated that although adverse events were not captured explicitly in the model as not enough information was available, adverse events were indirectly captured through the use of EQ5D in the trials, and response rates and all-cause discontinuation in the model. Table 8 shows base case utility values and selected alternative utility values.

**Table 8: Utility values: Base case (pooled secukinumab trials) and alternative values**

| | **PASI <50** | **50-74** | **75-89** | **>90** |
|---|---|---|---|---|
| **Utility value used in base case** | | | | |
| Pooled baseline | 0.642 | | | |
| Secukinumab trials pooled Change from baseline | 0.11 | 0.19 | 0.23 | 0.26 |
| **Highest and lowest values from alternative sources** | | | | |
| Lowest value all sources | -0.01 (PASI<25)<br>0.1 (PASI 25-50) | 0.102 | 0.102 | 0.13 |
| Highest value all sources | 0.66 | 0.861 | 0.892 | 0.892 |
| **Utility values used in previous NICE technology appraisals (change from baseline)** | | | | |
| Etanercept TA103 | 0.05 | 0.17 | 0.19 | 0.21 |
| Adalimumab TA146 | 0.054 | 0.14 | 0.14 | 0.219 |
| Adalimumab TA146 DLQI ≤10 | 0.045 | 0.102 | 0.102 | 0.13 |
| Adalimumab TA146 DLQI >10 | 0.063 | 0.178 | 0.178 | 0.308 |
| Infliximab TA134 | 0.12 | 0.29 | 0.38 | 0.41 |
| Ustekinumab TA180 | 0.04 | 0.17 | 0.22 | 0.25 |
| Note: base case utility values taken from pooled secukinumab trial data.<br>Values from alternative sources are values taken from either NICE technology appraisals for psoriasis or values taken from the literature.<br>Adalimumab utility values used in a scenario analysis | | | | |

### ERG comments

5.14 The ERG considered the company's approach to modelling quality of life, noting that:

- The company modelled EQ5D as a function of the associated PASI response at various points over time, rather than modelling the EQ5D relative to a PASI at a fixed week 12 time point. Therefore the resulting quality of life variables were more relevant for those maintaining a PASI response than those who lost their response over time.
- It was unlikely that, as asserted by the company (see section 5.13), EQ5D would have captured adverse events. This is because EQ5D data were stratified by PASI response, not by treatment arm. So, there was no obvious means by which the company could account for differential rates of serious adverse events by treatment reflected in the EQ5D values for a given PASI response.
- The company had assumed for the first year QALY calculations that patients maintained their response achieved by week 12 for the post-induction period up to 1 year. The ERG stated it would be more appropriate for people with a PASI 50-74 to accrue the quality of life for PASI 50-74 for the induction period (weeks 0-12), and the quality of life for PASI <50 for the remaining period of the first year. This is because people in the week 12 PASI 50-74 health state discontinue treatment from week 12.

5.15 The ERG noted that the health state determines a patient's utility value. It stated that, in reality, utility values within the same health state may differ depending on the treatment patients were receiving. The ERG noted this may have biased the analysis against secukinumab.

### Modelled resources

5.16 The company described the main areas of resource use for people with moderate to severe psoriasis, which primarily involved administrating pharmacological treatment and attending appointments with dermatologists or dermatological nurses. In addition, costs are associated

with teaching patients to self- administer the subcutaneous biologic treatments. The company used sources including NHS reference costs and the British National Formulary to populate costs in the model. The company conducted a systematic literature review for relevant costing studies (see section 5.18) and used the costing template for NICE CG153 both to validate the treatment pathway in the UK for psoriasis, and to inform resource use associated with best supportive care. The company used expert opinion to validate its assumptions on frequency of physician and monitoring visits.

5.17 The company also conducted a systematic literature review of relevant costing studies. One relevant study identified was by Fonia et al. (2010). This reported the results of a retrospective observational study that compared resource use, costs and disease severity for people with moderate to severe psoriasis in the 12 months before and the 12 months after treatment with biologics. The analysis demonstrated that mean annual hospital resource use costs decreased by £1,682 in the 12 months after starting biologic treatment, and mean annual drug costs increased by £9,456. The company stated that it did not use this study in its analyses of cost effectiveness when costing standard of care because CG153 and expert opinion were more up to date.

5.18 Table 10 outlines the costs included in the model. The company included information on costs and frequency of the following:

- individual health state costs consisting of:
  - drugs unit costs
  - physician and monitoring visits
  - hospitalisation because of serious adverse events

5.19 **Drug unit costs**. The company obtained the costs of drugs from British National Formulary (BNF) 64. Modelled patients accrued the costs of biologics at a frequency as outlined in Table 9 based on dosing schedules

in the statement of product characteristics. The company assumed that everyone receiving subcutaneous biologic treatments (secukinumab, adalimumab, ustekinumab and etanercept) administered their own treatment (after a one-off self-administration training cost of £39). For infliximab (administered intravenously), in addition to accruing the costs of the drug, people visited the dermatologist for administration (£92.39), with the frequency of specialist visits derived from the number of doses of infliximab required.

5.20 **Physician and monitoring visits**: All patients accrued the costs of monitoring, which included the costs of a physician (£98) and the cost of various monitoring tests based on NHS reference costs. In the induction period, the company estimated the frequency of physician visits for monitoring based on the advice of 2 consultant dermatologists. The company then used these to estimate the number of visits in the post-induction and annual phases. The company assumed that: in the induction period there were 3 to 4 visits to a physician for monitoring for standard of care and 4 to 5 for all other treatments; post-induction to 1 year there were 3 visits for all treatments; and annually there were 4 visits for all treatments. For all monitoring tests, in the induction phase there were 4 (12 week treatments) or 5 (16 week treatments); in the post induction period there were 3.46 (adalimumab and standard of care) or 3.08 (all other treatments); and in the annual phase there were either 6 (infliximab only) or 4 (all other treatments) of each of these tests. Patients on standard of care accrued costs for phototherapy (£91 at a frequency of: 1.18 visits in the induction period, 2.66 visits post induction, 3.84 visits annually) and day centre care (£460, at a frequency of: 1.54 visits in the induction period, 3.46 visits post induction, and 5 visits annually).

5.21 **Hospitalisation**: The company applied costs of hospitalisation because of flare-up of psoriasis, non-melanoma skin cancer, other malignancies, and severe infection. For a flare of psoriasis, the company applied a cost once annually of £5,337.20 to patients who either started treatment with standard of care, or switched to standard care because of nonresponse or

discontinuation of biologic treatment. This cost of hospitalisation was based on a weighted average of several psoriasis-related HRG codes which was calculated to an average rate per day (£498.80) and multiplied by average length of stay (10.7 days based on hospital episode statistics data). Rates for both non-melanoma skin cancer (£1,460.49) and other malignancies (lymphoma [£8,178.26] and melanoma [£1,460.49]) were taken from either trial data (secukinumab) or the statement of product characteristics, which varied at a rate of between 0.00043 and 0.0767 per patient year. For severe infection (sepsis [£2,101.72], tuberculosis [£2,403.15], pneumonia [£1,852.10], skin and soft tissue infection [£1,383.44], bone and joint infection [£3,087.03], and urinary tract infection [£1,754.08]), the company estimated rates from either trial data (secukinumab), the statement of product characteristics (ustekinumab), or a study by Dixon et al. (2006) (etanercept, infliximab and adalimumab) on rates of serious infection in people receiving anti-TNF for rheumatoid arthritis (based on results from the British Society for Rheumatology Biologics Register) and rates varied between 0.01 to 0.0513 per patient year. The company estimated the proportion of people receiving phototherapy from CG153.

5.22 **Health state costs**: For each health state in the model, the company presented a total cost associated with each treatment, which took into account costs of drugs, administration, monitoring and adverse events. In the induction period, all patients were in the same health state. In both the post-induction and annual periods, the company assumed that all patients receiving biologic treatments were in either PASI 75-89 or PASI 90+ (because patients moved to standard of care if they did not achieve PASI 75). Table 9 summarises the costs and frequencies used in the model:

**Table 9: Costs associated with treatments/health states costs**

| | Costs | Induction | Post induction | Annual |
|---|---|---|---|---|
| Self-admin training | £39 | One-off cost (subcutaneous treatments only) | | |
| *Secukinumab (health states: PASI 75-89 or PASI 90+)* | | | | |
| Drug costs per dose/ admin frequency | [redacted] | **0-12 weeks**: 6<br>**0-16 weeks**: 7 | **12- 52 weeks**: 10<br>**16-52 weeks**: 9 | 12 |
| Health state costs | | [redacted] | [redacted] | [redacted] |
| *Adalimumab (health states: PASI 75-89 or PASI 90+)* | | | | |
| Drug costs per dose/ admin frequency | £352.14 | **0-12 weeks**: 8<br>**0-16 weeks:** 9 | **12-52 weeks**: 20<br>**16-52 weeks**: 19 | 26 |
| Health state cost | | £3,738.31 | £7,012.39 | £9,579.68 |
| *Infliximab (health states: PASI 75-89 or PASI 90+)* | | | | |
| Drug costs per dose/ admin frequency | £419.62 | **0-12 weeks**: 3<br>**0-16 weeks**: 4 | **12-52 weeks**: 5<br>**16-52 weeks**: 4 | 6.5 |
| Physician visit IV | £92.39 | As above | | |
| Health state cost | | 6,731.49 | 10,831.06 | 14,106.20 |
| *Ustekinumab 45mg and 90mg (health states: PASI 75-89 or PASI 90+)* | | | | |
| Drug costs per dose/ admin frequency | £2,147 | **0-12 weeks**: 2<br>**0-16 weeks**: 2 | **12-52 weeks**: 4<br>**16-52 weeks**: 4 | 4.33 |
| Health state cost | | 4,757.04 | 8,906.65 | 9,727.71 |
| *Etanercept (health states: PASI 75-89 or PASI 90+)* | | | | |
| Drug costs per dose/ admin frequency | £89.38 | **0-12 weeks**: 24<br>**0-16 weeks**: 32 | **12-52 weeks**: 80<br>**16-52 weeks**: 72 | 104 |
| Health state cost | | 2,608.16 | 7,469.05 | 9,719.56 |
| *Best supportive care (health states: PASI <50)* | | | | |
| Methotrexate | £0.55 | **0-12 weeks**: 12<br>**0-16 weeks**: 16 | **12- 52 weeks**:40<br>**16-52 weeks**:36 | 52 |
| Ciclosporin | £33.94 | | | |
| Phototherapy | £91 | 1.18 | 2.66 | 3.84 |
| Day centre care | £460 | 1.54 | 3.46 | 5 |
| Health state cost | | 1,495.60 | 2,714.71 | 3,880.57 |
| *Monitoring costs (all treatments)* | | | | |
| Blood count | £3.01 | **0-12 weeks**: 4<br>**0-16 weeks**: 5 | 3.08 (other than ada & SoC, 3.46) | 4 (other than inf, 6 |
| U&E test | £1.25 | | | |
| Liver function test | £1.25 | | | |
| Total protein test | £1.25 | | | |
| Physician visit | £98 | 4 (5 for ADA) | 3 | 4 |
| *Hospitalisation costs* | | *Rate per patient year* | | |
| Psoriasis | £5337.2 | Once annually (only to people in/switching to SoC, based on LoS 10.7 days and £499 cost per day ) | | |
| Sepsis | £2101.72 | **SEC:** [redacted]; **ADA**: 0.052; **INF**: 0.0552<br>**UST45**: 0.01; **UST90**: 0.01; **ETN**: 0.051 | | |
| Tuberculosis | £2403.15 | | | |
| Pneumonia | £1852.1 | | | |
| Skin/soft tissue inf. | £1383.44 | | | |
| Bone & joint inf. | £3087.03 | | | |
| UTI | £1754.08 | | | |
| Lymphoma | £8178.26 | **SEC** [redacted]; **ADA** 0.006; **INF** 0.0767;<br>**UST45**: 0.0016; **UST90** 0.002; **ETN** 0.0043 | | |
| Melanoma | £1460.49 | | | |
| Non-melanoma skin cancer | £1460.49 | **SEC** [redacted]; **ADA** 0.01; **INF** 0.004;<br>**UST45** 0.0065; **UST90** 0.0065; **ETN** 0.035 | | |
| ADA adalimumab, ETN etanercept, INF infliximab, IV intravenous; LoS length of stay; SoC standard of care; SEC secukinumab, UST ustekinumab, UTI urinary tract infection, U&E urea & electrolyte | | | | |

***ERG comments***

5.23 The ERG noted a number of issues with the calculation of the costs of standard of care:

- The ERG noted that in the Fonia et al. (2010) study, which provided an alternative source for resource use for standard of care, adding a biologic reduced the duration of an inpatient admission by an average of 5 days, reduced phototherapy by 2.5 sessions, and increased the number of day centre care cases (psoriasis day case admission) required (0.14 to 1.16). Therefore, while Fonia et al. had demonstrated that biologics did have a significant impact on the use of healthcare resources, the net impact on hospital admissions was lower than used by the company derived from the costing template for NICE clinical guideline 153. Based on this costing template (and hospital episode statistics data to inform length of stay) the company assumed that when compared with biological treatments, best supportive care was associated with an average increase of 10.7 inpatient days, an average increase of 3.84 phototherapy sessions and an average increase of 5 day centre care attendances. The ERG considered the impact of this in its analyses.
- Costs of standard of care were higher in the first 2 years of the model than in the rest of the model. However, the majority of people who move to standard of care after discontinuing treatment would do so longer than 2 years after starting treatment, and therefore would miss the initially more expensive costs of standard of care. The ERG considered that this would bias the analysis against standard of care. The ERG explored the impact of this in its analyses by setting the first and second year costs of standard of care equal to the third and subsequent years.

5.24 The ERG considered it optimistic that all people receiving biologic treatments could inject themselves subcutaneously after only 1 hour of training. It considered the estimate from TA103 which assumed 3 one

hourly sessions of training for self-administration to be a more reasonable estimate, and used this in its base case.

5.25 The ERG questioned how sensibly the rates of modelled adverse events could be modelled differently between each biologic, and each biologic and standard of care. Further, the ERG noted that company had assumed that malignancies incurred a single inpatient stay (with costs derived from NHS reference costs) although this excluded a number of significant cost elements (for example ongoing drug costs) and did not account for people who may require no or more than one inpatient stay. The ERG stated that it was likely that the company had underestimated the costs of serious adverse events.

### *Company's base-case results and sensitivity analysis*

5.26 The company presented the base case results. The ICER for secukinumab compared with etanercept was £2,464 per QALY gained (incremental costs £573, incremental QALYs 0.23). Secukinumab dominated all other biological treatments (adalimumab, ustekinumab 45mg and 90mg, and infliximab). When compared with standard of care, the ICER was £7076 per QALY gained (incremental costs £2,515, incremental QALYs 0.39). Table 10 presents base case results.

**Table 10: Base case results**

| | Total costs | Total QALY | Inc. costs | Inc. QALY | ICER vs standard of care | ICER incremental analysis |
|---|---|---|---|---|---|---|
| SoC | £73,610 | 0.97 | | | | |
| Etanercept | £75,788 | 1.13 | £2,178 | 0.16 | £13,948 | £13,948 |
| Secukinumab | £76,361 | 1.36 | £2,752 | 0.39 | £7,076 | £2,464 |
| Adalimumab | £76,981 | 1.22 | £3,372 | 0.25 | £13,568 | Dominated by secukinumab |
| Ustekinumab 45mg | £79,544 | 1.30 | £5,934 | 0.33 | £17,971 | |
| Ustekinumab 90mg | £79,732 | 1.33 | £6,122 | 0.36 | £17,104 | |
| Infliximab | £93,539 | 1.36 | £19,929 | 0.38 | £51,802 | |
| Note: Incremental costs and QALYs shown are all treatments compared with secukinumab. | | | | | | |

**Company updated base case following clarification**

5.27 In response to clarification, the company noted that 689 observations about 10 patients had been excluded when calculating utility values. This had a minor impact on the ICERs. The ICER for secukinumab compared with etanercept was £2515 per QALY gained (incremental costs £573, incremental QALYs 0.23) and secukinumab dominated all other biological treatments (adalimumab, ustekinumab 45mg and 90mg, and infliximab). When compared with standard of care, the ICER for secukinumab was £7231 per QALY gained (incremental costs £2,515, incremental QALYs 0.39).

**Table 11: Base case results following clarification**

| | Total costs | Total QALY | Inc. costs | Inc. QALY | ICER vs standard of care | ICER incremental analysis |
|---|---|---|---|---|---|---|
| Standard of care | £73,610 | 1.01 | | | | |
| Etanercept | £75,788 | 1.17 | £2,178 | 0.15 | £14,282 | £14,282 |
| Secukinumab | £76,361 | 1.39 | £2,752 | 0.38 | £7,231 | £2,515 |
| Adalimumab | £76,981 | 1.26 | £3,372 | 0.24 | £13,883 | Dominated |
| Ustekinumab 45mg | £79,544 | 1.34 | £5,934 | 0.32 | £18,373 | Dominated |
| Ustekinumab 90mg | £79,732 | 1.36 | £6,122 | 0.35 | £17,482 | Dominated |
| Infliximab | £93,539 | 1.39 | £19,929 | 0.38 | £52,933 | Dominated |
| Note: Incremental costs and QALYs shown are all treatments compared with standard of care. | | | | | | |

## *Company scenarios*

### *One-way sensitivity analyses*

5.28 The company undertook 208 one-way sensitivity analyses based on a range of parameters including (see Table 12 for selected results, and for full results see section 7.7.7 company submission and tables 34 to 39 in ERG report):

- discounting of costs and health effects (0% and 5%)
- efficacy parameters in the network meta-analysis
- discontinuation rates
- adverse event rates

- costs (drug, monitoring and hospitalisation costs varied by +/- 20%)
- resource use (administration of treatments and monitoring were varied by +/-20%).

5.29 The one way sensitivity analyses showed that compared with either standard of care or with the other biologics, secukinumab continued to dominate in most scenarios. The company noted that the most common key drivers across all of the comparisons were:

- the costs of treatment,
- the number of treatment administrations
- the cost and length of stay associated with hospitalisation
- the relative treatment effects

Scenarios where the ICER for secukinumab compared with all other comparators was above £20,000 per QALY gained included:

- Acquisition cost of the comparators (20% less than list price):
  - Adalimumab (£23,908.78 per QALY gained).
  - Ustekinumab 45mg (£37,991.15 per QALY gained),
  - Ustekinumab 90mg (£76,417.65 per QALY gained)
- Secukinumab acquisition cost ([redacted] than patient access scheme price) compared with
  - Standard of care (£23,688 per QALY gained)
  - Etanercept (£30,226 per QALY gained)
  - Adalimumab (£41,607 per QALY gained)
  - Ustekinumab 45mg (£55,889 per QALY gained)
  - Ustekinumab 90mg (£99,990 per QALY gained)

***Scenario analyses***

5.30 The company undertook 5 scenario analyses to examine the structural assumptions and data sources used in its base-case (see Table 13). One scenario included partial responders (PASI 50-74), 2 scenarios used efficacy outcomes from different the different scenarios used in the

network meta analyses (either varying secukinumab distribution using 16 week data while leaving all other distributions the same, or using 12 week data for all comparators). Another scenario used utility values from TA146, and another used data from FIXTURE for secukinumab etanercept and placebo. Compared with standard of care, the ICER for secukinumab varied from £4834 (partial responders scenario) to £9166 (FIXTURE data scenario) per QALY gained. Compared with etanercept, the ICER for secukinumab varied from £2345 (utility values scenario) to £3732 (16 week scenario) per QALY gained. Secukinumab continued to dominate adalimumab, ustekinumab (45mg and 90mg) and infliximab, in all scenarios.

***Probabilistic sensitivity analyses***

5.31 The company conducted probabilistic sensitivity analyses with 5,000 simulations employing parameters including efficacy, adverse event rates, discontinuation rates, utility values, resource use and costs of monitoring. Compared with standard of care secukinumab was more effective and more costly in 88.8% of scenarios and dominant (more effective and less costly) in 11.2% of scenarios. Compared with infliximab (58.2%), ustekinumab 45mg (99.6%), ustekinumab 90mg (92.9%) and adalimumab (78.46%), secukinumab dominated the other treatments in the majority of scenarios. Compared with etanercept, secukinumab was more effective and more costly 69% of scenarios. The company also presented a cost effectiveness acceptability curve. At a maximum acceptable ICER of £20,000 per QALY gained, the probability of secukinumab being cost-effective was close to 100% when compared with standard of care, etanercept, adalimumab and ustekinumab 45mg. The probability compared with infliximab (58%) and ustekinumab 90mg (93%) was the same irrespective of the maximum acceptable ICER, because the majority of the remaining model iterations fell in the south west quadrant (that is, were less effective and less costly).

5.32 The company stated that it considered conducting subgroup analyses for cost effectiveness based on people who have previously received biologic treatments, and for people with a DLQI <10. However, it did not undertake these analyses. For patients who had values of DLQI<10, the company stated that there was a lack of data and also no statistically significant differences in effectiveness when comparing patients with a DLQI<10 to the whole population (see section 4.11). For people who had taken biologic treatments previously, the company undertook a cost-minimisation analysis using information on a pairwise meta-analysis of 3 randomised controlled trials comparing biologic treatments with placebo in CG153 (psoriasis). In the analysis most ICERs for secukinumab were less than £20,000 per QALY gained, but when compared with infliximab, the ICER was £52,907 per QALY gained. The company noted that there were several limitations to this analysis, including a lack of data on all comparators.

### *ERG exploratory analyses*

5.33 The ERG corrected the company's base case as follows:

- Removed the costs of 5 intravenous infusions that had been incorrectly attributed to secukinumab
- Included the costs of serious adverse events for those on biologics for the first year which the company had omitted from the model
- Updated the number of doses of secukinumab and ustekinumab, as the ERG interpreted the licensing information for dosing differently to the company:
  - For secukinumab, the ERG interpreted the dosing as 4-weekly, which would be 13 doses annually not 12 as modelled by the company.
  - For ustekinumab, it stated that the post induction dose would be 3 doses, and not 4 as modelled by the company.

- Corrected mortality calculations within the cohort flow (the model had originally assumed that those discontinuing treatment did not die, which was to the detriment of the more effective treatment
- Revised 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
- Removed the hospitalisation cost for those remaining on drug therapy in the standard of care arm with a PASI 75 response
- Removed the costs of hospitalisation in the first year among those with a PASI 50-74 response from week 0 to week 12 and instead calculated the costs from week 12 to week 52 (to remove hospitalisation costs included in the induction period)
- Revised the quality of life values to reflect those supplied at clarification
- Revised the number of nurse hours for self-administration of subcutaneous biologics from 1 to 3
- Revised the mean patient weight to 83.3kg from the FIXTURE trial

5.34 The ERG presented 2 different base cases which took into account their corrections to the model:

- Base case A: This scenario (the ERG's preferred scenario) used assumptions related to standard of care based on Fonia et al. (2010) (an average increase of 5 inpatient days, an average increase of 3 phototherapy sessions and no increase in the average number of day centre care attendances).
- Base case B: This scenario used assumptions related to standard of care based on the costing template for CG153 and hospital episode statistics data (an average increase of 10.7 inpatient days, an average increase of 3.84 phototherapy sessions and an average increase of 5 day centre care attendances)

5.35 **Base case A** (corrections and standard of care resource use from Fonia et al. 2010, ERG's preferred base case): when compared with standard of care, secukinumab had ICER of £52,760 per QALY gained (incremental

costs £20,087, incremental QALYs 0.381), and extendedly dominated etanercept, adalimumab and ustekinumab and dominated infliximab. The ICERs of secukinumab compared directly with etanercept, adalimumab, ustekinumab 45mg and ustekinumab 90mg were £42,367, £38,684, £26,321 and £17,717 per QALY respectively. The ERG explained that changing assumptions for standard of care worsens secukinumab' s ICER in comparison with other biologics because the model structure means that people move immediately to standard of care following the failure of 1 biologic. As secukinumab was the most effective treatment, it had the least amount of people transitioning to standard of care.

**Table 12: Base case A: ERG base case incremental analysis using Fonia et al. (2010) for standard of care resource assumptions**

| | Costs | QALYs | Inc. Cost | Inc. QALY | ICER |
|---|---|---|---|---|---|
| Standard of care | £28,453 | 6.479 | | | |
| Etanercept | £38,768 | 6.629 | £10,315 | 0.15 | £68,730 |
| Adalimumab | £43,084 | 6.719 | £4,316 | 0.09 | £48,165 |
| Ustekinumab 45 | £46,999 | 6.801 | £3,916 | 0.083 | £47,453 |
| Ustekinumab 90 | £47,993 | 6.829 | £994 | 0.028 | £35,919 |
| Secukinumab | £48,540 | 6.860 | £547 | 0.031 | £17,717 |
| Infliximab | £63,227 | 6.856 | £14,688 | -0.004 | Dominated |

5.36 **Base case B** (corrections and company's preferred source of standard of care data): when compared with standard of care, secukinumab had a cost effectiveness of £14,902 per QALY gained (incremental costs £5673, incremental QALYs 0.38). Secukinumab extendedly dominated etanercept and adalimumab, dominated ustekinumab and infliximab, and had an ICER compared with etanercept and adalimumab of £8,899 and £6,979 per QALY respectively.

**Table 13: Base case B: ERG base case incremental analysis using CG153 for standard of care resource assumptions**

| | Costs | QALYs | Inc. Cost | Inc. QALY | ICER |
|---|---|---|---|---|---|
| Standard of care | £72,064 | 6.479 | | | |
| Etanercept | £75,685 | 6.629 | £3,621 | 0.15 | £24,126 |
| Adalimumab | £76,753 | 6.719 | £1,068 | 0.09 | £11,921 |
| Secukinumab | £77,737 | 6.860 | £984 | 0.141 | £6,979 |
| Ustekinumab 45 | £78,028 | 6.801 | £291 | -0.059 | Dominated |
| Ustekinumab 90 | £78,141 | 6.829 | £404 | -0.031 | Dominated |
| Infliximab | £92,550 | 6.856 | £14,813 | -0.004 | Dominated |

5.37 Because of the sensitivity of the ICER to changes in resource use for standard of care, the ERG presented a cross tabulation (please see ERG report Table 59) of the cost effectiveness of secukinumab compared with standard of care for different annual combinations of day centre care admissions and inpatient days for those on standard of care. The ERG did not include phototherapy sessions which were consistent in both the ERG and company preferred scenarios. If standard of care treatment generates a combined 11 mean annual numbers of day centre care admissions and days as an inpatient together, the cost effectiveness estimate for secukinumab compared with standard of care approximated £30,000 per QALY gained. However, if the mean annual numbers of day centre care admissions and days as an inpatient together totalled around 14 with standard of care, the cost effectiveness estimate for secukinumab compared with standard of care was around £20,000 per QALY gained.

5.38 The ERG presented sensitivity analyses to explore the impact of:

- Etanercept requiring 1.33 administrations rather than 2.00 administrations after induction, as inferred by the ERG from TA103 (etanercept) (the ERG noted that 1.33 was likely to be an extreme value)
- Varying the discontinuation rate after the first year to 15% and 25% (from 20% in the company model)

- Setting the first year discontinuation rate to zero
- Using an arbitrary increase in mortality risk associated with psoriasis of 20%
- Equalising the standard of care costs throughout the model by reducing the costs of year 1 and 2 (instead of assuming years 1 and 2 were more expensive)
- Doubling the costs of serious adverse events for the biologics
- Revising the quality of life impacts to be from the various NICE assessments or EQ5D models submitted by the company

5.39 The ERG presented results base case A and B. The ERG noted that changing the dosing of etanercept to intermittent dosing worsened the costs effectiveness of secukinumab compared with etanercept from £42,368 per QALY to £59,268 per QALY gained (base case A), and from £8,899 per QALY to £25,800 per QALY gained (base case B).

5.40 The ERG noted that using utility values from other appraisals decreased the ICERs for secukinumab, particularly when using utility values from TA134 (infliximab) and TA180 (ustekinumab). Using utility values from TA134 led to ICERs below £23,000 per QALY gained for secukinumab compared with the other biologic agents, and £26,610 compared with standard care (using base case A, ERGs standard of care cost assumptions). The ERG noted that results were not particularly sensitive to the other variables it had explored, although varying the clinical effectiveness inputs and the direct drug costs of the biologics have an impact. The ERG noted that the ICER was not sensitive to an choosing an arbitrary value of 1.2 increase risk of mortality associated with psoriasis, equalising the costs of year 1 and 2 standard of care to the rest of the model, reducing the discontinuation rate for secukinumab, and using different EQ5D models of quality of life from the company. The full results of the ERG exploratory sensitivity analysis can be found in Tables 60a, 60b, 61a and 61b of the ERG report.

### *Innovation*

5.41 The company considered secukinumab to be innovative because:

- Secukinumab offers a step change in the management of psoriasis as it has a different, first in class, more targeted, mode of action compared with the other biologic treatments licensed for plaque psoriasis.
- More people experience at least a 75% reduction in their baseline PASI scores with secukinumab than currently available biologic treatments.
- More than 1 in 3 patients achieved a complete resolution of their disease with secukinumab 300 mg in the pivotal trials (FIXTURE and ERASURE).
- Secukinumab has a rapid onset of efficacy with the estimated time to 50% reduction in mean PASI score occurring at 3 weeks in the FIXTURE and ERASURE trials.

5.42 One of the patient organisations stated that secukinumab is innovative because it inhibits the protein interleukin-17A which is found in high concentrations in skin affected by psoriasis. This is the first treatment to target this protein. One of the patient organisations stated that secukinumab was not innovative.

# 6 Equality issues

6.1 No equalities issues were raised during scoping. A patient organisation commented that people with psoriatic arthritis affecting their fingers could find using the pre-filled syringe difficult, as could those with a needle phobia. The patient organisation hoped that the manufacturer has factored in additional support for those who require it.

# 7 Authors

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# Appendix A: Clinical efficacy section of the draft European public assessment report

- European Public Assessment Report (EPAR)

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003729/WC500183131.pdf

- Summary of product characteristics (SmPC)

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003729/WC500183129.pdf