# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

# Secukinumab for the treatment of moderate to severe plaque psoriasis

## Novartis Pharmaceuticals UK Ltd

## Manufacturer Submission of Evidence

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# Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (sections 10.1 to 10.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

**A submission should be as brief and informative as possible**. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission.

Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with ‘see appendix X’. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126]’ rather than ‘One trial[126]’).

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, section 11.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

## Abbreviations

| Abbreviation | Definition |
|---|---|
| A&E | Accident and Emergency |
| ABPI | Association of the British Pharmaceutical Industry |
| ACD | Appraisal consultation document |
| AE | Adverse event |
| BID | Twice daily |
| BNF | British National Formulary |
| CI | Confidence interval |
| CSR | Clinical study report |
| DLQI | Dermatology Life Quality Index |
| EQ-5D | EuroQoL five dimensions questionnaire |
| FAD | Final appraisal determination |
| FDA | Food and Drug Administration |
| HRQL | Health-related quality of life |
| ICER | Incremental cost-effectiveness ratio |
| ITT | Intention-to-treat |
| NHS | National Health Service |
| NHS EED | NHS Economic Evaluation Database |
| NICE | National Institute for Health and Care Excellence |
| NR | Not reported |
| NS | Not significant |
| PAS | Patient Access Scheme |
| PSA | Probabilistic sensitivity analysis |
| PSS | Personal Social Services |
| QALY | Quality-adjusted life year |
| RCT | Randomised controlled trial |
| SAE | Serious adverse event |
| SEM | Standard error mean |
| SF-36 | Short Form-36 |
| SMC | Scottish Medicines Consortium |
| SmPC | Summary of product characteristics |
| STA | Single technology appraisal |
| UK | United Kingdom |

# Executive summary

## Secukinumab

Secukinumab (brand name Cosentyx®) is a fully human monoclonal antibody that represents a new biologic treatment for moderate to severe plaque psoriasis. Secukinumab is a first-in-class biologic treatment. Based on its novel mechanism of action; secukinumab selectively binds and neutralises the proinflammatory cytokine interleukin-17A (IL-17A; Section 1.2). IL-17A is a naturally occurring cytokine that is involved in inflammatory and immune responses and plays a key role in the pathogenesis of plaque psoriasis.(1) Secukinumab has received positive CHMP opinion for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy when administered at a dose of 300 mg with initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4 (Section 1.4).(1) A licence for this indication is expected in January 2015. The CHMP recommended that consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment. Furthermore, some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.

The decision problem that has been addressed in this submission is for the use of secukinumab 300 mg for adults with moderate to severe plaque psoriasis (Psoriasis Area and Severity Index [PASI] ≥ 10 and Dermatology Life Quality Index [DLQI] >10) who have failed to respond to standard systemic therapies (including ciclosporin, methotrexate and phototherapy), are intolerant to, or have a contraindication to these treatments. Aligned with the current UK treatment pathway for psoriasis,(2, 3) the comparators to secukinumab in this submission are the currently licensed biologic therapies (etanercept, infliximab, adalimumab and ustekinumab) and best supportive care (for people in whom biologic therapies are not tolerated or contraindicated; Section 2.7).

## Psoriasis

Psoriasis is a common chronic, relapsing, immune-mediated, inflammatory skin disease, mediated by cytokines (Section 2.1).(4) Psoriasis manifests itself in various forms with plaque-type psoriasis being the most common form of the disease, occurring in more than 80% of cases.(5) Plaque psoriasis is characterised by well-delineated red, scaly plaques that vary in extent from a few patches to more generalised involvement.(6)

The prevalence of psoriasis has been suggested to lie between 1.3% and 3% in the UK.(6, 7) Psoriasis can occur at any age, although it is less common in children.(6) Psoriasis impacts on a patient's quality of life in terms of physical impairment, pain, and psychological distress.(8) In addition, patients with psoriasis have a greater risk of cardiovascular disease and metabolic syndrome among other comorbidities.(9-11) Psoriasis also has a negative impact on productivity at work, with over half of severe plaque psoriasis patients reporting that they are unable to work.(3, 12-14).

The treatment pathway for psoriasis, outlined by current UK clinical guidelines (NICE CG153 and the British Association of Dermatologists [BAD]), consists of initial treatment with topical therapies, followed by standard systemic therapy and/or phototherapy (Section 2.5).(2, 3) Biologic therapies are the standard of care for patients with moderate to severe plaque psoriasis who have not responded to or are intolerant of or contraindicated to standard systemic therapy. Currently licensed biologics for the treatment of psoriasis in adults are etanercept, infliximab, adalimumab and ustekinumab, all of which have been assessed and approved by NICE.(15-18) The treatment pathway for psoriasis, outlined by current UK clinical guidelines (NICE CG153 and the British Association of Dermatologists [BAD]), consists of initial treatment with topical therapies, followed

by standard systemic therapy and/or phototherapy (Section 2.5).(2, 3) Biologic therapies are the standard of care for patients with moderate to severe plaque psoriasis who have not responded to or are intolerant of or contraindicated to standard systemic therapy. Currently licensed biologics for the treatment of psoriasis in adults are etanercept, infliximab, adalimumab and ustekinumab, all of which have been assessed and approved by NICE.(15-18)

## Clinical Effectiveness

The clinical efficacy of secukinumab compared to placebo has been demonstrated in four phase III double-blind randomised placebo controlled trials (RCTs; Section 6.2): FIXTURE (N=1,306),(19) ERASURE (N=738),(19) JUNCTURE (N=182) (20) and FEATURE (N=177) (21). In addition secukinumab has been compared head-to-head with etanercept in the FIXTURE study. Secukinumab is the only biologic treatment to have been presented to NICE with direct head-to-head RCT evidence versus a relevant biologic comparator for 52 weeks.

All four studies included 52 weeks treatment with secukinumab 300 mg and a placebo-controlled period of 12 weeks. Results from these studies (see Section 6.5) demonstrate that:

- Secukinumab administered at a dose of 300 mg provided a clinically meaningful and statistically significant improvement compared to placebo based on the co-primary endpoints of PASI 75 response and Investigator Global Assessment for clear to almost clear skin (IGA mod 2011 0/1) at week 12 in all four trials.
- Secukinumab 300 mg achieved significantly superior PASI 75 and IGA mod 2011 0/1 responses compared to etanercept at week 12 (77.1% vs. 44.0% and 62.5% vs. 27.2%, respectively) and at all subsequent timepoints in the FIXTURE study.
- The proportions of patients achieving clear skin (PASI 100) and almost clear skin (PASI 90) were higher with secukinumab 300 mg compared to placebo at week 12 in FIXTURE, ERASURE, JUNCTURE and FEATURE studies.
- Secukinumab 300 mg achieved significantly superior PASI 90 and PASI 100 responses compared to etanercept at week 12 (54.2% vs. 20.7% and 24.1% vs. 4.3%, respectively) and at all subsequent timepoints in the FIXTURE study.
- In the studies that have reported outcomes to week 52 (FIXTURE and ERASURE) it was observed that the efficacy in terms of PASI 75, PASI 90, PASI 100, and IGA mod 0/1 continued to increase between week 12 and week 16, and in the large majority of patients was maintained through to week 52. Thus, supporting the CHMP recommendation to assess response to secukinumab at 16 weeks.

In order to compare the relative efficacy of secukinumab versus all the biologic treatment comparators a network meta-analysis (NMA) was conducted (Section 6.7). The proportions of patients across four mutually exclusive PASI outcome categories (0-49, 50-74, 75-89 and 90-100) were assessed at the primary clinical trial endpoint specific to each comparator as this provided the most robust comparative effectiveness data (Section 6.7.4). For secukinumab 300 mg, ustekinumab 45 mg and 90 mg the primary trial endpoint was at 12 weeks. For infliximab, etanercept and adalimumab, these trial endpoints were at 10, 12 and 16 weeks, respectively, which additionally align with the response assessment points recommended in NICE CG153 and BAD guidelines.(2, 3) Given the 16 week stopping rule recommended in the CHMP positive opinion draft SmPC (1) a 16 week assessment point was considered as a scenario analysis in the NMA. Results of the base-case NMA (see Section 6.7.6) demonstrate that:

- Secukinumab 300 mg is more efficacious than the biologics etanercept, ustekinumab 45 mg, and adalimumab and was comparable to ustekinumab 90 mg and infliximab.
- Secukinumab 300 mg was consistently ranked in the top two treatments among all studied

interventions.

## Safety

The safety of secukinumab has been assessed through adverse event reporting in the FIXTURE, ERASURE, JUNCTURE, FEATURE and SCULPTURE studies (Section 6.9). Overall, secukinumab was well tolerated when administered subcutaneously at a dose of 300 mg weekly for the first month followed by four weekly dosing in patients with moderate to severe plaque psoriasis, across the five RCTs. The majority of adverse events were mild, with the most commonly reported adverse drug reactions being upper respiratory tract infections (most frequently nasopharyngitis and rhinitis).

In the four placebo-controlled trials (FIXTURE, ERASURE, JUNCTURE and FEATURE) secukinumab 300 mg demonstrated a favourable safety profile in comparison to placebo. In the placebo-controlled periods of these clinical studies (a total of 1,382 patients treated with secukinumab, and 694 patients treated with placebo for up to 12 weeks), infections were reported in 28.7% of patients treated with secukinumab compared with 18.9% of patients treated with placebo. Serious infections occurred in 0.14% of patients treated with secukinumab and in 0.3% of patients treated with placebo (Ref SmPC). Generally, no increase in safety events was seen with the recommended 300 mg dose of secukinumab compared with the exploratory 150 mg dose.

Adverse event rates reported for the secukinumab 300 mg fixed dose arm in SCULPTURE were comparable with the other four clinical trials (203.1 cases per 100 patient-years at week 52).

## Cost-effectiveness

A *de novo* combined decision tree and Markov state-transition model was developed in Microsoft Excel® to compare secukinumab with relevant biologics , in line with current UK practice and the treatment pathway (adalimumab, infliximab, ustekinumab 45mg, ustekinumab 90 mg, and etanercept) and best supportive care in terms of cost per QALY gained, over a 10-year time horizon (Section 7.2.2). The model structure was based on cost-effectiveness models previously presented for appraisal by NICE in this indication.(22, 23) Clinical effectiveness data were obtained from the NMA (Section 7.3.1), with model health states corresponding to the four PASI outcome categories (0-49, 50-74, 75-89 and 90-100). Utilities were based on pooled EQ-5D data collected alongside the five secukinumab trials (FIXTURE, ERASURE, JUNCTURE, FEATURE, and SCULPTURE; Section 7.4.9). Resource use was based on clinical trial data, data systematically obtained from the literature, summaries of product characteristics, psoriasis national guidelines, and expert opinion (Section 7.5). Unit costs were taken from the national health service (NHS) reference costs and the British National Formulary (BNF; Section 7.5). Base-case deterministic results from the model are presented in Table 1 (see also Section 7.7.6). These show that:

- Compared with best supportive care, secukinumab was cost-effective at a willingness to pay threshold of £20,000 per QALY; ICER = £7,076 (incremental QALY gain of 0.39 and incremental costs of £2,752).
- Secukinumab 300 mg dominated adalimumab, ustekinumab (45mg and 90mg) and infliximab, and extendedly dominated etanercept.

**Table 1. Base-case Results**

| | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) | ICER (£) SEC300 vs. comparator |
|---|---|---|---|---|---|---|---|
| **SoC** | £73,610 | 0.97 | | | | | £7,076 |
| **Etanercept 25mg tw** | £75,788 | 1.13 | £2,178 | 0.16 | £13,948 | £13,948* | £2,464 |
| **Secukinumab 300 mg** | £76,361 | 1.36 | £2,752 | 0.39 | £7,076 | £2,464 | |
| **Adalimumab 40 mg** | £76,981 | 1.22 | £3,372 | 0.25 | £13,568 | DOMINATED | DOMINANT |
| **Ustekinumab 45 mg** | £79,544 | 1.30 | £5,934 | 0.33 | £17,971 | DOMINATED | DOMINANT |
| **Ustekinumab 90 mg** | £79,732 | 1.33 | £6,122 | 0.36 | £17,104 | DOMINATED | DOMINANT |
| **Infliximab 5mg/kg** | £93,539 | 1.36 | £19,929 | 0.38 | £51,802 | DOMINATED | DOMINANT |

***Etanercept 25mg tw is extendedly dominated by Secukinumab 300mg**

In univariate sensitivity analyses (Section 7.7.7), key drivers of the cost effectiveness of secukinumab were noted as cost of treatment; frequency of hospitalisations with associated cost and length of stay (LOS); along with the treatment discontinuation rate. From the probabilistic sensitivity analyses (Section 7.7.8), it is clear that uncertainties around cost (e.g. treatment cost) had a much larger impact on the model results than uncertainties in estimates of the relative treatment effects.

In scenario analyses (Section 7.7.9) the model results were similar to the base-case result when the following assumptions were considered: inclusion of partial responders, 16 week NMA results, utilities and FIXTURE head-to-head clinical data.

**Budget Impact Analysis**

- In 2015, an estimated 794,852 adult patients in England and Wales will have psoriasis, of whom 20,269 are eligible for treatment with a biologic (Section 8.1). This is estimated to rise to 20,823 by 2019.
- Secukinumab is estimated to have an initial market share in 2015 of [redacted] by 2019 (Section 8.2).
- The introduction of secukinumab is estimated to have a cumulative saving to the NHS of £4,989,596 between 2015 and 2019 (Section 8.7).

**Conclusions**

- Psoriasis presents a high disease burden for patients in terms of physical impairment, pain, and psychological distress together with an increased risk of comorbidities such as cardiovascular disease and metabolic syndrome.
- Secukinumab is a first in class anti-IL-17A treatment that has been recommended by the CHMP for the treatment of adults with moderate to severe plaque psoriasis.
- Secukinumab has demonstrated superior clinical efficacy to placebo and a favourable safety profile in four phase III RCTs including a total of over 2,400 patients. The RCTs provide placebo-controlled evidence up to a week 12 assessment point for primary endpoints. In both of the 52 week RCTs it was observed that efficacy with secukinumab continued to increase between week 12 and week 16, and on this basis the CHMP has recommended that response to secukinumab be assessed following up to 16 weeks of treatment.
- In an NMA, secukinumab achieved superior efficacy compared to the well-established biologics adalimumab, etanercept, ustekinumab 45 mg and was comparable to ustekinumab 90 mg and infliximab
- In cost-effectiveness analyses, secukinumab was cost-effective vs. best supportive care at a willingness to pay threshold of £20,000 per QALY; secukinumab 300 mg also dominated adalimumab, ustekinumab (45mg and 90mg) and infliximab, and extendedly dominated etanercept.
- Over the course of five years, the introduction of secukinumab is expected to result in substantial annual cost savings for the NHS of £4,989,596 cumulatively between 2015 and 2019.

**Secukinumab 300 mg, administered for a minimum of 16 weeks, therefore represents a cost effective option for the NHS for the treatment of moderate to severe plaque psoriasis that would benefit patients.**

# Section A – Decision problem

## 1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

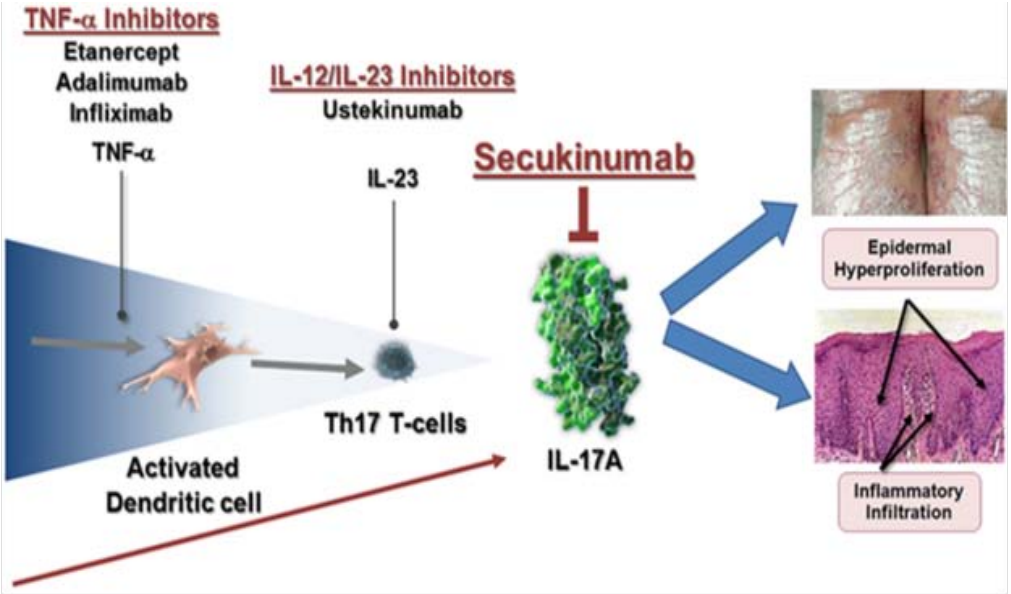
Brand Name: Cosentyx®
Approved name: secukinumab
Therapeutic Class: Monoclonal antibody selective for interleukin 17A

1.2 What is the principal mechanism of action of the technology?

Secukinumab offers an alternative, more targeted mode of action in the treatment of psoriasis compared to existing biologic treatments. Secukinumab is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises the pro-inflammatory cytokine interleukin 17A (IL-17A). IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. IL-17A plays a key role in the pathogenesis of plaque psoriasis and is found in much higher levels in psoriatic skin plaques in contrast to non-affected skin of plaque psoriasis patients (1).

Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes (as shown in Figure 1 below). As a result, secukinumab inhibits the release of pro-inflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A mediated contributions to autoimmune and inflammatory diseases. Clinically relevant levels of secukinumab reach the skin and reduce local inflammatory markers. As a direct consequence treatment with secukinumab reduces redness, thickness and skin shedding associated with plaque psoriasis lesions.

**Figure 1 Secukinumab mechanism of action and selective targetting through inhibition of IL-17A**




Secukinumab (AIN457) Advisory Committee Briefing Book (2014)(24)

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

A submission was made to the EMA in 2013. CHMP positive opinion was granted on 20th November 2014. Full licence approval is expected at the end of January 2015.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Cosentyx in the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy was favourable and therefore recommended the granting of the marketing authorisation. There are no special conditions, exceptional circumstances or conditions attached to the marketing authorisation (25).

The CHMP noted that “Robust and clinically relevant efficacy has been shown for secukinumab in the treatment of moderate to severe psoriasis. The 300 mg dose was consistently superior to the 150 mg dose. The overall safety profile of secukinumab is favourable. The safety profile of the 300 mg dose did not significantly differ from that of the 150 mg dose. Unfavourable effects typical for biologic psoriasis therapies have been observed, including infections, neutropenia and hypersensitivity, but no increase was observed in the rate of mycobacterial or serious opportunistic infections. In relation to other systemic treatments available for the treatment of psoriasis, no particular additional safety concerns have been raised. In addition, the magnitude of the beneficial effect was pronounced and superior to the effect of etanercept. The benefit-risk balance can be considered positive in all patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and therefore, the initially proposed indication: “Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA” was changed to “treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy” (25).

## 1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Based on the CHMP positive opinion the anticipated indication is as follows “Cosentyx is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy.”

## 1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The pivotal phase III studies for secukinumab for the treatment of moderate to severe psoriasis were the 2 studies FIXTURE and ERASURE. These studies are now completed and published (19). These 2 double-blind, multicentre, double-dummy, randomised, parallel-group, active (FIXTURE only) and placebo –controlled study (RCTs), where administration of secukinumab 300 mg (4 loading doses then fixed four weekly dosing) provided superior efficacy, in terms of PASI 75, PASI 90 and PASI 100 and IGA 0/1, to placebo and etanercept. Secukinumab 300 mg was well tolerated, with a comparable safety profile to etanercept (19). We expect further long term and sub-group data to be published in the next 12 months.

In addition, two studies were carried out to assess the efficacy of secukinumab using an auto injector device (JUNCTURE) and pre-filled syringes (FEATURE). Both of these studies confirmed the superior efficacy of secukinumab 300 mg to placebo, with respect to PASI75, 90 and 100, as well as IGA 0/1. Results from both of these studies have been published (26, 27) with further long term data is expected to be

published in the next 12 months. These studies also demonstrated a high usability of the pre-filled syringe and the auto injector pen to allow patients increased convenience in managing their psoriasis.

Two additional studies were carried out looking at dosing of secukinumab (SCULPTURE (28)and STATURE (29)). These studies have not been published in full to date, but have been presented as posters in International Congress, these studies are expected to be published in the next 12 months. The results of SCULPTURE study confirm the efficacy of secukinumab 300 mg when administered in accordance with its licensed dosing regimen. The primary endpoint was not met because the retreatment-as-needed regimen did not demonstrate non-inferiority to the fixed-interval regimen of secukinumab. STATURE was a sub-group follow on study for patients not achieving PASI 75 in the SCULPTURE Study. The results from STATURE are difficult to interpret due to the low numbers of subjects involved, as a result of the high numbers of patients achieving PASI 75 in the SCULPTURE study. 43 patients were recruited compared with planned number of 140 which resulted in the primary endpoint not being met and no definitive conclusions can be made regarding up titration. However, STATURE does show the safety of secukinumab given at high doses: 10 mg/kg via I.V. infusion.

There are 6 additional ongoing studies for secukinumab in psoriasis, listed below. These studies are ongoing. Therefore, data will not be included in this submission.

- CLEAR: Efficacy of Secukinumab Compared to Ustekinumab in Patients With Plaque-type Psoriasis. ClinicalTrials.gov Identifier: NCT02074982
- SIGNATURE: Secukinumab In Patients With Moderate to Severe Active, Chronic Plaque Psoriasis Who Have Failed on TNFα antaGoNists: A Clinical Trial EvalUating Treatment Results. ClinicalTrials.gov Identifier: NCT01961609
- TRANSFIGURE: A Randomized, Double-blind, Placebo-controlled, Multicentre, Study to Demonstrate the Efficacy at 16 Weeks of Secukinumab 150 and 300 mg s.c. and to Assess Safety, Tolerability and Long-term Efficacy up to 80 Weeks in Subjects With Moderate to Severe Nail Psoriasis. ClinicalTrials.gov Identifier: NCT01807520.
- GESTURE: Study of Safety, Tolerability, and Efficacy of Secukinumab in Subjects With Moderate to Severe Palmoplantar Psoriasis. ClinicalTrials.gov Identifier: NCT01806597
- SCALP: Efficacy and Safety of Subcutaneous Secukinumab in Adults with Moderate to Severe Scalp Psoriasis. Clinical Trials.gov Identifier: NCT02267135.
- 2PRECISE: Palmoplantar Pustular Psoriasis Efficacy and Safety with Secukinumab. Clinical Trials.gov.Identifier: NCT02008890

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Secukinumab is expected to be available in the UK in March 2015

## 1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Secukinumab has been recommended for use, unanimously by the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) to the US Food and Drug Administration (FDA) for use in the USA. Full FDA approval is expected imminently.

Following the Japanese drug commitee meeting on Friday 28th November 2014, we expect secukinumab approval in Japan between December 19th and 27th 2014.

The positive opinion from the EMA covers all EU member states and the licence is expected to be granted on 26th January 2015.

## 1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Yes, secukinumab 300 mg will be assessed by the Scottish Medicines Consortium. This is due to be completed and published in Q2 2015.

## 1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

**Table 2. Unit costs of technology being appraised**

| | |
|---|---|
| Pharmaceutical formulation | Cosentyx 150 mg solution for injection in pre-filled pen x 2<br>Cosentyx® 150 mg solution for injection in pre-filled syringe x 2 |
| Acquisition cost (excluding VAT) | **LIST PRICE**<br>COSENTYX®<br>150 mg solution for injection Pre Filled Pen x 2 - £1,218.78<br>COSENTYX®<br>150 mg solution for injection Pre Filled Syringe x 2 - £1,218.78<br>**PAS PRICE**<br>COSENTYX®<br>150 mg solution for injection Pre Filled Pen x 2_[redacted]<br>COSENTYX®<br>150 mg solution for injection Pre Filled Syringe x 2_-[redacted] |
| Method of administration | Administered by subcutaneous injection.<br>Patients may self-inject if a physician determines that this is appropriate. |
| Doses | The recommended dose of secukinumab is 300 mg, given |

| | |
|---|---|
| | as two subcutaneous injections of 150 mg |
| Dosing frequency | The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4.<br>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. |
| Average length of a course of treatment | Treatment continues for as long as patients are responding to treatment |
| Average cost of a course of treatment | [redacted] |
| Anticipated average interval between courses of treatments | N/A – Continuous treatment |
| Anticipated number of repeat courses of treatments | N/A – Continuous treatment |
| Dose adjustments | None |

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

N/A

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

There are no required additional tests or investigations for patients prior to receiving secukinumab or during therapy, compared to other available biologic therapies for psoriasis. There is a potential to reduce testing for secukinumab, as unlike other available biologic therapies, there is no requirement that patients should be evaluated for tuberculosis infection prior to initiation of secukinumab therapy. However, it is anticipated that clinicians will continue to test for tuberculosis infection prior to treating patients with secukinumab as this is a routine test for all existing biologics.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

There is no need for additional monitoring of patients receiving secukinumab. Secukinumab requires less frequent administration than anti-TNFalpha biologics for the treatment of psoriasis, being administered only once every month via subcutaneous injection following the initial induction period.

## 1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No additional therapies are anticipated based on the currently available clinical trial data or regulatory assessment.

# 2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Psoriasis is 'more than just a skin condition' and can affect a person's psychological and social wellbeing, not just their physical health (30). Psoriasis is a common ongoing life-long, chronic, relapsing, immune mediated, inflammatory skin disease, mediated by cytokines (4). The exact causes of psoriasis are not known, but it is believed to be influenced by both genetic and environmental factors(6). Psoriasis manifests itself in various forms with plaque-type psoriasis being the most common form of the disease, occurring in more than 80% of cases (5). Plaque psoriasis is characterised by well-delineated red, scaly plaques that vary in extent from a few patches to generalised involvement.

The prevalence of psoriasis has been suggested to lie between 1.3% and 3% in the UK, (6, 7). NICE publications estimate the prevalence of psoriasis to be 1.75% (3). The incidence rate of psoriasis is between 14 and 28 cases per 10,000 person years (31, 32). Psoriasis can occur at any age, although is uncommon in children and the majority of cases occur before 35 years.

**Figure 2. Psoriasis plaques**

Psoriatic lesions on hand

Psoriatic lesions on scalp

Psoriasis on back and arms

Psoriasis on foot

Nail psoriasis

©2014 Novartis Pharma Secukinumab Image Library July 2014

The severity of psoriasis is the UK is measured in 3 key ways: Psoriasis Area and Severity Index (PASI), the extent of body surface area affected (BSA), and the impact of the condition on patients' quality of life measured by the Dermatology Life Quality Index (DLQI). In moderate disease - 10% of the body is affected and in

severe disease it is more than 10%. In about one-fifth of people, their psoriasis is considered to be moderate to severe.

**Figure 3. Examples of Psoriasis by PASI assessment**

PASI: 12.6 PASI: 12.6 PASI: 20 PASI: 25.6

©2014 Novartis Pharma Secukinumab Image Library July 2014
*Images have been modified to protect patients' anonymity, and any distinguishing features concealed. Images are for illustrative purposes only to calculate PASI a full body assessment was performed.*

Psoriasis is also associated with a significant negative impact on health-related quality of life (HRQoL). Psoriasis impacts on a patient's quality of life in terms of physical impairment, pain, and psychological stress (Mattei 2014). Patients with psoriasis have a greater risk of significant co-morbidities including cardiovascular disease and metabolic syndrome, obesity and diabetes (Danielson, Papp, Young). This is shown in a cross-sectional study carried out in the US examining the impact of obesity and smoking on psoriasis showed that the prevalence of obesity in psoriasis patients was significantly higher than that of the general population (34% vs. 18%, respectively, $p<0.001$(33). Additionally, a retrospective analysis of more than 40,000 patients with psoriasis in Germany, showed that there was a 1.5-fold increase in the risk of developing diabetes ($p<0.05$ and a 2-fold increase in the risk of developing hypertension compared with matched individuals without psoriasis ($p<0.01$ ) (34). Finally, a large prospective, population-based cohort study in the UK of patients with psoriasis showed that the relative risk (RR) of myocardial infarction is higher than that of the general population, particularly in young patients. For a 30-year-old patient with mild or severe psoriasis, the adjusted RR of having a myocardial infarction is 1.29 (95% CI, 1.14–1.46) and 3.10 (95% CI, 1.98–4.86), respectively (35)Psoriasis is also closely linked to psoriatic arthritis, with one study suggesting that up to 13.8% of psoriasis patients also have psoriatic arthritis (36) (36). These factors can all influence the productivity of patients in education or at work and are harmful to their social interactions and emotional engagements (12).

Patients with more severe or uncontrolled psoriasis are the biggest psoriasis users of healthcare resource, through lengthy hospital stays, frequent clinic visits for specialist topical treatments, phototherapy and monitoring associated with systemic treatments (3). A UK study confirmed that mean length of stay increases with increasing disease severity, from 15.8 days per year for patients with a Psoriasis Area Severity Index (PASI) < 10 to 23.7 for patients with a PASI >20. (3). Recent NHS data suggests the

hospital stays for psoriasis continues to be substantial with an average stay length of 10.7 days (37).

Psoriasis can have a negative effect on the gaining and retaining of paid work, and lifetime earning potential. Psoriasis also has a negative impact on productivity at work. The condition commonly restricts the sufferer's choice of career and over half of patients with severe psoriasis report that they are unable to work at all (3, 13, 14).

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

The proportion of adult patients with psoriasis in the England and Wales is estimated to be approximately 800,000 or 1.75% of the total adult population(38). Of those patients, an estimated 20,000 (2.55%) are thought to be eligible to receive biologic therapy (14, 38).

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

In patients with severe psoriasis, life expectancy is reduced due to increased risk of cardiovascular disease, lymphoma and non melanoma skin cancer.(39) In addition there are data to show that 1 in 10 people with psoriasis contemplate suicide.(40) There is also an increased association with problems with alcohol for moderate to severe psoriasis sufferers which may also impact on life expectancy.(40)

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

There is a published NICE clinical guideline for the assessment and management of Psoriasis (Guideline 153 2012) and a NICE Quality Standard for Psoriasis: Quality Standard 40.

The following guidance is available for biologics use in psoriasis:

- Etanercept and efalizumab (subsequently withdrawn from the market) for the treatment of adults with psoriasis. TA 103. July 2006.
- Adalimumab for the treatment of adult patients with psoriasis. TA 146. June 2008.

- Ustekinumab for the treatment of adults with moderate to severe psoriasis. TA 180. September 2009.

The subgroups approved for the above 3 sets of guidance are: Patients with a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10, where 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.

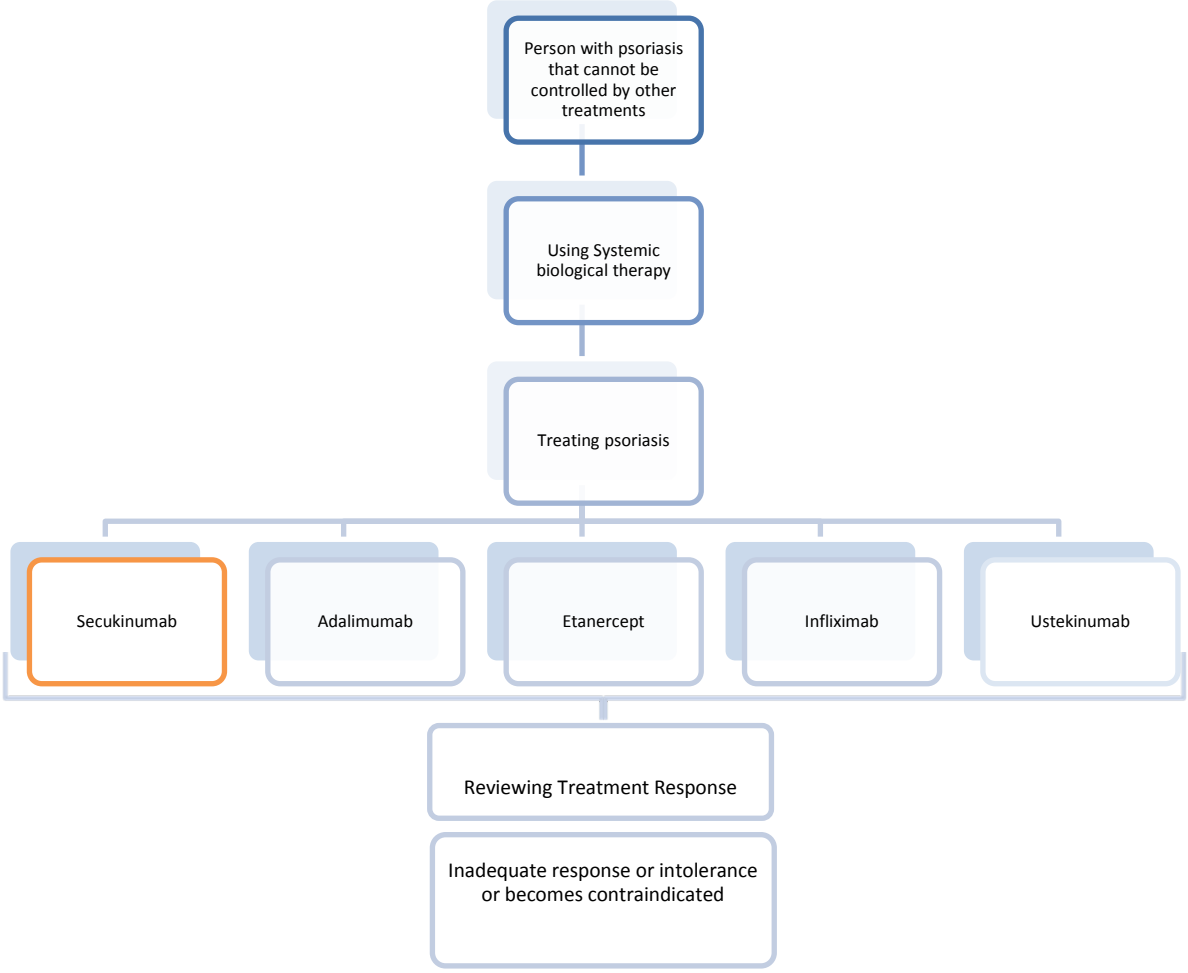
- Infliximab for the treatment of adult patients with psoriasis. TA 134. January 2008.

The subgroup approved for the above guidance is: Patients with a total Psoriasis Area Severity Index (PASI) of 20 or more and a Dermatology Life Quality Index (DLQI) of more than 18, where 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.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Secukinumab would be an additional and alternative option to current standard of care, anti-TNFalpha or IL-12/23 biologic options, for adults with plaque psoriasis with a PASI ≥10 and a DLQI >10. With higher levels of efficacy than current treatment options, secukinumab 300 mg would allow for superior treatment outcomes, without compromising on safety, in the current treatment pathway and should therefore be used ahead of other biologic agents.

**Figure 4. NICE clinical pathway adapted to show the proposed place in the pathway of secukinumab**




Adapted from NICE Clinical Guideline 53 (2012)(3)

## 2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Current clinical practice is limited by the options available to treat psoriasis. Current treatment options do not offer clinicians the opportunity to consistently provide patients with skin clear of psoriasis with PASI 90+ response rates. A recent retrospective observational study of patients with chronic plaque psoriasis aged >18 years, with data collected from 10 UK NHS secondary care dermatology departments from England, Scotland and Wales showed that 86% of patients either did not achieve or achieved and lost PASI 90 response (41). A significant proportion of patients, 67%, also did not achieve or achieved and lost PASI 75 response (41).

In comparison secukinumab 300 mg has been shown to achieve and sustain PASI 90 response for 60% of patients over 52 weeks (42).

The proportion of patients achieving a PASI 75 response in current clinical practice was shown to be only 67% (Bewley, Bishop-Bailey et al. 2014), in comparison

secukinumab 300 mg has been shown to deliver PASI 75 response in almost 20% more patients, with 86.7% of patents achieving PASI 75 in 16 weeks (42).

As a result of limited available efficacious treatment options, patients who do not achieve a PASI 75 response are sometimes left on treatments for at least 6 months. 15/56 (27%) of primary non-responders and 45/59 (76%) of secondary non-responders had no change in treatment for at least six months (41).

[redacted] The minority of these trials are in patients with non-plaque type psoriasis e.g palmarplantar pustular psoriasis, where there is a high unmet need. As these studies progress and end, it will be important that patients who are deemed to have benefited from secukinumab are able to continue to access treatment for as long as a clinical response is evident, even if these patients do not fulfil standard NICE criteria as a result of being treated by secukinumab (i.e. a patient with a PASI of 52 at the baseline of the trial, currently has a PASI of 0 and would therefore not meet the NICE entry criteria of PASI≥10 because of the effects of secukinumab). It would be unethical for clinicians to have to withdraw secukinumab treatment to allow patients to relapse in order to meet treatment funding thresholds. We ask that NICE considers recommending these patients are able to continue on treatment if clinically appropriate.

## 2.7 Please identify the main comparator(s) and justify their selection.

The main comparators for this submission, which have been discussed with NICE in reference to the draft scope and decision problem meeting are biologic therapies: Adalimumab (Humira®), Etanercept (Enbrel®), Infliximab (Remicade®), Ustekinumab (Stelara®) and best supportive care (for people in whom biologic therapies are not tolerated or contraindicated).

These comparators are the standard of care for the treatment of plaque psoriasis in the NHS in England and Wales in patients with a PASI≥10 and DLQI>10 in line with NICE guidance (TA103, 146,180). These comparators are also included in the NICE Clinical Pathway for Psoriasis. There are no other relevant comparators for treatment of plaque psoriasis with a PASI≥10 and DLQI>10.

## 2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The FIXTURE study showed secukinuamb to have a comparable safety profile to etanercept. Both etanercept and secukinumab are administered by subcutaneous injection. It is not anticipated that secukinumab 300 mg will routinely require any additional therapies to manage adverse events.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

In addition to drug acquisition cost, secukinumab does not require any additional resource use above that already in place for existing biologic therapy. In fact due to the lack of need to evaluate for tuberculosis infection prior to initiation of secukinumab, there is the potential for lower resource costs than current biologic therapies which require this evaluation. However, it is expected that clinicians will continue to test patients prior to initiation of secukinumab for tuberculosis infection and therefore a conservative approach has been taken and this potential cost reduction has not be accounted for in the cost effectiveness model. Costs to inform resource use are taken from NHS reference costs, PSSRU costs and previous NICE technology appraisals.

2.10 Does the technology require additional infrastructure to be put in place?

No. As with current practice, administration of secukinumab will be via self-administered subcutaneous injection. Monitoring of clinical outcomes will be using PASI and DLQI.

# 3 Equality

## *3.1 Identification of equality issues*

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

We do not think that this appraisal will exclude any people protected by the equality legislation, or lead to a recommendation that have a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

3.1.2 How has the analysis addressed these issues?

Not applicable as no issues identified.

# 4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a ‘step-change’ in the management of the condition.

Secukinumab 300 mg is innovative and offers a step change in the management of psoriasis as it has a different, first in class, more targeted, mode of action compared to the other biologic treatments licensed for plaque psoriasis. This more targeted

mode of action delivers higher levels of clinically highly relevant efficacy in terms of the percentage of patients achieving PASI 75, 90 and 100 than currently approved comparators with fast onset of action and good sustainability.

Secukinumab 300 mg delivers a higher number of PASI 75 responders than currently available biologic treatments. An estimate from NICE suggests that 57.3% of moderate to severe psoriasis patients will respond to their first biologic (38),however secukinumab 300 mg has been shown to achieve a PASI 75 response in over 86% of patients in 16 weeks. This represents a step change in efficacy levels for a sub-cutaneous biologic.

PASI 90 is an important outcome due to the improvements in DLQI associated with this level of psoriasis clearance. A recent pooled analysis of secukinumab phase 3 data demonstrated that significantly more patients achieving a PASI 90 response achieved a DLQI score of 0 or 1 (no impact of psoriasis on quality of life) than patients whose PASI response was between PASI 75-89 (43). The difference between PASI 75 and PASI 90 responses is shown below in Figure 5.

**Figure 5. Images of baseline PASI, PASI 75 and PASI 90 responses**

**Baseline PASI 27.4** **PASI 75 Response** **PASI 90 Response**

©2014 Novartis Pharma Secukinumab Image Library July 2014

Secukinumab 300 mg also gives patients and clinicians a real opportunity to achieve complete clearance of psoriasis with PASI 100. More than 1 in 3 patients achieved PASI 100 with secukinumab 300 mg in the two pivotal phase 3 trials (19). Complete clearance of psoriasis is the ultimate treatment goal for patients.

Another innovative aspect of secukinumab 300 mg is the rapid onset of efficacy with the estimated time to 50% reduction in mean PASI score occurring at 3 weeks with secukinumab 300 mg dose (19). This early response gives patients the benefit of symptom relief earlier than current options. It may also provide reassurance that the

treatment is working and motivate the patients to continue with treatment to achieve skin clear of psoriasis.

Secukinumab 300 mg has been proven to be efficacious regardless of age, weight, previous exposure to systemic or biologic treatment options and as a result the 300 mg maintenance dose is recommended for all patient populations.

### 4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

It is expected that due to the efficacy of secukinumab 300 mg there should be a reduction in cost to the NHS. This is primarily due to the higher proportion of patients achieving the threshold of PASI 75, thereby reducing the number of non-responders. With a greater number of patients achieving control of their psoriasis there should be less burden on dermatology services for example a reduction in dermatology outpatient appointments required. This reduction in dermatology services is unlikely to be captured by the QALY calculation.

An additional benefit of secukinumab that can result in health-related benefits for patients is the speed at which secukinumab works. Clinical studies (FIXTURE, ERASURE, JUNCTURE and FEATURE) have shown that responses to secukinumab 300 mg were observed early during the course of therapy with a 50% reduction in mean PASI from baseline by week 3. This compares to 7 weeks with etanercept (FIXTURE). This health related benefit is unlikely to be captured by the QALY calculation.

A further benefit of secukinumab that can results in health-related benefits is the number of patients able to achieve complete clearance of psoriasis: PASI 100. More than 1 in 3 patients achieved PASI 100 with secukinumab 300 mg in the two pivotal phase 3 trials. This health related benefit is unlikely to be captured by the QALY calculation.

### 4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Not applicable – see response above

# 5 Statement of the decision problem

| | Final scope issued by NICE | Decision problem addressed in the submission | Rationale if different from the scope |
|---|---|---|---|
| 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. | As per reference case |
| Intervention | Secukinumab 300 mg | Secukinumab 300 mg | As per reference case |
| 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). | As per reference case |
| 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. | In this submission, a range of outcome measures will be used to assess the clinical effectiveness of:<br>• Psoriasis Area and Severity Index (PASI) - including PASI 50/75/90/100. 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>• The efficacy of secukinumab will also be presented in terms of the Investigator's Global Assessment for psoriasis<br>• PASI 90 – As recommended by EMA the best evidence of efficacy is the % of patients who achieve the result of clear or almost clear skin (>PASI 90) on treatment.<br>• PASI 100 - this has been used as an indicator | As per reference case |

| | Final scope issued by NICE | Decision problem addressed in the submission | Rationale if different from the scope |
|---|---|---|---|
| | | of remission.<br>• Relapse prevention will be assessed based on sustainability of response at 52 weeks.<br>• Adverse events will be reported for secukinumab and comparators based on the results from the clinical trial programme<br>• Health-related quality of life is measured by EuroQol 5-Dimension (EQ-5D) and Dermatology Life Quality Index (DLQI) | |
| Economic analysis | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>Biosimilars are not expected to be in established NHS practice at the time of appraisal and are not included as comparators.<br>The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. | 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 |
| Subgroups to be considered | 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.<br>Guidance will only be issued in accordance with the marketing authorisation. | 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. | As per reference case where the evidence allows. |

| | Final scope issued by NICE | Decision problem addressed in the submission | Rationale if different from the scope |
|---|---|---|---|
| Special considerations, including issues related to equity or equality | No equity or equality issues identified. | No equity or equality issues identified. | As per reference case |

# Section B – Clinical and cost effectiveness

| Element of health technology assessment | Reference case | Section in 'Guide to the methods of technology appraisal' |
|---|---|---|
| Defining the decision problem | The scope developed by NICE | 5.2.5 and 5.2.6 |
| Comparator(s) | Therapies routinely used in the NHS, including technologies regarded as current best practice | 5.2.5 and 5.2.6 |
| Perspective costs | NHS and PSS | 5.2.7 to 5.2.10 |
| Perspective benefits | All health effects on individuals | 5.2.7 to 5.2.10 |
| Type of economic evaluation | Cost-effectiveness analysis | 5.2.11 and 5.2.12 |
| Synthesis of evidence on outcomes | Based on a systematic review | 5.3 |
| Measure of health effects | QALYs | 5.4 |
| Source of data for measurement of HRQL | Reported directly by patients and carers | 5.4 |
| Source of preference data for valuation of changes in HRQL | Representative sample of the public | 5.4 |
| Discount rate | An annual rate of 3.5% on both costs and health effects | 5.6 |
| Equity weighting | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | 5.12 |
| HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s) | | |

# 6 Clinical evidence

**Summary of Clinical Evidence**

- A systematic literature review was conducted to identify evidence of the clinical effectiveness and safety of secukinumab and relevant comparator biologics in moderate to severe plaque psoriasis.
- Six studies identified in the literature review considered treatment with secukinumab. Five of these were considered to be relevant to the decision problem:
  - FIXTURE was a phase III head-to-head, multi-centre, double-blind, randomised controlled trial (RCT) that compared secukinumab with placebo and etanercept in moderate to severe plaque psoriasis in 1,306 patients.
  - ERASURE was a phase III, multi-centre, double-blind, randomised, placebo-controlled study of secukinumab in 738 patients with moderate to severe plaque psoriasis.
  - JUNCTURE was a phase III multi-centre, double-blind, randomised, placebo-controlled study of secukinumab administered via an autoinjector in 182 moderate to severe plaque psoriasis patients.
  - FEATURE was a phase III multi-centre, double-blind, randomised, placebo-controlled study of secukinumab administered via a pre-filled syringe in 177 moderate to severe plaque psoriasis patients.
  - SCULPTURE was a phase III RCT designed to compare to secukinumab dosing regimens for maintaining response to treatment in 966 patients with moderate to severe plaque psoriasis. SCULPTURE assessed a primary study endpoint that does not align with the decision problem, but provides supporting evidence of the efficacy and safety of secukinumab in psoriasis patients.
- The phase III clinical trials of secukinumab in moderate to severe chronic plaque psoriasis patients consistently demonstrated very high skin clearance (PASI 75, PASI 90 and PASI 100 at week 12), sustained efficacy as far as week 52 and a favourable safety profile for secukinumab in these patients.
- A ≥50% mean decrease from baseline in PASI score was achieved as early as week 3 with secukinumab 300 mg compared to week 7 with etanercept (FIXTURE). It was not achieved at any visit with placebo (FIXTURE, ERASURE and JUNCTURE).
- In addition, there is evidence from FIXTURE and ERASURE that response to secukinumab continues to improve between 12 weeks and 16 weeks in efficacy over time analyses. Thus, the CHMP have recommended that response to secukinumab should be assessed at 16 weeks.
- Thirty nine further studies identified in the systematic literature review considered treatment with a relevant biologic comparator (etanercept, adalimumab, infliximab and ustekinumab).
- The 52 week head-to-head study of secukinumab and etanercept found secukinumab to demonstrate significantly superior efficacy compared to the highest approved dose of etanercept. Only one other relevant head-to-head study was identified; the ACCEPT study compared ustekinumab and etanercept for a period of only 12 weeks.

- As no further head-to-head studies beyond FIXTURE and ACCEPT were identified, network meta-analyses (NMA) were conducted to assess the relative effectiveness of secukinumab compared to relevant biologic comparators.
- The NMA results indicate that secukinumab has superior efficacy to etanercept, ustekinumab 45 mg and adalimumab and equal efficacy to ustekinumab 90 mg and infliximab.
- Secukinumab therefore represents an efficacious biologic therapy with a favourable safety profile.

## *6.1 Identification of studies*

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A systematic literature review (SLR) was conducted to identify evidence to support the clinical effectiveness and safety of secukinumab and relevant comparators in moderate to severe chronic plaque psoriasis. Eligible studies were randomised controlled trials (RCTs) with secukinumab and licensed biologics administered as monotherapy for the treatment of moderate to severe plaque psoriasis.

The initial search was conducted on 18 June 2013, and an update of this search was conducted on 8 October 2014. No language or date limits were applied in the initial searches. Thus, the two searches span from the inception of the databases to 8 October 2014. The searches encompassed the following electronic medical databases:

- MEDLINE and MEDLINE In-Process (using PubMed platform)
- Embase (using Embase Platform)
- The Cochrane Library, including:
    - The Cochrane Central Register of Controlled Trials
    - The Cochrane Database of Systematic Reviews
    - Database of Abstracts of Reviews of Effectiveness (DARE)

The updated searches were conducted in the same electronic databases but accessed via the OVID platform.

Full details on the search strings can be found in section 10.2. In addition to the searching of electronic databases, searching of congress abstracts was also performed. Conference abstracts of the American Academy of Dermatology (AAD), the European Academy of Dermatology and Venereology (EADV), the International Congress on Psoriasis (ICP), and the Society for Investigative Dermatology (SID) were published in journal supplements and indexed within Embase. However, publications from the World Congress of Dermatology (WCD) were not indexed in Embase. Thus, publications from WCD and clinicaltrials.gov were hand searched for completeness. Hand searching was limited to abstracts published in the last 5 years (2010-2014), as it was expected that high quality studies presented earlier would have been published.

Hand searching of reference lists of studies identified through searching of electronic databases was performed in order to capture any further potentially relevant studies. Additionally, a search of the Novartis Clinical Study Reports (CSRs) was conducted to identify non-published data.

## *6.2 Study selection*

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

For the initial search, the study selection process was performed in two phases. In level one screening, titles and abstracts of studies identified from the electronic databases and the hand searches were reviewed. In level two screening, the full text of studies selected at level one were obtained and reviewed. For both phases, two researchers determined eligibility according to the PICOS (Population, Intervention, Comparator, Outcomes and Study design) inclusion and exclusion criteria detailed in Table 3. If there was disagreement about study relevance, consensus was reached with a third researcher. The updated search was conducted in similar fashion to the initial searches with identical search strategy and PICOS criteria.

PICOS criteria were developed to capture studies that report the clinical efficacy and safety evidence of secukinumab in treating moderate to severe chronic plaque psoriasis. The PICOS criteria were also structured to capture potential comparators to inform a mixed treatment comparison.

**Table 3. Eligibility criteria used in clinical search strategy**

| Criteria | Inclusion | Exclusion |
|---|---|---|
| Population | • Adults (≥ 18 years) with moderate to severe chronic plaque-type psoriasis<br>• Adults with severe progressive or uncontrolled psoriasis | • Children with psoriasis<br>• Patients with types of psoriasis other than plaque psoriasis (i.e., nail, palmoplantar, pustular, erythrodermic, and guttate psoriasis); if population is mixed, exclude only if plaque psoriasis is not separately analysed<br>• Patients with mild psoriasis; if population is mixed, exclude only if moderate to severe psoriasis is not separately analysed<br>• Patients suffering from active, ongoing inflammatory diseases other than psoriasis as the primary population |
| Interventions | • Secukinumab (studies had to include a 300 mg dose treatment arm to be included) | • Non-biologic treatments for moderate to severe psoriasis as the main treatment of interest<br>• Phototherapy and photochemotherapy as the main treatment of interest<br>• Non-biologic systemics (i.e. methotrexate, ciclosporin) monotherapy or in combination with biologics |
| Comparators | • Etanercept (Enbrel®)<br>• Adalimumab (Humira®)<br>• Infliximab (Remicade®)<br>• Ustekinumab (Stelara®)<br>• Placebo | • Non-biologic treatments for moderate to severe plaque psoriasis as the main treatment of interest<br>• Phototherapy and photochemotherapy as the main treatment of interest<br>• Non-biologic systemics (i.e. methotrexate, ciclosporin) monotherapy or in combination with biologics<br>• Etanercept, adalimumab, infliximab, ustekinumab in combination with phototherapy, photochemotherapy, betamethasone/calcipotriol* |
| 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 (reduction in PASI score of at least 50%)<br>• PASI 75 (reduction in PASI score of at least 75%)<br>• PASI 90 (reduction in PASI score of at least 90%)<br>• PASI 100 (complete remission)<br>• Investigator's Global Assessment (or Physician's Global Assessment)[b]<br>• Time to response<br>• Primary non-responders to biologics<br>• Treatment failures due to non-response<br><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):**<br>• Occurrence of Grade 3 and Grade 4 hematological adverse events | |

| Criteria | Inclusion | Exclusion |
|---|---|---|
| | • 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>**HRQOL assessments:**<br>• Dermatology related quality of life (DLQI)<br>• EuroQol 5-Dimension Health Status Questionnaire (EQ-5D)<br>• Family and carer HRQOL (i.e., Family Dermatology Life Quality Index) | |
| Study design | • Phase 2/3 Randomised Controlled, Prospective Clinical Trials<br>• Systematic reviews (including meta-analyses)[a] | • Preclinical studies<br>• Phase 1 studies [a]<br>• Retrospective studies<br>• Case reports<br>• Commentaries and letters (publication type)<br>• Consensus reports<br>• Non-systematic reviews<br>• Non-randomised, controlled, prospective clinical trials*<br>• Long-term follow-up studies (e.g., open-label follow-up studies without a comparator arm) *<br>• Prospective observational studies (e.g., phase 4 studies) [a*] |
| Language | • All languages | • None |
| Date | • No limit | • None |

HRQOL = health-related quality of life; PASI = Psoriasis Area Severity Index.
* Criteria was listed as an inclusion criteria in Level 1 screening
[a] Systematic review and meta-analysis publications were used for identification of primary studies and were included at the level 1 and level 2 screens. Non-randomised studies, follow-up studies without a comparator arm, and observational studies were excluded from data extraction. Phase 1 and Phase 2 studies were excluded at full text screening. Phase 2 studies were included in the NMA.
[b] Definitions of Investigator's Global Assessment or Physician's Global Assessment, if reported in the publications, were captured.

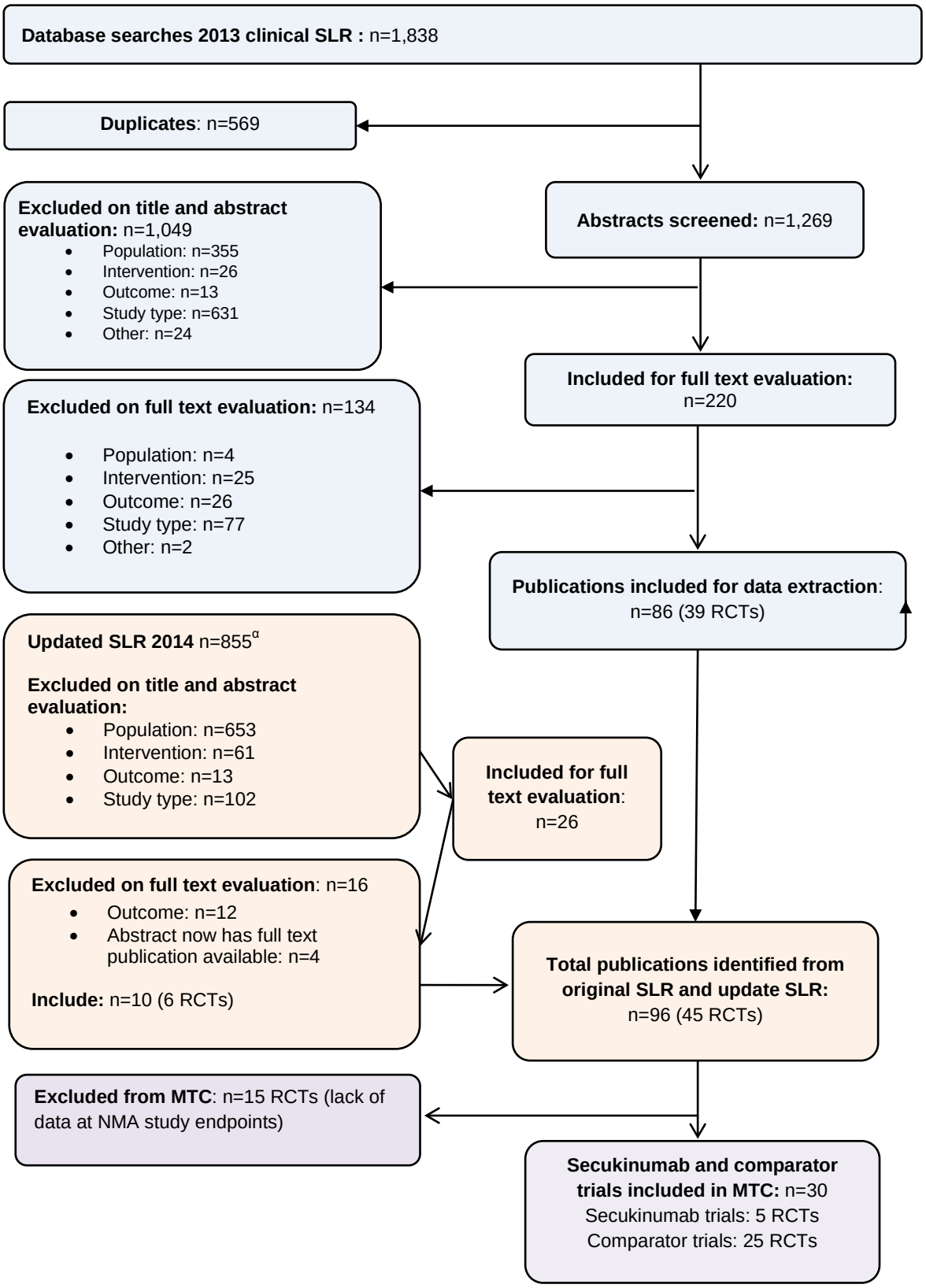
For each eligible study that passed level two screening, data of interest were extracted into a data extraction form that was developed for the review. Data extracted included the reference source, the study type, the patient populations, the interventions compared, the trial methods and a summary of results. At the time of data extraction, the quality of each RCT was assessed using the format recommended by NICE based on the CRD's guidance for undertaking reviews in health care. Quality assessments of included trials are presented in table format in section 10.4.

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-

statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

A PRISMA diagram of the clinical SLR (Figure 6) represents the flow of articles through the screening process. The SLR identified 45 RCTs overall (6 secukinumab RCTs, 39 comparator RCTs). However, during NMA feasibility assessment 15 RCTs were excluded due to lack of data at the endpoints considered in the analysis. Therefore, of the 45 RCTs identified, 30 RCTs were included in the NMA (5 secukinumab RCTs, 25 comparator RCTs).

**Figure 6. Clinical SLR: PRISMA Diagram**




α – updated systematic review 855 citations includes electronic database search and conference searches

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The primary sources for FIXTURE, ERASURE, JUNCTURE, and FEATURE were peer reviewed full text publications (19, 26, 27). Results from the placebo-controlled trial ERASURE and the active head-to-head trial FIXTURE were published in the New England Journal of Medicine in July 2014 (19). Twelve week results from the trial of secukinumab in an autoinjector device, JUNCTURE, were published in the Journal European Academy of Dermatology and Venereology,(26) and twelve week results from the trial of secukinumab in a pre-filled syringe, FEATURE, were published in the British Journal of Dermatology.(27)

Secondary references for these trials included conference abstracts reporting on subgroups within the trials (body weight (44, 45), prior biologic therapy(46) and sustainability of response(47-49). Novartis CSRs were the primary data source for the SCULPTURE trial as well as the SCULPTURE sub-group follow-on study, STATURE. Table 4 summarises the six secukinumab RCTs.

**Table 4. Summary of Relevant RCTs Sources**

| Trial Number | Trial Name | Primary Source | Secondary Source |
|---|---|---|---|
| CAIN457A2303 | FIXTURE | Langley 2014 (19) | Szepietowski 2014 (45)<br>Reich 2014 (48)<br>CSR (42)<br>Rivas 2014 (47) |
| CAIN457A2302 | ERASURE | Langley 2014(19) | Rich 2014 (44)<br>Papp 2014(46)<br>Gottlieb 2014 (50)<br>CSR (51) |
| CAIN457A2309 | JUNCTURE | Paul 2014 (26) | CSR (52) |
| CAIN457A2308 | FEATURE | Blauvelt 2014 (27) | CSR (53) |
| CAIN457A2304 | SCULPTURE | SCULPTURE CSR(28) | Mrowietz 2014 (39) |
| CAIN457A2307 | STATURE (subgroup follow on study from SCULPTURE) | STATURE CSR(29) | Thaci 2013 (54) |

## Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

A summary of the six relevant phase III RCTs have been provided below in Table 5.

**Table 5. Summary of Relevant RCTs**

| Trial no. (acronym) | Intervention | Comparator | Population | Primary study ref. |
|---|---|---|---|---|
| CAIN457A2303/ NCT01358578 (FIXTURE) | Secukinumab | Etanercept and placebo | 1,306 adult patients with moderate to severe, chronic, plaque-type psoriasis that had been diagnosed at least 6 months before randomisation | Langley 2014 (19) |
| CAIN457A2302/ NCT01365455 (ERASURE) | Secukinumab | Placebo | 738 adults patients with moderate to severe, chronic, plaque-type psoriasis that had been diagnosed at least 6 months before randomisation | Langley 2014(19) |
| CAIN 457A2309/ NCT01636687 (JUNCTURE) | Secukinumab | Placebo | 182 adults with moderate to severe, chronic, plaque-type psoriasis | Paul 2014(26) |
| CAIN 457A2308/ NCT01555125 (FEATURE) | Secukinumab | Placebo | 177 adults patients with moderate to severe, chronic, plaque-type psoriasis that had been diagnosed at least 6 months before randomisation | Blauvelt 2014 (27) |
| CAIN457A2304/ NCT01406938 (SCULPTURE) | Secukinumab | Placebo | 966 adults patients with moderate to severe, chronic, plaque-type psoriasis that had been diagnosed at least 6 months before randomisation | SCULPTURE CSR(28) |
| CAIN457A2307 (STATURE) | Secukinumab 10 mg/kg intravenous (i.v.) | Secukinumab 300 mg subcutaneous (s.c.) | 43 adults patients with moderate to severe, chronic, plaque-type psoriasis that were partial responders at 12 weeks in CAIN457A2304 study | STATURE CSR(29) |

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

With respect to the decision problem, secukinumab placebo-controlled or active-controlled studies are relevant evidence. There are four RCTs directly relevant to this submission as these directly compared secukinumab with etanercept and/or placebo: FIXTURE, ERASURE, JUNCTURE and FEATURE.

FIXTURE and ERASURE are two, large, primary RCTs supporting the safety and clinical evidence of secukinumab in the treatment of patients with moderate to severe chronic plaque psoriasis.(19) FIXTURE was a phase III head-to-head RCT comparing secukinumab with both placebo and etanercept. ERASURE was a phase III study comparing secukinumab with placebo.

JUNCTURE and FEATURE are two further RCTs, which present additional safety and clinical evidence for secukinumab in moderate to severe chronic plaque psoriasis patients.(26, 27) The population and primary endpoints of these RCTs align with those of FIXTURE and ERASURE.

In addition to the four RCTs discussed above, a fifth RCT, SCULPTURE, was also identified in the search as relevant to the decision problem (28). The aim of this study was to provide a comparison between secukinumab administered with a fixed dose regimen versus a retreatment at start of relapse (SoR) regimen (dosing as required in the event of a relaspse), with regards to the response and maintenance of response in subjects with moderate to severe chronic plaque-type psoriasis at 52 weeks. While the retreatment at start of relapse dosing regimen used within this trial is not in line with the draft secukinumab summary of product characteristics (SmPC), PASI 75 response was assessed at 12 weeks, and HRQoL data were collected alongside the trial. Thus, this RCT has been included as supporting evidence.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

One RCT was excluded from further discussion in this submission. STATURE was identified in the SLR (29) through hand searching; it is a sub-group follow-on study of SCULPTURE partial responders, and the aim was to assess the safety, tolerability and long-term efficacy of intravenous (10 mg/kg) and subcutaneous (300 mg) secukinumab in patients with moderate to severe chronic plaque-type psoriasis who are partial responders to secukinumab. STATURE has not been included due to the lack of placebo control and because the comparator dosing regimen used within this trial is not in line with the secukinumab draft SmPC. In addition the proportion of patients responding to secukinumab in SCULPTURE was higher than anticipated, therefore fewer patients were recruited into the STATURE study than expected (N=43). As a result the study was not statistically powered to meet the co-primary endpoints of PASI 75 and IGA 0 or 1 response at week 8 for secukinumab administered intravenously versus subcutaneously.

**List of relevant non-RCTs**

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

No non-RCTs were identified that were relevant to the decision problem.

## *6.3 Summary of methodology of relevant RCTs*

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Summaries of FIXTURE, ERASURE, JUNCTURE, FEATURE, and SCULPTURE are detailed in the sections below. Details of methodology include the following:

- Methods (study duration, blinding, randomisation, details of interventions and a study description)
- Participants (baseline characteristics and inclusion and exclusion criteria)
- Outcomes (primary and secondary outcomes, measures used, description of outcomes with relevance to the decision problem)
- Statistical analysis and definition of study groups (hypotheses, sample size calculation and statistical analysis)
- Patient numbers (number of patients eligible to enter the study and CONSORT flow chart)
- Critical appraisal of trials (allocation concealment, randomisation techniques, justification of sample size and adequacy of follow-up)

Results from FIXTURE, ERASURE, JUNCTURE and FEATURE have been published in peer reviewed journals. Data have been sourced from these publications

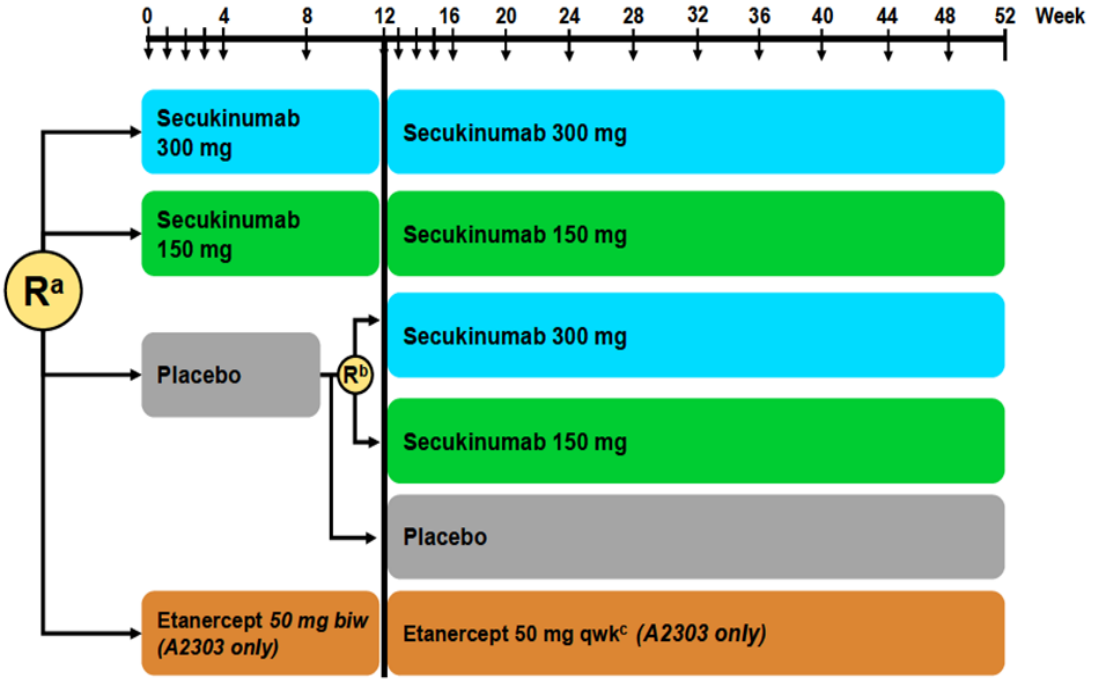
where possible. Where data that relate to the decision problem were not available in the literature the CSRs have been used for reference.

## Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

A trial schematic summarising the overall design of the four core trials FIXTURE, ERASURE, JUNCTURE and FEATURE is shown below in Figure 7. Tabular descriptions of the methodology of the five RCTs have been provided in Table 6. Study design diagrams for each trial have been provided in Appendix 3, Section 10.3.1.

**Figure 7. Overall trial schematics for FIXTURE, ERASURE, JUNCTURE and FEATURE**




[a] R, randomization at Week 0 to secukinumab (150 mg or 300 mg), etanercept 50 mg (Study A2303 only), or placebo with dosing at Weeks 0, 1, 2, 3, and 4, followed by maintenance dosing every 4 weeks

[b] Re-randomization of placebo patients that did not achieve PASI-75 response to secukinumab 150 mg or 300 mg administered at Weeks 12, 13, 14, 15, followed by dosing every 4 weeks maintenance dosing starting at Week 16

[c] Etanercept treatment qwk from Week 12 (A2303 only)

**Table 6. Comparative summary of methodology of the RCTs**

| Trial no. (acronym) | CAIN457A2303 (FIXTURE) (19, 42) | CAIN457A2302 (ERASURE)(19, 51) | CAIN457A2309 (JUNCTURE) (26, 52) | CAIN457A2308 (FEATURE) (27, 53) | CAIN457A2304 (SCULPTURE)(28) |
|---|---|---|---|---|---|
| Location | 231 centres in 26 countries (Argentina, Australia, Belgium, Brazil, Canada, Colombia, Egypt, Finland, France, Germany, Guatemala, Hungary, Iceland, India, Italy, Philippines, Poland, Republic of Korea, Romania, Russian Federation, Singapore, Spain, Sweden, Turkey, United Kingdom, United States). | 88 centres worldwide in 12 countries (Argentina, Canada, Columbia, Estonia, Iceland, Israel, Japan, Latvia, Lithuania, Mexico, Taiwan, and United States) | 38 study sites worldwide in 5 countries (USA, Canada, Estonia, France, Germany) | 32 centres worldwide: in 5 countries (Canada, Estonia, France, Germany and United States) | 133 centres worldwide in 16 countries: Austria , Bulgaria , Canada, Czech Republic, France, Germany, India, Italy, Japan, Poland, Singapore, Slovakia, Switzerland, United Kingdom, United States, Vietnam |
| Phase | 3 | 3 | 3 | 3 | 3 |
| N | 1,306 | 738 | 182 | 177 | 966 |
| Design | Double-blind, multicentre, double-dummy, randomised, parallel-group, active and placebo – controlled | Double-blind, double-dummy, randomised, multicentre, parallel-group, active and placebo -controlled | Double-blind, randomised, multicentre, parallel-group, and placebo-controlled | Double-blind, randomised, multicentre, parallel-group, and placebo-controlled | Double-blind, multicentre, randomised, parallel-group, and placebo-controlled |
| Duration of study | Overall: 52 weeks of active treatment<br>Induction period: 12 weeks<br>Maintenance period: 40 weeks | Overall: 52 weeks of active treatment<br>Induction period: 12 weeks<br>Maintenance period: 40 weeks | Overall: 52 weeks of active treatment<br>Induction period: 12 weeks<br>Maintenance period: 40 weeks<br>Optional Extension of a further 156 weeks | Overall: 52 weeks of active treatment<br>Induction period: 12 weeks<br>Maintenance period: 40 weeks<br>Optional Extension of a further 156 weeks | Overall: 52 weeks of active treatment<br>Induction period: 12 weeks<br>Maintenance period: 40 weeks |

| | | | | | |
|---|---|---|---|---|---|
| Method of randomisation | Eligible patients were randomised via IRT (V2)[a]<br>Randomisation was stratified by geographical region and body weight (≥ 90 kg or < 90 kg)[b]<br>Eligible subjects were randomized in a 1:1:1:1 ratio to receive secukinumab 300 mg or 150 mg or etanercept or placebo | Eligible patients were randomised via IRT (V2)[a]<br>Randomisation was stratified by geographical region and body weight (≥ 90 kg or < 90 kg)[b]<br>Eligible subjects were randomized in a 1:1:1 ratio to receive secukinumab 300 mg or 150 mg or placebo | Eligible patients were randomised via IRT (V2)[a]<br>Randomisation was stratified by body weight (≥ 90 kg or < 90 kg)[b]<br>Subjects were randomly allocated 1:1:1 to secukinumab 300 mg, secukinumab 150 mg or placebo delivered subcutaneously by autoinjector.<br>It was targeted to have at least approximately 30% of the patients in either of the 2 strata. | Eligible patients were randomised via IRT (V2)[a]<br>Randomisation was stratified by body weight (≥ 90 kg or < 90 kg)[b]<br>It was targeted to have at least approximately 30% of the patients in either of the 2 strata<br>Eligible subjects were randomised in a 1:1:1 ratio to receive secukinumab 300 or 150 mg or placebo | Eligible patients were randomised via IRT (V2)[a] and within dose group to fixed interval or treatment at start of relapse (V8)[a]<br>Randomisation was stratified by geographic region and body weight (≥ 90 kg or < 90 kg)[c]. It was targeted to have at least approximately 30% of the patients in either of the 2 strata |
| Method of blinding (care provider, patient and outcome assessor) | Double blind – patients, investigator staff, assessors, data analysts[1,2] | Double blind – patients, investigator staff, assessors, data analysts[1,2] | Double blind – patients, investigator staff, assessors, data analysts[1,2] | Double blind – patients, investigator staff, assessors, data analysts[1,2] | Double blind – patients, investigator staff, assessors, data analysts[1,3] |
| Intervention/Comparator | SEC 150 mg SC (n=327) vs SEC 300 mg SC (n= 327) vs ETAN (n=326) vs PBO (n=326) | SEC 150 mg SC (n=245) vs SEC 300 mg SC (n= 245) vs PBO (n=248) | SEC 150 mg SC (n=61) vs SEC 300 mg SC (n= 60) vs PBO (n=61) | SEC 150 mg SC (n=59) vs SEC 300 mg SC (n= 59) vs PBO (n=59) | **Induction:** SEC 150 mg SC (n=482) vs SEC 300 mg SC (n= 484)<br>**Maintenance:** Re-randomised to fixed dose interval (either SEC 150 mg or 300 mg depending on randomisation) every 4 Weeks to Week 48 vs. Start of relapse* (same dose as received in induction period & continued dosing until PASI 75 response was regained[†]) |
| Duration of follow-up | 8 weeks | 8 weeks | 8 weeks | 8 weeks | 8 weeks |
| Timing of assessments | Primary efficacy measures of PASI and IGA and AE safety assessments were carried out at:<br>Screening, randomisation<br>Weeks 1, 2, 3, 4, 8, 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60 | Primary efficacy measures of PASI and IGA and AE safety assessments were carried out at:<br>Screening, randomisation<br>Weeks 1, 2, 3, 4, 8, 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60 | Primary efficacy measures of PASI and IGA and AE safety assessments were carried out at:<br>Screening, randomisation<br>Weeks 1, 2, 3, 4, 8, 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60 | Primary efficacy measures of PASI and IGA and AE safety assessments were carried out at:<br>Screening, randomisation<br>Weeks 1, 2, 3, 4, 8, 12 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60 | Primary efficacy measures of PASI and IGA and AE safety assessments were carried out at:<br>Screening, randomisation<br>Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60 |

**Key:** ETAN = etanercept;; IRT = Interactive Response Technology; Maint. = maintenance PASI = Psoriasis Area and Severity Index; PBO = placebo; SC = subcutaneous; SEC = secukinumab; V = Visit; Wk(s) = week(s) , AE = Adverse Event, IGA = Investigators Global Assessment

**Notes: Randomisation: (a)** A patient randomisation list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomisation numbers. These randomisation numbers were linked to the different treatment groups, which in turn were linked to medication numbers; **(b)** Randomisation was stratified at initial randomisation (V2) by geographical region and by body weight collected at randomisation; **(c)** Randomisation was stratified at initial randomisation (V2) and at Wk 12 re-randomisation (V8) by geographical region and by body weight collected at randomisation. The latter stratification ensured balanced allocation of patients to treatment groups within the weight strata (≥ 90 kg or < 90 kg).**Blinding: (1)** Randomisation data were kept strictly confidential until the time of unblinding, and were not accessible by anyone else involved in the study; **(2)** The identity of the treatments was concealed by the use of investigational treatment that were all identical in packaging, labelling, schedule of administration, appearance, taste and odour. SEC 150 mg and SEC placebo were both labelled as "AIN457 150 mg/Placebo" to maintain the blind. Sponsor staff unblinded at Wk 12 and patients, investigator staff and assessors remained blinded until final database lock at Wk 60; **(3)** Placebo and active medication were prepared by an unblinded pharmacist or an unblinded qualified site personnel at each site in order to maintain the blind and to avoid unintentional unblinding, the results of hsCRP were not communicated to study site staff; Investigator up to primary endpoint analysis **Other:** * Defined as a loss of ≥20% of the maximum PASI gain achieved during the study compared to baseline, and a loss of PASI 75 response; [†] After Wk 12, if a patient did not fulfill the criteria of a start of relapse or was back to PASI 75 response after a start of relapse, they received placebo injections (two injections per dose) to maintain the blind. This treatment regimen was applied up to and including Wk 48

**Participants**

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

All trials included adult patients with chronic plaque-type psoriasis diagnosed for at least six months prior to randomisation. A summary of the inclusion/exclusion criteria from the relevant clinical trials has been provided in Table 7 to Table 11, with full details in Appendix 11, Section 10.11. The inclusion and exclusion criteria were consistent across the five RCTs.

**Table 7. FIXTURE Inclusion/Exclusion Criteria**

| FIXTURE (19, 42) | |
|---|---|
| **Inclusion** | **Exclusion** |
| - Men or women at least 18 years of age at time of screening<br>- Chronic plaque-type psoriasis diagnosed for at least 6 months before randomization<br>- Moderate to severe psoriasis as defined at randomization by:<br>• PASI score of 12 or greater and,<br>• IGA mod 2011 score of 3 or greater (based on a scale of 0 – 4) and,<br>• Body Surface Area (BSA) affected by plaque-type psoriasis of 10% or greater<br>- Candidate for systemic therapy, defined as having chronic plaque-type psoriasis considered inadequately controlled by:<br>• topical treatment and/or<br>• phototherapy and/or<br>• previous systemic therapy | - Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic and guttate psoriasis).<br>- Drug-induced psoriasis (i.e. new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium).<br>- Ongoing use of prohibited psoriasis treatments (e.g., topical or systemic corticosteroids (CS), ultraviolet (UV) therapy).<br>- Ongoing use of other non-psoriasis prohibited treatments<br>- Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor.<br>- Previous exposure to etanercept<br>- Pregnant or nursing (lactating) women.<br>- Women of child-bearing potential, unwilling to use effective contraception during the study and for 16 weeks after stopping treatment.<br>- Significant medical problems, including but not limited to the following: uncontrolled hypertension, congestive heart failure.<br>[redacted]<br>- Active systemic infections during the last two weeks (exception: common cold) prior to randomization or any infection that reoccurs on a regular basis.<br>- History of an ongoing, chronic or recurrent infectious disease (e.g. tuberculosis, HIV, hepatitis B, hepatitis C,lymphoproliferative disease, known malignancy or history of malignancy)<br>[redacted]<br>- Subjects who are allergic to rubber or latex;<br>-Any medical or psychiatric condition which, in the investigator's opinion would preclude the particpant from adherence to the protocol or completing the study per protocol.<br>-History or evidence of ongoing alcohol or drug abuse<br>- Plans for administration of live vaccines during the study period or 6 weeks prior to randomization.<br>[redacted]<br>-subjects not willing to limit UV light exposure (e.g.sunbathing and/or the use of tanning devices) during the course of this study |

**Table 8. ERASURE Inclusion/Exclusion Criteria**

| ERASURE (19, 51) | |
|---|---|
| **Inclusion** | **Exclusion** |
| The inclusion criteria were the same as FIXTURE (above). | The exclusion criteria were similar to FIXTURE (above) the main difference being that patients with previous exposure to etanercept were not excluded. |

**Table 9. JUNCTURE Inclusion/Exclusion Criteria**

| JUNCTURE(26, 52) | |
|---|---|
| **Inclusion** | **Exclusion** |
| The inclusion criteria were the same as FIXTURE (above). | The exclusion criteria were similar to FIXTURE (above) the differences being that patients with previous exposure to etanercept were not excluded and that patients with an inability or unwillingness to undergo repeated venipuncture or self-injection with the AI were also excluded from the study. |

**Table 10. FEATURE Inclusion/Exclusion Criteria**

| FEATURE (27, 53) | |
|---|---|
| **Inclusion** | **Exclusion** |
| The inclusion criteria were the same as FIXTURE (above). | The exclusion criteria were similar to FIXTURE (above) the differences being that patients with previous exposure to etanercept were not excluded and that patients with an inability or unwillingness to undergo repeated venipuncture or self-injection with a pre-filled syringe were also excluded from the study. |

**Table 11. SCULPTURE Inclusion/Exclusion Criteria**

| SCULPTURE (28) | |
|---|---|
| **Inclusion** | **Exclusion** |
| The inclusion criteria were the same as FIXTURE (above). | The exclusion criteria were the same as FIXTURE (above). |

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Patient age and gender are comparable across RCTs. Characteristics of participants in the five RCTs across randomised groups are presented in the tables below. Within the FEATURE study population, there was a lower proportion of Asian patients (1.7-3.4%) and a higher proportion of Caucasian patients (86.4-96.6%) when compared to the other RCTs. FEATURE and ERASURE also had higher proportions of patients who had failed on a prior biologic when compared to the other RCTs, however results from subgroup analyses in populations with failure to respond to prior biologic therapy in FIXTURE and ERASURE were generally consistent with the overall results from these studies.

**Table 12. Characteristics of participants in FIXTURE across randomised groups**

| CAIN457A2303 (FIXTURE)(19) | | | | |
|---|---|---|---|---|
| **N=1,306** | **SEC 300 mg (n=327)** | **SEC 150 mg (n=327)** | **ETAN (n=326)** | **PBO (n=326)** |
| Age (yrs), mean (SD) | 44.5 (13.2) | 45.4 (12.9) | 43.8 (13.0) | 44.1 (12.6) |
| Gender (male), n (%) | 224 (68.5) | 236 (72.2) | 232 (71.2) | 237 (72.7) |
| Race, n (%) | | | | |
| White, n (%) | 224 (68.5) | 219 (67.0) | 219 (67.2) | 218 (66.9) |
| Asian, n (%) | 73 (22.3) | 72 (22.0) | 74 (22.7) | 72 (22.1) |
| Other or unknown, n (%) | 30 (9.2) | 36 (11.0) | 33 (10.1) | 36 (11.0) |

| CAIN457A2303 (FIXTURE)(19) | | | | |
|---|---|---|---|---|
| **N=1,306** | **SEC 300 mg (n=327)** | **SEC 150 mg (n=327)** | **ETAN (n=326)** | **PBO (n=326)** |
| Weight (kg), mean (SD) | 83.0 (21.6) | 83.6 (20.8) | 84.6 (20.5) | 82.0 (20.4) |
| BMI (kg/m$^2$) mean (SD) | 28.4 (6.4) | 28.4 (5.9) | 28.7 (5.9) | 27.9 (6.1) |
| Time since psoriasis diagnosis (yr) | 15.8 (12.3) | 17.3 (12.2) | 16.4 (12.0) | 16.6 (11.6) |
| Baseline PASI score, mean (SD) | 23.9 (9.9) | 23.7 (10.5) | 23.2 (9.8) | 24.1 (10.5) |
| Baseline total BSA, mean (SD) | 34.3 (19.2) | 34.5 (19.4) | 33.6 (18.0) | 35.2 (19.1) |
| Baseline IGA mod 2011 score, n (%) | | | | |
| 3 moderate, n (%) | 203 (62.1) | 206 (63.0) | 195 (59.8) | 202 (62.0) |
| 4 severe, n (%) | 124 (37.9) | 121 (37.0) | 131 (40.2) | 124 (38.0) |
| Psoriatic arthritis, n (%) | 50 (15.3) | 49 (15.0) | 44 (13.5) | 49 (15.0) |
| Previous systemic treatment, n (%) | | | | |
| Any | 206 (63.0) | 212 (64.8) | 214 (65.6) | 204 (62.6) |
| Conventional agent | 195 (59.6) | 198 (60.6) | 204 (62.6) | 199 (61.0) |
| Biologic agent | 38 (11.6) | 45 (13.8) | 45 (13.8) | 35 (10.7) |
| TNF inhibitor | 12 (3.7) | 15 (4.6) | 21 (6.4) | 12 (3.7) |
| Anti−interleukin-12 and anti - interleukin-23 agent | 23 (7.0) | 23 (7.0) | 22 (6.7) | 21 (6.4) |
| No response to previous use of TNF inhibitor | 10 (3.1) | 9 (2.8) | 10 (3.1) | 3 (0.9) |

**Abbreviations**: yrs, years; kg, kilogram; BMI, body mass index; PASI, psoriasis area-and-severity index ; IGA, investigator's global assessment ;SD, standard deviation; yr, year; TNF, tumor necrosis factor.
**Note**: Race was self-reported. The body-mass index is the weight in kilograms divided by the square of the height in metres. Scores on the psoriasis area-and-severity index (PASI) range from 0 to 72, with higher scores indicating more severe disease. Scores on the modified investigator's global assessment range from 0 (clear skin) to 4 (severe disease); a score of 3 indicates moderate disease. Conventional systemic agents included methotrexate, ciclosporin, glucocorticoids, and fumaric acid esters.

## Table 13. Characteristics of participants in ERASURE across randomised groups

| CAIN457A2302 (ERASURE) (19) | | | |
|---|---|---|---|
| **N=738** | **SEC 300 mg (n=245)** | **SEC 150 mg (n=245)** | **PBO (n=248)** |
| Age (yrs), mean (SD) | 44.9 (13.5) | 44.9 (13.3) | 45.4 (12.6) |
| Gender (male), n (%) | 169 (69.0) | 168 (68.6) | 172 (69.4) |
| Race, n (%) | | | |
| White n (%) | 171 (69.8) | 171 (69.8) | 176 (71.0) |
| Asian, n (%) | 52 (21.2) | 54 (22.0) | 46 (18.5) |
| Other or unknown, n (%) | 22 (9.0) | 20 (8.2) | 26 (10.5) |
| Weight (kg), mean (SD) | 88.8 (24.0) | 87.1 (22.3) | 89.7 (25.0) |
| BMI (kg/m$^2$) mean (SD) | 30.3 (7.2) | 29.8 (6.8) | 30.3 (7.8) |
| Time since psoriasis diagnosis (yr) | 17.4 (11.1) | 17.5 (12.0) | 17.3 (12.4) |
| Baseline PASI score, mean (SD) | 22.5 (9.2) | 22.3 (9.8) | 21.4 (9.1) |
| Baseline total BSA, mean (SD) | 32.8 (19.3) | 33.3 (19.2) | 29.7 (15.9) |
| Baseline IGA mod 2011 score, n (%) | | | |
| 3 moderate, n (%) | 154 (62.9) | 161 (65.7) | 151 (60.9) |
| 4 severe, n (%) | 91 (37.1) | 84 (34.3) | 97 (39.1) |
| Psoriatic arthritis, n (%) | 57 (23.3) | 46 (18.8) | 68 (27.4) |
| Previous systemic treatment, n (%) | | | |
| Any | 163 (66.5) | 156 (63.7) | 146 (58.9) |
| Conventional agent | 128 (52.2) | 125 (51.0) | 108 (43.5) |
| Biologic agent | 70 (28.6) | 73 (29.8) | 73 (29.4) |
| TNF inhibitor | 48 (19.6) | 44 (18.0) | 51 (20.6) |
| Anti−interleukin-12 and anti-interleukin-23 agent | 32 (13.1) | 37 (15.1) | 31 (12.5) |
| No response to previous use of TNF inhibitor | 17 (6.9) | 18 (7.3) | 21 (8.5) |

**Abbreviations**: yrs, years; kg, kilogram; BMI, body mass index; PASI, psoriasis area-and-severity index ; IGA, investigator's global assessment ;SD, standard deviation; yr, year; TNF, tumor necrosis factor.
**Note**: Race was self-reported. The body-mass index is the weight in kilograms divided by the square of the height in metres. Scores on the psoriasis area-and-severity index (PASI) range from 0 to 72, with higher scores indicating more severe disease. Scores on the modified investigator's global assessment range from 0 (clear skin) to 4 (severe disease); a score of 3 indicates moderate disease. Conventional systemic agents included methotrexate, ciclosporin, glucocorticoids, and fumaric acid esters.

## Table 14. Characteristics of participants in JUNCTURE across randomised groups

| CAIN457A2309 (JUNCTURE) (26, 52) | | | |
|---|---|---|---|
| **N=182** | **SEC 300 mg (n=60)** | **SEC 150 mg (n=61)** | **PBO (n=61)** |
| Age (yrs), mean (SD) | 46.6 (14.2) | 43.9 (14.4) | 43.7 (12.7) |
| Gender (male), n (%) | 46 (76.7) | 41 (67.2) | 38 (62.3) |
| Caucasian, n (%) | 56 (93.3) | 58 (95.1) | 59 (96.7) |
| Weight (kg), mean (SD) | 91.0 (23.1) | 93.7 (31.7) | 90.2 (21.2) |
| BMI (kg/m$^2$) mean (SD) | 30.0 (6.9) | 30.6 (9.5) | 30.0 (6.8) |
| Time since psoriasis diagnosis (yr) | 21.0 (13.5) | 20.6 (14.5) | 19.86 (12.2) |
| Baseline PASI score, mean (SD) | 18.9 (6.4) | 22.0 (8.9) | 19.4 (6.7) |
| Baseline total BSA, mean (SD) | 26.4 (12.8) | 30.1 (16.7) | 25.7 (14.7) |
| Baseline IGA mod 2011 score, n (%) | | | |
| 3 moderate, n (%) | 39 (65.0) | 35 (57.4) | 38 (62.3) |
| 4 severe, n (%) | 21 (35.0) | 26 (42.6) | 23 (37.7) |
| Psoriatic arthritis, n (%) | 14 (23.3) | 16 (26.2) | 12 (19.7) |

| CAIN457A2309 (JUNCTURE) (26, 52) | | | |
|---|---|---|---|
| **N=182** | **SEC 300 mg (n=60)** | **SEC 150 mg (n=61)** | **PBO (n=61)** |
| Previous systemic treatment, n (%) | | | |
| Any | 34 (56.7) | 34 (55.7) | 33 (54.1) |
| Conventional agent | 30 (50.0) | 31 (50.8) | 29 (47.5) |
| Biologic agent | 15 (25.0) | 15 (24.6) | 13 (21.3) |
| **Abbreviations**: yrs, years; kg, kilogram; BMI, body mass index; PASI, psoriasis area-and-severity index ; IGA, investigator's global assessment ;SD, standard deviation; yr, year | | | |

## Table 15. Characteristics of participants in FEATURE across randomised groups

| CAIN457A2308 (FEATURE) (27, 53) | | | |
|---|---|---|---|
| **N=177** | **SEC 300 mg (n=59)** | **SEC 150 mg (n=59)** | **PBO (n=59)** |
| Age (yrs), mean (SD) | 45.1 (12.6) | 46.0 (15.1) | 46.5 (14.1) |
| Gender (male), n (%) | 38 (64.4) | 40 (67.8) | 39 (66.1) |
| Caucasian, n (%) | 54 (91.5) | 51 (86.4) | 57 (96.6) |
| Weight (kg), mean (SD) | 92.6 (25.9) | 93.7 (25.6) | 88.4 (21.5) |
| Time since psoriasis diagnosis (yr) | 18.0 (11.9) | 20.4 (13.0) | 20.2 (14.2) |
| Baseline PASI score, mean (SD) | 20.7 (8.0) | 20.5 (8.3) | 21.1 (8.5) |
| Baseline total BSA, mean (SD) | 33.3 (18.0) | 30.6 (16.6) | 32.2 (17.4) |
| Baseline IGA mod 2011 score, n (%) | | | |
| 3 moderate, n (%) | 40 (67.8) | 37 (62.7) | 34 (57.6) |
| 4 severe, n (%) | 19 (32.2) | 22 (37.3) | 25 (42.4) |
| Psoriatic arthritis, n (%) | 50 (15.3) | 49 (15.0) | 49 (15.0) |
| Previous systemic treatment, n (%) | | | |
| Any | 35 (59.3) | 45 (76.3) | 39 (66.1) |
| Conventional agent | 20 (33.9) | 39 (66.1) | 29 (49.2) |
| Biologic agent | 23 (39.0) | 28 (47.5) | 26 (44.1) |
| Failure on prior systemic biologic | 9/23 (39.1) | 18/28 (64.3) | 14/26 (53.8) |
| **Abbreviations**: yrs, years; kg, kilogram; BMI, body mass index; PASI, psoriasis area-and-severity index ; IGA, investigator's global assessment ;SD, standard deviation; yr, year | | | |

## Table 16. Characteristics of participants in SCULPTURE across randomised groups

| CAIN457A2304 (SCULPTURE) (28) | | |
|---|---|---|
| N=966 | SEC 300 mg [redacted] | SEC 150 mg [redacted] |
| Age (yrs), mean (SD) | [redacted] | [redacted] |
| <65 yrs, n (%) | [redacted] | [redacted] |
| ≥65 yrs, n (%) | [redacted] | [redacted] |
| ≥75 yrs, n (%) | [redacted] | [redacted] |
| Sex (male), n (%) | [redacted] | [redacted] |
| Race, n (%) | | |
| Asian, n (%) | [redacted] | [redacted] |
| Black, n (%) | [redacted] | [redacted] |
| Caucasian, n (%) | [redacted] | [redacted] |
| Other or unknown, n (%) | [redacted] | [redacted] |
| Weight (kg), mean (SD) | [redacted] | [redacted] |
| BMI (kg/m2), mean (SD) | [redacted] | [redacted] |
| Baseline PASI score | | |
| n | [redacted] | [redacted] |
| mean (SD) | [redacted] | [redacted] |
| PASI ≤20, n (%) | [redacted] | [redacted] |
| PASI >20, n (%) | [redacted] | [redacted] |
| Baseline total BSA) | | |
| n | [redacted] | [redacted] |
| mean (SD) | [redacted] | [redacted] |
| Baseline IGA mod 2011 score, n (%) | | |
| n | [redacted] | [redacted] |
| moderatea, n (%) | [redacted] | [redacted] |
| severeb, n (%) | [redacted] | [redacted] |
| Severity of psoriasis | | |
| n | [redacted] | [redacted] |
| moderatea, n (%) | [redacted] | [redacted] |
| severeb, n (%) | [redacted] | [redacted] |
| Duration of psoriasis - years | | |
| n | [redacted] | [redacted] |

| CAIN457A2304 (SCULPTURE) (28) | | |
|---|---|---|
| N=966 | SEC 300 mg [redacted] | SEC 150 mg [redacted] |
| mean (SD) | [redacted] | [redacted] |
| Psoriatic arthritis present, n (%)<br>Yes | [redacted] | [redacted] |
| Prior exposure to treatment (yes)<br>n<br>Systemic therapy, n (%)<br>Biologic therapy, n (%)<br>Non-biologic therapy, n (%) | [redacted] | [redacted] |
| Prior failure (yes)<br>n<br>Systemic therapy, n (%)<br>Biologic therapy, n (%)<br>Non-biologic therapy, n (%) | [redacted] | [redacted] |
| Baseline demographics and background characteristics for the induction period were representative of the psoriasis population and were well distributed between the treatment arms<br>Disease history and baseline characteristics for the induction period reflected the study inclusion and exclusion criteria, and overall were well distributed between the treatment arms | | |
| Key: BMI = body mass index; BSA = body surface area; IGA = Investigator's Global Assessment; PASI = Psoriasis Area Severity Index; PBO = placebo; SD = standard deviation; SEC = Secukinumab<br>Notes: In this table, all subset percentages of failures versus successes on prior psoriasis systemic therapy (biologic or non-biologic) for the induction period were calculated out of the total number of patients exposed to either 150 mg or 300 mg secukinumab; (a) PASI ≥10 or total BSA ≥10% and PASI ≤20 and total BSA ≤20%; b Total BSA >20% or PASI >20) | | |

## Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Outcome definitions were consistent across the RCTs. The outcome definitions used in the RCTs have been provided in Table 17. These outcome measures are in line with the EMA guidance on optimal outcomes in clinical studies: EMA position on efficacy outcomes in psoriasis (55). Descriptions of outcome measures have been provided in appendix 3, section 10.3.2.

In addition, one of the primary endpoints in FIXTURE, ERASURE, JUNCTURE and FEATURE aligns with the primary definition of response (i.e. PASI 75) assessed within NICE Clinical Guidance (NICE CG153)(3). DLQI was also assessed in the clinical trials, and this measure together with the PASI are used to define treatment efficacy and severity of disease in NICE CG153. A number of further outcomes were assessed in these studies, as summarised in Table 18.

**Table 17. Definition of outcomes used in the RCTs**

| Outcome | Definition |
|---|---|
| **Efficacy** | |
| IGA mod 2011 | The IGA mod 2011 tool 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 the psoriasis severity focusing on duration, erythema and scaling. The IGA mod 2011 scale used in the trials has been specifically developed taking into account feedback from the FDA. |
| PASI 50 response | Patients achieving ≥ 50% improvement (reduction) in PASI score compared to baseline were defined as PASI 50 responders. The PASI score is a standard and validated reference for chronic plaque-type psoriasis. |
| PASI 75 response | Patients achieving ≥ 75% improvement (reduction) in PASI score compared to baseline were defined as PASI 75 responders. |
| PASI 90 response | Patients achieving ≥ 90% improvement (reduction) in PASI score compared to baseline were defined as PASI 90 responders. The best evidence of efficacy is the percentage of patients who achieve the result of "clear or almost clear" (PASI>90%) on treatment. |
| PASI 100 response / remission | Complete clearing of psoriasis (PASI=0) |
| Relapse | When the achieved maximal PASI improvement from baseline was reduced by >50%. |
| Rebound-like event | An increase in PASI to >125% of baseline PASI, or presence of new pustular psoriasis, new erythrodermic psoriasis, or more inflammatory psoriasis occurring after the last dose of study treatment received |
| Rebound | Rebound-like event occurring within 8 weeks of stopping therapy |
| Maintenance of response | **For patients in the fixed interval regimens** PASI 75 response at Wk 52<br>**For patients in the start of relapse regimens** PASI 75 response at Wk 52 for patients who qualified for active treatment at Wk 40; & PASI 75 response at Wk 40 for patients who did not qualify for active treatment at Wk 40 |
| **QoL** | |
| DLQI | 10-item general dermatology disability index designed to assess health-related quality of life in adult subjects with skin diseases. Scores range from 0 to 30, and higher scores indicate greater health-related quality of life impairment. |
| EQ-5D | Generic instrument to assess subject's health status. It provides a simple descriptive profile and a single index value for health status. |
| HAQ-DI | Used measures to assess the long-term influence of chronic disease on a subject's level of functional ability and activity restriction. Scores range from 0 to 30, and higher scores indicate greater health-related quality of life impairment. |
| Psoriasis Symptom Diary | 16 items designed to evaluate a variety of psoriasis related characteristics that subjects have reported as important and relevant to their disease and treatment. More specifically, this instrument evaluates psoriasis-related itching, pain, scaling, stinging, burning, skin cracking and skin color. |
| **Key:** PASI = Psoriasis Area and Severity Index, IGA= investigator's global assessment, FDA= Food and Drug Administration, QoL= Quality of Life, DLQI= Dermatology Life Quality Index, EQ-5D= EuroQoL-5 Dimension, HAQ-DI= Health Assessment Questionnaire- Disability Index | |

**Table 18. Primary and Secondary Outcomes of the RCTs**

| Trial no. (acronym) | Primary outcome(s) and measures | Secondary/Other key outcome(s) and measures |
|---|---|---|
| **CAIN457A2303 (FIXTURE) (19, 42)** | Superiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to both PASI 75 and IGA mod 20110 or 1 response (co-primary endpoints) at Week 12, compared to placebo. | • Superiority of secukinumab with respect to:<br>• PASI 90 response at Week 12, compared to placebo.<br>• PASI 75 response at Week 12, compared to etanercept.<br>• PASI 75 response and IGA mod 2011 0 or 1 response at Week 12, compared to etanercept.<br>• Psoriasis related itching, pain and scaling as measured by the Psoriasis Symptom Diary at Week 12 compared to placebo and etanercept<br>• Superiority of secukinumab in maintaining PASI 75 response at Week 52 for subjects who were PASI 75 responders at Week 12, compared to etanercept.<br>• Superiority of secukinumab in maintaining IGA mod 2011 0 or 1 response at Week 52 for subjects who were IGA mod 2011 0 or 1 responders at Week 12, compared to etanercept.<br>• Efficacy of secukinumab with respect to:<br>• PASI 50 / 75 / 90 / 100 and IGA mod 20011 0 or 1 response over time up to week 12 compared to placebo and etanercept, and from week 12 to week 52 compared to etanercept.<br>• Time to PASI 75 response up to Week 12, compared to placebo and etanercept.<br>[redacted]<br>• Clinical safety and tolerability of secukinumab compared to placebo.<br>• Efficacy of secukinumab with respect to EQ-5D (EuroQOL 5-Dimension Health Status Questionnaire) score at Week 12, compared to placebo and etanercept, and over time up to Week 52, compared to etanercept.<br>• Effects of treatment with secukinumab with respect to changes in Dermatology Life Quality Index (DLQI) at Week 12, compared to placebo and etanercept, and over time up to Week 52, compared to etanercept.<br>• Effects of treatment of secukinumab with respect to DLQI 0 or 1 achievement at Week 12, compared to placebo and etanercept, and over time up to Week 52, compared to etanercept.<br>[redacted] |

| Trial no. (acronym) | Primary outcome(s) and measures | Secondary/Other key outcome(s) and measures |
|---|---|---|
| **CAIN457A2302 (ERASURE) (19, 51)** | The Primary outcome measure was the same as FIXTURE (above). | The secondary objectives were consistent with FIXTURE but with placebo as the only comparator:<br>• Superiority of secukinumab with respect to PASI 90 response at Week 12, as compared to placebo.<br>• Efficacy of secukinumab in maintaining PASI 75 response at Week 52 for patients who were PASI 75 responders at Week 12.<br>• Efficacy of secukinumab in maintaining IGA mod 2011 0 or 1 response at Week 52 for patients who were IGA mod 2011 0 or 1 responders at Week 12.<br>• Superiority of secukinumab with respect to psoriasis-related itching, pain and scaling as measured by the Psoriasis Symptom Diary at Week 12 compared to placebo.<br>• Clinical safety and tolerability of secukinumab compared to placebo.<br>• Efficacy of secukinumab with respect to PASI 50 / 75 / 90 / 100 and IGA mod 2011 0 or 1 response compared to placebo and over time up to Week 52.<br>• Efficacy of secukinumab with respect to PASI score and IGA mod 2011 score over time up to Week 12, compared to placebo and over time up to Week 52.<br>• Efficacy of secukinumab with respect to time to PASI 75 response up to Week 12 compared to placebo.<br>[redacted]<br>• Efficacy of secukinumab with respect to EQ-5D score at Week 12, compared to placebo, and over time up to Week 52.<br>• Effects of treatment with secukinumab with respect to changes in DLQI at Week 12 compared to placebo, and over time up to Week 52.<br>[redacted] |
| **CAIN457A2309 (JUNCTURE) (26, 52)** | To demonstrate the efficacy of autoinjector administered secukinumab in patients with moderate to severe chronic plaque-type psoriasis with respect to both PASI 75 and IGA 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo. | • Efficacy of secukinumab with respect to PASI 50 / 75 / 90 / 100 and IGA mod 2011 0 or 1 response, compared to placebo up to Week 12, and over time up to Week 52.<br>• Efficacy of secukinumab with respect to PASI score and IGA mod 2011 score at Week 12 compared to placebo, and over time up to Week 52.<br>[redacted]<br>• Development of immunogenicity against secukinumab. |

| Trial no. (acronym) | Primary outcome(s) and measures | Secondary/Other key outcome(s) and measures |
|---|---|---|
| **CAIN457A2308 (FEATURE) (27, 53)** | To demonstrate the efficacy of secukinumab in patients with moderate to severe chronic plaque-type psoriasis with respect to both PASI 75 and IGA 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo. | The secondary outcomes were the same as JUNCTURE listed above. |
| **CAIN457A2304 (SCULPTURE) (24, 28)** | To demonstrate the non-inferiority of 150 mg and 300 mg of secukinumab administered at the start of relapse versus fixed interval regimens of 150 mg and 300 mg of secukinumab respectively, in patients with moderate to severe chronic plaque-type psoriasis who were psoriasis area and severity index (PASI) 75 responders at Week 12, with respect to PASI 75 response: [redacted] | The secondary objectives applied to all patients for data up to Week 12 as well as to patients who were PASI 75 responders at Week 12: [redacted]<br>• Effects of treatment regimens with secukinumab with respect to PASI score and IGA mod 2011 score over time, up to Week 52<br>• Clinical safety and tolerability of secukinumab treatment regimens. [redacted] |

In addition to the pre-specified outcomes reported above, post-hoc analyses were carried out in FIXTURE and ERASURE to assess PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 0 or 1 responses at week 16 as a result of the observation from these trials that there continued to be increases in efficacy with secukinumab between weeks 12 and weeks 16.

## Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

A summary of the statistical analyses conducted in the RCTs has been provided in Table 19.

**Table 19. Summary of statistical analyses in RCTs**

| Primary hypothesis objective | Statistical analysis for testing the hypothesis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|
| **CAIN457A2303 (FIXTURE) (19, 42)** | | | |
| The statistical hypothesis for the co-primary efficacy variable (PASI 75 response at Wk 12 and IGA mod 2011 0 or 1 response at Wk 12) being tested was that there was no difference in the proportion of patients with PASI 75 response and IGA mod 2011 0 or 1 response at Wk 12 in any of the SEC groups vs. placebo. | Statistical analyses of efficacy variables were performed on an intent-to-treat basis, involving all randomised patients who were assigned to study treatment (FAS).<br>For response efficacy variables, the Cochran-Mantel-Haenszel (CMH)-test was performed for pairwise comparisons of SEC dose regimens vs. PBO or ETAN<br>For the non-inferiority comparison with regards | The sample size was determined by the key secondary objective to demonstrate the non-inferiority of SEC vs ETAN with respect to PASI 75 response at 12 wks.<br>The total sample size was 1,264 patients and using balanced randomisation 316 patients were randomised to each treatment group.<br>Since 2 SEC dose regimens were tested vs. PBO with respect to the co-primary endpoints | Missing values for the response variables were imputed with non-response, regardless of the reason of missing data. |

| Primary hypothesis objective | Statistical analysis for testing the hypothesis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|
| | to PASI 75 response at Wk 12, the stratified Mantel-Haenszel risk difference for each SEC dose minus ETAN and the associated CI was calculated and compared to the per-set non-inferiority margin of $\Delta$ 10%.<br>The tests were stratified by geographical region and body weight stratum.<br>Between-treatment differences for maintenance of PASI 75 response and IGA mod 2011 0 or 1 response after 52 wks of treatment for patients who were responders after 12 wks of treatment were evaluated for loss of response using a log-rank test, stratified by geographical region and body weight stratum.<br>The absolute changes from baseline to the Wk 12 for the Psoriasis Diary items pain, itching, and scaling were analysed in separate ANCOVAs with treatment, geographical region and body weight stratum as explanatory variables and baseline value as covariate. | (PASI 75 response and IGA mod 2011 0 or 1 response at Wk 12), the type-I-error was split to 2.5% 2-sided for each comparison. With 316 patients per group and assuming a response rate of 5% for PASI 75 response and IGA mod 2011 0 or 1 response in the PBO group, the power to show a response rate of 55% for PASI 75 response and 30% for IGA mod 2011 0 or 1 response in the SEC groups based on Fisher's exact test (nQuery Advisor 6.01, 2-group Fisher's-exact test of equal proportions) was above 99%. Placebo-response rates between 3% and 7% have been reported in Papp et al (2005), Menter et al (2008), Leonardi et al (2008), and Papp et al (2008). | |

**Key:** ANCOVAs = analysis of covariance FDI = fixed dose interval; IGA = Investigator's Global Assessment; ITT = intention-to-treat; LOCF = last observation carried forward; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; SIAQ = Self-assessment Injection Questionnaire; wk(s) = Week(s); ETAN = etanercept; FAS = full analysis set, mod = moderate

| Primary hypothesis objective | Statistical analysis for testing the hypothesis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|
| **CAIN457A2302 (ERASURE) (19, 51)** | | | |
| The statistical hypotheses for PASI 75 response at Wk 12 and IGA mod 2011 0 or 1 response at Wk 12 being tested was that there was no difference in the proportion of patients with PASI 75 response and IGA mod 2011 0 or 1 response at Wk 12 in any of the SEC groups vs PBO | Statistical analyses of efficacy variables were performed on an intent-to-treat basis, involving all randomized patients who were assigned to study treatment (full analysis set).<br>A sequentially rejective testing strategy was used to evaluate the study hypotheses for co-primary and key secondary variables while retaining a family-wise type I error of 5%. The co-primary efficacy variables were PASI 75 response at Wk 12 and IGA mod 2011 0 or 1 response at Wk 12. The statistical hypotheses for PASI 75 response at Week 12 and IGA mod 2011 0 or 1 | In order to fulfil registration and ICH E1 requirements on the number of patients treated for 6 mths and 12 mths in the development program, a sample size of 240 patients for each treatment group was targeted. Hence, the total sample size was 720 patients.<br>Since two SEC dose regimens were tested versus placebo with respect to the co-primary endpoints (PASI 75 response and IGA mod 2011 0 or 1 response at Week 12), the type-I-error were split to 2.5% two-sided for each comparison. With 240 patients per group and assuming a response rate of 5% for PASI 75 | Missing values for the co-primary variables were imputed with non-response regardless of the reason of missing data. |

| Primary hypothesis objective | Statistical analysis for testing the hypothesis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|
| | response at Wk 12 were that there was no difference in the proportion of patients with PASI 75 response and<br>IGA mod 2011 0 or 1 response at Week 12 in any of the SEC groups versus PBO. The primary analysis method was the stratified CMH test. The tests were stratified by geographical region and body weight stratum. SEC groups were compared to placebo in a pairwise fashion with respect to the proportion of patients with PASI 75 response and IGA mod 2011 0 or 1 response at Wk 12 using the CMH test statistics. As a supportive analysis, the co-primary variables were evaluated using a logistic regression model with treatment group, geographic region, body weight stratum, and baseline PASI score as effects.<br>For response efficacy variables, each SEC dose was compared to placebo by means of the stratified CMH test as well as by means of a logistic regression model at each visit up to Wk 12. Comparisons between SEC treatment groups were also made. Maintenance of PASI 75 and IGA 0/1 responses at 52 wks was reported using summary statistics and Kaplan-Meier estimates. | response and IGA mod 2011 0 or 1 response in the placebo group, the power to show a response rate of 55% for PASI 75 response and 30% for IGA mod 2011 0 or 1 response in the SEC groups based on Fisher's exact test (nQuery Advisor 6.01, 2 group Fisher's-exact test of equal proportions) is above 99%. | |
| **Key:** IGA = Investigator's Global Assessment; ITT = intention-to-treat; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; Wk(s) = Week(s) | | | |
| **CAIN457A2309 (JUNCTURE) (26, 52)** | | | |
| The statistical hypotheses for PASI 75 response at Wk 12 and IGA mod 2011 0 or 1 response at Wk 12 being tested was that there is no difference in the proportion of patients with PASI 75 response and IGA mod 2011 0 or 1 response at Week 12 in any of the SEC groups vs. PBO. | Primary analysis: stratified Cochran-Mantel-Haenszel test. The tests were stratified by body weight stratum. SEC treatment groups were to be compared to PBO in a pairwise fashion with respect to the proportion of patients with PASI 75 response and IGA mod 2011 0 or 1 response at Wk 12 using the Cochran-Mantel-Haenszel test statistics.<br>In case response rates were 0% or 100% in one of the treatment groups, the Fisher's | Since two SEC dose regimens were tested vs PBO with respect to the co-primary endpoints (PASI 75 response and IGA mod 2011 0 or 1 response at Wk 12), the type-I-error is split to 2.5% two-sided for each comparison. With 57 patients per group and assuming a response rate of 5% for PASI 75 response and IGA mod 2011 0 or 1 response in the PBO group, the power to show a response rate of 55% for PASI 75 response and 30% for IGA mod | If all efficacy post-baseline values were missing for one efficacy parameter, then missing values were not imputed and this patient was removed from the analysis of the corresponding variable. In addition, missing baseline values were not imputed.<br>Missing values with respect to response variables based on PASI score and IGA mod 2011 score were imputed with non-response. |

| Primary hypothesis objective | Statistical analysis for testing the hypothesis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|
| | exact test was applied.<br>The primary analysis set is the FAS. | 2011 0 or 1 response in the SEC groups based on Fisher's exact test (nQuery Advisor 6.01, two group Fisher's-exact test of equal proportions) is above 99% for PASI 75 response and 90% for IGA mod 2011 0 or 1 response. Placebo-response rates between 3% and 7% | [redacted] |
| **Key:** ANCOVAs = analysis of covariance FDI = fixed dose interval; IGA = Investigator's Global Assessment; LOCF = last observation carried forward; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; Wk(s) = Week(s) | | | |
| **Primary hypothesis objective** | **Statistical analysis for testing the hypothesis** | **Sample size, power calculation** | **Data management, patient withdrawals** |
| **CAIN457A2308 (FEATURE) (27, 53)** | | | |
| The statistical hypotheses for PASI 75 response at Wk 12 and IGA mod 2011 0 or 1 response at Wk 12 being tested was that there is no difference in the proportion of patients with PASI 75 response and IGA mod 2011 0 or 1 response at Week 12 in any of the SEC groups vs. PBO. | Primary analysis: stratified Cochran-Mantel-Haenszel test. The tests were stratified by body weight stratum. SEC treatment groups were to be compared to PBO in a pairwise fashion with respect to the proportion of patients with PASI 75 response and IGA mod 2011 0 or 1 response at Wk 12 using the Cochran-Mantel-Haenszel test statistics.<br>Following the database lock, the primary analysis method was changed to Fisher's exact test because there was 0% response rate for IGA mod 2011 and PASI 75 in the PBO group.<br>The primary analysis set is the FAS. | Since two SEC dose regimens were tested vs PBO with respect to the co-primary endpoints (PASI 75 response and IGA mod 2011 0 or 1 response at Wk 12), the type-I-error is split to 2.5% two-sided for each comparison. With 57 patients per group and assuming a response rate of 5% for PASI 75 response and IGA mod 2011 0 or 1 response in the PBO group, the power to show a response rate of 55% for PASI 75 response and 30% for IGA mod 2011 0 or 1 response in the SEC groups based on Fisher's exact test (nQuery Advisor 6.01, two group Fisher's-exact test of equal proportions) is above 99% for PASI 75 response and 90% for IGA mod 2011 0 or 1 response. [redacted] | [redacted]<br>Missing values with respect to response variables based on PASI score and IGA mod 2011 score were imputed with non-response.<br>[redacted] |

| Primary hypothesis objective | Statistical analysis for testing the hypothesis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|
| | | | [redacted] |

**Key:** ANCOVAs = analysis of covariance FDI = fixed dose interval; IGA = Investigator's Global Assessment; ITT = intention-to-treat; LOCF = last observation carried forward; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; SIAQ = Self-assessment Injection Questionnaire;; wk(s) = Week(s)

| Primary hypothesis objective | Statistical analysis for testing the hypothesis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|
| [redacted] | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |

| Primary hypothesis objective | Statistical analysis for testing the hypothesis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|
| | | [redacted] | [redacted] |

**Key:** ANCOVAs = analysis of covariance FDI = fixed dose interval; IGA = Investigator's Global Assessment; ITT = intention-to-treat; LOCF = last observation carried forward; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; SIAQ = Self-assessment Injection Questionnaire; SOR = start of relapse; wk(s) = Week(s)

### 6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Subgroup analyses undertaken within the relevant RCTs included: gender, age, weight, geographic location, age at diagnosis, disease duration, baseline measurements (e.g. DLQI), and previous experience of other treatments for psoriasis. These subgroups were selected, in line with comparator trials, on the basis that these are factors that may have the potential to influence the efficacy of psoriasis treatments.

As DLQI at baseline was not an exclusion criterion for the secukinumab clinical trials, an additional post-hoc analysis was conducted in alignment with the NICE definition of moderate to severe chronic plaque psoriasis patients (DLQI >10). This analysis examined whether there were differences in PASI 75 response at 12 weeks for patients with DLQI >10 versus those with DLQI ≤ 10 at baseline.

The subgroup analyses conducted and their rationale has been presented in Table 20.

**Table 20. Subgroup Analyses and Rationale**

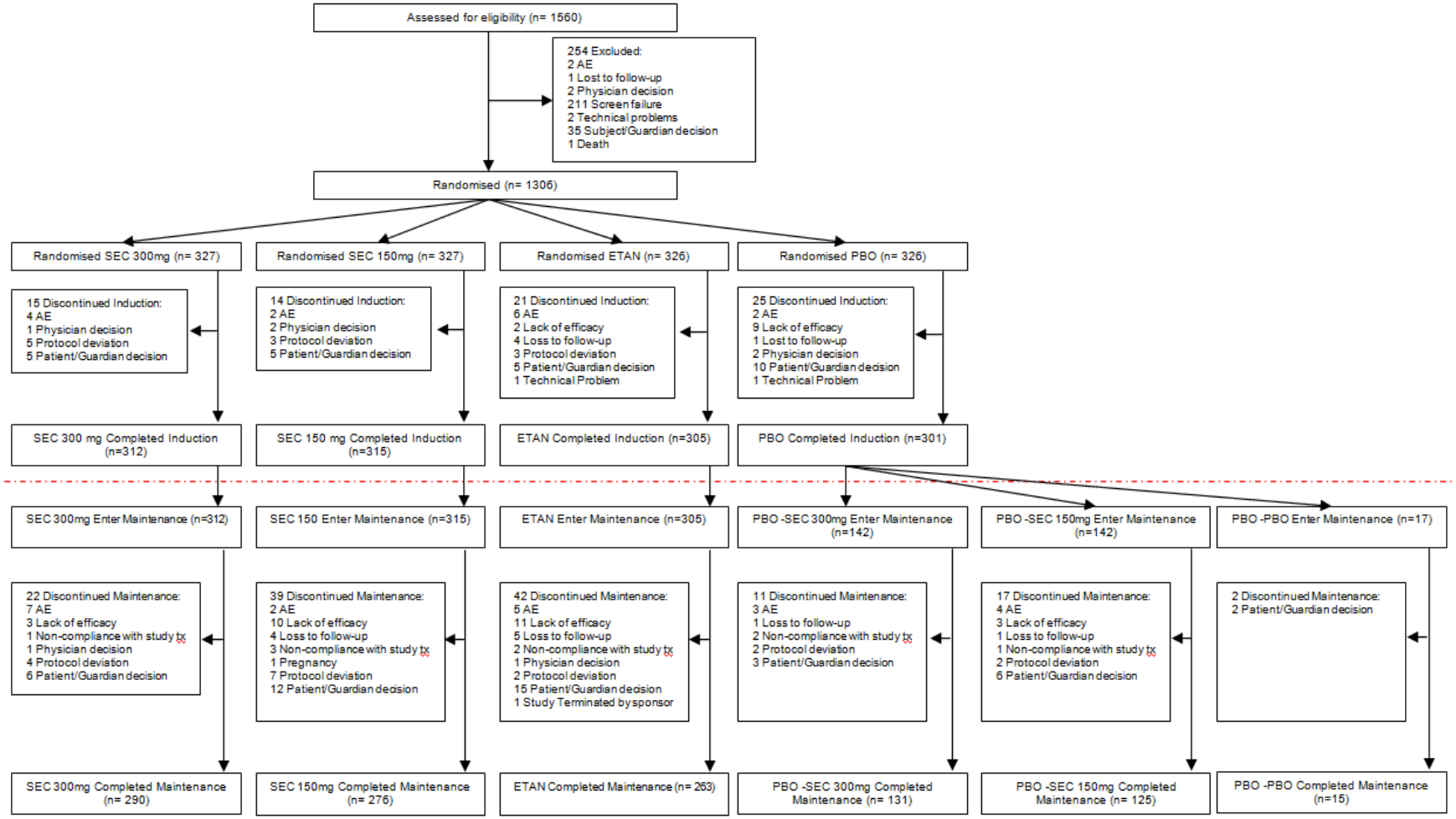
| Subgroup | Pre-planned or Post-hoc | Rationale | CAIN457A2303 (FIXTURE) (19, 42) | CAIN457A2302 (ERASURE) (19, 51) | CAIN457A2309 (JUNCTURE) (26, 52) | CAIN457A2308 (FEATURE) (27, 53) | CAIN457A2304 (SCULPTURE) (28) |
|---|---|---|---|---|---|---|---|
| Randomisation weight strata | Pre-planned | Potential to influence the efficacy of psoriasis treatments | x | x | x | x | x |
| Randomisation geographical region strata | Pre-planned | Stratified to maintain randomisation for the pre-planned subgroup analysis to consider different prior therapies and dosages for different geographies and differences in climate | x | x | | | x |
| Previous systemic therapy | Pre-planned | Potential to influence the efficacy of psoriasis treatments | x | x | x | x | x |
| Previous biologic therapy | Pre-planned | Potential to influence the efficacy of psoriasis treatments | x | x | x | x | x |
| Previous non-biologic therapy | Pre-planned | Potential to influence the efficacy of psoriasis treatments | x | x | x | x | x |
| Ongoing use of emollients | Pre-planned | Potential to influence the efficacy of psoriasis treatments | x | x | x | x | x |
| PsA at baseline | Pre-planned | Patients that have both psoriasis and psoriatic arthritis are considered to be more severe psoriasis patients. Thus, the presence of psoriatic arthritis is likely to influence the efficacy of psoriasis treatments. | x | x | | | x |
| Age | Pre-planned | Within psoriasis early onset and late onset psoriasis can be considered as 2 different conditions. Thus, age was analysed to help account for this. | x | x | x | x | x |
| Gender | Pre-planned | Potential to influence the efficacy of psoriasis treatments | x | x | x | x | x |
| Race | Pre-planned | Potential to influence the efficacy of psoriasis treatments | x | x | x | x | x |
| Time since psoriasis diagnosis | Pre-planned | Potential to influence the efficacy of psoriasis treatments | x | x | x | x | x |
| Baseline PASI score | Pre-planned | Potential to influence the efficacy of psoriasis treatments | x | x | x | x | x |
| Baseline IGA mod 2011 score | Pre-planned | Potential to influence the efficacy of psoriasis treatments | x | x | x | x | x |
| Baseline BSA | Pre-planned | Potential to influence the efficacy of psoriasis treatments | x | x | x | x | x |
| PASI 75 response at (Week 4 and Week 8) | Pre-planned | To explore early response to treatment | x | x | x | x | x |
| DLQI at baseline | Post-Hoc | Alignment with NICE population | x | x | | | |

**Participant flow**

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

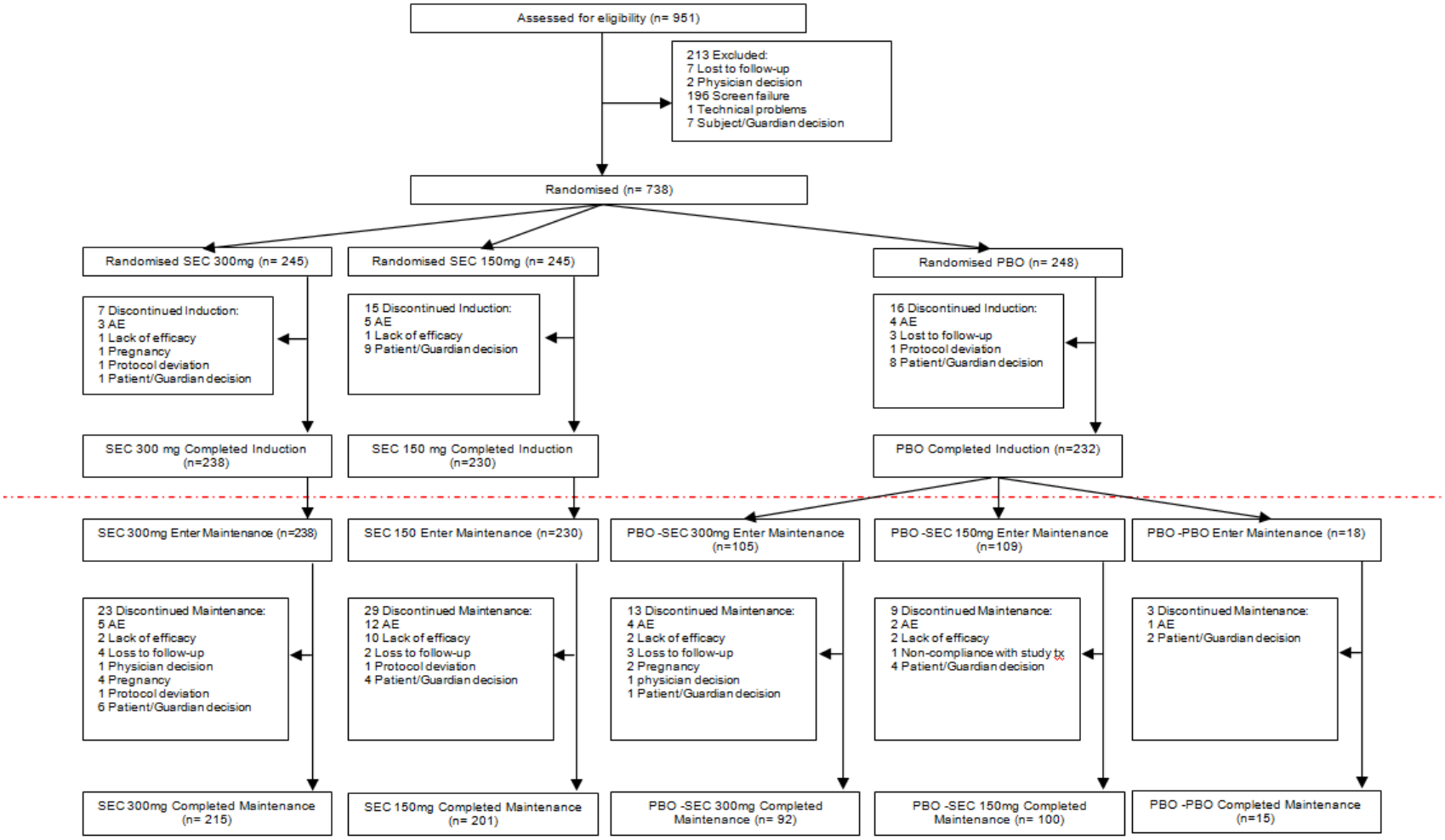
A summary of the patient flow for each of the RCTs has been provided in the CONSORT diagrams presented in Figure 8 to Figure 11 below.

**Figure 8. CONSORT Diagram - FIXTURE**




**Note**: dotted red line is the division of the induction and maintenance period

**Figure 9. CONSORT Diagram - ERASURE**




**Note**: dotted red line is the division of the induction and maintenance period

**Figure 10. CONSORT Diagram - JUNCTURE**

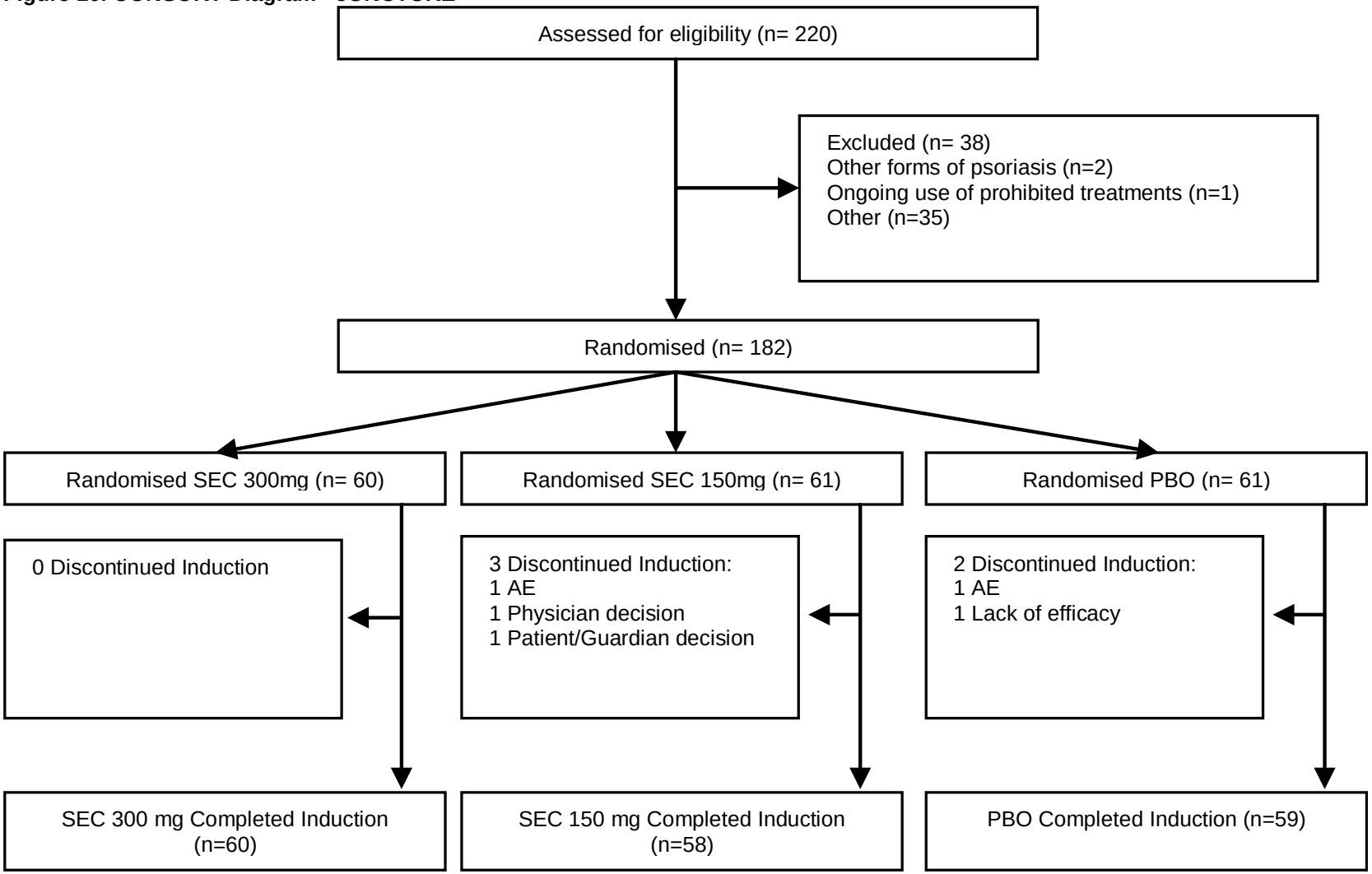


**Figure 11. CONSORT Diagram - FEATURE**

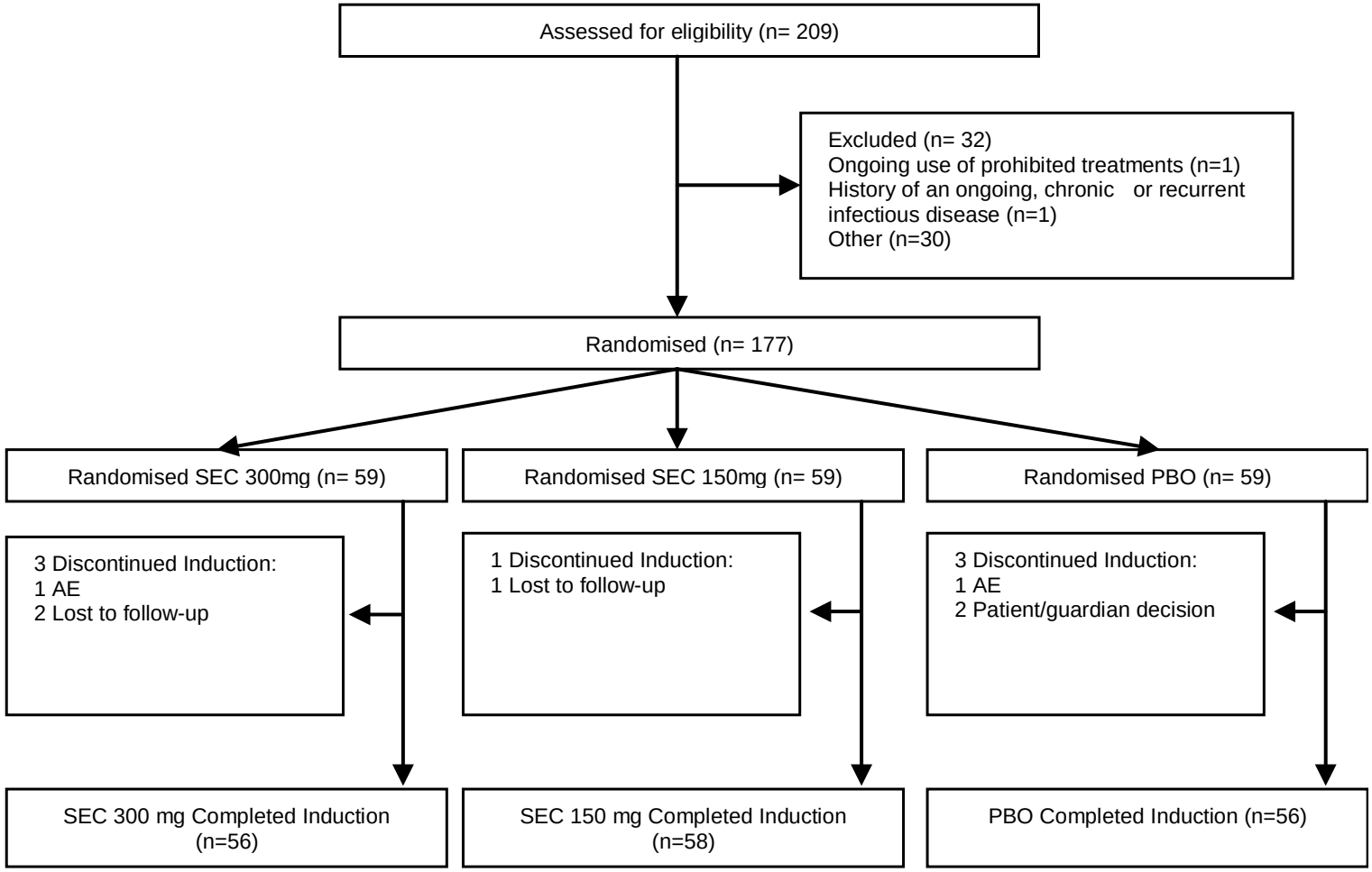


**Figure 12.** [redacted]

## *6.4 Critical appraisal of relevant RCTs*

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

For the critical appraisal of relevant RCTs, the NICE checklist for RCTs (adapted from the CRD (56)) was used as it has been tested for internal consistency, reliability and validity.

The RCTs were of good quality, of robust design and judged to have a low risk of bias as determined through quality assessment. Baseline demographics and patients characteristics were well balanced amongst all study groups. Concealment of treatment allocation and blinding of those involved with the RCTs were robust across

the five RCTs, In addition, there were no obvious imbalances in drop-out between groups or the RCTs as a whole. A summary of the quality assessments are provided in Table 21.

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

Detailed quality assessments of CAIN457A2303 (FIXTURE), CAIN457A2302 (ERASURE), CAIN457A2309 (JUNCTURE), CAIN457A2308 (FEATURE), and CAIN457A2304 (SCULPTURE) are provided in Section 10.3, Appendix 3.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

**Table 21. Quality assessment results for RCTs**

| **Trial no. (acronym)** | **CAIN457A2303 (FIXTURE) (19, 42)** | **CAIN457A2302 (ERASURE) (19, 51)** | **CAIN457A2309 (JUNCTURE) (26, 52)** | **CAIN457A2308 (FEATURE) (27, 53)** | [redacted] |
|---|---|---|---|---|---|
| Was randomisation carried out appropriately? | Yes | Yes | Yes | Yes | [redacted] |
| Was the concealment of treatment allocation adequate? | Yes | Yes | Yes | Yes | [redacted] |
| Were the groups similar at the outset of the study in terms of prognostic factors? | Yes | Yes | Yes | Yes | [redacted] |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | Yes | Yes | Yes | Yes | [redacted] |

| Trial no. (acronym) | CAIN457A2303 (FIXTURE) (19, 42) | CAIN457A2302 (ERASURE) (19, 51) | CAIN457A2309 (JUNCTURE) (26, 52) | CAIN457A2308 (FEATURE) (27, 53) | [redacted] |
|---|---|---|---|---|---|
| Were there any unexpected imbalances in drop-outs between groups? Were they adjusted in the analysis? | No | No | No | No | [redacted] |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | No | No | No | No | [redacted] |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Yes[a] | Yes[a] | Yes[a] | Yes[a] | [redacted] |
| **Notes: (a)** Efficacy data for all patients who underwent randomisation were analysed according to the assigned treatment | | | | | |

## 6.5 Results of the relevant RCTs

**Summary of Secukinumab Clinical Effectiveness**

**Overall, there is a strong clinical evidence base for the efficacy of secukinumab administered subcutaneously at a dose of 300 mg once weekly for the first month followed by every four weeks in patients with moderate to severe chronic plaque psoriasis.**

- The relative efficacy of secukinumab compared to an active comparator or placebo has been studied in four pivotal phase III double blind RCTs involving over 2,400 patients in total (FIXTURE, ERASURE JUNCTURE and FEATURE), and in a further phase III study comparing secukinumab dosing regimens (SCULPTURE).

*Primary endpoints*

- The co-primary endpoints of the FIXTURE, ERASURE, JUNCTURE and FEATURE trials were PASI 75 and IGA mod 2011 0/1 responses at week 12.
- Significantly higher PASI 75 and IGA mod 2011 0/1 responses were achieved with secukinumab 300 mg compared to placebo at week 12 in FIXTURE, ERASURE, JUNCTURE and FEATURE ($p<0.0001$ in all cases).
- SCULPTURE demonstrated similar efficacy of secukinumab to the other four trials, however non-inferiority of a secukinumab 'treatment on relapse' regimen

compared to a fixed treatment regimen for maintaining week 12 PASI response up to week 52 was not achieved in SCULPTURE.

*Efficacy versus etanercept*

- Significantly higher PASI 75 and IGA mod 2011 0/1 responses were achieved with secukinumab 300 mg compared to etanercept (given at the highest licensed dose) at week 12 (77.1% vs. 44.0% and 62.5% vs. 27.2%, respectively; p<0.0001 in all cases) and at all subsequent timepoints in FIXTURE.
- The proportions of patients achieving clear skin (PASI 100) and almost clear skin (PASI 90) were higher with secukinumab 300 mg compared to etanercept at week 12, and at every subsequent timepoint in FIXTURE.

*PASI 90 and PASI 100*

- The proportions of patients achieving clear skin (PASI 100) and almost clear skin (PASI 90) were higher with secukinumab 300 mg compared to placebo at week 12 in FIXTURE, ERASURE, JUNCTURE and FEATURE.
- When statistical analysis was conducted on the week 12 PASI 90 responses, these differences were significant (p<0.0001 in all cases).

*Efficacy over time*

- PASI 75, PASI 90, PASI 100, and IGA mod 0/1 response rates continued to increase from Week 12 to Week 16 in FIXTURE and ERASURE, supporting the CHMP recommendation to assess response to secukinumab 300 mg at 16 weeks.
- A ≥50% mean decrease from baseline in PASI score was achieved as early as week 3 with secukinumab 300 mg compared to week 7 with etanercept (FIXTURE). It was not achieved at any visit with placebo (FIXTURE, ERASURE FEATURE and JUNCTURE).
- In the three studies that have reported week 52 outcomes (FIXTURE, ERASURE and SCULPTURE) secukinumab 300 mg responses were maintained in the large majority of patients to week 52.

*Quality of life*

- DLQI reductions and EQ-5D improvements were consistently higher for secukinumab 300mg than placebo in FIXTURE, ERASURE, JUNCTURE and FEATURE.
- The FIXTURE study showed a more pronounced decrease in DLQI in the secukinumab 300 mg group than in the etanercept group.

*Subgroup analyses*

- In FIXTURE, ERASURE, JUNCTURE and FEATURE, pre-specified subgroup analyses by body weight and by previous exposure to systemic and to biologic therapies were consistent with overall study results.
- [redacted]

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.

- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Results for the key efficacy endpoints in FIXTURE, ERASURE, JUNCTURE, FEATURE and SCULPTURE are summarised in Table 22. Primary and secondary endpoints from FIXTURE, ERASURE, JUNCTURE and FEATURE are described in detail in Section 6.3.5. Results from SCULPTURE, which does not directly align with the decision problem (6.2.5), are presented in Section 10.7

FIXTURE, ERASURE, FEATURE and JUNCTURE achieved their primary endpoints. In addition, higher proportions of patients treated with secukinumab 300 mg achieved clear (PASI 100) or almost clear (PASI 90) skin compared to placebo or etanercept by week 12.

Efficacy data for secukinumab at weeks 16 and 52 have also been reported for FIXTURE and ERASURE. PASI and IGA mod 0/1 responses plotted over time in these studies show that response to secukinumab 300 mg continued to increase between weeks 12 and weeks 16. As a result of this observation, the Committee for Medicinal Products for Human Use (CHMP) have recommended that 16 weeks should be considered the appropriate induction treatment duration before evaluating response to secukinumab 300 mg (1).

**Table 22. Summary of results for key efficacy endpoints by study**

| | 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 (86.7%)** | 43 (71.7%)** | 2 (3.3%) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 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 | 0 (0.0%) | 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** |
| | | (45.8%) | | | | | | | | | | |
| 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 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [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 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.

## *FIXTURE Study (CAIN457A2303)*

### *Co-primary endpoints: PASI 75 and IGA mod 2011 0 or 1 response, Week 12, vs placebo*

This study achieved its primary objective: secukinumab 300 mg was superior to placebo with respect to PASI 75 response at Week 12 (OR 65.95; 95% CI [36.07, 20.59]; p<0.0001) and to IGA mod 2011 0 or 1 response at Week 12 (OR 79.13; 95% CI [35.97, 174.09]; p<0.0001) (19, 24, 42). 1,306 patients were randomised and results are presented from 1,297 patients. The results of the statistical analysis (Cochran-Mantel-Haenszel test) of IGA mod 2011 0 or 1 and PASI 75 response at Week 12 are shown below in Table 23.

**Table 23. Statistical analysis (Cochran-Mantel-Haenszel test) of IGA mod 2011 0 or 1 and PASI 75 responses at Week 12 (non-responder imputation) (FAS) (19, 24, 42)**

| | Treatment comparison "test" vs. "control" | "Test" n/m | "Control" n/m | Odds ratio estimate (95% CI) | P value | Outcome |
|---|---|---|---|---|---|---|
| IGA mod 2011 0 or 1 | SEC 300 mg vs PBO | 202/323 (62.5) | 9/324 (2.8) | 79.13 (35.97, 174.09) | <0.0001 | Superior to PBO |
| | SEC 150 mg vs PBO | 167/327 (51.1) | 9/324 (2.8) | 40.62 (19.80, 83.35) | <0.0001 | Superior to PBO |
| PASI 75 | SEC 300 mg vs PBO | 249/323 (77.1) | 16/324 (4.9) | 65.95 (36.07, 20.59) | <0.0001 | Superior to PBO |
| | SEC 150 mg vs PBO | 219/327 (67.0) | 16/324 (4.9) | 42.76 (23.57, 77.60) | <0.0001 | Superior to PBO |

**Key**: CI = confidence interval; FAS = full analysis set; IGA mod 2011 = Investigator's Global Assessment Modified 2011; m = number of patients evaluable; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab
**Notes**: The p-values for the differences between 300 mg vs. 150 mg secukinumab at Week 12, as assessed by the CMH test, were 0.0046 for PASI 75 and 0.0032 for IGA mod 2011 0 or 1. Missing values with respect to response variables based on PASI score and IGA mod 2011 score were imputed with non-response regardless of the reason for missing data. This is the most conservative way of assessing missing data.

### *Secondary Endpoints: PASI 50, PASI 90, and PASI 100 responses at Week 12, vs placebo*

Results of the statistical analysis on PASI 50 and 90 responses at Week 12 are shown in Table 24. PASI 90 response was greater and statistically significant for secukinumab 300 mg versus placebo (OR 118.48; 95% CI [41.34, 339.58]; p<0.0001) (24, 42). Similarly, PASI 50 response was significantly greater with secukinumab 300 mg compared to placebo (OR 57.35; 95% CI [34.36, 95.72]; p<0.0001).

**Table 24. Statistical analysis (Cochran-Mantel-Haenszel test) of PASI 50 and 90 response at Week 12 for secukinumab vs. placebo (non-responder imputation) (FAS) (19, 24, 42)**

| Response criterion | Treatment comparison "test" vs. "control" | "Test" n/m (%) | "Control" n/m (%) | Odds ratio estimate (95% CI) | P value | Outcome |
|---|---|---|---|---|---|---|
| PASI 50 | SEC 300 mg vs PBO | 296/323 (91.6) | 49/324 (15.1) | 57.35 (34.36, 95.72) | <0.0001 | Superior to placebo |
| | SEC 150 mg vs PBO | 266/327 (81.3) | 49/324 (15.1) | 24.69 (16.13, 37.80) | <0.0001 | Superior to placebo |
| PASI 90 | SEC 300 mg vs PBO | 175/323 (54.2) | 5/324 (1.5) | 118.48 (41.34, 339.58) | <0.0001 | Superior to placebo |
| | SEC 150 mg vs PBO | 137/327 (41.9) | 5/324 (1.5) | 56.10 (21.41, 147.03) | <0.0001 | Superior to placebo |

**Key:** CI = confidence interval; FAS = full analysis set; IGA mod 2011 = Investigator's Global Assessment modified 2011; m = number of patients evaluable; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab

PASI 100 response at Week 12 is shown in Table 25. The response with secukinumab 300 mg was greater than placebo, although no statistical analysis was conducted for this endpoint as this was not pre-planned on account of the fact that PASI 100 was not an established treatment target.

**Table 25. PASI 100 response at Week 12 for secukinumab vs. placebo (non-responder imputation) (FAS) (42)**

| Response criterion | SEC 300 mg (%) | SEC 150 mg (%) | Placebo (%) |
|---|---|---|---|
| PASI 100 | 78/323 (24.1%) | 47/327 (14.4%) | 0/324 (0.0%) |

### *Secondary Endpoints: PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 responses at Week 12, vs etanercept*

Response rates at Week 12 were higher and statistically significant (p<0.0001) for secukinumab 300 mg compared to etanercept (at highest licensed dose) for PASI 75, IGA mod 2011 0 or 1 and PASI 50 (Table 26) (42). As these outcomes were pre-planned in terms of the testing strategy and the planned sample size of the study, it is appropriate to conclude that secukinumab 300mg is superior to etanercept (42).

**Table 26. Statistical analysis (Cochran-Mantel-Haenszel test) of IGA mod 2011 0 or 1 and PASI 50, 75, and 90 response at Week 12 for secukinumab vs. etanercept (non-responder imputation) (FAS) (19, 24, 42)**

| Response criterion | Treatment comparison "test" vs. "control" | "Test" n/m (%) | "Control" n/m (%) | Odds ratio estimate (95% CI) | P value | Outcome |
|---|---|---|---|---|---|---|
| **12 weeks** | | | | | | |
| IGA mod 2011 0 or 1 | SEC 300 mg vs ETAN | 202/323 (62.5) | 88/323 (27.2) | 4.91 (3.46, 6.97) | <0.0001 | Superior to etanercept |
| | SEC 150 mg vs ETAN | 167/327 (51.1) | 88/323 (27.2) | 2.96 (2.11, 4.15) | <0.0001 | Superior to etanercept |
| PASI 50 | SEC 300 mg vs ETAN | 296/323 (91.6) | 226/323 (70.0) | 4.91 (3.06, 7.88) | <0.0001 | Superior to etanercept |
| | SEC 150 mg vs ETAN | 266 /327 (81.3) | 226/323 (70.0) | 1.91 (1.32, 2.77) | <0.0001 | Superior to etanercept |
| PASI 75 | SEC 300 mg vs ETAN | 249/323 (77.1) | 142/323 (44.0) | 4.69 (3.28, 6.70) | <0.0001 | Superior to etanercept |
| | SEC 150 mg vs ETAN | 219/327 (67.0) | 142/323 (44.0) | 2.73 (1.96, 3.79) | <0.0001 | Superior to etanercept |
| PASI 90 | SEC 300 mg vs ETAN | 175/323 (54.2) | 67/323 (20.7) | 4.67 (3.28, 6.66) | | n/a |
| | SEC 150 mg vs ETAN | 137/327 (41.9) | 67/323 (20.7) | 2.86 (2.01, 4.07) | | n/a |
| **Key:** CI = confidence interval; FAS = full analysis set; IGA mod 2011 = Investigator's Global Assessment modified 2011; m = number of patients evaluable; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab | | | | | | |

PASI 100 response at Week 12 was higher for secukinumab 300 mg compared to etanercept, although no statistical analysis was perfomed as this was not pre-planned on account of the fact that PASI 100 was not an established treatment target (Table 27).

**Table 27. PASI 100 response at Week 12 for secukinumab vs. etanercept (non-responder imputation) (FAS) (19).**

| Response criterion | SEC 300 mg (%) | SEC 150 mg (%) | Etanercept (%) |
|---|---|---|---|
| PASI 100 | 78/323 (24.1%) | 47/327 (14.4%) | 13/323 (4.0%) |

### *Secondary Endpoints: PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 responses over time*

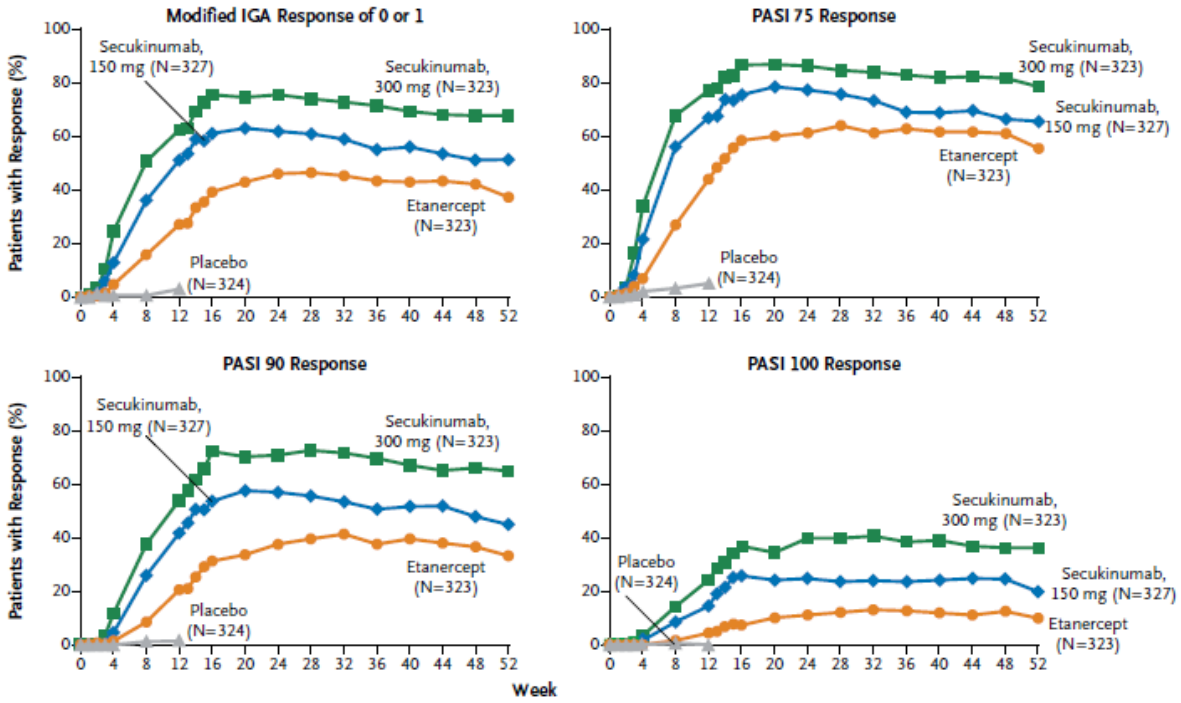
In the response over time analyses, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0/1 response rates were higher with secukinumab compared to etanercept at all timepoints up to Week 52 (Table 28 and Figure 13) (42).

**Table 28. IGA mod 2011 0 or 1 and PASI 50, 75, and 90 response at Week 16 and Week 52 for secukinumab vs. etanercept (FAS) (42)**

| Response criterion | SEC 300 mg (%) | SEC 150 mg (%) | Etanercept (%) |
|---|---|---|---|
| **16 weeks** | | | |
| IGA mod 2011 0 or 1 | 244/323 (75.5%) | 200/327 (61.2%) | 127/323 (39.3%) |
| PASI 50 | 302/323 (93.5%) | 290/327 (88.7%) | 257/323 (79.6%) |
| PASI 75 | 280/323 (86.7%) | 247/327 (75.5%) | 189/323 (58.5%) |
| PASI 90 | 234/323 (72.4%) | 176/327 (53.8%) | 101/323 (31.3%) |
| PASI 100 | 119/323 (36.8%) | 84/327 (25.7%) | 24/323 (7.4%) |
| **52 weeks** | | | |
| IGA mod 2011 0 or 1 | 219/323 (67.8) | 168/327 (51.4) | 120/323 (37.2) |
| PASI 50 | 274/323 (84.8) | 249/327 (76.1) | 234/323 (72.4) |
| PASI 75 | 254/323 (78.6) | 215/327 (65.7) | 179/323 (55.4) |
| PASI 90 | 210/323 (65.0) | 147/327 (45.0) | 108/323 (33.4) |
| PASI 100 | 117/323 (36.2%) | 65/327 (19.9%) | 32/323 (9.9%) |
| **Key:** CI = confidence interval; FAS = full analysis set; IGA mod 2011 = Investigator's Global Assessment modified 2011; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab | | | |

Two important trends were observed in the analyses of response over time. First, the proportions of patients who met the PASI 75, PASI 90, PASI 100, and IGA mod 2011 0/1 response criteria over time continued to increase from Week 12 to Week 16 (Figure 13). This supports the CHMP's recommendation that 16 weeks should be considered the appropriate induction treatment duration before evaluating response to secukinumab 300 mg.

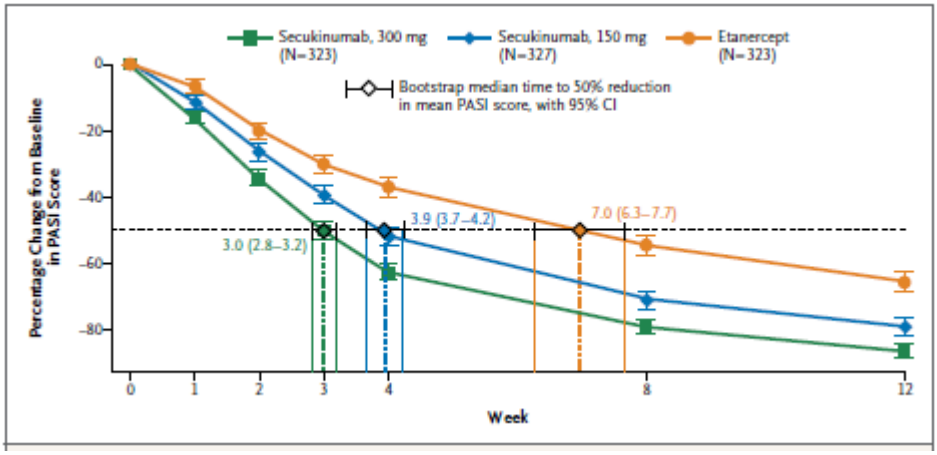
**Figure 13. PASI Response and IGA mod 2011 0 or 1 over trial duration**




Secondly, the response over time analysis showed that the speed at which patients respond to treatment was also considerably faster with secukinumab when compared to etanercept.

At Week 3 of the FIXTURE study, 50% of patients treated with secukinumab 300 mg were reported to have have a PASI 50 response. In comparison, it took 7 weeks for 50% of patients treated with etanercept to achieve PASI 50 (19)(Figure 14).

**Figure 14. FIXTURE Study: Speed of Response**




### *Secondary Endpoint: Dermatology Life Quality Index (DLQI)*

The DLQI total score improved continuously during the induction period in all active treatment groups, with a more pronounced decrease in the secukinumab 300 mg group than in the etanercept group (42). Changes in DLQI total score at Week 12 reached a mean of −10.4 (−78.8%) in the secukinumab 300 mg group and −7.9 (−56.0%) in the etanercept group. In contrast, total DLQI scores in the placebo group only improved by a mean score of –1.9 (−3.6%) (19, 42). More pronounced improvements in secukinumab 300 mg group than in the etanercept group were also seen for all individual scores (symptoms and feelings score, daily activities score, leisure score, work and school score, personal relationships score and treatment score) (42).

The relative improvement from baseline in DLQI total score at Week 4, Week 8 and Week 12 of the induction period was more pronounced in secukinumab 300 mg group than in the etanercept and placebo groups, and that difference was statistically significant at each assessed time point (42). The treatment differences compared to placebo and etanercept were always higher for the secukinumab 300 mg dose (42). Similarly, the treatment differences for absolute values of the DLQI total score at Week 4, Week 8, and Week 12 of the induction period were also statistically significant and in favour of secukinumab 300 mg at when compared to etanercept and placebo(42).

The proportion of patients with DLQI response (DLQI score of 0 or 1), that is a response showing no impact on daily living, was higher in the secukinumab 300 mg group than in the etanercept group and the placebo group at each assessed timepoint during the induction period (42). The difference between treatments was statistically significant from Week 4 onwards for secukinumab 300 mg vs. etanercept and placebo (42). At Week 12, DLQI response showing no impact on daily living (DLQI 0 or 1) was achieved by 56.7% of patients in the secukinumab 300 mg group, 34.5% of patients in the etanercept group, and 6.6% of patients in the placebo group (24, 42).

### *Secondary Endpoint: EuroQol 5-Dimension (EQ-5D)*

Mean absolute and relative changes from baseline were highest in the secukinumab 300 mg group at every assessed timepoint. Improvements during the induction period were reported for all EQ-5D categories in secukinumab 300 mg and in the etanercept group, whereas changes in the placebo group were less pronounced (42). The largest differences between baseline and Week 12 were seen in the EQ-5D categories pain/discomfort and anxiety/depression: the percentage of patients reporting no pain or discomfort increased from 23.6% to 71.8% for secukinumab 300 mg, from 24.3% to 65.1% for etanercept, and from 21.5% to 34.4% for placebo (42). The percentage of patients reporting not to be anxious or depressed increased between baseline and Week 12 from 43.1% to 78.0% for secukinumab 300 mg, from 46.7% to 71.3% for etanercept, and from 43.3% to 49.7% for placebo (42). Overall, the improvements in EQ-5D health assessments were consistently higher in the secukinumab 300 mg group than the etancept group.

Mean absolute (and relative) changes from baseline were highest in the secukinumab 300 mg group at each assessed timepoint (42). Mean changes from baseline in the EQ-5D health assessment (ranging from 0 [worst possible health state] to 100 [best possible health state]) increased continuously during the induction period in the secukinumab 300 mg group and in the etanercept group but not in the placebo group, indicating an improvement in all active treatment groups (42). Absolute changes from baseline reached a mean (±SD) score of 22.3 (±23.17) for secukinumab 300 mg, 14.4 (±20.17) for etanercept, and 2.2 (±19.65) for placebo (42). For both secukinumab dose groups, the comparison vs. placebo was favourable for secukinumab from Week 4 onwards ($p<0.0001$) (42). The comparison vs. etanercept was also favourable for secukinumab 300 mg from Week 8 onwards ($p=0.0008$) (42).

### *Subgroup analyses*

Results from the pre-specified subgroup analyses are summarised in Table 29 (42). Subgroup analyses by body weight, by previous exposure to systemic therapies, previous exposure to biologic therapies (including anti-tumour necrosis factor [TNF]α) and non-biologic systemic therapies were investigated. The results in populations with failure to respond to prior biologic, anti-TNF therapy or to non-biologic therapy were consistent with the overall results (42).

**Table 29. PASI 75, PASI 90 and IGA mod 2011 0 or 1 response at Week 12: subgroup analyses (42)**

| | Primary efficacy endpoints | | | | | | | | Key secondary endpoint | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IGA 0/1 | | | | PASI 75 | | | | PASI 90 | | | |
| | SEC 300 mg (%) | SEC 150 mg (%) | PBO (%) | ETAN (%) | SEC 300 mg (%) | SEC 150 mg (%) | PBO (%) | ETAN (%) | SEC 300 mg (%) | SEC 150 mg (%) | PBO (%) | ETAN (%) |
| **Body weight (non-responder imputation) (FAS)** | | | | | | | | | | | | |
| <90 kg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ≥90 kg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Previous exposure to systemic therapy (non-responder imputation) (FAS)** | | | | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Previous exposure to biologic systemic therapy (non-responder imputation) (FAS)** | | | | | | | | | | | | |
| Previous exposure, Y | 20/38 (52.6) | 15/45 (33.3) | 0/35 (0) | 12/45 (26.7) | 29/38 (76.3) | 24/45 (53.3) | 0/35 (0) | 24/45 (53.3) | 18/38 (47.4) | 15/45 (33.3) | 0/35 (0) | 8/45 (17.8) |
| Prior failure | 6/16 (37.5) | 3/15 (20.0) | 0/12 (0) | 4/16 (25.0) | 11/16 (68.8) | 7/15 (46.7) | 0/12 (0) | 6/16 (37.5) | 7/16 (43.8) | 3/15 (20.0) | 0/12 (0) | 2/16 (12.5) |
| **Previous exposure to anti-TNF-α therapy** | | | | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Non-biologic systemic therapy (non-responder imputation) (FAS)** | | | | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Previous exposure, ≥2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Ongoing emollient use** | | | | | | | | | | | | |
| Yes | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| No | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Key:** FAS = full analysis set; IGA = Investigator's Global Assessment; N = no; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; TEAN = etanercept; TNF-α = tumour necrosis factor alpha; Y = yes

Results of the post hoc subgroup analyses of patients with DLQI >10 score at baseline, analysed using the CMH test, are presented below (Table 30).

**Table 30.**

[redacted]

| Response criterion | Treatment comparison "test" vs. "control" | "Test" n/m (%) | "Control" n/m (%) | Odds ratio estimate (95% CI) | P value | Outcome |
|---|---|---|---|---|---|---|
| **DLQI ≤10** | | | | | | |
| IGA mod 2011 0 or 1 | SEC 300 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| IGA mod 2011 0 or 1 | SEC 300 mg vs ETAN | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs ETAN | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75 | SEC 300 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75 | SEC 300 mg vs ETAN | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs ETAN | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **DLQI > 10** | | | | | | |
| IGA mod 2011 0 or 1 | SEC 300 mg vs PBO | [redacted] | [redacted] | [redacted] | | |
| | SEC 150 mg vs PBO | [redacted] | [redacted] | [redacted] | | |
| IGA mod 2011 0 or 1 | SEC 300 mg vs ETAN | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs ETAN | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75 | SEC 300 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75 | SEC 300 mg vs ETAN | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs ETAN | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Key:** CI = confidence interval; FAS = full analysis set; IGA mod 2011 = Investigator's Global Assessment modified 2011; m = number of patients evaluable; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; ETAN = etanercept
**Notes:** *Note that the CMH test was not conducted if the response was less than 5 patients in either arm.
Missing values with respect to response variables based on PASI score and IGA mod 2011 score were imputed using the strictest criteria of non-response regardless of the reason for missing data

[redacted]

31 [redacted]

**Table 31.** [redacted]

| Response criterion | Variable | Estimate (SE) | P Value | P Value for Group Test | Outcome |
|---|---|---|---|---|---|
| Interaction Term, non-covariate adjusted model | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | | |
| | [redacted] | [redacted] | [redacted] | | |
| Interaction Term, covariate adjusted model* | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | | |
| | [redacted] | [redacted] | [redacted] | | |
| *[redacted] | | | | | |

### *FIXTURE Study Conclusion*

In this phase III multi-centre, double-blind, randomised, active and placebo-controlled study, secukinumab 300 mg demonstrated statistically and clinically significant efficacy in the treatment of moderate to severe chronic plaque psoriasis as measured by PASI 75 and IGA mod 0 or 1 responses. Secukinumab 300 mg also achieved a statistically and clinically significant increase in PASI 90 response (almost clear skin) compared with etanercept at highest licensed doses and placebo. Outcomes were higher and statistically significant for secukinumab 300 mg compared to etanercept for IGA mod 0 or 1, PASI 75 and PASI 90 in all pre-specified and post hoc subgroups by body weight, [redacted]

## *ERASURE Study (CAIN457A2302)*

### *Co-primary endpoints: PASI 75 and IGA mod 2011 0 or 1 response, Week 12 v placebo*

This study achieved its primary objective: secukinumab 300 mg was superior to placebo with respect to PASI 75 response at Week 12 (OR 82.69; 95% CI [38.70, 176.71]; p<0.0001) and to IGA mod 2011 0 or 1 response at Week 12 (OR 70.46; 95% CI [28.75, 172.70]; p<0.0001; Table 32) (19, 24, 51).

**Table 32. Statistical analysis (Cochran-Mantel-Haenszel test) of IGA mod 2011 0 or 1 and PASI 75 response at Week 12 (non-responder imputation) (FAS) (19, 24, 51)**

| | Treatment comparison "test" vs. "control" | "Test" n/m (%) | "Control" n/m (%) | Odds ratio estimate (95% CI) | P value | Outcome |
|---|---|---|---|---|---|---|
| IGA 0/1 | SEC 300 mg vs PBO | 160/245 (65.3) | 6/246 (2.4) | 70.46 (28.75, 172.70) | <0.0001 | Superior to PBO |
| | SEC 150 mg vs PBO | 125/244 (51.2) | 6/246 (2.4) | 44.18 (18.21, 107.18) | <0.0001 | Superior to PBO |
| PASI 75 | SEC 300 mg vs PBO | 200/245 (81.6) | 11/246 (4.5) | 82.69 (38.70, 176.71) | <0.0001 | Superior to PBO |
| | SEC 150 mg vs PBO | 174/243 (71.6) | 11/246 (4.5) | 57.64 (28.43, 116.86) | <0.0001 | Superior to PBO |

**Key:** CI = confidence interval; FAS = full analysis set; IGA mode 2011 = Investigator's Global Assessment modified 2011; m = number of patients evaluable; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab
**Notes:** Missing values with respect to response variables based on PASI score and IGA mod 2011 score were imputed using the most conservative method of assessing missing data using a non-response regardless of the reason for missing data.

### *Secondary Endpoints: PASI 50, PASI 90 and PASI 100 responses at Week 12*

Secukinumab 300 mg was superior to placebo in terms of PASI 90 response at Week 12, as demonstrated in the CMH test (p<0.0001 Table 33) (19, 24, 51).

**Table 33. Statistical analysis (Cochran-Mantel-Haenszel test) of PASI 90 response at Week 12 (non-responder imputation) (FAS) (19, 24, 51)**

| Response criterion | Treatment comparison "test" vs. "control" | "Test" n/m | "Control" n/m | Odds ratio estimate (95% CI) | P value | Outcome |
|---|---|---|---|---|---|---|
| PASI 90 | SEC 300 mg vs PBO | 145/245 (59.2) | 3/246 (1.2) | 186.13 (44.39, 780.52) | <0.0001 | Superior to PBO |
| | SEC 150 mg vs PBO | 95/243 (39.1) | 3/246 (1.2) | 59.50 (17.24, 205.35) | <0.0001 | Superior to PBO |

**Key:** CI = confidence interval; FAS = full analysis set; m = number of patients evaluable; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab

PASI 50 and PASI 100 responses were also greater with secukinumab 300 mg when compared to placebo at week 12 (Table 34).

**Table 34. PASI 50 and PASI 100 responses at Week 12 for secukinumab vs. placebo (non-responder imputation) (FAS) (19, 51)**

| Response criterion | SEC 300 mg (%) | SEC 150 mg (%) | PBO (%) |
|---|---|---|---|
| **12 weeks** | | | |
| PASI 50 | 222/245 (90.6%) | 203/243 (83.5%) | 22/246 (8.9%) |
| PASI 100 | 70/245 (28.6%) | 31/243 (12.8%) | 2/246 (0.8%) |
| **Key:** FAS = full analysis set; IGA mod 2011 = Investigator's Global Assessment modified 2011; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab | | | |

### *Secondary Endpoints: PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 responses over time*

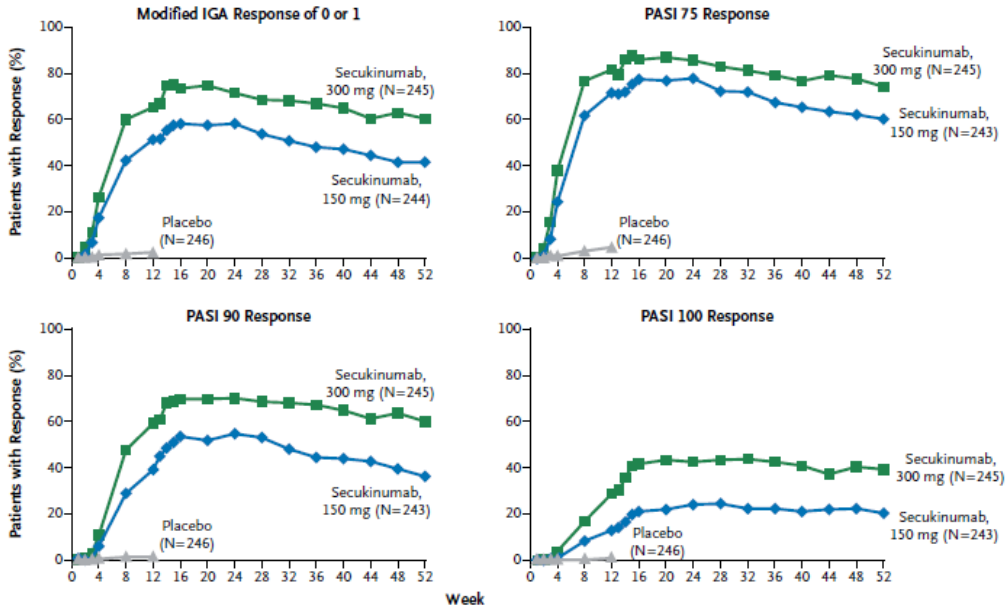
IGA mod 2011 0 or 1 and PASI responses in the secukinumab 300 mg arm at 16 and 52 weeks are reported below (Table 35). Consistent with FIXTURE, secukinumab 300 mg responses were higher at Week 16 compared to Week 12 and were sustained throughout 52 weeks of treatment in the large majority of patients. By week 16, 41.6% of patients achieved PASI 100 (complete remission).

**Table 35. IGA mod 2011 0 or 1 and PASI response over time (non-responder imputation) (FAS) (51)**

| Response criterion | SEC 300 mg (%) | SEC 150 mg (%) | PBO (%) |
|---|---|---|---|
| **16 weeks** | | | |
| IGA mod 2011 0 or 1 | 180/245 (73.5%) | 142/244 (58.2%) | N/A |
| PASI 50 | 224/245 (91.4%) | 212/243 (87.2%) | N/A |
| PASI 75 | 211/245 (86.1%) | 188/243 (77.4%) | N/A |
| PASI 90 | 171/245 (69.8%) | 130/243 (53.5%) | N/A |
| PASI 100 | 102/245 (41.6%) | 5/243 (21.0%) | N/A |
| **52 weeks** | | | |
| IGA mod 2011 0 or 1 | 148/245 (60.4%) | 101/244 (41.4%) | N/A |
| PASI 50 | 207/245 (84.5%) | 187/243 (77%) | N/A |
| PASI 75 | 182/245 (74.3%) | 146/243 (60.1%) | N/A |
| PASI 90 | 147/245 (60.0%) | 88/243 (36.2%) | N/A |
| PASI 100 | 96/245 (39.2%) | 49/243 (20.2%) | N/A |
| **Key:** FAS = full analysis set; IGA mod 2011 = Investigator's Global Assessment modified 2011; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab | | | |

As was observed in FIXTURE, the proportions of patients who met the PASI 75, PASI 90, PASI 100 and IGA mod 0/1 response criteria over time continued to increase from Week 12 to Week 16 (Figure 15). This supports the CHMP's recommendation that 16 weeks should be considered the appropriate assessment period before evaluating response to secukinumab.

**Figure 15. PASI Response and IGA mod 2011 0 or 1 over trial duration**




The response over time analysis showed that the speed at which patients responded was also considerably faster with secukinumab 300 mg than placebo. Higher response rates with secukinumab relative to placebo appeared as early as Week 2, with [redacted] of patients on secukinumab 300 mg achieving PASI 50 compared with only [redacted] of placebo patients. Secukinumab 300 mg showed greater PASI 75 and IGA mod 2011 0 or 1 responses than placebo from Week 3 and superior PASI 90 response from Week 4.(51) Rapid onset of response for secukinumab 300mg was also demonstrated by the percentage change in PASI score. A ≥ 50% mean decrease from baseline in PASI score was achieved by Week 3 in the secukinumab 300 mg group, but was not observed at any visit in the placebo group.

### *Secondary Endpoint: DLQI*

The percentage of patients with a DLQI 0 or 1 response, indicating no impairment of health-related quality of life, was higher with secukinumab 300 mg (58.8%) than with placebo (10.3%) (p<0.001) at Week 12 (24, 51). The responses were sustained throughout the maintenance period with secukinumab treatment (19, 51). At Week 52, the proportion of subjects achieving DLQI score of 0 or 1 was 66.3% for the secukinumab 300 mg group (51).

[redacted]

**Table 36. Percentage changes from baseline to Week 12 in the Dermatology Life Quality Index total score by visit (LOCF) induction period (FAS) (51)**

| | | Treatment difference | | | |
|---|---|---|---|---|---|
| **DLQI** | **Hodges-Lehmann estimate** | **Comparison** | **Hodges-Lehmann estimate** | **P value*** | **Outcome** |
| **SEC 300 mg** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **SEC 150 mg** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **PBO** | [redacted] | | | | |
| **Key:** CI = confidence interval; DLQI = Dermatology Life Quality Index; FAS = full analysis set; LOCF = last observation carried forward; PBO = placebo; SEC = secukinumab<br>**Notes:** * Van-Elteren test; Scores on the Dermatology Life Quality Index (DLQI) range from 0 to 30, with higher scores indicating a greater effect of the disease on quality of life | | | | | |

### *Secondary Endpoint: EQ-5D*

In the induction period, the repeated measures analysis of the absolute change from baseline in the EQ-5D health state assessment showed significant improvements with 300 mg secukinumab compared with placebo (p<0.0001) at Visit 12 (Table 37). A clear effect of secukinumab 300 mg treatment was seen in the category of "Pain/Discomfort," where the proportion of secukinumab 300 mg treated patients reporting no pain or discomfort increased from 26.2% at baseline to 72.8 at Week 12 (51). For the placebo group, the extent of improvement was considerably lower, with 18.9% at baseline reporting no pain or discomfort compared with 28.4% at Week 12 (51).

[redacted]

**Table 37. Repeated measurement analysis of the absolute change from baseline to Week 12 in EQ-5D health state assessment (from 0 to 100) induction period (FAS) (51)**

| | | Treatment contrast in adjusted mean (change) | | | |
|---|---|---|---|---|---|
| **EQ-5D** | **Adjusted mean** | **Comparison** | **Difference in adjusted means** | **P value** | **Outcome** |
| **SEC 300 mg** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **SEC 150 mg** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **PBO** | [redacted] | | | | |
| **Key:** CI = confidence interval; EQ 5D = Eurol Qol tool; PBO = placebo; SE = standard error; SEC = secukinumab | | | | | |

### *Subgroup analyses*

Results from the pre-specified subgroup analyses are summarised in Table 38 (51). The superior efficacy of secukinumab 300 mg versus placebo with respect to PASI 75 and IGA mod 2011 0 or 1 responses at Week 12 observed in the overall population was consistently demonstrated in both body weight subgroups and in all subgroups by previous exposure to systemic, biologic systemic (including anti-TNF)

and non-biologic systemic therapies (51). Secukinumab 300 mg demonstrated better efficacy than placebo regardless of whether the patient had failed prior biologic or non-biologic systemic therapies (51).

**Table 38. PASI 75, PASI 90 and IGA mod 2011 0 or 1 response at Week 12: subgroup analyses (51)**

| | Primary efficacy endpoints | | | | | | Key secondary endpoint | | |
|---|---|---|---|---|---|---|---|---|---|
| | IGA 0/1 | | | PASI 75 | | | PASI 90 | | |
| | SEC 300 mg | SEC 150 mg | PBO | SEC 300 mg | SEC 150 mg | PBO | SEC 300 mg | SEC 150 mg | PBO |
| **Body weight (non-responder imputation) (FAS)** | | | | | | | | | |
| <90 kg | 103/142 (72.5) | 75/141 (53.2) | 3/142 (2.1) | 126/142 (88.7) | 104/140 (74.3) | 6/142 (4.2) | 99/142 (69.7) | 63/140 (45.0) | 2/142 (1.4) |
| ≥90 kg | 57/103 (55.3) | 50/103 (48.5) | 3/104 (2.9) | 74/103 (71.8) | 70/103 (68.0) | 5/104 (4.8) | 46/103 (44.7) | 32/103 (31.1) | 1/104 (1.0) |
| **Previous exposure to systemic therapy (non-responder imputation) (FAS)** | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Previous exposure to biologic systemic therapy (non-responder imputation) (FAS)** | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Anti-TNF-α therapy** | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Non-biologic systemic therapy (non-responder imputation) (FAS)** | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Previous exposure, ≥2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Ongoing emollient use** | | | | | | | | | |
| Yes | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| No | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Key:** FAS = full analysis set; IGA = Investigator's Global Assessment; N = no; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; TNF-α = tumour necrosis factor alpha; Y = yes

[redacted] The results of the CMH test of IGA mod 2011 0 or 1 and PASI 75 response in these subgroups at Week 12 are shown below (Table 39).

**Table 39.** [redacted] **(51)**

| Response criterion | Treatment comparison "test" vs. "control" | "Test" n/m (%) | "Control" n/m (%) | Odds ratio estimate (95% CI) | P value |
|---|---|---|---|---|---|
| **DLQI ≤10** | | | | | |
| IGA mod 2011 0 or 1 | SEC 300 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75 | SEC 300 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] |
| **DLQI > 10** | | | | | |
| IGA mod 2011 0 or 1 | SEC 300 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75 | SEC 300 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs PBO | [redacted] | [redacted] | [redacted] | [redacted] |

**Key**: CI = confidence interval; IGA mod 2011 = Investigator's Global Assessment modified 2011; m = number of patients evaluable; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab
**Notes**: *Note that the CHM test was not conducted if the response was less than 5 patients in either arm.
Missing values with respect to response variables based on PASI score and IGA mod 2011 score were imputed with non-response regardless of the reason for missing data.

[redacted]

40 [redacted]

**Table 40.** [redacted]

| Response criterion | Variable | Estimate (SE) | P Value | P Value for Group Test | Outcome |
|---|---|---|---|---|---|
| Interaction Term, non-covariate adjusted model | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | | |
| Interaction Term, covariate adjusted model* | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | | |
| [redacted] | | | | | |

### *ERASURE Study Conclusions*

In this phase III multi-centre, double-blind, randomised, placebo-controlled study, secukinumab 300 mg demonstrated statistically and clinically significant efficacy in the

treatment of moderate to severe chronic plaque psoriasis as measured by PASI 75 and IGA mod 0 or 1 responses. Secukinumab 300 mg also achieved a statistically and clinically significant increase in PASI 90 response (almost clear skin) compared with placebo. Outcomes were higher for secukinumab 300 mg than placebo for IGA mod 0 or 1, PASI 75 and PASI 90 in all pre-specified and post hoc subgroups by body weight, previous exposure to systemic therapy, non-systemic therapy, anti-TNF therapy, [redacted]

## *JUNCTURE Study (CAIN457A2309)*

### *Co-primary endpoints: PASI 75 and IGA 2011 0 or 1 responses, Week 12 v placebo*

This study achieved its primary objective: secukinumab 300 mg was superior to placebo with respect to PASI 75 response (RD 83.4; 95% CI [70.7, 91.7]; p<0.0001) and IGA mod 2011 0 or 1 response at Week 12 (RD 73.3; 95% CI [58.8, 83.9]; p<0.0001; Table 41) (24, 26, 52).

**Table 41. Statistical analysis (Risk-difference and Fisher's exact test) of IGA mod 2011 0 or 1 and PASI 75 at Week 12 (non-responder imputation) (FAS) (24, 26, 52)**

| Response criterion | Treatment comparison "test" vs. "control" | "Test" n/m (%) | "Control" n/m (%) | Risk difference estimate (%) (95% CI) | P value* | Outcome |
|---|---|---|---|---|---|---|
| IGA mod 20110/1 | SEC 300 mg vs PBO | 44/60 (73.3) | 0/61 (0.0) | 73.3 (58.8, 83.9) | <0.0001 | Superior to PBO |
| | SEC 150 mg vs PBO | 32/60 (53.3) | 0/61 (0.0) | 53.3 (36.6, 66.7) | <0.0001 | Superior to PBO |
| PASI 75 | SEC 300 mg vs PBO | 52/60 (86.7) | 2/61 (3.3) | 83.4 (70.7, 91.7) | <0.0001 | Superior to PBO |
| | SEC 150 mg vs PBO | 43/60 (71.7) | 2/61 (3.3) | 68.4 (53.1, 79.8) | <0.0001 | Superior to PBO |

**Key:** CI = confidence interval; FAS = full analysis set; IGA = Investigator's Global Assessment; m = number of patients evaluable; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; * unadjusted p-values
**Notes**: As none of the placebo-treated patients achieved an IGA mod 2011 0 or 1 response at Week 12 (52), the Fisher's exact test was applied as the primary analysis method for the primary endpoint analysis rather than the CMH test (52).

### *Secondary endpoints: PASI 50 and PASI 90 responses, Week 12*

Secukinumab 300 mg was superior to placebo with respect to PASI 90 response at Week 12.

**Table 42. Statistical analysis (Risk-difference and Fisher's exact test) of PASI 90 response at Week 12 (non-responder imputation) (FAS) (24, 26, 52)**

| Response criterion | Treatment comparison "test" vs. "control" | "Test" n/m (%) | "Control" n/m (%) | Risk difference estimate (%) (95% CI) | P value* | Outcome |
|---|---|---|---|---|---|---|
| PASI 90 | SEC 300 mg vs PBO | 33/60 (55.0) | 0/61 (0.0) | 55.0 (38.4, 68.1) | <0.0001 | Superior to PBO |
| | SEC 150 mg vs. PBO | 24/60 (40.0) | 0/61 (0.0) | 40.0 (22.5, 55.0) | <0.0001 | Superior to PBO |

**Key:** CI = confidence interval; FAS = full analysis set; IGA = Investigator's Global Assessment; m = number of patients evaluable; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; * unadjusted p-values
**Notes**: As none of the placebo-treated patients achieved a response at Week 12 (52), the Fisher's exact test was applied as the primary analysis method for the primary endpoint analysis rather than the CMH test (52).

The CMH test and logistic regression analysis of PASI 50 response at Week 12 showed that the secukinumab 300 mg response rate was statistically significantly higher compared to placebo (p < 0.0001).

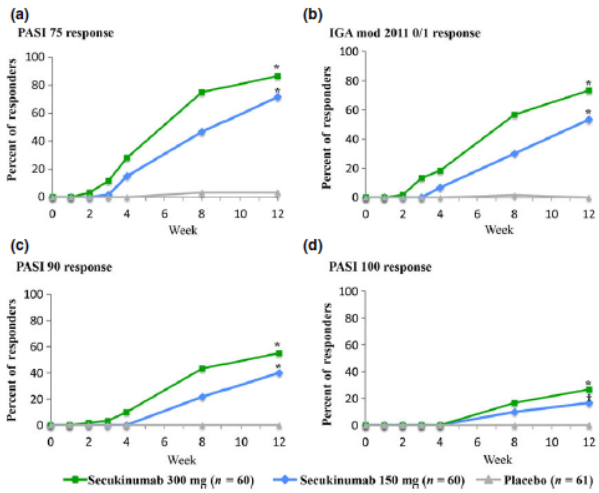
**Table 43. Statistical analysis (CMH test and logistic regression) of PASI 50 response at Week 12 (non-responder imputation) (FAS) ) (52)**

| Response criterion | Treatment comparison "test" vs. "control" | "Test" n/m (%) | "Control" n/m (%) | Odds ratio estimate (95% CI) | P value* | Outcome |
|---|---|---|---|---|---|---|
| PASI 50 | SEC 300 mg vs PBO | 58/60 (96.7) | 5/61 (8.2) | Not reported | <0.0001 | Superior to PBO |
| | SEC 150 mg vs. PBO | 48/60 (80.0) | 5/61 (8.2) | Not reported | <0.0001 | Superior to PBO |
| **Key:** CI = confidence interval; FAS = full analysis set; IGA = Investigator's Global Assessment; m = number of patients evaluable; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; * unadjusted p-values | | | | | | |

### *Secondary endpoints: PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 responses over time*

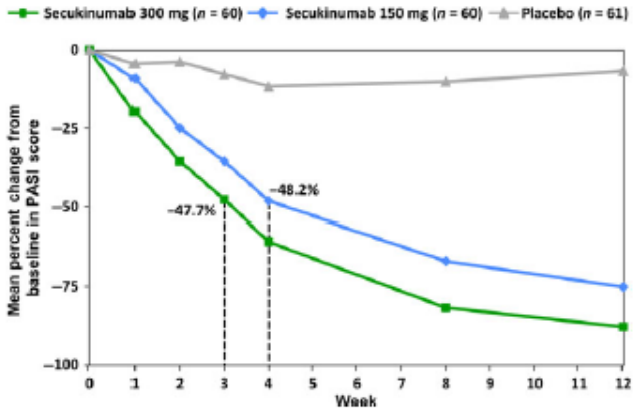
PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 responses from baseline to week 12 for secukinumab 300 mg and placebo are shown in Figure 16 below.

**Figure 16. JUNCTURE Study: IGA mod 2011 0/1 and PASI 75, 90, and 100 Response over time**




Reponses to secukinumab were observed early during the course of therapy with a 50% reduction in mean PASI from baseline being achieved by week 3 in the secukinumab 300 mg group (Figure 17). Furthermore differences in response between secukinumab 300 mg and placebo are observed from as early as week 1.

**Figure 17. JUNCTURE Study: Speed of Response, secukinumab v. placebo**




### *Secondary endpoint: DLQI*

The proportions of patients achieving DLQI 0 or 1 response (i.e., no impact on daily living) at Week 12 were 74.6% for secukinumab 300 mg compared with 15.3% in the placebo group (24, 52). The difference in DLQI 0 or 1 response was statistically superior for secukinumab 300 mg compared to placebo ($p < 0.0001$) (24, 52).

[redacted]

[redacted]

### *Secondary endpoint: EQ- 5D*

More patients in the secukinumab groups reported improvements on each of the questions of the EQ-5D health state assessment. The EQ-5D questions where improvements in secukinumab groups were most evident were on pain/discomfort, usual activities, anxiety/depression, walking, and self-care. At Week 12, the overall change from Baseline on the EQ-5D health state assessment (from 0 to 100) indicated an improved health status in secukinumab 300 mg (+14.3%) compared with placebo (0%) (52).

Overall health status, assessed as difference in adjusted means, improved over time for secukinumab 300 mg vs. placebo and was statistically significant in favour of secukinumab at all visits in which EQ-5D assessments were made (Weeks 4, 8 and 12) (52).

### *Subgroup analyses*

Results from the pre-specified subgroup analyses are summarised in Table 44 and Table 45 (52). Due to a small number of patients in some of the subgroups, the results should be interpreted with caution (52).

**Table 44. Risk difference and Fisher's exact test of PASI 75, PASI 90, and IGA mod 2011 0 or 1 response at Week 12 by weight strata (non-responder imputation) (FAS) (52)**

| Response criterion | Treatment comparison "test" vs. "control" | "Test" n/m (%) | "Control" n/m (%) | Risk difference estimate (%) (95% CI) | Fisher's test P value* | Outcome |
|---|---|---|---|---|---|---|
| **Weight stratum <90 kg** | | | | | | |
| IGA mod 2011 0/1 | SEC 300 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75 | SEC 300 mg vs.PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs.PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 90 | SEC 300 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Weight stratum ≥ 90 kg** | | | | | | |
| IGA mod 2011 0/1 | SEC 300 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75 | SEC 300 mg vs.PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs.PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 90 | SEC 300 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Key:** FAS=full analysis set; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index n=number of patients with response, m=number of patients evaluable

**Table 45. PASI 75, PASI 90 and IGA mod 2011 0 or 1 response at Week 12: subgroup analyses (52)**

| | IGA 0/1 | | | PASI 75 | | | PASI 90 | | |
|---|---|---|---|---|---|---|---|---|---|
| | SEC 300 mg (%) | SEC 150 mg (%) | PBO (%) | SEC 300 mg (%) | SEC 150 mg (%) | PBO (%) | SEC 300 mg (%) | SEC 150 mg (%) | PBO (%) |
| **Systemic therapy (non-responder imputation) (FAS)** | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Biologic systemic therapy (non-responder imputation) (FAS)** | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Anti-TNFα therapy** | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Non-biologic systemic therapy (non-responder imputation) (FAS)** | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Key:** FAS = full analysis set; IGA = Investigator's Global Assessment; N = no; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; TNF-α = tumour necrosis factor alpha; Y = yes

### *JUNCTURE Study Conclusions*

In this phase III multi-centre, double-blind, randomised, placebo-controlled study, secukinumab administered via an autoinjector demonstrated statistically and clinically significant efficacy in the treatment of moderate to severe chronic plaque psoriasis as measured by PASI 75, PASI 90 and IGA mod 0 or 1 compared with placebo.

## *FEATURE Study (CAIN457A2308)*

### *Co-primary endpoints: PASI 75 and IGA mod 2011 0 or 1 responses, Week 12 v placebo*

The co-primary efficacy endpoint of PASI 75 response and IGA mod 2011 0 or 1 response at Week 12 was achieved. Secukinumab 300 mg was superior to placebo with respect to PASI 75 response (RD 75.9; 95% CI [61.5, 86.1]; p<0.0001) and IGA mod 2011 0 or 1 response at Week 12 (RD 69.0; 95% CI [53.5, 80.5]; p<0.0001) (27, 53).

**Table 46. Statistical analysis (Risk-difference and Fisher's exact test) of IGA mod 2011 0 or 1 and PASI 75 response at Week 12 (non-responder imputation) (FAS) (53)**

| Response criterion | Treatment comparison "test" vs. "control" | "Test" n/m (%) | "Control" n/m (%) | Risk difference estimate (%) (95% CI) | P value* | Outcome |
|---|---|---|---|---|---|---|
| IGA mod 2011 0/1 | SEC 300 mg vs PBO | 40/ 58 (69.0) | 0/ 59 (0.0) | 69.0 (53.5, 80.5) | <0.0001 | Superior to PBO |
| | SEC 150 mg vs PBO | 31/ 59 (52.5) | 0/ 59 (0.0) | 52.5 (35.1, 67.2) | <0.0001 | Superior to PBO |
| PASI 75 | SEC 300 mg vs PBO | 44/ 58 (75.9) | 0/ 59 (0.0) | 75.9 (61.5, 86.1) | <0.0001 | Superior to PBO |
| | SEC 150 mg vs PBO | 41/ 59 (69.5) | 0/ 59 (0.0) | 69.5 (53.9, 81.4) | <0.0001 | Superior to PBO |

**Key:** CI = confidence interval; FAS = full analysis set; IGA = Investigator's Global Assessment; m = number of patients evaluable; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; * unadjusted p-values
**Notes: As none of the placebo-treated patients achieved an IGA mod 2011 0 or 1 response at Week 12 (53) the Fisher's exact test was applied as the primary analysis method for the primary endpoint analysis rather than the CMH test (53)**

### *Secondary endpoints: PASI 50 and PASI 90 responses, Week 12*

Secukinumab 300 mg was superior to placebo with respect to PASI 50 and PASI 90 responses at Week 12.

**Table 47. Statistical analysis (Risk-difference and Fisher's exact test) of PASI 50 and PASI 90 response at Week 12 (non-responder imputation) (FAS) (53)**

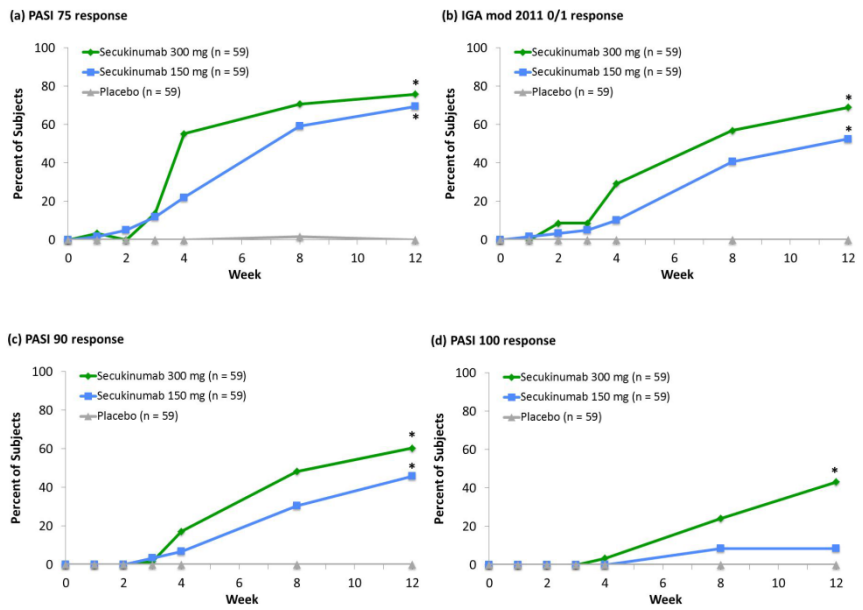
| Response criterion | Treatment comparison "test" vs. "control" | "Test" n/m (%) | "Control" n/m (%) | Risk difference estimate (%) (95% CI) | P value* | Outcome |
|---|---|---|---|---|---|---|
| PASI 50 | SEC 300 mg vs PBO | 51/58 (87.9%) | 3/59 (0.0) | Not calculated | Not calculated | Not calculated |
| | SEC 150 mg vs. PBO | 51/59 (86.4%) | 3/59 (0.0) | Not calculated | Not calculated | Not calculated |
| PASI 90 | SEC 300 mg vs PBO | 35/58 (60.3) | 0/59 (0.0) | 60.3 (43.9, 73.0) | <0.0001 | Superior to PBO |
| | SEC 150 mg vs. PBO | 27/59 (45.8) | 0/59 (0.0) | 45.8 (27.8, 61.3) | <0.0001 | Superior to PBO |

**Key:** CI = confidence interval; FAS = full analysis set; IGA = Investigator's Global Assessment; m = number of patients evaluable; n = number of patients with response; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; * unadjusted p-values
**Notes:** As none of the placebo-treated patients achieved a response at Week 12 ,(53) the Fisher's exact test was applied as the primary analysis method for the primary endpoint analysis rather than the CMH test (53)

### *Secondary endpoints: PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 responses over time*

Secukinumab 300 mg demonstrated a higer response than placebo with respect to IGA mod 2011 0 or 1, PASI 75, PASI 90 and PASI 100 measures across all time points from week 2 (Figure 18).

**Figure 18. FEATURE Study: IGA mod 2011 0/1, PASI 75, PASI 90, and PASI 100 Response, Baseline to 12 weeks**




### *Secondary endpoint: DLQI*

The difference in DLQI 0 or 1 response was significantly higher for secukinumab 300 mg compared to placebo (p<0.0001) (24, 53). [redacted]

### *Secondary endpoint: EQ- 5D*

More patients in secukinumab 300 mg reported improvements on each of the questions of the EQ-5D health state assessment (53). The EQ-5D questions where improvements in secukinumab 300 mg were most evident were on pain/discomfort, usual activities, and anxiety/depression questions. Benefit of secukinumab treatment over placebo was statistically significant in the EQ-5D questions on self-care, usual activities, and pain/discomfort (53). At Week 12, the overall change from Baseline on the EQ-5D health state assessment (from 0 to 100) indicated an improved health state in secukinumab 300 mg (mean percent change of +24.7% for secukinumab 300 mg) compared with placebo (+6.8%) (53).

Overall health status, assessed as difference in adjusted means, improved over time for secukinumab 300 mg vs. placebo and was statistically significant in favour of secukinumab at all visits EQ-5D assessments were made (Weeks 4, 8 and 12) (53).

### *Subgroup analyses*

Subgroup analyses were performed for co-primary endpoints and PASI 90. [redacted] 48 [redacted]

**Table 48. Risk difference and Fisher's exact test of PASI 75, PASI 90, and IGA mod 2011 0 or 1 response at Week 12 by weight strata (non-responder imputation) (FAS) (53)**

| Response criterion | Treatment comparison "test" vs. "control" | "Test" n/m (%) | "Control" n/m (%) | Risk difference estimate (%) (95% CI) | Fisher's test P value* | Outcome |
|---|---|---|---|---|---|---|
| **Weight stratum <90 kg** | | | | | | |
| IGA mod 20110/1 | SEC 300 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75 | SEC 300 mg vs.PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs.PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 90 | SEC 300 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Weight stratum >90 kg** | | | | | | |
| IGA mod 2011 0/1 | SEC 300 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 75 | SEC 300 mg vs.PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs.PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PASI 90 | SEC 300 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | SEC 150 mg vs. PBO | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Key:** FAS=full analysis set; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index n=number of patients with response, m=number of patients evaluable

[redacted]

**Table 49. PASI 75, PASI 90 and IGA mod 2011 0 or 1 response at Week 12: subgroup analyses (53)**

| | IGA 0/1 | | | PASI 75 | | | PASI 90 | | |
|---|---|---|---|---|---|---|---|---|---|
| | SEC 300 mg | SEC 150 mg | PBO | SEC 300 mg | SEC 150 mg | PBO | SEC 300 mg | SEC 150 mg | PBO |
| **Systemic therapy (non-responder imputation) (FAS)** | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Biologic systemic therapy (non-responder imputation) (FAS)** | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Anti-TNFα therapy** | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Non-biologic systemic therapy (non-responder imputation) (FAS)** | | | | | | | | | |
| Previous exposure, Y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior failure | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Key:** FAS = full analysis set; IGA = Investigator's Global Assessment; N = no; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab; TNF-α = tumour necrosis factor alpha; Y = yes

### *FEATURE Study Conclusions*

In this phase III multi-centre, double-blind, randomised, placebo-controlled study, secukinumab administered via a pre-filled syringe demonstrated statistically and clinically significant efficacy in the treatment moderate to severe chronic plaque psoriasis as measured by PASI 75, PASI 90 and IGA mod 0 or 1 compared with placebo.

### *SCULPTURE Study (CAIN457A2304)*

The primary endpoint of the SCULPTURE study was not met, and therefore non-inferiority of the experimental secukinumab 'treatment on relapse' regimen compared to the (recommended) fixed treatment regimen was not demonstrated.(24) [redacted]

[redacted]Further information on the results of SCULPTURE are provided in the appendices, Section 10.5.

## *6.6 Meta-analysis*

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

No pairwise meta-analyses were conducted as a network meta-analysis was performed.

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Head-to-head evidence was available for the 52 week comparison of secukinumab with etanercept(19) and the 12 week ustekinumab with etanercept (57); however head-to-head studies between other comparator biologics have not been conducted, thus a network meta-analysis (NMA) was conducted to estimate the relative efficacy between treatments. All evidence synthesis was conducted by network meta-analysis (NMA), as described in Section 6.7. The rationale for this is that NMA can provide relative measures of effect for all relevant comparators given the absence of head-to-head evidence. It is also most suitable when, as is the case here, there are multiple-arm trials within the network. Use of an NMA in preference to pairwise meta-analysis allowed all available and relevant evidence to be included, allowing more precise treatment effects to be calculated.

Consistency between direct and indirect estimates has been evaluated. The conclusions reached by the NMA are not likely to be substantially different from those that would be derived from pairwise meta-analysis in those instances where the latter would be feasible.

This approach has been adopted in a previous STA submission in psoriasis for a biologic (ustekinumab)(23).

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

The five secukinumab phase III trials (FIXTURE, ERASURE, JUNCTURE, FEATURE and SCULPTURE) were included in the network meta-analsyis (NMA). STATURE (29) was identified in the SLR but it did not meet the inclusion criteria of the NMA as it did not have a placebo comparator arm, it was a sub-group follow-on study of SCULPTURE partial responders and used different dosing regimens which are not in line with the draft secukinumab licence or SmPC.

## *6.7 Indirect and mixed treatment comparisons*

**Summary of Network Meta-analyses**

**Overall, secukinumab 300 mg has superior efficacy to well established treatments, etanercept 50 mg, ustekinumab 45 mg and adalimumab, and equal efficacy to ustekinumab 90 mg and infliximab for the treatment of moderate to severe plaque psoriasis.**

- A network meta-analysis (NMA) was conducted to evaluate the relative efficacy of secukinumab 300 mg compared with biologics licensed for the treatment of psoriasis in England and Wales (etanercept, adalimumab, infliximab and ustekinumab).
- From 45 studies identified in the clinical systematic review, 30 were included in the NMA following feasibility assessment.
- The proportions of patients across four mutually exclusive PASI outcome categories (0-49, 50-74, 75-89 and 90-100) were assessed at each trial's primary endpoint specific to each comparator (referred to as 'NICE 12 week endpoint' in this submission) :
    - For secukinumab and ustekinumab this was at 12 weeks, as aligned with the primary endpoints in the secukinumab ustekinumab and RCTs (the point up to which a placebo comparator was used, thus providing the most robust comparative effectiveness data).
    - For infliximab, etanercept and adalimumab, these were at 10, 12 and 16 weeks, respectively, for which comparative data versus placebo were available and in alignment with NICE CG153 and BAD guidelines.
- Results of the base-case NMA (26 RCTs) showed that secukinumab 300 mg is more efficacious than etanercept, ustekinumab 45 mg and adalimumab, and has equal efficacy to ustekinumab 90 mg (when used in all weights and not in line with weight based dosing in the SmPC) and infliximab, as represented by higher or similar proportions of patients, respectively, in the 50-74 (PASI 50), 75-89 (PASI 75) and 90-100 (PASI 90) categories.
- Scenario analyses were conducted for all trials reporting 12 week data (referred to as '12 week analysis')(23 RCTS) and for the NICE endpoint analysis with the inclusion of secukinumab 300 mg data at 16 weeks (referred to as the 'NICE 16 week endpoint analysis')(27 RCTs). These analyses reported similar findings to the base-case

results.

- Sensitivity analyses explored the effect of heterogeneity between included trials by: a) excluding studies with a high baseline PASI score, b) excluding studies with low psoriasis duration, c) excluding studies with a proportion of patients with prior biologic exposure and d) conducting a sub-analysis of trials with DLQI >10. Similar findings to the base-case analysis were obtained in the sensitivity analyses.
- Secukinumab 300 mg can therefore be considered of either equivalent or better clinical effectiveness than all comparator biologic treatments.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

The data used in the NMA (58) were extracted from studies identified in the systematic literature review described above in sections 6.1 to 6.5. The interventions and doses of interest for the different treatments are presented in Table 50. Studies and/or arms reporting on irrelevant doses or comparators were excluded.

**Table 50 Interventions and doses of interest, network meta-analysis**

| 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.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Trials included in the NMA were identified and selected via the systematic literature review as described in sections 6.1 to 6.5. A feasibility assessment of forty-five trials was undertaken to assess their eligibility for the NMA. Seven trials included patients on secukinumab, of which two trials incorporated doses below that of interest and were excluded (Rich and Papp). An additional 13 comparator trials were excluded as doses or timepoints were not of interest (Appendix 6, Section 10.6).

The base-case for the NMA was the analysis based on each trial's primary endpoint (referred to as NICE 12 week endpoints analysis) as this provided the most robust comparative effectiveness data. These consisted of:

- For ustekinumab and secukinumab this was at 12 weeks.
- For infliximab, etanercept and adalimumab, these were at 10, 12 and 16 weeks, respectively, which additionally align with NICE CG153 and BAD guidelines.(2, 3)

In addition, two scenario analyses were conducted:

1. Network of all trials reporting data at 12 weeks to enable comparison with the 12 week comparative timepoint base-case (referred to as 12 week analysis).
2. Repeat of the 12 week NICE endpoint analysis with the inclusion of 16 week secukinumab data to explore the efficacy of secukinumab at 16 week timepoint (referred to 16 week NICE endpoint analysis).

Sub group and sensitivity analyses were planned for:

- Baseline PASI score (high if >25)
- Psoriasis duration (less or greater than 15 years)
- Percent with prior biologic exposure, trials with >20% prior biologic exposure patients
- Trials including patients with DLQI>10

Trial characteristics and baseline patient characteristics are presented in, section 6.7.5 along with the outcomes data relevant to the NMAs. The appendix, Section 10.6 contains the list of included trials in the NMA (n=30), excluded trials from the NMA (n=15) with exclusion reasons and full quality assessment of the NMA included trials.

### 6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

**Table 51. Summary of the trials used to conduct the NMA all analyses**

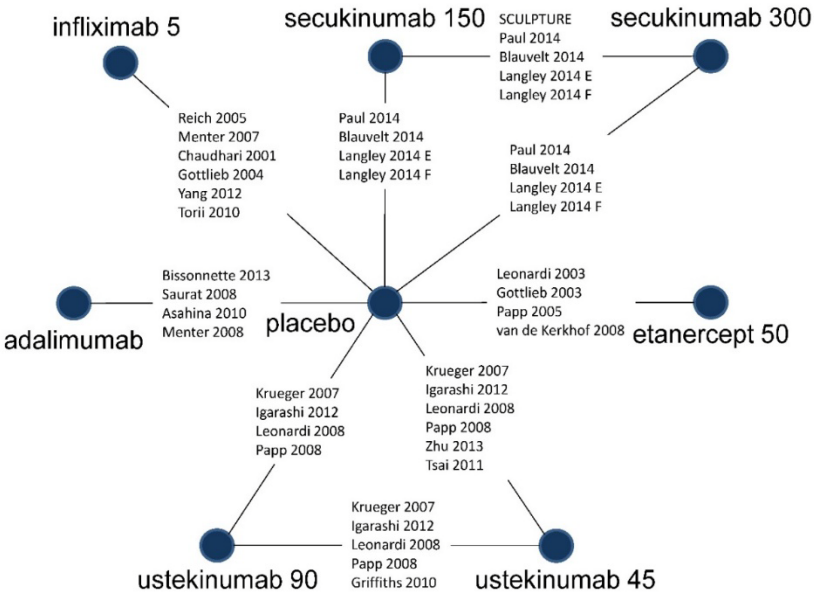
| No. trials | References of trials | Secukinumab (dose) | Adalimumab (dose) | Etanercept) [β] (dose | Infliximab (dose) | Ustekinumab (dose) | Placebo |
|---|---|---|---|---|---|---|---|
| 5 | ERASURE (Langley 2014) | ✓ (150, 300) | | | | | ✓ |
| | FIXTURE (Langley 2014) | ✓ (150, 300) | | | | | ✓ |
| | SCULPTURE (CAIN457A2304) | ✓ (150, 300) | | | | | |
| | JUNCTURE (Paul 2014) | ✓ (150, 300) | | | | | ✓ |
| | FEATURE (Bluavelt 2014) | ✓ (150, 300) | | ✓ | | | ✓ |
| 4 | Bissonnette 2013 | | ✓ | | | | ✓ |
| | CHAMPION (Sauret 2008) | | ✓ | | | | ✓ |
| | Asahina 2010 | | ✓ (standard, 80x0, 80x3+) | | | | ✓ |
| | REVEAL (Menter 2008) | | ✓ | | | | ✓ |
| 8 | Leonardi 2003 | | | ✓ (25, 50,100) | | | ✓ |
| | Bagel 2012 | | | ✓ (100) | | | ✓ |
| | Gottlieb 2003 | | | ✓ (50) | | | ✓ |
| | Papp 2005 | | | ✓ (50, 100) | | | ✓ |
| | Gottlieb 2011 | | | ✓ (100) | | | ✓ |
| | Tyring 2006 | | | ✓ (100) | | | ✓ |
| | Strober 2011 | | | ✓ (100) | | | ✓ |
| | Van de Kerkhof 2008 | | | ✓ (50) | | | ✓ |
| 6 | EXPRESS (Reich 2005) | | | | ✓ (5) | | ✓ |
| | EXPRESS II (Menter 2007) | | | | ✓ (3, 5) | | ✓ |
| | Chaudari 2001 | | | | ✓ (5, 10) | | ✓ |
| | SPIRIT (Gottlieb 2004) | | | | ✓ (3, 5) | | ✓ |
| | Torii 2010 | | | | ✓ (5) | | ✓ |
| | Yang 2012 | | | | ✓ (5) | | ✓ |
| 7 | ACCEPT (Griffiths 2010) | | | ✓ (100) | | ✓ (45, 90) | |
| | Kruger 2007 | | | | | ✓ (45, 45x1, 90, 90x1) | ✓ |
| | Igarashi 2012 | | | | | ✓ (45, 90) | ✓ |
| | LOTUS (Zhu 2013) | | | | | ✓ (45) | ✓ |
| | PEARL (Tsai 2011) | | | | | ✓ (45) | ✓ |
| | PHOENIX 1 (Leonardi 2008) | | | | | ✓ (45, 90) | ✓ |
| | PHOENIX 2 (Papp 2008) | | | | | ✓ (45, 90) | ✓ |

Adapted from Caldwell et al. (2005) Simultaneous comparison of multiple treatments combining direct and indirect evidence. BMJ 331: 897–900, All doses mg unless otherwise stated.

β – etanercept 100 mg was not a relevant comparator however it was necessary to include this to provide a network to link relevant comparators for the 16 week analysis

A network diagram for the base case NMA is presented below. Each node represents a treatment regimen included in the network. Lines represent the direct comparisons between nodes. Labels along each edge represent the author of the primary reference contributing to the respective direct comparison.

**Figure 19. Network of trials for the comparison of secukinumab versus other biologics for PASI response (NICE 12 week endpoint, base-case)**




### 6.7.4 For the selected trials, provide a summary of the data used in the analysis.

After NMA feasibility, 26 RCTs were eligible for inclusion in the base case (NICE 12 week network analysis), 23 RCTs in the 12 week analysis (scenario 1) and 27 RCTs in the NICE 16 week network analysis (scenario 2). Therefore 30 RCTs were included overall but not all trials were used in every analysis. To enable a 16 week network to be formed it was necessary to include etanercept 100 mg treatment arms even though this dose is not recommend by NICE for use in the UK.

Treatment and patient characteristics are presented in Table 52 and outcomes data in Table 53. In this analysis, the PASI outcome, a continuous measure, was reported as overlapping nested categories (i.e. PASI j = reduction in PASI score of at least j%, j=50, 75, 90, where PASI 50 > PASI 75 > PASI 90). The number of PASI cut-offs varied from trial to trial. In order to perform the analysis, the data for each trial were transformed into mutually exclusive categories at the reported cut-offs. For example, a trial reporting on all cut-offs would have categories 0-49, 50-74, 75-89 and 90-100, while a trial reporting only PASI 50 would have categories 0-50 and 51-100.

**Table 52 Baseline patient characteristics of RCTs included in NMA**

| 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 | |
| Krueger 2007 | Placebo | 64 | 44 | 72 | 92.8 | 16.9 | Yes | | 95 | | 61 | 19.9 | 12 | |

| 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 |
| 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 | |

| 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 | | |

**Table 53 PASI outcome response as reported in the included RCTs**

| Trial | Author | Treatment | Time point (weeks)_ | N | PASI 50 (n) | PASI 50 (%) | PASI 75 (n) | PASI 75 (%) | PASI 90 (n) | PASI 90 (%) | PASI 100 (n) | PASI 100 (%) | 12 week (NICE endpoint) | 12 week | 16 week (NICE endpoint) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ACCEPT | Griffiths 2010 | etanercept 100 | 12 | 347 | | | 197 | 56.8 | 80 | 23.1 | | | YES | YES | YES |
| ACCEPT | Griffiths 2010 | ustekinumab 45 | 12 | 209 | | | 141 | 67.5 | 76 | 36.4 | | | YES | YES | YES |
| ACCEPT | Griffiths 2010 | ustekinumab 90 | 12 | 347 | | | 256 | 73.8 | 155 | 44.7 | | | YES | YES | YES |
| Bagel | Bagel 2012 | etanercept 100 | 12 | 62 | 52 | 85 | 36 | 59 | 15 | 25 | | | | | YES |
| Bagel | Bagel 2012 | placebo | 12 | 62 | 4 | 7 | 3 | 5 | 1 | 2 | | | | | YES |
| Bissonnette | Bissonnette 2013 | adalimumab | 16 | 20 | | | 14 | 70 | | | | | YES | | YES |
| Bissonnette | Bissonnette 2013 | placebo | 16 | 10 | | | 2 | 20 | | | | | YES | | YES |
| CHAMPION | Saurat 2008 | adalimumab | 16 | 108 | 96 | 89 | 85 | 79.6 | 56 | 51.9 | 18 | 16.7 | YES | | YES |
| CHAMPION | Saurat 2008 | placebo | 16 | 53 | 16 | 30.2 | 10 | 18.9 | 5 | 11.3 | 1 | 1.3 | YES | | YES |
| CHAMPION | Saurat 2008 | adalimumab | 12 | 108 | 97 | 90.7 | 83 | 76.9 | 53 | 49.1 | 11 | 11.1 | | YES | |
| CHAMPION | Saurat 2008 | placebo | 12 | 53 | 13 | 26.4 | 8 | 15.1 | 3 | 7.5 | 0 | 0 | | YES | |
| CNTO 1275 Psoriasis Study | Krueger 2007 | placebo | 12 | 64 | 7 | 11 | 1 | 2 | 1 | 2 | 0 | 0 | YES | YES | YES |
| CNTO 1275 Psoriasis Study | Krueger 2007 | ustekinumab 45 | 12 | 64 | 59 | 92 | 43 | 67 | 28 | 44 | 10 | 16 | YES | YES | YES |
| CNTO 1275 Psoriasis Study | Krueger 2007 | ustekinumab 90 | 12 | 64 | 59 | 92 | 52 | 81 | 33 | 52 | 13 | 20 | YES | YES | YES |
| ERASURE | Langley 2014 | placebo | 12 | 246 | 22 | 8.9 | 11 | 4.5 | 3 | 1.2 | 2 | 0.8 | YES | | |
| ERASURE | Langley 2014 | secukinumab 150 | 12 | 243 | 203 | 83.5 | 174 | 71.6 | 95 | 39.1 | 31 | 12.8 | YES | | |
| ERASURE | Langley 2014 | secukinumab 300 | 12 | 245 | 222 | 90.6 | 200 | 81.6 | 145 | 59.2 | 70 | 28.6 | YES | | |
| ERASURE | Langley 2014 | secukinumab 150 | 16 | 243 | 212 | 87.2 | 188 | 77.4 | 130 | 53.5 | 51 | 21 | | | YES |
| ERASURE | Langley 2014 | secukinumab 300 | 16 | 245 | 224 | 91.4 | 211 | 86.1 | 171 | 69.8 | 102 | 41.6 | | | YES |
| EXPRESS | Reich 2006 | infliximab 5 | 10 | 301 | 274 | 91 | 242 | 80 | 172 | 57 | | | YES | | YES |
| EXPRESS | Reich 2006 | placebo | 10 | 77 | 6 | 8 | 2 | 3 | 1 | 1 | | | YES | | YES |
| EXPRESS II | Menter 2007 | infliximab 5 | 10 | 314 | | | 237 | 75.5 | 141 | 45.2 | | | YES | | YES |
| EXPRESS II | Menter 2007 | placebo | 10 | 208 | | | 4 | 1.9 | 1 | 0.5 | | | YES | | YES |
| Etanercept Psoriasis Study group | Leonardi 2003 | etanercept 100 | 12 | 164 | 121 | 74 | 81 | 49 | 36 | 22 | | | YES | YES | YES |
| Etanercept Psoriasis Study group | Leonardi 2003 | etanercept 50 | 12 | 162 | 94 | 58 | 55 | 34 | 19 | 12 | | | YES | YES | YES |
| Etanercept Psoriasis Study group | Leonardi 2003 | placebo | 12 | 166 | 24 | 14 | 6 | 4 | 1 | 1 | | | YES | YES | YES |
| FIXTURE | Langley 2014 | placebo | 12 | 324 | 49 | 15.1 | 16 | 4.9 | 5 | 1.5 | 0 | 0 | YES | YES | |

| Trial | Author | Treatment | Time point (weeks)_ | N | PASI 50 (n) | PASI 50 (%) | PASI 75 (n) | PASI 75 (%) | PASI 90 (n) | PASI 90 (%) | PASI 100 (n) | PASI 100 (%) | 12 week (NICE endpoint) | 12 week | 16 week (NICE endpoint) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FIXTURE | Langley 2014 | secukinumab 150 | 12 | 327 | 266 | 81.3 | 219 | 67 | 137 | 41.9 | 47 | 14.4 | YES | YES | |
| FIXTURE | Langley 2014 | secukinumab 300 | 12 | 323 | 296 | 91.6 | 249 | 77.1 | 175 | 54.2 | 78 | 24.1 | YES | YES | |
| FIXTURE | Langley 2014 | etanercept 100 | 16 | 323 | 257 | 79.6 | 189 | 58.5 | 101 | 31.3 | 24 | 7.4 | | | YES |
| FIXTURE | Langley 2014 | secukinumab 150 | 16 | 327 | 290 | 88.7 | 247 | 75.5 | 176 | 53.8 | 84 | 25.7 | | | YES |
| FIXTURE | Langley 2014 | secukinumab 300 | 16 | 323 | 302 | 93.5 | 280 | 86.7 | 234 | 72.4 | 119 | 36.8 | | | YES |
| SCULPTURE | Novartis CSR | secukinumab 150 | 12 | 481 | 448 | 93.1 | 406 | 84.4 | 237 | 49.3 | 78 | 16.2 | YES | YES | |
| SCULPTURE | Novartis CSR | secukinumab 300 | 12 | 483 | 464 | 96.1 | 435 | 90.1 | 310 | 64.2 | 124 | 25.7 | YES | YES | |
| FEATURE (Blauvelt 2014) | Blauvelt 2014 | secukinumab 150 | 12 | 59 | 3 | 5.1 | 0 | 0 | 0 | 0 | 0 | 0 | YES | YES | |
| FEATURE (Blauvelt 2014) | Blauvelt 2014 | secukinumab 300 | 12 | 59 | 51 | 86.4 | 41 | 69.5 | 27 | 45.8 | 5 | 8.5 | YES | YES | |
| FEATURE (Blauvelt 2014) | Blauvelt 2014 | Placebo | 12 | 58 | 51 | 87.9 | 44 | 75.9 | 35 | 60.3 | 24 | 43.1 | YES | YES | |
| Gottlieb | Gottlieb 2003 | etanercept 50 | 12 | 57 | 39 | 70 | 17 | 30 | 6 | 11 | | | YES | YES | YES |
| Gottlieb | Gottlieb 2003 | placebo | 12 | 55 | 6 | 11 | 1 | 2 | 0 | 0 | | | YES | YES | YES |
| Gottlieb - A | Chaudhari 2001 | infliximab 5 | 10 | 11 | | | 9 | 81.8 | | | | | YES | | YES |
| Gottlieb - A | Chaudhari 2001 | placebo | 10 | 11 | | | 2 | 18.2 | | | | | YES | | YES |
| Japanese Ustekinumab Study | Igarashi 2012 | placebo | 12 | 31 | 4 | 12.9 | 2 | 6.5 | 1 | 3.2 | | | YES | YES | YES |
| Japanese Ustekinumab Study | Igarashi 2012 | ustekinumab 45 | 12 | 64 | 53 | 82.8 | 38 | 59.4 | 21 | 32.8 | | | YES | YES | YES |
| Japanese Ustekinumab Study | Igarashi 2012 | ustekinumab 90 | 12 | 62 | 52 | 83.9 | 42 | 67.7 | 27 | 43.5 | | | YES | YES | YES |
| LOTUS | Zhu 2013 | placebo | 12 | 162 | 32 | 19.8 | 18 | 11.1 | 5 | 3.1 | 1 | 0.6 | YES | YES | YES |
| LOTUS | Zhu 2013 | ustekinumab 45 | 12 | 160 | 146 | 91.3 | 132 | 82.5 | 107 | 66.9 | 38 | 23.8 | YES | YES | YES |
| M04-688 | Asahina 2010 | adalimumab | 12 | 43 | | | 23 | 53.5 | 13 | 30.2 | | | YES | YES | |
| M04-688 | Asahina 2010 | placebo | 12 | 46 | | | 1 | 2.2 | 0 | 0 | | | YES | YES | |
| M04-688 | Asahina 2010 | adalimumab | 16 | 43 | 35 | 81.4 | 27 | 62.8 | 17 | 39.5 | | | YES | | YES |
| M04-688 | Asahina 2010 | placebo | 16 | 46 | 9 | 19.6 | 2 | 4.3 | 0 | 0 | | | YES | | YES |
| M10-114 | Gottlieb 2011 | etanercept 100 | 12 | 141 | | | 78 | 56 | 32 | 23 | 9 | 6.7 | | | YES |
| M10-114 | Gottlieb 2011 | placebo | 12 | 68 | | | 5 | 7.4 | 1 | 1.4 | 0 | 0 | | | YES |
| PEARL | Tsai 2011 | placebo | 12 | 60 | 8 | 13.3 | 3 | 5 | 1 | 1.7 | 0 | 0 | YES | YES | YES |
| PEARL | Tsai 2011 | ustekinumab 45 | 12 | 61 | 51 | 83.6 | 41 | 67.2 | 30 | 49.2 | 5 | 8.2 | YES | YES | YES |
| PHOENIX 1 | Leonardi 2008 | placebo | 12 | 255 | 26 | 10.2 | 8 | 3.1 | 5 | 2 | 0 | 0 | YES | YES | YES |
| PHOENIX 1 | Leonardi 2008 | ustekinumab 45 | 12 | 255 | 213 | 83.5 | 171 | 67.1 | 106 | 41.6 | 32 | 12.5 | YES | YES | YES |

| Trial | Author | Treatment | Time point (weeks)_ | N | PASI 50 (n) | PASI 50 (%) | PASI 75 (n) | PASI 75 (%) | PASI 90 (n) | PASI 90 (%) | PASI 100 (n) | PASI 100 (%) | 12 week (NICE endpoint) | 12 week | 16 week (NICE endpoint) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PHOENIX 1 | Leonardi 2008 | ustekinumab 90 | 12 | 256 | 220 | 85.9 | 170 | 66.4 | 94 | 36.7 | 28 | 10.9 | YES | YES | YES |
| PHOENIX 2 | Papp 2008 | placebo | 12 | 410 | 41 | 10 | 15 | 3.7 | 3 | 0.7 | 0 | 0 | YES | YES | YES |
| PHOENIX 2 | Papp 2008 | ustekinumab 45 | 12 | 409 | 342 | 83.6 | 273 | 66.7 | 173 | 42.3 | 74 | 18.1 | YES | YES | YES |
| PHOENIX 2 | Papp 2008 | ustekinumab 90 | 12 | 411 | 367 | 89.3 | 311 | 75.7 | 209 | 50.9 | 75 | 18.2 | YES | YES | YES |
| Papp | Papp 2005 | etanercept 100 | 12 | 194 | 150 | 77 | 96 | 49 | 40 | 21 | | | | | YES |
| Papp | Papp 2005 | etanercept 50 | 12 | 196 | 126 | 64 | 67 | 34 | 21 | 11 | | | YES | YES | YES |
| Papp | Papp 2005 | placebo | 12 | 193 | 18 | 9 | 6 | 3 | 1 | 1 | | | YES | YES | YES |
| REVEAL | Menter 2008 | adalimumab | 16 | 814 | | | 578 | 71 | 366 | 45 | 162 | 20 | YES | | YES |
| REVEAL | Menter 2008 | placebo | 16 | 398 | | | 26 | 7 | 7 | 2 | 3 | 1 | YES | | YES |
| SPIRIT | Gottlieb 2004 | infliximab 5 | 10 | 99 | 96 | 97 | 87 | 87.9 | 57 | 57.6 | | | YES | | YES |
| SPIRIT | Gottlieb 2004 | placebo | 10 | 51 | 11 | 21.6 | 3 | 5.9 | 1 | 2 | | | YES | | YES |
| Strober (M10-315) | Strober 2011 | etanercept 100 | 12 | 139 | | | 55 | 39.6 | 19 | 13.7 | 8 | 5.8 | | | YES |
| Strober (M10-315) | Strober 2011 | placebo | 12 | 72 | | | 4 | 6.9 | 3 | 4.2 | 0 | 0 | | | YES |
| Torii | Torii 2010 | infliximab 5 | 10 | 35 | 29 | 83.1 | 26 | 73.8 | 19 | 55.5 | | | YES | | YES |
| Torii | Torii 2010 | placebo | 10 | 19 | 2 | 11 | 0 | 0 | 0 | 0 | | | YES | | YES |
| Tyring | Tyring 2006 | etanercept 100 | 12 | 311 | 229 | 74 | 147 | 47 | 65 | 21 | | | | | YES |
| Tyring | Tyring 2006 | placebo | 12 | 307 | 43 | 14 | 15 | 5 | 4 | 1 | | | | | YES |
| Yang | Yang 2012 | infliximab 5 | 10 | 84 | 79 | 94 | 68 | 81 | 48 | 57.1 | | | YES | | YES |
| Yang | Yang 2012 | placebo | 10 | 45 | 6 | 13.3 | 1 | 2.2 | 0 | 0 | | | YES | | YES |
| van de Kerkhof | van de Kerkhof 2008 | etanercept 50 | 12 | 96 | 66 | 68.8 | 36 | 37.5 | 13 | 13.5 | | | YES | YES | YES |
| van de Kerkhof | van de Kerkhof 2008 | placebo | 12 | 46 | 4 | 8.7 | 1 | 2.2 | 1 | 2.2 | | | YES | YES | YES |

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method as implemented in the OpenBUGS software package (59, 60). All analyses were performed using R version 3.0.3 (http://www.r-project.org/) and OpenBugs version 3.2.3 (OpenBUGS Project Management Group). The OpenBugs code is provided in the appendix, Section 10.8. The methods recommended by DSU for ordered categorical data were used for this analysis.

**Evaluation of inconsistency**

Prior to the NMA, the evidence networks were examined to determine if there was inconsistency between direct and indirect comparisons for the closed loops in the network. In principle, the available information for each of the comparisons (i.e. contrasts) that were part of a closed loop, was split into direct and indirect information to assess consistency. For each contrast in question, a pooled relative treatment effect estimate was obtained using only the studies providing direct evidence for this comparison, as well as an estimate using only studies that provide indirect evidence for this comparison by means of a NMA. This approach is called 'edge-splitting' (61). For synthesis of direct evidence standard random effects meta-analysis models were used (same syntax as the NMA models). Where this approach was not feasible, consistency was evaluated by comparing findings of two models: one with an NMA using the full evidence network (i.e. two and three-arm trial results), and one based on an NMA excluding two-arm trials from the loops in question.

**NMA methodology and models**

Based on the findings of the feasibility assessment and evaluation of consistency, the results of the RCTs that were part of one evidence network and deemed sufficiently similar were synthesised by means of NMAs by population and outcome of interest. Under the assumption of consistency, the NMA model relates data from the individual studies to basic parameters reflecting the (pooled) relative treatment effect of each intervention compared to placebo. Based on these parameters, the relative treatment effects between each of the contrasts in the network were obtained.

Meta-regression models were investigated by meta-regression and sensitivity analysis. The plausibility of model assumptions should guide model choice and, in general, we deemed that the assumptions of random effects models are more plausible than of the fixed effect model. For completeness, both fixed and random effects NMA were conducted (fixed-effects analyses are not presented but are available on request). In this analysis, the overlapping nested PASI categories were transformed into mutually exclusive categories at the reported cut-offs. A multinomial likelihood NMA setup with probit link function (62) was used to simultaneously calculate probability of PASI 50, 75 and 90 response and relative risk between each comparison in the network.

In order not to influence the observed results by the prior distribution, non-informative prior distributions were used for the model parameter(s): for (pooled) treatment effects with NMA models, for cut-off effects with NMA models, and for treatment-by-covariate interaction term with meta-regression models; for between study heterogeneity with *u* set at 5 times the range of

observed treatment effects across studies included in the NMA, and
for nuisance parameters of the models (62).

The goodness-of-fit of model predictions to the observed data were measured by calculating the posterior mean residual deviance. Subsequently the deviance information criterion (DIC) was obtained which provides a measure of the trade-off between model fit and parsimony (the fixed effect model being the most parsimonious). However, DIC is not the sole criterion for selection, and the random effects model was considered more plausible.

**Table 54. DIC estimates for different models.**

| Model | DIC |
|---|---|
| NICE 12 week endpoint analysis fixed effects<br>NICE 12 week endpoint analysis random effects | 942.8<br>942.7 |
| 12 week analysis fixed effects<br>12 week analysis random effects (RE) | 885.0<br>885.0 |
| NICE 16 week endpoint analysis fixed effects<br>NICE 16 week endpoint analysis random effects | 421.7<br>423.3 |

### Presentation of results

The primary outputs of the Bayesian NMA are the posterior distributions of the (pooled) relative treatment effects between all interventions in the networks. For each PASI cut-off, relative treatment effects are presented as relative risks. The probability of PASI response for each intervention has also been estimated for each PASI cut-off. In addition, the predictive distributions based on the treatment effect estimates and heterogeneity estimate were calculated as this better represents the uncertainty about the comparative effectiveness of treatments in a future roll out of a particular intervention (62).

The posterior distributions of each outcome or effect measure of interest are summarised by the median as reflection of the “point estimate” of effect and 95% credible intervals (CrIs), which are constructed from the 2.5$^{th}$ and 97.5$^{th}$ percentiles of the posterior distribution.

For each outcome and research question, the rank-probabilities and expected rank for all treatments were calculated, as well as the probability that any given intervention is better than the comparator of interest. In addition, rankograms are presented for each treatment. Rankograms plot the probability of being best, second best, etc. against the rank, thereby creating a graphical display the hierarchy of the interventions studied.

Note: Given the use of non-informative prior distributions for all analyses, the 95% CrIs are similar to what 95% confidence intervals (CIs) would have looked like if the analyses were performed in a frequentist framework. Accordingly, one can take the position to interpret the 95% CrI in a similar way as 95% CIs when interpreting relative treatment effect, if that is considered more familiar.

## 6.7.6 Please present the results of the analysis.

### Base-case analysis: 12 week NICE endpoints

PASI response for the base-case NICE Endpoints analysis was reported in 26 trials. The evidence network is presented in Figure 19. The results of the random effects multinomial NMA (DIC=942.7) are presented in tables and figures below. All treatments had significantly better PASI 50, 75 and 90 responses than placebo.

The base case analysis showed secukinumab 300 mg is more efficacious than etanercept 50 and adalimumab, ustekinumab 45 and equal efficacy to ustekinumab 90 and infliximab as represented by higher or similar proportions of patients, respectively, in the 50-74 (PASI 50), 75-89 (PASI 75) and 90-100 (PASI 90) categories.

The estimated probability of ranking (1st, 2nd, etc.) based on the NMA results are displayed in the rankogram in Figure 23. Considering the complete rankogram for each treatment, it can be observed that the "mass" of the rankograms for secukinumab 300 and infliximab are mostly at the left, which indicates that these treatments are most likely to be most efficacious. The "mass" of the rankogram for etanercept is mostly on the right, indicating that it is most likely the least efficacious.

Similar findings as obtained with the base-case analysis were observed with the sensitivity analyses excluding trials with low psoriasis duration; high baseline PASI score; and high percentage with prior biologic exposure. Among trials with DLQI>10, it was not possible to evaluate comparisons involving adalimumab, but the other effect estimates were consistent with base case results. In the meta-regression adjusting for prior biologic exposure (>20% vs. other), the findings were also similar as for the base-case analysis.

**Table 55. Random effects multinomial NMA for PASI 50 response**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **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** |

**Figure 20. Modelled probability of PASI 50 response**

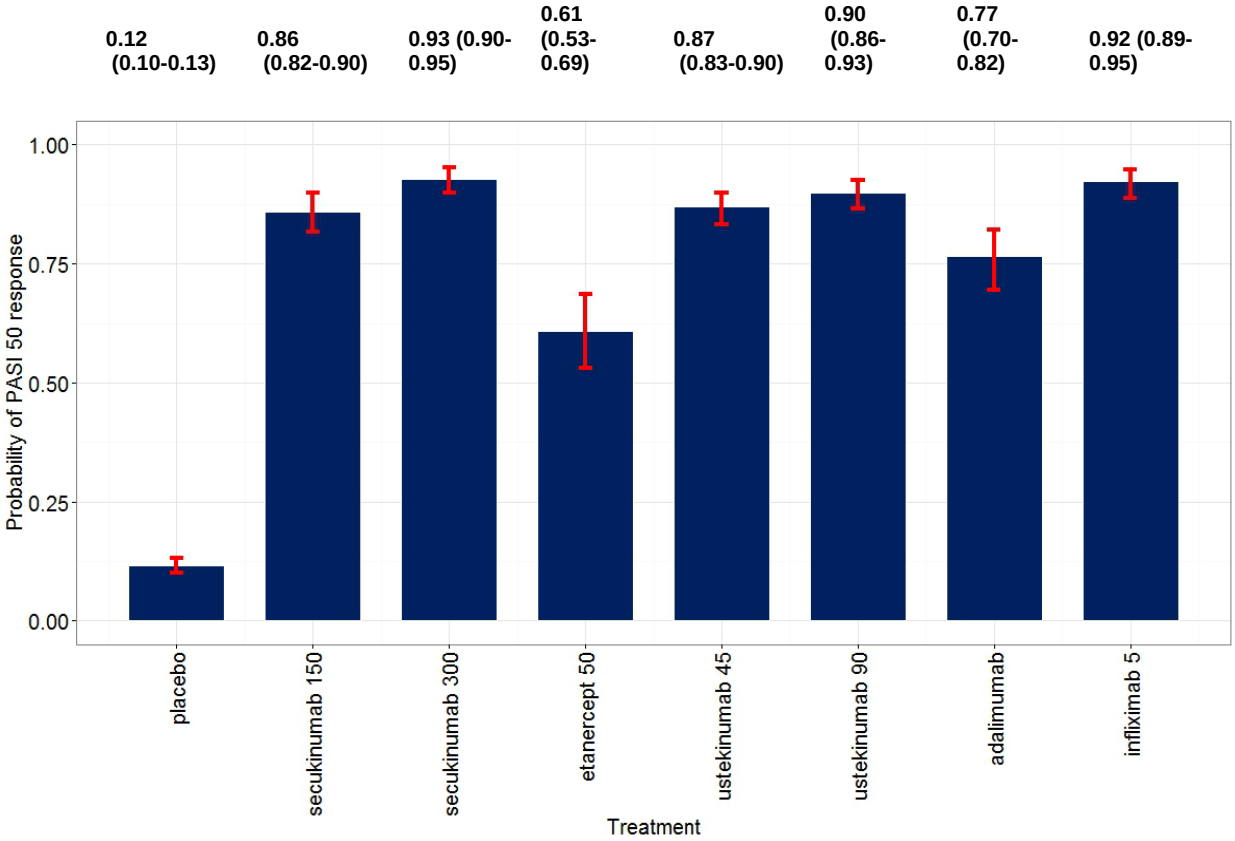



**Table 56. Random effects multinomial NMA for PASI 75 response**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **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** |

**Figure 21. Modelled probability of PASI 75 response**

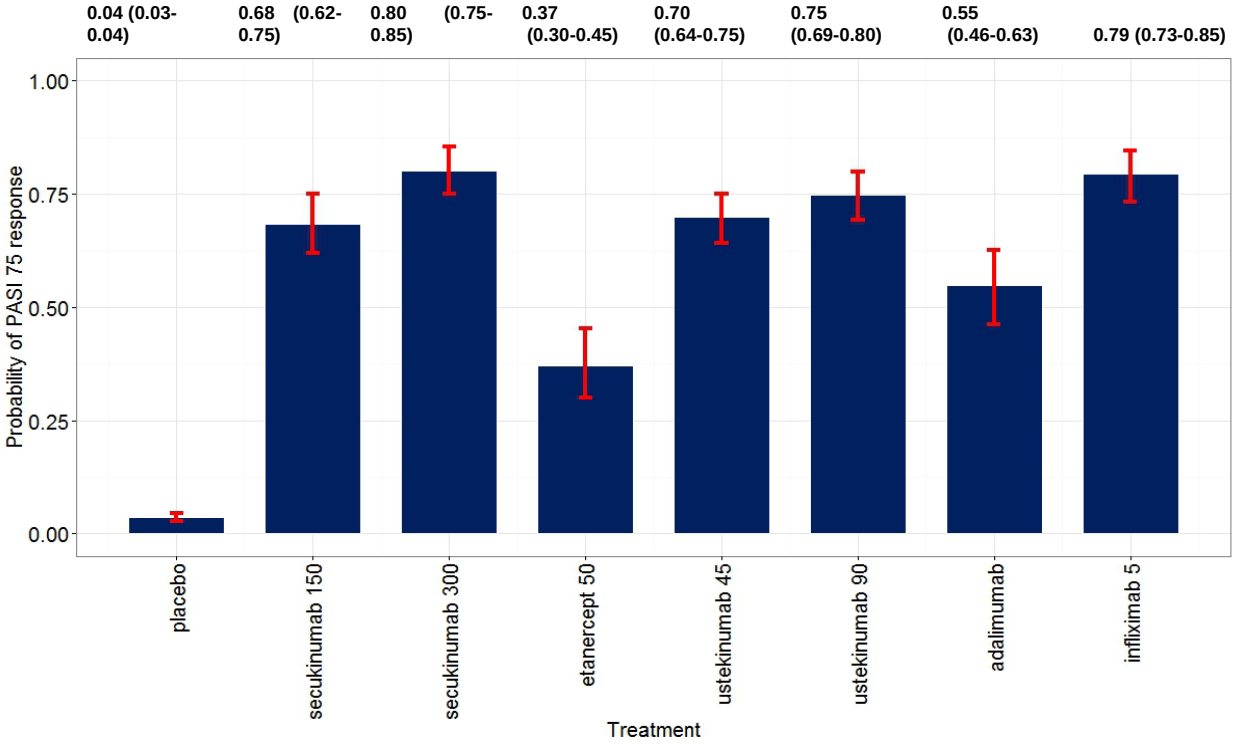



**Table 57. Random effects multinomial network meta-analysis for PASI 90 response**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **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** |

**Figure 22. Modelled probability of PASI 90 response**

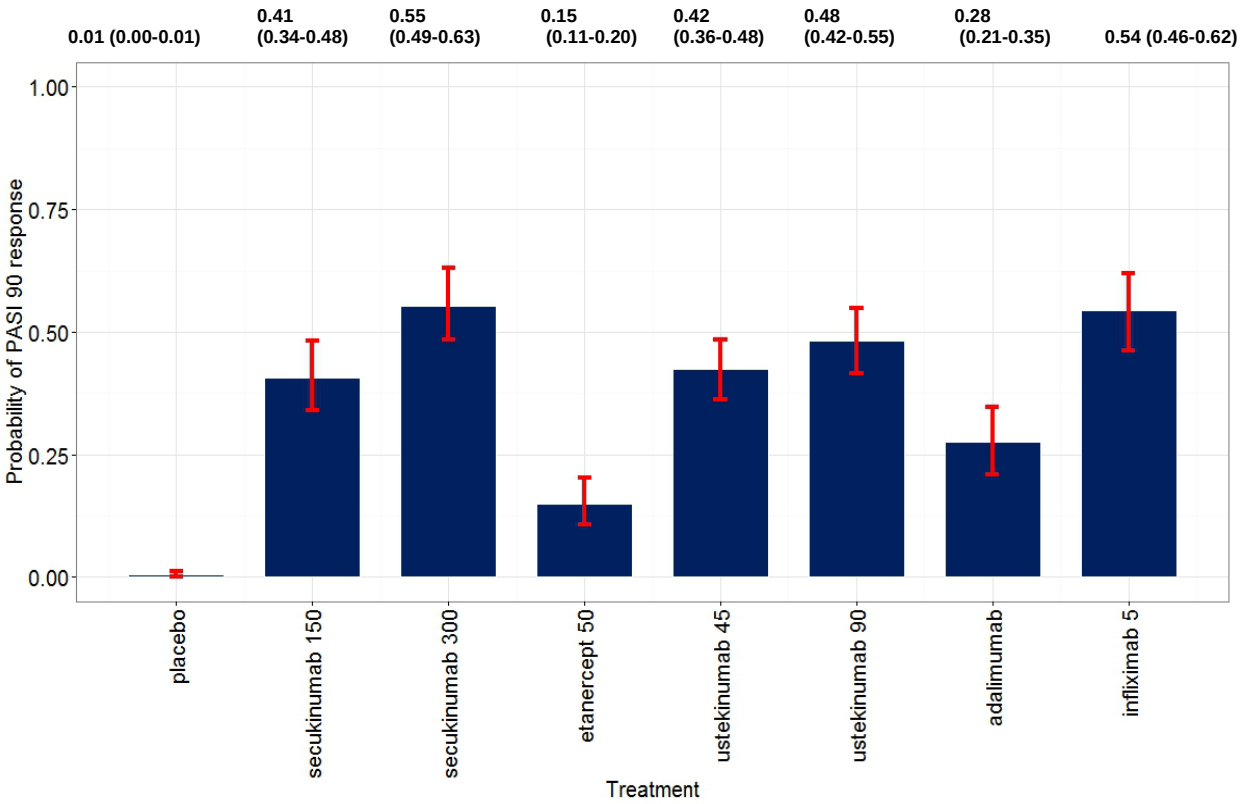
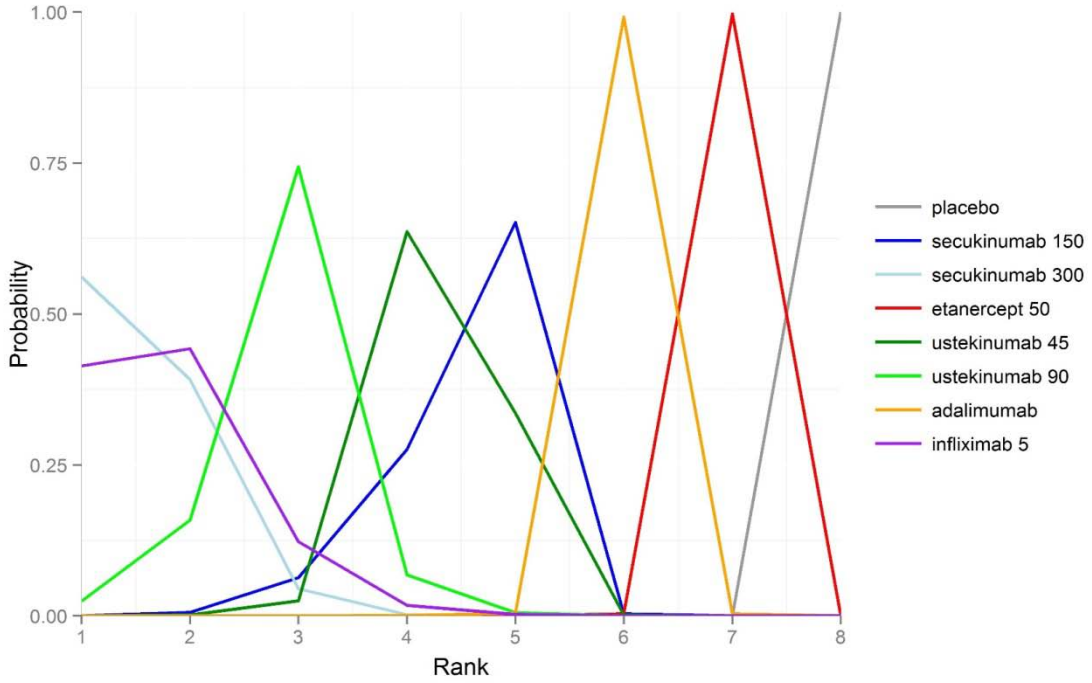



**Figure 23. Base-case NMA: Rankogram**



6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

The data were examined to assess the distribution of potential effect modifiers across studies, within and between direct comparisons. Sensitivity analyses were conducted where studies deemed to be at increased risk of effect modification were excluded, and robustness of results tested. Effect modifiers were tested by sensitivity analysis and meta-regression as follows:

- Baseline PASI score was high in three trials (63-65). Sensitivity analyses were performed to determine if the results were altered by their exclusion. The results were consistent with the base-case NMA.
- Psoriasis duration was low in four trials (63, 65-67). Sensitivity analyses were performed to determine if the results were altered by their exclusion. The results were consistent with the base-case NMA.
- Percent with prior biologic exposure was high in four trials (26, 63, 68, 69). Sensitivity analyses were performed by exclusion as well as by meta-regression with prior biologic exposure (>20% vs. other) as a covariate. The results were consistent with the base-case NMA.
- DLQI was reported in approximately half the trials. Sensitivity analyses were performed to determine if the results were altered in a sub-analysis of trials with DLQI>10. The results were consistent aside from adalimumab, which was not in the network for this sub-analysis.

**Scenario Analyses**

In addition to the sensitivity analyses conducted above, two further scenarios were conducted to investigate the effect of varying the response assessment points for the biologic comparators. Results from these analyses are included as scenario analyses in the cost-effectiveness model (Section 7.6.1).

In Scenario 1, 12 week trial data was used for all comparators. The network for this scenario is presented in Figure 24 below.

In Scenario 2, a 16 week assessment point was used for secukinumab, and base case assessment points for all other comparators (infliximab: 10 weeks, etanercept: 12 weeks, ustekinumab: 12 weeks and adalimumab: 16 weeks). The network for this scenario is presented in Figure 25 below.

Results from the scenario analyses were consistent with the base case and are presented in the appendix, Section 10.9.

**Figure 24. Network of trials for the comparison of secukinumab versus other biologics for PASI response (12 week analysis, scenario analysis)**

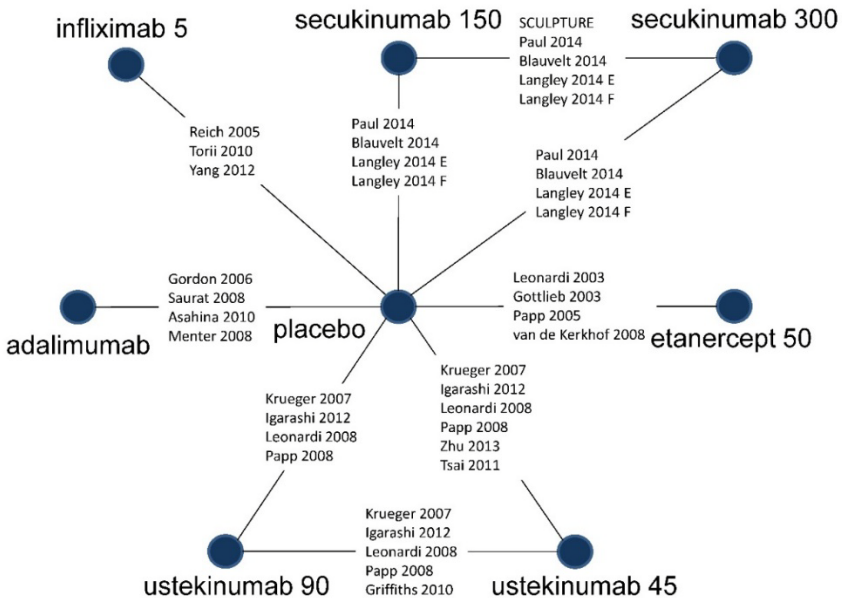
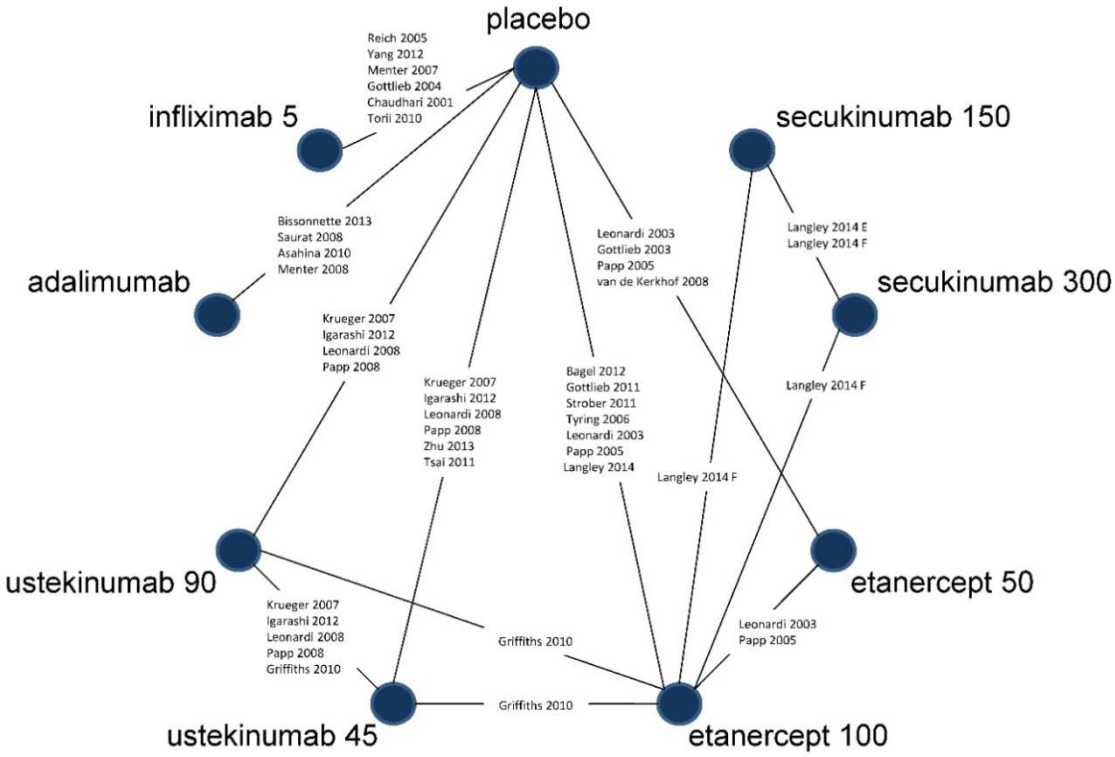



**Figure 25. Network of trials for the NICE 16 week endpoint analysis (secukinumab 16 week data)**



6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

All trials used were relevant, and no additional sensitivity analyses were required.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

As noted above, no pairwise meta-analysis was carried out. However, the consistency between direct and indirect estimates was assessed. This assessment is described in section 6.7.5 under the heading 'Evaluation of inconsistency'.

## *6.8 Non-RCT evidence*

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

RCT evidence is considered the highest form of evidence in the hierarchy of evidence. As there were sufficient RCT evidence identified to address the decision problem, non-RCT evidence was not included.

## 6.9 *Adverse events*

**Summary of Secukinumab Adverse Events**

**Overall, secukinumab administered subcutaneously at a dose of 300 mg once weekly for the first month followed by every four weeks was well tolerated across five phase III RCTs, constituting over 2,400 evaluated patients in total.**

- The safety of secukinumab has been robustly assessed through adverse event reporting in one head-to-head RCT (FIXTURE), in comparison to etanercept and placebo, and in three further RCTs in comparison to placebo (ERASURE, JUNCTURE and FEATURE). Data from the SCULPTURE study, which did not include a placebo comparator, provide supportive evidence.
- In all five studies the rate of serious AEs was low, and similar for all treatment arms. A total of 8 major adverse cardiovascular events were reported across the five trials for patients treated with secukinumab at any dose.
- The most commonly reported AEs across all five trials were nasopharyngitis, headache, diarrhoea, upper respiratory tract infection, pruritus and pyrexia.
- The rate of AEs reported for secukinumab 300 mg at week 12 was favourable compared to placebo in FIXTURE (55.5% vs. 49.8%, respectively), ERASURE (55.1% vs. 47.0%, respectively) and FEATURE (50.8% vs. 47.5%, respectively).
- In general, the incidence of AEs was similar for secukinumab 300 mg and etanercept up to week 52 in FIXTURE (number of cases per 100 patient-years: 252.0 and 243.4, respectively).
- [redacted]
- Discontinuation rates were low for secukinumab 300 mg, etanercept and placebo, with a slightly higher rate of discontinuation reported in FIXTURE for etanercept compared to secukinumab 300 mg at week 12 (1.9% vs 1.2% respectively).
- Overall, across all five trials no increase in safety events was seen with the recommended 300 mg secukinumab dose compared with the exploratory 150 mg secukinumab dose.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the

search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

The five secukinumab RCTs (FIXTURE, ERASURE, JUNCTURE, FEATURE and SCULPTURE) were designed primarily to investigate efficacy outcomes for secukinumab but adverse event reporting were key secondary endpoints in all five trials. Adverse events (AEs) reported in these studies are described below.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

The safety profile of secukinumab has been determined by analysis of adverse event rates reported in the five RCTs of secukinumab in psoriasis referred to in this submission (see Section 6.3 for trial descriptions). In addition, secukinumab has been studied in doses up to 10 mg/kg via intravenous infusion in psoriasis patients with no new or unexpected safety findings identified(29).

Secukinumab was well tolerated in patients with moderate to severe psoriasis in the clinical trials. In these studies, the safety profile of secukinumab 300 mg was comparable with the active comparator etanercept, and to placebo. Overall no increase in safety events was seen with the recommended 300 mg secukinumab dose compared with the exploratory 150 mg secukinumab dose.

### *FIXTURE Study (CAIN457A2303)*

Table 58 shows the adverse events (AEs) in FIXTURE as reported in the primary study publication (19). The incidence of AEs was similar in the secukinumab and etanercept groups. The most commonly occurring AEs in the secukinumab arms were nasopharyngitis, headache, and diarrhoea. A similar proportion of patients in the secukinumab 300 mg treatment arm reported infections and infestations during the induction period: 26.7% in the secukinumab 300 mg arm compared with 24.5% receiving etanercept and 19.3% in the placebo arm. *Candida* infections were more common in the secukinumab groups: reported in 22 (4.7%) patients in the secukinumab 300 mg group and were reported as mild to moderate. In the etanercept group four (1.2%) patients reported *Candida* infection, two of which were classified as severe. None of the infections resulted in treatment discontinuation and all cases resolved with either no treatment or standard therapy.

The rate of SAEs was low during the 12 week induction period (<2.5% of patients experienced an SAE in any treatment group) and remained similar across all groups for the duration of the entire study: 6.8 events per 100 patient-years in the secukinumab 300 mg arm and 7.0 events per 100 patient-years in the etanercept arm, and 8.3 events per 100

patient-years in the placebo arm. There were no clinically apparent differences in the type of serious adverse events in the study groups. There were no deaths in the study, and there were no AEs of special interest.

There were no cases of major adverse cardiac events (MACE) in the secukinumab 300 mg arm (24). One cerebrovascular accident and one myocardial infarction were reported in the secukinumab 150 mg group and one myocardial infarction for the etancercept group. Note that these were reported as SAEs.

Grade 3 neutropenia was reported in nine patients (1%) in the combined secukinumab dose groups, no patients in the etanercept group. No infections were reported in the patients with Grade 3 neutropenia. Grade 4 neutropenia was reported in one patient (0.3%) in the etanercept group and no patients in the secukinumab groups. The rate of discontinuation due to adverse events was more frequent in the etanercept group compared to any secukinumab dose.

**Table 58. Adverse events across randomised groups, FIXTURE (CAIN457A2303) (19, 42)**

| | Induction (12 weeks) | | | | Entire study period (52 weeks) | | | |
|---|---|---|---|---|---|---|---|---|
| | Secukinumab 300 mg (n = 326) | Secukinumab 150 mg (n = 327) | Etanercept 50 mg (n = 323) | Placebo patients (n = 327) | Any Secukinumab 300 mg (n = 467) | Any Secukinumab 150 mg (n = 469) | Etanercept (n = 323) | Placebo (n = 327) |
| | Number of patients with event (%) | | | | Number of patients with event (number of cases per 100 patient-year) | | | |
| Any adverse event | 181 (55.5) | 191 (58.4) | 186 (57.6) | 163 (49.8) | 376 (252.0) | 364 (236.4) | 253 (243.4) | 168 (329.7) |
| Death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nonfatal serious adverse event | 4 (1.2) | 7 (2.1) | 3 (0.9) | 6 (1.8) | 27 (6.8) | 24 (6.0) | 20 (7.0) | 7 (8.3) |
| Discontinuation due to AE[+] | 4 (1.2) | 2 (0.6) | 6 (1.9) | 3 (0.9) | 14 | 10 | 12 | 3 |
| Infection or infestation | 87 (26.7) | 101 (30.9) | 79 (24.5) | 63 (19.3) | 269 (105.4) | 240 (91.9) | 170 (91.4) | 65 (89.5) |
| Common adverse events* | | | | | | | | |
| Nasopharyngitis | 35 (10.7) | 45 (13.8) | 36 (11.1) | 26 (8.0) | 122 (35.2) | 108 (31.4) | 86 (35.7) | 26 (32.8) |
| Headache | 30 (9.2) | 16 (4.9) | 23 (7.1) | 23 (7.0) | 58 (15.7) | 47 (12.4) | 40 (15.2) | 24 (29.6) |
| Diarrhoea | 17 (5.2) | 12 (3.7) | 11 (3.4) | 6 (1.8) | 38 (9.9) | 36 (9.3) | 22 (7.9) | 7 (8.4) |
| Pruritus | 8 (2.5) | 12 (3.7) | 8 (2.5) | 11 (3.4) | 16 (4.0) | 21 (5.3) | 16 (5.7) | 11 (13.2) |
| Arthralgia | 5 (1.5) | 14 (4.3) | 12 (3.7) | 10 (3.1) | 24 (6.0) | 33 (8.5) | 23 (8.2) | 10 (12.1) |
| Upper respiratory tract infection | 7 (2.1) | 10 (3.1) | 7 (2.2) | 3 (0.9) | 26 (6.6) | 26 (6.6) | 18 (6.4) | 3 (3.5) |
| Back pain | 8 (2.5) | 8 (2.4) | 9 (2.8) | 6 (1.8) | 31 (7.9) | 20 (5.1) | 26 (9.3) | 6 (7.1) |
| Cough | 11 (3.4) | 5 (1.5) | 4 (1.2) | 4 (1.2) | 30 (7.6) | 15 (3.7) | 12 (4.2) | 4 (4.8) |
| Hypertension | 5 (1.5) | 10 (3.1) | 5 (1.5) | 4 (1.2) | 20 (5.0) | 22 (5.6) | 14 (4.9) | 4 (4.7) |
| Nausea | 8 (2.5) | 6 (1.8) | 4 (1.2 | 7 (2.1) | 11 (2.7) | 10 (2.5) | 7 (2.4) | 7 (8.3) |
| Oropharyngeal pain | 9 (2.8) | 5 (1.5) | 4 (1.2) | 7 (2.1) | 25 (6.3) | 20 (5.0) | 10 (3.5) | 7 (8.3) |

Source: Table 4, Langley et al 2014 (19)
The induction period was defined as the period from baseline through week 12, and the entire study period as the period from baseline through week 52.
*Occurring at an incidence ≥2% in the combined secukinumab arms during the induction period or at an incidence rate ≥5 per 100 subject-years in the combined secukinumab arms during the entire treatment period; listed in descending order of frequency.
[+]Exposure-adjusted incidence rates were not calculated for AEs leading to discontinuation;

### *ERASURE Study (CAIN457A2302)*

Table 59 shows the observed AEs in ERASURE as reported in the primary study publication (19, 51). Nasopharyngitis, headache and upper respiratory tract infection were the most commonly reported AEs throughout the study period. The proportion of patients who experienced an AE during induction was slightly higher in the secukinumab 300 mg arm (55.1%) compared to the placebo group (47%). The incidence of infections and infestations was higher in the secukinumab arm compared with placebo in both the induction period (29.4% vs 16.2%) and the entire treatment period (rate per 100 patient-years: 100.0% vs 83.9% respectively). *Candida* infections were reported in 11 patients over the entire study period and were graded mild or moderate (7 in secukinumab 300 mg arm, 3 in secukinumab 150 mg arm and 1 in the placebo group).

Rates of SAEs were low for secukinumab and comparable to placebo across groups (6.3 per 100 subject-years secukinumab 300 mg, 6.4 per 100 subject-years for secukinumab 150 mg and 7.4 for placebo) (19). There were four potential cases of MACE during the study, two were in the secukinumab arm 300 mg (0.7%) and two were in the secukinumab arm 150 mg (0.7%) (24). No cases were reported in the placebo arm. All cases of MACE, except one, were reported as SAEs. No deaths were reported during the study.

**Table 59.Adverse events across randomised groups, ERASURE (19, 51)**

| | **Induction (12 weeks)** | | | **Entire study period (52 weeks)** | | |
|---|---|---|---|---|---|---|
| | **Secukinumab 300 mg (n = 245)** | **Secukinumab 150 mg (n = 245)** | **Placebo patients (n = 247)** | **Secukinumab 300 mg (n = 349)** | **Secukinumab 150 mg (n = 353)** | **Placebo (n = 247)** |
| | Number of patients with event (percentage) | | | Number of patients with event (number of cases per 100 patient-year) | | |
| Any adverse event | 135 (55.1) | 148 (60.4) | 116 (47.0) | 286 (245.5) | 287 (269.5) | 124 (323.0) |
| Death | 0 | 0 | 0 | 0 | 0 | 0 |
| Nonfatal serious adverse event | 6 (2.4) | 4 (1.6) | 4 (1.6) | 19 (6.3) | 19 (6.4) | 5 (7.4) |
| Discontinuation due to AE[+] | 3 (1.2) | 5 (2.0) | 4 (1.6) | 12[+] | 18[+] | 5[+] |
| Common adverse events* | | | | | | |
| Infection or infestation | 72 (29.4) | 66 (26.9) | 40 (16.2) | 193 (100.0) | 185 (95.4) | 48 (83.9) |
| Nasopharyngitis | 22 (9.0) | 23 (9.4) | 19 (7.7) | 57 (20.9) | 69 (26.2) | 20 (30.8) |
| Headache | 12 (4.9) | 13 (5.3) | 7 (2.8) | 31 (10.9) | 24 (8.4) | 10 (15.1) |
| Upper respiratory tract infection | 9 (3.7) | 10 (4.1) | 0 | 32 (11.1) | 36 (12.7) | 2 (3.0) |
| Pruritus | 9 (3.7) | 8 (3.3) | 5 (2.0) | 15 (5.1) | 14 (4.8) | 5 (7.4) |
| Oropharyngeal pain | 4 (1.6) | 10 (4.1) | 3 (1.2) | 12 (4.0) | 12 (4.1) | 3 (4.4) |
| Fatigue | 2 (0.8) | 8 (3.3) | 2 (0.8) | 3 (1.0) | 10 (3.4) | 2 (2.9) |
| Hypertension | 0 | 9 (3.7) | 3 (1.2) | 16 (5.3) | 21 (7.3) | 3 (4.4) |
| Influenza like illness | 5 (2.0) | 3 (1.2) | 3 (1.2) | 14 (4.7) | 17 (5.8) | 3 (4.5) |

The induction period was defined as the period from baseline through week 12, and the entire study period as the period from baseline through week 52.
*Occurring at an incidence ≥2% in the combined secukinumab arms during the induction period or at an incidence rate ≥5 per 100 subject-years in the combined secukinumab arms during the entire treatment period; listed in descending order of frequency.
[+]Exposure-adjusted incidence rates were not calculated for AEs leading to discontinuation. NR: Not Reported

### *JUNCTURE Study (CAIN457A2309)*

Safety evaluations for JUNCTURE are based on the data collected up to the end of week 12 of the study (26, 52). Table 60 shows the observed AEs in JUNCTURE.

The most frequently reported AEs in JUNCTURE were nasopharyngitis, headache, and pruritus. The overall incidence of AEs was higher in the secukinumab 300 mg arm compared to the placebo arm (70.0% and 54.1% respectively). *Candida* infections were reported in two patients in the placebo group; this was non-serious, and it did not result in discontinuation. There were no deaths or MACE events reported during the study period. Discontinuation due to AEs during the induction period was low in all treatment groups. One SAE leading to discontinuation occurred in a placebo treated patient ([redacted]) and another discontinuation in the secukinumab 300 mg group was due to [redacted]; these were both considered to be related to the study medication.

The safety profile of secukinumab delivered via auto-injector was consistent with the safety profile seen in FIXTURE and ERASURE.

**Table 60. Adverse events across randomised groups, JUNCTURE (CAIN457A2309) (26, 52)**

| | **Induction 12 weeks** | | |
|---|---|---|---|
| | **Secukinumab 300 mg (n = 60)** | **Secukinumab 150 mg (n = 61)** | **Placebo patients (n = 61)** |
| Number of patients with event (percentage) | | | |
| Any adverse event | 42 (70) | 39 (63.9) | 33 (54.1) |
| Death | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Nonfatal serious adverse event | 1 (1.7) | 3 (4.9) | 1 (1.6) |
| Discontinuation due to AE | 0 | 0 | 1 (1.6) |
| Common adverse events* | | | |
| Nasopharyngitis | 19 (31.7) | 4 (23.0) | 10 (16.4) |
| Headache | 3 (5.0) | 5 (8.2) | 3 (4.9) |
| Pruritus | 5 (8.3) | 1 (1.6) | 2 (3.3) |
| Sinusitis | 3 (5.0) | 1 (1.6) | 0 (0.0) |
| Cough | 3 (5.0) | 0 (0.0) | 2 (3.3) |
| Hypertension | 1 (1.7) | 2 (3.3) | 4 (6.6) |
| Toothache | 2 (3.3) | 1 (1.6) | 2 (3.3) |
| Blepharitis | [redacted] | [redacted] | [redacted] |
| Dysphonia | [redacted] | [redacted] | [redacted] |
| Gastroenteritis | [redacted] | [redacted] | [redacted] |
| Nausea | [redacted] | [redacted] | [redacted] |
| Rhinitis | [redacted] | [redacted] | [redacted] |
| Seborrhoeic dermatitis | [redacted] | [redacted] | [redacted] |
| Bronchitis | [redacted] | [redacted] | [redacted] |
| Oropharyngeal pain | [redacted] | [redacted] | [redacted] |
| Injection site haematoma | [redacted] | [redacted] | [redacted] |

*Occurred in at least 2% of treatment group.

## *FEATURE Study (CAIN457A2308)*

Safety evaluations for FEATURE are based on the data collected up to the end of week 12 of the study (induction period) (27, 53). Table 61 shows the observed AEs in FEATURE.

The most commonly reported AEs in FEATURE over the 12 week treatment period for secukinumab 300 mg were diarrhoea, nasopharyngitis, headache, and pyrexia. The overall incidence of AEs was similar between secukinumab 300 mg (30/59; 50.8%) and placebo (28/59; 47.5%).(27)

The overall incidence of SAEs was low in both secukinumab 300 mg and placebo treated patients (3/59, 5.1% vs 1/59, 1.7% respectively). Most AEs were reported as mild to moderate in severity.

Potential MACE cases (acute MI and cerebrovascular accident) were reported in two patients in the secukinumab 300 mg group in both cases the subject had multiple CV risk factors that the investigators considered to be primarily responsible. There were

no MACE events reported in the placebo arm. No deaths were reported during the study period.

Overall, the safety profile seen in FEATURE was consistent with that reported in ERASURE and FIXTURE.

**Table 61. Adverse events across randomised groups, FEATURE (CAIN457A2308) (27, 53)**

| | Induction 12 weeks | | |
|---|---|---|---|
| | **Secukinumab 300 mg (n =59 )** | **Secukinumab 150 mg (n =59 )** | **Placebo patients (n = 59)** |
| Number of patients with event (percentage) | | | |
| Any adverse event | 30 (50.8) | 34 (57.6) | 28 (47.5) |
| Death | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Nonfatal serious adverse event | 3 (5.1) | 0 (0.0) | 1 (1.7) |
| Discontinuation due to AE | 1 (1.7) | 0 (0.0) | 1 (1.7) |
| Common adverse events* | | | |
| Diarrhoea | 5 (8.5) | 2 (3.4) | 1 (1.7) |
| Nasopharyngitis | 3 (5.1) | 3 (5.1) | 5 (8.5) |
| Headache | 0 (0.0) | 4 (6.8) | 3 (5.1) |
| Pyrexia | 2 (3.4) | 2 (3.4) | 2 (3.4) |
| Back pain | 3 (5.1) | 0 (0.0) | 0 (0.0) |
| Bursitis | 2 (3.4) | 1 (1.7) | 0 (0.0) |
| Cough | 1 (1.7) | 2 (3.4) | 0 (0.0) |
| Depression | 1 (1.7) | 2 (3.4) | 0 (0.0) |
| Nausea | 3 (5.1) | 0 (0.0) | 1 (1.7) |
| Oropharyngeal pain | 1 (1.7) | 2 (3.4) | 0 (0.0) |
| Rhinitis | 1 (1.7) | 2 (3.4) | 0 (0.0) |
| Asthenia | [redacted] | [redacted] | [redacted] |
| Dermatitis contact | [redacted] | [redacted] | [redacted] |
| Dysmenorrhoea | [redacted] | [redacted] | [redacted] |
| Hypercholesterolaemia | [redacted] | [redacted] | [redacted] |
| Sciatica | [redacted] | [redacted] | [redacted] |
| Toothache | [redacted] | [redacted] | [redacted] |
| Upper respiratory tract infection | [redacted] | [redacted] | [redacted] |
| Vomiting | [redacted] | [redacted] | [redacted] |
| Psoriasis | [redacted] | [redacted] | [redacted] |

*Occurred in at least 3% of treatment group.

### *SCULPTURE Study (CAIN457A2304)*

AEs reported for SCULPTURE are given in Table 62 (28). AEs for SCULPTURE were consistent with FIXTURE and ERASURE. The most frequently reported AEs during the induction period were nasopharyngitis, headache, and upper respiratory tract infections. The overall incidence of AEs during the induction period was comparable across all treatment groups, and no dose-relationship was observed.

[redacted]

There were two potential MACE events reported in the study, one during the induction period (acute MI) and one during the maintenance period (cerebral haemorrhage).(24) [redacted]

**Table 62. Adverse events across randomised groups, SCULPTURE (CAIN457A2304) (28)**

| | Induction (12 weeks) | | Entire study period (52 weeks) | | | |
|---|---|---|---|---|---|---|
| | **Secukinumab 300 mg FI (n = 483)** | **Secukinumab 150 mg FI (n = 482 )** | **Secukinumab 300 mg FI (n = 216)** | **Secukinumab 300 mg SoR(n = 217)** | **Secukinumab 150 mg FI (n = 203)** | **Secukinumab 150 mg SoR (n = 205)** |
| | Number of patients with event (percentage) | | Number of patients with event (incident rate per 100 patient-years) | | | |
| Any adverse event | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Death | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Nonfatal serious adverse event | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Discontinuation due to SAE | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Common adverse events* | | | | | | |
| Nasopharyngitis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Headache | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Upper respiratory tract infection | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Pruritus | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Hypertension | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cough | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Back pain | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Nausea | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Influenza | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Pharyngitis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Bronchitis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

The induction period was defined as the period from baseline through week 12, and the entire study period as the period from baseline through week 52.
*****Occurring at incidence ≥2% in any treatment group; FI: fixed interval; SoR: start of relapse; NR: not reported

### 6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Overall, results from the five primary trials demonstrate that secukinumab was well tolerated when administered subcutaneously at a dose of 300 mg weekly for the first month followed by four weekly intervals in patients with moderate to severe plaque psoriasis. To analyse the results from these studies further, a pooled analysis of the placebo-controlled studies (FIXTURE, ERASURE, JUNCTURE and FEATURE) was conducted. Results from this analysis are discussed below.

#### *Analysis of Pooled Clinical Trial Data*

A total of 4,498 patients have been treated with secukinumab in blinded and open-label clinical studies in various indications (plaque psoriasis and other autoimmune conditions). Of these, 1,900 patients were exposed to secukinumab for at least one year, representing 3,588 patient years of exposure (1).

The four placebo-controlled phase III studies in plaque psoriasis were pooled to evaluate the safety of secukinumab in comparison to placebo up to 12 weeks after treatment initiation (19, 26, 27, 42, 51-53). In total, 2,076 patients were evaluated (692 patients on 150 mg, 690 patients on 300 mg and 694 patients on placebo).

**Adverse Events**

The most frequently reported single adverse drug reactions (ADRs) were upper respiratory tract infections (most frequently nasopharyngitis and rhinitis). Most of the events were mild or moderate in severity.

ADRs from clinical studies (Table 63) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, ADRs are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

**Table 63. Summary of Adverse Events in Clinical Studies**

| 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 | | | | |

### Infections

In the placebo-controlled period of the clinical trials (a total of 1,382 patients treated with secukinumab and 694 patients treated with placebo for up to 12 weeks), infections were reported in 28.7% of patients treated with secukinumab compared with 18.9% of patients treated with placebo.(24) The majority of infections consisted of non-serious and mild to moderate upper respiratory tract infections, such as nasopharyngitis, which did not necessitate treatment discontinuation. There was an increase in mucosal or cutaneous candidiasis, consistent with the mechanism of action, but the cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation.

Serious infections occurred in 0.14% of patients treated with secukinumab and in 0.3% of patients treated with placebo.(24) Over the entire treatment period (a total of 3,430 patients treated with secukinumab for up to 52 weeks for the majority of patients), infections were reported in [redacted]

### *Conclusions*

The safety of secukinumab has been directly compared with that of etanercept. The evidence from the RCTs described above indicates that the adverse event profiles of secukinumab and etanercept are comparable.

## *6.10 Interpretation of clinical evidence*

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

In the FIXTURE study versus etanercept:

- Secukinumab 300 mg significantly increased PASI 75 rates versus etancercept p<0.0001 (77.1% of subjects achieved a PASI 75 response rate versus 44.0% with etanercept) at week 12.
- 54% of secukinumab 300 mg patients achieved at least a 90% reduction in skin redness, thickness and scaling (PASI 90) as early as Week 12, compared to 21% of etanercept patients (p<0.0001). At week 16, 72% of secukinumab 300 mg patients achieved this higher standard of efficacy (PASI 90).
- Secukinumab 300 mg patients were also more likely to experience completely clear skin compared to those taking etanercept, as measured by PASI 100 at Week 16 (36.8% versus 7.4%).
- Both doses of secukinumab showed improved efficacy compared to etanercept throughout the 52 week study. Secukinumab efficacy was sustained over the full one year duration of the study.
- In FIXTURE, the incidence of AEs was similar for secukinumab 300 mg and etanercept up to week 52 (number of cases per 100 patient-years: 252.0 and 243.4, respectively).

There is also an extensive evidence base for secukinumab in placebo-controlled trials (four studies):

- The proportion of patients treated with secukinumab 300 mg reaching PASI 75 at 12 weeks in these trials ranged from to 73.3% to 81.6%, whereas the rate with placebo did not exceed 5%.
- PASI 75, PASI 90, PASI 100, and IGA mod 0/1 response rates continued to increase from Week 12 to Week 16 in FIXTURE and ERASURE, supporting the CHMP recommendation to assess response to secukinumab at 16 weeks.
- A ≥50% mean decrease from baseline in PASI score was achieved as early as week 3 with secukinumab 300 mg compared to week 7 with etanercept (FIXTURE). It was not achieved at any visit with placebo (FIXTURE, ERASURE and JUNCTURE).

- Other end points, where measured, were consistent with the efficacy seen in FIXTURE (Figure 26).

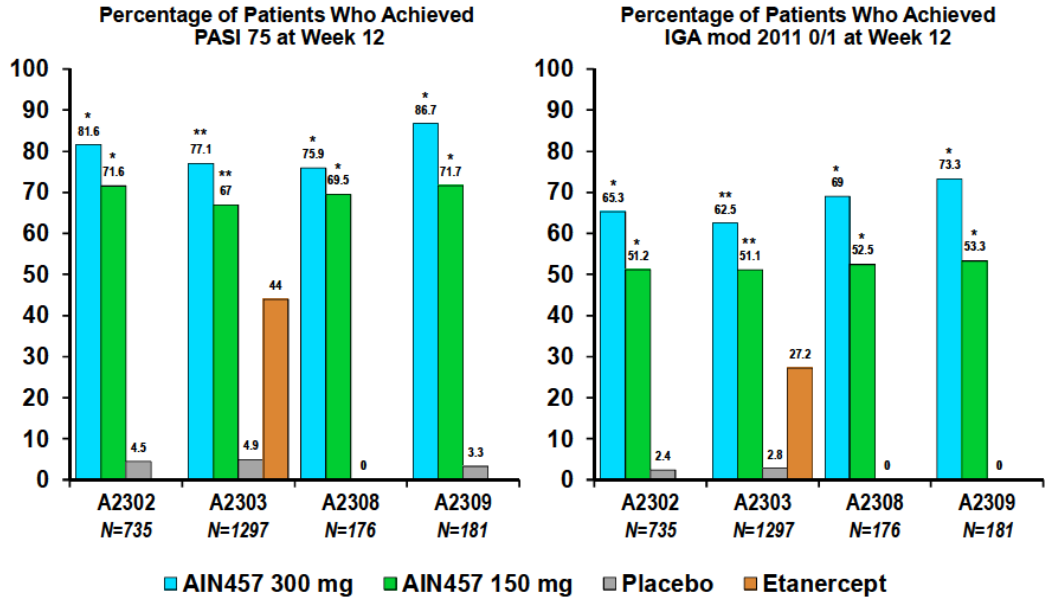
There were no major safety signals identified in the phase 3 trial programme:

- The incidence of adverse events (AEs) was similar between secukinumab 300 mg and etanercept.
- The most common exposure adjusted AEs in any treatment group (including placebo) throughout the 52 week treatment period were nasopharyngitis and headache (occurring in between 12-36% of patients in all groups).
- At the same time point, non-fatal serious AEs were experienced by 5.8% of secukinumab 300 mg, 5.1% of secukinumab 150 mg and 6.2% of etanercept and 2.1% of placebo patients.
- The FEATURE and JUNCTURE studies demonstrate the acceptability of both delivery mechanisms for secukinumab 300 mg.

### 6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

There is a strong clinical evidence base for secukinumab 300 mg in the treatment of psoriasis, consisting of five phase III trials. The four core randomised placebo controlled trials (FIXTURE, ERASURE, JUNCTURE and FEATURE) met their primary and pre-specified key secondary endpoints, and all showed consistent levels of efficacy with regard to PASI 75 and PASI 90. The consistency of findings across these four trials is a major strength of the evidence base.

**Figure 26. FIXTURE primary efficacy outcomes (24)**




* p < 0.0001 versus placebo. Treatment comparisons for studies A2302 and A2303 were based on Cochran-Mantel-Haenszel testing and for studies A2308 and A2309 on Fisher's exact test.

** p <0.0001 versus etanercept

A limitation of the evidence base is the lack of direct head-to-head evidence versus active comparators other than etanercept. However, this has also been a similar issue for all biologics for psoriasis reviewed by NICE to date and an extensive evidence network was available with which to make indirect comparisons, and this was used in a network meta-analysis.

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The evidence base is highly relevant to the decision problem, although indirect comparison (network meta-analysis) techniques were required to extend this to active comparators other than etanercept. The primary outcome measure in the trials was the PASI score in line with UK clinical practice. The PASI score measures both the size and severity of psoriasis lesions, and therefore directly reflects the patient's symptom burden. Improvements in PASI score equate to a reduced symptom burden.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Based on the evidence from the clinical trials, the criteria that should be applied to psoriasis patients to identify eligibility for treatment with secukinumab are a PASI ≥10 and DLQI >10. Note that the evidence base provides support for both the 150 mg and 300 mg doses of secukinumab. However, the 300 mg dose of secukinumab has been recommended by the CHMP and is the only dose listed in the proposed SmPC, which is why it was used throughout.

# 7 Cost effectiveness

**Summary of Cost-effectiveness**

**Overall, secukinumab administered subcutaneously at a dose of 300 mg once weekly for the first month followed by monthly dosing is dominant or extendedly dominant compared to all other biologics and is cost-effective vs. best supportive care at a willingness to pay threshold of £20,000 per QALY (ICER: £7,076).**

- A *de novo* combined decision tree and Markov state-transition model was developed in Microsoft Excel® to estimate the outcomes and costs of using secukinumab 300 mg for the treatment of patients with moderate to severe plaque psoriasis. The model design was based on those used in previous appraisals of biologics in moderate to severe psoriasis.
- All biologics licensed for the treatment of psoriasis in England and Wales (etanercept, adalimumab, infliximab and ustekinumab) were included as comparators in the model. A best supportive care comparator was also included.
- The model was structured as three phases:
  - i) **Induction period** in which all patients received biologic therapy until initial response to treatment was assessed.
  - ii) **Post-induction to 1 year** in which patients who achieved PASI 75 response by the end of phase i) continued biologic treatment. Non-responders switched to best supportive care.
  - iii) **1 year to 10$^{th}$ year** in which patients continued treatment from phase iii) or discontinued treatment due to loss of efficacy, adverse events or other reasons. Discontinuation was applied on a yearly cycle (model cycle length of 1 year).
- Patients were assigned to one of four health states at the induction period based on PASI response criteria (0-49, 50-74, 75-89 and 90-100).
- Clinical efficacy parameters were derived using results of a pooled analysis of PASI response data from the response assessment points defined in the base-case NMA for phase i). In phases ii) and iii) treatment discontinuation rates were applied based on ERASURE and the literature.
- In the base-case, utility values were derived using pooled EQ-5D data from five secukinumab RCTs (FIXTURE, ERASURE, FEATURE, JUNCTURE and SCULPTURE).
- Costs and resource use associated with administering and monitoring treatment, as well as serious adverse events were included in the model. Cost sources included NHS reference costs, the British National Formulary, and published literature.
- Cost and resource use were applied from the perspective of the NHS and personal social services, and both costs and outcomes were discounted at 3.5%.
- Univariate and probabilistic sensitivity analyses were performed to assess uncertainty around key parameters included in the model. In addition five scenario analyses were conducted: a) continuing biologic treatment in partial responders; b) using NMA data where the response assessment points were set to 12 weeks for all comparators; c) using NMA data with a 16 week response assessment point for secukinumab; d) using utility values from the adalimumab

NICE TA146; e) using head-to-head data from FIXTURE to inform the PASI distributions.

- Base-case deterministic results show that secukinumab 300 mg is dominant compared to adalimumab, ustekinumab 45 mg, ustekinumab 90 mg and infliximab 5 mg/kg, extendedly dominant compared to etanercept and cost-effective at a willingness to pay threshold of £20,000 per QALY gained, compared to standard of care (ICER: £7,076).
- In univariate sensitivity analyses, key drivers of the cost-effectiveness of secukinumab were noted as the cost of treatment; frequency of hospitalisations, their cost and associated length of stay (LOS); and treatment discontinuation rate.
- From the probabilistic sensitivity analyses, it is clear that uncertainty around cost (e.g. treatment cost) had a much larger impact on the model results than uncertainty around estimates of the relative treatment effects.
- In scenario analyses, the model results were robust to changes in the inclusion of partial responders to continue initial treatment after the induction period, treatment response time points, FIXTURE head-to-head clinical data and utilities.

## *7.1 Published cost-effectiveness evaluations*

**Identification of studies**

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

A systematic literature review was conducted on 04 December 2013 to identify economic evaluations (EE), including cost-effectiveness, cost-benefit, cost-utility, and cost-minimisation studies, published in the area of moderate to severe plaque psoriasis. The EE review was further limited to studies published in the English language between 01 January 1998 and 04 December 2013, as this was the timepoint after which biologic interventions for chronic plaque psoriasis became available. The search was updated on 02 October 2014. The EE review was also tailored to identify resource use (RU) and costing papers (e.g. burden-of-illness analyses) reporting resource use for the targeted population as required in Section 7.5.3 of this submission.

Articles and abstracts were identified through searches using the following databases on the OVID platform[1]:

- Embase
- Medline (including Medline (R) in process),
- EconLit
- NHS EED

For each database, a search was developed combining disease terms for psoriasis, study design terms (e.g. cost-effectiveness, cost-utility), and outputs of interest (costs and RU). The relevance of references identified by the search across the four databases was assessed against eligibility criteria that were defined following enhanced PICOS criteria.

The search strings can be found in Section 10.11, Appendix 11. The search strings were developed through reviewing prior technology appraisals (TAs) and Cochrane guidelines, and they are consistent with previous search strings with one exception; previously, TAs had included specific drug names within the search strings. The present review was designed to reflect the therapeutic area as a whole, therefore it was not appropriate to restrict the search to specific interventions. The review included the broader psoriasis population (i.e. not limited to plaque psoriasis), which is consistent with precedent set by Woolacott et al. 2005(70).

All references captured by the combined search were reviewed by two reviewers based on their abstracts and titles against the eligibility criteria presented in Table 64.

All publications where there was disagreement about inclusion at this stage were discussed and managed between the two reviewers until a consensus was reached, and a third reviewer was not required. Included publications were retained for full text review. Publications that were not relevant were marked as excluded. The full texts of the publications retained after the abstracts review were judged once more by the two reviewers against the eligibility criteria presented. The approach to resolve any disagreement was the same as for the abstracts review process. All papers included after the full text review were retained for data extraction.

The updated search was conducted in a similar fashion to the initial searches with identical search strategy and PICOS criteria.

[1] Ovid is a platform that provides standardised access to a wide range of economic and clinical literature databases

**Table 64: Eligibility criteria for economic evaluation (and resource use) search**

| Economic evidence | Inclusion | Exclusion |
|---|---|---|
| Population | -Adults (≥18 years) with moderate to severe chronic plaque-type psoriasis(CPP) including those in whom chronic plaque-type psoriasis is poorly controlled by topical treatments and/or phototherapy and/or previous systemic therapy;<br><br>-For identification of data on Adverse Events (rates, associated costs and utilities), intermittent dosing, relapse rates, adherence, and dose titration; adult subjects with other autoimmune diseases treated with biologics | - Children with psoriasis;<br><br>- Patients with types of psoriasis other than plaque psoriasis (i.e. pustular, erythrodermic, and guttate psoriasis); if population is mixed, exclude only if plaque psoriasis is not separately analysed;<br><br>-Patients with mild psoriasis; if population is mixed, exclude only if moderate to severe psoriasis is not separately analysed;<br><br>-Patients suffering from active, ongoing inflammatory diseases other than psoriasis |
| Interventions | -Any biologic<br>-Etanercept<br>-Adalimumab<br>-Ustekinumab<br>-Infliximab<br>-Efalizumab***<br>-Alefacept*** | -Systemic non-biological treatments for moderate to severe psoriasis;<br><br>-Phototherapy and photochemotherapy as the main treatment of interest |
| Comparators | -Any comparator | |
| Outcome measures | -Direct and indirect medical costs and resource utilisation associated with managing patients with moderate to severe psoriasis (including management of adverse events);<br>-Cost-effectiveness results for studies that included biologic treatments -The value of health effects (quality of life, HRQoL);<br>-Utility or preference weights;<br>-Disutility associated with adverse events;<br>-Indirect costs; | |
| Study design | -Cost-benefit analysis;<br>-Cost-effectiveness analysis;<br>-Cost-minimisation analysis;<br>-Cost-utility analysis;<br>-Costing analysis;<br>-Burden/ Cost of illness studies;<br>-Studies reporting resource utilization and costs;<br>-Systematic reviews of EE**;<br>-Retrospective observational studies | -Editorials;<br>-Notes;<br>-Comments;<br>-Letters;<br>-Abstracts only* |
| Restrictions | Language: English<br>Date: 1998- present | |

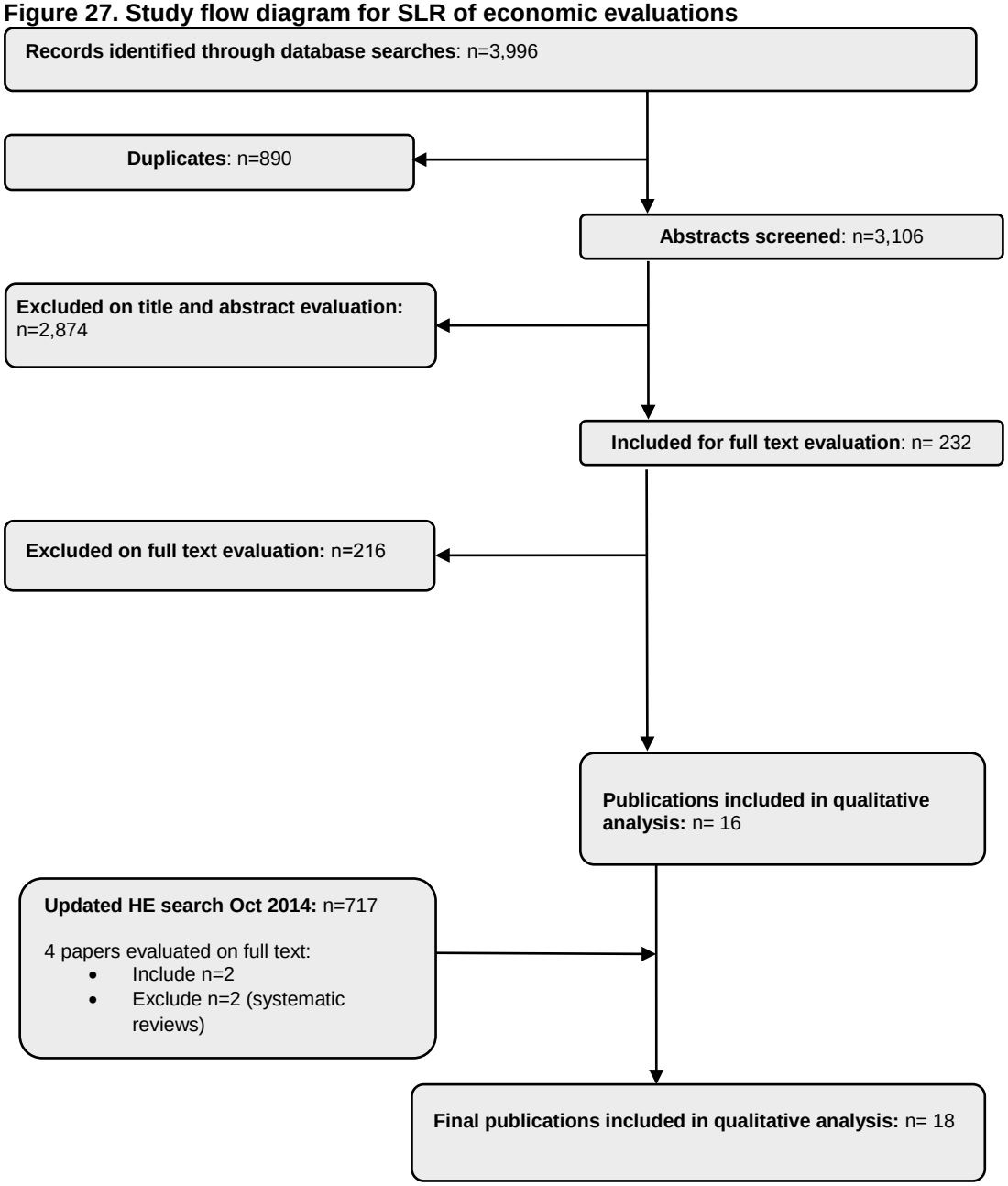
* applies at the full-text review stage only.
**to be kept on file as a cross-reference to ensure that we have captured all relevant papers.
***Were excluded at full-text review as are not UK relevant comparators

Overall, the EE and RU search yielded a total of 3,996 hits, of which 890 were duplicates, leaving 3,106 records to be reviewed against the eligibility criteria. After screening 3,106 titles and abstracts, 232 studies were selected for full-text review. Of these, 16 were retained for data extraction.

This search was updated on 02 October 2014 generating 707 hits of which 60 were duplicates, leaving 647 records to be reviewed against the eligibility criteria. After screening 647 titles and abstracts, 4 studies were selected for full-text review. Of these 2 were excluded because they were systematic reviews and 2 were retained for data extraction. The reference lists of the two systematic reviews were cross-checked for completeness.

A PRISMA flow diagram summarising the process of study selection and the final results of the search is given below in Figure 27.

**Figure 27. Study flow diagram for SLR of economic evaluations**



In addition to the SLR of databases, a search for prior NICE technology appraisals (TAs) for treatment of moderate to severe plaque psoriasis was conducted to identify earlier models developed for this indication. Four TAs were identified for the treatment of moderate to severe plaque psoriasis with etanercept/ efalizumab, infliximab, adalimumab and ustekinumab respectively:

- Etanercept (Enbrel®) and efalizumab (please note no longer marketed) for the treatment of adults with psoriasis (TA 103) in 2006(70)
- Infliximab (Remicade®) for the treatment of adults with psoriasis (TA 134) in 2008(71)
- Adalimumab (Humira®) for the treatment of adults with psoriasis (TA 146) in 2008 (22)
- Ustekinumab (Stelara®) for the treatment of adults with psoriasis (TA 180) in 2009(23)

In addition to prior TAs, a search for guidelines on the treatment of moderate to severe plaque psoriasis relevant to the UK setting was undertaken. The treatment guideline for psoriasis (CG153)(3) and the British Association of Dermatologists' guidelines for biologic interventions for psoriasis(2) were identified and validated the treatment pathway.

### Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Of the 232 papers initially identified for full text review in the EE SLR (see Figure 27), 16 relevant studies were identified. Of these, one was relevant for the RU literature review, and 15 were considered relevant for the EE review. No secukinumab studies were identified in the EE SLR. Note that abstracts were not included as there was sufficient fully published data available.

The updated search that was conducted on 02 October 2014 (see Figure 27) identified 4 papers for full text review, 2 papers were excluded (due to 'other reasons') resulting in 2 relevant studies that were considered relevant for the economic evaluation review in addition to the 16 identified in the initial review.

The 18 studies identified by the EE search included:

- Sixteen cost-effectiveness analyses (CEA), cost-utility analyses (CUA), and cost-efficacy analyses: (Woolacott *et al.* 2006(72), Lloyd *et al.* 2008(73), Nelson *et al.* 2008(74), Greiner *et al.* 2009(75), De Portu *et al.* 2010 (76),

Schmitt-Rau *et al*. 2010 (77), Anis *et al*. 2011 (78), Knight *et al.* 2012 (79), Villacorta *et al*. 2013 (80),Heinen-Kammerer *et al.* 2007 (81), Colombo *et al.* 2009 (82), Pan *et al.* 2011 (83), Menter et al. 2005 (84), Ferrandiz et al. 2012 (85), Chi 2014 (86), Wang 2014(87));

- One budget impact anal*ysis* (BIA) (Avgerinou *et al.* 2012 (88));
- One retrospective observational study (Fonia *et al.* 2010 (89)) reporting resource use data.

Sixteen of the relevant publications were not UK based studies. These publications have been summarised and critically appraised in the appendix (Section 10.12) but are not discussed further in the submission.

Two remaining publications were specific to the United Kingdom (UK); they have been summarised and critically appraised below (Table 65).

**Table 65. Summary of Economic Evaluation (EE) studies**

| **Reference** | **Woolacott et al. 2006** | **Lloyd et al. 2008** | **Etanercept (Enbrel®)- NICE TA103 (Jul 2006)-** | **Infliximab (Remicade®)- NICE TA134 (May 2007)** | **Adalimumab (Humira®)- NICE TA146 (Sep 2007)-** | **Ustekinumab (Stelara®)- NICE TA 180 (Jan 2009)** |
|---|---|---|---|---|---|---|
| Country(ies) where study was performed | UK | UK | UK | UK | UK | UK |
| Study population | Moderate to severe psoriasis | Moderate to severe psoriasis | Moderate to severe psoriasis | Moderate to severe psoriasis | Adults with moderate to severe chronic plaque psoriasis | Moderate to severe psoriasis |
| Model characteristics /Type of evaluation | Cost-effectiveness analysis (Markov model) | Cost-effectiveness analysis (Markov model) | MTA | STA | STA | STA |
| Intervention | Efalizumab, (not available in UK)<br>Etanercept (25mg intermittent, 25mg continuous and 50 mg intermittent) | Etanercept 50 mg biw | Etanercept 25mg<br>Etanercept 50 mg<br>Etanercept 25mg (intermittent)<br>Efalizumab (not available) | Infliximab 5mg/kg | Adalimumab 40 mg | Ustekinumab 45mg/90 mg |
| Comparator | Best supportive care | No systemic therapy, etanercept 25mg biw | The addition of etanercept to other management strategies compared to the strategies excluding etanercept. | • Etanercept<br>• Efalizumab (no longer available)<br>• Standard treatment without a TNF-inhibitor or efalizumab | • Standard therapies: Acitretin, ciclosporin, hydroxycarbamide, methotrexate, PUVA<br>• etanercept<br>• efalizumab<br>• infliximab | • Adalimumab<br>• Efalizumab (no longer available)<br>• Etanercept<br>• Infliximab<br>• Best supportive care |
| Time horizon | 10 years | 10 years | Manufacturer - 12-week + longer-term outcomes (eight 12-week treatment periods).<br>ERG - Intermittent etanercept, assumed time between 12-week treatment cycles would be 29 days, resulting in 3.2 treatment cycles per year | 10 years | Considers use of standard & biologic therapies over time as per the York model (TA103) | 10 years |
| Outcomes | Cost-utility | 10-year treatment cost, QALY gain per patient over 10 years, and incremental cost per QALY gain | Average improvement in utility multiplied by time between visits to estimate QALY gain between the visits. ERG - Utilities estimated by mapping mean change in DLQI score (conditional PASI response) to changes in EQ-5D | Utilities were based on values from etanercept trials that linked the DLQI with the PASI | QALYs are primary outcome used in cost-utility analysis. The QALY gain determined by level of PASI response | Mean costs and QALYs are presented per unit time a patient spends on treatment. |
| Sensitivity analysis | Probabilistic sensitivity analyses | Subgroup analyses, scenario analyses, and stochastic analysis using bootstrap re-sampling to generate 95% CIs | Deterministic sensitivity analyses and probabilistic sensitivity analyses | One-way sensitivity analyses and probabilistic sensitivity analyses | Deterministic sensitivity analyses and probabilistic sensitivity analyses | Cost-effectiveness analysis. Univariate and Probabilistic sensitivity analyses |
| **Results** | | | | | | |

| Reference | Woolacott et al. 2006 | Lloyd et al. 2008 | Etanercept (Enbrel®)- NICE TA103 (Jul 2006)- | Infliximab (Remicade®)- NICE TA134 (May 2007) | Adalimumab (Humira®)- NICE TA146 (Sep 2007)- | Ustekinumab (Stelara®)- NICE TA 180 (Jan 2009) |
|---|---|---|---|---|---|---|
| Total cost (for each intervention) | • Etanercept 50 mg (intermittent): £14,102 annual cost per patient<br>• Etanercept 25mg(continuous): £9,562<br>• Efalizumab: £9,070 | Etanercept 50 mg biw: £47, 587 | • Annual per-patient drug cost for etanercept (25 mg/kg twice weekly) = £4,290 if patients received two twelve week courses per year<br>• Etanercept continuously, cost rises to £9,296. | Infliximab £419.62 per 100-mg vial given as a 5-mg/kg IV infusion over 2-hours Followed by 5-mg/kg infusion doses at 2 & 6 weeks after first infusion, then every 8 weeks thereafter. Manufacturer estimated average annual cost/patient = £11,750. | Adalimumab costs £357.50 per 40 mg prefilled syringe/pen. Average annual cost per patient of is estimated to be £10,010 in the first year and £9295 in subsequent years. | Average annual cost of ustekinumab is estimated to be £9,336 compared to £9,327 for etanercept 25mg (continuous) and £9,327 for adalimumab. |
| *Incremental outcome ratio* | • Basecase (etanercept 25mg): £66,703/QALY<br>• Scenario 1 (pts on etanercept 25mg with poor DLQI): £34,834/QALY<br>• Scenario 2 (pts on etanercept 25mg with poor DLQI and high risk of hospitalisation): £29,420/QALY | Etanercept 50 mg : £6,217/QALY | 12-week analysis :<br>• Etanercept 25 mg over no systemic therapy almost £125,000<br>• Etanercept 50 mg substantially higher.<br>96-week analysis:<br>• Intermittent 25 mg etanercept vs placebo estimated £37,200.<br>• PASI >10 + DLQI >15 - ICERs for etanercept vs systemic therapy declined markedly. For intermittent 25 mg etanercept therapy, ICER around £24,000 per QALY, respectively.<br>ERG<br>• Supportive care only cost-effective strategy until threshold reaches £70,000 /QALY.<br>• Intermittent low-dose (25 mg) etanercept £65,320/QALY<br>• Intermittent high-dose (50 mg) etanercept treatment was substantially higher.<br>• Results of several alternative scenarios presented indicated cost effectiveness of etanercept varied considerably according to baseline DLQI & assumption all non-responders hospitalised for 21 days annually. In all cases, ICERs of the biologics found to be lower than in the base-case.<br>• In scenario that considered both poor baseline quality of life and hospitalisation for non-responders, the ICER for intermittent etanercept 25 mg was £14,460 per QALY gained | • Using 4th-quartile DLQI utilities vs continuous etanercept £26,095/QALY<br>• Infliximab compared with supportive care was £22,240/QALY<br>ERG<br>• Infliximab compared with continuous etanercept £41,000/QALY when the alternative drop-out rate and inpatient costs assumptions were combined. When all-patient utility included, ICER increased to approximately £77,000. | • Adalimumab compared with supportive care was £30,500/QALY.<br>• Etanercept given continuously was dominated by adalimumab and etanercept given intermittently (assumed to be 88% of the cost of continuous etanercept)<br>ERG<br>• £27,300/QALY gained for intermittent etanercept compared with supportive care<br>• £36,700/QALY gained for adalimumab compared with intermittent etanercept | • Ustekinumab vs. supportive care, (ICER) of £29,587/QALY<br>• Etanercept 25 mg given intermittently (assuming 88% of the cost of continuous etanercept) £27,105/QALY<br>• Infliximab vs.ustekinumab was £304,566/QALY<br>• Adalimumab and etanercept given continuously rather than intermittently were dominated by ustekinumab<br>ERG<br>• Ustekinumab vs. supportive care £40,952/QALY<br>• intermittent etanercept 25 mg in £41,449/QALY |

**Abbreviations**: biw: Biweekly; QALY: quality-adjusted life year; UK: United Kingdom; DLQI: dermatology life quality index; mg: milligram ; PSA: probabilistic sensitivity analysis

**UK Studies:**

**Woolacott et al. 2006** (72) reported the results of a systematic literature review for clinical data, a systematic literature review of economic evaluations, and a cost-effectiveness analysis comparing etanercept, efalizumab and supportive care based on the UK setting. This paper is the Assessment Report for NICE TA 103. This paper was published after the NICE TA 103 submission. As the manufacturers' submissions did not consider all the relevant treatment options available it was deemed necessary to construct a *de-novo* cost-effectiveness model as per the ERG report for TA 103, commonly known as the York model. This *de-novo* cost-effectiveness model, which will be referred to as the 'York' model from here onwards, was used for the cost-effectiveness analysis described in this publication.

The York model included a broad range of comparators including systemic therapies. Patients entering the model were assessed after a trial period and continued treatment if they had responded (achieving a PASI 75 response) or discontinued if they had not responded. The trial period was assessed based on the clinical trials for each treatment included (10, 12, and 16 weeks). After the trial period, patients entered a Markov model with annual cycles over a 10 year time horizon.

The inputs used for the main cost-effectiveness analysis were reported including medical, drug costs and resource use. These were derived from the British National Formulary (BNF)(90), British Society of Rheumatology's Guidelines (91), Chalmers *et al.* 2005 (92), the Personal Social Services Research Unit (PSSRU(93)), and expert opinion. The DLQI in relation to PASI response were reported at baseline and week 12 from the etanercept trials and mapped to EQ-5D gain using data from the HODaR database (94). The main outcomes of the cost-effectiveness analysis were QALYs for each comparator, the costs associated with each comparator and the ICERs. In addition, as this model did not account for treatment sequencing, ICERs compared to supportive care were calculated in order to indicate the cost-effectiveness threshold at which a drug would be included in the sequence.

Probabilistic sensitivity analyses were performed. The results of the base case analysis were relatively high ranging from £66,703/QALY (etanercept 25 mg) to £120,855 (etanercept 50 mg). The scenario analysis showed etanercept 25mg would be cost-effective for patients with the worst baseline DLQI ($4^{th}$ quartile) with an ICER of £34,834/ QALY. Further scenario analysis showed that etanercept 25mg for patients with poor baseline DLQI and not responding to therapy with a higher risk of hospitalisation assumed to be 21 days per year had an ICER of £29,420/QALY.

*Critical appraisal*

This study uses systematic methods to synthesize evidence in order to populate the decision model used to compare various biologic and non-systemic treatments for the treatment of patients with moderate to severe psoriasis. The evidence synthesis of clinical data in the form of a Bayesian network meta-analysis of randomised controlled trials (RCTs) has been reported clearly and includes studies of appropriate design which reinforce the internal validity of this study. The model structure is composed of 2 components; the first of which is a decision tree model for the initial trial period (3 months), followed by a Markov model which extrapolates up to a 10 year time horizon. Patients are assessed at the 3 month period and dependent on

their response enter the long-term model. However, the long-term Markov model did not account for the initial 3 month trial period. Therefore, the total time horizon is actually 10 years and 3 months.

Further to that, the EQ-5D data used in this analysis were not directly elicited from the etanercept trials. Rather, DLQI data from the trials was elicited according to PASI response and mapped to change in EQ-5D using the HODaR database. Probabilistic sensitivity analysis (PSA) was conducted using the standard error from the OLS regression of EQ-5D and DLQI and the standard error from the change in DLQI conditional on PASI response and assumed normal distributions in both instances. The yearly cost of hospitalisation for non-responding patients was an assumption based on survey data, as there was no published data available, and scenario analysis was conducted around it that estimated that the model was sensitive to this assumption.

The key assumptions made throughout the study have been justified and varied using PSA except for the annual discontinuation rate for those patients that responded to treatment. This was a fixed parameter within the analysis based on expert opinion. The number of annual laboratory tests and outpatient visits were also based on expert opinion due to lack of published or patient-level data, however, the sensitivity analysis carried out around these 2 variables is not clarified within the analysis.

Further limitations discussed within the study are around the mixed treatment comparison which has limitations due to the restricted data available and related to short term use. Sequential modelling was considered a challenge in the model and was addressed in the appendix. The best treatment sequence was reported based on the assumption that effectiveness is not related of the position in the treatment sequence and that patients benefit whilst on treatment.

**Lloyd et al. 2008(73)** presented the results of a cost-effectiveness analysis comparing initial dosing of etanercept 50 mg twice weekly to no systemic therapy and etanercept 25mg twice weekly in patients with moderate to severe chronic plaque psoriasis. The analysis time horizon was ten years. The main outcomes were 10-year treatment cost, QALY gain per patient over 10 years, and incremental cost per QALY gain.

This analysis was based on a de novo economic model that combined a decision tree with a Markov model after 12 weeks of treatment. At 12 weeks, patients who did not achieve a reduction in PASI of at least 50% were deemed non-responders, and patients who achieved a PASI 75 response were deemed responders. Patients who had a reduction in PASI of 50-74% at 12 weeks received another 12 weeks of treatment, and they were deemed responders if they achieved a PASI 75 by week 24. All responding patients were given a treatment-free period (29 days) followed by an additional 12 weeks of treatment. This assumption was taken from NICE appraisal (3) followed by a retreatment period of 12 weeks.

Clinical data were taken from three randomised clinical trials (RCTs) (95-97). PASI and DLQI data were also retrieved from these three RCTs for patients with psoriasis that received an initial dose of etanercept treatment for 12 weeks, of which one had been designed to incorporate re-treatment after dose interruption. The DLQI was

mapped to EQ-5D according to methods applied in Currie et al. 2007(98). The medical costs were collected from the UK NHS perspective. The drug utilization and resource use assumptions were captured from the pooled study dataset from the 3 RCTs (95-97), the BNF(90), the Department of Health (DOH), and the literature (2). The base case population included patients with a PASI of 10 or more and a DLQI of ≥ 10 at baseline.

Sensitivity analysis was undertaken. When comparing etanercept 50 mg twice weekly with no systemic therapy the incremental cost per QALY was determined to be £6,217.

*Critical Appraisal*

This study clearly reported the methodology followed to assess the cost-effectiveness of etanercept 50 mg twice weekly to no systemic therapy and etanercept 25mg twice weekly in patients with moderate to severe chronic plaque psoriasis. The evidence synthesis for clinical data used had some limitations around the fact that although the populations and design of these trials are comparable, most likely uncertainty was introduced into the model due to unnoticed differences within the patient population. The sensitivity analysis that was conducted around this showed that the impact on results was low.

The model structure and retreatment were not assessed in uncertainty analyses. The model structure was composed of an initial phase of 12 weeks, after which those patients who have responded (reduction in PASI of 50-74%) are given a treatment-free period followed by an additional 12 weeks of treatment. After 24 weeks, patients who achieve a PASI score of 75 were considered responders and initiate a treatment-free period followed by a retreatment period of 12 weeks. As the PASI response after retreatment was less than one point different to the PASI score after the first 12 weeks of treatment (95% confidence interval (CI) that includes 0) the PASI response in subsequent cycles was considered to be the same as in the initial cycle. A similar approach was undertaken for QALY gain, where the mean utility change for the initial 12 weeks for responding patients was used to calculate utility gain for the retreatment phase. Sensitivity analysis was not conducted around this and may be a point to consider when interpreting the results.

Most assumptions that were made within the model were assessed using sensitivity analysis such as the treatment-free period between cycles of treatment, the PASI response achieved using the retreatment phase and the number of outpatient visits required per cycle of treatment.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2]

[2] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

or Philips et al. (2004)[3]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

Quality assessment of the eighteen full EE studies has been provided in section 10.12. This assessment follows the format of the Drummond and Jefferson checklist.

## *7.2 De novo analysis*

**Patients**

7.2.1 What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The population included in the economic model consists of adult patients with moderate to severe plaque psoriasis, aligned with the definition from NICE clinical guidelines (CG 153)(3) (PASI ≥10 and DLQI >10).

The patient population enrolled in the FIXTURE, ERASURE, JUNCTURE, FEATURE, and SCULPTURE trials, as described in Section 6.3, were those with PASI ≥12 at baseline.

Although this definition differs from that defined in NICE CG 153, subgroup analyses conducted to examine patients with DLQI >10 at baseline in the FIXTURE and ERASURE studies did not find a statistically significant difference in the efficacy of the DLQI > 10 subgroup when compared to the total study populations (see section 6.5.3). As this population was demonstrated to be not statistically different to that of the NICE population, the full trial populations were considered appropriate for the economic model.

The patients included in the economic analyses are also in line with the expected licensed indication for secukinumab, as described in Section 1.5.

[3] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

## Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

A *de novo* economic model was developed to estimate the outcomes and costs of using secukinumab 300 mg for the treatment of patients with moderate to severe plaque psoriasis. The model was a combined decision tree and Markov state-transition model developed in Microsoft Excel®.

The model includes four health states (HS) based on the PASI response of patients receiving treatment. In addition, the model includes an absorbing HS for death. Diagrammatical representation of the model is provided in Figure 28 and Figure 29.

**Figure 28. Illustration of the structure of the cost-effectiveness analysis**

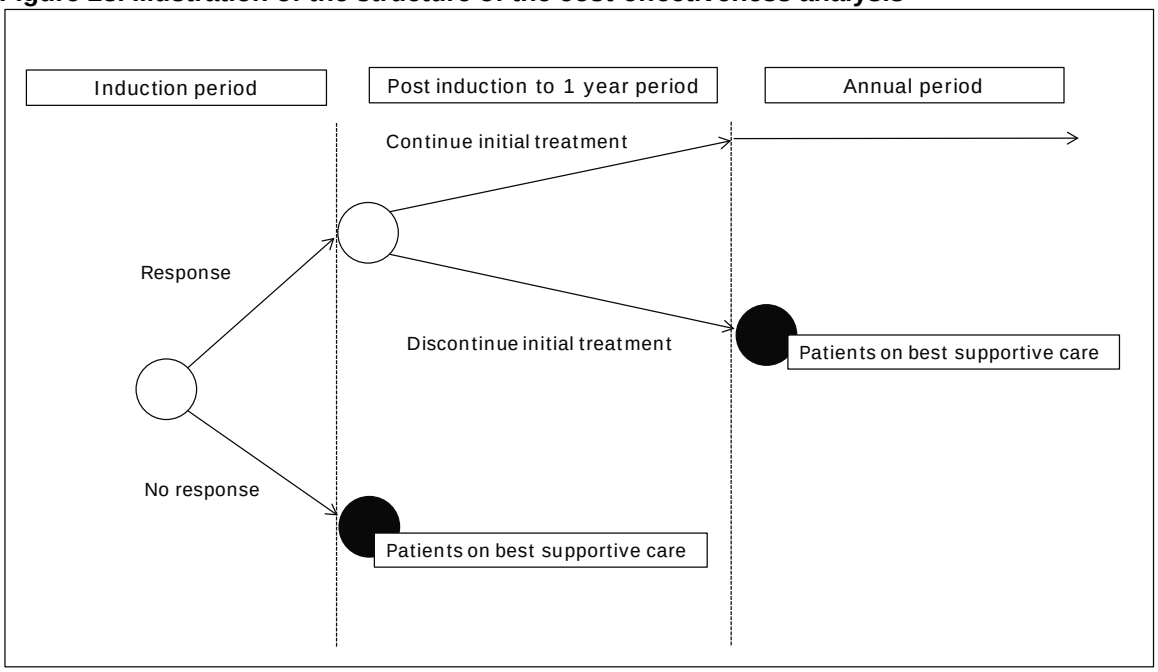
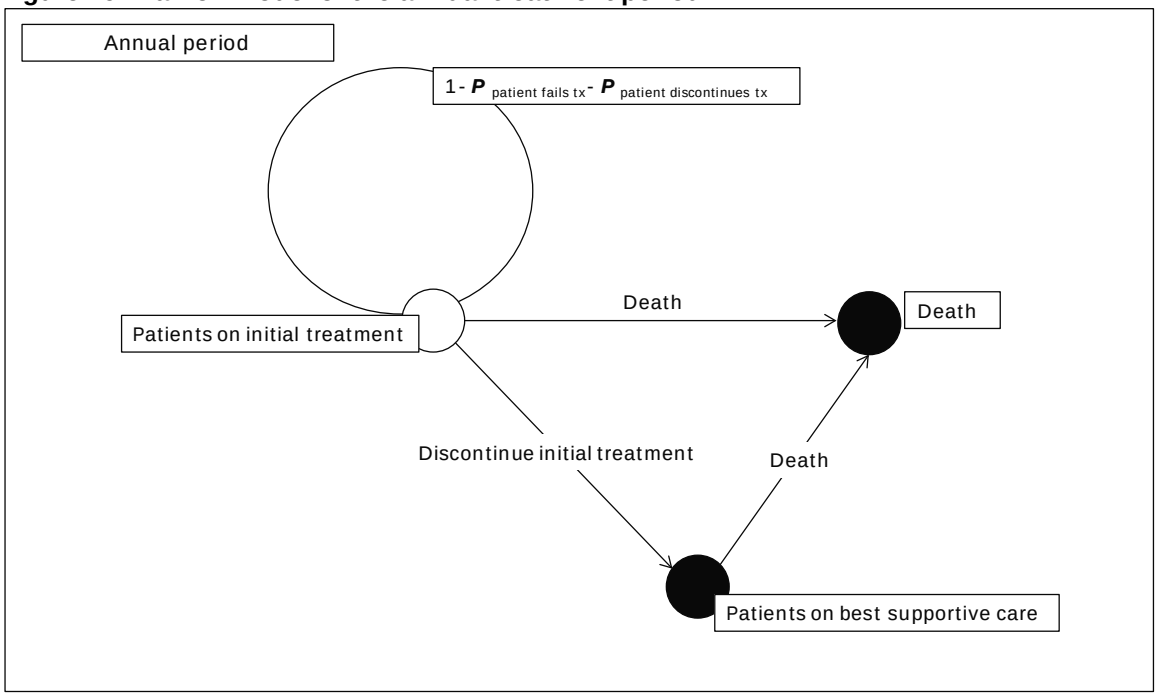


**Figure 29. Markov model of the annual treatment period**




Patients entered the model on treatment initiation and underwent an initial 'trial' period referred to in this analysis as the induction period. The response to treatment, which was defined as achieving a PASI 75 or higher response, was made at the end of this induction period. The duration of this period was defined as the primary clinical trial endpoint specific to each comparator. For secukinumab 300 mg, ustekinumab 45 mg and 90 mg the primary trial endpoint was at 12 weeks. For infliximab, etanercept and adalimumab, these trial endpoints were at 10, 12 and 16 weeks, respectively, which additionally align with the response assessment points recommended in NICE CG153 and BAD guidelines.(2, 3) To explore the effect of varying these assessment points, two scenarios were investigated (Section 7.6.1): a scenario based on the NMA conducted with a 16 week assessment point for secukinumab and a scenario based on the NMA conducted with a 12 week assessment point for all comparators.

Those patients who had achieved a PASI 75 or higher response after the induction period continued on treatment and those who had not discontinued biologic treatment and switched to best supportive care. At the end of the first year, a trial-based discontinuation rate was applied to those that continued on biologic treatment after induction. Patients that continued after the first year continued into the Markov model with annual cycles. Discontinuations of responders were estimated at an annual rate of 20% over the remainder of the time horizon. As there are no long-term data on the discontinuation of or loss of efficacy in patients treated for moderate to severe plaque psoriasis, the discontinuation rate was based upon expert opinion (Section 7.3.5) and is consistent with prior TAs. The discontinuation rate is considered to be "all-cause" discontinuation.

It was assumed that a patients' PASI score is constant over time across all treatment arms after the induction period as there are no data to suggest that PASI score changes beyond the trial period. This assumption was validated by expert opinion (Section 7.3.5), and it is consistent with the assumptions used in prior TAs. Each HS

represents a PASI response for patients treated for moderate to severe plaque psoriasis. The model uses the PASI <50, PASI 50-74, PASI 75-89, and PASI 90+ response rates to define utility in the first year decision tree model and then throughout the Markov model.

### 7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

While CHMP opinion recommends secukinumab for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy, secukinumab 300 mg is expected to be used similarly to existing biologic treatments within the current clinical pathway; in patients who have failed at least two standard systemic therapies. The use of secukinumab represents an alternative option within the range of biological treatments currently available for this patient population in line with the clinical pathway of care identified in Section 2.5.

The chosen model structure directly captures the treatment target recommended in NICE CG153 and BAD guidelines (an improvement in PASI response), by incorporating health states based on PASI scores.(2, 3) Patients are allowed to transit through health states over time according to their response to biologic treatment. This structure is in line with the modelling approaches used in previous HTA submissions for the treatment of moderate to severe plaque psoriasis.(22, 23)

This cost-effectiveness model has some similarities to the structure and methods used in the York model developed for NICE TA103 (70). As in the York model, this model structure also combines a decision tree and Markov model with a 10 year time horizon.

Some changes compared to the York model were implemented in the present analysis to represent the clinical pathway for psoriasis more accurately. These are summarised in Table 66.

**Table 66. Summary of the key differences between the present cost-effectiveness model and the York model developed for TA103**

| Approach in the York model | Approach in the present analysis | Rationale |
|---|---|---|
| A decision tree structure was used up to the induction phase, after which patients continued on treatments assigned at the end of the induction phase | A decision tree structure was extended beyond the induction phase to 1 year in the present model | Including an additional decision point in the model at 1 year takes into account the fact that patients may lose response to treatment after the induction phase |
| A fixed induction period of 12 weeks was used | The present model was designed to allow for induction periods of 10, 12 or 16 weeks | The analysis could be adapted to take into account varying induction period lengths in line with the different primary trial endpoints between comparators |
| A 20% discontinuation rate was used throughout the model | Trial-based discontinuation rates were applied at the end of the first year of the model, and the 20% rate was included beyond this point | Discontinuation rates reported in the clinical trial are considered to be a more accurate estimate of 1 year discontinuation in clinical practice |
| After the induction period, partial responders were considered in the same way as non-responders and discontinued biologic treatment | In a scenario analysis, after the induction period, partial responders (PASI 50-74) could continue on the initial treatment prescribed | There is some uncertainty in clinical practice over how best to treat patients with a partial response treatment, as these patients may benefit from an improved response if biologic therapy is continued beyond the induction period |
| The costs of adverse events were not considered | Costs and resource use associated with managing adverse events due to biologic therapy were included in the model | Including the costs of treating adverse events in patients treated with a biologic is a more realistic model of clinical practice |
| Mortality was not considered in the model | Background mortality was applied | It is unrealistic to assume there would be no mortality over the course of the 10 year time horizon |

### 7.2.4 Please define what the health states in the model are meant to capture.

Mutually exclusive PASI categories were used to define the health states illustrated in Figure 29: PASI <50, PASI 50-74, PASI 75-89 and PASI 90+. These four health states refer to the PASI response of patients and capture the QoL and cost associated with each specific PASI response over the duration of the model.

At the induction period assessment point, those patients achieving a PASI <50 response were defined as failing treatment and, therefore, discontinued initial treatment and switched to best supportive care. Best supportive care was adapted

from the NICE Psoriasis guidelines which recognised the continued intensity of ongoing care required by patients with moderate to severe psoriasis not on biologic therapy (see Section 7.5.3). Those patients achieving a PASI 50-74 response were defined as partial responders and therefore discontinued initial treatment and switched to best supportive care (see also Section 7.7.9) as this was included as a scenario analysis). Patients achieving a PASI 75-89 or PASI 90+ response were defined as responders and therefore continued on the initial treatment that was administered.

At 52 weeks, patients were able to maintain the health state defined at induction period or discontinue based on a trial-based discontinuation rate derived from FIXTURE and ERASURE and therefore switch to best supportive care.

From 52 weeks to the 10$^{th}$ year, patients entering the Markov model were able to maintain the health state of the first year or discontinue based on a long term discontinuation rate and therefore switch to best supportive care. In addition, the model included an absorbing health state for death.

### 7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

In clinical practice, as aligned with NICE CG153 and BAD guidelines, psoriasis severity is measured by PASI score.(2, 3) The model health states are structured around PASI response to treatment, and resource use, costs and QALYs were thus assigned depending on change in severity of disease following treatment.

Not all patients continue long-term biologic treatment due to lack or loss of efficacy, adverse events, or for other reasons. Therefore the model was structured around three phases to capture all cause discontinuation at various points in the treatment pathway.

These phases represent:

- **Induction period**: a period of potential response to treatment, justified by good quality RCT, NMA data, and licencing recommendations.
- **Post-induction to 52 weeks**: a period where treatment is expected to continue to maintain PASI response. The post induction period was included to address criticism of prior models.
- **52 weeks to 10$^{th}$ year**: annual cycles that extrapolate the long term decline in PASI response and discontinuation of treatment occurs. The 9 year extrapolation period is justified by expert opinion (Section 7.3.5) and publications/TAs conducted.

Beyond the loss of efficacy accounted for in the applied discontinuation rates, underlying disease progression was not included in the model as there are insufficient data available to map out the progression of moderate to severe psoriasis over time.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

The key features of the model used to conduct the base-case analysis are summarised in Table 67.

**Table 67. Key features of base case analysis**

| Factor | Values | Justification | Reference |
|---|---|---|---|
| Time horizon | 10 years | Time horizon is reflective of the duration of treatment of moderate to severe plaque psoriasis. This assumption was based on expert opinion, and it is consistent with prior TAs in this indication. | Expert Opinion, TA 103, TA 134, TA 146,TA 180(22) (23, 70, 71) |
| Cycle length | Annual | Annual cycle length was based on the secukinumab trial durations (approximately 52 weeks of active treatment). Annual cycle length in the Markov structure was validated with expert opinion and it is consistent with the York model used in prior TAs. | Expert Opinion TA 103, TA 134, TA 146, TA 180(22) (23, 70, 71) |
| Cohort age | 45 years | Cohort age was assumed to align with a pooled estimate of the FIXTURE & ERASURE clinical trial populations (mean – 45 years). This was consistent with other secukinumab clinical trials (range: 43.7-46.7), and generally representative of the RCTs included in the NMA. | FIXTURE & ERASURE(19) |
| Half-cycle correction | Not applied | Half cycle correction was not applied in the model due to the non-cyclical nature of the model structure. | TA 103, TA 134, TA 146, TA 180 (22) (23, 70, 71) |
| Were health effects measured in QALYs; if not, what was used? | QALYs | NICE reference case | NICE Guide to the Methods of Technology Appraisal 2013(99) |
| Discount of 3.5% for utilities and costs | 3.5% | NICE reference case | NICE Guide to the Methods of Technology Appraisal 2013(99) |
| Perspective (NHS/PSS) | NHS/PSS Perspective | NICE reference case | NICE Guide to the Methods of Technology Appraisal 2013(99) |
| NHS, National Health Service; NICE: National Institute for Health and Care Excellence; PSS, personal social services; QALYs, quality-adjusted life years | | | |

## Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The CEA includes the treatments outlined below for the treatment of adults with moderate to severe plaque psoriasis.

The intervention is included in the model is as per recommendations from the CHMP.

- The intervention is 300 mg secukinumab subcutaneous injection once weekly for 4 weeks followed by monthly dosing, starting at Week 4 (1)

The CHMP also noted that consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment and that some patients with initially partial response may subsequently improve with continued treatment beyond 16 weeks.(1) To account for these considerations, scenario analyses were conducted using a 16 week assessment point for secukinumab, and to allow partial responders to continue treatment beyond the initial assessment point (Section 7.6.1)

The comparators in the model are as per marketing authorisation, NICE endpoints and doses which are summarised in the table below.

**Table 68. Summary of SmPC & NICE stopping rules**

| | Etanercept | Adalimumab | Infliximab | Ustekinumab |
|---|---|---|---|---|
| Dose | 25 mg twice weekly or 50 mg once weekly. Alternatively, 50 mg twice weekly for up to 12 weeks then, if necessary, 25 mg twice weekly or 50 mg once weekly. | Initially, 80 mg, then 40 mg every other week starting 1 week after initial dose. | 5mg/kg over 2 hours repeated 2 weeks and 6 weeks after 1st infusion, then every 8 weeks. | < 100 kg, initially 45 mg. >100 kg, initially 90 mg. Repeat dose after 4 weeks, then every 12 weeks. |
| SmPC | Discontinue if no response after 12 weeks, continue with treatment for up to 24 weeks until remission | Therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period | If a patients shows no response after 14 weeks (4 doses) no additional treatment should be given | Considerations should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment |
| NICE | Discontinue at 12 weeks if no adequate response | Discontinue at 16 weeks if no adequate response | Discontinue at 10 weeks if no adequate response | Discontinue at 16 weeks if no adequate response |
| Criteria | Adequate Response: 75% reduction in the PASI score (PASI 75) from when treatment started or a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in the DLQI score from when the treatment started | | | |
| NICE Discussion | Trial endpoint at PASI 75 at 12 weeks. Clinical experts indicated that 12 weeks was a sufficient period of time in which to determine whether a patient was likely to respond. This experience was also in accordance with BAD guidelines. Response definition was driven by EMEA criteria and BSR guidelines for use of biologics in PsA. Expert testimony indicated QoL in some patients may improve in patients not showing PASI 75 at 12 weeks, hence inclusion | Phase III trial endpoint PASI75 at 16 weeks, 16 week timepoint used as assessment point in the CE model, therefore committee concluded treatment beyond 16 weeks only for patients who had responded | Principal trial endpoint was PASI75 at 10 weeks, CE model assumed treatment discontinued if this response was not achieved at 10 weeks. Therefore 10 week criteria was considered appropriate. PASI 50 criteria was included for consistency | Trial endpoint PASI 75 at 12 weeks. Clinical experts indicated that the treatment continuation rules from TA103 (etanercept) remained relevant, however response should be measured at 16 weeks rather than 12 and before the 3rd (16 week) dose is given |

| | | | | |
|---|---|---|---|---|
| | of DLQI criteria | | | |

All biologic treatments have been incorporated into the economic evaluation in line with their current UK marketing authorisations and NICE endpoints as stated in sections 1.3 and 1.5. Best supportive care has been incorporated into the economic evaluation based on data from the NICE psoriasis guidelines (CG153)(3)(Table 87).

Monitoring frequency for all treatments included in the economic evaluation have been estimated based on expert opinion. See section 7.5.4 for further details.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the ‘response’ criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

A 16 week treatment continuation rule has been assumed. This treatment continuation rule is stated in the draft SmPC *"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."(1)*

This continuation rule in the SmPC was based on the observation in 2 large placebo controlled RCTs (FIXTURE and ERASURE) investigating secukinumab 300 mg that treatment response continues to increase from week 12 to week 16.

This 16 week continuation rule is also consistent with the continuation rules of the two treatments most recently reviewed by NICE (ustekinumab TA180 and adalimumab TA146) and therefore no additional monitoring and or assessments will be required over current clinical practice.(22, 23) As per routine clinical practice is it anticipated that an assessment of response to secukinumab 300 mg will take place prior to the dose due at week 16.

Response has been defined in the analyses in line with previous comparators reviewed by NICE as:

- Achievement of a minimum of PASI 75 from baseline or
- PASI 50 reduction accompanied by a five-point reduction in DLQI from start of treatment.

A scenario analysis using 16 week secukinumab trial data was conducted to examine both the efficacy in an NMA analysis (Section 6.7.7) and the cost effectiveness in the economic model (Section 7.6.1). Both analyses showed similar results to the 12 week base case and thus demonstrate that secukinumab 300 mg administered in line with the draft SmPC, with a continuation rule at 16 weeks is a cost-effective option for the NHS.

## *7.3 Clinical parameters and variables*

### 7.3.1 Please demonstrate how the clinical data were implemented into the model.

Clinical data used to model treatment effectiveness over the induction period were incorporated into the model using data from the network meta-analysis (NMA) using different time endpoints for the induction period (please see section 6.7.2).

For the induction period, efficacy data for the intervention and comparator arms were incorporated in the model using the results of a pooled analysis of PASI response data from the NMA. The outcome of interest used the PASI response reported at the response assessment points: secukinumab at 12 weeks, infliximab at 10 weeks, adalimumab at 16 weeks, ustekinumab at 12 weeks, and etanercept at 12 weeks. As described in Section 6.7.5, the random effects model was considered more appropriate for use in the economic model, based on the statistical tests conducted. The overlapping nested PASI categories derived from the NMA were transformed into mutually exclusive categories at the reported cut-offs (0-49, 50-74, 75-89, 90-

100) and a multinomial likelihood NMA setup with probit link function (61) was used to simultaneously calculate the probability of achieving PASI 50, 75 or 90 response and the relative risk between each comparison in the network (see Section 6.7.5).

The *de-novo* model is based on PASI response distributions after the induction period and therefore the median response rates for the reported PASI cut-offs are not used directly within the model structure.

### 7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Transition probabilities were applied differently in the three model phases (induction, post-induction [post-induction to 52 weeks], and annual; see Section 7.2.2). In the induction phase, transitions to different clinical health states are based on response at the primary endpoints defined for each comparator within the NMA (e.g. 12 weeks for secukinumab). The post induction phase of the model is based on transition probabilities of discontinuation at 52 weeks. The transition probabilities in the annual phase of the model are based on probabilities of discontinuation and all-cause mortality. The model distinguishes between on-treatment and off-treatment phases for the post induction period and the annual period; during the induction period all patients are considered to be on-treatment.

**Induction period assessment point**

In the base-case analysis, treatment was assumed to continue for the duration of the induction period. After the induction period ended, patients continued treatment if they had a PASI response of 75 or above (defined as full response) and entered an ‘on treatment’ arm. Patients were treated with best supportive care if they had a PASI < 75 and entered an ‘off treatment’ arm. The on-treatment arm consisted of two PASI categories above 75; PASI 75-89 and PASI 90 +. The off-treatment arm consisted of two PASI categories below 75; PASI <50 and PASI 50-74. In the model base-case, the distribution of patients across the PASI response categories was calculated from random effects multinomial NMA parameter estimates from the base-case NMA (6.7.6).

The overlapping nested PASI categories were transformed into mutually exclusive categories at the reported cut-offs (Section 6.7.4). A multinomial likelihood NMA setup with probit link function (61) was used to simultaneously calculate the probability of PASI 50, 75 and 90 response and the relative risk between each comparison in the network (See section 6.7.5)

**Table 69. Calculated PASI distributions from random effects multinomial network NMA parameter estimates for cost-effectiveness analysis, base-case analysis**

| Treatment | Treatment effect estimate (SE) | PASI <50 | PASI 50-74 | PASI 75-89 | PASI 90+ |
|---|---|---|---|---|---|
| SoC | 0(-) | 88.4% | 8.0% | 3.0% | 0.6% |
| Secukinumab 300 mg | -2.65(0.1) | 7.3% | 12.5% | 24.8% | 55.4% |
| Adalimumab 40 mg | -1.92(0.11) | 23.4% | 21.7% | 27.2% | 27.7% |
| Infliximab 5 mg/kg | -2.62(0.12) | 7.7% | 12.8% | 25.1% | 54.4% |
| Ustekinumab 45 mg | -2.32(0.08) | 13.0% | 17.0% | 27.5% | 42.4% |
| Ustekinumab 90 mg | -2.47(0.08) | 10.1% | 15.0% | 26.6% | 48.3% |
| Etanercept 50 mg | -1.47(0.11) | 39.1% | 23.7% | 22.3% | 14.9% |
| **Parameter** | **Estimate (SE)** | | | | |
| PASI cut point 50 | 1.2(0.04) | | | | |
| PASI cut point 75 | 1.8(0.04) | | | | |
| PASI cut point 90 | 2.512(0.04) | | | | |

### Post induction period

At the end of the first year, an ‘all-cause’ discontinuation rate was applied to account for those patients that were not continuing on their initial treatment after the first year.

### Annual treatment period

In the annual treatment period, the model distinguished between the on-treatment arm, off-treatment arm and death. The on-treatment arm was further distinguished by PASI category (PASI 75-89 and PASI 90+). In the base-case analysis, patients who responded (PASI >75) and who do not discontinue (all cause discontinuation) at the end of the first year were assumed to retain this level of efficacy until they dropped out. This applied for all treatments.

Beyond loss of treatment efficacy accounted for in the all-cause discontinuation rates applied, the model assumed that treatment efficacy mas maintained during the annual treatment period. The same assumption was made by Woolacott et al. 2006(72), where treatment was assumed to continue after the post induction period, unless patients discontinued due to all-cause discontinuation reasons. This assumption was also validated by clinical experts (Section 7.3.5).

The formulas used to calculate the distribution of patients across the off-treatment phase, the on-treatment phase (PASI 75-89, PASI 90+) and death from the 2nd year onwards are presented below.

- $pPASI <50_t = pPASI<50_{t-1} + (pPASI\ 50\text{-}74_{t-1} + pPASI\ 75\text{-}89_{t-1} + pPASI\ 90+_{t-1}) * d_t - pPASI<50_{t-1} * m_t$
- $pPASI\ 50\text{-}74_t = pPASI\ 50\text{-}74_{t-1} + (pPASI\ 50\text{-}74_{t-1}) * d_t - pPASI\ 50\text{-}74_{t-1} * m_t$
- $pPASI\ 75\text{-}89_t = p\ PASI\ 75\text{-}89_{t-1} + (p\ PASI\ 75\text{-}89_{t-1}) * d_t - pPASI\ 75\text{-}89_{t-1} * m_t$
- $pPASI\ 90+_t = p\ PASI\ 90+_{t-1} + (p\ PASI\ 90+_{t-1}) * d_t - pPASI\ 90+_{t-1} * m_t$
- $pdeath_t = pdeath_{t-1} + (p\ PASI<50_{t-1} + p\ PASI\ 50\text{-}74_{t-1} + p\ PASI\ 75\text{-}89_{t-1} + PASI\ 90+_{t-1}) * m_t$

where $p_t$:proportion

$m_t$: mortality rate

$d_t$: discontinuation rate

and the first formula assumes that any patient discontinuing treatment after the induction period (i.e. due to annual discontinuation rates, rather than an efficacy assessment) is assumed to move the PASI<50 state.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Age-specific all-cause mortality was obtained from the UK life tables (100) and applied to the model as underlying risk of death to all patients and varied over time according to patient age. There is currently no other evidence to indicate that transition probabilities should vary over time for psoriasis, therefore no further variations were considered.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Surrogate outcome measures were not used in the model.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Two consultant dermatologists with experience in treating patients with moderate to severe plaque psoriasis in the UK setting were identified by Novartis and participated in the validation. These two were experts selected for their expertise in UK psoriasis practice. Declarations of conflicts of interest were obtained. Expert advice was sought regarding assumptions on the clinical relevance of partial response in the treatment of psoriasis. As the clinical experts were in the same telephone meeting together (but in separate locations), no iteration was required to collate the feedback as they discussed topics with one another in real time.

**Methods**

The interview was conducted over a teleconference and participants were allowed to review the questionnaire prior to the interview.

**Questions**

The following questions regarding partial response were asked:

1. Is partial response clinically relevant in the treatment of psoriasis?

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

2. For patients who have responded, would another response assessment at 52 weeks be clinically relevant (e.g. due to loss of response)? Or would accounting for discontinuation at 52 weeks suffice?
3. In prior submissions, the “Induction to one year” period was not included, and there is no precedent on how to model the treatment discontinuation over this period. We believe that the secukinumab discontinuation rate would be approximately11.7% of patients, which was taken from the secukinumab clinical trials (ERASURE and FIXTURE). Would this be a valid assumption?
4. 20% treatment discontinuation was used as the estimated annual discontinuation rate in prior submissions (see question 2 annual discontinuation). Have discontinuation rates changed in the last 5-8 years? Would this be a valid assumption with current treatment of psoriasis?
5. In your clinical opinion, what is the average length-of-stay (LOS) of a psoriasis hospitalisation in the UK?

**Results**

The answers to the questions above are summarised below:

1. Yes, PASI 50 (and 5pt decrease in DLQI) is considered “response” by the NICE guidelines(3, 38)
2. No clinical assessment at 52 weeks is necessary, patient discontinuation at this time point for all reasons (e.g. loss of efficacy, adverse events) is acceptable.
3. Yes, that’s fine. Although not a real world estimate, it is the most robust value available.
4. 20% may be outdated, but in the absence of registry data for the UK population this may be used.
5. Inpatient stays for psoriasis are very rare and have diminished in the last 5 years. A LOS of 14-15 days would be likely, but this is not supported by data. Therefore, the use of 10.7 days as per our HES data assumption for this calculation is approved. (see section 7.5.5)

Based on the response to Question 1, the current base case analysis accounts for the inclusion of partial responders in the scenario analysis only (see section 7.3.5).

Based on the response to Question 2, no efficacy assessment at 52 weeks is included and only an all-cause discontinuation rate is applied.

Based on the response to Questions 3 and 4, a discontinuation rate of 11.7% calculated from ERASURE and FIXTURE has been applied after the first year to all biologic comparators and a discontinuation rate of 20% has been applied from year 2 onwards (annually) in the absence of long term registry data applicable to the UK population.

Based on the response to Question 5, a LOS of 10.7 days has been used to calculate the cost of hospitalisation due to psoriasis.

## Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

The variables used in the *de novo* economic model are summarised in Table 70 Below.

**Table 70. Summary of variables applied in the economic model**

| Variable | Value | CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Age | 45 years | 95%CI:43-47(fixed) | Patient characteristics section 6.3.4 |
| Efficacy parameters | | | |
| Median (PASI 50) | 1.20 | 95%CI:1.118-1.274(CODA*) | Indirect and mixed treatment comparisons section 6.7 |
| Median (PASI 75) | 0.60 | 95%CI:0.574-0.633 (CODA*) | Indirect and mixed treatment comparisons section 6.7 |
| Median (PASI 90) | 1.32 | 95%CI:1.277-1.359 (CODA*) | Indirect and mixed treatment comparisons section 6.7 |
| Median (SoC) | 0 | (Fixed) | Indirect and mixed treatment comparisons section 6.7 |
| Median (SEC 300) | -2.648 | 95%CI:-2.852--2.477 (CODA*) | Indirect and mixed treatment comparisons section 6.7 |
| Median (ADA) | -1.92 | 95%CI:-2.127--1.703 (CODA*) | Indirect and mixed treatment comparisons section 6.7 |
| Median (INF) | -2.623 | 95%CI:-2.839--2.393 (CODA*) | Indirect and mixed treatment comparisons section 6.7 |
| Median (UST 45) | -2.321 | 95%CI:-2.475--2.167 (CODA*) | Indirect and mixed treatment comparisons section 6.7 |
| Median (UST 90) | -2.469 | 95%CI:-2.633--2.302 (CODA*) | Indirect and mixed treatment comparisons section 6.7 |
| Median (ETN) | -1.471 | 95%CI:-1.682--1.272 (CODA*) | Indirect and mixed treatment comparisons section 6.7 |
| Adverse event rates | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| ADA rate of malignancies/ patient year | 0.006 | 95%CI:0.0037-0.0098(BETA) | Intervention and comparator cost section 7.5.5 |
| ADA rate NMSC/ patient year | 0.010 | 95%CI:0.0066-0.0143(BETA) | Intervention and comparator cost section 7.5.5 |
| ADA rate of severe infections/ patient year | 0.052 | 95%CI:0.04-0.066(BETA) | Intervention and comparator cost section 7.5.5 |
| INF rate of malignancies/ patient year | 0.0767 | CI assumed to be± 20% of mean value (BETA) | Intervention and comparator cost section 7.5.5 |

| Variable | Value | CI (distribution) | Reference to section in submission |
|---|---|---|---|
| INF rate NMSC/ patient year | 0.004 | CI assumed to be± 20% of mean value (BETA) | Intervention and comparator cost section 7.5.5 |
| INF rate of severe infections/ patient year | 0.0552 | 95%CI:0.049-0.062(BETA) | Intervention and comparator cost section 7.5.5 |
| UST45 rate of malignancies/ patient year | 0.0016 | CI assumed to be± 20% of mean value (BETA) | Intervention and comparator cost section 7.5.5 |
| UST45 rate NMSC/ patient year | 0.0065 | CI assumed to be± 20% of mean value (BETA) | Intervention and comparator cost section 7.5.5 |
| UST45 rate of severe infections/ patient year | 0.01 | CI assumed to be± 20% of mean value (BETA) | Intervention and comparator cost section 7.5.5 |
| UST90 rate of malignancies/ patient year | 0.002 | CI assumed to be± 20% of mean value (BETA) | Intervention and comparator cost section 7.5.5 |
| UST90 rate NMSC/ patient year | 0.007 | CI assumed to be± 20% of mean value (BETA) | Intervention and comparator cost section 7.5.5 |
| UST90 rate of severe infections/ patient year | 0.010 | CI assumed to be± 20% of mean value (BETA) | Intervention and comparator cost section 7.5.5 |
| ETN rate of malignancies/ patient year | 0.000 | CI assumed to be± 20% of mean value (BETA) | Intervention and comparator cost section 7.5.5 |
| ETN rate NMSC/ patient year | 0.035 | CI assumed to be± 20% of mean value (BETA) | Intervention and comparator cost section 7.5.5 |
| ETN rate of severe infections/ patient year | 0.051 | 95%CI:0.045-0.059(BETA) | Intervention and comparator cost section 7.5.5 |
| Discontinuation rates | | | |
| Biologics year discontinuation rate | 0.117 | 95%CI:0.092-0.145(BETA) | Intervention and comparator cost section 7.5.5 |
| SoC discontinuation rate | 0 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Annual discontinuation rate | 0.20 | 95%CI:0.047-0.428(BETA) | Intervention and comparator cost section 7.5.5 |
| Costs | | | |
| Treatment unit costs | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| Adalimumab (80 mg pack) (£) | 704.28 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Infliximab (100) (£) | 419.62 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Ustekinumab (45mg) (£) | 2,147.00 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Etanercept (25mg) (£) | 89.38 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Methotrexate (2.5mg, 100 tablets) (£) | 2.77 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Methotrexate (10 mg, 100 tablets) (£) | 35.02 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Ciclosporin (100 mg, 30 tablets) (£) | 48.49 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Monitoring costs | | | |
| Cost of complete blood count (£) | 3.01 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Cost of urea, creatinine and electrolytes test (£) | 1.25 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Cost of liver function test (£) | 1.25 | (Gamma) | Intervention and comparator cost section 7.5.5 |

| Variable | Value | CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Cost of total protein test (£) | 1.25 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Cost of self-admin training (£) | 39.00 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Cost of physician visit for IV (£) | 92.39 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Cost of day centre care (£) | 460.00 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Cost of UVB phototherapy (£) | 91.00 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Hospitalisation costs | | | |
| Psoriasis | 5337.20 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Sepsis | 2101.72 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Lymphoma | 8178.26 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Melanoma | 1460.49 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| NMSC | 1460.49 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Tuberculosis | 2403.15 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Pneumonia | 1852.10 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Skin and soft tissue infection | 1383.44 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Bone and joint infection | 3087.03 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Urinary tract infection | 1754.08 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Average LOS for Psoriasis patients | 10.7 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Administration frequency | | | |
| Number of admin (SEC) – 12wk | 6 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Number of admin (SEC) – Post induction | 10 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Number of admin (ADA) – 16wk | 9 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Number of admin (ADA) – Post induction | 19 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Number of admin (INF) – 12wk | 3 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Number of admin (INF) – Post induction | 5 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Number of admin (UST45) – 12wk | 2 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Number of admin (UST45) – Post induction | 4 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Number of admin (UST90) – 12wk | 2 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Number of admin (UST90) – Post induction | 4 | (Fixed) | Intervention and comparator cost section 7.5.5 |

| Variable | Value | CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Number of admin (ETN) – 12wk | 24 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Number of admin (ETN) – Post induction | 80 | (Fixed) | Intervention and comparator cost section 7.5.5 |
| Monitoring frequency | | | |
| Number of self-admin training (non-IV biologics)-12wks | 1 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of IV infusions (INF) | 3 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of physician visits (All biologics)-12wk | 4 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of physician visits (SoC)-12wk | 3 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of FBC -12wk | 4 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of LFT- 12wk | 4 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of U&E -12wk | 4 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of TP -12wk | 4 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of SC -12wk | 4 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of self-admin training (non-IV biologics)-16wks | 1 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of physician visits (All biologics)-16wk | 5 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of physician visits (SoC)-16wk | 4 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of FBC -16wk | 5 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of LFT- 16wk | 5 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of U&E -16wk | 5 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of TP -16wk | 5 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of SC -16wk | 5 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Number of physician visits-post induction | 3 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Frequency of day care (SoC) – post induction | 4 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Frequency of NBUVB (SoC) – post induction | 3 | (Gamma) | Intervention and comparator cost section 7.5.5 |
| Utility values | | | |
| Utility gain: PASI <50 | 0.11 | (Multivariate normal distribution) | Section 7.4.9 |
| Utility gain: PASI 50-74 | 0.19 | (Multivariate normal distribution) | Section 7.4.9 |
| Utility gain: PASI 75-89 | 0.23 | (Multivariate normal distribution) | Section 7.4.9 |
| Utility gain: PASI 90+ | 0.26 | (Multivariate normal distribution) | Section 7.4.9 |

| Variable | Value | CI (distribution) | Reference to section in submission |
|---|---|---|---|
| ***Note: CI and sampling of NMA parameters (i.e. treatment effects, PASI cut points) was derived from the CODA output of the NMA. CODA (Convergence Diagnostic and Output Analysis) is a menu-driven set of S-Plus functions which serves as an output processor for the BUGS software. It may also be used in conjunction with Markov chain Monte Carlo output from a user's own programs. In the model, the CODA output represents the 40,000 iterations that were used to calculate the NMA inputs for the model. So, the mean of CODA output for treatment effect is equal to the mean treatment effect of the NMA. In the PSA, the CODA output is being sampled via a random draw to maintain the relative relationship of treatment effect and cut points for each comparator within the iteration of PSA.**<br><br>**ADA: adalimumab; CI: confidence interval; ETN: etanercept; cut-off point 1: PASI 50; cut-off point 2: PASI 75; cut-off point 3: PASI 90 FBC: Full Blood Count; INF: infliximab; IV: Intravenous; LFT: Liver Function Test; NBUVB: Narrowband Ultraviolet B; NMSC: Non-Melanoma Skin Cancer; OWSA: One-way sensitivity analysis; SC: Serum Creatinine;SEC: secukinumab; SoC: standard of care; TP: Total Protein; U&E: Urine and Electrolyte tests; UST: ustekinumab;** | | | |

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Both costs and outcomes are extrapolated beyond the initial induction period for all treatments as there are no long term data to account for PASI response beyond the induction period after which efficacy is measured. If patients responded to treatment after the induction period they were assumed to continue on treatment and maintain their PASI response (PASI 75-89, PASI 90+), until they dropped out. The drop-out rate after the first year for all biologic treatment comparators was considered to be equal to that of secukinumab 300 mg, which from the FIXTURE and ERASURE trials was calculated at 0.117. The long term drop-out rate, which was applied from the 2$^{nd}$ year onwards and has been validated by clinical experts (Section 7.3.5), was 20%. The all-cause mortality rate was also applied from the 2$^{nd}$ year onwards and was retrieved from the Office of National Statistics (100).

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table 71 below lists all the assumptions made in the economic model.

**Table 71. List assumptions in the economic model**

| Parameter | Assumptions | Consistent with prior TAs | Justification |
|---|---|---|---|
| Time horizon | Model time horizon is 10 years | Yes | 10 year time horizon is selected to reflect the chronic nature of the condition. See section 7.2.6 |
| Health states | Defined by PASI response | Yes | PASI response was used as a primary endpoint in the trials and it is considered the standard measure of psoriasis in clinical practice. See section 6.3.5. |
| Treatment efficacy | PASI response is maintained | Yes | In the absence of long term data on maintenance of PASI response, it was assumed that patients maintain PASI response after the trial period. Current clinical practice assumes that those who stop responding would be included in the patients who discontinue each year, and those who continue treatments do so while their response is maintained. This was validated by the clinical experts. See Sections 7.2.2 and 7.3.5. |
| Mortality | All- cause mortality is applied in the Markov. | No | All-cause mortality is applied in the annual treatment period to account for those patients that die throughout the 10 year time horizon. See Section 7.3.3. |
| Discontinuation | A discontinuation rate is applied at the end of the 1st year and every year after that. | Yes | It is unrealistic to assume that all patients who were on treatment at the end of induction would continue treatment for the duration of the model; discontinuation rates were therefore based on data available from the RCTs and estimates of annual discontinuation. Both rates were validated by expert opinion. See Section 7.3.5. |
| Adverse events | Adverse event rates were modelled | No | Costs in the model were adjusted for cost of adverse events, which were calculated using the AE rates and cost of hospitalisation for that AE. Efficacy was not adjusted for AEs. See Section 7.5.7 |
| Psoriasis hospitalisation | Psoriasis hospitalisation was applied annually for those patients treated with SoC | Yes | The cost of psoriasis hospitalisation was applied once a year for those patients on SoC and the length of stay was 10.7 days. See Section 7.5.5. |

## *7.4 Measurement and valuation of health effects*

### Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Psoriasis is an inflammatory skin disease that typically follows a relapsing and remitting course. It is characterised by well-delineated red, scaly plaques that vary in extent from a few patches to generalised involvement.(6) Psoriasis impacts patient's body image and self-esteem, leading to patients experiencing feelings of shame, stigma and embarrassment regarding their appearance (101). People with milder cases of psoriasis also seem to be affected and more severe cases of the disease have been linked to depression.(12)

Psoriasis also impacts work productivity since patients often limit their daily activity and physical function due to discomfort and pain, and take time off leading to reduced levels of employment and income (102, 103).

In patients with severe psoriasis, life expectancy is reduced due to increased risk of cardiovascular disease, lymphoma and non melanoma skin cancer (39) with quality of life being affected to an extent seen in other chronic diseases such as myocardial infarction, hypertension, congestive heart failure or type 2 diabetes (104). Note that this has not been account for within the model as the there is a lack of robust granular data.

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Generally, increased severity of psoriasis is associated with decreased health related quality of life. To grade psoriasis on the basis of severity (mild, moderate and severe), a Psoriasis Area Severity Index (PASI) scale is used. This scale takes into account the proportion of body surface area affected and redness, thickness and scaling of the plaques resulting in a score which ranges from 0 (no disease) to 72 (maximal disease). However, PASI does not assess the patient's quality of life. Thus, a patient with relatively minimal psoriasis may be more severely impacted psychologically if the psoriasis is on their face (i.e. very visible) versus their upper arm (i.e. not visible/easily covered), but they would have the same PASI score (43).

Patients with chronic psoriasis will experience deterioration in HQOL over the course of the condition if left untreated. A concept called "Cumulative Life Course Impairment" (CLCI) has been developed to measure the cumulative effect of psoriasis by taking into consideration the burden of stigmatization, physical and psychological co-morbidities as well as a patient's coping strategies and how this can impact on a patient to achieve a "full life potential."(105)

**HRQL data derived from clinical trials**

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

Multiple patient- reported outcome (PRO) instruments, including the Euroqol-5 dimensions health status questionnaire (EQ-5D) and Dermatology Life Quality Index

(DLQI), were administered in the five phase III clinical trials for secukinumab (FIXTURE (19), ERASURE (19), JUNCTURE (20),FEATURE (21) and SCULPTURE (28).

The EQ-5D assessment schedule for each trial is presented in Table 72. This schedule shows the time points at which the EQ-5D questionnaire was administered.

**Table 72. Assessment Schedule for the EQ-5D**

| Study | Analysis Week | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | Follow-up |
| Fixture (CAIN457A2303) | x | | x | x | x | | | x | | | x | | | | x | |
| Erasure (CAIN457A2302) | x | | x | x | x | | | x | | | x | | | | x | |
| Juncture (CAIN457A2309) | x | | x | x | x | | | | | | | | | | | |
| Feature (CAIN457A2308) | x | | x | x | x | | | | | | | | | | | |
| Sculpture (CAIN457A2304) | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

The EQ-5D is a generic instrument to assess a patient's health status (The EuroQoL Group, 1990), and it is the preferred measure of HRQoL within the NICE reference case. The instrument provides a simple descriptive profile and a single index value for health status.

Dermatology life quality index (DLQI) is a validated dermatology specific health related quality of life (HRQL) questionnaire most frequently used in studies of randomised controlled trials in dermatology. The aim of the questionnaire is to measure the extent to which a patient's skin condition has affected their life over the last week. Each question is scored from 0 to 3 and the scores summed, giving a range from 0 (no impairment of life quality) to 30 (maximum impairment). A score of greater than 10 is considered to correspond to a substantial effect on a person's HRQoL. Further detail related to interpretation of scores can be found in Table 73.

**Table 73: Interpretation of DLQI scores**

| Score (106) | Definition |
|---|---|
| 0-1 | No effect at all on patient's life |
| 2-5 | Small effect on patient's life |
| 6-10 | Moderate effect on patient's life |
| 11-20 | Very large effect on patient's life |
| 21-30 | Extremely large effect on patient's life |

Observations pertaining to EQ-5D utility score and DLQI baseline score were available for 3,286 and 3,293 patients across the secukinumab studies, respectively. Table 74 summarises utility scores by trials and pooled data from all time points. The mean utility baseline scores were generally comparable across four out of five studies (ERASURE, FIXTURE, SCULPTURE, and FEATURE). In the case of JUNCTURE, mean utility score was higher at baseline.

**Table 74: Summary of Baseline EQ-5D Utility scores**

| | FIXTURE (CAIN457A2303) | ERASURE (CAIN457A2302) | JUNCTURE (CAIN457A2309) | FEATURE (CAIN457A2308) | SCULPTURE (CAIN457A2304) | Pooled |
|---|---|---|---|---|---|---|
| EQ-5D utility score | | | | | | |
| N | 1,261 | 730 | 171 | 175 | 949 | 3,286 |
| Mean (SD) | 0.640 (0.3074) | 0.632 (0.3224) | 0.717 (0.2650) | 0.631 (0.3011) | 0.640 (0.2965) | 0.642 (0.3057) |
| Median | 0.725 | 0.725 | 0.796 | 0.725 | 0.725 | 0.725 |
| Min, Max | –0.594, 1.000 | –0.358, 1.000 | –0.181, 1.000 | –0.349, 1.000 | –0.484, 1.000 | –0.594, 1.000 |
| Missing | 0 | 0 | 0 | 0 | 0 | 0 |
| DLQI utility score | | | | | | |
| N | 1,263 | 732 | 172 | 175 | 951 | 3,293 |
| Mean (SD) | 13.375 (6.970) | 13.112 (7.511) | 11.157 (6.957) | 12.914 (7.239) | 13.502 (7.153) | 13.213 (7.174) |
| Median | 13 | 12 | 10 | 12 | 13 | 13 |
| Min, Max | 0,30 | 0,30 | 0,30 | 1,30 | 0,30 | 0,30 |
| Missing | 42 | 5 | 10 | 2 | 14 | 73 |
| **Abbreviations**: EQ-5D, EuroQol 5 Dimensions; Min, minimum; Max, maximum; DLQI, Dermatology Life Quality Index; SD, standard deviation | | | | | | |

## Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping was needed to assess health state utility values as EQ-5D data were collected at the same time points in the relevant clinical trials.

## HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

An initial systematic literature review was conducted to identify HRQL studies including health utility elicitation/validation studies, and reports of economic evaluations using utility measures gathered during the studies. Studies published in the area of plaque psoriasis in the English language between 01 January 2004 and 23 December 2013 were included, as it was considered that the search could be limited to the timepoint after which biologic interventions for chronic plaque psoriasis became available. An update of this search was conducted on 02 October 2014.

The purpose of this search was more specifically to identify studies providing the following:

- Provide alternative utility values to those collected and analysed from the clinical trial that can be used to derive an alternate set of inputs to be used as a sensitivity analysis
- Provide a better understanding of the generalisability of the trial-based utility values used in the base-case analysis.

Articles and abstracts were identified through searches using the following databases on the OVID platform:

- Embase
- Medline (including Medline (R) in process),
- EconLit
- NHS EED.

For each database, a search was developed combining disease terms study design terms and outputs of interest. The relevance of references identified by the search across the four databases was assessed against eligibility criteria that were defined following enhanced PICOS criteria (Table 75).

The search strings were developed from prior technology TAs and Cochrane guidelines and are consistent with previous search strings. The systematic literature review was designed to include the broader psoriasis population (i.e. not limited to plaque psoriasis), which is in line with the precedent sent by Woolacott et al. 2005 (70).

The search strings can be found in Section 10.13, Appendix 13. During the study selection process, all references captured by the combined search were reviewed by two researchers based on their abstracts and titles against the eligibility criteria presented in Table 75 .

**Table 75. Eligibility criteria for HRQL search**

| Quality of life | Inclusion | Exclusion |
|---|---|---|
| Population | -Adults (≥18 years) with moderate to severe chronic plaque-type psoriasis;<br>-For identification of data on Adverse Events (rates, associated costs and utilities), intermittent dosing, relapse rates, adherence, and dose titration; adult subjects with other autoimmune diseases treated with biologics | -Children with psoriasis;<br>-Patients with types of psoriasis other than plaque psoriasis (i.e. pustular, erythrodermic and guttate psoriasis); if population is mixed, exclude only if plaque psoriasis is not separately analysed;<br>-Patients with mild psoriasis; if population is mixed, exclude only if moderate to severe psoriasis is not separately analysed;<br>-Patients suffering from active, ongoing inflammatory diseases other than psoriasis |

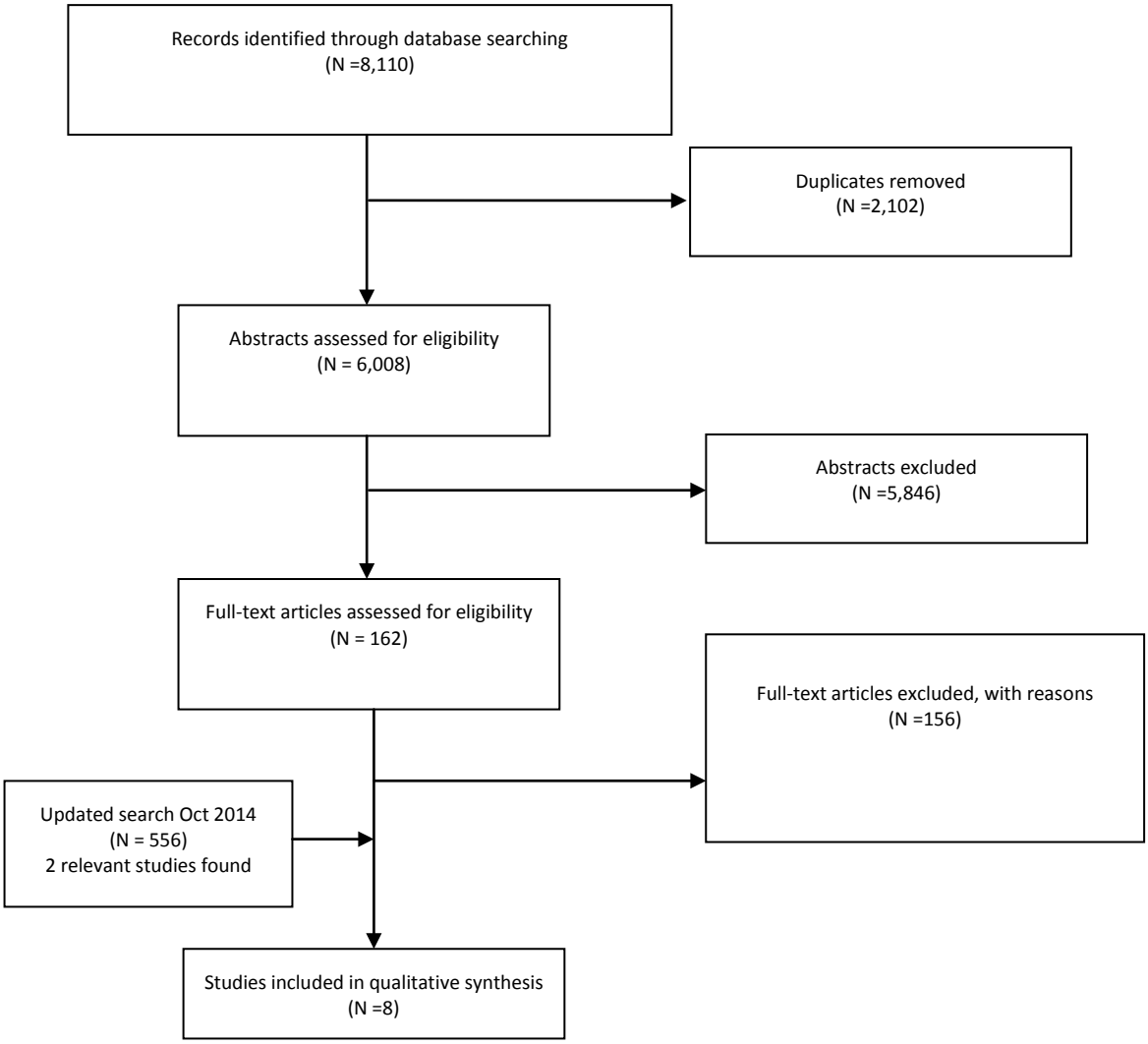
| Quality of life | Inclusion | Exclusion |
|---|---|---|
| Interventions | -Biologics of interest (adalimumab, etanercept, infliximab, ustekinumab) | -Systemic non-biological treatments for moderate to severe psoriasis;<br>-Phototherapy and photochemotherapy as the main treatment of interest;<br>- Biologics not of interest as not available in UK (alefacept, efalizumab and briakinumab) |
| Comparators | -Any comparator | |
| Outcome measures | -Severity of psoriasis (change in PASI score or static score);<br>-Adverse effects of treatment;<br>-Health-related quality of life (Dermatology Life Quality Index (DLQI);<br>-Euroqol 5-Dimension health status questionnaire (EQ-5D, SF-36, SF-6D);<br>-Health utility index (HUI);<br>-Psoriasis Disability Index (PDI);<br>-Utility or preference weights | -Health assessment questionnaire- disability Index (HAQ-DI), for individuals with psoriatic arthritis);<br>-Clinical studies that report the DLQI *de facto* but not for use to measure quality of life<br><br>Note: If study does not report an outcome listed in the inclusion criteria, the study will be excluded. |
| Study design | -Reports of utility elicitation exercises;<br>-Reports of utility validation exercises;<br>-Studies reporting utility estimates or preference weights;<br>-Reports of economic evaluations using utility measures gathered during the studies;<br>-Systematic reviews of utility studies* | -Editorials;<br>-Notes;<br>-Comments;<br>-Letters;<br>-Pharmacokinetic/Pharmacodynamic (PKPD) studies;<br>-*In Vitro* studies;<br>-Guidelines;<br>-Case Studies |
| Restrictions | Language: English<br>Date: Published 2004 – December 2013 | |
| *to be kept on file as a cross-reference to ensure that we have captured all relevant papers | | |

All publications where there was disagreement about inclusion at this stage were resolved through discussion between the two reviewers, and a third reviewer was not required. Included publications were retained for full text review. Publications that were not relevant were marked as excluded. The full texts of the publications retained after the abstracts review were judged once more by the two reviewers against the eligibility criteria presented. The approach to resolve any disagreement was the same as for the abstracts review process. All papers included after the full text review were retained for data extraction.

Overall, the HRQL search yielded a total of 8,110 hits, of which 2,102 were duplicates, leaving 6,008 records to be reviewed against the eligibility criteria. A total of 5,846 abstracts were excluded leaving 162 studies for full-text review. Of these, 156 were excluded, and 6 were retained for data extraction. In addition, an updated electronic database search conducted in October 2014 yielded a total of 615 hits, of which 59 were duplicates. Of the 556 remaining articles, 2 were retained for data extraction. Therefore, 8 articles in total were included for data extraction.

The process of study selection and the final results of the search are illustrated below in Figure 30 using the PRISMA Flow diagram.

**Figure 30. Study flow diagram for systematic review of HRQL studies**




7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.

- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

At full text review, eight studies were retained for data extraction. These are presented in order of relevance with the first two studies (Woolacott et al. 2006 (72) and Sizto et al. 2009(107)) comprising those studies most relevant to the UK setting. The remaining six studies included are listed in chronological order (Shikiar et al. 2006 (108), Anis et al. 2011(78), Pan et al. 2011(83), Knight et al. 2012 (79), Mattei 2014 (8) and Heredi 2014(109)). As the objective of the QoL systematic review was to provide context to the utility values collected alongside the clinical trials, these eight publications were included. A summary for each study is provided below.

**Table 76. Woolacott et al. 2006**

| | |
|---|---|
| **Reference** | Woolacott et al. 2006 (72) |
| **Population** | Adult patients with moderate to severe chronic plaque psoriasis |
| **Information on recruitment** | N/A |
| **Interventions and comparators** | The base case analysis compared etanercept 25mg intermittent, efalizumab continuous, etanercept 25mg continuous and etanercept 50 mg intermittent with supportive care. |
| **Sample size** | N/A |
| **Response rates** | N/A |
| **Description of health states** | The health states were categorized according to PASI response:<br>• PASI response <50<br>• PASI ≥ 50 and <75<br>• PASI ≥ 75 and <90<br>• PASI ≥ 90 |
| **Adverse events** | N/A |
| **Method of elicitation** | Not reported |
| **Method of valuation** | DLQI, EQ-5D |
| **Mapping** | Mapping was used in order to calculate the mean gain in utility for the various PASI response categories. The calculation process consisted of various steps.<br>Initially the mean difference in DLQI score was calculated between baseline and week 12 for patients with different levels of PASI response and differing baseline DLQI scores taken from the etanercept trials. These calculations were feasible due to access to patient-level data by Wyeth and by the fact that both placebo and active treatment groups were pooled.<br>The next step involved using data from the Health Outcomes Data Repository (HODaR) database (which was comprised of patients who had completed both questionnaires for DLQI and EQ-5D) to map the difference in DLQI related to PASI response to differences in EQ-5D utility. Lastly, ordinary least-squares regression analysis was used to produce EQ-5D utilities from the DLQI-EQ-5D data from HODaR. This was further used to calculate the mean gain in utility for the various PASI response categories. |
| **Results (mean)** | Mean gains in utility for the different PASI response categories for all patients:<br>• PASI response <50: 0.05 (SE 0.01)<br>• PASI ≥ 50 and <75: 0.17 (SE 0.04)<br>• PASI ≥ 75 and <90: 0.19 (SE 0.04)<br>• PASI ≥ 90: 0.21 (SE 0.05)<br>Mean gains in utility for the different PASI response categories for patients in the 4th quartile DLQI:<br>• PASI response <50: 0.12 (SE 0.03)<br>• PASI ≥ 50 and <75: 0.29 (SE 0.06)<br>• PASI ≥ 75 and <90: 0.38 (SE 0.08)<br>• PASI ≥ 90: 0.41 (SE 0.09) |
| **Appropriateness for use in CEA** | Yes. |

**Table 77. Sizto et al. 2009**

| | |
|---|---|
| **Reference** | Sizto et al. 2009 (107) |
| **Population** | Patients with moderate to severe psoriasis following a treatment pathway established in UK guidelines |
| **Information on recruitment** | N/A |
| **Interventions and comparators** | Methotrexate, ciclosporin, etanercept 25mg intermittent, etanercept 50 mg intermittent, efalizumab, adalimumab, etanercept continuous, infliximab vs. supportive care. |
| **Sample size** | N/A |
| **Response rates** | N/A |
| **Description of health states** | The health states were categorised according to PASI response:<br>• No response (< PASI 50)<br>• Moderate response (≥ PASI 50 to < PASI 90)<br>• Good response (≥ PASI 90) |
| **Adverse events** | N/A |
| **Method of elicitation** | Not reported |
| **Method of valuation** | EQ-5D. The utility data was taken from the adalimumab trials CHAMPION (110) and REVEAL (111) trials and calculated applying UK specific population weights using a normal distribution. |
| **Mapping** | N/A |
| **Results (mean)** | Change in health utility (EQ-5D):<br>• No response (< PASI 50): 0.06 (SEM 0.03)<br>• Moderate response (≥ PASI 50 to < PASI 90): 0.18 (SEM 0.02)<br>• Good response (≥ PASI 90): 0.31 (SEM 0.03) |
| **Appropriateness for use in CEA** | Publication does not provide enough detail to answer this. |

**Table 78. Shikiar et al. 2006**

| | |
|---|---|
| **Reference** | Shikiar et al. 2006 (108) |
| **Population** | Patients with moderate to severe plaque psoriasis and an affected BSA of ≥ 5% for at least 1 year. |
| **Information on recruitment** | The patients included in this study were enrolled at 18 sites in the United States and Canada. |
| **Interventions and comparators** | Two doses of subcutaneously administered adalimumab vs. placebo for 12 weeks. |
| **Sample size** | 147 patients |
| **Response rates** | Blinded data were available for 147 patients at baseline and 140 patients at Week 12. |
| **Description of health states** | The health states were categorized according to improvement in PASI score:<br>• PASI Improvement <25%<br>• PASI improvement 25-49%<br>• PASI improvement 50-74%<br>• PASI improvement ≥75% |
| **Adverse events** | N/A |
| **Method of elicitation** | Not reported |
| **Method of valuation** | EQ-5D, DLQI, SF-36 |
| **Mapping** | |
| **Results (mean)** | Change in Index EQ-5D score<br>• PASI Improvement <25%: -0.01 (SD 0.26)<br>• PASI improvement 25-49%: 0.1 (SD 0.24)<br>• PASI improvement 50-74%:0.2 (SD 0.21)<br>• PASI improvement ≥75%: 0.25 (SD 0.30) |
| **Appropriateness for use in CEA** | Not suitable as patient population is North American. |

**Table 79. Anis et al. 2011**

| | |
|---|---|
| **Reference** | Anis et al. 2011 (78) |
| **Population** | Patients with moderate to severe psoriasis in the US |
| **Information on recruitment** | N/A |
| **Interventions and comparators** | The treatments included in the analysis were comprised of tumor necrosis factor (TNF)-antagonists adalimumab, etanercept, and infliximab. T-cell inhibitors alefacept and efalizumab were also discussed, but are not available in the UK. |
| **Sample size** | N/A |
| **Response rates** | N/A |
| **Description of health states** | The health states were categorised according to PASI response:<br>• No response (< PASI 50)<br>• Moderate response (≥ PASI 50 to < PASI 90)<br>• Good response (≥ PASI 90) |
| **Adverse events** | N/A |
| **Method of elicitation** | Not reported |
| **Method of valuation** | EQ-5D |
| **Mapping** | Health utilities had not been measured during the majority of trials, the main outcome measured had been response to treatment measured with the PASI. Therefore, the QALYs used in this analysis were estimated from defining the relation between EQ-5D and PASI response from two adalimumab trials (110, 112). Once the relationship was established it was applied to the response rates of each drug included in the analysis, which had been calculated using a mixed-treatment evidence synthesis. |
| **Results (mean)** | The utilities for each health state were calculated to be:<br>• No response (< PASI 50): 0.04 (SE 0.02)<br>• Moderate response (≥ PASI 50 to < PASI 90): 0.12 (SE 0.02)<br>• Good response (≥ PASI 90): 0.21 (SE 0.02) |
| **Appropriateness for use in CEA** | Publication does not provide enough detail to answer this. |

**Table 80. Pan et al. 2011**

| | |
|---|---|
| **Reference** | Pan et al. 2011 (83) |
| **Population** | Clinical efficacy data was retrieved from the ACCEPT trial which was comprised solely of adult chronic plaque psoriasis patients. These patients had either failed to respond to standard systemic therapies (e.g., methotrexate and ciclosporin), had become intolerant of these, or had contraindications. |
| **Information on recruitment** | Not reported |
| **Interventions and comparators** | The intervention in this cost-utility analysis was ustekinumab 45mg and the comparator was etanercept 50 mg. |
| **Sample size** | The ACCEPT trial had incorporated 903 patients (randomised to etanercept= 347, ustekinumab 45 mg=209, ustekinumab 90 mg=347) |
| **Response rates** | Not reported |
| **Description of health states** | The health states were categorized according to PASI response:<br>• PASI < 50 at week 12<br>• PASI ≥50 and <75 at week 12<br>• PASI ≥75 and <90 at week 12<br>• PASI ≥90 at week 12 |
| **Adverse events** | N/A |
| **Method of elicitation** | Not reported |
| **Method of valuation** | EQ-5D, DLQI |
| **Mapping** | PASI data that had been retrieved from clinical trials did not provide utility values, therefore the DLQI data, retrieved from PHOENIX 1 and PHOENIX 2 trials as well as data from the adalimumab HTA, was adapted to utilities using an ordinary least squares linear regression calculation. The mean difference in DLQI score between baseline and week 12 were estimated and mapped using the regression to EQ-5D. Hence, utility gains were reported related to each PASI response level. |
| **Results (mean)** | Utility gains for all patients based on calculation from the PHOENIX trial<br>• PASI < 50 at week 12: 0.04<br>• PASI ≥50 and <75 at week 12: 0.17<br>• PASI ≥75 and <90 at week 12: 0.22<br>• PASI ≥90 at week 12: 0.25<br>Utility gains for all patients based on calculation from the adalimumab HTA:<br>• PASI < 50 at week 12: 0.063<br>• PASI ≥50 and <75 at week 12: 0.1780<br>• PASI ≥75 and <90 at week 12: 0.1780<br>• PASI ≥90 at week 12: 0.3080 |
| **Appropriateness for use in CEA** | Yes. |

**Table 81. Knight et al. 2012**

| | |
|---|---|
| **Reference** | Knight et al. 2012 (79) |
| **Population** | Patients with moderate to severe plaque psoriasis |
| **Information on recruitment** | N/A |
| **Interventions and comparators** | Etanercept 50 mg once weekly was set as the intervention and compared with adalimumab 40 mg every other week or non-systemic therapy. |
| **Sample size** | The data for the etanercept arm was retrieved from two RCTs (96, 97).Combining these two trials included a total of 1283 patients with chronic plaque psoriasis.<br>The data for the adalimumab arm was retrieved from a 12-week clinical controlled trial as well as two Phase III trials for which a sample size was not reported within this study. |
| **Response rates** | Not reported |
| **Description of health states** | The health states were categorised according to PASI response:<br>• PASI response < 50 (low response)<br>• PASI ≥75 response,<br>• PASI 50-74 response,<br>• PASI 14-74 response |
| **Adverse events** | Not included in analysis |
| **Method of elicitation** | Not reported |
| **Method of valuation** | EQ-5D |
| **Mapping** | Mapping was undertaken from DLQI to EQ-5D utility using the statistically significant association that was calculated in the Wyeth submission and the HTA submission for etanercept in psoriasis (72). The formula used was 0.956–0.0248*DLQI. The data used for this mapping exercise was taken from the Health Outcomes Data Repository (HODaR) database which is linked to HRQoL data and therefore relevant to the UK. |
| **Results (mean)** | The utility scores that were derived from mapping from DLQI scores for each health state were:<br>• PASI response < 50 (low response): 0.66<br>• PASI ≥75 response: 0.892<br>• PASI 50-74 response: 0.861<br>• PASI 14-74 response: 0.761 |
| **Appropriateness for use in CEA** | Yes. |

**Table 82. Mattei et al. 2014**

| | |
|---|---|
| **Reference** | **Mattei 2014 (8)** |
| **Population** | Psoriasis patients in included RCTs published between 2001 and 2010 in a systematic review |
| **Information on recruitment** | N/A – no detail on RCT individual patient recruitment |
| **Interventions and comparators** | Adalimumab, alefacept, efalizumab, etanercept, infliximab, ustekinumab. (alefacept, efalizumab which are both not available in the UK.) |
| **Sample size** | Not reported |
| **Response rates** | Not reported |
| **Description of health states** | PASI and DLQI measured at baseline and at 10-16 weeks following treatment |
| **Adverse events** | Not reported |
| **Method of elicitation** | DLQI collected through RCTs |
| **Method of valuation** | N/A – utilities were not collected, the study focus was to compare change in PASI with change in DLQI |
| **Mapping** | N/A |
| **Results (mean)** | Grouped by treatment arms with PASI <50% had a mean DLQI reduction of 5.17 (SD 1.01, CI 1.14), treatment arms PASI 50 -75% reduction in PASI had mean DLQI reduction of 6.12 (SD 1.52, CI 0.94). Treatment arms PASI >75% had a mean DLQI reduction of 9.36 (SD 0.89, CI 0.58). When mean per cent reduction in PASI was plotted against mean reduction in DLQI across 22 treatment arms, a correlation coefficient value of 0.898 was observed (p>0.01). |
| **Appropriateness for use in CEA** | Although not directly useful for CEA, this study shows a correlation between DLQI and PASI reduction |

**Table 83. Heredi et al. 2014**

| Reference | Heredi 2014 (109) |
|---|---|
| **Population** | Consecutive adult psoriasis patients from two Hungarian university clinics, mean age 51 years, 68.5% males, mean disease duration 22 years |
| **Information on recruitment** | Patient questionnaire on demographic data, health state, quality of life (EQ-5D, EQ VAS, DLQI, VAS) and dermatologist questionnaire based on disease activity (PASI, PGA,VAS). |
| **Interventions and comparators** | Not reported |
| **Sample size** | 200 |
| **Response rates** | Not reported. |
| **Description of health states** | EQ-5D, EQ-5D VAS, DLQI, PASI |
| **Adverse events** | Not reported |
| **Method of elicitation** | Patient's DLQI was used to describe the health states, and this was mapped to the EQ-5D. |
| **Method of valuation** | Due to lack of evaluated Hungarian tariffs, the UK weights were applied to calculate global EQ-5D scores (Dolan 1997). |
| **Mapping** | Firstly, a simple linear regression of DLQI onto both EQ-5D score and EQ VAS was performed, then variables were applied and a final stepwise regression looking at predictors was applied. |
| **Results (mean)** | Median EQ-5D, DLQI and PASI scores were 0.73, 3.0 and 3.45 respectively. EQ-5D showed a moderate correlation with DLQI and PASI. Strong correlation was found between DLQI and PASI |
| **Appropriateness for use in CEA** | Although not directly used in a CEA, this study shows there is a strong correlation between DLQI and PASI. |

In addition, all publications underwent a formal quality assessment that was carried out for each individual study and can be found in section 10.13. This assessment was done through adapting the Drummond and Jefferson checklist to fit HRQoL publications.

### 7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Utility values identified from the systematic review are presented, together with values reported from the previous NICE technology appraisals for psoriasis in adults and the present submission, in Table 84.

Since EQ-5D scores were collected in the five secukinumab clinical trials alongside the efficacy measures that inform the model, these were considered the most robust source of utility values for the model. As described in Section 7.4.9, the EQ-5D data from these trials were converted into utility increments which were applied to the four PASI health states.

The utilities chosen for the present submission lie between the range of estimates identified in the literature and in prior NICE technology appraisals (Table 84).

**Table 84: A comparison of identified EQ-5D utility values from the literature, previous technology appraisals and the present submission**

| | PASI <50 | PASI 50-74 | PASI 75-89 | PASI 90 and above | Comment |
|---|---|---|---|---|---|
| **Utility Values by Health State** | | | | | |
| Knight et al. 2012 [d] | 0.66 | 0.861 | 0.892 | 0.892 | PASI 14-74 response was given a utility value of 0.761<br><br>Utility scores that were derived from mapping from DLQI scores for each health state (Table 74) |
| **Utility Gains from Baseline** | | | | | |
| Woolacott et al. 2006[a] | 0.05 (SE 0.01) | 0.17 (SE 0.04) | 0.19 (SE 0.04) | 0.21 (SE 0.05) | Mapping was used in order to calculate the mean gain in utility for the various PASI response categories. |
| Woolacott et al. 2006 | 0.12 (SE 0.03) | 0.29 (SE 0.06) | 0.38 (SE 0.08) | 0.41 (SE 0.09) | Mean gains in utility for the different PASI response categories for patients in the 4th quartile DLQI: (a proxy for moderate to severe psoriasis) |
| Sizto et al. 2009 [e] | 0.06 (SEM 0.03) | 0.18 (SEM 0.02)[c] | 0.31 (SEM 0.03) | 0.31 (SEM 0.03) | Change in health utility derived from EQ-5D collected in RCTs (Table 70) |
| Shikiar et al. 2006[b] | -0.01 (SD 0.26, PASI < 25)<br>0.1 (SD 0.24, PASI 25-49) | 0.2 (SD 0.21) | 0.25 (SD 0.30) | 0.25 (SD 0.30) | Change in Index EQ-5D score (Table 71) |
| Anis et al. 2011 [e] | 0.04 (SE 0.02) | 0.12 (SE 0.02) | 0.12 (SE 0.02) | 0.21 (SE 0.02) | Change in Index EQ-5D score(Table 72) |
| Pan et al. 2011[c] | 0.04 | 0.17 | 0.22 | 0.25 | Utility gains for all patients based on calculation from the PHOENIX trial (Table 73) |
| | 0.063 | 0.178 | 0.178 | 0.308 | Utility gains for all patients based on calculation from the patients in TA 146 (Table 73) |
| Etanercept and Efalizumab (TA103)[d] | 0.05(SE 0.01) | 0.17(SE 0.04) | 0.19(SE 0.04) | 0.21(SE 0.05) | Same as Woolacott 2006 |
| Adalimumab (TA146) [d] | 0.054 | 0.14 | 0.14 | 0.219 | EQ-5D collected alongside RCTs, utility gains used within the CEA |
| Adalimumab (TA146) [d,]<br>DLQI ≤ 10 | 0.045 | 0.102 | 0.102 | 0.13 | EQ-5D collected alongside RCTs, utility gains used within the CEA |
| Adalimumab (TA146)d,<br>DLQI > 10 | 0.063 | 0.178 | 0.178 | 0.308 | EQ-5D collected alongside RCTs, utility gains used within the CEA |
| Infliximab (TA134) [e] | 0.12 | 0.29 | 0.38 | 0.41 | EQ-5D collected alongside RCTs, utility gains used within the CEA |
| Ustekinumab (TA180) [e] | 0.04 | 0.17 | 0.22 | 0.25 | Mapping was used in order to calculate the mean gain in utility for the various PASI response categories. |
| Secukinumab (present submission) | 0.11 | 0.19 | 0.23 | 0.26 | Methodology similar to TA 146 was used |

[a] Data from all patients used

[b] Different PASI response levels used. These are PASI <25, PASI 25-49, PASI 50-74 and PASI 75 and above

[c] PHOENIX trial only

[d] Change in EQ-5D is the dependent variable in the regression analysis

[e] Absolute EQ-5D is the dependent variable in the regression analysis

## Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Adverse events were captured indirectly through the collection of EQ-5D data alongside the clinical trials; they were also taken into consideration through response rate and all cause discontinuation. It is known that adverse events have a negative impact on HRQL. However, the magnitude of impact an adverse event has on HRQL is unclear.

## Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

EQ-5D data collected in the five secukinumab RCTs were used for the utility values in the base-case. This was the most appropriate data source as these were recent trials of robust quality, and EQ-5D data were collected alongside PASI measurements used to inform the distributions of patients across the PASI health states.

Utility values were estimated using a mixed effects regression model to account for the longitudinal nature of the secukinumab RCT data.(113) The regression model assessed the relation between change in EQ-5D, PASI response levels, and baseline DLQI within the RCTs. A random intercept model was fitted including a categorical variable for PASI response, baseline DLQI, and an interaction term between PASI response and baseline DLQI. The baseline DLQI variable was centred to lessen correlation with the interaction term and allow easier interpretation. The reason for including the interaction term was to assess how responsive changes in EQ-5D are to PASI response categories depending on patient's baseline DLQI. This methodology follows what has been previously used in TA 146 and the literature.

A complete case analysis approach resulted in regression model being made using 3,231 patients in the base-case analysis. The regression equation was:

$$\Delta EQ\text{-}5D_{ij} = \alpha + \beta_1 PASI_{ij} + \beta_2 DLQI_{ij} + \beta_3 PASI{*}DLQI_{ij} + u_i + w_{ij}$$

where $\beta_1$ represents change in $\Delta$EQ-5D$_{ij}$ for a given PASI response level keeping PASI < 50 as the reference category. In this equation, i stands for the patient and j stands for the time point. Results from this regression model have been reported in Table 85.

**Table 85. Results of the utility analysis: ΔEQ-5D by Health State**

| CEM Health States | Base-case utility values |
|---|---|
| Pooled baseline EQ 5D score | 0.642 |
| PASI <50 | 0.109 |
| PASI 50-74 | 0.193 |
| PASI 75-89 | 0.226 |
| PASI 90+ | 0.264 |

From the results in Table 85, the regression suggested that patients in HS with higher PASI scores saw larger improvements in HRQL.

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No opinions from clinical experts were solicited.

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

A constant HRQL is associated with each health state. However, health state utility values are discounted at an annual rate of 3.5% in the base-case analysis.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

As EQ-5D data were collected alongside efficacy measurements in the secukinumab RCTs, these were considered the most robust source of utility data. Utility values identified from the SLR were therefore not included in the model base-case.

As discussed in Section 7.4.7, utility values derived from the clinical trials were similar to those identified in the literature, however to investigate the effect of changing the utility values in the model, a scenario analysis was conducted using the utility values from NICE TA 146 (Section 7.6.1).

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is considered to be constant within the model. The utility values are discounted using the reference case discount rate of 3.5% for health effects in the base-case.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

## *7.5 Resource identification, measurement and valuation*

### NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Moderate to severe plaque psoriasis management broadly includes administration of pharmacological treatment and monitoring visits, and this is conducted by dermatologists or nurses in a dermatology clinic. For administration of pharmacological treatment, self-administration training is provided to patients to administer the subcutaneous biologic treatments.

All costs associated with moderate to severe plaque psoriasis management and their sources are presented in Section 7.5.5) (Intervention and comparator) 7.5.6 (health-state) and 7.5.7 (adverse events). Cost sources included NHS reference costs, British National Formulary, and published literature. These are the most appropriate sources of information as they as they represented the most current national sources for costs to the NHS.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS reference costs (2012-13) were chosen for this economic evaluation rather than PbR tariffs in the base-case and the scenario analyses. NHS reference costs were selected as they provide relevant costs and volume that reflect the pattern of care delivered in the NHS. NHS reference costs represent the cost burden to the NHS rather than internal reimbursement between NHS organisations and allow for a greater level of granularity to be assessed.

### Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A systematic literature review was conducted to identify sources to populate the resource use model inputs. This systematic literature review was conducted alongside the EE systematic literature review (see methods in Section 7.1.1 and Appendix 11, Section 10.11).

One publication (Fonia et al. 2010) was identified and is specific to the UK setting. This study is summarised in Table 86 and described below. As mentioned in 7.1, the NICE psoriasis guideline (CG 153 (38)) was identified and used to validate the treatment pathway for the UK. Upon further review, the resource use associated with best supportive care was extracted for the economic model (Table 87).

**Table 86. Summary of resource use studies identified**

| | | | | |
|---|---|---|---|---|
| Reference | Fonia et al. 2010 (89) | | | |
| Type of analysis | Retrospective observational study | | | |
| Study population | Patients with psoriasis that had commenced biologic therapy and had visited a specialist at St John's institute in the UK. Patients were required to be over the age of 18 years and to have commenced treatment with biologics at least 6 months prior to data collection of this study. Of the 96 patients who met the inclusion criteria, 94 had records that were useful and of those 76 had fully recorded medical history 12 months or more prior to biologic treatment. | | | |
| Country/setting | UK setting | | | |
| Interventions | Biologics including: adalimumab, efalizumab (not used in the UK), etanercept or infliximab | | | |
| Patient age | Mean age was 47.3 years. | | | |
| Source of cost data (currency year) | Costs were representative of 2008 GBP and were collected from the NHS Reference Costs and the BNF. | | | |
| **Results** | | | | |
| Direct medical costs | **Resource** | | **Mean cost £ (SE) per patient 12 months before biologic treatment** | **Mean cost £ (SE) per patient 12 months after biologic treatment** |
| | Adalimumab | | - | 405.3 (190.6) |
| | Efalizumab | | - | 464.8 (209.5) |
| | Etanercept | | - | 6920.1 (619.9) |
| | Infliximab | | - | 2633.0 (535.4) |
| | Acitretin | | 81.0 (20.3) | 10.1 (7.7) |
| | Ciclosporin | | 628.9 (97.5) | 212.5 (67.7) |
| | Fumaric acid esters | | 509.5 (150.6) | 43.8 (25.7) |
| | Hydroxycarbamide | | 3.6 (1.8) | - |
| | Methotrexate | | 15.5 (3.4) | 11.9 (6.2) |
| | Mycophenolate mofetil | | 10.8 (7.2) | 278.2 (70.9) |
| | Inpatient admissions | | 1887.7 (578.4) | 451.8 (206.3) |
| | ICU admissions | | - | - |
| | HDU admissions | | - | - |
| | A&E visits | | 2.26 (2.26) | 3.39 (2.52) |
| | Outpatient visits | | 232.1 (8.0) | 234.0 (6.8) |
| | Day ward admission | | 63.8 (22.9) | 510.6 (98.1) |
| | Phototherapy | | 770.8 (336.0) | 74.5 (74.5) |
| Resource use | **Resource** | | **Mean resource unit (SE) per patient before biologic treatment** | **Mean resource unit (SE) per patient after biologic treatment** |
| | Acitretin | No. of patients | 18 | 1 |
| | | No. of days on tx | 58.0 (13.9) | 7.6 (5.5) |
| | Ciclosporin | No. of patients | 36 | 17 |
| | | No. of days on tx | 119.5 (17.3) | 36.9 (10.8) |

| Reference | Fonia et al. 2010 (89) | | | |
|---|---|---|---|---|
| | Fumaric acid | No. of patients | 19 | 3 |
| | | No. of days on tx | 45.7 (10.8) | 2.9 (1.7) |
| | Hydrocarbamide | No. of patients | 5 | 0 |
| | | No. of days on tx | 15.1 (7.5) | - |
| | Methotrexate | No. of patients | 31 | 27 |
| | | No. of days on tx | 104.3 (17.2) | 100.2 (17.3) |
| | Mycophenolate mofetil | No. of patients | 3 | 0 |
| | | No. of days on tx | 2.6 (1.8) | - |
| | **Resource** | | **Mean days on treatment (SE) per patient after 12 month of biologic treatment** | |
| | | | **All patients** | **Patients treated with specific biologic** |
| | adalimumab | No. of patients | 6 | - |
| | | No. of days on tx | 15.9 (7.5) | 201.0 (56.0) |
| | efalizumab | No. of patients | 9 | - |
| | | No. of days on tx | 18.5 (8.3) | 156.0 (52.8) |
| | etanercept | No. of patients | 54 | -- |
| | | No. of days on tx | 229.3 (18.6) | 322.8 (10.9) |
| | infliximab | No. of patients | 24 | - |
| | | No. of days on tx | 82.2 (16.1) | 260.4 (25.5) |

**Fonia et al. 2010 (89)** reported the results of a retrospective observational study that sought to estimate the consequences of commencing biologic treatment on medical resource utilisation and costs for patients with moderate to severe plaque psoriasis. The main outcomes of this study were the comparisons of healthcare resource use and related costs in patients 12 months before biologic treatment and 12 months after, as well as the comparison disease severity before and after. All the data was collected from patients' notes, electronic patient records, pharmacy records and other relevant databases from Guy's and St Thomas' Hospitals NHS Trust in the UK for 12 months prior and 12 months after initiating therapy with biologics. The statistical analysis applied to this data included descriptive statistics to determine the frequencies of medical resource utilisation, inferential statistics to assess the disparities in resource utilisation and related costs and disease severity between the 12 months prior and 12 months post biologic initiation, $\chi^2$ (chi-squared) test for changes in weight, and a bootstrap analysis for all costs based on a sample of 5000 repetitions. The analysis showed a significant decline in all hospital resource use categories in the 12 months after initiation of biologic treatment, with mean annual costs decreased by £1,682. In contrast, mean annual drug costs increased as expected by £9,456. Note that these estimates were not used within the CEA, as more up-to-date inputs from NICE CG 153 and expert opinion were instead used.

Assumptions for best supportive care were adapted from the NICE Psoriasis guidelines (CG 153 (38)) which recognizes the continued intensity of ongoing care required by patients with moderate to severe psoriasis not on biologic therapy. These are summarised in Table 87.

**Table 87. Resource use for best supportive care based on NICE treatment guideline (3, 38)**

| Component | Proportion receiving | Resource use components | |
|---|---|---|---|
| Drugs | | | |
| Methotrexate | 45% (a) | | |
| Ciclosporin (b) | 45% (a) | | |
| No drug | 10% (a) | 5 OP visits | |
| **Other treatment** | | | |
| Day centre care | 100% (a) | 5 visits | |
| NBUVB | 16% (b) | 1 course | 24 sessions |
| **Inpatient care** | | | |
| High need | 82% (c) | 1 admission (a) | 20.8 days per admission (e) |
| Very high need | 18% (c) | 2.55 admission (d) | |

| Component | Proportion receiving | Resource use components |
|---|---|---|
| NBUVB: Narrowband UVB<br>[a] Based on GDG opinion<br>[b] Based on proportion receiving PUVA in year before starting biological therapy in Driessen(114) and colleagues<br>[c] Based on split in Driessen and colleagues (under/over 30 days in hospital per annum)<br>[d] Calculated based on mean length of stay from Woods (20.8) and mean hospital days per annum in the very high need group in Driessen (53.0);<br>[e] Based on mean length of stay for patients admitted with baseline PASI 10 to 20 in Woods. 23.7 days used in sensitivity analysis | | |

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Two consultant dermatologists were approached and participated in the validation. These two were experts selected for their expertise in UK psoriasis practice. Declarations of conflicts of interest were obtained. Expert advice was sought regarding assumptions on the frequency of physician's visits for drug administration and monitoring visits (including frequency of tests such as full blood count (FBC), liver function test (LFT), urea and electrolyte (U&E), total protein (TP) and serum creatinine) for each of the following periods: induction, post induction to year 1, and annual. As the clinical experts were in the same telephone meeting together (but in

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

separate locations), no iteration was required to collate the feedback as they discussed topics with one another in real time.

**Methods**

It was assumed that the opinions of these consultants were generalisable to the UK setting. The interview was conducted over a teleconference and participants were allowed to review the questionnaire prior to the interview.

**Questions**

The following questions regarding resource use for physicians' visits and monitoring visits were asked:

Frequency of physician visits:

- What frequency of physician visits for each treatment included in this analysis (secukinumab 300 mg, adalimumab 40 mg, etanercept 25mg, infliximab 5mg/kg, ustekinumab 45mg, ustekinumab 90 mg and standard of care (SoC)) reflects current clinical practice in the induction period, the post induction to 1 year period and the annual period?
- Does the frequency of physician visits change if the induction period changes from 12 to 16 weeks?
- What assumption would you recommend for secukinumab visits? (e.g. equal to ustekinumab, reflective of the trial for the first year, etc.)
- Do different regimens of etanercept require different assumptions for physician visits?
- Is it correct to assume that the physician visits during the "induction to 1 year" period is a linear proportion of the annual physician visits?

Frequency of monitoring tests in the induction period:

- What frequency of monitoring tests including: FBC, LFT, U&E, Total protein, and serum creatinine for each treatment included in this analysis (listed above) reflects current clinical practice in the induction period?
- Was the proposed treatment regimen for TA 180 (Table 88 below) relevant to current clinical practice for the first 12 weeks of treatment on the given biologic therapy?

**Table 88. Frequency of monitoring tests from TA 180**

| Treatment | FBC | LFT | U&E | Total Protein | Serum Creatinine |
|---|---|---|---|---|---|
| Adalimumab 40 mg[b] | 2 | 2 | 2 | - | 1 |
| Etanercept 25mg[a] | 2 | 2 | 2 | - | 1 |
| Ustekinumab 45mg[a] | 2 | 2 | 2 | - | 1 |
| Ustekinumab 90 mg[c] | 2 | 2 | 2 | - | 1 |
| **Note:** All values were taken from TA 180 (23). Source: a Woolacott et al, 2006; b BAD guidelines, c Expert opinion | | | | | |

- If the induction period changes from 12 to 16 weeks, how would the monitoring regimen change for the "induction" period?

- What assumption would you recommend for secukinumab monitoring regimen? (e.g. equal to ustekinumab, reflective of the trial for the first 12 weeks)
- Do different regimens of etanercept require different assumptions for monitoring regimen?
- Is the monitoring regimen done at a physician visit or in addition to a physician visit? If monitoring is done in addition to physician visits, who conducts the monitoring? (e.g. nurse, GP, specialist)
- Is there a component on the monitoring regimen that we have not accounted for?

Frequency of monitoring tests in the annual period:

- What frequency of monitoring tests including: FBC, LFT, U&E, Total protein, and serum creatinine for each treatment included in this analysis (listed above) reflects current clinical practice in the annual period?
- Is it appropriate to assume a linear relationship in the monitoring regimen from the "induction to 1 year" period to the "annual" period?

  ***Example**: 12 week induction period would equate to 75% of annual monitoring regimen for the "induction to 1 year" period in the model.*
- What assumption would you recommend for secukinumab monitoring regimen? (e.g. equal to ustekinumab)
- Do different regimens of etanercept require different assumptions for annual monitoring regimen?

### Results

The values for frequency of physician visits derived from the physician validation meeting are described below in Table 89.

**Table 89. Frequency of physician visits (12 and 16 week induction period)**

| Treatment | Induction Period (12 weeks/16 weeks) | Post induction to 1 year | Annual |
|---|---|---|---|
| Secukinumab 300 mg | 4/5 | 3 | 4 |
| Adalimumab 40 mg | 4 /5 | 3 | 4 |
| Etanercept (25 mg cont.) | 4 /5 | 3 | 4 |
| Infliximab 5mg/kg | 4 /5 | 3 | 4 |
| Ustekinumab 45mg | 4 /5 | 3 | 4 |
| Ustekinumab 90 mg | 4 /5 | 3 | 4 |
| SoC | 3 /4 | 3 | 4 |

The values for frequency of monitoring tests for the induction period and annual monitoring period that were derived from the physician validation meeting are described below in Table 90, Table 91 and Table 92.

**Table 90. Frequency of monitoring tests – Induction period (12 weeks)**

| Treatment | FBC | LFT | U&E | TP | SC |
|---|---|---|---|---|---|
| Secukinumab 300 mg | 4 | 4 | 4 | 4 | 4 |
| Adalimumab 40 mg | 4 | 4 | 4 | 4 | 4 |

| | | | | | |
|---|---|---|---|---|---|
| Etanercept (25 mg tw) | 4 | 4 | 4 | 4 | 4 |
| Infliximab 5mg/kg | 4 | 4 | 4 | 4 | 4 |
| Ustekinumab 45mg | 4 | 4 | 4 | 4 | 4 |
| Ustekinumab 90 mg | 4 | 4 | 4 | 4 | 4 |
| SoC | 4 | 4 | 4 | 4 | 4 |

**Table 91. Frequency of monitoring tests – Induction period (16 weeks)**

| Treatment | FBC | LFT | U&E | TP | SC |
|---|---|---|---|---|---|
| Secukinumab 300 mg | 5 | 5 | 5 | 5 | 5 |
| Adalimumab 40 mg | 5 | 5 | 5 | 5 | 5 |
| Etanercept (25 mg tw) | 5 | 5 | 5 | 5 | 5 |
| Infliximab 5mg/kg | 5 | 5 | 5 | 5 | 5 |
| Ustekinumab 45mg | 5 | 5 | 5 | 5 | 5 |
| Ustekinumab 90 mg | 5 | 5 | 5 | 5 | 5 |
| SoC | 5 | 5 | 5 | 5 | 5 |

**Table 92. Frequency of monitoring tests – Annual monitoring period**

| Treatment | FBC | LFT | UE | TP | SC |
|---|---|---|---|---|---|
| Secukinumab 300 mg | 4 | 4 | 4 | 4 | 4 |
| Adalimumab 40 mg | 4 | 4 | 4 | 4 | 4 |
| Etanercept (25 mg tw) | 4 | 4 | 4 | 4 | 4 |
| Infliximab 5mg/kg | 6 | 6 | 6 | 6 | 6 |
| Ustekinumab 45mg | 4 | 4 | 4 | 4 | 4 |
| Ustekinumab 90 mg | 4 | 4 | 4 | 4 | 4 |
| SoC | 4 | 4 | 4 | 4 | 4 |

The values for frequency of monitoring tests for the post induction to year 1 period were calculated as linear calculation of the values used for the induction period.

Note that these findings were used for the base case.

## Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The cost of each treatment option included the cost of treatment, the cost of monitoring and the cost of SAEs. The cost of treatment covered the pharmacological cost of the intervention (drug unit cost). The expected cost of treatment was subsequently calculated by multiplying the treatment unit costs by the frequency of treatment. The cost of monitoring was calculated by multiplying the costs of each of the monitoring tests by the frequency of monitoring which has been discussed in section 7.5.4. The cost of SAEs was calculated by multiplying the hospitalisation cost of each type of SAE by the rate at which these SAEs occurred.

### *Drug unit cost*

The unit drugs costs are presented in Table 93. Drug costs were obtained from the British National Formulary (BNF) prices (BNF 64 (115)) and MIMS (116).

**Table 93: Unit costs associated with the technology in the economic model**

| Treatment | Pack cost (£) | Number in pack | Form | Strength | Cost per tablet | Cost per dose (£) | Reference |
|---|---|---|---|---|---|---|---|
| Secukinumab | [redacted] | 1 | Pre-filled syringe or auto injector | 300mg | | [redacted] | Assumption/ PAS price |
| Adalimumab | 704.28 | 2 | pre-filled syringe (sc) | 40 mg/0.8ml | | 352.14 | BNF October 2014 |
| Infliximab | 419.62 | 1 | Vial | 100 | | 419.62 | BNF October 2014 |
| Ustekinumab | 2,147.00 | 1.00 | Pre-filled syringe 45 mg/0.5 ml | 45 mg | | 2147 | BNF October 2014 |
| Etanercept | 89.38 | 1 | Pre-filled syringe | 25mg | | 89.38 | BNF October 2014 |
| SoC: Methotrexate | 2.77 | 28 | Tablette | 2.5 | 0.10 | 0.55* | BNF-October 2014 |
| | 35.02 | 100 | Tablette | 10 | 0.35 | | BNF-October 2014 |
| SoC: Ciclosporin | 25.59 | 30 | soft tablettes | 50 | 0.85 | 33.94* | BNF-October 2014 |
| | 48.49 | 30 | soft tablettes | 100 | 1.62 | | BNF-October 2014 |

*Weekly cost, assumes 15 mg taken each week
** Weekly cost, assumed 2100 mg taken each week

### *Cost of administration and monitoring*

Table 94 presents the unit costs associated with administration and monitoring in the economic model. It was assumed that each patient on a subcutaneously administered biologic received one self-administration training in order to administer the injection themselves. Patients that were administered infliximab through IV were assumed to visit the specialist (dermatologist) for this administration, and the frequency of these visits was based on the number of doses of infliximab required.

Other components of monitoring included specialist visits, full blood count (FBC), liver function tests (LFT), urea and electrolytes tests (U&E), total protein tests, and serum creatinine and these were applied according to the number recommended by clinical experts.

Patients on SoC were also assumed to accrue costs for UVB phototherapy (NBUVB) and a day centre care cost.

**Table 94: Unit costs associated with administration and monitoring in the economic model**

| Items | Unit cost (£) | Reference |
|---|---|---|
| **Self-Administration Training** | 39 | PSSRU 2013, Section 10b, average of cost (without qualifications) of an hour for Nurse Education |
| **Physician (Specialist)** | 98 | NHS Reference Cost 2012-2013 (Service Code: 330) |
| **Specialist visit for IV administration** | 92.39 | NHS Reference Cost 2012-2013, Outpatient Procedure (Currency Code: WF01A) |
| **FBC** | 3.01 | NHS Reference Cost 2012-2013, Currency Code: DAPS01 (Haematology) |
| **LFT** | 1.25 | NHS Reference Cost 2012-2013, Currency Code: DAPS04 (Clinical Biochemistry) |
| **U&E** | 1.25 | NHS Reference Cost 2012-2013, Currency Code: DAPS04 (Clinical |

| | | |
|---|---|---|
| | | Biochemistry) |
| **Total Protein** | 1.25 | NHS Reference Cost 2012-2013, Currency Code: DAPS04 (Clinical Biochemistry) |
| **Serum Creatinine** | 1.25 | NHS Reference Cost 2012-2013, Currency Code: DAPS04 (Clinical Biochemistry) |
| **Day Centre Care** | 460 | NHS Reference Cost 2012-2013 (Service Code: 330), Weighted Average for Day Costs |
| **NBUVB** | 91 | NHS Reference Cost 2012-2013, Outpatient Procedure (Currency Code: JC47A, Service Code: 330) |
| **Abbreviations**:FBC: Full blood count; LFT: Liver Function tests; U&E: Urea, creatinine, Electrolytes; NBUVB: UVB phototherapy | | |

### *Hospitalisation costs due to SAEs*

Hospitalisation costs in this analysis included costs for and are described in detail in section 7.5.7, Table 100:

- Psoriasis
- Non-melanoma skin cancer (NMSC)
- Malignancy other than NMSC
- Severe infection

The hospitalisation cost due to psoriasis (£5,337.20) was calculated by multiplying the average length of stay (10.7 days as per HES data (37)) by the average day cost of a hospitalisation for psoriasis taken from the NHS reference cost database (117). The average day cost of a hospitalisation due to psoriasis (£498.80) was calculated from the weighted average cost of the diagnosis “skin disorders with interventions” within the NHS reference cost database divided by the average LOS recorded. For more details around the calculations of the average day cost, refer to Table 95.

**Table 95. Cost of average day in hospital due to psoriasis (NHS Reference costs)**

| Diagnosis | Currency Code | Currency Description | Number of Procedures | Average Cost (£) | Average LOS | Weighted Average (£) | Average Day Cost (£) |
|---|---|---|---|---|---|---|---|
| **Psoriasis** | JD07A | Skin Disorders with Interventions, with CC Score 12+ | 9 | £7,274.25 | 28.89 | £2,906.46 | £498.80 |
| | JD07B | Skin Disorders with Interventions, with CC Score 8-11 | 20 | £9,119.74 | 17.75 | | |
| | JD07C | Skin Disorders with Interventions, with CC Score 4-7 | 85 | £4,766.83 | 10.99 | | |
| | JD07D | Skin Disorders with Interventions, with CC Score 0-3 | 372 | £2,055.03 | 3.63 | | |
| | JD07F | Skin Disorders without Interventions, with CC Score 14-18 | 5 | £6,774.10 | 22.20 | | |
| | JD07G | Skin Disorders without Interventions, with CC Score 10-13 | 22 | £7,513.26 | 14.00 | | |
| | JD07H | Skin Disorders without Interventions, with CC Score 6-9 | 96 | £4,412.25 | 10.35 | | |
| | JD07J | Skin Disorders without Interventions, with CC Score 2-5 | 417 | £3,097.60 | 6.63 | | |
| | JD07K | Skin Disorders without Interventions, with CC Score 0-1 | 433 | £2,098.32 | 3.29 | | |
| **Source**: NHS Reference Costs 2012-2013 | | | | | | | |

### *Frequency of treatment*

Table 96 describes the mean number of doses administered per type of treatment for each model time period and these are defined as per the SmPC for each treatment.

**Table 96: Frequency of treatment injections**

| Items | Induction (0-12 weeks) | Post induction (12- 52 weeks) | Induction (0-16 weeks) | Post induction (16-52 weeks) | Annual | Source |
|---|---|---|---|---|---|---|
| **Secukinumab** | 6 | 10 | 7 | 9 | 12 | SMPC |
| **Adalimumab** | 8 | 20 | 9 | 19 | 26 | SMPC |
| **Infliximab** | 3 | 5 | 4 | 4 | 6.5 | SMPC |
| **Ustekinumab** | 2 | 4 | 2 | 4 | 4.33 | SMPC |
| **Etanercept** | 24 | 80 | 32 | 72 | 104 | SMPC |
| **SoC*** | 12 | 40 | 16 | 36 | 52 | NICE Psoriasis guidelines |
| Note that resource use for ustekinumab 45mg and 90 mg was assumed to be the same<br>*Note SoC is not an injection | | | | | | |

### *Frequency of administration and monitoring*

During the induction period (week 0- 12 or week 0-16), resource use assumptions for patient monitoring tests and administration were validated by clinical experts. For the post induction to year 1 period, resource use was calculated as a linear function of the induction period calculations. Resource use estimates were similar across all the biologic treatments. Table 97 provides detailed estimates of the frequency of administration and monitoring used within this analysis.

**Table 97. Frequency of administration and monitoring**

| Items | Self Admin | IV infusion | Physician | FBC | LFT | U&E | Total Protein | Serum Creatinine | Day Centre Care | NBUVB |
|---|---|---|---|---|---|---|---|---|---|---|
| **Induction NICE endpoints** | | | | | | | | | | |
| Secukinumab | 1 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 0 | 0 |
| Adalimumab | 1 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 0 | 0 |
| Etanercept | 1 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 0 | 0 |
| Infliximab | 0 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 0 | 0 |
| Ustekinumab 45mg | 1 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 0 | 0 |
| Ustekinumab 90 mg | 1 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 0 | 0 |
| SoC | 0 | 0 | 4 | 5 | 5 | 5 | 5 | 5 | 1.54 | 1.18 |
| **Post induction (NICE endpoints)** | | | | | | | | | | |
| Secukinumab | 0 | 0 | 3 | 3.08 | 3.08 | 3.08 | 3.08 | 3.08 | 0.00 | 0.00 |
| Adalimumab | 0 | 0 | 3 | 3.46 | 3.46 | 3.46 | 3.46 | 3.46 | 0.00 | 0.00 |
| Etanercept | 0 | 0 | 3 | 3.08 | 3.08 | 3.08 | 3.08 | 3.08 | 0.00 | 0.00 |
| Infliximab | 0 | 5 | 3 | 3.08 | 3.08 | 3.08 | 3.08 | 3.08 | 0.00 | 0.00 |
| Ustekinumab 45mg | 0 | 0 | 3 | 3.08 | 3.08 | 3.08 | 3.08 | 3.08 | 0.00 | 0.00 |
| Ustekinumab 90 mg | 0 | 0 | 3 | 3.08 | 3.08 | 3.08 | 3.08 | 3.08 | 0.00 | 0.00 |
| SoC | 0 | 0 | 3 | 3.46 | 3.46 | 3.46 | 3.46 | 3.46 | 3.46 | 2.66 |
| **Annual** | | | | | | | | | | |
| Secukinumab | 0 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 0 | 0 |
| Adalimumab | 0 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 0 | 0 |
| Etanercept | 0 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 0 | 0 |
| Infliximab | 0 | 6.5 | 4 | 6 | 6 | 6 | 6 | 6 | 0 | 0 |
| Ustekinumab 45mg | 0 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 0 | 0 |
| Ustekinumab 90 mg | 0 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 0 | 0 |
| SoC | 0 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | 3.84 |
| **Source**: Expert opinion | | | | | | | | | | |

### *Frequency of hospitalisation due to adverse events*

Hospitalisation costs due to psoriasis were applied to patients that had either initiated treatment on SoC or were switched to SoC due to non-response or discontinuation with a biologic treatment. Psoriasis hospitalisation costs were applied once annually as per prior submissions (23) for the treatment of a flare up of psoriasis.

Hospitalisation costs due to a) malignancies other than NMSC, b) NMSC and c) severe infection were applied to each treatment arm as per the rates of these events occurring. The rates for malignancies other than NMSC were taken from trial data (42) for secukinumab and SmPCs for the remaining biologics.(15-18) The rates applied for non-melanoma skin cancer were retrieved from Novartis data on file for secukinumab and the SmPCs for the other biologics (15-18). The rates of severe infection were taken from Novartis data on file for secukinumab, SmPC for ustekinumab (17), and Dixon et al. 2006(118) for etanercept, infliximab and adalimumab.

**Table 98. Adverse Event Rates**

| Adverse events | SEC 300 | ADA | INF | UST 45 | UST 90 | ETN |
|---|---|---|---|---|---|---|
| Malignancies other than NMSC (rate /patient year) | [redacted] | 0.006 | 0.0767 | 0.0016 | 0.0016 | 0.00043 |
| Non-melanoma skin cancer (rate /patient year) | [redacted] | 0.0097 | 0.004 | 0.0065 | 0.0065 | 0.0354 |
| Severe infections (rate /patient year) | [redacted] | 0.0519 | 0.0552 | 0.01 | 0.01 | 0.0513 |
| Sources | CSR | SPC and Dixon et al. 2006 | INF Product information, assumption based on secukinumab and Dixon et al. 2006 | SPC | SPC | Etanercept Product Information and Dixon et al. 2006 |

## Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Health state costs were calculated for the induction period, for the maintenance period and the annual period separately. These costs were calculated for the following health states:

- PASI <50
- PASI 50-74
- PASI 75-89
- PASI 90-100

The costs are presented in Table 99 for the base case, where partial response is not accounted for. Costs for the scenario considering continued treatment for partial

responders are given in Section 7.6.1. Health state cost are representative of drug costs, administration costs, monitoring costs, and AE costs.

**Table 99. Health State Costs - Base case (Partial responders discontinue)**

| | Induction | Maintenance | | | | Annual | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI 90-100 | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI 90-100 |
| Secukinumab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Ustekinumab 45mg | 4,757.04 | - | - | 8,906.65 | 8,906.65 | - | - | 9,727.71 | 9,727.71 |
| Ustekinumab 90 mg | 4,757.04 | - | - | 8,906.65 | 8,906.65 | - | - | 9,727.71 | 9,727.71 |
| Adalimumab 40 mg | 3,738.31 | - | - | 7,012.39 | 7,012.39 | - | - | 9,579.68 | 9,579.68 |
| Etanercept 25mg | 2,608.16 | - | - | 7,469.05 | 7,469.05 | - | - | 9,719.56 | 9,719.56 |
| Infliximab 5mg/kg IV | 6,731.49 | - | - | 10,831.06 | 10,831.06 | - | - | 14,106.20 | 14,106.20 |
| SoC | 1,495.60 | 2,714.71 | 2,714.71 | 2,714.71 | 2,714.71 | 3,880.57 | 3,880.57 | 3,880.57 | 3,880.57 |

## Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Only serious adverse events that required hospitalisation were included in the model as it was assumed these would be cost-drivers for treatment of moderate to severe plaque psoriasis with biologics. The following adverse events are included in the model:

- Psoriasis (occurs only in patients on SoC)
- Malignancy other than NMSC
- Non-melanoma skin cancer
- Severe infection

The unit costs for each AE are described in Table 100. Full details of the source costs used to derive these costs are presented in the appendices, Section 10.16.

**Table 100: List of adverse events and summary of costs included in the economic model**

| Adverse events | Items | Value (£) | Reference |
|---|---|---|---|
| Malignancy other than NMSC | Lymphoma (Hospital costs) | 8,178.26 | NHS reference costs 2013 (PA41Z) |
| | Melanoma (Hospital costs) | 1,460.49 | NHS reference costs 2013 (JC42A) |
| Non-melanoma skin cancer | Non-melanoma skin cancer (Hospital costs) | 1,460.49 | NHS reference costs 2013 (JC42A) |
| Severe infection. | Sepsis | 2,101.72 | NHS reference costs 2013 (Weighted average:WA03A; WA03B, WA03C) |
| | Tuberculosis | 2,403.15 | NHS reference costs 2013 (Weighted average: DZ14C; DZ14D, DZ14E) |
| | Pneumonia | 1,852.10 | NHS reference costs 2013 (Weighted average: DZ23D; DZ23E; DZ23F; DZ23G; DZ11D; DZ11E; DZ11F; DZ11G; DZ11H; DZ11J) |
| | Skin and soft tissue infection | 1,383.44 | NHS reference costs 2013 (Weighted average: PA16A; PA16B; PA17A; PA17B; PA18A; PA18B) |
| | Bone and joint infection | 3,087.03 | NHS reference costs 2013 (Weighted average: HD25D; HD25E; HD25F; HD25G; HD25H) |
| | Urinary tract infection | 1,754.08 | NHS reference costs 2013 (Weighted average: LA04H;LA04J;LA04K LA04L;LA04M;LA04N LA04P; LA04Q; LA04R; LA04S |
| Psoriasis | Psoriasis | 5,337.20 | NHS reference costs 2013 (Weighted average: JD07A; JD07B; JD07C; JD07D; JD07F; JD07G JD07H; JD07J JD07K) |

## Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Not applicable.

## 7.6 Sensitivity analysis

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Four scenario analyses were undertaken to examine the impact of structural assumptions and the robustness of data sources used in the base-case of the model.

### *Inclusion of partial responders*

In the base-case analysis, partial responders (PASI response 50-74) were not considered to continue on biologic treatment after the induction period. Instead they discontinued and continued on SoC. Given the uncertainty around whether patients with PASI 50-74 would continue treatment in clinical practice, a scenario analysis was conducted to account for partial responders continuing on treatment. In this scenario analysis, all other settings remain equal to the base case.

When modelling so as to account for partial responders continuing on treatment after the induction period, the costs assigned to these patients are those of the initial treatment (Table 101). *Note that in the base-case, where partial responders discontinued after the induction period, the cost of SoC was assigned to patients with partial response after the induction period.*

**Table 101. Health State Costs – Scenario analysis (Partial responders continue)**

| | Induction | Maintenance | | | | Annual | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI 90-100 | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI 90-100 |
| Secukinumab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Ustekinumab 45mg | 4757.04 | - | 8,906.65 | 8,906.65 | 8,906.65 | - | 9,727.71 | 9,727.71 | 9,727.71 |
| Ustekinumab 90 mg | 4757.04 | - | 8,906.65 | 8,906.65 | 8,906.65 | - | 9,727.71 | 9,727.71 | 9,727.71 |
| Adalimumab 40 mg | 3738.31 | - | 7,012.39 | 7,012.39 | 7,012.39 | - | 9,579.68 | 9,579.68 | 9,579.68 |
| Etanercept 25mg | 2608.16 | - | 7,469.05 | 7,469.05 | 7,469.05 | - | 9,719.56 | 9,719.56 | 9,719.56 |
| Infliximab 5mg/kg IV | 6731.489 | - | 10,831.06 | 10,831.06 | 10,831.06 | - | 14,106.20 | 14,106.20 | 14,106.20 |
| SoC | 1495.598 | 2,714.71 | 2,714.71 | 2,714.71 | 2,714.71 | 3,880.57 | 3,880.57 | 3,880.57 | 3,880.57 |

### *12 week NMA analysis*

In the base-case analysis, the distribution of patients across the PASI response categories were calculated from random effects multinomial NMA parameter estimates for the cost-effectiveness analysis for the primary trial endpoints (Section 7.2.2; adalimumab: 16 weeks; infliximab: 10 weeks; ustekinumab: 12 weeks; etanercept: 12 weeks and secukinumab at 12 weeks).

To explore the effect of varying the length of the induction period for the biologic comparators, a scenario analysis was conducted where the distribution of patients

across the PASI response categories was calculated from random effects multinomial NMA parameter estimates for the cost-effectiveness analysis for 12 week time endpoints across all the comparators (Section 6.7.9).

In this scenario, efficacy and resource use had to be projected to accrue only a 12 week induction period for all comparators. Table 102 shows the outputs of the NMA and the calculated distributions described above for the 12 week end point across all comparators.

**Table 102. Calculated PASI distributions from random effects multinomial NMA parameter estimates for CEA, 12 week analysis**

| | | PASI Distribution | | | |
|---|---|---|---|---|---|
| **Treatment** | **Treatment effect estimate (SE)** | **PASI <50** | **PASI 50-74** | **PASI 75-89** | **PASI 90+** |
| placebo | 0 (-) | 89.3% | 7.5% | 2.7% | 0.5% |
| secukinumab 300mg | -2.649(0.1) | 7.9% | 13.1% | 25.2% | 53.7% |
| adalimumab 40mg | -1.97(0.11) | 23.3% | 21.8% | 27.0% | 27.9% |
| infliximab 5mg/kg | -2.45(0.16) | 11.3% | 16.0% | 26.9% | 45.8% |
| ustekinumab 45mg | -2.319(0.08) | 14.0% | 17.8% | 27.5% | 40.7% |
| ustekinumab 90mg | -2.47(0.09) | 11.0% | 15.7% | 26.8% | 46.6% |
| etanercept 50mg | -1.47(0.11) | 40.9% | 23.7% | 21.5% | 13.9% |

| **Parameter** | **Estimate (SE)** |
|---|---|
| PASI cut point 50 | 1.24(0.04) |
| PASI cut point 75 | 1.85(0.04) |
| PASI cut point 90 | 2.56(0.04) |

### *16 week NICE endpoints NMA analysis*

A scenario analysis was conducted using random effects multinomial NMA parameter estimates for the cost-effectiveness analysis for a 16 week assessment point for secukinumab, and the primary trial timepoints for the other biologic comparators (Section 6.7.9) (adalimumab: 16 weeks; infliximab: 10 weeks; ustekinumab: 12 weeks; etanercept: 12 weeks and secukinumab at 16 weeks).

This scenario aimed to investigate the effect of using a 16 week response assessment point given that the efficacy of secukinumab has been demonstrated to increase between week 12 and 16 in FIXTURE and ERASURE, and in line with the CHMP opinion.(1)

Table 103 present the outputs of the NMA and the calculated distributions described above for the 12 week end point across all comparators.

**Table 103. Calculated PASI distributions from random effects multinomial NMA parameter estimates for CEA, NICE 16 week endpoint analysis (16 weeks for SEC 300)**

| | | PASI Distribution | | | |
|---|---|---|---|---|---|
| **Treatment** | **Treatment effect estimate (SE)** | **PASI <50** | **PASI 50-74** | **PASI 75-89** | **PASI 90+** |
| placebo | 0 | 89.03% | 7.93% | 2.48% | 0.56% |
| secukinumab 300mg | -2.776(0.15) | 6.08% | 12.30% | 22.09% | 59.52% |
| adalimumab 40mg | -1.93(0.11) | 24.13% | 23.68% | 24.93% | 27.26% |
| infliximab 5mg/kg | -2.625(0.12) | 8.12% | 14.55% | 23.75% | 53.59% |
| ustekinumab 45mg | -2.27(0.07) | 14.87% | 19.78% | 25.80% | 39.55% |
| ustekinumab 90mg | -2.409(0.08) | 11.88% | 17.79% | 25.34% | 44.99% |
| etanercept 50mg | -1.454(0.09) | 41.06% | 25.26% | 19.70% | 13.98% |

| **Parameter** | **Estimate (SE)** |
|---|---|
| PASI cut point 50 | 1.23(0.04) |
| PASI cut point 75 | 1.88(0.04) |
| PASI cut point 90 | 2.54(0.05) |

### Resource Use

In this scenario, all patients are assessed at 12 weeks across all comparators and therefore resource use for 12 weeks is used for drug treatment cost calculations (section 6.7.9, Table 104) and monitoring cost calculations (section 7.5.5).

**Table 104. Frequency of treatment injections**

| Items | Induction (NICE endpoints) | Post induction (NICE endpoints) | Source |
|---|---|---|---|
| Secukinumab | 6 | 10 | SMPC |
| Adalimumab | 10 | 18 | SMPC |
| Infliximab | 3 | 5 | SMPC |
| Ustekinumab | 2 | 4 | SMPC |
| Etanercept | 24 | 80 | SMPC |
| Standard of Care | 12 | 40 | NICE Psoriasis guidelines (CG 153) |

### *Utility values from TA146*

Utility values from a previous appraisal (TA146(22)) were tested as a scenario analysis. In this previous appraisal, the relationship between utility changes and PASI response was assessed using pooled data from the two main trials for adalimumab (CHAMPION, MO2-528) and presented below in Table 105.

**Table 105. Changes of EQ-5D by PASI response (TA146)**

| | Δ EQ-5D | |
|---|---|---|
| **PASI Response** | **Mean** | **SE** |
| PASI <50 | 0.054 | 0.017 |
| PASI 50-74 | 0.140 | 0.016 |
| PASI 75-89 | 0.140 | 0.016 |
| PASI 90-99 | 0.219 | 0.021 |

### *Head-to-head efficacy data from FIXTURE*

A scenario analysis, where trial data from FIXTURE were used to define the distribution of patients across the PASI categories, was undertaken. The data from FIXTURE included head-to-head 12 week induction PASI response for patients treated with secukinumab 300 mg vs. etanercept and SoC.

The overlapping nested PASI categories reported in the FIXTURE trial were transformed into mutually exclusive categories at the reported cut-offs and converted into distributions of patients across the PASI categories.

**Table 106. Efficacy data (FIXTURE) for PASI distribution after 12 weeks**

| PASI Response | Placebo | Secukinumab 300 mg | Etanercept |
|---|---|---|---|
| PASI <50 | 85% | 8% | 30% |
| PASI 50-74 | 10% | 15% | 26% |
| PASI 75-89 | 3% | 23% | 23% |
| PASI 90+ | 2% | 54% | 21% |

### 7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Uncertainty around values for key parameters and the implications of using different estimates has been examined through one way sensitivity analyses (OWSA). Parameter ranges used in the OWSA can be found in Table 107. The rationale for including parameters in the OWSA is as follows:

- **Discounting**: Sensitivity analyses using rates of 0%-5% for both costs and health effects were assumed
- **Efficacy parameters**: Outputs of the NMA including the treatment effect of each comparator and the mean cut-off points were varied by using 95% CIs.
- **Discontinuation rates**: Inputs varied using data from ERASURE and FIXTURE CSRs
- **Adverse event rates**: The adverse event rates for severe infection for etanercept, infliximab and adalimumab were taken from the 95% CI found in Dixon et al. 2006(118). All other inputs were varied by ±20%.
- **Costs**: Drug unit costs, monitoring unit costs, and hospitalisation costs were varied by ±20%.
- **Resource use:** Administration of treatments and monitoring were varied by ±20%.

Utility values were not varied in OWSA as the base-case utility value for each PASI category was dependent on the utility value of the PASI <50, that is, they are estimated as changes from the reference utility of the PASI<50 state. As all utility values were inter-dependent, it was not deemed appropriate to vary each one individually. The impact of utility values is therefore evaluated through Scenario 4 above, using utilities from TA146.

Variables included in the OWSA are presented in Table 107.

**Table 107. Variables included in the OWSA**

| Parameter | Base-case value | Lower value | Upper value | Reference |
|---|---|---|---|---|
| Median (PASI 50) | 1.195 | 1.118 | 1.274 | NMA Section 6.7 |
| Median (PASI 75) | 0.603 | 0.574 | 0.633 | NMA Section 6.7 |
| Median (PASI 90) | 1.317 | 1.277 | 1.359 | NMA Section 6.7 |
| Median (SoC) | 0.000 | 0.000 | 0.000 | NMA Section 6.7 |
| Median (SEC 300) | -2.648 | -2.852 | -2.477 | NMA Section 6.7 |
| Median (ADA) | -1.920 | -2.127 | -1.703 | NMA Section 6.7 |
| Median (INF) | -2.623 | -2.839 | -2.393 | NMA Section 6.7 |
| Median (UST 45) | -2.321 | -2.475 | -2.167 | NMA Section 6.7 |
| Median (UST 90) | -2.469 | -2.633 | -2.302 | NMA Section 6.7 |
| Median (ETN) | -1.471 | -1.682 | -1.272 | NMA Section 6.7 |
| *Discontinuation rates* | | | | |
| Biologic year 1 discontinuation rate | 0.117 | 0.092 | 0.145 | ERASURE and FIXTURE CSR |
| Annual discontinuation rate (year 2+) | 0.200 | 0.047 | 0.428 | Expert Opinion/Woolacott et al. 2006 |
| *Adverse event rates* | | | | |
| SEC 300 rate of malignancies/ patient | [redacted] | [redacted] | [redacted] | [redacted] |

| Parameter | Base-case value | Lower value | Upper value | Reference |
|---|---|---|---|---|
| [redacted] | | | | |
| SEC 300 rate NMSC/ patient year | [redacted] | [redacted] | [redacted] | ±20% of mean value |
| SEC 300 rate of severe infections/ patient year | [redacted] | [redacted] | [redacted] | ±20% of mean value |
| ADA rate of malignancies/ patient year | 0.006 | 0.004 | 0.010 | SMPC |
| ADA rate NMSC/ patient year | 0.010 | 0.007 | 0.014 | SMPC, |
| ADA rate of severe infections/ patient year | 0.052 | 0.040 | 0.066 | Dixon et al. 2006 |
| INF rate of malignancies/ patient year | 0.077 | 0.061 | 0.092 | ±20% of mean value |
| INF rate NMSC/ patient year | 0.004 | 0.003 | 0.005 | ±20% of mean value |
| INF rate of severe infections/ patient year | 0.055 | 0.049 | 0.062 | Dixon et al. 2006 |
| UST45 rate of malignancies/ patient year | 0.002 | 0.001 | 0.002 | ±20% of mean value |
| UST45 rate NMSC/ patient year | 0.007 | 0.005 | 0.008 | ±20% of mean value |
| UST45 rate of severe infections/ patient year | 0.010 | 0.008 | 0.012 | ±20% of mean value |
| UST90 rate of malignancies/ patient year | 0.002 | 0.001 | 0.002 | ±20% of mean value |
| UST90 rate NMSC/ patient year | 0.007 | 0.005 | 0.008 | ±20% of mean value |
| UST90 rate of severe infections/ patient year | 0.010 | 0.008 | 0.012 | ±20% of mean value |
| ETN rate of malignancies/ patient year | 0.00043 | 0.00034 | 0.00052 | ±20% of mean value |
| ETN rate NMSC/ patient year | 0.035 | 0.028 | 0.042 | ±20% of mean value |
| ETN rate of severe infections/ patient year | 0.051 | 0.045 | 0.059 | Dixon et al. 2006 |
| *Drug unit costs* | | | | |
| Secukinumab (300 mg) - PAS price (£) | [redacted] | [redacted] | [redacted] | ±20% of mean value |
| Adalimumab (80 mg pack) (£) | 704.28 | 563.42 | 845.14 | ±20% of mean value |
| Infliximab (100) (£) | 419.62 | 335.70 | 503.54 | ±20% of mean value |
| Ustekinumab (45mg) (£) | 2147.00 | 1717.60 | 2576.40 | ±20% of mean value |
| Etanercept (25mg) (£) | 89.38 | 71.50 | 107.26 | ±20% of mean value |
| Methotrexate (2.5mg, 100 tablets) (£) | 2.77 | 2.22 | 3.32 | ±20% of mean value |
| Methotrexate (10 mg, 100 tablets) (£) | 35.02 | 28.02 | 42.02 | ±20% of mean value |
| Ciclosporin (100 mg, 30 tablets) (£) | 48.49 | 38.79 | 58.19 | ±20% of mean value |
| *Monitoring unit costs* | | | | |
| Cost of complete blood count (£) | 3.01 | 2.41 | 3.61 | ±20% of mean value |
| Cost of urea, creatinine and electrolytes test (£) | 1.25 | 1.00 | 1.50 | ±20% of mean value |
| Cost of liver function test (£) | 1.25 | 1.00 | 1.50 | ±20% of mean value |
| Cost of total protein test (£) | 1.25 | 1.00 | 1.50 | ±20% of mean value |
| Cost of self-admin training (£) | 39.00 | 31.20 | 46.80 | ±20% of mean value |
| Cost of physician visit for IV (£) | 92.39 | 73.91 | 110.87 | ±20% of mean value |
| Cost of specialist visit (£) | 98.00 | 78.40 | 117.60 | ±20% of mean value |
| Cost of day centre care (£) | 460.00 | 204.10 | 590.03 | NHS Reference costs based on lower and upper quartile weighted averages |
| Cost of UVB phototherapy (£) | 91.00 | 72.80 | 109.20 | ±20% of mean value |
| *Hospitalisation costs* | | | | |
| Psoriasis | 5337.20 | 4269.76 | 6404.64 | ±20% of mean value |
| Sepsis | 2101.72 | 1681.38 | 2522.07 | ±20% of mean value |
| Lymphoma | 8178.26 | 6542.61 | 9813.92 | ±20% of mean value |
| Melanoma | 1460.49 | 1168.39 | 1752.58 | ±20% of mean value |
| NMSC | 1460.49 | 1168.39 | 1752.58 | ±20% of mean value |

| Parameter | Base-case value | Lower value | Upper value | Reference |
|---|---|---|---|---|
| Tuberculosis | 2403.15 | 1922.52 | 2883.78 | ±20% of mean value |
| Pneumonia | 1852.10 | 1481.68 | 2222.52 | ±20% of mean value |
| Skin and soft tissue infection | 1383.44 | 1106.76 | 1660.13 | ±20% of mean value |
| Bone and joint infection | 3087.03 | 2469.63 | 3704.44 | ±20% of mean value |
| Urinary tract infection | 1754.08 | 1403.26 | 2104.89 | ±20% of mean value |
| Average LOS for Psoriasis patients | 10.70 | 8.56 | 12.84 | ±20% of mean value |
| *SoC weightings* | | | | |
| Day Centre Care | 1.00 | 0.80 | 1.20 | ±20% of mean value |
| NVUVB | 0.16 | 0.13 | 0.19 | ±20% of mean value |
| *Monitoring frequency* | | | | |
| Number of self-admin training (non-IV biologics)-12wks | 1.00 | 0.80 | 1.00 | Lower: -20% of mean value<br>Upper: Assumption |
| Number of IV infusions (INF)- 12 wks | 3.00 | 2.40 | 3.60 | ±20% of mean value |
| Number of physician visits (All biologics)-12wk | 4.00 | 3.20 | 5.00 | Lower: ±20% of mean value<br>Upper: Assumption |
| Number of physician visits (SoC)-12wk | 3.00 | 2.40 | 8.00 | Lower: -20% of mean value<br>Upper: Assumption |
| Number of FBC -12wk | 4.00 | 3.20 | 4.80 | ±20% of mean value |
| Number of LFT- 12wk | 4.00 | 3.20 | 4.80 | ±20% of mean value |
| Number of U&E -12wk | 4.00 | 3.20 | 4.80 | ±20% of mean value |
| Number of TP -12wk | 4.00 | 3.20 | 4.80 | ±20% of mean value |
| Number of SC -12wk | 4.00 | 3.20 | 4.80 | ±20% of mean value |
| Number of self-admin training (non-IV biologics)-16wks | 1.00 | 0.80 | 1.00 | Lower: -20% of mean value<br>Upper: Assumption |
| Number of physician visits (All biologics)-16wk | 5.00 | 4.00 | 5.00 | Lower: -20% of mean value<br>Upper: Assumption |
| Number of physician visits (SoC)-16wk | 4.00 | 3.20 | 4.00 | Lower: -20% of mean value<br>Upper: Assumption |
| Number of FBC -16wk | 5.00 | 4.00 | 6.00 | ±20% of mean value |
| Number of LFT- 16wk | 5.00 | 4.00 | 6.00 | ±20% of mean value |
| Number of U&E -16wk | 5.00 | 4.00 | 6.00 | ±20% of mean value |
| Number of TP -16wk | 5.00 | 4.00 | 6.00 | ±20% of mean value |
| Number of SC -16wk | 5.00 | 4.00 | 6.00 | ±20% of mean value |
| Number of physician visits- post induction | 3.00 | 2.40 | 3.60 | ±20% of mean value |
| Frequency of day care (SoC) – post induction | 4.00 | 3.20 | 4.80 | ±20% of mean value |
| Frequency of NBUVB (SoC) – post induction | 4.00 | 3.20 | 4.80 | ±20% of mean value |
| Number of physician visits - Annual | 4.00 | 3.20 | 4.80 | ±20% of mean value |
| Number of infusions-(INF) | 6.50 | 5.20 | 7.80 | ±20% of mean value |
| Number of FBC (non-IV tx)-Annual | 4.00 | 3.20 | 4.80 | ±20% of mean value |
| Number of FBC (INF)-Annual | 6.00 | 4.80 | 7.20 | ±20% of mean value |
| Number of LFT(non-IV tx)- Annual | 4.00 | 3.20 | 4.80 | ±20% of mean value |
| Number of LFT (INF) -Annual | 6.00 | 4.80 | 7.20 | ±20% of mean value |
| Number of U&E (non-IV tx)- Annual | 4.00 | 3.20 | 4.80 | ±20% of mean value |
| Number of U&E (INF)-Annual | 6.00 | 4.80 | 7.20 | ±20% of mean value |
| Number of TP (non-IV tx)- Annual | 4.00 | 3.20 | 4.80 | ±20% of mean value |
| Number of TP (INF)-Annual | 6.00 | 4.80 | 7.20 | ±20% of mean value |
| Number of SC (non-IV tx) -Annual | 4.00 | 3.20 | 4.80 | ±20% of mean value |
| Number of SC (INF) -Annual | 6.00 | 4.80 | 7.20 | ±20% of mean value |
| Frequency of day care (SoC) – Annual | 5.00 | 4.00 | 6.00 | ±20% of mean value |
| *Discounting* | | | | |
| Discounting of costs | 3.50% | 0.00% | 5.00% | Assumption |
| Discounting of outcomes | 3.50% | 0.00% | 5.00% | Assumption |
| Cut-off point 1: PASI 50; Cut-off point 2: PASI 75; Cut-off point 3: PASI 90; FBC: Full Blood Count; LFT: Liver Function Test; U&E: Urine and Electrolyte tests; TP: Total Protein; SC: Serum Creatinine; NBUVB: Narrowband Ultraviolet B; IV: Intravenous; tx: treatments; INF: Infliximab; NMSC: Non-Melanoma Skin Cancer | | | | |

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was conducted in order to simultaneously reflect uncertainty associated with parameters in the results of the model (parameter uncertainty). Distributions were assigned to characterise the uncertainty associated with the (precision of) mean parameter values or second order uncertainty. The distributions chosen for PSA were selected to represent the available evidence on the parameter of interest.

Variables and statistical distributions used in the probabilistic sensitivity analyses are reported in Table 108 below.

**Table 108. Probabilistic parameters**

| Input | Mean | Distribution type | Source |
|---|---|---|---|
| ***Efficacy*** | | | |
| Median (PASI 50) | 1.195 | CODA | NMA section 6.7 |
| Median (PASI 75) | 0.603 | CODA | NMA section 6.7 |
| Median (PASI 90) | 1.317 | CODA | NMA section 6.7 |
| Median (SoC) | 0 | CODA | NMA section 6.7 |
| Median (SEC 300) | -2.648 | CODA | NMA section 6.7 |
| Median (ADA) | -1.92 | CODA | NMA section 6.7 |
| Median (INF) | -2.623 | CODA | NMA section 6.7 |
| Median (UST 45) | -2.321 | CODA | NMA section 6.7 |
| Median (UST 90) | -2.469 | CODA | NMA section 6.7 |
| Median (ETN) | -1.471 | CODA | NMA section 6.7 |
| ***Adverse event rates*** | | | |
| SEC 300 rate of malignancies/ patient year | [redacted] | BETA | Intervention and comparator cost section 7.5.5 |
| SEC 300 rate NMSC/ patient year | [redacted] | BETA | Intervention and comparator cost section 7.5.5 |
| SEC 300 rate of severe infections/ patient year | [redacted] | BETA | Intervention and comparator cost section 7.5.5 |
| ADA rate of malignancies/ patient year | 0.006 | BETA | Intervention and comparator cost section 7.5.5 |
| ADA rate NMSC/ patient year | 0.010 | BETA | Intervention and comparator cost section 7.5.5 |
| ADA rate of severe infections/ patient year | 0.052 | BETA | Intervention and comparator cost section 7.5.5 |
| INF rate of malignancies/ patient year | 0.077 | BETA | Intervention and comparator cost section 7.5.5 |
| INF rate NMSC/ patient year | 0.004 | BETA | Intervention and comparator cost section 7.5.5 |
| INF rate of severe infections/ patient year | 0.055 | BETA | Intervention and comparator cost section 7.5.5 |
| UST45 rate of malignancies | 0.002 | BETA | Intervention and comparator cost section 7.5.5 |
| UST45 rate NMSC/ patient year | 0.007 | BETA | Intervention and comparator cost section 7.5.5 |
| UST45 rate of severe infections/ patient year | 0.010 | BETA | Intervention and comparator cost section 7.5.5 |
| UST90 rate of malignancies/ patient year | 0.002 | BETA | Intervention and comparator cost section 7.5.5 |
| UST90 rate NMSC/ patient year | 0.007 | BETA | Intervention and comparator cost section 7.5.5 |
| UST90 rate of severe infections/ patient year | 0.010 | BETA | Intervention and comparator cost section 7.5.5 |
| ETN rate of malignancies/ patient year | 0.00043 | BETA | Intervention and comparator cost section 7.5.5 |
| ETN rate NMSC/ patient year | 0.035 | BETA | Intervention and comparator cost section 7.5.5 |
| ETN rate of severe infections/ patient year | 0.051 | BETA | Intervention and comparator cost section 7.5.5 |
| ***Discontinuation rates*** | | | |
| Biologics year 1 drop-out rate | 0.117 | BETA | 95%CI:0.092-0.145 |
| year 2-10 drop-out rate | 0.2 | BETA | 95%CI:0.047-0.428 |
| ***Utilities*** | | | |

| | | | |
|---|---|---|---|
| Utility gain: PASI <50 | 0.1091 | (Multivariate normal distribution) | Section 7.4.9 |
| Utility gain: PASI 50-74 | 0.1932 | (Multivariate normal distribution) | Section 7.4.9 |
| Utility gain: PASI 75-89 | 0.2258 | (Multivariate normal distribution) | Section 7.4.9 |
| Utility gain: PASI 90+ | 0.2641 | (Multivariate normal distribution) | Section 7.4.9 |
| ***Resource use - monitoring*** | | | |
| Number of physician visits (All biologics)-12wk | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of physician visits (SoC)-12wk | 3.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of FBC -12wk | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of LFT- 12wk | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of U&E -12wk | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of TP -12wk | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of SC -12wk | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of physician visits (All biologics)-16wk | 5.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of physician visits (SoC)-16wk | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of FBC -16wk | 5.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of LFT- 16wk | 5.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of U&E -16wk | 5.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of TP -16wk | 5.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of SC -16wk | 5.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of physician visits-post induction | 3.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Frequency of day care (SoC) – post induction | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Frequency of NBUVB (SoC) – post induction | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of physician visits - Annual | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of FBC (non-IV tx)-Annual | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of FBC (INF)-Annual | 6.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of LFT(non-IV tx)-Annual | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of LFT (INF) -Annual | 6.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of U&E (non-IV tx)-Annual | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of U&E (INF)-Annual | 6.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of TP (non-IV tx)-Annual | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of TP (INF)- Annual | 6.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of SC (non-IV tx) - Annual | 4.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Number of SC (INF) -Annual | 6.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| Frequency of day care (SoC) – Annual | 5.00 | GAMMA | Intervention and comparator cost section 7.5.5 |
| ***Costs of monitoring*** | | | |
| Cost of complete blood count (£) | 3.01 | GAMMA | Section 7.5.5 and 7.5.6 |
| Cost of urea, creatinine and electrolytes test (£) | 1.25 | GAMMA | Section 7.5.5 and 7.5.6 |
| Cost of liver function test (£) | 1.25 | GAMMA | Section 7.5.5 and 7.5.6 |
| Cost of total protein test (£) | 1.25 | GAMMA | Section 7.5.5 and 7.5.6 |
| Cost of self-admin training (£) | 39.00 | GAMMA | Section 7.5.5 and 7.5.6 |
| Cost of physician visit for IV (£) | 92.39 | GAMMA | Section 7.5.5 and 7.5.6 |
| Cost of day centre care (£) | 460.00 | GAMMA | Section 7.5.5 and 7.5.6 |
| Cost of UVB phototherapy (£) | 91.00 | GAMMA | Section 7.5.5 and 7.5.6 |
| *Adverse Events* | | | |
| LOS of psoriasis hospitalisation | 10.70 | GAMMA | Hospital Episode Statistics (HES) , Primary diagnosis: 4 Character L40.0 Psoriasis Vulgaris |
| **Note:** CI and sampling of NMA parameters (i.e. treatment effects, PASI cut points) was derived from the CODA output of the NMA. Cut-off point 1: PASI 50; Cut-off point 2: PASI 75; Cut-off point 3: PASI 90; FBC: Full Blood Count; LFT: Liver Function Test; U&E: Urine and Electrolyte tests; TP: Total Protein; SC: Serum Creatinine; NBUVB: Narrowband Ultraviolet B; IV: Intravenous; tx: treatments; INF: Infliximab; NMSC: Non-Melanoma Skin Cancer | | | |

## 7.7 Results

### Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Outcomes from the four primary secukinumab RCTs (FIXTURE, ERASURE, JUNCTURE, and FEATURE) at 12 and 52 weeks (where reported) have been listed below. The base-case model results for these time points for secukinumab, etanercept (FIXTURE only), and placebo have also been reported for comparison. As the base-case does not use data elicited directly from the trial (i.e. the base-case uses the NMA conducted to align with decision problem and is inclusive of additional comparisons), the estimates were not expected to directly correlate to those listed below.

**Table 109. Summary of model results compared with clinical data**

| Outcome | Clinical trial result-FIXTURE (%) | Clinical trial result-ERASURE (%) | Clinical trial result-JUNCTURE (%) | Clinical trial result-FEATURE (%) | Model result (%) |
|---|---|---|---|---|---|
| Secukinumab, 12 weeks | | | | | |
| PASI < 50 | 8.36% | 9.39% | 12.07% | 3.33% | 7.31% |
| PASI 50-74 | 14.55% | 8.98% | 12.07% | 10.00% | 12.46% |
| PASI 75-89 | 22.91% | 22.45% | 15.52% | 31.67% | 24.82% |
| PASI 90+ | 54.18% | 59.18% | 60.34% | 55.00% | 55.41% |
| Etanercept, 12 weeks | | | | | |
| PASI < 50 | 30.03% | N/A | N/A | N/A | 39.13% |
| PASI 50-74 | 26.01% | N/A | N/A | N/A | 23.69% |
| PASI 75-89 | 23.22% | N/A | N/A | N/A | 22.29% |
| PASI 90+ | 20.74% | N/A | N/A | N/A | 14.89% |
| Placebo, 12 weeks | | | | | |
| PASI < 50 | 84.88% | 91.06% | 94.92% | 91.80% | 88.40% |
| PASI 50-74 | 10.19% | 4.47% | 5.08% | 4.92% | 8.00% |
| PASI 75-89 | 3.40% | 3.25% | 0.00% | 3.28% | 3.01% |
| PASI 90+ | 1.54% | 1.22% | 0.00% | 0.00% | 0.60% |
| Secukinumab, 52 weeks | | | | | |
| PASI < 50 | 15.17% | 15.51% | N/A | N/A | 7.31% |
| PASI 50-74 | 6.19% | 10.20% | N/A | N/A | 12.46% |
| PASI 75-89 | 13.62% | 14.29% | N/A | N/A | 24.82% |
| PASI 90+ | 65.02% | 60.00% | N/A | N/A | 55.41% |
| Etanercept, 52 weeks | | | | | |
| PASI < 50 | 27.55% | N/A | N/A | N/A | 39.13% |
| PASI 50-74 | 17.03% | N/A | N/A | N/A | 23.69% |
| PASI 75-89 | 21.98% | N/A | N/A | N/A | 22.29% |
| PASI 90+ | 33.44% | N/A | N/A | N/A | 14.89% |

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The tables below provide the detail of the proportion of the model cohort occupying each individual health state over the model's time horizon.

**Table 110. Markov Trace: Secukinumab 300 mg**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ | Death |
|---|---|---|---|---|---|
| Year 1 | 0.0731 | 0.1246 | 0.2482 | 0.5541 | 0.0000 |
| Year 2 | 0.4327 | 0.0000 | 0.1749 | 0.3903 | 0.0021 |
| Year 3 | 0.5448 | 0.0000 | 0.1395 | 0.3114 | 0.0042 |
| Year 4 | 0.6337 | 0.0000 | 0.1113 | 0.2484 | 0.0066 |
| Year 5 | 0.7040 | 0.0000 | 0.0887 | 0.1981 | 0.0092 |
| Year 6 | 0.7594 | 0.0000 | 0.0707 | 0.1579 | 0.0120 |
| Year 7 | 0.8028 | 0.0000 | 0.0564 | 0.1258 | 0.0150 |
| Year 8 | 0.8364 | 0.0000 | 0.0449 | 0.1002 | 0.0185 |
| Year 9 | 0.8622 | 0.0000 | 0.0358 | 0.0798 | 0.0222 |
| Year 10 | 0.8818 | 0.0000 | 0.0285 | 0.0635 | 0.0262 |

**Table 111. Markov Trace: SoC**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ | Death |
|---|---|---|---|---|---|
| Year 1 | 0.8840 | 0.0800 | 0.0301 | 0.0060 | 0.0000 |
| Year 2 | 0.9619 | 0.0000 | 0.0300 | 0.0060 | 0.0021 |
| Year 3 | 0.9598 | 0.0000 | 0.0300 | 0.0060 | 0.0042 |
| Year 4 | 0.9575 | 0.0000 | 0.0299 | 0.0060 | 0.0066 |
| Year 5 | 0.9551 | 0.0000 | 0.0298 | 0.0059 | 0.0092 |
| Year 6 | 0.9524 | 0.0000 | 0.0297 | 0.0059 | 0.0120 |
| Year 7 | 0.9494 | 0.0000 | 0.0296 | 0.0059 | 0.0150 |
| Year 8 | 0.9461 | 0.0000 | 0.0295 | 0.0059 | 0.0185 |
| Year 9 | 0.9425 | 0.0000 | 0.0294 | 0.0059 | 0.0222 |
| Year 10 | 0.9386 | 0.0000 | 0.0293 | 0.0058 | 0.0262 |

**Table 112. Markov Trace: Ustekinumab 45mg**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ | Death |
|---|---|---|---|---|---|
| Year 1 | 0.1301 | 0.1704 | 0.2753 | 0.4243 | 0.0000 |
| Year 2 | 0.5052 | 0.0000 | 0.1939 | 0.2989 | 0.0021 |
| Year 3 | 0.6026 | 0.0000 | 0.1547 | 0.2385 | 0.0042 |
| Year 4 | 0.6798 | 0.0000 | 0.1234 | 0.1902 | 0.0066 |
| Year 5 | 0.7408 | 0.0000 | 0.0984 | 0.1517 | 0.0092 |
| Year 6 | 0.7887 | 0.0000 | 0.0784 | 0.1209 | 0.0120 |
| Year 7 | 0.8261 | 0.0000 | 0.0625 | 0.0963 | 0.0150 |
| Year 8 | 0.8550 | 0.0000 | 0.0498 | 0.0767 | 0.0185 |
| Year 9 | 0.8770 | 0.0000 | 0.0396 | 0.0611 | 0.0222 |
| Year 10 | 0.8936 | 0.0000 | 0.0315 | 0.0486 | 0.0262 |

**Table 113. Markov Trace: Ustekinumab 90 mg**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ | Death |
|---|---|---|---|---|---|
| Year 1 | 0.1013 | 0.1498 | 0.2660 | 0.4829 | 0.0000 |
| Year 2 | 0.4704 | 0.0000 | 0.1874 | 0.3402 | 0.0021 |
| Year 3 | 0.5749 | 0.0000 | 0.1495 | 0.2714 | 0.0042 |
| Year 4 | 0.6577 | 0.0000 | 0.1193 | 0.2165 | 0.0066 |
| Year 5 | 0.7231 | 0.0000 | 0.0951 | 0.1726 | 0.0092 |
| Year 6 | 0.7746 | 0.0000 | 0.0758 | 0.1376 | 0.0120 |
| Year 7 | 0.8149 | 0.0000 | 0.0604 | 0.1097 | 0.0150 |
| Year 8 | 0.8461 | 0.0000 | 0.0481 | 0.0873 | 0.0185 |

| | | | | | |
|---|---|---|---|---|---|
| Year 9 | 0.8699 | 0.0000 | 0.0383 | 0.0695 | 0.0222 |
| Year 10 | 0.8879 | 0.0000 | 0.0305 | 0.0553 | 0.0262 |

**Table 114. Markov Trace: Adalimumab**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ | Death |
|---|---|---|---|---|---|
| Year 1 | 0.2342 | 0.2172 | 0.2716 | 0.2769 | 0.0000 |
| Year 2 | 0.6115 | 0.0000 | 0.1914 | 0.1951 | 0.0021 |
| Year 3 | 0.6875 | 0.0000 | 0.1527 | 0.1556 | 0.0042 |
| Year 4 | 0.7475 | 0.0000 | 0.1218 | 0.1241 | 0.0066 |
| Year 5 | 0.7947 | 0.0000 | 0.0971 | 0.0990 | 0.0092 |
| Year 6 | 0.8317 | 0.0000 | 0.0774 | 0.0789 | 0.0120 |
| Year 7 | 0.8604 | 0.0000 | 0.0617 | 0.0629 | 0.0150 |
| Year 8 | 0.8823 | 0.0000 | 0.0491 | 0.0501 | 0.0185 |
| Year 9 | 0.8988 | 0.0000 | 0.0391 | 0.0399 | 0.0222 |
| Year 10 | 0.9109 | 0.0000 | 0.0311 | 0.0317 | 0.0262 |

**Table 115. Markov Trace: Etanercept**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ | Death |
|---|---|---|---|---|---|
| Year 1 | 0.3913 | 0.2369 | 0.2229 | 0.1489 | 0.0000 |
| Year 2 | 0.7360 | 0.0000 | 0.1570 | 0.1049 | 0.0021 |
| Year 3 | 0.7868 | 0.0000 | 0.1253 | 0.0837 | 0.0042 |
| Year 4 | 0.8267 | 0.0000 | 0.0999 | 0.0668 | 0.0066 |
| Year 5 | 0.8579 | 0.0000 | 0.0797 | 0.0532 | 0.0092 |
| Year 6 | 0.8821 | 0.0000 | 0.0635 | 0.0424 | 0.0120 |
| Year 7 | 0.9005 | 0.0000 | 0.0506 | 0.0338 | 0.0150 |
| Year 8 | 0.9143 | 0.0000 | 0.0403 | 0.0269 | 0.0185 |
| Year 9 | 0.9242 | 0.0000 | 0.0321 | 0.0214 | 0.0222 |
| Year 10 | 0.9311 | 0.0000 | 0.0255 | 0.0171 | 0.0262 |

**Table 116. Markov Trace: Infliximab**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ | Death |
|---|---|---|---|---|---|
| Year 1 | 0.0766 | 0.1280 | 0.2511 | 0.5442 | 0.0000 |
| Year 2 | 0.4377 | 0.0000 | 0.1769 | 0.3834 | 0.0021 |
| Year 3 | 0.5488 | 0.0000 | 0.1411 | 0.3059 | 0.0042 |
| Year 4 | 0.6369 | 0.0000 | 0.1126 | 0.2440 | 0.0066 |
| Year 5 | 0.7065 | 0.0000 | 0.0898 | 0.1945 | 0.0092 |
| Year 6 | 0.7614 | 0.0000 | 0.0716 | 0.1551 | 0.0120 |
| Year 7 | 0.8043 | 0.0000 | 0.0570 | 0.1236 | 0.0150 |
| Year 8 | 0.8377 | 0.0000 | 0.0454 | 0.0984 | 0.0185 |
| Year 9 | 0.8633 | 0.0000 | 0.0362 | 0.0784 | 0.0222 |
| Year 10 | 0.8826 | 0.0000 | 0.0288 | 0.0624 | 0.0262 |

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The tables below show the cumulative discounted QALYs for the treatments included in the model using the base case assumptions. A similar presentation has been

provided to the Markov traces above, where cumulative QALYs are shown for the end of the decision tree (year 1) and the annual cycles (year 2-10).

**Table 117. QALY Trace: Secukinumab 300 mg**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ |
|---|---|---|---|---|
| Year 1 | 0.0080 | 0.0241 | 0.0561 | 0.1463 |
| Year 2 | 0.0456 | 0.0000 | 0.0382 | 0.0996 |
| Year 3 | 0.0555 | 0.0000 | 0.0294 | 0.0768 |
| Year 4 | 0.0623 | 0.0000 | 0.0227 | 0.0592 |
| Year 5 | 0.0669 | 0.0000 | 0.0175 | 0.0456 |
| Year 6 | 0.0697 | 0.0000 | 0.0135 | 0.0351 |
| Year 7 | 0.0712 | 0.0000 | 0.0104 | 0.0270 |
| Year 8 | 0.0717 | 0.0000 | 0.0080 | 0.0208 |
| Year 9 | 0.0714 | 0.0000 | 0.0061 | 0.0160 |
| Year 10 | 0.0706 | 0.0000 | 0.0047 | 0.0123 |

**Table 118. QALY Trace: SoC**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ |
|---|---|---|---|---|
| Year 1 | 0.0964 | 0.0154 | 0.0068 | 0.0016 |
| Year 2 | 0.1014 | 0.0000 | 0.0066 | 0.0015 |
| Year 3 | 0.0977 | 0.0000 | 0.0063 | 0.0015 |
| Year 4 | 0.0942 | 0.0000 | 0.0061 | 0.0014 |
| Year 5 | 0.0908 | 0.0000 | 0.0059 | 0.0014 |
| Year 6 | 0.0875 | 0.0000 | 0.0057 | 0.0013 |
| Year 7 | 0.0842 | 0.0000 | 0.0054 | 0.0013 |
| Year 8 | 0.0811 | 0.0000 | 0.0052 | 0.0012 |
| Year 9 | 0.0781 | 0.0000 | 0.0050 | 0.0012 |
| Year 10 | 0.0751 | 0.0000 | 0.0049 | 0.0011 |

**Table 119. QALY Trace: Ustekinumab 45mg**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ |
|---|---|---|---|---|
| Year 1 | 0.0142 | 0.0329 | 0.0622 | 0.1120 |
| Year 2 | 0.0532 | 0.0000 | 0.0423 | 0.0763 |
| Year 3 | 0.0614 | 0.0000 | 0.0326 | 0.0588 |
| Year 4 | 0.0669 | 0.0000 | 0.0251 | 0.0453 |
| Year 5 | 0.0704 | 0.0000 | 0.0194 | 0.0349 |
| Year 6 | 0.0724 | 0.0000 | 0.0149 | 0.0269 |
| Year 7 | 0.0733 | 0.0000 | 0.0115 | 0.0207 |
| Year 8 | 0.0733 | 0.0000 | 0.0088 | 0.0159 |
| Year 9 | 0.0726 | 0.0000 | 0.0068 | 0.0123 |
| Year 10 | 0.0715 | 0.0000 | 0.0052 | 0.0094 |

**Table 120. QALY Trace: Ustekinumab 90 mg**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ |
|---|---|---|---|---|
| Year 1 | 0.0111 | 0.0289 | 0.0601 | 0.1275 |
| Year 2 | 0.0496 | 0.0000 | 0.0409 | 0.0868 |
| Year 3 | 0.0585 | 0.0000 | 0.0315 | 0.0669 |
| Year 4 | 0.0647 | 0.0000 | 0.0243 | 0.0516 |
| Year 5 | 0.0687 | 0.0000 | 0.0187 | 0.0397 |

| | | | | |
|---|---|---|---|---|
| Year 6 | 0.0711 | 0.0000 | 0.0144 | 0.0306 |
| Year 7 | 0.0723 | 0.0000 | 0.0111 | 0.0236 |
| Year 8 | 0.0725 | 0.0000 | 0.0085 | 0.0181 |
| Year 9 | 0.0721 | 0.0000 | 0.0066 | 0.0139 |
| Year 10 | 0.0711 | 0.0000 | 0.0051 | 0.0107 |

**Table 121. QALY Trace: Adalimumab**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ |
|---|---|---|---|---|
| Year 1 | 0.0255 | 0.0420 | 0.0613 | 0.0731 |
| Year 2 | 0.0644 | 0.0000 | 0.0417 | 0.0498 |
| Year 3 | 0.0700 | 0.0000 | 0.0322 | 0.0384 |
| Year 4 | 0.0735 | 0.0000 | 0.0248 | 0.0296 |
| Year 5 | 0.0755 | 0.0000 | 0.0191 | 0.0228 |
| Year 6 | 0.0764 | 0.0000 | 0.0147 | 0.0175 |
| Year 7 | 0.0763 | 0.0000 | 0.0113 | 0.0135 |
| Year 8 | 0.0756 | 0.0000 | 0.0087 | 0.0104 |
| Year 9 | 0.0744 | 0.0000 | 0.0067 | 0.0080 |
| Year 10 | 0.0729 | 0.0000 | 0.0052 | 0.0062 |

**Table 122. QALY Trace: Etanercept**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ |
|---|---|---|---|---|
| Year 1 | 0.0427 | 0.0458 | 0.0503 | 0.0393 |
| Year 2 | 0.0776 | 0.0000 | 0.0343 | 0.0268 |
| Year 3 | 0.0801 | 0.0000 | 0.0264 | 0.0206 |
| Year 4 | 0.0813 | 0.0000 | 0.0204 | 0.0159 |
| Year 5 | 0.0815 | 0.0000 | 0.0157 | 0.0123 |
| Year 6 | 0.0810 | 0.0000 | 0.0121 | 0.0094 |
| Year 7 | 0.0799 | 0.0000 | 0.0093 | 0.0073 |
| Year 8 | 0.0784 | 0.0000 | 0.0072 | 0.0056 |
| Year 9 | 0.0766 | 0.0000 | 0.0055 | 0.0043 |
| Year 10 | 0.0745 | 0.0000 | 0.0042 | 0.0033 |

**Table 123. QALY Trace: Infliximab**

| Year | PASI < 50 | PASI 50-74 | PASI 75-89 | PASI-90+ |
|---|---|---|---|---|
| Year 1 | 0.0084 | 0.0247 | 0.0567 | 0.1437 |
| Year 2 | 0.0461 | 0.0000 | 0.0386 | 0.0978 |
| Year 3 | 0.0559 | 0.0000 | 0.0298 | 0.0754 |
| Year 4 | 0.0626 | 0.0000 | 0.0229 | 0.0581 |
| Year 5 | 0.0672 | 0.0000 | 0.0177 | 0.0448 |
| Year 6 | 0.0699 | 0.0000 | 0.0136 | 0.0345 |
| Year 7 | 0.0714 | 0.0000 | 0.0105 | 0.0265 |
| Year 8 | 0.0718 | 0.0000 | 0.0081 | 0.0204 |
| Year 9 | 0.0715 | 0.0000 | 0.0062 | 0.0157 |
| Year 10 | 0.0706 | 0.0000 | 0.0048 | 0.0121 |

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table 124 below reports discounted life years (LY) and discounted QALYs accrued for each model HS for the treatments presented in the model. Costs associated with each model health state are also presented. Results are presented for the base-case analysis.

**Table 124. Model outputs by clinical outcomes**

| Secukinumab | LY | QALY | Cost |
|---|---|---|---|
| PASI < 50 | 5.44 | 0.5929 | [redacted] |
| PASI 50-74 | 0.12 | 0.0241 | [redacted] |
| PASI 75-89 | 0.91 | 0.2064 | [redacted] |
| PASI 90+ | 2.04 | 0.5387 | [redacted] |
| Death | 0.00 | 0.0000 | [redacted] |
| Placebo | | | |
| PASI < 50 | 8.13 | 0.8865 | £70,194.49 |
| PASI 50-74 | 0.08 | 0.0154 | £763.37 |
| PASI 75-89 | 0.26 | 0.0578 | £2,210.73 |
| PASI 90+ | 0.05 | 0.0135 | £441.06 |
| Death | 0.00 | 0.0000 | £0.00 |
| Ustekinumab 45mg | | | |
| PASI < 50 | 5.77 | 0.6292 | £49,554.65 |
| PASI 50-74 | 0.17 | 0.0329 | £2,182.70 |
| PASI 75-89 | 1.01 | 0.2288 | £10,941.43 |
| PASI 90+ | 1.56 | 0.4125 | £16,864.81 |
| Death | 0.00 | 0.0000 | £0.00 |
| Ustekinumab 90 mg | | | |
| PASI < 50 | 5.61 | 0.6117 | £48,044.37 |
| PASI 50-74 | 0.15 | 0.0289 | £1,918.51 |
| PASI 75-89 | 0.98 | 0.2212 | £10,575.28 |
| PASI 90+ | 1.78 | 0.4694 | £19,193.74 |
| Death | 0.00 | 0.0000 | £0.00 |
| Adalimumab 40 mg | | | |
| PASI < 50 | 6.28 | 0.6847 | £54,141.51 |
| PASI 50-74 | 0.22 | 0.0420 | £2,561.11 |
| PASI 75-89 | 1.00 | 0.2258 | £10,041.39 |
| PASI 90+ | 1.02 | 0.2692 | £10,237.32 |
| Death | 0.00 | 0.0000 | £0.00 |
| Etanercept 25mg | | | |
| PASI < 50 | 6.91 | 0.7536 | £59,638.10 |
| PASI 50-74 | 0.24 | 0.0458 | £2,525.29 |
| PASI 75-89 | 0.82 | 0.1853 | £8,167.19 |
| PASI 90+ | 0.55 | 0.1448 | £5,457.26 |
| Death | 0.00 | 0.0000 | £0.00 |
| Infliximab 5mg/kg IV | | | |
| PASI < 50 | 5.46 | 0.5954 | £46,805.79 |
| PASI 50-74 | 0.13 | 0.0247 | £1,892.86 |

| | | | |
|---|---|---|---|
| PASI 75-89 | 0.92 | 0.2088 | £14,158.33 |
| PASI 90+ | 2.00 | 0.5291 | £30,681.64 |
| Death | 0.00 | 0.0000 | £0.00 |

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Disaggregated discounted costs and QALYs are reported by health state in the tables below.

**Table 125. Summary of QALY gain by health state**

| | Secukinumab | SoC | Increment | Absolute Increment | % absolute increment |
|---|---|---|---|---|---|
| PASI < 50 | 0.59 | 0.89 | -0.29 | -0.29 | -75.49% |
| PASI 50-74 | 0.02 | 0.02 | 0.01 | 0.01 | 2.22% |
| PASI 75-89 | 0.21 | 0.06 | 0.15 | 0.15 | 38.20% |
| PASI 90+ | 0.54 | 0.01 | 0.53 | 0.53 | 135.07% |
| Death | 0.00 | 0.00 | 0.00 | 0.00 | 0.00% |
| Total | 1.36 | 0.97 | 0.39 | 0.39 | 100.00% |
| | Secukinumab | Ustekinumab 45mg | Increment | Absolute Increment | % absolute increment |
| PASI < 50 | 0.59 | 0.63 | -0.04 | -0.04 | -61.89% |
| PASI 50-74 | 0.02 | 0.03 | -0.01 | -0.01 | -15.11% |
| PASI 75-89 | 0.21 | 0.23 | -0.02 | -0.02 | -38.29% |
| PASI 90+ | 0.54 | 0.41 | 0.13 | 0.13 | 215.28% |
| Death | 0.00 | 0.00 | 0.00 | 0.00 | 0.00% |
| Total | 1.36 | 1.30 | 0.06 | 0.06 | 100.00% |
| | Secukinumab | Ustekinumab 90 mg | Increment | Absolute Increment | % absolute increment |
| PASI < 50 | 0.59 | 0.61 | -0.02 | -0.02 | -0.61 |
| PASI 50-74 | 0.02 | 0.03 | 0.00 | 0.00 | -0.16 |
| PASI 75-89 | 0.21 | 0.22 | -0.01 | -0.01 | -0.48 |
| PASI 90+ | 0.54 | 0.47 | 0.07 | 0.07 | 2.24 |
| Death | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Total | 1.36 | 1.33 | 0.03 | 0.03 | 1.00 |
| | Secukinumab | Adalimumab | Increment | Absolute Increment | % absolute increment |
| PASI < 50 | 0.59 | 0.68 | -0.09 | -0.09 | -65.41% |
| PASI 50-74 | 0.02 | 0.04 | -0.02 | -0.02 | -12.76% |
| PASI 75-89 | 0.21 | 0.23 | -0.02 | -0.02 | -13.85% |
| PASI 90+ | 0.54 | 0.27 | 0.27 | 0.27 | 192.02% |
| Death | 0.00 | 0.00 | 0.00 | 0.00 | 0.00% |
| Total | 1.36 | 1.22 | 0.14 | 0.14 | 100.00% |
| | Secukinumab | Etanercept | Increment | Absolute Increment | % absolute increment |
| PASI < 50 | 0.59 | 0.75 | -0.16 | -0.16 | -69.03% |
| PASI 50-74 | 0.02 | 0.05 | -0.02 | -0.02 | -9.33% |
| PASI 75-89 | 0.21 | 0.19 | 0.02 | 0.02 | 9.06% |

| | | | | | |
|---|---|---|---|---|---|
| PASI 90+ | 0.54 | 0.14 | 0.39 | 0.39 | 169.30% |
| Death | 0.00 | 0.00 | 0.00 | 0.00 | 0.00% |
| Total | 1.36 | 1.13 | 0.23 | 0.23 | 100.00% |
| | Secukinumab | Infliximab | Increment | Absolute Increment | % absolute increment |
| PASI < 50 | 0.59 | 0.60 | 0.00 | 0.00 | -59.22% |
| PASI 50-74 | 0.02 | 0.02 | 0.00 | 0.00 | -16.36% |
| PASI 75-89 | 0.21 | 0.21 | 0.00 | 0.00 | -58.00% |
| PASI 90+ | 0.54 | 0.53 | 0.01 | 0.01 | 233.58% |
| Death | 0.00 | 0.00 | 0.00 | 0.00 | 0.00% |
| Total | 1.36 | 1.36 | 0.00 | 0.00 | 100.00% |

### Table 126. Summary of costs by health state

| | Secukinumab | SoC | Increment | Absolute Increment | % absolute increment |
|---|---|---|---|---|---|
| PASI < 50 | £46,434.10 | £70,194.49 | -£23,760.38 | -£23,760.38 | -863.52% |
| PASI 50-74 | £1,573.81 | £763.37 | £810.44 | £810.44 | 29.45% |
| PASI 75-89 | £8,772.69 | £2,210.73 | £6,561.96 | £6,561.96 | 238.48% |
| PASI 90+ | £19,580.63 | £441.06 | £19,139.57 | £19,139.57 | 695.58% |
| Death | £0.00 | £0.00 | £0.00 | £0.00 | 0.00% |
| Total | £76,361.23 | £73,609.65 | £2,751.58 | £2,751.58 | 100.00% |
| | | | | | |
| | Secukinumab | Ustekinumab 45mg | Increment | Absolute Increment | % absolute increment |
| PASI < 50 | £46,434.10 | £49,554.65 | -£3,120.55 | -£3,120.55 | 98.06% |
| PASI 50-74 | £1,573.81 | £2,182.70 | -£608.89 | -£608.89 | 19.13% |
| PASI 75-89 | £8,772.69 | £10,941.43 | -£2,168.74 | -£2,168.74 | 68.15% |
| PASI 90+ | £19,580.63 | £16,864.81 | £2,715.82 | £2,715.82 | -85.34% |
| Death | £0.00 | £0.00 | £0.00 | £0.00 | 0.00% |
| Total | £76,361.23 | £79,543.59 | -£3,182.36 | -£3,182.36 | 100.00% |
| | | | | | |
| | Secukinumab | Ustekinumab 90 mg | Increment | Absolute Increment | % absolute increment |
| PASI < 50 | £46,434.10 | £48,044.37 | -£1,610.27 | -£1,610.27 | 47.77% |
| PASI 50-74 | £1,573.81 | £1,918.51 | -£344.69 | -£344.69 | 10.23% |
| PASI 75-89 | £8,772.69 | £10,575.28 | -£1,802.59 | -£1,802.59 | 53.48% |
| PASI 90+ | £19,580.63 | £19,193.74 | £386.89 | £386.89 | -11.48% |
| Death | £0.00 | £0.00 | £0.00 | £0.00 | 0.00% |
| Total | £76,361.23 | £79,731.90 | -£3,370.66 | -£3,370.66 | 100.00% |
| | | | | | |
| | Secukinumab | Adalimumab 40 mg | Increment | Absolute Increment | % absolute increment |
| PASI < 50 | £46,434.10 | £54,141.51 | -£7,707.41 | -£7,707.41 | 1242.93% |
| PASI 50-74 | £1,573.81 | £2,561.11 | -£987.30 | -£987.30 | 159.22% |
| PASI 75-89 | £8,772.69 | £10,041.39 | -£1,268.70 | -£1,268.70 | 204.60% |
| PASI 90+ | £19,580.63 | £10,237.32 | £9,343.31 | £9,343.31 | -1506.74% |
| Death | £0.00 | £0.00 | £0.00 | £0.00 | 0.00% |
| Total | £76,361.23 | £76,981.34 | -£620.10 | -£620.10 | 100.00% |
| | | | | | |
| | Secukinumab | Etanercept 25mg | Increment | Absolute Increment | % absolute increment |
| PASI < 50 | £46,434.10 | £59,638.10 | -£13,204.00 | -£13,204.00 | -2302.75% |
| PASI 50-74 | £1,573.81 | £2,525.29 | -£951.47 | -£951.47 | -165.93% |

| | | | | | |
|---|---|---|---|---|---|
| PASI 75-89 | £8,772.69 | £8,167.19 | £605.50 | £605.50 | 105.60% |
| PASI 90+ | £19,580.63 | £5,457.26 | £14,123.37 | £14,123.37 | 2463.09% |
| Death | £0.00 | £0.00 | £0.00 | £0.00 | 0.00% |
| Total | £76,361.23 | £75,787.83 | £573.40 | £573.40 | 100.00% |
| | | | | | |
| | Secukinumab | Infliximab 5mg/kg IV | Increment | Absolute Increment | % absolute increment |
| PASI < 50 | £46,434.10 | £46,805.79 | -£371.69 | -£371.69 | 2.16% |
| PASI 50-74 | £1,573.81 | £1,892.86 | -£319.05 | -£319.05 | 1.86% |
| PASI 75-89 | £8,772.69 | £14,158.33 | -£5,385.64 | -£5,385.64 | 31.35% |
| PASI 90+ | £19,580.63 | £30,681.64 | -£11,101.01 | -£11,101.01 | 64.63% |
| Death | £0.00 | £0.00 | £0.00 | £0.00 | 0.00% |
| Total | £76,361.23 | £93,538.61 | -£17,177.38 | -£17,177.38 | 100.00% |

**Table 127. Summary of predicted resource use by category of cost**

| | Secukinumab | SoC | Increment | Absolute Increment | % absolute increment |
|---|---|---|---|---|---|
| Treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Medical | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SAEs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | £76,361.23 | £73,609.65 | £2,751.58 | £2,751.58 | 100.00% |
| | | | | | |
| | Secukinumab | Ustekinumab 45mg | Increment | Absolute Increment | % absolute increment |
| Treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Medical | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SAEs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | £76,361.23 | £79,543.59 | -£3,182.36 | -£3,182.36 | 100.00% |
| | | | | | |
| | Secukinumab | Ustekinumab 90 mg | Increment | Absolute Increment | % absolute increment |
| Treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Medical | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SAEs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | £76,361.23 | £79,731.90 | -£3,370.66 | -£3,370.66 | 100.00% |
| | | | | | |
| | Secukinumab | Adalimumab 40 mg | Increment | Absolute Increment | % absolute increment |
| Treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Medical | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SAEs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | £76,361.23 | £76,981.34 | -£620.10 | -£620.10 | 100.00% |
| | | | | | |
| | Secukinumab | Etanercept 25mg | Increment | Absolute Increment | % absolute increment |
| Treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Medical | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SAEs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | £76,361.23 | £75,787.83 | £573.40 | £573.40 | 100.00% |
| | | | | | |
| | Secukinumab | Infliximab 5mg/kg IV | Increment | Absolute Increment | % absolute increment |
| Treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Medical | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SAEs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | £76,361.23 | £93,538.61 | -£17,177.38 | -£17,177.38 | 100.00% |

## Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The results of the base-case analysis showed that compared with SoC, secukinumab was associated with gains in QALYs (incremental QALYs: 0.39) and costs (incremental costs: £2,752). Compared to SoC, secukinumab was a cost-effective option in treating moderate to severe plaque psoriasis (ICER: £7,076 per QALY).

The results of the base-case also showed that when compared to other biologic treatments, secukinumab was dominant versus adalimumab, ustekinumab 45 mg, ustekinumab 90 mg and infliximab. Compared to etanercept, secukinumab was associated with gains in QALYs (incremental QALYs: 0.23) and costs (incremental costs:) resulting in an ICER of £2,464 per QALY.

**Table 128. Base-case results**

| | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) | ICER (£) SEC300 vs. comparator |
|---|---|---|---|---|---|---|---|
| **SoC** | £73,610 | 0.97 | | | | | £7,076 |
| **Etanercept 25mg tw** | £75,788 | 1.13 | £2,178 | 0.16 | £13,948 | £13,948* | £2,464 |
| **Secukinumab 300 mg** | £76,361 | 1.36 | £2,752 | 0.39 | £7,076 | £2,464 | |
| **Adalimumab 40 mg** | £76,981 | 1.22 | £3,372 | 0.25 | £13,568 | DOMINATED | DOMINANT |
| **Ustekinumab 45 mg** | £79,544 | 1.30 | £5,934 | 0.33 | £17,971 | DOMINATED | DOMINANT |
| **Ustekinumab 90 mg** | £79,732 | 1.33 | £6,122 | 0.36 | £17,104 | DOMINATED | DOMINANT |
| **Infliximab 5mg/kg** | £93,539 | 1.36 | £19,929 | 0.38 | £51,802 | DOMINATED | DOMINANT |

***Etanercept 25mg tw is extendedly dominated by Secukinumab 300mg**

It is important to note that life years were not presented in Table 128 as the life years across all treatments were the same (9.88 LY). These results were based on the treatment effects calculated in the NICE endpoints NMA detailed in section 6.7.6.

## Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Deterministic sensitivity analyses were performed by means of one-way sensitivity analyses, where one parameter was varied relative to its base case value. The method adopted and the parameters tested were described in Section 7.6.2.
A summary of the results is presented in Table 129 below using NMBs and ICERs.

Overall, there were 208 sensitivity analyses conducted for the base-case analysis. A tornado plot for the top 15 most sensitive parameters based on the ICER measure at a willingness-to-pay (WTP) of £20,000 per QALY was used to illustrate the results of the analyses.

## Table 129. OWSA Summary Table

| Secukinumab versus | Values for OWSA variation | | SoC | | UST 45 | | UST 90 | | ADA | | ETAN | | INFL | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter varied** | **Low Variation** | **High Variation** | **NMB with lower variation** | **NMB with upper variation** | **NMB with lower variation** | **NMB with upper variation** | **NMB with lower variation** | **NMB with upper variation** | **NMB with lower variation** | **NMB with upper variation** | **NMB with lower variation** | **NMB with upper variation** | **NMB with lower variation** | **NMB with upper variation** |
| ***Base case NMB*** | | | 8,913.48 | | 4,941.29 | | 4,297.31 | | 4,830.22 | | 6,406.65 | | 17,300.97 | |
| Acquisition cost | 20 % less than list price | 20 % more than list price | - | - | -468.53 | 10,351.11 | -1,433.76 | 10,028.38 | 854.82 | 8,805.61 | 3,654.49 | 9,158.81 | 9,110.67 | 25,491.28 |
| Discount Rate for costs | 0% | 5% | 8,876.95 | 8,926.90 | 5,174.74 | 4,854.77 | 4,552.52 | 4,202.77 | 4,990.70 | 4,770.61 | 6,510.35 | 6,367.94 | 18,892.25 | 16,711.73 |
| Discount Rate for outcomes | 0% | 5% | 9,910.90 | 8,542.11 | 5,115.63 | 4,876.74 | 4,389.41 | 4,263.21 | 5,243.50 | 4,677.18 | 7,082.15 | 6,156.52 | 17,313.29 | 17,296.41 |
| Length of stay for a hospitalisation (days) | 8.56 | 12.84 | 5,899.30 | 11,927.66 | 4,550.07 | 5,332.51 | 4,093.95 | 4,500.66 | 3,864.62 | 5,795.81 | 4,768.69 | 8,044.61 | 17,274.25 | 17,327.70 |
| Day Centre Care Days (annual) | 4 | 6 | 7,923.80 | 9,903.16 | 4,814.46 | 5,068.12 | 4,231.38 | 4,363.24 | 4,517.17 | 5,143.26 | 5,875.63 | 6,937.67 | 17,292.31 | 17,309.64 |
| Annual Discontinuation | 5% | 43% | 17,415.59 | 3,677.21 | 8,086.80 | 3,021.78 | 6,977.72 | 2,664.74 | 9,251.40 | 2,122.24 | 12,407.10 | 2,723.51 | 29,687.07 | 9,778.87 |
| **Secukinumab versus** | **Values for OWSA variation** | | **SoC** | | **UST 45** | | **UST 90** | | **ADA** | | **ETAN** | | **INFL** | |
| **Parameter varied** | **Low Variation** | **High Variation** | **ICER with lower variation** | **ICER with upper variation** | **ICER with lower variation** | **ICER with upper variation** | **ICER with lower variation** | **ICER with upper variation** | **ICER with lower variation** | **ICER with upper variation** | **ICER with lower variation** | **ICER with upper variation** | **ICER with lower variation** | **ICER with upper variation** |
| ***Base case ICER*** | | | 7,076.47 | | Dominant | | Dominant | | Dominant | | 2,464.45 | | Dominant | |
| Acquisition cost | 20 % less than list price | 20 % more than list price | - | - | 37,991.15 | Dominant | 76,417.65 | Dominant | 23,908.78 | Dominant | 14,293.13 | Dominant | Dominant | Dominant |
| Discount Rate for costs | 0% | 5% | 7,170.41 | 7,041.95 | Dominant | Dominant | Dominant | Dominant | Dominant | Dominant | 2,018.77 | 2,630.81 | Dominant | Dominant |
| Discount Rate for outcomes | 0% | 5% | 6,519.06 | 7,309.17 | Dominant | Dominant | Dominant | Dominant | Dominant | Dominant | 2,247.00 | 2,556.05 | Dominant | Dominant |
| Length of stay for a hospitalisation (days) | 8.56 | 12.84 | 14,828.28 | Dominant | Dominant | Dominant | Dominant | Dominant | 2,461.90 | Dominant | 9,504.35 | Dominant | Dominant | Dominant |
| Day Centre Care Days (annual) | 4 | 6 | 9,621.71 | 4,531.24 | Dominant | Dominant | Dominant | Dominant | Dominant | Dominant | 4,746.77 | 182.13 | Dominant | Dominant |
| Annual Discontinuation | 5% | 43% | 4,855.78 | 12,006.00 | Dominant | Dominant | Dominant | Dominant | Dominant | 1,972.60 | Dominant | 8,564.21 | Dominant | Dominant |

The tornado diagrams below show the variation in base-case model results from OWSA (secukinumab versus comparator). For the comparisons in which secukinumab 300 mg does not dominate the comparator (i.e. vs. SoC and etanercept), ICER-based tornado diagrams are presented. For the remaining comparisons in which secukinumab 300 mg dominates the comparator, NMB-based diagrams are presented.

No two comparisons showed identical rankings of key drivers of the cost-effectiveness. However, 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 (LOS) associated with hospitalisation, and the relative treatment effects.

**Figure 31. OWSA Results: Secukinumab v SoC, ICER**

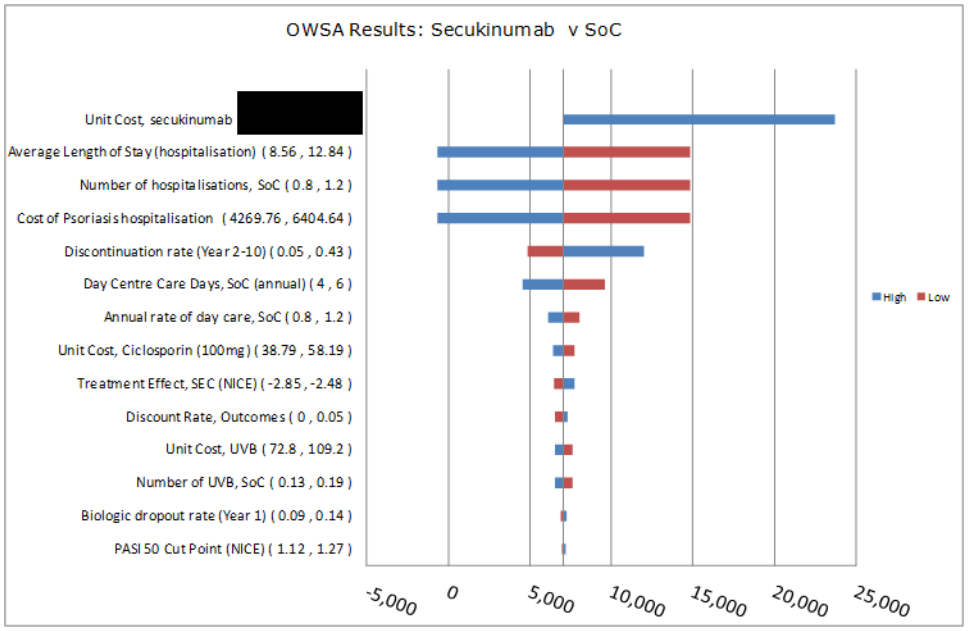


**Figure 32. OWSA Results: Secukinumab v Ustekinumab 45mg, NMB**

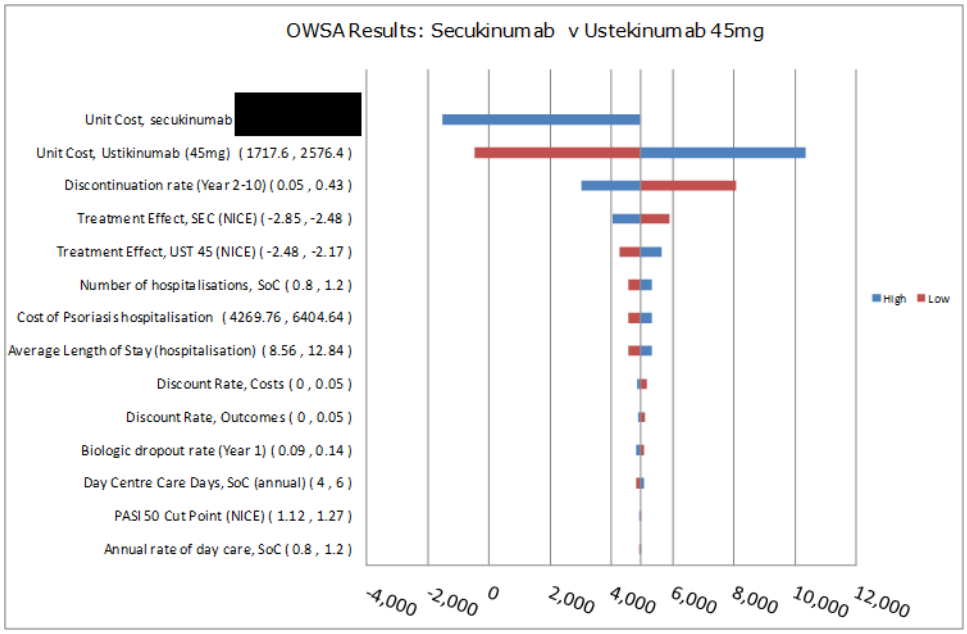



**Figure 33. OWSA Results: Secukinumab v Ustekinumab 90mg, NMB**

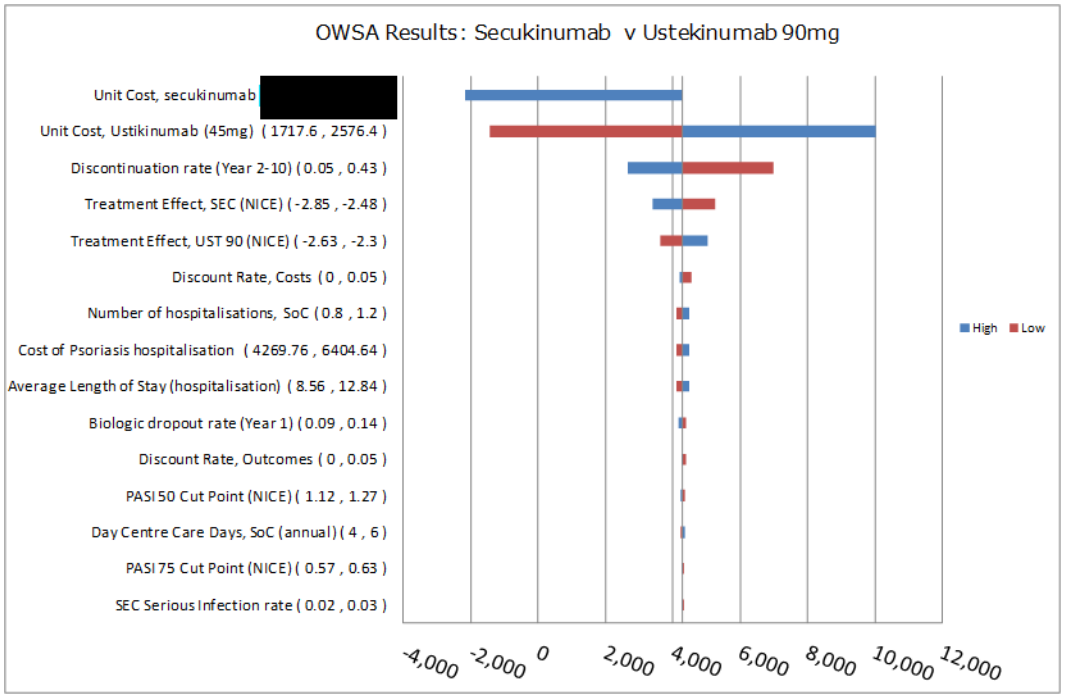


**Figure 34. OWSA Results: Secukinumab v Adalimumab, NMB**

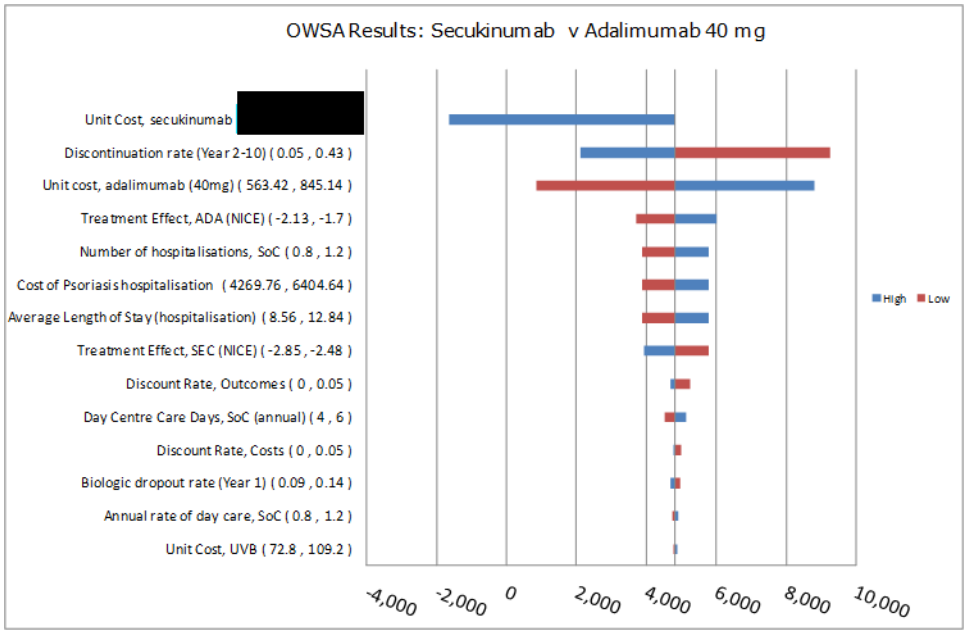



**Figure 35. OWSA Results: Secukinumab v Etanercept, ICER**

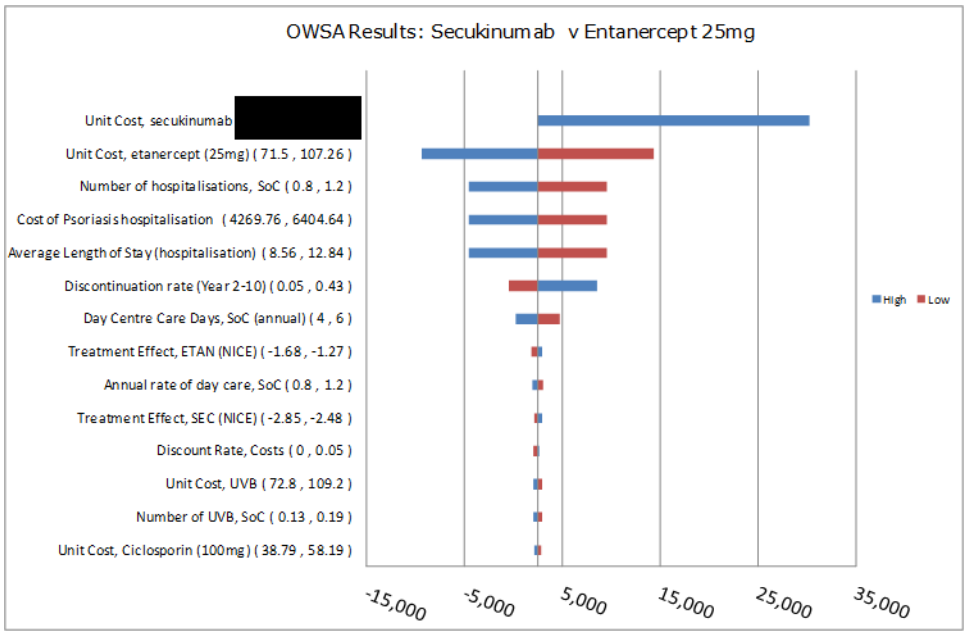
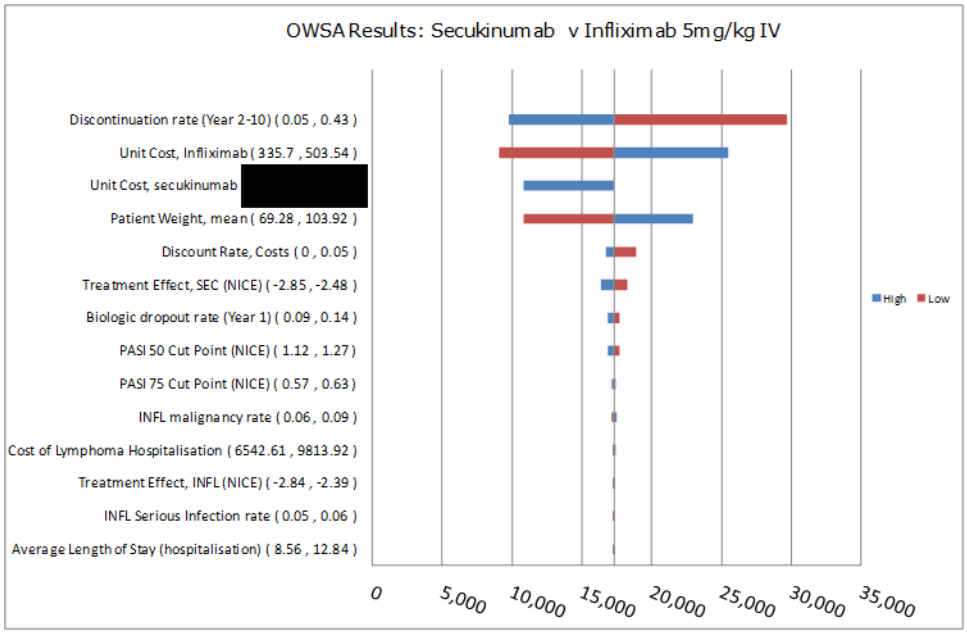


**Figure 36. OWSA Results: Secukinumab v Infliximab, NMB**




7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The probabilistic sensitivity analysis (PSA) was run with 5,000 simulations. PSA outputs are represented graphically by plotting incremental cost and effectiveness pairs on the cost-effectiveness plane and presenting the likelihood of secukinumab being cost-effective at a range of willingness-to-pay (WTP) thresholds.

The results of the PSA graphed as scatter plots are presented in the figures below. The ellipses on the scatterplots represent the 95% and 99% CIs.

**Figure 37. Scatterplot for secukinumab vs. SoC**

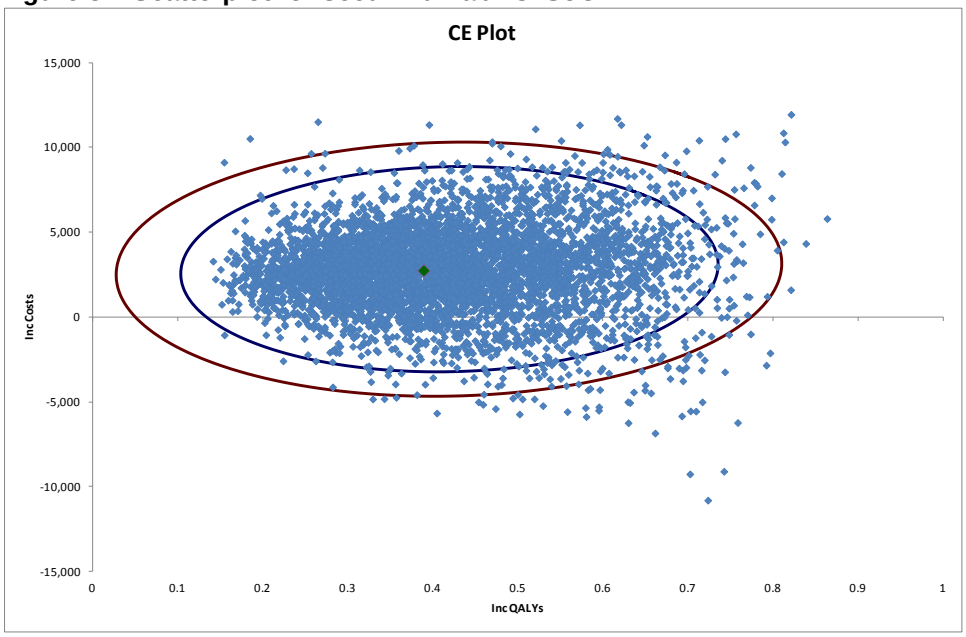



**Figure 38. Scatterplot for secukinumab vs. ustekinumab 45 mg**

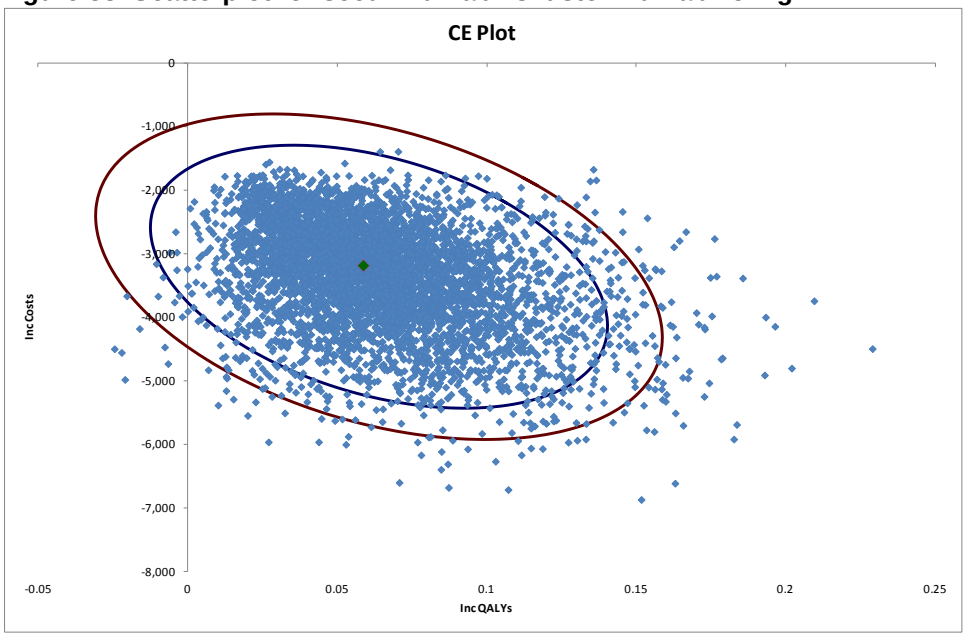


**Figure 39. Scatterplot for secukinumab vs. ustekinumab 90 mg**

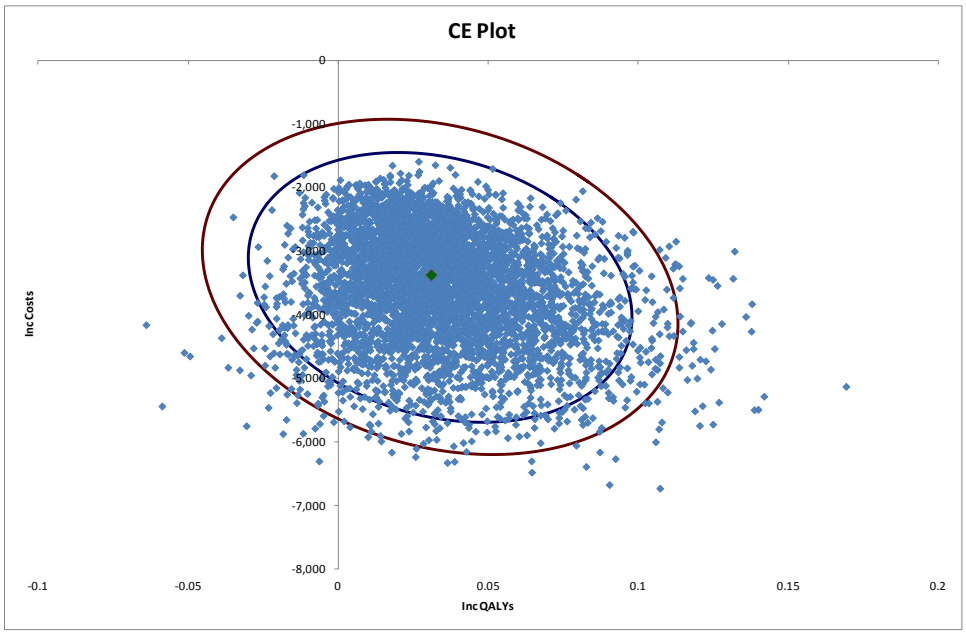



**Figure 40. Scatterplot for secukinumab vs. adalimumab**

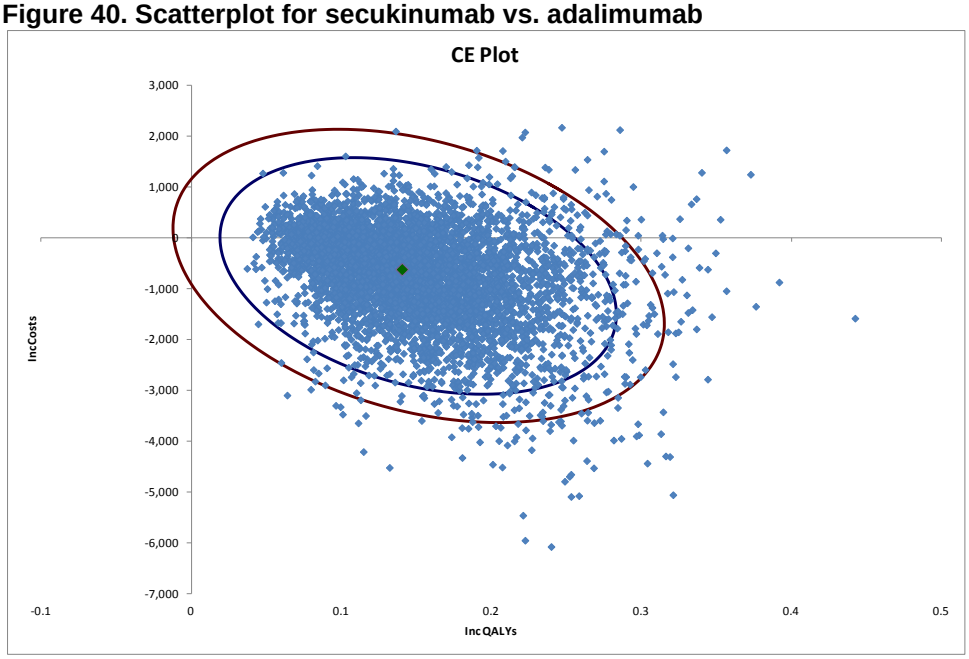


**Figure 41. Scatterplot for secukinumab vs. etanercept**

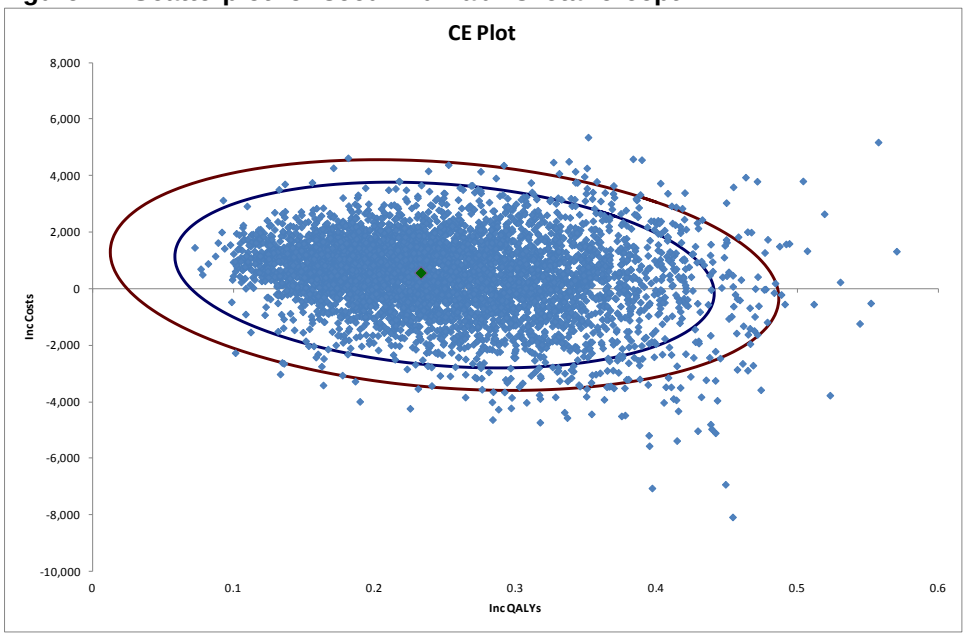
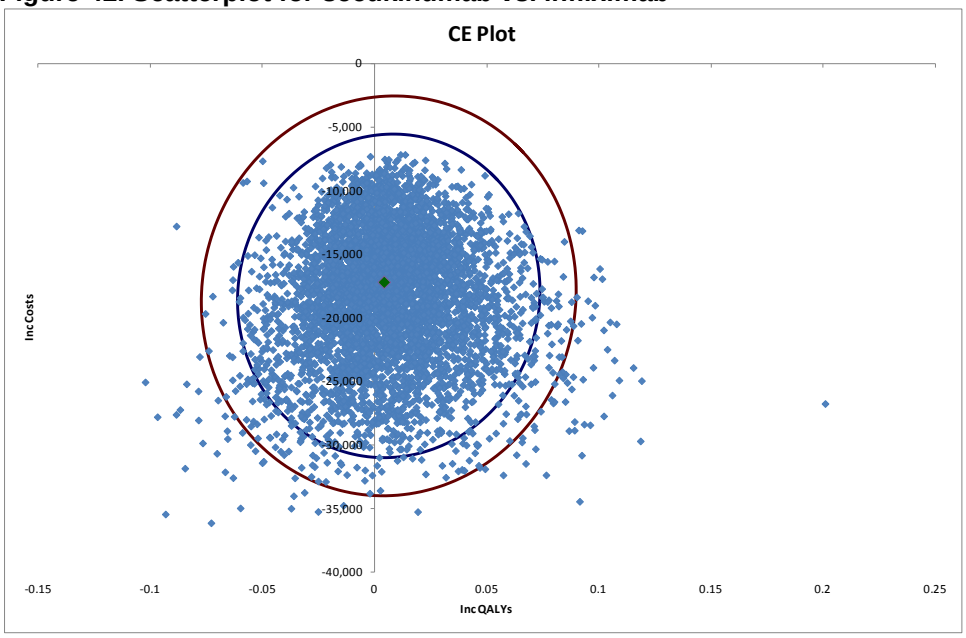



**Figure 42. Scatterplot for secukinumab vs. infliximab**



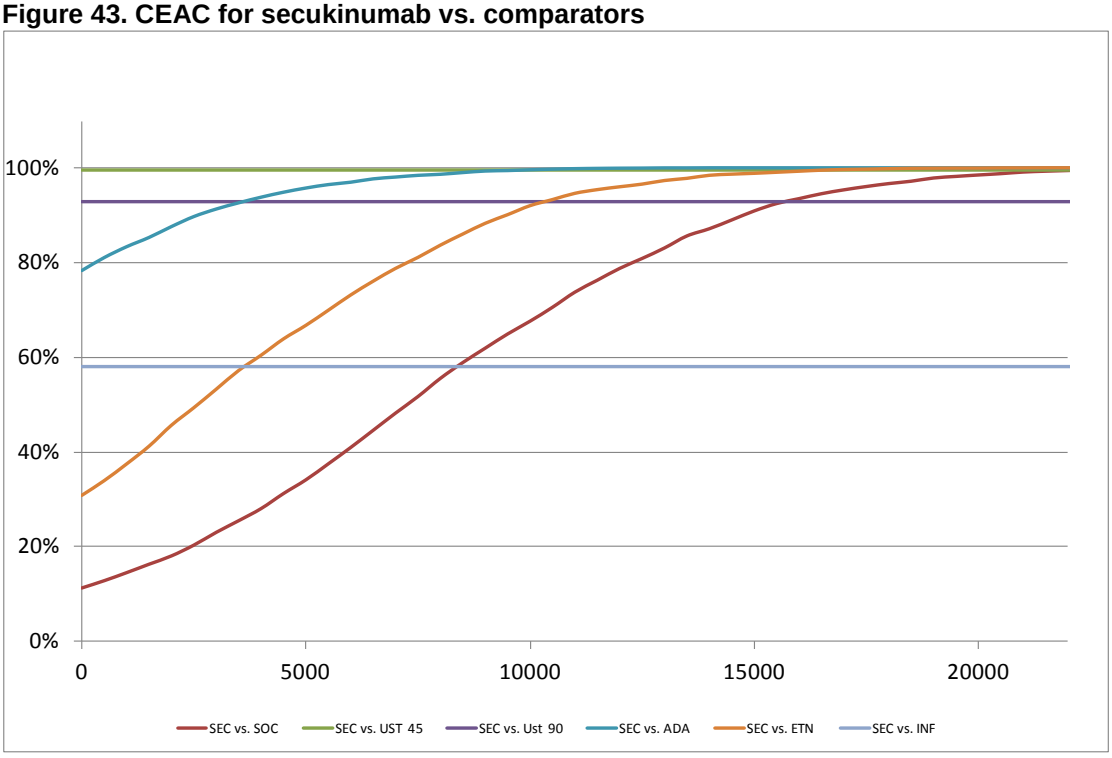

The PSA demonstrated that compared to SoC, the likelihood that secukinumab is more effective and more costly (and potentially cost-effective) is 88.8%, and the likelihood secukinumab is more effective and less costly (i.e. dominant) is 11.20%. With the exception of etanercept, the majority of model iterations for secukinumab versus biologic comparators are in the South East quadrant (i.e. where secukinumab is dominant). Complete details of the proportion of simulations within each CE quadrant have been provided below.

**Table 130. PSA simulations per CE quadrant for secukinumab vs. comparators**

| Secukinumab vs. | South East | North East | South West | North West |
|---|---|---|---|---|
| SoC | 11.20% | 88.80% | 0.00% | 0.00% |
| Ustekinumab 45mg | 99.60% | 0.00% | 0.36% | 0.04% |
| Ustekinumab 90 mg | 92.98% | 0.00% | 6.90% | 0.12% |
| Adalimumab | 78.46% | 21.54% | 0.00% | 0.00% |
| Etanercept | 30.96% | 69.04% | 0.00% | 0.00% |
| Infliximab | 58.20% | 0.00% | 41.46% | 0.34% |

In addition, a cost effectiveness acceptability curve (CEAC) was used to assess the cost effectiveness of secukinumab across a range of hypothetical WTP thresholds. At a threshold of £20,000 per QALY, the probability of secukinumab being cost-effective was close to 100% when compared to SoC, etanercept and adalimumab (Figure 43). Due to model iterations falling in the South West quadrant there was a ceiling on the probability of cost effectiveness versus ustekinumab (45mg & 90mg) and infliximab. (Figure 43).

**Figure 43. CEAC for secukinumab vs. comparators**




7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The results of the scenario analyses described in 7.6.1 are presented below:

### *Inclusion of Partial Responders*

As the NICE definition of response to psoriasis treatment is a PASI 75 response or a PASI 50 response with 5 point improvement in DLQI, a scenario analysis was

conducted to account for partial responders (PASI 50-74) continuing on treatment past the induction period. The results of this scenario analysis showed that compared to SoC, secukinumab was associated with higher QALYs (incremental QALYs: 0.36) and higher costs (incremental costs : £1,752). This results in an ICER of £4,834 per QALY (versus base case ICER of £7,076 per QALY). As in the base case analysis secukinumab dominates adalimumab, ustekinumab (45mg and 90mg) and infliximab, and extendedly dominates etanercept.

**Table 131. Deterministic Results: Inclusion of partial responders**

| | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) | ICER (£) SEC300 vs. comparator |
|---|---|---|---|---|---|---|---|
| SoC | £73,262 | 1.00 | | | | | £4,834 |
| Etanercept 25mg tw | £74,356 | 1.14 | £1,094 | 0.13 | £8,170 | £8,170* | £2,879 |
| Secukinumab 300 mg | £75,014 | 1.37 | £1,752 | 0.36 | £4,834 | £2,879 | |
| Adalimumab 40 mg | £75,365 | 1.23 | £2,102 | 0.23 | £9,325 | DOMINATED | DOMINANT |
| Ustekinumab 45 mg | £78,138 | 1.31 | £4,876 | 0.31 | £15,963 | DOMINATED | DOMINANT |
| Ustekinumab 90 mg | £78,496 | 1.34 | £5,234 | 0.33 | £15,747 | DOMINATED | DOMINANT |
| Infliximab 5mg/kg | £93,918 | 1.36 | £20,656 | 0.36 | £57,642 | DOMINATED | DOMINANT |

* Etanercept 25mg tw is extendedly dominated by secukinumab 300 mg

### *12-week NMA*

The second scenario analysis was conducted to examine the impact of the efficacy estimates and induction period with respect to the results. In this analysis, the distribution of patients across the PASI response categories was calculated from random effects multinomial NMA with parameter estimates at a 12 week endpoint across all the comparators. This time endpoint reflects the endpoint of the trials for which data was available. The results of this scenario analysis showed that compared to SoC, secukinumab was associated with higher QALYs (incremental QALYs: 0.39) and higher costs (incremental costs: £3,267. This results in an ICER of £8,473 (versus base case ICER of £7,076 per QALY). As in the base case analysis secukinumab dominates adalimumab, ustekinumab (45mg and 90mg) and infliximab, and extendedly dominates etanercept.

**Table 132. Deterministic Results: 12 week NMA**

| | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) | ICER (£) SEC300 vs. comparator |
|---|---|---|---|---|---|---|---|
| SoC | £73,501 | 0.97 | | | | | £8,473 |
| Etanercept 25mg tw | £75,917 | 1.12 | £2,416 | 0.15 | £15,976 | £15,976* | £3,632 |
| Secukinumab 300 mg | £76,768 | 1.35 | £3,267 | 0.39 | £8,473 | £3,632 | |
| Adalimumab 40 mg | £76,830 | 1.22 | £3,329 | 0.25 | £13,130 | DOMINATED | DOMINANT |
| Ustekinumab 45 mg | £79,582 | 1.29 | £6,081 | 0.33 | £18,706 | DOMINATED | DOMINANT |
| Ustekinumab 90 mg | £79,766 | 1.32 | £6,265 | 0.35 | £17,710 | DOMINATED | DOMINANT |
| Infliximab 5mg/kg | £92,377 | 1.32 | £18,876 | 0.35 | £53,895 | DOMINATED | DOMINANT |

* Etanercept 25mg tw is extendedly dominated by secukinumab 300 mg

### *NICE 16 week endpoints NMA*

The third scenario analysis was conducted to examine the impact of the efficacy estimates and induction period with respect to the results. In this analysis, the distribution of patients across the PASI response categories was calculated from random effects multinomial NMA with parameter estimates using the 16 week NICE endpoint analysis (a 16 week assessment point was used for secukinumab, and base case assessment points for all other comparators (infliximab: 10 weeks, etanercept: 12 weeks, ustekinumab: 12 weeks and adalimumab: 16 weeks).The results of this scenario analysis showed that compared to SoC, secukinumab was associated with higher QALYs (incremental QALYs 0.41) and higher costs (incremental costs £3,045). This results in an ICER of £7,495 (versus base case ICER of £7,076 per QALY). As in the base case analysis secukinumab dominates adalimumab, ustekinumab (45mg and 90mg) and infliximab, and extendedly dominates etanercept.

**Table 133. Deterministic Results: NICE (16 weeks SEC 300)**

| | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) | ICER (£) SEC300 vs. comparator |
|---|---|---|---|---|---|---|---|
| SoC | £73,610 | 0.97 | | | | | £7,495 |
| Etanercept 25mg tw | £75,688 | 1.11 | £2,077 | 0.15 | £14,133 | £14,133* | £3,732 |
| Secukinumab 300 mg | £76,656 | 1.37 | £3,045 | 0.41 | £7,495 | £3,732 | |
| Adalimumab 40 mg | £76,927 | 1.21 | £3,316 | 0.24 | £13,596 | DOMINATED | DOMINANT |
| Ustekinumab 45 mg | £79,368 | 1.28 | £5,758 | 0.31 | £18,306 | DOMINATED | DOMINANT |
| Ustekinumab 90 mg | £79,558 | 1.31 | £5,947 | 0.34 | £17,395 | DOMINATED | DOMINANT |
| Infliximab 5mg/kg | £93,132 | 1.35 | £19,522 | 0.38 | £51,185 | DOMINATED | DOMINANT |

* **Etanercept 25mg tw is extendedly dominated by secukinumab 300mg**

### *TA 146 Utilities*

The fourth scenario analysis was conducted to examine the impact of different utility estimates on the CE results. In this analysis, the utility estimates from TA 146 were used. The results of this scenario analysis showed that compared to SoC, secukinumab was associated with higher QALYs (incremental QALYs: 0.39) and higher costs (incremental costs: £2,752). This results in an ICER of £7,082 (versus base case ICER of £7,076 per QALY). As in the base case analysis secukinumab dominates adalimumab, ustekinumab (45mg and 90mg) and infliximab, and extendedly dominates etanercept

**Table 134. Deterministic Results: TA 146 Utilities**

| | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) | ICER (£) SEC300 vs. comparator |
|---|---|---|---|---|---|---|---|
| SoC | £73,610 | 0.50 | | | | | £7,082 |
| Etanercept 25mg tw | £75,788 | 0.64 | £2,178 | 0.14 | £15,118 | £15,118* | £2,345 |
| Secukinumab 300 mg | £76,361 | 0.89 | £2,752 | 0.39 | £7,082 | £2,345 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Adalimumab 40 mg | £76,981 | 0.73 | £3,372 | 0.24 | £14,314 | DOMINATED | DOMINANT |
| Ustekinumab 45 mg | £79,544 | 0.82 | £5,934 | 0.32 | £18,418 | DOMINATED | DOMINANT |
| Ustekinumab 90 mg | £79,732 | 0.85 | £6,122 | 0.35 | £17,340 | DOMINATED | DOMINANT |
| Infliximab 5mg/kg | £93,539 | 0.88 | £19,929 | 0.38 | £51,932 | DOMINATED | DOMINANT |

* Etanercept 25mg tw is extendedly dominated by secukinumab 300mg

### *FIXTURE Study Data*

The final scenario analysis was conducted using head-to-head RCT data from FIXTURE. In this analysis, the response estimates for placebo, secukinumab, and etanercept at 12 weeks were taken from the FIXTURE RCT results. The results of this scenario analysis showed that compared to SoC and etanercept, secukinumab was a cost effective treatment option.

**Table 135. Deterministic Results: FIXTURE Study Results**

| | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) | ICER (£) SEC300 vs. comparator |
|---|---|---|---|---|---|---|---|
| SoC | £73,499 | 0.99 | | | | | £9,166 |
| Etanercept 25mg tw | £76,142 | 1.17 | £2,643 | 0.18 | £14,903 | £14,903 | £3,508 |
| Secukinumab 300 mg | £76,773 | 1.35 | £3,274 | 0.36 | £9,166 | £3,508 | |

## 7.7.10 What were the main findings of each of the sensitivity analyses?

- The deterministic sensitivity analysis has shown that base-case results were most sensitive to changes in the cost of treatment (secukinumab and comparators), cost of treatment administration (secukinumab and comparators), and the costs and LOS associated with hospitalisation in the model.
- At a threshold of £20,000 per QALY, the probability of secukinumab being cost-effective was close to 100% when compared to SoC, etanercept and adalimumab.
- Scenario analyses were performed to test how key model assumptions impacted the base case results. Inputs tested in the scenarios included allowing partial responders (PASI 50-74) to remain on active treatment after the induction period, and using different sources of efficacy and utilities values. Results have shown that secukinumab remains a cost effective treatment option in almost all the scenarios tested with ICERs similar to those of the base case.

Overall, the base-case results demonstrated that secukinumab is cost effective in the treatment of patients with moderate to severe chronic plaque psoriasis. The robustness of these results was confirmed by the outputs of both the OWSA and the PSA.

### 7.7.11 What are the key drivers of the cost-effectiveness results?

From the sensitivity analyses, it was clear the key drivers of cost effectiveness of secukinumab were as follows:

- **Cost of treatment**

The cost of secukinumab was shown to be a driver in the CEAs with its comparators. This was one of the top two drivers in five of the six one-way sensitivity analyses. The cost of the relevant comparator was also one of the top three drivers in five of the six analyses.

- **Cost and length of stay (LOS) associated with hospitalisation**

The cost of hospitalisation and the LOS associated with hospitalisation was shown to be a driver in three of the six one-way sensitivity analyses.

- **Relative treatment effects**

There are two components to this driver. The first is the cut points, which establish the distribution of PASI response across all treatments within the model. The second component is the treatment effect associated with each treatment. The treatment effect was seen to be a key driver in each of the analyses.

From the tornado diagram, it is clear that the magnitude of the impact the changes in cost (e.g. treatment cost) had on the CEA results were much larger than that of the relative treatment effects.

## *7.8 Validation*

### 7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Two clinicians were involved in the development of the CEM to ensure the underlying assumptions were robust and/or reflective of UK clinical practice (e.g. model structure, disease progression). In addition, these clinicians validated values for resource use inputs which are detailed in section 7.5.4 and Appendix 15, Section 10.15.

The CEM underwent two measures of quality control to ensure internal and external validity. This was conducted by the model developers and an experienced health economist outside the team of developers in which extreme value scenarios were tested to cross check that the model behaved logically.

## 7.9 Subgroup analysis

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

Subgroup analyses were not part of the current evaluation. As discussed in Section 7.9.5, a subgroup based on prior biologic experience was not included due to the lack of robust efficacy data.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable.

7.9.3 Please describe how the statistical analysis was undertaken.

Not applicable.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Not applicable.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

Subgroup analyses for the biologically experienced patient subgroup and the subgroup of patients with a DLQI>10 were not considered in the main analyses.

### *Biologically Experienced Patient Subgroup*

Although this patient subgroup was identified as part of the scope of the decision problem (section 5), this subgroup was not included due to the lack of robust efficacy data. The data available from the secukinumab RCTs was based upon very small sample sizes, and the trials were not powered to observe differences in treatment effect within this subgroup. In addition, there was limited data on this subgroup for the comparators listed within the NICE scope, which made the comparison unviable.

However, there was an effort made to look at this subgroup using data from Appendix O of the psoriasis guideline CG 153 (38), which included PASI response

rates from a pairwise meta-analysis of three RCTs. A fixed-effect ordered probit model was utilised in order to model the trial outcomes when comparing biologic treatment vs. placebo (Table 136).

**Table 136. Appendix O data for biologically experienced patients**

| Response criterion | SoC | Biologic |
|---|---|---|
| PASI 50 | 3.8% | 79.4% |
| PASI 75 | 0.8% | 57.3% |
| PASI 90 | 0.1% | 31.9% |
| **Proportion of biologically experienced patients** | | |
| PASI < 50 | 96.2% | 20.6% |
| PASI 50-74 | 3% | 22.1% |
| PASI 75-89 | 0.7% | 25.4% |
| PASI 90-100 | 0.1% | 31.9% |

It is clear that the primary limitation of this data is that the response data for biologically experienced patients is not as granular (i.e. biologic treatments were grouped together). As data on each comparator was not available, a cost minimisation analysis was undertaken. All other data applied in this analysis were that of the base-case (see sections 7.3.6, 7.4.9, and 7.5).

### Results

Table 137 presents the results when running the subgroup analysis using the settings specified above.

**Table 137. Cost-minimisation results for biologically experienced patients**

| | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) versus baseline (QALYs) |
|---|---|---|---|---|---|
| | | | | | |
| SoC | [redacted] | 0.94 | [redacted] | [redacted] | [redacted] |
| Etanercept 25mg tw | [redacted] | 1.24 | £2,748 | 0.30 | £9,191 |
| Secukinumab 300 mg | [redacted] | 1.24 | [redacted] | 0.30 | £9,516 |
| Adalimumab 40 mg | [redacted] | 1.24 | £3,418 | 0.30 | £11,431 |
| Ustekinumab 45 mg | [redacted] | 1.24 | £5,448 | 0.30 | £18,219 |
| Ustekinumab 90 mg | [redacted] | 1.24 | £5,448 | 0.30 | £18,219 |
| Infliximab 5mg/kg | [redacted] | 1.24 | £15,819 | 0.30 | £52,907 |

### *Patient Subgroup with DLQI>10*

Patients with a DLQI>10 were not considered for subgroup analysis for two reasons. First, there were no statistically significant differences between the subgroup and the total population with respect to co-primary endpoint (see section 6.5), which suggests that the result of the total population are likely to be representative of this subgroup. Second, there was limited data on this subgroup for the comparators listed within the NICE scope.

## *7.10 Interpretation of economic evidence*

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the

submission be given more credence than those in the published literature?

There are currently no other studies investigating the cost effectiveness of secukinumab in patients with moderate to severe plaque psoriasis in the UK. However, prior TAs and publications have analysed the primary comparators in this analysis (i.e. ustekinumab, inflixumab, adalimumab, and etanercept).

Prior UK cost effectiveness publications are summarised in section 7.1. TA 180 appears to be the most relevant comparison to this analysis as it is the most recent TA conducted in this indication, it uses a similar time horizon, and it includes the majority of the comparators included in this analysis. However, TA 180 uses a different model structure, and the utilities were mapped using DLQI values. The incremental costs reported in TA 180 are broadly in line with those from the base-case deterministic results for secukinumab. However, the incremental QALYs for interventions in TA 180 are lower, which could be a result of the differences in approach described above.

The *de novo* model presented includes improvements upon the York model used in previous TAs in response to criticism from prior ERG reports. Changes to the model structure were made to address previous ERG comments on the time horizon in particular. The induction and post induction periods are flexible to align with NICE endpoints or straight endpoints (i.e. 12 weeks), which allow for alignment with the endpoints used in prior TAs (NICE endpoint analysis), the primary endpoint of the secukinumab clinical trials (i.e. 12 week) and the time at which peak efficacy for secukinumab was seen in the clinical trials (NICE endpoints with secukinumab at 16 weeks). In addition, the data used for the utility estimate in the base-case analysis was taken from the secukinumab clinical trials, which directly collected EQ-5D information . This elicitation method was an improvement on the less robust methods used in TA 103 and TA180 when such information was not available and mapping from DLQI data was necessary.

### 7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

The scope of this appraisal considers adults with moderate to severe plaque psoriasis, and this is defined by NICE as patients with PASI ≥10 and DLQI >10. Based upon the secukinumab trial population (i.e. PASI ≥12) and the lack of statistically significant differences in outcomes in the post-hoc analysis of the DLQI >10 subgroup vs. the full trial population (see section 6.5), this economic evaluation is relevant to all groups of patients who could potentially use secukinumab as identified in the decision problem.

### 7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The primary strength of this analysis is the robustness of the clinical data. For secukinumab, there were five phase III clinical trials (n=3,369) that were used to provide efficacy and utility estimates for this submission. The magnitude and direction of the results for PASI response and EQ-5D were broadly similar across the five secukinumab clinical trials, which provided secukinumab with a substantial, robust foundation for the economic evaluation.

The underlying weakness of the data available for this indication and evaluation is the lack of long term data for extrapolation of clinical and economic outcomes. In the evaluation, the discontinuation rate in the Markov cycles was in line with expert opinion and prior TAs, however, there are no publicly available data or information to support this assumption (e.g. UK registry data). In addition, it is assumed that patients maintain their PASI response past 52 weeks. Although this aligns with prior TAs and expert opinion, there are limited data to prove or dispute this assumption.

### 7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

As mentioned above, long term data that could be used to validate assumptions of extrapolation would increase the robustness of this evaluation and future evaluations.

In addition, there are limited data available on patients who are biologically experienced (i.e. failure on prior biologic). From discussions with the clinical experts, this patient population is growing, and additional data would help to support the evaluations in this sub-set of the moderate to severe plaque psoriasis patient population.

# Section C – Implementation

## 8 Assessment of factors relevant to the NHS and other parties

**Summary of Budget Impact Analysis**

- A *de novo* budget impact analysis was developed in order to evaluate the total budget impact of introducing secukinumab 300 mg into the market in England and Wales.
- Out of a projected population of 45,420,099 adults in England and Wales in 2015, 794,852 were estimated to have psoriasis, 2.55% of whom were estimated to receive treatment with a first biologic, giving a total eligible population in 2015 of 20,269 patients.
- Overall, it was estimated that of these eligible patients [redacted] are currently receiving treatment with a biologic therapy. Of these it is anticipated that [redacted] of patients will receive secukinumab 300 mg in England and Wales in 2015 rising to [redacted] or [redacted] patients in 2019.
- **With a patient access scheme in place, the net budget impact of introducing secukinumab 300 mg in England and Wales is estimated to have a cumulative saving to the NHS of £4,989,596 between 2015 and 2019 (Section 8.7).**

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

One population was used in this Budget Impact Analysis: The number of eligible patients for biologic treatment in the UK. This is in line with current, and expected future, clinical practice in the UK.

In order to estimate a projected eligible psoriasis population that require treatment with a biologic 2015 to 2019, the following parameters have been considered:

- Total projected population in England and Wales from 2015 to 2019: Office of National Statistics (100) 2013 figures for the England and Wales population were used (100). To this, an average annual population growth rate for the UK of 0.68%, was applied, calculated using data projections from the ONS (100).
    - Output – the number of people living in England and Wales in 2015 was estimated to be 57,721,574

- From the total projected population, the adult (18 years+ population) was calculated to reflect that the majority of biologic treatments are licensed for

use in adults only. 78.69% of the population in England and Wales are estimated to be adults.
    - Output – The adult population in the England and Wales equates to 45,420,099 adults

- The proportion of people with plaque type psoriasis in UK as a whole was calculated using the rate of 1.75% from NICE Guideline 153.
    - Output - 794,852 adults in England and Wales are estimated to have psoriasis
- The proportion of moderate to severe plaque type psoriasis patients, meeting NICE criteria, eligible to receive a biologic treatment was then calculated, using the rate of 2.55%, from the costing template accompanying NICE Clinical Guideline 153
    - Output - 20,269 are the number psoriasis patients eligible to receive biologic treatment in England and Wales

- The proportion of moderate to severe plaque type psoriasis patients, meeting NICE criteria, estimated to be currently receiving biologic treatment for moderate to severe plaque type psoriasis was then calculated, using the rate of [redacted] from Freedom of Information request data (NHiS Oct 2013)
    - Output – [redacted] people with psoriasis are estimated to be receiving biologic treatment in England and Wales.

5 year estimates have been provided in the table below.

**Table 138. Estimated and projected adult population of the England and Wales, 2015 to 2019**

| | 2015 | 2016 | 2017 | 2018 | 2019 |
|---|---|---|---|---|---|
| **Population size of England & Wales** | 57,721,574 | 58,112,191 | 58,505,451 | 58,901,372 | 59,299,973 |
| **Adult Population (+18)** | 45,420,099 | 45,727,468 | 46,036,918 | 46,348,461 | 46,662,113 |
| **Adults with psoriasis** | 794,852 | 800,231 | 805,646 | 811,098 | 816,587 |
| **Proportion of patients eligible with first biologic** | 20,269 | 20,406 | 20,544 | 20,683 | 20,823 |
| **Proportion of patients treated with first biologic** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

## 8.2 What assumption(s) were made about current treatment options and uptake of technologies?

To help understand the economic impact of secukinumab 300 mg use in the NHS, cost savings were estimated using two scenarios; the NHS with secukinumab 300 mg and the NHS without secukinumab 300 mg. The uptake of secukinumab 300 mg

was assumed to increase over time and displace the other biologic treatments currently used to treat psoriasis in the UK market.

Treatment options included in the model are all biologics currently approved for use in the UK and recommended by NICE- adalimumab, etanercept, infliximab and ustekinumab.

**Uptake of secukinumab 300 mg**

Not all patients who are estimated to receive a biologic will receive secukinumab 300 mg. Overall, it was estimated that of these patients [redacted] or [redacted] patients will receive secukinumab 300 mg in England and Wales in 2015 rising to [redacted] or [redacted] patients in 2019.

## What assumption(s) were made about market share (when relevant)?

Market share estimates for the current biologic treatments were obtained from NHiS {NHiS Oct 2013} and were assumed to be applicable to 2015. As market share data for the next five years were not available for these biologic treatments, the market shares in future years were assumed to remain constant from 2015-2019 and equal to those of 2015 (Table 139).

**Table 139. Current market share distributed by regimens (without secukinumab 300 mg) {NHiS Oct 2013}**

| | 2015 | 2016 | 2017 | 2018 | 2019 |
|---|---|---|---|---|---|
| Secukinumab | 0% | 0% | 0% | 0% | 0% |
| Adalimumab (Humira) | 50% | 50% | 50% | 50% | 50% |
| Etanercept (Enbrel) | 21% | 21% | 21% | 21% | 21% |
| Infliximab (Remicade) | 7% | 7% | 7% | 7% | 7% |
| Ustekinumab (Stelara) | 22% | 22% | 22% | 22% | 22% |
| Total annual market distribution | **100%** | **100%** | **100%** | **100%** | **100%** |

[redacted] 140 [redacted]

**Table 140. Projected market share distributed by regimens (with secukinumab 300 mg)**

| | 2015 | 2016 | 2017 | 2018 | 2019 |
|---|---|---|---|---|---|
| Secukinumab 300 mg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Adalimumab (Humira) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Etanercept (Enbrel) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Infliximab (Remicade) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Ustekinumab (Stelara) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total annual market distribution | **100%** | **100%** | **100%** | **100%** | **100%** |

8.3 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Treatment of moderate to severe plaque psoriasis with biologics is already established in the UK and the costs for routine tests and monitoring are currently accounted for in commissioning budgets. Treatment with secukinumab 300 mg in the UK will not require additional monitoring or routine tests compared to the comparator biologic treatments, as mentioned in Section 1.12.

Given the comparable efficacy of secukinumab 300 mg in comparison with infliximab given via IV infusion there is a potential that secukinumab 300 mg may be given in place of infliximab for some patients. This would lead to a reduction in infusion costs for the NHS. The annual average weighted treatment administration cost for infliximab given via IV infusion is estimated to be £1,232.40 per dose (119).

If, for example, [redacted] of those psoriasis patients treated with secukinumab 300 mg in 2015, were treated with secukinumab 300 mg in place of infliximab given via IV infusion, this would save the NHS infusion costs of £552,731 in 2015.

[redacted]

8.4 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Costs considered in the budget impact analysis were [redacted] As the costs associated with monitoring, routine testing and administration apply to all biologic treatments. Treatment with secukinumab 300 mg in the UK will not require additional monitoring or routine tests compared to the comparator biologic treatments. As discussed above there are potential resource savings when secukinumab 300 mg is used in preference to infliximab administered via IV infusion [redacted].

Unit cost for the comparator treatments included in the model were taken from the BNF (120) (Table 142, Table 143).

**Table 141. Unit Costs Assumptions: Year 1**

| Treatment regimen | Pack cost | Doses per pack | Number of Doses (Year 1 ) | Cost (Year 1 ) |
|---|---|---|---|---|
| Secukinumab | [redacted] | [redacted] | [redacted] | [redacted] |
| Adalimumab | £704.28 | 2 | 28 | £9,859.92 |

| | | | | |
|---|---|---|---|---|
| Etanercept ** | £357.50 | 4 | 104 | £9,295 |
| Infliximab | £419.62 | 1 | 32 | £13,427.84 |
| Ustekinumab | £2,147 | 1 | 6 | £12,882.00 |

** NICE do not currently recommend the use of etanercept 50 mg twice weekly, however, there is evidence to suggest that this higher dose is used in clinical practice (41). Therefore the estimates for the cost of etanercept presented here are likely to be underestimates.

**Table 142. Unit Costs Assumptions: Year 1+**

| Treatment regimen | Pack cost | Doses per pack | Number of Doses (Year 1+) | Cost (Year 1+ ) |
|---|---|---|---|---|
| Secukinumab | [redacted] | [redacted] | [redacted] | [redacted] |
| Adalimumab | £704.28 | 2 | 26 | £9,155.64 |
| Etanercept** | £357.50 | 4 | 104 | £9,295.00 |
| Infliximab | £419.62 | 1 | 26.0 | £10,910.12 |
| Ustekinumab | £2,147 | 1 | 4.3 | £9,296.51 |

** NICE do not currently recommend the use of etanercept 50 mg twice weekly, however, there is evidence to suggest that this higher dose is used in clinical practice (41). Therefore the estimates for the cost of etanercept presented here are likely to be underestimates.

## 8.5 Were there any estimates of resource savings? If so, what were they?

[redacted]

As discussed above in Section 8.4 there are potential resource savings when secukinumab 300 mg is used in preference to infliximab administered via IV infusion, [redacted]. The annual average weighted treatment administration cost for infliximab given via IV infusion is estimated to be £1,232.40 per dose (119).

There may also be additional resource savings for secukinumab 300 mg due to the high levels of efficacy. Based on the higher PASI 75 and PASI 90 responses rate for secukinumab 300 mg compared to other subcutaneous biologics (etanercept, adalimumab and ustekinumab) as estimated from the mixed treatment comparison in Section 6.6. The increase in the number of responders for secukinumab 300 mg leads to a corresponding reduction in the number of non-responders. With a greater number of patients achieving control of their psoriasis there should be less burden on dermatology services for example a reduction in dermatology outpatient appointments required. This resource reduction estimate has not been included for the sake of simplicity.

## 8.6 What is the estimated annual budget impact for the NHS in England and Wales?

The annual budget impact for years 2015-2019 has been provided in Table 143. The cumulative budget impact of secukinumab 300 mg over the next 5 years is expected to deliver savings of £4,989,597 to the NHS.

**Table 143. England and Wales Budget Impact Results**

| Treatment | 2015 | 2016 | 2017 | 2018 | 2019 |
|---|---|---|---|---|---|
| **NHS without secukinumab 300 mg** | | | | | |
| Adalimumab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Etanercept | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Infliximab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Ustekinumab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Total** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | | | | |
| Secukinumab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Adalimumab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Etanercept | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Infliximab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Ustekinumab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Total** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Net Budget Impact** | **£217,310** | **-£279,082** | **-£1,056,322** | **-£1,346,834** | **-£2,524,668** |

## 8.7 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Psoriasis can have a negative effect on the gaining and retaining of paid work, and lifetime earning potential. Psoriasis also has a negative impact on productivity at work. The condition commonly restricts the sufferer's choice of career and over half of patients with severe psoriasis report that they are unable to work at all (9, 11, 12). The impact of psoriasis on work time and lost productivity has an indirect cost to the UK economy. There are no UK studies that have quantified these indirect costs but a new highly effective treatment option, such as secukinumab 300 mg, could reduce the number of people whose work is impaired as a result of psoriasis and provide another opportunity for resource savings in the UK.

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Please use a recognised referencing style, such as Harvard or Vancouver.


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