## Section A: Clarification on effectiveness data

**A1. PRIORITY For subgroups with a week 12 PASI 50 – 75, please present patient numbers with a PASI < 50, PASI 50 – 74, PASI 75 – 89, PASI 90+ (inclusive of PASI 100) and PASI 100 at week 52 for each arm of the FIXTURE trial. A suggested table template is provided below.**

CIC data supplied in other document.

**A2. PRIORITY Given that placebo patients in most secukinumab studies were 're-randomised' at 12 weeks according to their response status, please confirm whether the inclusion of data in the 16 week scenario network meta-analysis was based on the original or secondary (week 12) randomisation. Was secondary randomisation performed for any other trials in the network and, if so, how was this handled in the network meta-analysis (NMA)?**

The inclusion of secukinumab data in the 16 week scenario was based on the original randomisation and there was no corresponding data collected for the placebo arm at 16 weeks. The number of patients in the dataset analyzed at 12 weeks is the same as 16 weeks (N=323 FIXTURE, N=245 ERASURE). We confirm that data for NMA comparators (ustekinumab, infliximab, etanercept and adalimumab) that had undergone a secondary randomisation was not included in the NMA.

**A3. PRIORITY Please provide a copy of reference 58 by Redwood.**

Two reports have been attached: one report with results of network meta-analyses focused on 12 week data (secukinumab NMA 12 week report) and one with results of 16 week data analyses (secukinumab NMA 16 week report).

**A4. PRIORITY For Table 69:**

- **The table contains a column for treatment effect estimates: 0 for SoC, - 2.65 for secukinumab 300mg etc. Please explain what the numbers in the 'treatment effect estimate' column mean.**
- **The table includes a section for "PASI cut point 50/75/100" with cut point estimates of 1.2, 1.8 and 2.512 respectively. Please explain what these numbers mean.**
- **If relevant please include cross references to any appropriate sections/tables in the submission.**

**Table 1 (Table 69 from NICE submission). 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) | | | | |

In the table above:

- The numbers in the column treatment effect estimate are the $d_{Ak}$ in the model below and reflect the underlying relative treatment effect of each biologic versus placebo (SoC) regardless of the PASI cutoff on the probit scale.
- PASI cut point 50 is calculated as the average of $\mu_{jb}$ when *b* = treatment A (i.e. placebo/SoC).
- PASI cut point 75 equals the estimate for PASI cut point 50 + $z_2$.
- PASI cut point 90 equals the estimate for PASI cut point 50 + $z_3$.

We used the network meta-analysis model for ordered categorical data as presented in example 6 in the appendix of the NICE DSU technical support document for evidence synthesis (Dias et al 2014)

PASI data is continuous but the outcome measure is categorized using three pre-defined cut-offs (i.e. PASI 50, PASI 75, PASI 90), which were aligned with the model health states. The model we used assumes that the relative treatment effect is the same regardless of the PASI cut-off.

The different studies used for the NMA report the number of patients in the different PASI categories for all arms of a trial. More specific, studies report $r_{jki}$, which is the number of patients in arm *k* of trial *j* in category *i*. The likelihood can be expressed as a series of conditional binomial distributions as shown by Dias et al 2014:

$$r_{jki} \sim binomial\left(q_{jki}, N_{jki}\right) \qquad i = 1,\ldots, I_j - 1$$

$$\text{with} \quad N_{jki} = n_{jk} - \sum_{u=1}^{i-1} r_{jku}$$

$q_{jki}$ is the probability of belonging to category *i,* in arm *k* of trial *j*:

$$q_{jki} = \Pr\left(\text{PASI score in category } i\right) = \Pr\left(C_i < \text{PASI score} < C_{i+1}\right)$$

where $C_i$ and $C_{i+1}$ are the lower and upper bound of category *i (*=lower bound of category *i+1)*, with *C* defined as the PASI cut- offs.

Accordingly $q_{jki}$ can be expressed as follows :

$$q_{jki} = 1 - \frac{\Pr\left(\text{PASI score} > C_{i+1}\right)}{\Pr\left(\text{PASI score} > C_i\right)} = 1 - \frac{p_{jkc+1}}{p_{jkc}}$$

A probit link function, which is the inverse of the normal cumulative distribution function, was used to map the probabilities $p_{jkc}$ onto the real underlying scale. The random effects NMA model used can be described as follows:

$$\Phi^{-1}\left(p_{jkc}\right)=\begin{cases}\mu_{jb}+z_c & b=\mathrm{A,B,C,}\quad \text{if } k=b\\ \mu_{jb}+z_c+\delta_{jbk} & \text{if } k \text{ alphabetically after } b\end{cases}$$

$$\delta_{jbk}\sim normal\left(d_{bk},\sigma^2\right)=normal\left(d_{Ak}-d_{Ab},\sigma^2\right)$$

$$d_{AA}=0$$

Where: $\Phi^{-1}$ is the inverse of the normal cumulative distribution. There are *k* treatments labelled as A, B, C, etc., and treatment A is taken to be the reference treatment for the analysis (i.e. placebo). $\mu_{jb}$ is the (transformed) outcome in study *j* with 'baseline' treatment *b* for PASI 50. $z_c$ represent the different cut offs that categorize the underlying continuous PASI scores and is assumed fixed across all trials. We set $z_1$=0 reflecting the cutpoint for PASI 50, $z_2$ reflects PASI 75, and $z_3$ reflects PASI 90. $z_c$ are the differences between the response categories on the standard normal scale. $\delta_{jbk}$ is the trial-specific treatment effect of *k* relative to treatment *b*. These trial-specific effects are drawn from a random effects distribution: $\delta_{jbk}\sim N\left(d_{bk},\sigma^2\right)$. $d_{bk}$ is the treatment effect of treatment *k* relative to 'baseline treatment' *b*. $d_{bk}$ are identified by expressing them in terms of the reference treatment A: $d_{bk}=d_{Ak}-d_{Ab}$ with $d_{AA}=0$.The heterogeneity $\sigma^2$ is assumed constant for all treatment comparisons.

The probabilities of non-overlapping PASI response categories provided in the last 4 columns are calculated based on the relative treatment effects vs placebo/SoC and the PASI cut point estimates.

For example, to calculate the probabilities for PASI 50, PASI 75, and PASI 90 in the secukinumab 300 mg arm, we used the following:

- Pr (PASI<50) = Normal (0,1) cumulative distribution function for treatment effect (-2.65) and the PASI 50 cut point (1.2). Note that in excel, this is equivalent to the formula =NORMDIST(-2.65+1.2,0,1,TRUE).

- Pr (PASI<75) = Normal (0,1) cumulative distribution function for treatment effect (-2.65) and the PASI 75 cut point (1.8).

- Pr (PASI<90) = Normal (0,1) cumulative distribution function for treatment effect (-2.65) and the PASI 90 cut point (2.5).

From the above 3 values, we can calculate the proportion of patients in each health state:

- PASI < 50 = Pr (PASI < 50)
  = NORMDIST(-2.65+1.2,0,1,TRUE)
  = 7.3%

- PASI 50-74 = Pr (PASI < 75) - Pr (PASI < 50)
  = NORMDIST(-2.65+1.8,0,1,TRUE) - NORMDIST(-2.65+1.2,0,1,TRUE)
  = (19.8%) – (7.3%)
  = 12.5%

- PASI 75-89 = Pr(PASI < 90) - Pr(PASI<75)
  = NORMDIST(-2.65+2.5,0,1,TRUE) - NORMDIST(-2.65+1.8,0,1,TRUE)
  = (44.5%) - (19.8%)
  = 24.8%

- PASI > 90 = 1- Prob(PASI<90)
  = 1 - NORMDIST(-2.65+2.5,0,1,TRUE)
  = 1- (44.5%)
  = 55.4%

In the network meta-analysis report, relative risk estimates are reported. The relative risks were obtained by calculating the Pr (PASI > 50) = 1-Pr (PAS I< 50), Pr (PASI > 75) = 1 – Pr (PASI < 75), and Pr (PASI > 90) = 1 – Pr (PASI < 90) for each treatment and subsequently dividing these estimates for comparisons of interest using Markov Chain Monte Carlo (MCMC).

*Ref: Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011; last updated April 2014; available from http://www.nicedsu.org.uk)*

**A5. Please explain why a formal meta-analysis was not attempted for all relevant outcomes specified in the NICE final scope.**

During meta-analysis feasibility a thorough analysis of all included trials was undertaken to determine what outcomes could be included in the NMA. Although NICE final scope outlined additional outcomes of interest such as relapse and remission rates, adverse events and health-related quality of life, it was not possible to include these in the NMA due to the lack of data reported across trials or the differences in reporting outcomes across trials.
The severity of psoriasis measured by PASI response is commonly reported in psoriasis trials as a standard endpoint. Therefore, this outcome was deemed the most suitable to use as an efficacy comparison for use in the economic model.

**A6. Please present Figure 13 separately for the subgroups of week 12 PASI < 50, PASI 50 – 74, PASI 75 – 89, PASI 90+ (inclusive of PASI 100) and PASI 100. *It is recognised that this is a non-trivial request therefore please provide as much information on this issue as possible prior to 2nd of February 2015*.**

Response to question A6 has not been included at this time, but it will be addressed prior to 2 February 2015.

**A7. NICE only recommends infliximab for those with very severe psoriasis with a PASI score of at least 20. Please clarify if it is possible to determine from the trial data the**

**proportion of people who have very severe psoriasis (those with a PASI>20 as per NICE infliximab guidance), and to carry out a comparison of secukinumab with infliximab in this subgroup?**

***Secukinumab, PASI > 20 data:***

We can confirm that we were able to determine from the trials data the proportion with very severe psoriasis (i.e. baseline PASI > 20), and we have tabulated this in Table 2 below.

**Table 2. Results from PASI >20, Pooled analysis from FIXTURE, ERASURE, FEATURE and JUNCTURE at Week 12**

| Patients with baseline PASI > 20 | Placebo | Secukinumab 300 mg | Etanercept |
|---|---|---|---|
| **N** | **325** | **334** | **162** |
| **IGA mod 2011 0/1** | 7/325 (2.2%) | 208/334 (62.3%) | 45/162 (27.8%) |
| **PASI 75** | 14/325 (4.3%) | 271/334 (81.1%) | 78/162 (48.1%) |
| **PASI 90** | 5/325 (1.5%) | 191/334 (57.2%) | 43/162 (26.5%) |
| **PASI 100** | 1/325 (0.3%) | 83/334 (24.9%) | 6/162 (3.7%) |

Note that an analysis pertaining to the treatment effect of secukinumab in patients with PASI >20 and PASI ≤ 20 has been conducted and published at the European Academy of Dermatology and Venerology (EADV) conference in 2014. The conclusions of this analysis were as follows:

- Regardless of disease severity (PASI ≤ 20 or PASI > 20), secukinumab achieved higher clinical response rates, including clear/almost clear skin (PASI 90/100), vs. etanercept and placebo in pooled, placebo-controlled phase 3 studies over 52 weeks
- The efficacy of secukinumab in disease severity subgroups was consistent with that in the overall population receiving secukinumab

***Indirect Comparison:***
We were unable to conduct an indirect comparison of secukinumab with infliximab in this subgroup as the data for infliximab are unavailable.

However, if we were to conduct an indirect comparison of secukinumab and infliximab within this subgroup, we would want to ensure that we accounted for the differences in clinical trial populations. For example, in the secukinumab clinical trials there is a significant proportion of subjects who had biologics exposure and/or failure on prior biologic. As infliximab was one of first biologics indicated for the treatment of psoriasis, we would expect a large proportion if not all of the patients in the infliximab clinical trials to be biologic-naïve. However, this information is not consistently reported in the infliximab trial publications. This would be one of the effect modifiers that we would recommend controlling for if conducting an indirect comparison in this subgroup.

***Reference****: Spelman LJ, Blauvelt A, Loffler J, Papavassilis C, Fox T. Secukinumab Shows Efficacy Regardless of Baseline Disease Severity in Subjects With Moderate to Severe Plaque Psoriasis: A Pooled Analysis From Four Phase 3 Studies. EADV*

**A8. Please describe the process used to determine whether a particular treatment dose was included as a comparator in the NMA (Table 50). Was this process consistent for both the intervention and comparator arms? Specifically, in Table 51, footnote 'a' explains that the non-licenced dose of 150mg is included in the NMA as long as the trial also included a 300mg arm. Was this rule also applied to the comparators?**

To be included in the NMA, studies had to include the treatments/ doses as outlined in the table below. Studies and/or arms reporting on irrelevant doses or comparators were excluded, unless they provided indirect evidence for comparisons of the interventions of interest as shown in the table below. The non-licensed secukinumab dose of 150mg was included for completeness and transparency and all secukinumab phase III trials contain both the 300mg and 150mg treatment arms.

**Table 3. Doses of biologics included in the NMA**

| Drug | Loading dose | Maintenance dose |
|---|---|---|
| Secukinumab | 150 or 300 mg week 0,1,2,3,4 | 150 or 300 mg every month |
| Etanercept | NA | 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 |

**A9**. **The submission contains several figures/tables outlining relevant trials, however the sources described as included/excluded are inconsistent. For example, Blauvelt 2014 and SCULPTURE are included in Figure 19 and Table 52 but not Table 53; Chaudhari 2001 is listed as both included and excluded on page 296/297 and is included in Figure 25; Gordon 2006 is not in the list of included studies but it is included in Figure 24. Please clarify which trials have been included in the NMA, and if Figures 19, 24, 25 and Table 53 are incomplete or inaccurate, please provide corrected versions. When doing so, please use consistent names for the studies in the figures and tables.**

Novartis apologises for some inconsistencies in the reporting of trials. This was due to conducting two separate NMAs (12 week timepoint and 16 week timepoint) and then combining the data into one table to present in the submission (Table 52 and Table 53). Blauvelt 2014 and SCULPTURE should have been included in Table 53 and a revised Table 53 has been inserted in appendix 1 of this document. Likewise, the list of included and excluded studies has been revised to contain the correct references with Chaudari 2001 and Gordon 2006 listed as included studies.

**A10. For the base-case NMA (NICE 12-week analysis) PASI was assessed at variable time points specific to each comparator: 12 weeks for most comparators but 10 and 16 week time points for infliximab and adalimumab respectively. Please clarify why the base case analysis was not based on a standard assessment time - Figure 24 suggests that 12-week data were available for all comparators.**

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:

- 12 weeks for ustekinumab and secukinumab
- 10, 12 and 16 weeks for infliximab, etanercept and adalimumab respectively, which additionally align with NICE CG153 and BAD guidelines.

The variable time points analysis was used as the base-case instead of 12 weeks standard assessment time because infliximab trials report their primary endpoint at 10 weeks and adalimumab trials report their primary endpoint at 16 weeks. Data were available for three infliximab trials at 12 weeks and for four adalimumab trials at 12 weeks although these were not primary endpoint data and sometimes data were extrapolated from a graph within the manuscript e.g. Torii 2010. A sensitivity analysis was conducted using trial data at 12 weeks which demonstrated similar results to the base case.

**A11. The OPENBUGS code (Appendix 8) includes two models with covariates. Please clarify which covariates were adjusted for.**

A random effects meta-regression with prior biologic exposure (>20% vs. other) as a study level covariate was performed. For each study, the study-level covariate was assigned a value of 1 if >20% of the population had prior exposure to biologics, otherwise a value of 0 was assigned. For studies not explicitly reporting the distribution of prior biologic exposure or not reporting in/exclusion criteria regarding prior biologic exposure we assumed no prior exposure. As such, all studies were included in the meta-regression analysis.

## Section B: Clarification on cost-effectiveness data

Please note that in addressing question A23 we detected an unusual pattern of missing observations when conducting this analysis. During the analysis, it was apparent that there were observations that should have been included in the original analysis. This is due to the way the way the baseline DLQI variable was recorded, and it led to 689 observations on 10 patients for which baseline DLQI was available to be excluded.

The original and corrected regression coefficients are shown in Table 4. In turn, we have also presented the updated utility weights (Table 5) and the updated base case results (Table 6). **The changes to the ICERs are negligible.**

**Table 4. Corrected coefficients from utility regression**

| EQ-5D quality of life regression | Original | Corrected |
|---|---|---|
| Constant | 0.109 | 0.1139 |
| PASI_50-74 | 0.084 | 0.0820 |
| PASI_75-89 | 0.117 | 0.1135 |
| PASI_90+ | 0.155 | 0.1520 |
| cntr_dlqt~l | 0.010 | 0.0098 |
| cntr_dlqt~l_ PASI_50-74 | 0.005 | 0.0050 |
| cntr_dlqt~l_ PASI_75-89 | 0.006 | 0.0062 |
| cntr_dlqt~l_ PASI_90+ | 0.009 | 0.0086 |

**Table 5. Utility Weights**

| PASI Response | Original Utility Weights | Corrected Utility Weights |
|---|---|---|
| PASI <50 | 0.109 | 0.114 |
| PASI 50-74 | 0.193 | 0.196 |
| PASI 75-89 | 0.226 | 0.227 |
| PASI 90-99 | 0.264 | 0.266 |
| PASI 100 | 0.264 | 0.266 |
| Source | IMS analysis | IMS analysis |

**Table 6. 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 | 1.01 | | | | | £7,231 |
| **Etanercept 25mg tw** | £75,788 | 1.17 | £2,178 | 0.15 | £14,282 | £14,282* | £2,515 |
| **Secukinumab 300 mg** | £76,361 | 1.39 | £2,752 | 0.38 | £7,231 | £2,515 | |
| **Adalimumab 40 mg** | £76,981 | 1.26 | £3,372 | 0.24 | £13,883 | DOMINATED | DOMINANT |
| **Ustekinumab 45 mg** | £79,544 | 1.34 | £5,934 | 0.32 | £18,373 | DOMINATED | DOMINANT |
| **Ustekinumab 90 mg** | £79,732 | 1.36 | £6,122 | 0.35 | £17,482 | DOMINATED | DOMINANT |
| **Infliximab 5mg/kg** | £93,539 | 1.39 | £19,929 | 0.38 | £52,933 | DOMINATED | DOMINANT |

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

**A12. PRIORITY Please provide a worked example of the arithmetic underlying the calculation of the PASI response distributions of Table 69, with an explanation of the underlying logic to this calculation. For instance, how is the 24.8% for the PASI 75-89 for secukinumab 300mg calculated?**

As mentioned in the response to A4, the probabilities for achieving a PASI 50, PASI 75, and PASI 90 were calculated for each comparator based upon the relevant treatment effect and cut point. These probabilities were used to calculate the proportion of patients in each health state.

To align with the example mentioned in the question, 24.8 % for the PASI 75-89 health state was calculated as follows:

- Pr (PASI<75) = Normal (0,1) cumulative distribution function for treatment effect (-2.65) and the PASI 75 cut point (1.8).

- Pr (PASI<90) = Normal (0,1) cumulative distribution function for treatment effect (-2.65) and the PASI 90 cut point (2.5).

- PASI 75-89 = Pr(PASI < 90) - Pr(PASI<75)
  = NORMDIST(-2.65+2.5,0,1,TRUE) - NORMDIST(-2.65+1.8,0,1,TRUE)
  = (44.5%) - (19.8%)
  = 24.8%

**A13. Please provide a copy of reference 113 (*IMS Health. Secukinumab NICE submission: Utility analysis. Novartis Internal Report 2014*).**

Note this report has been updated to reflect the revision found while conducting the response to A23. The updated report has been attached and is dated January 2015.

**A14. The electronic model in the Drop_Out_Calculations worksheet contains data labelled as PASI < 75 suggesting that 23+7+15+22 patients dropped out from a total of 245+327. Please clarify which trial(s) these data are drawn from and the reason for the choice of trial(s).**

Yes. We can confirm that is the correct calculation. The number of patients was taken from the secukinumab 300mg arms of the two key pivotal trials of ERASURE and FIXTURE.

Of the five secukinumab clinical trials, only three clinical trials (ERASURE, FIXTURE, and SCULPTURE) reported discontinuation at 52 weeks. The dosing regimen used within the SCULPTURE trial is not in line with the secukinumab summary of product characteristics (SmPC) and the dosing of the model. Thus, SCULPTURE was excluded from this calculation.

**A15. The electronic model provides the following coefficients for the quality of life function:**

| EQ-5D quality of life regression | Coef. |
|---|---|
| Constant | 0.109 |
| PASI_50-74 | 0.084 |
| PASI_75-89 | 0.117 |
| PASI_90+ | 0.155 |
| cntr_dlqit~l | 0.010 |
| c.cntr_dlq~l_(PASI_50-74) | 0.005 |
| c.cntr_dlq~l _(PASI_75-89) | 0.006 |
| c.cntr_dlq~l_(PASI_90+) | 0.009 |

**The quality of life function for e.g. PASI 75-89 is given as the sum of:**
- **0.109 = Constant**
- **0.117 = PASI_75-89**
- **0.000 = (Input_DLQI-Average_DLQI)*( cntr_dlqit~l + c.cntr_dlq~l_(PASI_50-74)+ c.cntr_dlq~l _(PASI_75-89))**

**This results in a sum of 0.226 as per Table 85 of the submission. The sum (cntr_dlqit~l + c.cntr_dlq~l_(PASI_50-74)+ c.cntr_dlq~l _(PASI_75-89)) = 0.021 but because Input_DLQI = Average_DLQI = 13.213, the cntr_dlq terms drops out of all of the quality of life value calculations. Please explain these results.**

The explanation of the equation presented in the submission is somewhat truncated. A more succinct version of the equation used in the model is explained in detail below:

Terms in the above equation should be interpreted as follows:

Data related terms:

denotes the absolute EQ-5D utility for patient i at timepoint j

denotes the observed change in EQ-5D utility for patient i at timepoint j

denotes the baseline DLQI associated with patient i (i.e. DLQI score at time 0)

denotes the average baseline DLQI for all patients in the dataset

Parameters estimated by model:

is the average change in EQ5D utility associated with patients achieving a PASI<50 response and average DLQI at baseline ( )

, and represent the mean changes in EQ-5D associated with a PASI 50-74, PASI 75-89 and PASI 90+ response respectively in patients with average DLQI at baseline compared to patients with a PASI<50 response

represents the change in EQ5D utility associated with a one unit increase in DLQI at baseline from the average for patients with a PASI<50 response

, and represent the difference in change in EQ5D utility associated with a one unit increase in baseline associated with a PASI 50-74, PASI 75-89 and PASI 90+ response respectively compared to patients with a PASI<50 response, i.e. the difference in slopes associated with each level of PASI response

is a residual error term

is a random intercept term to account for between patient variability:

Note: is the between patient variance parameter estimated by the model

The DLQI variable was centred according to the average DLQI calculated from the dataset (13.213) in order to ensure that the utility values outputted were reflective of the dataset used (since this is where efficacy data is taken from). This value was put into the equation so that the utility values used in the model correspond to patients with the average DLQI in the dataset. As can be seen from the regression equation, any terms multiplied by the centred DLQI variable disappear when the average DLQI from the dataset is inputted into the equation.

The table from question A15 has been updated (Table 7) and it now includes the terms in the regression equation above.

**Table 7. Coefficients in the regression model**

| EQ-5D quality of life regression | Coefficient | Symbol in regression equation |
|---|---|---|
| Constant | 0.1139 | |
| PASI_50-74 | 0.0820 | |
| PASI_75-89 | 0.1135 | |
| PASI_90+ | 0.1520 | |
| cntr_dlqt~l | 0.0098 | |
| cntr_dlqt~l_ PASI_50-74 | 0.0050 | |
| cntr_dlqt~l_ PASI_75-89 | 0.0062 | |
| cntr_dlqt~l_ PASI_90+ | 0.0086 | |

Using the coefficients in the table above to calculate the change in EQ-5D utility for a PASI 75-89 assuming they had the average DLQI, the equation becomes:

**A16. A categorical variable for PASI response is described in the submission, and is used, for example, in the β1PASIij term. Please provide more detail for this categorical variable. For example, does '0', '1', '2', '3' represent a PASI response of '<50', '50-74', '75-89' and '90+'. Has some other categorisation been used? Or does the calculation use a number of dummy variables, and use β1PASI_50-74ij + β2PASI_75-89ij + β3PASI_90ij within which for a patient i with a PASI response of 75-89 at time point j would see PASI_50-74ij =0, PASI_75-89ij = 1 and PASI_90ij = 0?**

As mentioned in A15, the functional form is:

Where

To align with the example given in the question, we confirm that patient i with a PASI response of 75-89 at time j would be coded in the dataset as PASI_50-74ij =0, PASI_75-89ij = 1 and PASI_90ij = 0.

**A17. Please clarify how the arithmetic bulleted above under A15 is in line with the functional form given on page 187 of the submission, and how the coefficients of the electronic model correspond with the *α, β1, βj* and *β3* of the functional form on page 187 of the submission.**

Aligning with the response given in A15, the coefficients in the Table 4 were used to calculate the change in EQ-5D utility for a PASI 75-89, and this assumes patient i had the average DLQI.

The calculation is as follows:

**A18. Please confirm whether *ΔEQ-5Dij* represents the change from baseline.**

We can confirm that represents change from baseline in EQ-5D utility. Please see equation in the response to question A15 for a more complete description.

**A19. Please clarify whether data from multiple studies were included in the utility model. Was any study level effect explored and, if so, what were the results of this?**

We can confirm that the analysis was conducted using pooled data from 5 studies (ERASURE, FIXTURE, SCULPTURE, FEATURE, and JUNCTURE). The effect of including a categorical level covariate for study was explored. The functional form of this model is shown below:

Where, for example:

Note that ERASURE was used as the reference case in this regression model. The corresponding results for this model are shown in Table 8 .

**Table 8. Coefficients in the regression model including a categorical variable for study**

| EQ-5D quality of life regression | Coefficient | Symbol in regression equation |
|---|---|---|
| Constant | 0.103 | |
| FIXTURE | 0.007 | |
| SCULPTURE | 0.025 | |
| FEATURE | 0.019 | |
| JUNCTURE | -0.001 | |
| PASI_50-74 | 0.082 | |
| PASI_50-89 | 0.114 | |
| PASI_90+ | 0.152 | |
| cntr_dlqt~l | 0.01 | |
| cntr_dlqt~l_ PASI_50-74 | 0.005 | |
| cntr_dlqt~l_ PASI_75-89 | 0.006 | |
| cntr_dlqt~l_ PASI_90+ | 0.009 | |

A chi-squared test was carried out on the study coefficients which gave a p-value 0.2342 indicating that study does not have an effect on the change in EQ-5D. We also note that the coefficients associated with PASI response and DLQI are the same to 3 decimal places and therefore adjusting for study is unlikely to produce materially different predicted utilities.

Furthermore, the regression was used to predict utility weights for the economic model, and it is not obvious which study coefficient to use while making predictions. Therefore we believe using the model without adjusting for study is the correct approach.

**A20. The text states that only the baseline DLQI is used, in which case the functional form would be:**

$$\Delta EQ\text{-}5D_{ij} = \alpha + \beta_1 PASI_{ij} + \beta_2 DLQI_{i0} + \beta_3 PASI_{ij} * DLQI_{i0} + u_i + w_{ij}$$

**Please outline which functional form has been adopted. If *$DLQI_{i0}$* has been used, what is the purpose of the *$\beta_2 DLQI_{i0}$* term given α and $u_i$?**

From question A15, the functional form is:

Where:

denotes the baseline DLQI associated with patient i (i.e. DLQI score at time 0)

denotes the average baseline DLQI for all patients in the dataset

is the average change in EQ5D utility associated with patients achieving a PASI<50 response and average DLQI at baseline ( )

is a random intercept term to account for between patient variability:

Note: is the between patient variance parameter estimated by the model

We can confirm that baseline DLQI was used as a covariate and centred at the mean value in the dataset. Please see the response to A15 for additional context of the regression and interpretation of the coefficients.

**A21. If *DLQIij* is used (rather than baseline DLQI), with this value varying with both i and j within the quality of life regression, please describe the extent to which the contemporaneous DLQI is taken into account within the electronic model, and the impact that this may have upon results.**

We confirm that baseline DLQI was used.

**A22. Please provide more information on (Input_DLQI-Average_DLQI), including how it should be interpreted, why it is zero for all the calculated values and why it is correct for all the cntr_dlq coefficients to drop out of all the quality of life calculations as a result.**

As mentioned in the response to A15, the DLQI variable was centred according to the average DLQI calculated from the dataset (13.213) in order to ensure that the utility values outputted were reflective of the dataset used (since this is where efficacy data is taken from). This value was put into the equation so that the utility values used in the model correspond to patients with the average DLQI in the dataset. As can be seen from the regression equation, any terms multiplied by the centred DLQI variable disappear when the average DLQI from the dataset is inputted into the equation.

**A23. Please provide a justification for using a complete case analysis approach. Please also present a summary of the total number of observations available at each time point, the number of missing observations at each time point (also enumerating which of the data elements are missing) and the resulting number of complete cases that are available for analysis within the complete case analysis.**

We believe the complete case analysis approach is justified on the basis that only 125/3366 (<5%) of patients in the original dataset are omitted from the analysis due to missing covariate values. We also considered the number of patients who were missing from the analysis at each time point. It should be noted that the number of patients missing from the analysis at each time point is also a function of how EQ-5D was collected in each trial and therefore we consider the number of patients who were missing at each time point due to missing covariates separately. The schedule for EQ-5D collection in each trial is shown in Table 9 and the number of missing observations by time point is shown in Table 10.

**Table 9. EQ-5D collection schedule in included trials**

| | Analysis Week | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Baseline** | **2** | **4** | **8** | **12** | **16** | **20** | **24** | **28** | **32** | **36** | **40** | **44** | **48** | **52** | **Follow-up** |
| ERASURE | x | | x | x | x | | | x | | | x | | | | x | |
| FIXTURE | x | | x | x | x | | | x | | | x | | | | x | |
| SCULPTURE | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| FEATURE | x | | x | x | x | | | x | | | x | | | | x | |
| JUNCTURE | x | | x | x | x | | | x | | | x | | | | x | |

EQ-5D = EuroQol-5 Dimensions Health Status Questionnaire.

**Table 10. Missing observations**

| Week | Number of patients | Number of missing EQ-5D observations | Number of missing DLQI observations[1] | Number of missing PASI observations[1] | Number of observations omitted[1] |
|---|---|---|---|---|---|
| **0** | 3365 | 79 | N/A | N/A | N/A |
| **1** | 3353 | 3353 | 0 | 0 | 0 |
| **2** | 3353 | 2425 | 13 | 1 | 13 |
| **4** | 3353 | 78 | 65 | 3 | 67 |
| **8** | 3353 | 30 | 65 | 3 | 67 |
| **12** | 3353 | 24 | 66 | 3 | 68 |
| **16** | 2835 | 2835 | 0 | 0 | 0 |
| **20** | 2835 | 2835 | 0 | 0 | 0 |
| **24** | 2835 | 868 | 39 | 2 | 41 |
| **28** | 2835 | 2835 | 0 | 0 | 0 |
| **32** | 2835 | 2835 | 0 | 0 | 0 |
| **36** | 2835 | 857 | 40 | 2 | 42 |
| **40** | 2835 | 2835 | 0 | 0 | 0 |
| **44** | 2835 | 2835 | 0 | 0 | 0 |
| **48** | 2835 | 2835 | 0 | 0 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| **52** | 2835 | 856 | 40 | 2 | 42 |
| [1]Assuming EQ-5D available | | | | | |

**A24. Please clarify what correlation structures were explored for the linear mixed model, and what was used for the final model?**

We attempted to fit models using the following correlation structures:

1. Independent
2. Exchangeable
3. Unstructured

When fitting the exchangeable variance model the likelihood ratio test for the null hypothesis that the random effects variance=0 has p-value<0.001. This means that the independent correlation model is unlikely to be appropriate compared to the exchangeable variance model since the estimation of a non-zero random effects variance cannot be attributed to chance. When testing the unstructured correlation model, it did not converge in Stata using the command "xtreg," and we are unable to report meaningful results from this analysis. Therefore, the exchangeable variance model is the most appropriate, and this was used in the final model.

**A25. Section 7.5.5 notes a hospitalisation cost of £5,337. Table 100 suggests that this is a cost associated with psoriasis, based upon the 10.7 average hospital days for people with psoriasis. Please confirm which PASI health states this cost applies to within the model, and please give more detail on the rationale for the assumptions made around this health state cost.**

Yes, we confirm that the cost of hospitalisation was based on an average LoS of 10.7 days. The cost of hospitalisation, which was calculated to be £5,337 when applying 10.7 days to the average day cost of a psoriasis hospitalisation (£498.80).

***Calculation of Hospitalisation Cost:***
The methodology for this calculation is aligned with that of prior submissions using the latest available data. The LoS was taken from HES and per diem cost of hospitalisation was taken from NHS reference costs.

The LoS reported by HES has effectively reduced by half from 2002/03 to 2012/13 (i.e. 19.6 days in HES 2002/03 to 10.7 days in 2013/14). Over the same period, the per diem cost of hospitalization using NHS reference costs has doubled (£ 248.31 to £498.80).

Given the changes in the treatment paradigm over the past 10 years and inflation, we were initially unsure if this estimate was in-line with UK clinical practice. Thus, we consulted with two expert dermatologists about the methodology of costing and the cost of hospitalization. Both clinicians confirmed that the method and cost of hospitalisation was appropriate and in-line with their clinical experience.

***Frequency of Hospitalisation:***
The frequency of hospitalisation in the model was aligned with CG 153 which specified that 82% of the patient population on standard of care (SoC) were considered high need and admitted

once per year. The remaining 18% were considered very high need and admitted 2.55 times per year.

During model development, a weighted average of “high need” and “very high need” admissions was considered. If the weighted average had been considered, the hospitalisation cost would have been more than 25% higher. However, we decided to use the more conservative estimate of £5,337 in the base case as we knew this was a key driver of model results.

***Hospitalisation within health states:***
In the first year, the cost of one hospitalisation was applied to patients that discontinue active treatment. As such, the cost of hospitalisation was applied in the following health states: PASI<50, PASI 50-74, PASI 75-89, and PASI 90+.

In years 2-10, the cost of one hospitalisation was applied to patients who were on SoC. For active treatment arms, this was applied to PASI <50 and PASI 50-74 in the base case. For the SoC arm, this was applied to the following health states in the base case: PASI<50, PASI 50-74, PASI 75-89, and PASI 90+.

**A26. The source of the average length of stay (LoS) for psoriasis (10.7 days) is given as reference 37, which provides an HTML link to the HSCIC website, however no further relevant information is available. Please provide detail on how the 10.7 days average LoS for psoriasis has been calculated, including a table at the most disaggregate level possible of the data underlying this calculation coupled with the relevant HES categories and codes. Please also clarify whether the LoS data are specific to each of the four health states within the model.**

Various codes and combinations of LoS for psoriasis hospitalization were explored on the HES website during model development. Ultimately, the code L40.0 for Psoriasis Vulgaris was selected as it was the most specific to plaque psoriasis and aligned with analyses conducted in NICE CG153 (appendix P, Table 59). The most recent version of HES was used (i.e.2012/13), which specified 10.7 days as the mean LoS for code L40.0. The LoS of 10.7 days was also validated during a consultation with two expert dermatologists.

This worksheet was retrieved from the HSCIC website on the 5 of November 2013 using the link: http://www.hscic.gov.uk/article/2021/Website-Search?productid=13264=primary+diagnosis+ICD&sort=Relevance&size=10&page=1&area=both#top. Unfortunately, this link does not lead to the same section of the website and therefore we are not able to access the excel file during the time of response to the clarification questions.

Apologies that the relevant information was not on the website, but we do have a hard copy of the HSCIC workbook, that was used during model development. Please find attached an excel document which highlights the value that was used labeled ‘A26. HES-admi-diag-2012-2013-tab_MARKED.xlsx’. Code L40.0 is situated on the sheet labeled “Primary Diagnosis – 4 char” and highlighted in yellow for ease of validation.

**A27. Please tabulate what hospitalisation data and resource use data, if any, were collected during each of the secukinumab trials. If hospitalisation data and resource use data were collected during any of the studies periods, please provide answers to the following questions:**

a. **What proportions of patients within each trial were from countries where hospitalisation rates might be expected to be reasonably similar to that of the UK?**

This data was not collected during the clinical trials.

b. **To what extent would it have been possible to map this resource use data to the PASI response categories of the model?**

This data was not collected during the clinical trials.

**A28. Please provide more detailed references for the NHS reference costs cited within the electronic model, including the name of the reference cost spreadsheet, together with an HTML link to this spreadsheet and the worksheet.**

Please find an excel spreadsheet attached with detail of all the NHS reference costs used in the electronic model and linked to the relevant spreadsheet from which it was sourced. The HTML link to access the workbook is https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013 and the workbook that was selected was the 'National schedule of reference costs: the main schedule'.

## Appendix 1 – revised included/excluded study lists and Table 53

**Table 11 List of included RCTs across all NMAs**

| Trial | Citation |
|---|---|
| ACCEPT<br>(Griffiths 2010) | Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. The New England journal of medicine. Jan 14 2010;362(2):118-128. |
| Bagel<br>(Bagel 2012) | Bagel J, Lynde C, Tyring S, Kricorian G, Shi Y, Klekotka P. Moderate to severe plaque psoriasis with scalp involvement: a randomized, double-blind, placebo-controlled study of etanercept. Journal of the American Academy of Dermatology. Jul 2012;67(1):86-92.- dose not relevant |
| Bissonnette<br>(Bissonnette 2013) | Bissonnette R, Tardif JC, Harel F, Pressacco J, Bolduc C, Guertin MC. Effects of the tumor necrosis factor-alpha antagonist adalimumab on arterial inflammation assessed by positron emission tomography in patients with psoriasis: results of a randomized controlled trial. Circ Cardiovasc Imaging 2013 Jan 1;6(1):83-90. |
| ERASURE/CAIN457A2302 | Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. The New England journal of medicine. Jul 24 2014;371(4):326-338. |
| FIXTURE/CAIN457A2303 | Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. The New England journal of medicine. Jul 24 2014;371(4):326-338. |
| SCULPTURE/<br>CAIN457A2304 | No publication. Data provided by Novartis. |
| FEATURE/CAIN457A2308 | Paul C. Secukinumab efficacy and safety: Results from the First study of sEcukinumAb in prefilled syringes in subjecTs with chronic plaqUe-type psoriasis REsponse at 12 weeks (FEATURE). 2014 Conference abstract # P8053. |
| JUNCTURE/CAIN457A2309 | Blauvelt A. Secukinumab efficacy and safety in subjects with moderate to severe plaque psoriasis: Results from the Judging the efficacy of secUkinumab in patients with psoriasis using autoiNjector: a Clinical Trial evalUating treatment REsults trial (JUNCTURE). 2014 Conference abstract # P8054. |
| CHAMPION<br>(Saurat 2008) | Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008 Mar;158(3):558-66. |
| CNTO 1275 Psoriasis Study<br>(Krueger 2007) | Krueger GG, Langley RG, Leonardi C, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 2007 Feb 8;356(6):580-92. |
| Etanercept Psoriasis Study group<br>(Leonardi 2003) | Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003 Nov 20;349(21):2014-22. |
| EXPRESS<br>(Reich 2006)[1] | Reich K, Nestle FO, Papp K, et al. Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. Br J Dermatol 2006 Jun;154(6):1161-8. |

| Trial | Citation |
|---|---|
| EXPRESS II<br>(Menter 2007) | Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol 2007 Jan;56(1):31-15. |
| Gottlieb<br>(Gottlieb 2003) | Gottlieb AB, Matheson RT, Lowe N, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol 2003 Dec;139(12):1627-32. |
| Gottlieb – A<br>(Chaudari 2001) | Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomized trial. Lancet 2001;357:1842-7.<br>Gottlieb AB, Matheson RT, Lowe N, et al. Infliximab monotherapy provides rapid and sustained benefit for plaque-type psoriasis. J Am Acad Dermatol 2003 Jun;48(6):829-35. |
| Japanese Ustekinumab Study<br>(Igarashi 2012) | Igarashi A, Kato T, Kato M, Song M, Nakagawa H. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. J Dermatol 2012 Mar;39(3):242-52. |
| LOTUS<br>(Zhu 2013) | Zhu X, Zheng M, Song M, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). J Drugs Dermatol 2013 Feb;12(2):166-74. |
| M04-688<br>(Asahina 2010) | Asahina A, Nakagawa H, Etoh T, Ohtsuki M. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a Phase II/III randomized controlled study. J Dermatol 2010 Apr;37(4):299-310. |
| M02-528<br>(Gordon 2006) | Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol 2006 Oct;55(4):598-606. |
| M10-315<br>(Strober 2011) | Strober BE, Crowley JJ, Yamauchi PS, Olds M, Williams DA. Efficacy and safety results from a phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. Br J Dermatol 2011 Sep;165(3):661-8. |
| M10-114<br>(Gottlieb 2011) | Gottlieb AB, Leonardi C, Kerdel F, Mehlis S, Olds M, Williams DA. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. Br J Dermatol 2011 Sep;165(3):652-60. |
| Papp<br>(Papp 2005) | Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, et al A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 2005 Jun;152(6):1304-12. |
| PEARL<br>(Tsai 2011) | Tsai TF, Ho JC, Song M, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). J Dermatol Sci 2011 Sep;63(3):154-63. |
| PHOENIX 1<br>(Leonardi 2008) | Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients |

| Trial | Citation |
|---|---|
| | with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008 May 17;371(9625):1665-74. |
| PHOENIX 2<br>(Papp 2008) | Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008 May 17;371(9625):1675-84. |
| REVEAL<br>(Menter 2008) | Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. J Am Acad Dermatol 2008 Jan;58(1):106-15. |
| SPIRIT<br>(Gottlieb 2004) | Gottlieb AB, Evans R, Li S, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 2004 Oct;51(4):534-42. |
| Torii<br>(Torii 2010) | Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. J Dermatol Sci 2010 Jul;59(1):40-9. |
| Tyring<br>(Tyring 2006) | Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006 Jan 7;367(9504):29-35. |
| van de Kerkhof<br>(van de Kerkhof 2008) | van de Kerkhof PC, Segaert S, Lahfa M, Luger TA, Karolyi Z, Kaszuba A, et al Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. Br J Dermatol 2008 Nov;159(5):1177-85. |
| Yang<br>(Yang 2012) | Yang HZ, Wang K, Jin HZ, et al. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. *Chinese medical journal.* Jun 2012;125(11):1845-1851. |

1 incorrectly labelled Reich 2005 in network diagrams

**Table 12 List of studies excluded from the NMA**

| Trial | Citation |
|---|---|
| Gottlieb - NCT01001208 | Gottlieb AB, Langley RG, Strober BE, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. Br J Dermatol 2012 Sep;167(3):649-57**.- dose not relevant** |
| RESTORE1 | Barker J, Hoffmann M, Wozel G, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). Br J Dermatol 2011 Nov;165(5):1109-17**.- timepoint not of interest** |
| REACH | Leonardi C, Langley RG, Papp K, Tyring SK, Wasel N, Vender R, et al. Adalimumab for treatment of moderate to severe chronic plaque psoriasis of the hands and feet: efficacy and safety results from REACH, a randomized, placebo-controlled, double-blind trial. Arch |

| Trial | Citation |
|---|---|
| | Dermatol 2011 Apr;147(4):429-36.- **trial timepoint not of interest** |
| TRANSIT | Weissenseel P. Ustekinumab is well-tolerated & effective in patients with psoriasis inadequately responsive to methotrexate: Week 12 results from the TRANSIT study. JDDG - Journal of the German Society of Dermatology 2011;9(11):984. **data not relevant for NMA** |
| Revicki | Revicki D, Willian MK, Saurat JH, Papp KA, Ortonne JP, Sexton C, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16- week randomized controlled trial in patients with moderate to severe plaque psoriasis. Br J Dermatol 2008 Mar;158(3):549-57 **data not relevant for NMA** |
| Krueger | Krueger GG, Langley RG, Finlay AY, Griffiths CE, Woolley JM, Lalla D, et al. Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized phase III trial. Br J Dermatol 2005 Dec;153(6):1192-9. **data not relevant for NMA** |
| Papp | Papp KA, Langley RG, Sigurgeirsson B, et al. Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. Br J Dermatol 2013 Feb;168(2):412-21. **dose not relevant** |
| PRISTINE | Strohal R, Puig L, Robertson D, Estojak J, Pedersen R, Melin J, et al. Efficacy and safety of etanercept for the treatment of moderate-to-severe psoriasis when used with adjunctive topical therapy as needed: the PRISTINE Trial (Abstract 404) 40th Meeting of the European Society for Dermatological Research, 08- 11 September 2010, Helsinki, Finland. Journal of Investigative Dermatology 2010;130:S68. **data not relevant for NMA** |
| Revicki | Revicki DA, Willian MK, Menter A, Gordon KB, Kimball AB, Leonardi CL, et al. Impact of adalimumab treatment on patient- reported outcomes: results from a Phase III clinical trial in patients with moderate to severe plaque psoriasis. J Dermatolog Treat 2007;18(6):341-50. **data not relevant for NMA** |
| Reich | Reich K, Puig L, Luger T, Lambert J, Chimenti S, Girolomoni G, et al. Long-term improvement in patient-reported outcomes after transition from methotrexate to ustekinumab in moderate to severe psoriasis: Transit week 52 results. Value in Health 2012;15(7):A573. **data not relevant for NMA** |
| Rich | Rich P, Sigurgeirsson B, Thaci D, et al. Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled, phase II regimen-finding study. Br J Dermatol 2013 Feb;168(2):402-11. **dose not relevant** |
| Kimball | Kimball A, Chen L, Mulani P, Gupta S The benefits of adalimumab on clinical and patient-reported outcomes among moderate to severe psoriasis patients with comorbidities. Journal of the American Academy of Dermatology 2009;60(3):AB95. **data not relevant for** |

| Trial | Citation |
|---|---|
| | **NMA** |
| Kumari | Kumari N Secukinumab for treatment of moderate-to-severe plaque psoriasis: Results of a double-blind, parallel group, placebo-controlled, phase II dose ranging study. Dermatology and Therapy 2012;2:S39-S40. **dose not relevant** |
| Weissenseel | Weissenseel P. Ustekinumab improves quality of life outcomes in psoriasis patients transitioned from methotrexate regardless of transition strategy: Week 16 results from the TRANSIT study. JDDG - Journal of the German Society of Dermatology 2011;9(11):983. **data not relevant for NMA** |
| Lebwohl | Lebwohl M, Gordon K, Okun M, Blum R Efficacy and safety of a second adalimumab treatment cycle in psoriasis patients who relapsed after adalimumab discontinuation or dosage reduction. Journal of the American Academy of Dermatology 2010;62(3):AB129. **data not relevant for NMA** |

## Table 13 Summary of data used in NMA (updated Table 53 from submission)

| 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 primary trial endpoint) | 12 week | 16 week (NICE primary trial 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 | |
| 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 | |

| 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 primary trial endpoint) | 12 week | 16 week (NICE primary trial endpoint) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 | secukinumab 150 | 12 | 59 | 3 | 5.1 | 0 | 0 | 0 | 0 | 0 | 0 | YES | YES | |
| FEATURE | Blauvelt 2014 | secukinumab 300 | 12 | 59 | 51 | 86.4 | 41 | 69.5 | 27 | 45.8 | 5 | 8.5 | YES | YES | |
| FEATURE | Blauvelt 2014 | Placebo | 12 | 58 | 51 | 87.9 | 44 | 75.9 | 35 | 60.3 | 24 | 43.1 | YES | YES | |
| JUNCTURE | Paul 2014 | placebo | 12 | 61 | 5 | 8.2 | 2 | 3.3 | 0 | 0 | 0 | 0 | YES | YES | |
| JUNCTURE | Paul 2014 | secukinumab 150 | 12 | 60 | 48 | 80 | 43 | 71.7 | 24 | 40 | 10 | 16.7 | YES | YES | |
| JUNCTURE | Paul 2014 | secukinumab 300 | 12 | 60 | 58 | 96.7 | 52 | 86.7 | 33 | 55 | 16 | 26.7 | 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 |
| M02-528 | Gordon 2006 | placebo | 12 | | | | 2 | 4.0 | | | 0 | 0.0 | | YES | |
| M02-528 | Gordon 2006 | adalimumab | 12 | | | | 23 | 53.0 | | | 4 | 11.0 | | YES | |
| PEARL | Tsai 2011 | placebo | 12 | 60 | 8 | 13.3 | 3 | 5 | 1 | 1.7 | 0 | 0 | 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 primary trial endpoint) | 12 week | 16 week (NICE primary trial endpoint) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 |
| 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 |