NICE National Institute for Health and Care Excellence

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**Single Technology Appraisal (STA)**

**Secukinumab for treating moderate to severe plaque psoriasis ID718**

Dear [redacted],

The Evidence Review Group, Aberdeen Health Technology Assessment Group and the technical team at NICE have now had an opportunity to take a look at the submission received on the 2 December 2014 by Novartis. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on 16 January 2015. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Carl Prescott, Technical Lead (carl.prescott@nice.org.uk ). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk) in the first instance.

Yours sincerely

Dr Elisabeth George
Associate Director – Appraisals
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**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.

| Patients with week 12 PASI 50-74 | SoC | Secukinumab 300 | Etanercept |
|---|---|---|---|
| Week 52 PASI | | | |
| PASI < 50 | N=??? | N=??? | N=??? |
| PASI 50 - 74 | N=??? | N=??? | N=??? |
| PASI 75-89 | N=??? | N=??? | N=??? |
| PASI 90+ | N=??? | N=??? | N=??? |
| PASI 100 | N=??? | N=??? | N=??? |

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)?

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

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.

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

A6. Please present Figure 14 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*.

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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?

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?

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.

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.

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

**Section B: Clarification on cost-effectiveness data**

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?

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

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

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total of 245+327. Please clarify which trial(s) these data are drawn from and the reason for the choice of trial(s).

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.

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?

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.

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

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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?

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 $u_i$?

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.

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.

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.

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

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.

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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?

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

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.