NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria

Dear [redacted],

The Evidence Review Group, Southampton Health Technology Assessment Centre (SHTAC), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 24 July 2014 by Novartis Pharmaceuticals UK. 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 **6pm** on **28 August 2014**. 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 Pilar Pinilla-Dominguez, Technical Lead (pilar.pinilla-dominguez@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

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority question:** Please clarify the definition for the outcome 'Number of weekly ISS MID responders' (Table B9 p78).

A2. **Priority question:** Please clarify the number of participants in each treatment group (omalizumab 300 mg and placebo) with data included in these secondary efficacy analyses from the GLACIAL trial (Table B9 p78).

A3. **Priority question:** Sub-analysis of GLACIAL trial (p80):

a. Please provide a clearer explanation for why the subgroup (concurrent treatment with H1antihistamines and LTRA and H2 antihistamines) is more aligned to the manufacturer's decision problem. The positioning of omalizumab in the submission described in Figure A3 p30 shows four current treatment groups with omalizumab as an option for each of these groups (not just the group on the far right of the figure treated with H1antihistamines and LTRA and H2 antihistamines). Similarly the decision problem (on p40) describes the population as having inadequate response despite combinations of up to 4x dose of H1antihistamines +/- LTRA +/- H2 antihistamines.

b. What was the proportion of missing data for these analyses? The cited reference (ref 90) for the subgroup analysis indicates that all the analyses were performed on observed data, there was no imputation of missing data. However Table B10 on p80 and Table B6 on p65-66 do not seem to corroborate one another. Table B6 with baseline characteristics for number (%) CSU medication use on study day 1 of H1+H2+LTRA gives n=64 in the omalizumab group and n=25 in the placebo group but in the subgroup analyses n=[redacted](UAS7)/n=[redacted](DLQI & AE) for the omalizumab at 12 weeks group. Please explain this discrepancy.

c. What method of data analysis was used to determine that there was no significant difference in efficacy for the subgroup compared to the whole study population?

Meta-analysis

A4. **Priority question:** No meta-analysis was conducted because studies were not considered sufficiently similar or equally relevant to the decision problem. However, in the economic analysis EQ-5D values were based on patient-level EQ-5D data pooled across all phase III trials (GLACIAL, ASTERIA I and ASTERIA II) and all treatment groups within the trials. Please explain why the approach to combining data differs between the two sections of the submission (p84).

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

A5. On p373 it is stated that 'only a small number of patients in both ASTERIA I and ASTERIA II had been previously treated with LTRA and H2 antihistamines'. Please provide a breakdown of the number of patients previously treated with LTRA and H2 antihistamines for each of the arms in the trials.

Decision problem

A6. Please explain what is meant by "the submission represents a selective submission (p22)".

A7. The decision problem addressed in the submission differs from the scope issued by NICE. The proposed decision problem matches the eligibility criteria for the GLACIAL trial (CSU with inadequate response despite combinations of up-dosed H1 antihistamines, with/out LTRA with/out H2 antihistamines), but does not mention that the economic analysis is limited to patients with moderate or severe disease (defined by UAS7 score of 16-27 for moderate urticaria and 28-42 severe urticaria). Should this initial severity-based condition also be specified in the decision problem? (Section 5, Decision Problem p39-43).

A8. Please confirm whether or not randomisation was stratified by prior or concomitant therapy (Table B4 p63).

A9. In Figure B2 (p74) the number of patients excluded is n=144 and the reasons for excluding patients sum to 86. Please provide further details of the reasons for excluding the other 58 patients (Figure B2 p74).

A10. In Figure B2 (p74) it is not clear why the one patient in the placebo group who was not treated was not taken into account when calculating the number who completed the study drug (stated as 63, but should be 62?) and number who completed the study (stated as 66, but should be 65?). Please provide further details on this.

A11. In Figure B3 (p77) (also presented as Figure 2 in Kaplan et al [2013]), please can you indicate, for each trial arm, at each observation point how many baseline observations carried forward (BOCF) are contributing to the reported mean values?

A12. Please supply a list of the 15 included records shown in the flow diagram shown in Figure B6 p101.

Indirect comparison

A13. Please provide further justification as to why the severity scoring system used in Vena et al. (2006) is different to the one used in the omalizumab trials (p92).

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Missing data and imputation

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

a. **Priority question:** Please clarify if the baseline observation carried forward (BOCF) and last observation carried forward (LOCF) were the only imputation methods attempted in the development of the manufacturer's submission. The appendix to the Kaplan et al (2013) paper describes use of additional multiple imputation methods, which are not discussed in the manufacturer's submission.

b. Please provide a reason why mixed-model repeated-measures analyses were not undertaken.

c. Standard texts (Glick HA et al Economic Evaluation in Clinical Trials. Oxford Handbook in Health Economic Evaluation. OUP, Oxford. 2007. Willan AR, Briggs AH. Statistical Analysis of Cost-effectiveness Data. John Wiley and Sons Ltd, England. 2006) describe analytical approaches to dealing with missing and/or censored data for economic evaluations. Please provide the rationale for using alternative approaches to analysis and imputation of missing/censored observations?

d. **Priority question:** Please provide the rationale for using the last observation carried forward (LOCF) method for estimating the proportion of patients in each health state at each time point for populating the economic model (section 7.3.1, p162).

B2. **Priority question:** In Table A1, p 20 of the manufacturer's submission, the average length of a course of treatment is stated as "20 weeks, adjusted for early discontinuation of non-responders".

a. **Priority question:** Please provide a clear explanation of how this is implemented in the economic model

b. **Priority question:** Please also indicate which worksheets and cells in the submitted electronic model are used to produce this adjustment

c. Please provide further justification for assuming that following re-treatment the response to omalizumab is similar to the original response.

d. Please provide further justification for assuming that patients whose disease relapses do not get re-treatment immediately.

Utility values

B3. **Priority question:** The utility values used in the model are based on pooled EQ-5D responses in the ASTERIA I, ASTERIA II and GLACIAL trials. None of the trial references provided in the submission have reported any EQ-5D-based data – none of the included references have made any mention of the collection of EQ-5D data within the trials. EQ-5D is not listed as an outcome evaluated in the

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

GLACIAL trial in the description of primary and secondary outcomes included in the trial (see Table B7, pp 68 to 70) while other quality of life measures such as DLQI and CU-Q2oL are described and their inclusion justified. There is no reference to the administration of the EQ-5D in the GLACIAL trial in the clinical effectiveness section of the manufacturer's submission. Please confirm whether any of the EQ-5D data from the ASTERIA I, ASTERIA II or GLACIAL trials have been presented/peer reviewed, and if so please provide references

B4. **Priority question:** The manufacturer's submission states on p182 that the EQ-5D was administered at baseline, week 12 and week 40:

a. Please state whether administration of the EQ-5D was specified in the trial protocols for the GLACIAL trial (this outcome is not listed in the entry for NCT01264939 on clinicaltrials.gov) and for the ASTERIA I and ASTERIA II trials (this outcome is not listed in entry for NCT01287117 or for NCT01292473 on clinicaltrials.gov).

b. Please state how and when the EQ-5D was administered at baseline in the GLACIAL, ASTERIA I and ASTERIA II trials. For example, did patients complete the EQ-5D during baseline clinical assessment and was this done alongside the DLQI & CU-Q2oL or were they completed separate from the clinical assessment?

c. Please state how and when the EQ-5D was administered at week 12 and week 40 – alongside or separate from clinical assessments? Please provide this information for the GLACIAL, ASTERIA I and ASTERIA II trials.

d. Please state whether the EQ-5D was completed at the same time as other quality of life assessments in the GLACIAL, ASTERIA I and ASTERIA II trials.

B5. **Priority question:** The manufacturer's submission contains no information on completion or response rates for the EQ-5D in the ASTERIA I, ASTERIA II and GLACIAL trials. Please provide details of the response rates, and item completion for the EQ-5D in the ASTERIA I, ASTERIA II and GLACIAL trials for each time-point that the questionnaires were administered.

B6. **Priority question:** The manufacturer's submission contains very limited methodological detail on the analysis conducted to generate the mean utility values for health states used in the model, other than to state that a "mixed effect regression model was … used to estimate utility values for each of the health states …." (p182). Please provide a detailed analysis report including details of the inclusion of imputed values for UAS7 (to define health state) or EQ-5D responses, if relevant.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

B7. **Priority question:** Table B31 (p183), includes a column headed "N" against each health state.

a. Please confirm whether this indicates the total number of completed questionnaires providing data for each state (and not number of patients)?

b. The sum of the "N"s is 2,030 (783+538+211+209+289) which is greater than the number of patients in the three trials that are reported as being the source for these data (ASTERIA I = 323, ASTERIA II = 318, GLACIAL = 335, total patients = 976). This suggests that the analysis contains multiple observations for patients in the trials (presumably from the three indicated time-points: baseline, week 12 and week 40). Please confirm whether this is correct.

c. Please indicate whether you consider it appropriate to include multiple observations for patients in the analysis. How does the regression analysis account for the inclusion of repeated measures?

d. Please indicate how you have dealt with missing values in the analysis. Was any imputation attempted (to deal with item non-response or missing observations) or is this a complete case analysis?

B8. Distribution of EQ-5D responses for patients within each health state.

a. Please indicate the minimum and maximum EQ-5D index score in each health state.

b. Please present a chart showing individual EQ-5D index scores within each health state, in ascending order. Please also indicate whether there are any imputed (carried forward) values in these analyses.

Distribution of UAS7 scores

B9. Distribution of UAS7 scores for patients within each health state.

a. Please provide the mean, standard deviation, standard error and number of observations for UAS7 scores by health state.

b. Please also provide the median, minimum & maximum values and 2.5th, 25th, 75th and 97.5th percentiles.

Drop outs and discontinuations

B10. In the GLACIAL trial publications it is reported that 28 participants in the omalizumab arm and 18 participants in the placebo arm dropped out. In the manufacturer's submission (Tables B27 and B29) the data do not concur with this. For the omalizumab arm there were 8 drop outs in the moderate group and 39 drop outs in the severe group (therefore n=47). For the placebo group there

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

were 5 drop outs in the moderate group and 17 in the severe group (therefore n=22).

a. Please provide further explanation of where the additional 19 omalizumab drop outs and 4 additional placebo drop outs come from?

b. The ERG note that using the proportions of moderate:severe participants used elsewhere in the manufacturer's submission (that is 29%:71% in the omalizumab group and 39%:61% in the placebo arm) and the trial data for drop-outs, there would be 8 moderate and 20 severe participants dropping out of the omalizumab arm and 7 moderate and 11 severe participants dropping out of the placebo arm. In your response to the above question please also provide an explanation as to why the additional drop outs observed in the manufacturer's submission appear mostly in the two severe participant groups.

Probability of relapse

B11. Please provide a rationale for not adopting standard survival analysis techniques to model the probability of relapse – using relapse as the event of interest and using standard approaches to censored observations. The potential appropriateness of such an approach is not discussed in the relevant sub-section of 7.3.7 (pp175 to 176).

B12. The "Relapse" sub-section of 7.3.7 in the manufacturer's submission cross-refers to two CiC documents (Novartis Data on File references) which have been provided to the ERG. However neither of these appears to include the exact data illustrated in the figures in this section.
[redacted]

a. Please clarify the approach taken for modelling probability of relapse and the data used to conduct this analysis. Please provide the data used to conduct these analyses or indicate how these can be derived from the tabulations provided in the CiC reference "Analyses for Xolair in Chronic Spontaneous Urticaria: Final Results Report". 18th July 2014.

B13. Please provide a rationale for deriving linear functions (linear in log time) for the relapse probabilities, but using apparently uncorrelated sampled values from beta distributions for probabilities of relapse in the probabilistic evaluation of the model (see Table B28, section on "Cumulative relapse proportions post-treatment" p170 of the manufacturer's submission).

Costs and use of resources

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

B14. Tables B35 – 37 (p 192) with the calculation of total mean costs include a single value indicating resource use.

a. It is not clear whether this indicates the number of patients using a given resource, the number of units of the resource used by each patient or the total number of units of the resource used across all patients. Please indicate which of these is correct.

b. The tables indicate that the cost for each health state is a mean weighted cost. This is, presumably, determined from the units of resource used, the total number of patients and unit costs. However the numbers of patients in each health state are not reported. Please provide the total numbers of patients in each health state.