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)**

**Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis (ID539)**

Dear [redacted],

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have now had an opportunity to take a look at the submission from Genzyme received on 22 July 2013. In general terms they felt that it is well presented and clear, albeit very long, which we discussed in a separate communication with you. 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 28 August. 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 '[redacted]' in turquoise, and all information submitted under '[redacted]' 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 Richard Diaz, Technical Lead (richard.diaz@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

Encl. checklist for in confidence information

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

**Section A: Clarification on clinical effectiveness data**

A1. Please provide the clinical study reports for CARE MS I and CARE MS II and CAMSS 223 (phase II and open label extension), together with their protocols. The CSRs were referenced in the manufacturer's submission, but were not provided with the references.

**Questions regarding the CAMS223 trial and extension**

A2. The submission and journal papers outline the details of a dosing suspension that occurred in September 2005 during the extension phase of CAMS223 study. Dosing of alemtuzumab was later resumed. There are a number of questions of clarification relating to this study about when the dosing of alemtuzumab was resumed and how this impacted on planned endpoint evaluations:

- On page 80 and elsewhere in the submission, it is stated that dosing of alemtuzumab was suspended after three cases of immune thrombocytopenic purpura (ITP) but that dosing of alemtuzumab was later resumed. Please provide further details of how the decision to resume treatment was made.

The submission refers to [redacted] but there is no table B.5 in the submission. Please provide table B.5.

- Were any participants who did not receive second or third cycles of alemtuzumab given retreatment prior to the 36-month evaluation?

- Figure B6.3.1 on page 81 shows the trajectory of the participants in the trial and extension period. Could you [redacted] only occurred after the 36 month efficacy and safety evaluations for all participants and not at the time of the dosing suspension? Also, please confirm that Figure B6.3.1 is not commercial in confidence, since some of this information appears to be supplied as commercial-in-confidence in the preceding highlighted paragraphs.

- What was the mean follow-up of participants at the point of the alemtuzumab dosing suspension? Please confirm whether clinical efficacy analyses were carried out for the period up to the dosing suspension and if so, please provide these data.

A3. The patient disposition in CAMMS223 appears to differ between the trial publication (Coles 2008) (used in the submission) and the publication of the extension study (Coles 2012), see Figures 1 in each publication. Please provide details as to the number of patients randomised to the alemtuzumab 12 mg group and the total number completing the study at 36 months?

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

A4. Table B6.3.4 on pages 87-89 shows that in the CAMMS223 trial approximately 10% of participants had 1 or no relapses in the 2 years prior to entering the trial? Similarly, there were participants in the CARE MS I and II trials who also do not appear to meet the inclusion criteria based on the number of relapses in the previous two years. Please explain why these patients were included in the trials.

A5. In table B6.3.4 on page 87-89 of the submission, please could you clarify in the row EDSS >2.0-4.0 if all participants had EDSS <3 as per the inclusion criteria for CAMMS 223 and CARE MS I? Similarly, please clarify whether all the participants in the CARE MS II study had an EDSS <5 as per the inclusion criteria for the study.

A6. In table B6.5.1 on page 117-118 of the submission, the percentage of patients experiencing 6-month sustained accumulation of disability (SAD) at 3 years in CAMMS223 is reported twice but with different data. Please clarify if the second mention of the data represents the percentage of patients experiencing 3-month SAD at 3 years?

**Meta-Analysis**

A7. Please provide the justification for using a random effects meta-analysis.

A8. Page 131 of the submission states that 'the results of the direct meta-analysis demonstrated that alemtuzumab 12 mg was consistently superior to placebo for the analysed efficacy and safety outcomes.' Please clarify if this comparison is indeed with placebo, because in other instances (for example on page 132), alemtuzumab was compared with other disease modifying therapies.

A9. On page 130 of the submission, it states that 'few signs of heterogeneity were found using informal classical meta-analyses of direct and one-bridge-indirect evidence'. Please explain where one-bridge-indirect evidence was applied.

**Adverse Events**

A10. Table B6.9.1 on page 187 of the submission shows the incidence of adverse events (AEs) over time up to Year 4 for people receiving alemtuzumab. Are incidence data of AEs available for the subgroup of patients that received a third or fourth cycle of alemtuzumab? If so, please provide those data.

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

A11. Please identify the model inputs and source of baseline EDSS distribution data for both in base-case and sensitivity analyses. The EDSS UK RSS data presented in table B7.3.24 do not match those presented in either Pickin et al. 2009 or Boggild et al. 2009. If another source of data for EDSS distribution were used, please provide those data.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

A12. Please clarify how the annual administration costs for natalizumab were derived (table B7.5.3 page 304). There is a discrepancy between the cost shown in the submission (£6162) and the cost used in the model (£6611). Please identify which cost is most accurate and how that cost was calculated.

A13. Please clarify how the costs associated with relapses not leading to hospitalisation were calculated (B7.5.10 and B7.5.11 page 319). The value of £844.65 shown in the table B7.5.11 differs significantly from the value of €2705 in Dee et al. 2012.

A14. The rules for discontinuing alemtuzumab treatment are given on page 242 of the submission. Please clarify the stopping rules for fingolimod and natalizumab used in your economic evaluation. Also, please provide the justification for all treatment stopping rules for secondary-progressive MS (SPMS).

**Section C: Textual clarifications and additional points**

A15. On page 85 there appear to be errors in the labelling of CAMMS223 and CARE MS I and II, for example, CARE MS I is referred to as CAMMS323. Please check this for accuracy and provide the correct wording.

A16. Please provide details of studies that were potentially eligible but then excluded or not reported for the MTC, systematic review of cost effectiveness, and systematic review of HRQol?