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)

Teriflunomide for treating relapsing forms of multiple sclerosis [ID548]

Dear [redacted]

The Evidence Review Group, the Centre for Reviews & Dissemination and Centre for Health Economics at the University of York, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 28th May 2013 by Genzyme. NICE and the ERG note that the submission by far exceeds the recommended length of STA submissions. The ERG has exceptionally agreed to critique your submission as it is, in order to avoid any delays in the schedule of this appraisal. However, we have to emphasise at this stage to you that because of the length of your submission we cannot guarantee that Committee members are able to review your entire submission, and that the ERG is able to go through all aspects of your submission to the same degree of detail.

Despite the length of the submission, 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 **28th June 2013**. 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 Martyn Burke, Technical Lead (martyn.burke@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk) in the first instance.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Section A: Clarification on effectiveness data

Design and conduct of the clinical trials

A1. **Priority Question:** Please provide the Clinical Study Reports (CSRs) for the TEMSO, TOWER and TENERE trials, together with their protocols. The CSRs are referenced in the manufacturer's submission (MS), but were not provided with the references.

A2. On page 53 of the MS, the trial outcome inclusion criteria used in the manufacturer's search strategy is presented. Please can the manufacturer clarify if results for all outcomes from the included trials are presented in the MS?

A3. Adjusted annualised relapse rate (ARR) results are reported in the MS for the TEMSO, TOWER and TENERE trials. Please provide details of what variables were adjusted for and comment on the significance of any differences in the adjustments between the trials. Please clarify how the adjusted ARR results are used in the MTC? Also, please provide the number of events and time at risk for each group.

A4. Please provide the Kaplan-Meier plots for the phase III trials (TESMO, TENERE and TOWER) for the time to the first 3 month sustained accumulation of disability (SAD), time to first 6 month SAD and time to first relapse (or remaining relapse free).

A5. In the MS, 3 month SAD is defined as "… as an increase from baseline of at least 1.0 point in the Expanded Disability Status Scale (EDSS) score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 weeks." Please provide details of how the change in EDSS score, representing disability progression, was linked to the occurrence of a relapse? If this was not the case, please explain why this approach was not used?

Design, conduct and results of the TESMO trial

A6. **Priority Question:** Please provide any data available on 6 month SAD? The European Medicines Agency (EMA) guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis stipulates that, "accurate and reliable definition of sustained worsening is important and should include two consecutive examinations carried out by the same physician at least 6 months apart."

A7. Please provide summary results for the severity of relapse outcome to supplement the data reported on page 121 of the MS? This includes the actual reductions and confidence intervals (CIs) for each treatment arm, and the CIs for the relative treatment difference.

A8. Please clarify why the results for change from baseline in EDSS score are not available for the TEMSO trial (page 122 of the MS), despite this being listed as an

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

outcome (page 91 of the MS)? Please provide the results for this outcome from the TEMSO trial?

A9. On page 130 of the MS, it states that for the TEMSO trial "no statistically significant treatment differences were observed in SF-36 or EQ-5D scores". Please provide the summary results (for both value and VAS scores): at baseline, at each follow-up and the end of the study, change from baseline and details of statistical comparison, with patient numbers and mean follow-up. Also, please clarify which valuation (tariff) was used for the EQ-5D.

Design, conduct and results of the TESMO extension trial

A10. Please provide the results relating to MSQOL-54 instrument and the timescale over which these data were collected?

Design, conduct and results of the TENERE trial

A11. **Priority Question:** Time to failure is the primary endpoint of the TENERE trial, which is a composite of relapse or discontinuation due to any cause. Please confirm whether all the results are available and reported for both components of the primary endpoint in the MS? If this is not the case, please provide this data. Also, the TENERE trial results, as presented in the PowerPoint presentation (Vermersch et al. 2012), suggest inconsistent effects of the 2 doses of teriflunomide on relapse rate. Please provide further information to explain this?

A12. Please provide summary results for the Fatigue Impact Scale (FIS)?

A13. **Priority Question:** Please provide the summary results of adverse events (safety data) reported in the TENERE trial?

A14. **Priority Question:** Please explain how the results for 3 month SAD are derived in the TENERE trial. EDSS and SAD are not listed as outcomes in the published PowerPoint (Vermersch et al. 2012) or conference abstract (Vermersch et al. 2012). Please clarify whether they were pre-specified (planned) outcomes or post-hoc analyses?

A15. In the TENERE trial, freedom from relapse (disease activity) at the end of study period is reported. Please confirm the time point here.

Design, conduct and results of the TOWER trial

A16. Please confirm that the results for 3 month SAD are correct, as reported in the MS as HR [redacted]. Please clarify how a p-value of [redacted] was estimated?

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

A17. Please provide summary results for the SF-36: at baseline, follow-up and end of study, change from baseline and details of statistical comparison, with patient numbers and mean follow-up.

A18. Subgroup analyses have been presented for the TEMSO trial only. Please clarify whether subgroup analyses are available for the TOWER trial? If they are available, please provide the results of the subgroup analyses for the TOWER trial.

Search strategy

A19. Please clarify the time span of the effectiveness search? In section 10.2.3 page 369 of the MS, the endpoint is given as 30 June 2012. Table C10.2.1 on page 370 of the MS, states 29 May 2012 and within the PubMed search strategy on the same page the date is given as 2011/05/20.

Mixed treatment comparisons

A20. To help the Evidence Review Group understand the face validity of the mixed treatment comparison (MTC) analyses, please provide a clear comparison of the direct trials results and results from the MTC (both including and excluding the pre-2000 studies).

a) **Priority Question:** Please complete the triangular matrix below, with the upper part reporting the direct comparisons for the various pairwise comparisons reporting direct evidence and the lower part reporting the MTC results for all possible pairwise comparisons (with specific attention to teriflunomide, rebif and placebo). Please provide this table for each of the outcomes included in the economic model (ARR, 3 month SAD and all cause discontinuations). Please provide the mean and 95% confidence intervals/credible intervals, as well as the DIC statistics and results from both fixed and random effects analyses. Please provide the MTC code used. Please clarify whether the baseline effect is included in the MTC model to calculate absolute effects or does it just estimate relative effects?

	Comparator 1	Comparator 2	Comparator 3	Comparator 4
Comparator 1		Trial Results	Trial Results	Trial Results
Comparator 2	MTC Result		Trial Results	Trial Results
Comparator 3	MTC Result	MTC Result		Trial Results
Comparator 4	MTC Result	MTC Result	MTC Result	

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

b) **Priority Question:** Please provide a MTC with all years (including pre-2000 studies) for each of the outcomes included in the economic model but controlling for baseline relapse.

c) Data from the MTC for the ARR outcome lists the time point for the TEMSO trial as "ALL". Please clarify what is meant here?

d) The EMA guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis stipulates that for confirmatory trials, "two years is considered the minimum duration to demonstrate efficacy". Please confirm whether any steps were taken to take trial duration into account in the MTC? Also, please confirm whether any steps were taken to take into account for factors such as: baseline ARR rate, baseline EDSS score, mean age of patients, time since diagnosis?

e) Please provide details of how hazard ratios for 3 month SAD are calculated from the MTC inputs, presented in Table B6.7.6 (page 165 of the MS)?

f) Please confirm whether total discontinuations in the MTC are odds ratios (as stated on page 173 of the MS) or hazard ratios as stated in Table AA2.4 (Additional Appendix 2). If hazard ratios, please clarify how these are calculated from the data presented?

g) Please explain the apparent discrepancy between the flow diagram on page 54 of the MS (that states an additional 11 trials were included in the sensitivity analysis MTC) and the Additional Appendix 2 (where details of only 6 additional trials are provided). Please confirm the details of the other 5 trials and explain the reasoning for their exclusion from the MTC?

Section B: Clarification on cost-effectiveness data

Natural history data

B1. **Priority Question:** Please provide the proportion of patients from each of the 3 teriflunomide trials (TESMO, TENERE and TOWER) who experienced SAD but later regressed.

B2. **Priority Question:** Please provide an equivalent annual relapsing-remitting multiple sclerosis (RRMS) transition matrix for EDSS using the placebo arms of the TEMSO and TOWER trials – allowing for regression as well. Please present the details of the statistical model used. If this is not feasible, please provide the EDSS distributions from the placebo arms of the teriflunomide trials at baseline, 12 and 24 months.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

B3. Please provide additional details of patient characteristics in the Ontario data used to calculate the transitions (for example patient numbers, baseline characteristics, time at risk etc) for all people with RRMS, people with active RRMS and people with secondary progressive multiple sclerosis (SPMS).

B4. Please provide additional details on the statistical approaches used to derive transition matrices from the Ontario data or at least the number of events (transitions from one state to another) and time at risk for each of the transitions in the matrix.

B5. Please provide the number of patients in each EDSS state of the Ontario data allowing for regression.

Economic analysis

B6. **Priority Question:** Please provide clinical trial and model results at 1 year and 2 years for: average number of relapses, EDSS scores (actual mean scores and change in baseline), EQ-5D value scores (actual mean scores and change in baseline). Please provide comparisons for teriflunomide, rebif and placebo. Please ensure that the model results use the baseline characteristics of the trial populations and not the characteristics of the Ontario data (please clarify which characteristics have been changed to make it reflective of the trial population).

B7. **Priority Question:** Please confirm the source and price year for the acquisition costs of the disease-modifying treatments (DMTs) reported in Table B7.5.1 (page 284 of the MS).

B8. Please provide the number of patients, mean utilities and standard errors for each EDSS health state and by treatment arm in the TEMSO trial. Please clarify whether these values are the EQ-5D scores or VAS scores.

B9. Please provide additional details on what is being reported in Table B7.7.1 (page 307 of the MS). Please clarify that the results reported in Table B7.7.1 (both the clinical trial and model results) are for the teriflunomide arm?

B10. Please explain why the number of liver function tests and full blood counts are much higher for teriflunomide compared with the other treatments, Table B7.5.3 (page 286 of the MS). Please clarify whether these monitoring tests are required as part of the anticipated marketing authorisation recommended by the EMA?

Safety

B11. Please clarify why only adverse events that occurred at a rate of >4% more than placebo are included in the economic model. Please explain the rationale behind this 4% cut off? Please clarify whether there are any clinically significant or costly

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

adverse events (albeit less common) that have not been included in the economic model?