Single Technology Appraisal (STA)

Teriflunomide for treating relapsing forms of multiple sclerosis [ID548]

## 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.

Response

These are attached to the accompanying e mails. Please note they are both academic and commercial in confidence.

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?

Response

Within the MS, outcomes for the trials of teriflunomide 14mg vs. placebo or interferon beta-1a (IFNβ-1a) are presented in direct response to the decision problem, see table B6.5.1 of the submission. A comprehensive summary of all trial outcomes is presented in Additional Appendix 1 (Tabulated teriflunomide trial data) that was sent with the original submission.

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.

Response part a:

For each of the three mentioned studies (TEMSO, TOWER, TENERE) the primary analysis of ARR was performed using a Poisson regression model with robust error variance to appropriately accommodate for the potential for over-dispersed data.

[redacted]

The only difference between the three studies is the list of region (due to difference in countries' recruitment) with TEMSO: Americas, Eastern Europe, Western Europe; TOWER: Americas, Asia and Australia, Eastern Europe, Western Europe and Africa and TENERE: Americas, Eastern Europe, Western Europe and Africa.

The treatment group had 3 levels (placebo, teriflunomide 7 mg, and teriflunomide 14 mg). In order to account for different treatment durations among patients [redacted]

[redacted]

Table A1. Summary of covariates significance from the GEE Model in the TEMSO study

| Analysis Of GEE Parameter Estimates | | | | | | | |
|---|---|---|---|---|---|---|---|
| Empirical Standard Error Estimates | | | | | | | |
| Parameter | | Estimate | Standard Error | 95% Confidence Limits | | Z | Pr > \|Z\| |
| Intercept | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ARMN | 0 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ARMN | 7 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ARMN | 14 | [redacted] | [redacted] | [redacted] | [redacted] | | |
| STRATUAN | 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| STRATUAN | 2 | [redacted] | [redacted] | [redacted] | [redacted] | | |
| REGION | AMERICAS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| REGION | EASTERN EUROPE | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| REGION | WESTERN EUROPE | [redacted] | [redacted] | [redacted] | [redacted] | | |

Extracted from the GENMOD procedure in SAS

Table A2. Summary of covariates significance from the GEE Model in the TOWER study

| Analysis Of GEE Parameter Estimates | | | | | | | |
|---|---|---|---|---|---|---|---|
| Empirical Standard Error Estimates | | | | | | | |
| Parameter | | Estimate | Standard Error | 95% Confidence Limits | | Z | Pr > \|Z\| |
| Intercept | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ARMN | 0 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ARMN | 7 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ARMN | 14 | [redacted] | [redacted] | [redacted] | [redacted] | | |
| STRATUAN | 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| STRATUAN | 2 | [redacted] | [redacted] | [redacted] | [redacted] | | |
| REGION | AMERICAS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| REGION | ASIA AND AUSTRALIA | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| REGION | EASTERN EUROPE | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| REGION | WESTERN EUROPE AND AFRICA | [redacted] | [redacted] | [redacted] | [redacted] | | |

Extracted from the GENMOD procedure in SAS

Table A3. Summary of covariates significance from the GEE Model in the TENERE study

| Analysis Of GEE Parameter Estimates | | | | | | | |
|---|---|---|---|---|---|---|---|
| Empirical Standard Error Estimates | | | | | | | |
| Parameter | | Estimate | Standard Error | 95% Confidence Limits | | Z | Pr > \|Z\| |
| Intercept | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ARMN | 0 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ARMN | 7 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ARMN | 14 | [redacted] | [redacted] | [redacted] | [redacted] | | |
| STRATUAN | 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| STRATUAN | 2 | [redacted] | [redacted] | [redacted] | [redacted] | | |
| REGION | AMERICAS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| REGION | EASTERN EUROPE | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| REGION | WESTERN EUROPE AND AFRICA | [redacted] | [redacted] | [redacted] | [redacted] | | |

Extracted from the GENMOD procedure in SAS

Part b: Adjusted ARRs were used in the MTC analyses for ARR.

Part c: The number of relapses and the patient-year used to analyse the ARR are presented for each of the studies in the following tables.

Table A4. Summary of Number of relapses and patient-year in TEMSO and TOWER

| | Placebo | Teriflunomide 14 mg |
|---|---|---|
| TEMSO | | |
| Number of patients | 363 | 358 |
| Number of patients with at least one relapse | 184 (50.7%) | 141 (39.4%) |
| Number of relapses | [redacted] | [redacted] |
| Patient-year follow up | [redacted] | [redacted] |
| TOWER | | |
| Number of patients | 388 | 370 |
| Number of patients with at least one relapse | 186 (47.9%) | 122 (33.0%) |
| Number of relapses | [redacted] | [redacted] |
| Patient-year follow up | [redacted] | [redacted] |

Table A5. Summary of Number of relapses and patient-year in TENERE

| | Rebif | Teriflunomide 14 mg |
|---|---|---|
| Number of patients | 104 | 111 |
| Number of patients with at least one relapse | [redacted] | [redacted] |
| Number of relapses | [redacted] | [redacted] |
| Patient-year follow up | [redacted] | [redacted] |

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).

Response

Kaplan Meier curves of the first event as requested in the question are displayed in the following for TEMSO study.

**Figure A1. Kaplan-Meier plot of time to disability progression sustained for 12 weeks intent-to-treat population in TEMSO [TEMSO CSR]**

**Figure A2. Kaplan-Meier plot of time to disability progression sustained for 24 weeks intent-to-treat population in TEMSO [TEMSO CSR]**

**Figure A3. Kaplan-Meier plot of time to first MS relapse: intent-to-treat population in TEMSO [TEMSO CSR]**

Kaplan Meier curves of the first event as requested in the question are displayed in the following for TOWER study.

**Figure A4. Kaplan-Meier plot of time to disability progression sustained for 12 weeks intent-to-treat population in TOWER [TOWER CSR p103]**

**Figure A5. Kaplan-Meier plot of time to disability progression sustained for 24 weeks intent-to-treat population in TOWER [TOWER CSR p110]**

**Figure A6. Kaplan-Meier plot of time to first MS relapse: intent-to-treat population in TOWER [TOWER CSR p112]**

Kaplan Meier curves of the first event as requested in the question are displayed in the following for TENERE study.

**Figure A7. Kaplan-Meier plot of time to disability progression sustained for 12 weeks intent-to-treat population in TENERE**

**Figure A8. Kaplan-Meier plot of time to disability progression sustained for 24 weeks intent-to-treat population in TENERE**

**Figure A9. Kaplan-Meier plot of time to first MS relapse: intent-to-treat population in TENERE**

**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?**

Response

All EDSS measurements (with or without relapse) were used to determine the onset of a disability progression.

However, for the purpose of confirmation, only EDSS scores measured more than 30 days *after* the onset of a confirmed relapse were used for the confirmation of disability progression (to avoid confusing this with a temporary relapse).

1. Disability progression was defined as at least a 1-point increase on the EDSS from the baseline if the baseline was EDSS ≤5.5 or at least a 0.5-point increase from the baseline on the EDSS if the baseline was EDSS >5.5 and was persistent for at least 12 weeks
2. Only EDSS measurements on more than 30 days from the onset of a confirmed relapse were used to confirm a sustained disability progression and to reduce false confirmations based on temporary relapse. [TEMSO CSR, Section 6.5.1.1]

Therefore, disability progression criteria have been implemented in order to not be polluted by a temporary EDSS increase due to a confirmed relapse.

This definition was used in the TEMSO, TOWER and TENERE studies.

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."

Response

The key secondary objective of the TEMSO trial was to determine the efficacy of teriflunomide in delaying the progression of disability over the study period, as assessed on the basis of changes in the EDSS score. Sustained disability progression was defined as in increase from baseline of at least 1.0 point in the 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, i.e. 3-month SAD. [O'Connor, 2011]

However, the Clinical Study Report for the TEMSO trial does report 24-week/6-month SAD (Table A6). See also Figure A2 in answer to question A4 above.

Table A6: Analysis of time to disability progression sustained for 24-weeks (intention-to-treat population) in TEMSO

| | Placebo N=363 | Teriflunomide 14mg N=358 |
|---|---|---|
| No. of patients with disability progression | [redacted] | [redacted] |
| No. of patients who were censored | [redacted] | [redacted] |
| Probability of disability progression (derived from Kaplan-Meier estimates (95% CI) at: | | |
| 24 weeks | [redacted] | [redacted] |
| 48 weeks | [redacted] | [redacted] |
| 108 weeks | [redacted] | [redacted] |
| Hazard ratio (95% CI)* | | [redacted] |
| P-value† | | [redacted] |

[redacted]

For completion, results for TOWER are provided too. See Table A7. 24-week/6-month SAD was not a reported in the trial CSR.

Table A7: Analysis of time to disability progression sustained for 24-weeks (intention-to-treat population) in TOWER

| | Placebo N=388 | Teriflunomide 14mg N=370 |
|---|---|---|
| No. of patients with disability progression | [redacted] | [redacted] |
| No. of patients who were censored | [redacted] | [redacted] |

| Probability of disability progression (derived from Kaplan-Meier estimates (95% CI) at: | | |
|---|---|---|
| 24 weeks | [redacted] | [redacted] |
| 48 weeks | [redacted] | [redacted] |
| 108 weeks | [redacted] | [redacted] |
| 132 weeks | [redacted] | [redacted] |
| Hazard ratio (95% CI)* | | [redacted] |
| P-value† | | [redacted] |

[redacted]

For completion, results for TENERE are provided too. See Table A8. 24-week/6-month SAD was not a reported in the trial CSR.

Table A8: Analysis of time to disability progression sustained for 24-weeks (intention-to-treat population) in TENERE

| | Rebif N=104 | Teriflunomide 14mg N=111 |
|---|---|---|
| No. of patients with disability progression | [redacted] | [redacted] |
| No. of patients who were censored | [redacted] | [redacted] |
| Probability of disability progression (derived from Kaplan-Meier estimates (95% CI) at: | | |
| 24 weeks | [redacted] | [redacted] |
| 48 weeks | [redacted] | [redacted] |
| 96 weeks | [redacted] | [redacted] |
| Hazard ratio (95% CI)* | | [redacted] |
| P-value† | | [redacted] |

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.

Response

As mentioned in the submission, it was not possible to supply full answers to some elements of the decision problem, including 'severity of relapse' as they were not defined endpoints in the trial program for teriflunomide. Data regarding hospitalisation due to relapses and sequelae of relapse outcome are presented below, however confidence intervals for each treatment arm and for the relative treatment difference are not available.

Table A9. Relapse leading to hospitalisation and relapses sequelae in TEMSO and TOWER

| | Placebo | Teriflunomide 14mg | Teri. 14mg vs Placebo RR [95%CI] p value |
|---|---|---|---|
| TEMSO [O'Connor et al. 2013; Miller A et al. 2012] | (n=363) | (n=358) | |

| | | | |
|---|---|---|---|
| Annualised rate of relapse leading to hospitalisation | 0.14 [0.11;0.18] | 0.06 [0.04;0.08] | 0.407 [0.272;0.609] p<0.0001 |
| Patients free of relapse leading to hospitalisation | 80.4% (76.2%;84.6%) | 90.8% (88.5%;93.1%) | 0.87 (0.801;0.938) p<0.0001 |
| The risk of hospitalisation per relapse | 30.7% (24.5%;37.0%) | 17.6% (11.4%;23.9%) | 0.57 (0.415;0.792) P=0.0005 |
| Relapse with sequelae - investigator (end of relapse) | 0.17 [0.13;0.21] | 0.08 [0.06;0.11] | 0.474 [0.33;0.681] p<0.0001 |
| Patients free of relapse with sequelae | 77.4% (72.7%;82.1%) | 86.9% (83.7%;90.0%) | 0.88 (0.798;0.952) p=0.0009 |
| The risk of sequelae per relapse | 33.1% (26.7%;39.6%) | 22.9% (15.3% ;30.5%) | 0.69 (0.521;0.918) p=0.01 |
| TOWER [O'Connor et al. 2013] | (n=388) | (n=370) | |
| Annualised rate of relapse leading to hospitalisation | 0.15 (0.106 ;0.213) | 0.10 (0.071;0.14) | 0.664 (0.476 ;0.925) p=0.0155 |
| Nights in hospital for relapse (per patient) Mean (95%CI) (a) | 3.4 (2.2;4.7) | 1.7 (1.2 ;2.3) | -1.7 (-3.197 ;-0.178) p=0.0285 |
| ARR with sequelae based on an EDSS/FS increase at least 30 days post relapse | 0.21 (0.174 ;0.262) | 0.14 (0.107 ;0.172) | 0.634 (0.474 ;0.848) p=0.0021 |
| ARR with sequelae based on investigator assessment at the end of relapse | 0.17 (0.137 ;0.22) | 0.08 (0.056 ;0.116) | 0.465 (0.303 ;0.712) p=0.0004 |
| ARRs requiring IV corticosteroid treatment | 0.43 (0.363 ;0.5) | 0.27 (0.226 ;0.332) | 0.643 (0.508 ;0814) p=0.0002 |

(a) For nights in hospital for relapse per patient risk difference is presented for the comparison between teriflunomide 14 mg and placebo

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

Response

In this context it is worth noting that in existing EMA guidelines on the assessment of MS treatments and also in the revised draft guidelines, it is stated "the mean change in EDSS score from the baseline is not an appropriate efficacy parameter. Based on EDSS scores, treatment failure or progression should be predefined e.g. as the achievement of a specified degree of disability or of a sustained worsening of relevant magnitude. Acceptable efficacy parameters endpoints are the time to reach progression or the proportion of individuals who have shown progression at a pre-specified time" [EMA 2006, EMA 2012].

[redacted]

**Figure 1 Plot of change from baseline in EDSS over time – ITT population**

**Table A10. Analysis of EDSS, intent-to-treat-population**

[redacted]

[redacted]

[redacted]

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.

Response

For the SF-36, the changes from baseline for the 8 scales (range between 0 and 100) and 2 component summaries (physical and mental component summaries) were analysed using a mixed-effect model with repeated measures (MMRM) on untransformed data.

For the EQ-5D quantitative variables (visual analogue scale and single index utility), the change from baseline was analysed using a mixed-effect model with repeated measures (MMRM) on untransformed data. The qualitative variables (5-dimensional 3-level system) were summarised by visit, baseline status, and the treatment group using the number and percentage of patients; the denominator (/N) was the number of ITT patients for the treatment group who had the variable assessed at baseline and the corresponding visit. [TEMSO CSR p63]

For detailed results see Appendix 1 [TEMSO CSR, Appendix 15.2 Efficacy data, Table 6-9].

The valuation used for the EQ-5D is the one proposed by Dolan et al [Dolan et al 1997].

## 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?

Response

The MSQOL-54 was not an outcome measure in TEMSO. The MSQOL-54 instrument was used in the teriflunomide phase II extension study. Overall patients treated with 14 mg teriflunomide maintained their quality of life as measured by MS-QoL-54 [Phase II Extension CSR p83].

## 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?

Response (part 1 of question)

Results for both components of the primary endpoint are shown in Tables A11-A14 and Figures A11 & A12 below.

[redacted]

[redacted]

Table A11: Analysis of time to failure (confirmed relapse or permanent study treatment discontinuation) intention to treat population [CSR page 76]

| | Teriflunomide 14mg (N=111) | Rebif (N=104) |
|---|---|---|
| No. of patients with primary outcome (first occurrence of relapse, permanent treatment discontinuation for any cause or other reason whichever occurs first) | 42 (37.8%) | 44 (42.3%) |
| Relapse | [redacted] | [redacted] |
| Permanent treatment discontinuation | [redacted] | [redacted] |
| Other reason for failure* | [redacted] | [redacted] |
| No. of patients who were censored | [redacted] | [redacted] |
| Kaplan-Meier estimates of probability of failure (95%) CI at: | | |
| 24 weeks | [redacted] | [redacted] |
| 48 weeks | [redacted] | [redacted] |
| 96 weeks | [redacted] | [redacted] |
| Hazard ratio (95% CI)† | [redacted] | [redacted] |
| P-value¥ | [redacted] | [redacted] |

[redacted]

Table A12: Analysis of time to confirmed relapse - intention to treat population [CSR Appendix 16.2.6.1.5]

| | Teriflunomide 14mg (N=111) | Rebif (N=104) |
|---|---|---|
| No. of patients with confirmed relapse | [redacted] | [redacted] |
| No. of patients who were censored | [redacted] | [redacted] |
| Kaplan-Meier estimates of probability of failure (95%) CI at: | | |
| 24 weeks | [redacted] | [redacted] |
| 48 weeks | [redacted] | [redacted] |
| 96 weeks | [redacted] | [redacted] |
| Hazard ratio (95% CI)† | [redacted] | [redacted] |
| P-value¥ | [redacted] | [redacted] |

[redacted]

**Figure A11. Kaplan-Meier plot of time to confirmed relapse – ITT population**

**Table A13. Analysis of time to treatment discontinuation - randomised population [CSR Appendix 16.2.1.2.1]**

| | Teriflunomide 14mg (N=111) | Rebif (N=104) |
|---|---|---|
| Overall | | |
| Number assessed | | |
| Number censored, n (%) | | |
| Number of events, n (%) | | |
| Week 0 | | |
| Number at risk | | |
| Number of events | | |
| Probability of discontinuation (95% CI) | | |
| Week12 | | |
| Number at risk | | |
| Number of events | | |
| Probability of discontinuation (95% CI) | | |
| Week 24 | | |
| Number at risk | | |
| Number of events | | |
| Probability of discontinuation (95% CI) | | |
| Week 36 | | |
| Number at risk | | |
| Number of events | | |
| Probability of discontinuation (95% CI) | | |
| Week 48 | | |
| Number at risk | | |
| Number of events | | |

| | | |
|---|---|---|
| Probability of discontinuation (95% CI) | [redacted] | [redacted] |
| Week 60 | | |
| Number at risk | [redacted] | [redacted] |
| Number of events | [redacted] | [redacted] |
| Probability of discontinuation (95% CI) | [redacted] | [redacted] |
| Week 72 | | |
| Number at risk | [redacted] | [redacted] |
| Number of events | [redacted] | [redacted] |
| Probability of discontinuation (95% CI) | [redacted] | [redacted] |
| Week 84 | | |
| Number at risk | [redacted] | [redacted] |
| Number of events | [redacted] | [redacted] |
| Probability of discontinuation (95% CI) | [redacted] | [redacted] |
| Week 96 | | |
| Number at risk | [redacted] | [redacted] |
| Number of events | [redacted] | [redacted] |
| Probability of discontinuation (95% CI) | [redacted] | [redacted] |
| Stratified Log Rank test p-value | [redacted] | [redacted] |

**Figure A12. Kaplan-Meier plot of time to treatment discontinuation - randomised population**

Response (part 2 of question)

Compared to TEMSO and TOWER studies, we observed in TENERE study a greater difference between the two doses 7 and 14mg (see Table 14 below). We do not have further information to explain this, however this in accordance with a greater effect for the 14mg dose observed in other studies, especially in the TOWER study. In addition, the licensed dose for teriflunomide in England and Wales is 14mg and the 7mg dose is not expected to be used in clinical practice.

Table A14. Analysis of relapse rates in the TENERE study [Vermersch, 2012]

| | **SC IFNβ**-1a (n=104) | Teriflunomide 7mg (n=109) | Teriflunomide 14mg (n=111) |
|---|---|---|---|
| ≥1 confirmed relapse, % | 15.4 | 42.2 | 23.4 |
| Adjusted ARR, confirmed relapse | | | |
| Estimate (95% CI) | 0.22 (0.11, 0.42) | 0.41 (0.27, 0.64) | 0.26 (0.15, 0.44) |
| Relative risk (95% CI) | | 1.90 (1.05, 3.43) | 1.20 (0.62, 2.30) |
| p-value vs SC IFNβ-1a | | 0.03 | 0.59 |

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

Response

At Week 48, the mean (SD) changes from baseline in FIS score was [redacted] for the 14 mg teriflunomide group and [redacted] for the SC IFNβ-1a group. In the MMRM analysis, the model adjusted LS-mean difference from SC IFNβ-1a for the change from baseline [redacted] for the 14 mg teriflunomide group (p-value [redacted] Table A14).

Table A15. Analysis of change from baseline in FIS total score at Week 48 (MMRM analysis) – ITT Population [TENERE CSR p84]

| | Teriflunomide 14mg (N=111) | **IFNβ**-1a (N=104) |
|---|---|---|
| Baseline (Week 0) | | |
| Number | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] |
| Median (Min: Max) | [redacted] | [redacted] |
| Week 48 | | |
| Number | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] |
| Median (Min: Max) | [redacted] | [redacted] |
| Change from baseline | | |
| Number | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] |
| Median (Min: Max) | [redacted] | [redacted] |
| Change from baseline (MMRM) | | |
| Number | [redacted] | [redacted] |
| LS Mean (SE) | [redacted] | [redacted] |
| LS Mean Difference from IFNβ-1a (SE) | [redacted] | |
| 95% CI | [redacted] | |
| P-value (vs. IFNβ-1a) | [redacted] | |

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

Response

[redacted]

[redacted]

Table A16. Overview of safety profile: treatment-emergent adverse events – safety population

| | Teriflunomide | | |
|---|---|---|---|
| n (%) | 7mg (n=110) | 14mg (n=110) | Rebif (n=101) |
| Patients with any TEAE | [redacted] | [redacted] | [redacted] |
| Patients with any treatment emergent SAE | [redacted] | [redacted] | [redacted] |
| Patients with any TEAE leading to death | [redacted] | [redacted] | [redacted] |
| Patients with any TEAE leading to permanent treatment discontinuation | [redacted] | [redacted] | [redacted] |

TEAE: treatment emergent adverse event, SAE: serious adverse event.

[redacted]

[redacted]

[redacted]

Table A17. **Number (%) of patients with TEAE(s) with a frequency of ≥5%** by PT – Safety population

| Preferred Term n (%) | Teriflunomide 14 mg (N=110) | **SC IFNβ**-1a (N=101) |
|---|---|---|
| Any class | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] |
| Alopecia | [redacted] | [redacted] |
| Nasopharyngitis | [redacted] | [redacted] |
| Headache | [redacted] | [redacted] |
| Alanine aminotranferase increased | [redacted] | [redacted] |
| Back pain | [redacted] | [redacted] |
| Paraesthesia | [redacted] | [redacted] |
| Nausea | [redacted] | [redacted] |
| Influenza | [redacted] | [redacted] |
| Vomiting | [redacted] | [redacted] |
| Abdominal pain | [redacted] | [redacted] |
| Upper respiratory tract infection | [redacted] | [redacted] |
| Arthralgia | [redacted] | [redacted] |
| Pain in extremity | [redacted] | [redacted] |
| Abdominal pain upper | [redacted] | [redacted] |
| Dysmenorrhoea | [redacted] | [redacted] |
| Fatigue | [redacted] | [redacted] |
| Neutropenia | [redacted] | [redacted] |
| Influenza like illness | [redacted] | [redacted] |
| Myalgia | [redacted] | [redacted] |
| Asthenia | [redacted] | [redacted] |
| Dizziness | [redacted] | [redacted] |
| Insomnia | [redacted] | [redacted] |
| Injection-site erythema | [redacted] | [redacted] |

Extracted from Appendix 16.2.7.1.8.

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?

Response

3-month SAD was not a pre-specified outcome in the TENERE study, and results from this endpoint were derived by a post-hoc analysis. Its derivation follows exactly the protocol used for the TEMSO and TOWER studies. Disability progression was defined as at least a 1-point increase in the EDSS from baseline if baseline was EDSS ≤5.5 or at least a 0.5-point increase from baseline in the EDSS if baseline was EDSS >5.5 that was persistent for at least 12 weeks. Only EDSS measurements recorded more than 30 days from the onset of a confirmed relapse were used to confirm sustained disability progression in order to reduce false confirmations by discriminating events that occurred due to relapses.

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

Response

The treatment study duration as per protocol has a minimal duration of 48 weeks and the maximum duration went up to 118 weeks. Actual study treatment duration was slightly under 115 weeks (804 days).

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?

Response

Correct. The p-value was derived from a log-rank test with stratification of EDSS strata at baseline and region.

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.

Response

[redacted]

Complete tables of results can be found in pages 213 -352 of Appendix 2 [Appendix 16.2.6.5 TOWER CSR].

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.

Response

Subgroup analyses are available for the highly active (HA) and rapidly evolving severe (RES) populations within the TOWER study and are presented below. These analyses were not included within the original submission since the definitions used for HA and RES disease do not include any specifications regarding MRI outcomes as per the marketing authorisation for natalizumab and fingolimod and the definitions used in previous NICE guidance. In TOWER specifically, unlike in TEMSO, gadolinium-enhancing lesions were not measured at baseline which form part of the definition both for RES and HAD populations and TEMSO derived data was assumed to provide a closer fit to these subgroups. For HA disease, the TOWER study recorded patients who had at least one relapse within one year before randomisation, and with previous DMT intake (only interferon or glatiramer/ only interferon) for at least 12 months. For RES, the TOWER study recorded patients who had at least two relapses within one year before randomisation.

Table A18. Relapse-free data for the HA-disease sub-analysis (TOWER, ITT population)

| Treatment | Time point | **IFNβ or glatiramer only** | | Treatment | **IFNβ only** | |
|---|---|---|---|---|---|---|
| | | Number (%) | Odds ratio vs. placebo | | Number (%) | Odds ratio vs. placebo |
| Placebo (n=78) | All | [redacted] | | Placebo (n=38) | [redacted] | |
| Teriflunomide 14 mg (n=78) | | [redacted] | [redacted] | Teriflunomide 14 mg (n=38) | [redacted] | [redacted] |

Table A19. Relapse-free data for the RES-disease sub-analysis (TOWER, ITT population)

| Treatment | Number (%) | Odds ratio vs. placebo |
|---|---|---|
| Placebo (n=128) | [redacted] | |
| Teriflunomide 14 mg (n=125) | [redacted] | [redacted] |

Table A20. Three-month sustained accumulation of disability (SAD) data for the HA-disease sub-analysis (TOWER, ITT population)

| | Previous DMT intake | | | | |
|---|---|---|---|---|---|
| Treatment | **IFNβ or glatiramer only** | | Treatment | **IFNβ only** | |
| | Number (%) with SAD | HR vs. placebo (95% CI) | | Number (%) with SAD | HR vs. placebo (95% CI) |
| Placebo (n=78) | [redacted] | | Placebo (n=38) | [redacted] | |
| Teriflunomide 14 mg (n=78) | [redacted] | [redacted] | Teriflunomide 14 mg (n=38) | [redacted] | [redacted] |

Table A21. Three Month sustained accumulation of disability (SAD) data for the RES-disease sub-analysis (TOWER, ITT population)

| Treatment | Number (%) with SAD | HR vs. placebo (95% CI) |
|---|---|---|
| Placebo (n=128) | [redacted] | |
| Teriflunomide 14 mg (n=125) | [redacted] | [redacted] |

Table A22. Overall Discontinuation data for the HA-disease sub-analysis (TOWER, ITT population)

| | Previous DMT intake | | | | |
|---|---|---|---|---|---|
| Treatment | **IFNβ or glatiramer only** | | Treatment | **IFNβ only** | |
| | Number (%) discontinuing | Odds ratio vs. placebo (95% CI) | | Number (%) discontinuing | Odds ratio vs. placebo (95% CI) |
| Placebo (n=78) | [redacted] | | Placebo (n=38) | [redacted] | |
| Teriflunomide 14 mg (n=78) | [redacted] | [redacted] | Teriflunomide 14 mg (n=38) | [redacted] | [redacted] |

Table A23. Overall Discontinuation data for the RES-disease sub-analysis (TOWER, ITT population)

| Treatment | Number (%) discontinuing | Odds ratio vs. placebo (95% CI) |
|---|---|---|
| Placebo (n=128) | [redacted] | |
| Teriflunomide 14 mg (n=125) | [redacted] | [redacted] |

Table A24. Discontinuation due to adverse events data for the HA-disease sub-analysis (TOWER, ITT population)

| | Previous DMT intake | | | | |
|---|---|---|---|---|---|
| Treatment | **IFNβ or glatiramer only** | | Treatment | **IFNβ only** | |
| | Number (%) discontinuing | Odds ratio vs. placebo (95% CI) | | Number (%) discontinuing | Odds ratio vs. placebo (95% CI) |
| Placebo (n=78) | [redacted] | | Placebo (n=38) | [redacted] | |
| Teriflunomide 14 mg (n=78) | [redacted] | [redacted] | Teriflunomide 14 mg (n=38) | [redacted] | [redacted] |

Table A25. Discontinuation due to adverse events data for the RES-disease sub-analysis

| Treatment | Number (%) discontinuing | Odds ratio vs. placebo (95% CI) |
|---|---|---|
| Placebo (n=128) | [redacted] | |
| Teriflunomide 14 mg (n=125) | [redacted] | [redacted] |

Subgroups analyses were also performed in the TOWER study report for the primary endpoint, annualised relapse rate (ARR)[TOWER CSR Section 10.1.3 p98].

[redacted] Results are summarized in the following forest plot (Figure A13).

**Figure A13. Summary of MS relapse for all subgroups (TOWER, ITT population)**

[redacted]

**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.**

Response

The original search was done with a cut-off of May 2011. It was subsequently updated twice – one in June 2012 and once in November 2012. Each search was overlapped to allow for any discrepancies in the database indexing process. The final search cut-off should be listed as November 12, 2012.

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 | |

Response

Please see attached Appendix 3 for all trial results as requested.

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.

We do not have a MTC analysis as requested available in time for 28th June 2013.

If NICE wish us proceed with a de novo analysis, we confirm that it will be completed by 31st July. It would be carried out in two phases:

- Phase I: Feasibility assessment for two options a) meta-regression and b) stratified MTCs by baseline relapse rate. This
- Phase II: Assuming one of the two options are feasible, we proceed with the analysis. Our thought is that the preference would be for meta regression, if feasible.

In the absence of this MTC analysis, Forest plots indicating subgroup analyses of endpoints from the TEMSO, TOWER AND TENERE studies based on the baseline relapse rate are presented below.

In general, the subgroup results were consistent with the overall results (i.e. disease outcomes with teriflunomide were improved vs. placebo and similar to Rebif). This provides some indication of what an MTC may reveal.

Figure A14. Subgroup analysis of relapse rate by baseline relapse, TEMSO ITT population

| Subgroup | Teriflunomide vs Placebo | Relative risk (95% CI) | Plb Worse | Plb Better |
|---|---|---|---|---|

Figure A15. Subgroup analysis of accumulation of disability by baseline relapse, TEMSO ITT population

| Subgroup | Teriflunomide vs Placebo | Hazard ratio (95% CI) | Plb Worse | Plb Better |
|---|---|---|---|---|

Figure A16. Subgroup analysis of relapse rate by baseline relapse, TOWER ITT population

Figure A17. Subgroup analysis of accumulation of disability by baseline relapse, TOWER ITT population

Figure A18. Subgroup analysis of the primary endpoint (time to failure) by baseline relapse, TENERE ITT population

**Figure A19. Subgroup analysis of relapse rate (all MS relapses) by baseline relapse, TENERE ITT population**

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?**

Response

The time-point for the TEMSO trial should be marked as the latest time-point which averaged 27 months duration.

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?**

Response

The inclusion criteria for the systematic literature review and thus the mixed treatment comparison analysis was to exclude trials shorter than 6 months in duration (during the randomized phase). Per the suggestion of clinical experts, specifically Professor Vermersch, a sensitivity analysis that excluded trials less than one year in duration was carried out. An analysis excluding trials less than two years duration was considered, however differences between the study sets did not warrant this so a one year cut-off was used.

**Table A26. Duration of trials considered for the MTC**

| Duration of Randomized Phase | Studies |
|---|---|
| **6 Months** | FTY720 D2201 Study Group, BG-12 Phase IIb Study, Laquinimod in Relapsing MS, Japanese Phase II Study (FTY720) |
| **9 Months** | LAQ/5062, Teri in MS, Dose Comparison 9006 Study Group |
| **11 Months** | HERMES Trial Group |
| **12 Months** | EVIDENCE, TRANSFORMS, FORTE Study Group, SELECT |
| **24 Months or Longer** | FREEDOMS, Etemadifar 2006, BEYOND, BECOME, ALLEGRO, CARE-MS I, CARE-MS II, CombiRx, DEFINE, REGARD, AFFIRM, BRAVO, CONFIRM, FREEDOMS II, TEMSO, TENERE, TOWER, CAMMS223 |

As shown in the table above studies included in the networks which were 12 months in length which included data for the comparators in the decision problem were EVIDENCE (SC IFNβ-1a vs intramuscular IFNβ-1a) and TRANSFORMS (fingolimod vs intramuscular IFNβ-1a).

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)?

The table shows the raw proportion data which wasn't used (for the most part) in the MTC analyses. Instead the HRs reported by the studies were used within the MTC. For the teriflunomide and alemtuzumab trials, internal data which may not be published, for example, the post hoc analysis of 3-month SAD for TENERE was used.

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?

Response

The discontinuation analyses are odds ratios, not hazard ratios. We apologise that one of the tables was mislabeled.

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?

Response

In the flow diagram on page 54, where there is no restriction on year of recruitment *or* % RRMS, 11 trials are removed from the potential pool for the base-case. Of these, 5 trials drop out of the sensitivity analysis for all-years with ≥80% RRMS (due to having <80% RRMS), leaving 6 studies that are before the year 2000 with ≥80% RRMS.

Section B: Clarification on cost-effectiveness data

## CORRECTION TO THE HEALTH ECONOMIC MODEL

- During review of the below questions an error was spotted and corrected in the model submitted to NICE on 28th May 2013. The error and correction regarded incorrect formulas for the duration of injection-site reactions and influenza like symptoms for the blended comparator treatment option. In addition, it was noted that waning of effectiveness only applied to the treatment effect for delaying disability progression in the model submitted. The number of relapses treatment prevents in terms of the ARR is now also subject to the waning of effectiveness. Given the relatively small impact relapses has on the overall results, changes to the results are negligible, and the base case does not change since no waning is assumed in the base case.

Cells G384 and G389 have been amended in the defaults sheet with the correct formula. The denominators were previously divided by the sum of the durations as opposed to the sum of the market shares for the blended comparator. The impact on results is negligible and in favour of teriflunomide:

- The ICER for teriflunomide without PAS vs. the blended comparator improves from [redacted] per QALY to [redacted] per QALY.
- The ICER for teriflunomide with PAS vs. the blended comparator remains dominant.

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.

Response

Please note that we have provided the information required for each of the three studies, however, it is important to take into consideration that these analyses are not protected by the original randomisation and should be interpreted with caution.

TEMSO

In the TEMSO study, [redacted] patients experienced at least one instance of sustained accumulation of disability progression for 3 months (3-month SAD). Among these, [redacted] had this first 3-month SAD defined as persistent (SAD is maintained up to the end of the study) and [redacted] experienced a regression (their first 3-month SAD was not persistent). Results are presented in the following Table B1

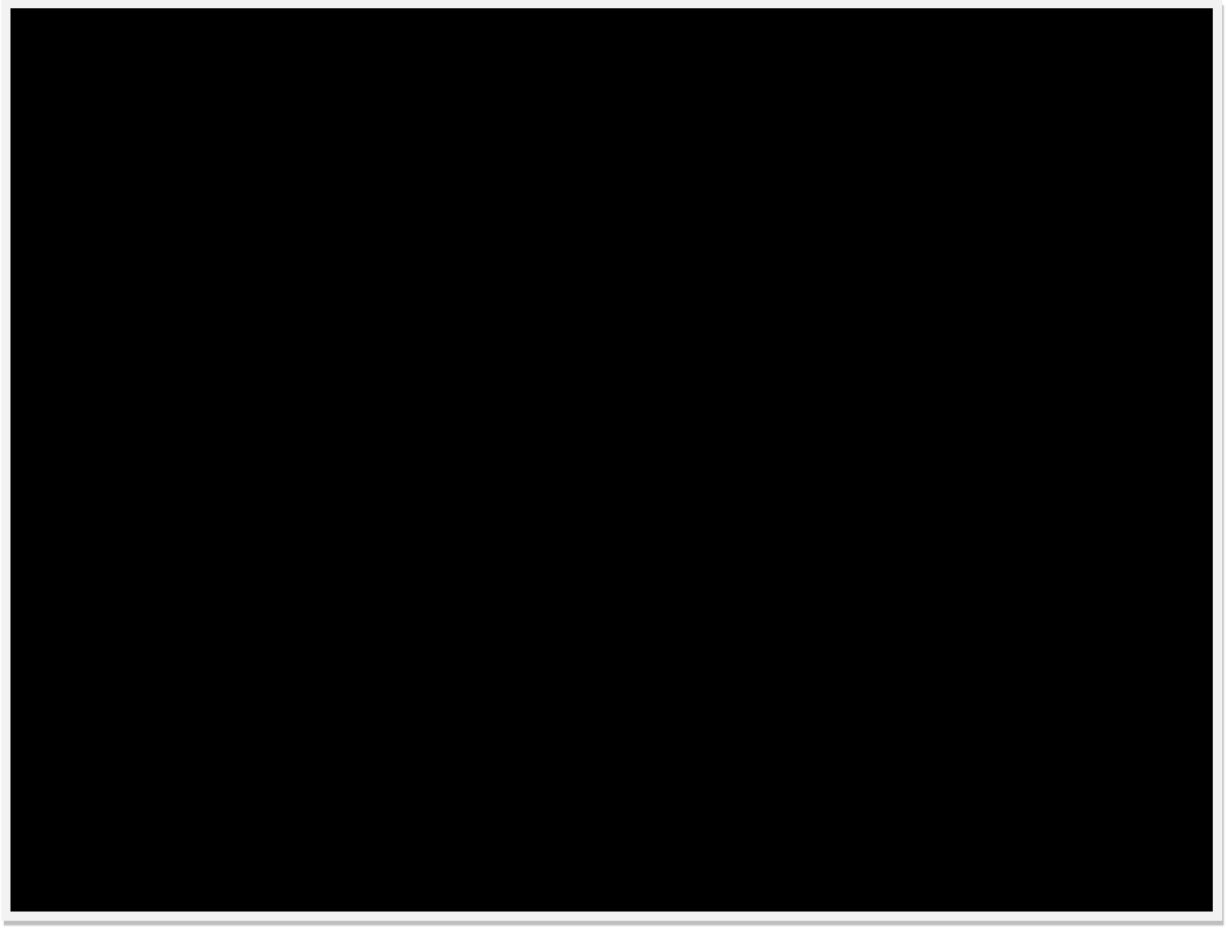
Table B1 Number (%) of patients experiencing a regression after their first SAD 3 months (TEMSO)

| Status of first Disability Progression for 12-Weeks | Placebo (N=86) | 7 mg (N=68) | 14 mg (N=62) | Total (N=216) |
|---|---|---|---|---|
| Patient experienced a regression after the first 3-month SAD (i.e. 3-month SAD was not persistent) | [redacted] | [redacted] | [redacted] | [redacted] |
| Persistent SAD | [redacted] | [redacted] | [redacted] | [redacted] |

N.B. Not persistent means that the progression is not maintained till the End of Study (i.e. regression before the EOS)

The follow-up of patients having experienced a regression after their first SAD 3 months is summarised in the following Figure B1.

**Figure B1 Summary of patients that experienced a regression after the first 3-month SAD (TEMSO)**



**TOWER**

In the TOWER study [redacted] patients experienced at least one instance of 3-month SAD. SAD persisted for [redacted] of these patients (SAD is maintained up to the end of the study) and [redacted] experienced a regression (their first 3-month SAD was not persistent). Results are presented in the following Table B2.

**Table B2– Number (%) of patients experiencing a regression after their first 3-month SAD (TOWER)**

| Status of first Disability Progression for 12-Weeks | Placebo (N=65) | 7 mg (N=65) | 14 mg (N=44) | Total (N=174) |
|---|---|---|---|---|
| Patient experienced a regression after the first 3-month SAD (i.e. 3-month SAD was not persistent) | [redacted] | [redacted] | [redacted] | [redacted] |
| Persistent SAD | [redacted] | [redacted] | [redacted] | [redacted] |

N.B. Not persistent means that the progression is not maintained till the End of Study (i.e. regression before the EOS)

The follow-up of patients having experienced a regression after their first SAD 3 months is summarised in the following Figure B2

**Figure B2 Summary of patients having experienced a regression after the first 3-month SAD (TOWER)**

**TENERE**

In the TENERE study, [redacted] patients experienced at least one instance of 3-month SAD. Among these, [redacted] had this first 3-month SAD defined as persistent (SAD is maintained up to the end of the study) and [redacted] experienced a regression (their first 3-month SAD was not persistent). Results are presented in the following Table B3.

**Table B3– Number (%) of patients experiencing a regression after their first SAD 3 months (TENERE)**

| Status of first Disability Progression for 12-Weeks | Rebif (N=9) | 7 mg (N=10) | 14 mg (N=10) | Total (N=29) |
|---|---|---|---|---|
| Patient experienced a regression after the first 3-month SAD (i.e. 3-month SAD not persistent) | [redacted] | [redacted] | [redacted] | [redacted] |
| Persistent SAD | [redacted] | [redacted] | [redacted] | [redacted] |

N.B. Not persistent means that the progression is not maintained till the End of Study (i.e. regression before the EOS)

Among the [redacted] patients who experienced a regression after the first 3-month SAD, [redacted] remained regressed to the end of the study. [redacted]

[redacted]

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.**

Table B4 is an annual RRMS transition matrix of probabilities through EDSS states derived from the placebo arms of the TOWER and TEMSO trials, which allows for regression. No patients reached EDSS state 9 and EDSS 10 is equivalent to death. Mortality is captured separately in the model thus there are no probabilities to transitioning to EDSS 10.

**Table B4 Natural history transition matrix derived from placebo arms of TOWER and TEMSO**

[redacted]

The natural transition matrix was derived using the msm-package using individual data (extracted from pooled data) from the placebo arms of the two studies TEMSO and TOWER. The programming was done in R software and has followed the same approach than the one presented in question B4 for the LO transition matrix.

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).**

Response

A full exploratory analysis of the London Ontario data set was performed to evaluate the relevant parameters for use in the full Multi-State Markov analysis. From this exploratory analysis the following patient characteristics were reported for all RRMS, active RRMS and highly active RRMS groups ( Table ). Definitions of All RRMS group and RRMS sub-groups are listed below:

Active RRMS: 2 relapse events during the 2-year pre-study period, but <2 relapses in the first pre-study year.

Highly Active RRMS: 2 relapse events during the first year of the pre-study period.

All RRMS: Includes active, highly active and benign RRMS (defined as one confirmed relapse event during the 2-year pre-study period)

Baseline characteristics for SPMS group were not available as patients were followed from MS onset. Data used for SPMS transitions were those of patients who had progressed to SPMS during their follow-up in the London Ontario dataset, which is why it was possible to estimate the mean time from MS onset to SPMS.

**Table B.5. Patient characteristics for all RRMS and active RRMS groups from exploratory analysis of London Ontario data (This data cannot be published and is ACADEMIC-IN-CONFIDENCE)**

| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
|---|---|---|---|---|---|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

DSS: Disability status scale; RRMS: Relapsing remitting multiple sclerosis; Sd: Standard deviation

B.6. gives the number of patients feasible for the calculation of the transition intensity matrices for the full data set and for the validation data set. All observations with only one observation were excluded due to having no transition.

**Table B.6. Sample size of groups from London Ontario data used in generation of transition matrices (This data cannot be published and is ACADEMIC-IN-CONFIDENCE)**

| [redacted] | [redacted] |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

RRMS: Relapsing remitting multiple sclerosis

*Including both active and highly active RRMS patients

**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.**

Response

The EDSS states were modelled as homogeneous continuous-time Markov process with a transition matrix Q. For example, a transition matrix for a disease with three progression states and one absorbing state (e.g. Death) is:

$$Q = \begin{pmatrix} -(q_{01} + q_{02}) & q_{01} & q_{02} \\ 0 & -q_{12} & q_{12} \\ 0 & 0 & 0 \end{pmatrix}$$

The transition probability matrix *P(t)* for transition after time *t* was calculated using the matrix exponential

$$P(t) = Exp(t \cdot Q)$$

Incorporating at covariate *k* was done by estimated *Q(k)* and a proportion hazards model was used to estimate *Q(k)*.

$$q_{rs}(k(t)) = q_{rs}^{(0)} \cdot exp(\beta_{rs}^{T} \cdot k(t))$$

All calculations to generate transition probability matrices for all patient groups (including all RRMS, pooled active RRMS and SPMS) were made using R statistical programming software using the msm package.

B.7. lists the number of transitions and the mean number of transitions by group. I.e. for All RRMS group, 109 patients experienced 1 transition, 91 patients experienced 2 transitions, etc. in follow-up period.

**Table B.7: Number of transitions per group and mean number of transitions (This data cannot be published and is ACADEMIC-IN-CONFIDENCE)**

| [redacted] | [redacted] | | | | | | | | [redacted] |
|---|---|---|---|---|---|---|---|---|---|
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

RRMS: Relapsing remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

*Including both active and highly active RRMS patients

Table B.8. and B.9. list the observed transitions in the follow-up period for all RRMS and SPMS groups, respectively. This data was not available for the pooled active RRMS population.

**Table B.8: Observed transitions in the All RRMS state (This data cannot be published and is ACADEMIC-IN-CONFIDENCE)**

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EDSS: Expanded Disability Status Scale RRMS: Relapsing remitting multiple sclerosis

**Table B.9.: Observed transitions in the SPMS state (This data cannot be published and is ACADEMIC-IN CONFIDENCE)**

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|---|---|---|---|---|---|---|---|---|---|---|
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EDSS: Expanded Disability Status Scale; SPMS: Secondary progressive multiple sclerosis

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

Response

The transition matrices generated from London Ontario data for RRMS, active RRMS and SPMS patient populations do not allow for regression. This was due to the elimination of short-term variations in EDSS when dataset was analysed retrospectively, resulting in no EDSS improvement in the final dataset.

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).

Table B5 contains comparisons between the pooled TEMSO, TOWER and TENERE clinical trial outcomes, with the model results. Data were captured in 24 intervals in the clinical trial, so it is not possible to obtain the trial results at years 1 and 2; week 48 and week 96 results have been used as a proxy. EQ-5D data were only collected in TEMSO, not TOWER or TENERE.

The model results have been obtained when using the baseline characteristics from pooled treatment arms of the TEMSO and TOWER trials, in terms of initial EDSS distribution, male to female ratio and starting age for treatment. The treatment transition probabilities are derived using London Ontario natural history transition matrix, supplemented by TOWER and TEMSO placebo arms for probabilities from EDSS 0, as detailed in the main submission (Section B7.2.5). In comparison, the clinical trial results consider baseline characteristics split by treatment arm for the pooled TEMSO, TOWER and TENERE trials. Since the model results and clinical trial results effectively consider different starting populations (split treatment arms vs. pooled treatment arms) and trial data (TEMSO + TOWER + TENERE vs. TEMSO + TOWER) there is deviation between the results.

Table B10: Comparison of clinical trial and model results

| Parameter | Clinical trial results Pooled TEMSO, TOWER & TENERE | | Model results per patient | |
|---|---|---|---|---|
| *Teriflunomide 14mg* | *Year 1* | *Year 2* | *Year 1* | *Year 2* |
| Average number of relapses* | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean EDSS score | [redacted] | [redacted] | [redacted] | [redacted] |
| Change in baseline EDSS score | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean EQ-5D score | [redacted] | [redacted] | [redacted] | [redacted] |
| Change in baseline EQ-5D score | [redacted] | [redacted] | [redacted] | [redacted] |
| *Rebif 44mcg* | *Year 1* | *Year 2* | *Year 1* | *Year 2* |
| Average number of relapses* | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean EDSS score | [redacted] | [redacted] | [redacted] | [redacted] |

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| Change in baseline EDSS score | [redacted] | [redacted] | [redacted] | [redacted] |
| *Placebo* | *Year 1* | *Year 2* | *Year 1* | *Year 2* |
| Average number of relapses* | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean EDSS score | [redacted] | [redacted] | [redacted] | [redacted] |
| Change in baseline EDSS score | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean EQ-5D score | [redacted] | [redacted] | [redacted] | [redacted] |
| Change in baseline EQ-5D score | [redacted] | [redacted] | [redacted] | [redacted] |

*Estimated using Nelson-Aalen curves

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).

Table B11 below confirms the acquisition costs listed in the original submission (Table B7.5.1). The annual costs of beta-interferons and glatiramer acetate are listed directly in the DoH Health Service Circular, 2002. The net price of 7-cap pack of fingolimod is £367.50 [BNF Gilenya, 2013], leading to an annual cost of (367.50*52) = £19,110. The net price of 15-mL vial of natalizumab is £1130.00 [BNF Tysabri, 2013], leading to an annual cost of (1130*52/4) £14,690.

Table B11: Acquisition costs sources and price year

| Treatment | Dosage | Treatment regimen | Total annual cost | Source | Price year |
|---|---|---|---|---|---|
| Teriflunomide | 14 mg | Teriflunomide 14mg once daily in oral form | £13,529 | Genzyme | 2013 |
| IFNβ-1a 44µg (Rebif) | 44 µg | 44µg 3 times per week, self-injected subcutaneously | £8,942 | DoH Health Service Circular, 2002 | 2002 |
| IFNβ-1a 22µg (Rebif) | 22 µg | 22µg 3 times per week, self-injected subcutaneously | £7,513 | DoH Health Service Circular, 2002 | 2002 |
| IFNβ-1a (Avonex) | 30 µg | 30 µg once a week, self-injected subcutaneously | £8,502 | DoH Health Service Circular, 2002 | 2002 |
| IFNβ-1b | 250 µg | 250 µg every other day, self-injected subcutaneously | £7,259 | DoH Health Service Circular, 2002 | 2002 |
| Glatiramer acetate | 1 mL vial 20mg/mL | 20 mg per day, self-injected subcutaneously | £5,823 | DoH Health Service Circular, 2002 | 2002 |
| Fingolimod | 52 x 7-tab pack 0.5mg capsule | 0.5 mg once daily in oral form | £367.50 * 52 = £19,110 | British National Formulary | 2013 |
| Natalizumab | 15 mL vial 20 mg/mL | 300 mg intravenous injection by a health professional every 4 weeks | £14,690 | British National Formulary | 2013 |

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.

Table B12: EQ-5D scores for each EDSS state

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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?

Table B7.7.1 of the submission reports the results of the 2-year clinical trials for the teriflunomide 14mg arm compared to the 2-year results for teriflunomide 14mg projected by the cost-effectiveness model. Outcomes considered are change in EDSS from baseline, average number of relapses leading to hospitalisation and not leading to hospitalisation, change in EQ-5D and mortality. The clinical trials evaluated in the comparison are TEMSO and TOWER. Table 1 presented above provides a similar comparison. The model considers results for teriflunomide alone. The purpose of the table is to show how model results differ from those recorded in the clinical trial (as requested in question B6 above), the reasons for which are discussed in Section 7.7.1.

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?

Elevations of liver enzymes and blood pressure have been observed in patients receiving teriflunomide (see section 6.9.2 of main submission). The draft summary of product characteristics (Appendix 1 of main submission) states:

- Liver enzymes should be assessed before initiation of teriflunomide therapy - every two weeks during the first 6 months of treatment, and every 8 weeks thereafter
- Blood pressure must be checked before the start of teriflunomide treatment and periodically thereafter

Therefore, within the first year, liver function tests and blood counts are taken every two weeks for the first 6 months (52/2/2 = 13) and every 8 weeks thereafter (52/2/8 = 3) equating to 16 tests in the first year. Subsequent years require tests every 8 weeks, equating to (52/8) 7 tests per year.

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

To identify treatment-related adverse events for the purposes of including associated costs and quality of life decrements in the model, adverse events had to be identified which would not have otherwise occurred with placebo. Therefore, any adverse event which occurred at a rate of 4% of more compared to placebo were included in the model, and considered to be treatment-related adverse events. The 4% cut off is an arbitrary value, but is felt to capture a broad range of treatment-related adverse events. Adverse events that occurred between 0% and 4% would likely have negligible impact on cost and quality of life. Sensitivity analyses showed that results were insensitive to changes in costs or quality of life due to adverse events, thus inclusion of clinically significant or less common but more costly adverse events would have negligible impact.

The 4% cut off may also be considered unfavourable to teriflunomide since this criterion excluded progressive multifocal leukoencephalopathy (PML), a clinically significant and costly adverse event associated with natalizumab treatment. Otherwise, all clinically significant or costly adverse events are included in the model based on this cut off.