Single Technology Appraisal (STA)

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

## 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.

See covering e mail and attachments

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:

Response

We would like to raise a point of clarification in this question. The dosing suspension occurred in September 2005 after the results were issued to the Data Safety Monitoring Board (DSMB) for the pre-planned first interim analysis. The DSMB conducted 2 pre-planned interim analyses of safety and efficacy at 1 (results issued September 2005) and 2 years (results issued September 2006) after all patients had received initial treatment (equivalent to Month 0 for alemtuzumab treated patients). The Sponsor's designated statistician and supporting programmer performed the interim analyses, prepared the report, and communicated the results to the DSMB in accordance with the DSMB Charter and Statistical Analysis Plan.

A timeline of events describing relevant changes to the conduct of the study is shown in figure A2.1.

Figure A2.1: Chronology of relevant changes to the conduct of the CAMMS223 study [Genzyme CSR 2010]

| Timeline | Event |
|---|---|
| September 2005 | Results of first interim analysis issued. Interim analysis was performed when all patients had completed at least one year of follow up from initial treatment (i.e. had reached ≥Month 12 for alemtuzumab treated patients) |
| 16 September 2005 | Alemtuzumab dosing suspension initiated |
| 30 August 2006 | Amendment 6 – confirmation of no further alemtuzumab treatment for the remainder of the study. Additional two years of follow up (i.e. to month 60) for all patients subsequent to the 36 month treatment period |
| September 2006 | Results of second interim analysis issued. Interim analysis was performed when all patients had completed at least two years of follow up from initial treatment (i.e. had reached ≥Month 24 for alemtuzumab treated patients) |
| September 2007 | All patients complete 36 month treatment period |
| 7th April 2008 | Extension Phase |

| | |
|---|---|
| | Protocol amendment 8 – Randomisation of consenting alemtuzumab patients to either fixed dose or as needed retreatment |
| 18th March 2009 | Extension Phase<br>Protocol amendment 10 – Patient/investigator selection of fixed dose or as needed retreatment |

- 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.

Response

An independent, unblinded Data Safety Monitoring Board (DSMB) provided ongoing, expert, safety review to assess potential safety issues associated with alemtuzumab in this study. The Sponsor provided all treatment-emergent safety data to the DSMB at quarterly intervals, and provided the DSMB with all deaths and serious, unexpected and related serious adverse event (SAE) data on a timely basis. The DSMB was authorised to make recommendations to the Sponsor regarding study continuation, stopping, or modification based on safety findings.

Procedures governing the convening and execution of the responsibilities of the DSMB were specified separately in a prospectively written DSMB Charter document. The DSMB was appointed by the Sponsor and initially had 6 members. Following the recognition in 2005 of immune thrombocytopenic purpura (ITP) as a potential complication, a haematologist was added to the panel. The panel also included a statistician.

When alemtuzumab dosing was suspended a risk minimisation action plan (RiskMAP) for proactive identification and treatment of ITP patients was designed with an external expert panel to minimise morbidity through early identification and rapid treatment of patients with significant thrombocytopenia. The RiskMAP involved comprehensive investigator (and other site personnel) and patient education about the signs and symptoms of ITP (including pictures exemplifying the petechiae and ecchymoses from ITP), monthly testing of FBCs with platelets for all patients, a monthly questionnaire inquiring about signs and symptoms of ITP, and quarterly anti-platelet antibody testing. Each site was instructed to identify a local haematologist who specialised in the treatment of ITP. Patients were given the option to re-enter the study as long as they did not have any of the disqualifying criteria (Table B.5, presented in response the next point for clarification). The DSMB were sufficiently reassured by the stringent measures put in place through the RiskMAP and were able to subsequently advise the lifting of the dosing suspension

- The submission refers to Table B.5 which describes disqualifying criteria for alemtuzumab retreatment, but there is no table B.5 in the submission. Please provide table B.5.

Response

Table A2.1: Table B.5 – disqualifying criteria for retreatment with alemtuzumab following the lifting of the dosing suspension.[Genzyme CSR 2010]

| |
|---|
| • Exposure within past 28 days to interferon-beta or glatiramer acetate.<br>[redacted] |

[redacted]

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

<u>Response</u>

Only [redacted] eligible patients ([redacted]%) did not receive the second cycle of alemtuzumab at Month 12 due to the dosing suspension. [redacted] alemtuzumab-treated patients discontinued treatment after the first cycle ([redacted] due to the [redacted], [redacted] due to [redacted] and [redacted] due to [redacted]).[Genzyme CSR 2010]

Table A2.2 shows that [redacted] received a third cycle, with [redacted] ([redacted] patients on the 12 mg dose and [redacted] on the 24 mg dose) receiving the third cycle at Month 24, and [redacted] receiving the third cycle (all received 12 mg) after retreatment was in place under Amendments 8 or 10. [redacted] patients who had each received their third cycle at Month 24 received a fourth cycle (of 12 mg/day for 3 days) during the retreatment period (range, 37 to 54 months after the last/prior infusion).

Table A2.2: Alemtuzumab exposure at complete follow-up [Genzyme CSR 2010]

| Time | Exposure | Alemtuzumab 12mg/day (N=108) | Alemtuzumab 24mg/day (N=108) | Alemtuzumab Pooled (N=216) |
|---|---|---|---|---|
| Initial 3 years | Received cycle 1<br>Received cycle 2<br>Received cycle 3<br>Did not receive cycle 2 due to dose suspension | [redacted] | [redacted] | [redacted] |
| Amendment 8 | Randomised for re-treatment<br>As needed treatment<br>Eligible for retreatment cycle 1<br>Received retreatment cycle 1<br>Fixed treatment<br>Received retreatment cycle 1 | [redacted] | [redacted] | [redacted] |
| Amendment 10 | Elected for re-treatment<br>As needed treatment<br>Eligible for retreatment cycle 1<br>Received retreatment cycle 1<br>Fixed treatment<br>Received retreatment cycle 1 | [redacted] | [redacted] | [redacted] |
| Total cycles received | 1<br>2<br>3<br>4 | [redacted] | [redacted] | [redacted] |

The timeline of events shown above confirms that participants who did not receive second or third cycles of alemtuzumab could not have be given retreatment prior to the 36-month evaluation as the lifting of the dosing suspension occurred subsequently to the time at which all patients would have reached ≥36 months follow up since their initial treatment.

- Figure B6.3.1 on page 81 shows the trajectory of the participants in the trial and extension period. Could you confirm the re-randomisation/choice between the fixed or as needed treatment 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.

Response

Confirmed, as shown in figure A2.2, the re-randomisation/choice between fixed or as needed treatment only occurred after the 36 month efficacy and safety evaluations for all participants. None of the data in Figure B6.3.1. is commercial in confidence

- 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.

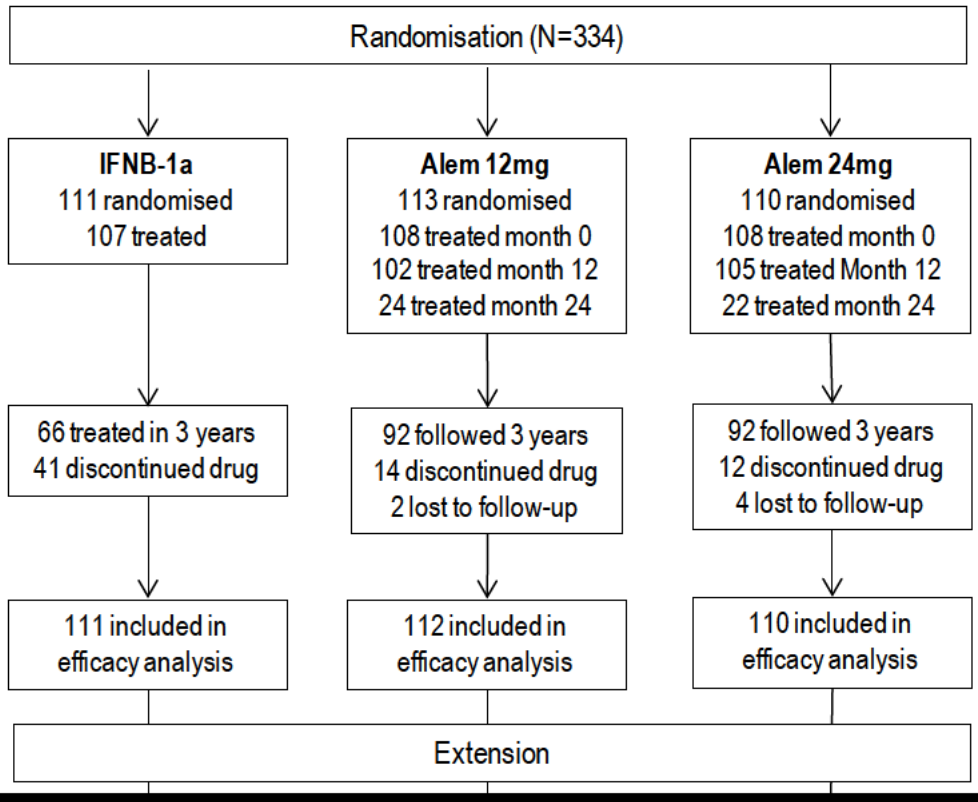
Response

Data analysis of clinical efficacy was carried out on a yearly basis as outlined on pages 121-122 in Tables B.6.5.2.2-4 in our submission. No efficacy analysis relating specifically to the point of alemtuzumab dosing suspension has been identified within the CSR or upon internal enquiries regarding analyses undertaken.

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?

Response

The patient disposition detailing the number of patients randomised to the alemtuzumab 12mg group and the total number completing the study at 36 months is described in the submission on page 104, Figure B6.3.2. They are reproduced again below for confirmation purposes.




[redacted]

**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.**

Response

As shown in table B6.3.4 of the submission, for a small number of patients there was a discrepancy between patient recruitment and inclusions criteria for CAMMS223, CARE-MS I and CARE-MS II in relation to meeting the required inclusion criteria for frequency of MS episodes prior to trial entry. For example in terms of CAMMS 223, patients were recruited on the basis of having two episodes in the previous two years, but on review of their notes it became clear that these episodes did not fulfil the protocol definition of a relapse.

In all three trials, the full analysis (FA) set was used for the primary efficacy analyses and consisted of all patients who were randomised to treatment and had received any amount of study drug.

The Per-Protocol (PP) set is a subset of the FA set and included all:

- Patients who had no major protocol deviations or inclusion/exclusion criteria deviations that might potentially affect efficacy.
    - With regard to MS episode history prior to trial entry, only patients who had no relapses in the previous two years were excluded from the per protocol analysis. Patients with 1 relapse in the last two years were included in the full analysis set as this was not thought likely to potentially affect efficacy.
- Alemtuzumab-treated patients who received alemtuzumab at 0 and 12 months without any major protocol deviations at either dose, or if SAD was experienced in the first 12 months, who had received alemtuzumab at Month 0 without any major protocol deviations
- IFNB-1a-treated patients who took at least 80% of the required IFNB-1a doses and remained on therapy for at least 12 months, or if SAD was experienced, who took at least 80% of the required IFNB-1a doses prior to that event.

The PP set was defined and approved prior to database lock and final analysis.

According to the statistical analysis plans for the three trials, analysis of the co-primary endpoints would be performed for the PP set if it was <90% of the FA Set.

For CAMMS223 and CARE-MS II the PP analysis was completed as the per-protocol set included [redacted]% ([redacted] out of [redacted]) and [redacted]% ([redacted] out of [redacted]) of the full analysis set respectively

For CARE-MS I the PP analysis was not completed as the PP set included [redacted]% ([redacted] out of [redacted]) of the full analysis set.

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.

Response

Table A5.1 shows the number of patients with an EDSS of ≤3.0 in CAMMS223 and CARE-MS I and ≤5.0 in CARE-MS II. It is important to clarify that the results presented below are the EDSS scores recorded at baseline and could differ from screening values which were used to determine eligibility for trial inclusion. It is not possible to provide the screening EDSS scores.

Table A5.1: Amended Table B6.3.4. Baseline characteristics of patients in Phase II and Phase III Alemtuzumab Studies

| Trial | NCT0050778 (CAMMS223) [Coles *et al*. 2008; Genzyme CSR 2008] | | | NCT00530348 (CAMMS323, CARE-MS I) [Genzyme CSR 2012a] | | NCT00548405 (CAMMS324, CARE-MS II) [Coles et al. 2012; Genzyme CSR 2012b] | | |
|---|---|---|---|---|---|---|---|---|
| Baseline characteristics | SC IFNβ-1a (44µg 3x/week) | Alemtuzu-mab (12mg annual cycle) | Alemtuzu-mab (24mg annual cycle) | SC IFNβ-1a (44µg 3x/week) | Alemtuzu-mab (12mg annual cycle) | SC IFNβ-1a (44µg 3x/week) | Alemtuzu-mab (12mg annual cycle) | Alemtuzu-mab (24mg annual cycle) |
| Mean EDSS score | 1.9 (0.83) | 1.9 (0.74) | 2.0 (0.73) | 2.0 (1.3) | 2.1 (1.4) | 2.7 (1.21) | 2.7 (1.26) | 2.7 (1.17) |
| 0 | - | 4 (3.6) | 5 (4.5) | 9 (5) | 15 (4) | 5 (2) | 16 (4) | 4 (2) |
| >0-1.5 | | 40 (35.7) | 36 (32.7) | 60 (32) | 126 (34) | 44 (22) | 89 (21) | 31 (18) |
| >1.5-2.0 | | 30 (26.8) | 30 (27.3) | 50 (27) | 87 (23) | 34 (17) | 63 (15) | 29 (17) |
| >2.0-3.0 | | 38 (33.9) | [redacted] | 65 (35) | 140 (37) | 48 (24) | 112 (26) | 52 (31) |
| >3.0-4.0 | | 0 | [redacted] | 3 (2) | 8 (2) | 50 (25) | 98 (23) | 38 (22) |
| >4.0-5.0 | - | - | [redacted] | - | | 19 (9) | 42 (10) | 14 (8) |
| >5.0-6.0 | - | - | [redacted] | - | | 2 (1) | [redacted] | [redacted] |
| >6.0-7.0 | - | - | [redacted] | - | | 0 | [redacted] | [redacted] |

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?

<u>Response</u>

The first occurrence is reported incorrectly. The percentage of patients experiencing 6-month SAD at 3 years was 26.2% for SC INFβ-1a and 8.5% in the alemtuzumab 12mg group. The percentage of patients experiencing three-month SAD at 3

years was 32.7% for SC IFNβ-1a and 16.3% in the alemtuzumab 12mg group. The figures first reported are those patients with no relapse at 3 years (51.6% for SC IFNβ-1a and 77.0% for the 12mg alemtuzumab group) [Coles, 2008].

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

Response

The choice was between a fixed-effects and a random-effects meta-analysis, and fixed-effects analyses have the strong assumption that there is no heterogeneity in effect sizes. Furthermore, when there is enough power to detect heterogeneity, and there is none, the random-effects and fixed-effects results are quite similar. Thus, the conservative choice is to implement *a priori* a random-effects analysis. (There are exceptions to this rule, for instance when analyzing rare safety events, but they are not germane to this particular set of analyses.) The Cochrane Collaboration (http://www.cochrane-net.org/openlearning/html/mod13-4.htm) recommends generally using the more conservative option when making this choice. However, the question is probably moot in this case, given the low amount of random-effects variance: fixed-effects and random-effects results were similar.

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.

Response

Confirmed, this is a typographical error. The sentence should state that the results of the meta-analysis demonstrated that alemtuzumab was consistently superior to SC IFNβ-1a for the analysed efficacy and safety outcomes.

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.

Response

Consider the general case of comparing two treatments, A and B, within the MTC. There might be three sources of information for connecting A to B: two studies that test A vs B (two instances of direct evidence), and one study of A vs C, and one study of B vs C (which, when combined using a Bucher indirect comparison, give us one instance of one-bridge indirect evidence comparing A and B).

The direct A vs B evidence and the "one-bridge" A vs B evidence (3 data points in all, in this example) were meta-analyzed and also visually examined to see if:

1) There was meaningful heterogeneity, and
2) The indirect evidence looked substantively different than the direct evidence.

We found few signs of heterogeneity, which matched up with the low estimates of random-effects variance found in the MTCs.

The primary focus of comparison of the results of the MTC to direct trial data related to the SAD 3 month HR outcome since the HE model was most sensitive to the estimates of this parameter derived from the MTC. Below is a table comparing the outputs of the base case and sensitivity analysis MTC and direct trial evidence in relation to this outcome. The conclusion of such a comparison are that:

- The greatest difference between the outputs of the two MTCs relate to the estimate of GA vs placebo where the base case MTC appears to be closer than the all years MTC to the estimate from the two larger trials of GA vs placebo – CONFIRM and the Copolymer I Study)
- Betaferon is substantially worse in both MTCs than the estimate from direct trial data. This is in part because it does worse than GA in a trial in the indirect network matrix (BEYOND SAD 21% vs 20% betaferon vs GA; n=897 vs 448; O'Connor et al 2009).
- The alemtuzumab 12mg vs Rebif 44 output in both MTCs is similar to the direct metanalysis output and the results of CARE MS II. CAMMS 223 provides better results and CARE MS I worse results than from the MTCs.

Table A10.1 MTC Results

| | Basecase MTC | All years MTC | Direct results (all references included in original submission) |
|---|---|---|---|
| Comparison | Hazard ratio (95% CI) | Hazard ratio (95% CI) | |
| Alemtuzumab 12mg vs Rebif 44 | [redacted] | [redacted] | CAMMS 223: 0.42 (0.23,0.77) (n=112 vs 111) (Coles et al 2008)<br>CARE MS I: 0.78 (0.47,1.29) (n=376 vs 187) (Coles et al 2012)<br>CARE MS II: 0.72 (0.49,1.05)(n=426 vs 202) (Coles et al 2012)<br>Direct meta analysis [redacted] |
| Alemtuzumab 12mg vs placebo | [redacted] | [redacted] | No relevant data found |
| Rebif 44 vs placebo | 0.79 (0.51,1.24) | [redacted] | PRISMS: 0.65 (0.45,0.94) (n=184 vs 187) (Ebers 1198) |
| Rebif 22 vs placebo | | [redacted] | PRISMS: 0.76 (0.53,1.08) (n=189 vs 187) (Ebers 1998) |
| Avonex vs placebo | 0.91(0.61,1.33) | [redacted] | No relevant data found |
| Betaferon vs placebo | 1.21 (0.68,2.16) | [redacted] | IFNB MS Study: 0.68 (0.4,1.17) (n=124 vs 125) (Duquette 1993) |
| GA 20mg vs placebo | 0.93(0.59,1.45) | [redacted] | CONFIRM: 0.93(0.63,1.37) (n=350 vs 363) (Fox et al 2011)<br>Coploymer 1 MSSG: 0.86 (0.51,1.45) (n=125 vs 126) (Johnson 1995)<br>Bornstein 1987: 0.32* (0.09, 1.09) (n=25 vs 25) (Bornstein et al 1987) |
| Fingolimod 0.5 mg vs placebo | 0.75 (0.58,0.96) | [redacted] | FREEDOMS: 0.7 (0.52,0.96) (n=425 vs 418) (Kappos et al 2010)<br>FREEDOMS II: 0.83 [0.61–1.12];(n=358 vs 355) (Calabresi et al 2012) |
| Natalizumab 300mg vs placebo | 0.58 (0.4,0.84) | [redacted] | AFFIRM: 0.58 (0.43,0.77)(n=627 vs 315) (Polman et al 2006) |

*HR estimated from the published KM curve

## 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.

We only have to date AE data analysed by third or fourth cycle for first ITP events, infusion associated reactions, anaphylactic reactions, thyroid disorders in the format of analysis provided in Table B6.9.1. (all active controlled studies) . This is shown in table A10.1-4.

**Table A10.1. Thyroid Disorders in Alemtuzumab 12mg -Treated Patients (All Available Follow Up, Pool C)**

| | Overall | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 |
|---|---|---|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Patients at Risk | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Any Thyroid AE | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Abnormal TSH Result with | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Any Thyroid AE or Abnormal TSH Result with Simultaneous Abnormal free T3 or free T4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Table A10.2 : Incidence of Potential Anaphylactic Reactions Overall and by Cycle in All Alemtuzumab 12mg –Treated Patients (All Available Follow Up, Pool C)**

| | Overall n (%) | Cycle 1 n (%) | Cycle 2 n (%) | Cycle 3 n (%) | Cycle 4 n (%) | Cycle 5 n (%) | Cycle 6 n (%) |
|---|---|---|---|---|---|---|---|
| Patients at Risk | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Standard MedDRA Query | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Sampson Method | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Table A.10.3: Incidence of Infusion-Associated Reactions by Cycle and Severity in All Alemtuzumab 12mg -Treated Patients (All Available Follow Up, Pool C)**

| System Organ Class | Overall | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 |
|---|---|---|---|---|---|---|
| Patients at risk | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Any IAR | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Grade 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Grade 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Grade 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Grade 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Grade 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Table A10.4. First Immune Thrombocytopenic Purpura Event by Cycle in All Alemtuzumab 12mg -Treated Patients, All Available Follow Up (Pool C)

| | Alemtuzumab 12 mg/day (N=1216) n (%) |
|---|---|
| Cycle | |
| 1 | [redacted] |
| 2 | [redacted] |
| 3 | [redacted] |
| 4 | 0 |
| 5 | 0 |

Note: Percentages are based on the number of treated patients meeting the platelet-based or AE-based definition of ITP in the corresponding treatment group. ITP = immune thrombocytopenic purpura; AE = adverse event

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.

Response

Table A11.1 shows the model inputs and source of baseline EDSS distribution data for both the base case and sensitivity analyses correctly reported.

Table A11.1: Summary of baseline EDSS distribution data applied in the base case economic model and explored in sensitivity analysis (SA)

| Variable | Value | Source |
|---|---|---|
| Age at baseline | UK RSS: 39.3 years | Pickin et al. 2009 |
| | (SA) CARE-MS: [redacted] | Cohen et al. 2012<br>Coles et al. 2012a |
| Female to male ratio | UK RSS: 2.98 : 1 | Pickin et al. 2009 |
| | (SA) CARE-MS: [redacted] | Cohen et al. 2012<br>Coles et al. 2012a |
| Baseline EDSS distribution | UK RSS<br>0: 3%<br>1: 7%<br>2: 20%<br>3: 19.5%<br>4: 20.5%<br>5: 10%<br>6: 15.5%<br>7: 4.5% | Pickin et al. 2009 |
| | (SA) CARE-MS<br>[redacted] | Cohen et al. 2012<br>Coles et al. 2012a |

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.

Response

The administration costs for natalizumab are as stated in the submission (£6,162). This is derived as shown in Table A12.1.

Table A12.1: Annual administration cost of natalizumab

| Treatment | Year 1 cost | Year 2 cost | Source | Justification |
|---|---|---|---|---|
| Natalizumab | £6,162 | £6,162 | NHS Reference Costs AA30C Medical Care of Patients with Multiple Sclerosis without CC Day Case @ £474 per visit. | 13 infusions per year |

An incorrect cost of £6,611 was used in the model so the impact of changing the cost to £6,162 has been explored and found to have negligible results. With regards to the incremental base-case results, natalizumab still remains the most expensive treatment with this updated administration cost, therefore the cost-effectiveness of alemtuzumab remains unchanged. Considering the subgroup analysis of alemtuzumab versus natalizumab in RES RRMS, the results remain the same whereby natalizumab still remains dominated by alemtuzumab.

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.

Response

Resource use associated with a relapse are sourced from Dee et al. 2012 which used data collected from Irish neurology centres. Relapses not leading to hospitalisation require 5 days steroid treatment as a day case [Dee et al. 2012]. UK NHS reference costs have been substituted for the HIPE Irish costs used in the publication to gain a UK equivalent cost. Table A13.1 shows the cost calculation for relapses not leading to hospitalisation (Table B7.5.10 in the submission).

Table A13.1 Cost calculation for relapses not leading to hospitalisation [Dee et al. 2012]

| Parameter | Resource use | Number of days | Source of cost | Cost per day |
|---|---|---|---|---|
| Cost calculation for relapses not leading to hospitalisation | Days of steroid treatment | 5 | National Reference Costs 2011-12-Outpatient Attendances Data. Service code 400: Neurology | £168.93 |

Table A13.1 shows that the cost per day of steroid treatment is £168.93, resulting in 5 days costing £844.65 and this is used in the base case.

Dee et al. 2012 does state that the cost of a relapse not leading to hospitalisation is €2705 but this is an Irish cost and it is preferable to derive a cost relevant to the UK using UK NHS reference costs.

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).

Response

A patient can remain on a treatment with fingolimod or natalizumab whilst the following conditions are met:

- Patient does not discontinue treatment (estimated using outputs from the MTC)
- Patient has RRMS with an EDSS < 7
- Patient does not have SPMS.

The patient population considered within the base case economic evaluation is adults with active RRMS defined by clinical or imaging features. This is in line with the anticipated license following positive recommendation for alemtuzumab made by the Committee for Medicinal Products for Human Use (CHMP) on 27th June 2013 [EMA 2013]. Since the MAA submitted for alemtuzumab does not include the SPMS population, the cost-effectiveness of alemtuzumab within the SPMS population is not relevant. A SPMS stopping rule was implemented for all comparators at EDSS 0 such that no patients were treated with a DMT upon conversion to SPMS in the base case model. However, sensitivity analyses were performed to evaluate the impact of modelling SC IFNβ-1a and IFNβ-1b according to their licence in SPMS up to EDSS 7, in line with NICE guidance [NICE 2003]. The results of the sensitivity analysis showed that modelling SPMS treatment where licensed has very little impact on the ICER.

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.

Response

To confirm CAMMS323 is CARE-MS I, CAMMS324 is CARE-MS II and CAMMS223 is the phase II trial. P85 has been checked for accuracy and the results presented are correct.

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?

Response

MTC

As shown in the PRISMA diagram (figure B6.7.1), 19 of 52 trials were excluded as recruitment occurred prior to 2000 and/or <80% RRMS and were therefore outside the context of the base case. Details for these 19 trials is provided in Table A16.1

Table A16.1: Trials which did not fulfil recruitment year and disease characteristic base case criteria

| Study | Year | Intervention |
|---|---|---|
| Baum et al. | 2006 | Interferon β-1b |
| Bornstein et al. | 1987 | Copolymer 1 |
| Bornstein | 1991 | Copolymer 1 |

| | | |
|---|---|---|
| Johnson et al. | 1995 | Copolymer 1 |
| Kappos et al. | 1998 | Interferon β-1b |
| Comi et al. | 2001 | Glatiramer acetate |
| Duquette et al. | 1993 | Interferon β-1b |
| Cohen et al. | 2002 | Interferon β-1a |
| Miller et al. | 2003 | Natalizumab |
| Millefiorini et al. | 1997 | Mitoxantrone |
| Hartung et al. | 2002 | Mitoxantrone |
| Jacobs et al. | 1996 | Interferon β-1a |
| Andersen et al. | 2004 | Interferon β-1a |
| Ebers et al. | 1999 | Interferon β-1a |
| Ebers et al. | 1998 | Interferon β-1a |
| Saida et al. | 2005 | Interferon β-1b |
| Li et al. | 2001 | Interferon β-1a |
| Panitch | 2004 | Interferon β-1b |
| Tubridy | 1999 | Anti-alpha4 integrin antibody |

Of the remaining 33 trials, a further three were excluded because the trial used dosing and scheduling outside the context of approved product indications. Details for these three trials is provided in Table A16.2

Table A16.2: Trials which included dosing and scheduling outside of approved product indications

| Study | Year | Intervention |
|---|---|---|
| Filippi et al. | 2006 | Glatiramer acetate |
| Polman et al. | 2003 | Interferon β-1a |
| Clanet et al. | 2002 | Interferon β-1a |

All 30 of the remaining trials were included in the MTC and are listed in appendix 5 of the submission.

### Cost-effectiveness systematic review

The results of the systematic review are discussed in Section 10.10.4 of the submission whereby overall 33 studies were identified as evaluating cost-effectiveness in MS.

Of these cost-effectiveness studies, no studies for alemtuzumab were identified. However, two cost-effectiveness studies from the UK NHS perspective have recently been published for MS DMTs and used in NICE assessments. These studies are Chilcott et al. 2003 and Gani et al. 2008 and a quality assessment for each of these studies is provided in Section 7.1.3, Table B7.1.1 of the submission.

The 33 studies which were identified as evaluating cost-effectiveness in MS are detailed in Table A16.3.

Table A16.3: Studies identified as evaluating cost-effectiveness in MS from the cost-effectiveness systematic review

| Study | Year | Population | Intervention |
|---|---|---|---|
| Agashivala et al. | 2012 | RRMS | Fingolimod |
| Sánchez-de la Rosa et al. | 2012 | RRMS | Beta interferon; glatiramer acetate |
| Pan et al. | 2012 | RRMS | Beta interferon |
| Caloyeras et al. | 2012 | Patients with a first clinical event suggestive of MS | Beta interferon |
| Agashivala et al. | 2011 | RRMS | Fingolimod |

| Study | Year | Population | Intervention |
|---|---|---|---|
| O'Day et al. | 2011 | RMS | Natalizumab |
| Noyes et al. | 2011 | RRMS and SPMS | Beta interferon; glatiramer acetate |
| Nuijten et al. | 2010 | RRMS | Beta interferon |
| Tappenden et al. | 2010 | SPMS | Haematopoietic stem cell transplantation |
| Goldberg et al. | 2009 | RRMS | Beta interferon; glatiramer acetate |
| Earnshaw et al. | 2009 | RRMS | Glatiramer acetate; Natalizumab |
| Guo et al. | 2009 | RMS | Beta interferon |
| Chiao et al. | 2009 | RMS | Natalizumab |
| Tappenden et al. | 2009 | RRMS and SPMS | Beta interferon; glatiramer acetate |
| Janković et al. | 2009 | RRMS | Beta interferon; glatiramer acetate |
| Kobelt et al. | 2008 | MS | Natalizumab |
| Gani et al. | 2008 | RRMS and SPMS | Natalizumab |
| Bell et al. | 2007 | RRMS | Beta interferon; glatiramer acetate |
| Prosser et al. | 2004 | RRMS, SPMS and PRMS | Beta interferon; glatiramer acetate |
| Chilcott et al. | 2003 | RRMS and SPMS | Beta interferon; glatiramer acetate |
| Touchette et al. | 2003 | SPMS and PRMS | Mitoxantrone; beta interferon |
| Kobelt et al. | 2003 | RRMS and SPMS | Beta interferon |
| Lepen et al. | 2003 | RRMS | Beta interferon |
| Nuijten et al. | 2002 | RRMS and SPMS | Beta interferon |
| Bose et al. | 2001 | RRMS | Glatiramer acetate |
| Phillips et al. | 2001 | RRMS | Beta interferon |
| Brown et al. | 2000 | RRMS | Beta interferon |
| Kobelt et al. | 2000 | SPMS | Beta interferon |
| Kendrick et al. | 2000 | RRMS | Beta interferon |
| Forbes et al. | 1999 | SPMS | Beta interferon |
| Parkin et al. | 1998 | RRMS | Beta interferon |
| Novartis (Fingolimod) | 2011 | RRMS | Fingolimod |
| PenTAG | 2007 | RRMS and SPMS | Natalizumab |

HRQoL systematic review

The results of the systematic review are discussed in Section 10.12.7 of the submission whereby overall 10 studies were identified as evaluating quality of life in MS.

Of these studies, 2 were implemented in the model. These studies are Orme et al. 2007 and Gani et al. 2008 and a quality assessment for each of these studies is provided in Section 7.4.6, Table B7.4.1 of the submission.

The 10 studies which were identified as evaluating quality of life in MS are detailed in Table A16.4.

Table A16.4: Studies identified as evaluating quality of life in MS from the HRQoL systematic review

| Study | Year | Country |
|---|---|---|

| | | |
|---|---|---|
| Karampampa et al. | 2012 | UK |
| Naci et al. | 2010 | UK |
| Gray et al. | 2009 | Ireland |
| Boggild et al. | 2009 | UK |
| Holmoy et al. | 2008 | UK |
| Gani et al. | 2008 | UK |
| McCrone et al. | 2008 | UK |
| Forbes et al. | 2007 | UK |
| Orme et al. | 2007 | UK |
| Novartis (Fingolimod) | 2011 | UK |

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