Genzyme's Response to the alemtuzumab ACD sent to NICE on 9th January 2014

Genzyme's Response is related to the following areas (which we bullet point below and reference to the relevant pages):

- A.1. Relevant evidence has not been considered in describing the expected use of alemtuzumab (page 2)
- A.2. Relevant evidence has not been considered in determining whether alemtuzumab is clinically effective in patients with highly active (HA) RRMS despite interferon use (page 2-19)
- A.3. Relevant evidence has not been considered in the Committee's decision whether alemtuzumab is clinically effective in patients with RES RRMS (page 20-41)
- A.4. Relevant evidence has not been considered relating to the request to use the TEMSO TOWER placebo arm to derive natural history disease progression transition probabilities for the model in the additional analyses request in the ACD. (page 42-43)
- A.5. Relevant evidence has not be considered to support the inclusion of direct non-health care costs sourced from Tyas et al 2007 within the additional requested cost effectiveness analyses in the ACD (page 43-44)
- A.6.. Relevant evidence has not been considered in requesting as part of the ACD additional analyses applying a waning of efficacy solely to alemtuzumab and not to the comparators (page 45-46)
- B.1. Genzyme do not believe that the summary of clinical effectiveness which states that alemtuzumab 12mg does not have persuasive evidence that it is clinically effective in HA RRMS despite interferon use patients is a reasonable interpretation of the evidence (page 46-47)
- B.2. Genzyme do not believe that the summary of clinical effectiveness which states that alemtuzumab does not have persuasive evidence that it is clinically effective in RES RRMS patients is a reasonable interpretation of the evidence (page 47-48)
- C. Genzyme do not believe that the provisional recommendations are a sound and a suitable basis for guidance to the NHS (page 48-49)

Section A: Has all of the relevant evidence been taken into account?

A.1. Relevant evidence has not been considered in describing the expected use of alemtuzumab 12mg (in Section 4.4. of the ACD).

The description of the use of alemtuzumab does not capture that neurology clinical experts expect that alemtuzumab will be used primarily in place of natalizumab and fingolimod for patients with both RES RRMS and HAD despite interferon use.

This was indicated in our submission to NICE in the following statements on positioning in STA submission:

- PAGE 18 / 52 / 224: "Initially, it is anticipated that alemtuzumab will be used primarily in patients showing a high degree of disease activity (eg. presenting with two or more relapses in the prior year or with one relapse in the prior year despite treatment with interferons or glatiramer acetate) and primarily in place of natalizumab or fingolimod. It should be recognised that the definition of "highly active" for use of alemtuzumab would not need to be as restrictive as that contained within the licences of fingolimod and natalizumab and would be aligned to the more inclusive definition used amongst clinicians in England and Wales treating MS)."

- PAGE 239: 73% of those who will receive alemtuzumab 12mg will be patients with RES RRMS or HA disease despite treatment with a beta interferon.

A.2. Relevant evidence has not been considered in determining whether alemtuzumab is clinically effective in patients with highly active (HA) RRMS despite interferon use (this relates to the opinion expressed in Section 4.9. of the ACD that further evidence was needed by the Committee to persuade it of the clinical effectiveness of alemtuzumab in this subgroup).

Two sets of evidence are provided to support the efficacy of alemtuzumab in the HA RRMS despite interferon use subgroup from the CARE MS II study:

- Part A.2.1: Discussion of the results based on this subgroup from CARE MS II (for 3 and 6 month sustained accumulation of disability (SAD) hazard ratios (HR) and annualised response rate (ARR) rate ratios (RR). CARE MS II is the only study of the 3 main studies with treatment experienced patients and so the only one from which a HA RRMS despite beta interferon use subgroup analysis is possible.

- Part A.2.2: A discussion of the HA RRMS despite interferon use MTC networks which includes this subgroup from the CARE MS II study in terms of the results and their interpretation. This includes an assessment of clinical heterogeneity and a statistical assessment of heterogeneity, an assessment of heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies and the weakness and strengths of the networks (this is done both for the ARR RR and 3 month SAD HR networks. No 6 month SAD HR MTC network is presented because no such data was identified for fingolimod on our literature search for this outcome)

- Part A.2.3. The additional cost effectiveness analyses requested in the ACD for active RRMS has been run for alemtuzumab versus fingolimod in the HA RRMS despite interferon subgroup. This is so that if the

Committee accept the clinical effectiveness of alemtuzumab in this subgroup they have available the same associated cost effectiveness analyses as they have requested for active RRMS. This data plus the associated models was also sent to NICE as part of the additional information request so that its validity could be assessed by the ERG on 9th January 2014.

A.2.1: Evidence based on HA RRMS despite interferon use subgroup from CARE MS II results (for 3 and 6 month SAD HRs and ARR RRs)

The clinical effectiveness of alemtuzumab 12mg vs SC IFNβ-1a 44µg in HA RRMS despite interferon use patients in relation to 6 months SAD HRs based on a subgroup analyses of CARE MS II is shown in Table A.2.1.1. It provides the following supportive evidence:

- The 6 months SAD HRs shows alemtuzumab 12mg to be statistically significantly better than SC IFNβ-1a 44µg: 0.55 [0.32, 0.95] (n=334).
    - These results are comparable to those in the full trial data set 0.58 [0.38, 0.87] (n=628).
    - This is consistent with the assessment of alemtuzumab 12mg by the regulatory authority, the European Medicines Agency (EMA), which did not identify any difference between highly active and non-highly active subgroups in the efficacy of alemtuzumab 12mg as shown in the European Public Assessment Report for the drug.[EMA (Lemtrada EPAR), 2013]
- No 6 month SAD HR results of a subgroup analysis of fingolimod in the highly active despite interferon subgroup has been identified in the literature to allow a comparison based on this outcome.

A.2.1.1: Six month SAD HRs for alemtuzumab 12mg for HA RRMS despite interferon use subgroup compared to full trial data sets

Comparison	Data Source	Subgroup Sample size	Full trial sample size	Sample size as % of full trial data set	SAD 6 mth HR (HAD despite INF use subgroup) [95% CI]	SAD 6 mth HR (full trial data) [95% CI]
Alemtuzumab 12mg versus **SC IFNβ**-1a	Data on file [Genzyme 2013] / CARE MS II [Coles et al 2012]	334	628	53%	0.55* [0.32, 0.95]	0.58 [0.38, 0.87]

* CARE MS II HAD definition: > 365 days interferon (IFN) with IFN exposure in year prior to treatment and gadolinium enhancing lesion positive (Gad+) OR T2 > 0.5 mL and 1 or more relapses in prior year

The clinical effectiveness of alemtuzumab 12mg vs SC IFNβ-1a 44µg in HA RRMS despite interferon use patients in relation to 3 months SAD HRs based on a subgroup analysis of the CARE MS II study are shown in Table A.2.1.2 and provides the following supportive evidence:

- The 3 months SAD HRs of the subgroup from CARE MS II shows alemtuzumab 12mg to be numerically but not statistically significantly better than SC IFNβ-1a 44µg: 0.61 [0.37, 1.01] (n=334).
    - These results are comparable to those in the full trial data set: [redacted].
    - These results need to be considered in light of the fact that 6 month SAD is considered to be the more robust measure of sustained disability accumulation than 3 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 six months apart".[EMA, 2009]

- As shown in Table A.2.1.2., the clinical efficacy of fingolimod 0.5mg versus placebo in relation to 3 month HRs in the HA RRMS despite interferon use trial subpopulation is comparable to that of alemtuzumab 12mg versus an active comparator (SC IFNβ-1a 44µg): 0·68 [0·29, 1·62] (n=114) or 0.73 [0.29, 1.84] (n=70) (depending on the definition of HA RRMS despite interferon use) compared to 0.61 [0.37, 1.01] (n=334) respectively.
    - A fingolimod 0.5 mg highly active RRMS despite interferon use subgroup analysis against placebo from the FREEDOMS trial (n= 169; 20% of the full trial data set) and versus IM IFNβ-1a 30mg from TRANSFORMS (n=374; 43% of the full trial data set) were accepted by NICE as proof of the efficacy of fingolimod 0.5 mg in this subgroup.
    - Alemtuzumab 12mg has data from a similar sized subgroup population as the TRANSFORM subgroup (n=334; 53% of full trial data set) and also against an active comparator.
    - It was reported in the fingolimod NICE guidance that no statistically significant difference in disability progression between treatment groups in these subgroup populations was observed vs either placebo or an active comparator (although the actual figures were not stated).[NICE, 2012 – Section 4.7]. The measure used was 3 month SAD HRs and no 6 month SAD HR data was presented. Alemtuzumab has statistically significantly better results in this subgroup for disability progression using the more robust measure of 6 months SAD HRs.

A.2.1.2: 3 month SAD HR for alemtuzumab 12mg and fingolimod HA RRMS despite interferon use trial subgroups compared to the full trial data sets

Comparison	Data Source	Reference	Subgroup Sample size	Full trial sample size	Sample size as % of full trial data set	SAD 3 mth HR (HAD despite INF use subgroup)	SAD 3 mth HR (full trial data)
Alemtuzumab 12mg versus **SC IFNβ**-1a	CARE MS II	Data on file	334	628	53%	0.61 [0.37, 1.01]*	[redacted]
Fingolimod 0.5 mg vs placebo	FREEDOMS [Devonshire et al, 2012]	Devonshire et al	114	843	14%	0·68 [0·29, 1·62]**	0.70 [0.52, 0.96]
Fingolimod 0.5 mg vs placebo	FREEDOMS [EMA, (Fingolimod EPAR) 2011]	Fingolimod EPAR	70	843	8%	0.73 [0.29, 1.84]***	0.70 [0.52, 0.96]

* CARE MS II HAD definition: > 365 days interferon (IFN) with IFN exposure in year prior to treatment and gadolinium enhancing lesion positive (Gad+) OR T2 > 0.5 mL and 1 or more relapses in prior year
**FREEDOMS HAD definition used: Group C in Devonshire et al paper: Patients who received interferon beta during the year before study enrolment and had at least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or nine T2 lesions at baseline
** *FREEDOMS HAD definition from fingolimod EPAR: Patients who had been on treatment with an approved disease-modifying MS drug for at least 6 months (sufficient duration to evaluate efficacy), were still on treatment in the year before starting study drug, and had at least 1 relapse during the last year. The relapse may or may not have occurred while on the MS disease modifying therapy and at least one Gd-enhancing lesion on baseline MRI.

The clinical effectiveness of alemtuzumab 12mg vs SC IFNβ-1a 44µg in HA RRMS despite interferon use patients in relation to annualised relapse rates rate ratios (ARR RR) based on a subgroup analysis of CARE MS II is shown in Table A.2.1.3. It provides the following supportive evidence:

- The subgroup analysis of ARR RR shows alemtuzumab 12mg to be statistically significantly better than SC IFNβ-1a 44µg: 0.4 [0.28, 0.56] (n=334).
    - These results are comparable to those in the full trial data set: 0.5 [0.41, 0.61] (n=628).
    - This is consistent with the assessment of alemtuzumab 12mg by the regulatory authority, the European Medicines Agency (EMA), which did not identify any difference between highly active and non-highly active subgroups in the efficacy of alemtuzumab 12mg as shown in the European Public Assessment Report for the drug.
- The clinical efficacy of fingolimod 0.5mg versus placebo in relation to ARR RRs in the HA RRMS despite interferon use subpopulation is comparable to that of the alemtuzumab 12mg versus an active comparator

(SC IFNβ-1a 44µg): 0.38 [0.21, 0.68] (n=114) or 0.44 [0.25, 0.77] (n=187) (dependent upon the definition of the HA RRMS despite interferon subgroup definition for fingolimod 0.5mg) compared to 0.4 [0.28, 0.56] (n=334) respectively.

- Fingolimod 0.5mg HA RRMS despite interferon use subgroup analyses against placebo from the FREEDOMS trial (n= 169; 20% of the full trial data set) and versus IM IFNβ-1a 30mg from TRANSFORMS (n=374; 43% of the full trial data set) were accepted by NICE as proof of the efficacy of fingolimod 0.5mg in this subgroup.
- In the highly active RRMS despite interferon use subgroup analysis ARR of 0.21 compared with 0.54 (p< 0.001) for fingolimod 0.5mg versus placebo and of 0.25 compared with 0.51 (p < 0.001) for fingolimod 0.5mg compared with IM IFNβ-1a 30mg are quoted in the fingolimod 0.5mg NICE guidance
- Alemtuzumab 12mg has data from a similar sized subgroup population as the TRANSFORM subgroup (n=334; 53% of full trial data set) and also against an active comparator.
- (in the fingolimod EPAR ARR outcome data for a HA despite interferon use subgroup of TRANSFORM is presented but the outcome used is negative binomial rate ratios which make comparison to the alemtuzumab data difficult so these results are not presented here)

Table A.2.1.3: ARR – RR alemtuzumab 12mg and fingolimod 0.5mg HA RRMS despite interferon use trial subgroup analyses compared to the full trial data sets

Comparison	Data Source	Subgroup Sample size	Full trial sample size	Sample size as % of full trial data set	ARR RR (HAD despite INF use subgroup) [95% CI]	ARR RR (full trial data)
Alemtuzumab 12mg versus **SC IFNβ**-1a	CARE MS II Data on file [Genzyme 2013]	334	628	53%	0.4* [0.28, 0.56]	0.5 [0.41, 0.61]
Fingolimod 0.5 mg vs placebo	FREEDOMS [Devonshire et al, 2012]	114	843	13%	0·38** [0·21, 0·68]	0·46 [0·37, 0·57]

* CARE MS II HAD definition: > 365 days interferon (IFN) with IFN exposure in year prior to treatment and gadolinium enhancing lesion positive (Gad+) OR T2 > 0.5 mL and 1 or more relapses in prior year

**FREEDOMS HAD definition used: Group C in Devonshire et al paper: Patients who received interferon beta during the year before study enrolment and had at least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or nine T2 lesions at baseline

A.2.2: A discussion of the MTC networks for HA RRMS despite interferon use in terms of the results and their interpretation.

This includes the following:

- A.2.2.1. – A.3.2.2. A presentation and discussion of the results of the MTCs for 3 month SAD HRs and ARR RRs. No results are presented for the 6 month SAD HR MTC because this analysis only provided data for comparisons of alemtuzumab versus SC IFNβ-1a 44µg (for which direct evidence exists) and versus teriflunomide which is not a comparator. It did not provide data versus fingolmod 0.5 mg which is the comparator against which alemtuzumab is required by the NICE scope to be compared in this group since no 6 month SAD HR data for fingolimod 0.5mg in highly active RRMS despite interferon use was identified in the literature.
- A.2.2.3. An assessment of clinical heterogeneity
- A.2.2.4. A statistical assessment of heterogeneity
- A.2.2.5. An assessment of heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies
- A.2.2.6. The weakness and strengths of the networks

A.2.2.1. A presentation and discussion of the results of the three month SAD HR MTC for the HA RRMS despite interferon subgroups.

The following key points are noted in relation to the effectiveness of alemtuzumab 12mg for HA RRMS despite interferon use patients in relation to 3 month SAD HR as estimated using the associated MTC (output described in Table A.2.2.1.1 and network and inputs described in Figure A.2.2.1.1 and Table A.2.2.1.2:

- Alemtuzumab is [redacted]
    - This result should be seen in the context of the HA RRMS despite interferon subgroup of the CARE MS II which forms the direct evidence input into this network in which alemtuzumab 12mg although showing non-statistically significant results versus an active comparator (SC IFNβ-1a 44 µg) was associated with a narrower CI: 0.61 [0.37, 1.01].
    - The wider credible intervals associated with alemtuzumab 12mg versus placebo estimations based on the MTC results in contrast to the narrower 95% CIs around alemtuzumab versus SC IFNβ-1a 44 µg based on the direct evidence is primarily because of the high uncertainty associated with the data that forms the links between alemtuzumab 12mg and placebo in the network (see Figure A.3.2.1.1 below).
        - The link from alemtuzumab to placebo is alemtuzumab to SC IFNβ-1a 44 µg then SC IFNβ-1a 44 µg to teriflunomide 14mg and then teriflunomide 14mg to placebo. The trial

subgroup data associated with the SC IFNβ-1a 44 μg vs teriflunomide 14mg and teriflunomide 14mg to placebo adds uncertainty as can be inferred from the confidence intervals of [redacted] and [redacted]] respectively (see Table A2.2.1.2 below)

- Alemtuzumab is numerically but not statistically significantly better than fingolimod 0.5mg based on the MTC results: 0.65 [0.11, 3.72].
    - The wide CI around alemtuzumab versus fingolimod is primarily because of the high uncertainty associated with the data that forms the links between alemtuzumab 12mg and fingolimod 0.5mg in the network (see Figure A.2.2.1.1 below) and the number of links needed to make this comparison.
    - The link from alemtuzumab to fingolimod 0.5mg is alemtuzumab to SC IFNβ-1a 44 μg then SC IFNβ-1a 44 μg to teriflunomide 7/14mg and then teriflunomide 7/14mg to placebo and then placebo to fingolimod 0.5mg; the trial subgroup data associated with the SC IFNβ-1a 44 μg vs teriflunomide 14mg and teriflunomide 14mg to placebo is associated with a degree of uncertainty as described in the bullet point directly above.
    - These results should be seen in the context of the direct trial HA despite interferon subgroup evidence in which the fingolimod 0.5mg versus placebo in relation to 3 month HRs is comparable to that of alemtuzumab 12mg versus an active comparator (SC IFNβ-1a 44μg): 0·68 [0·29, 1·62] (n=114) or 0.73 [0.29, 1.84] (n=70) (depending on the definition of HA RRMS despite interferon use) compared to 0.61 [0.37, 1.01] (n=334) respectively.
    - The MTC analysis has been carried out to provide parameter estimates for the HE model with cost effectiveness being driven primarily by SAD HRs. Taking the highly conservative assumption that the alemtuzumab vs SC IFNβ-1a 44μg results from the CARE MS II subgroup analysis for 3 month SAD HRs and ARR RR are equivalent to alemtuzumab vs placebo results and populating the HE model with parameter values based on this assumption (together with using fingolimod versus placebo results from the FREEDOMS subgroup) still provides preferential ICER of £7,089 to £17,232 for alemtuzumab versus fingolimod (See Table A.2.3.2. below for details). This ICER is based on an assumed annual PAS price for fingolimod of £13,000. This suggests at even the most conservative assumption that SC IFNβ-1a 44μg and placebo efficacy are equivalent in HA RRMS despite interferon use patients that alemtuzumab remains cost effective .

- These 3 month SAD results need to be considered in the context of the fact that the 6 month SAD is considered to be the more robust measure of sustained disability accumulation than the 3 month SAD, and 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 six months apart”.
    - In this regard, it is worth noting that the 6 months SAD HRs shows alemtuzumab 12mg to be statistically significantly better than SC IFNβ-1a 44μg: 0.55 [95% CI: 0.32, 0.95] (n=334).
    - No 6 month SAD HR results of a subgroup analysis of fingolimod in the highly active despite interferon subgroup has been identified in the literature to allow a comparison based on this outcome.

Table A.2.2.1.1: Output from 3 month SAD HR MTC

	Alemtuzumab 12 mg	Placebo
	Hazard Rate [95% CrI]	
Alemtuzumab 12 mg	N/A	[redacted]
SC IFNβ-1a 44 µg	[redacted]	[redacted]
Fingolimod 0.5 mg	0.65 [0.11, 3.72]	[redacted]

Figure A.2.2.1.1: 3 month SAD HR MTC network:

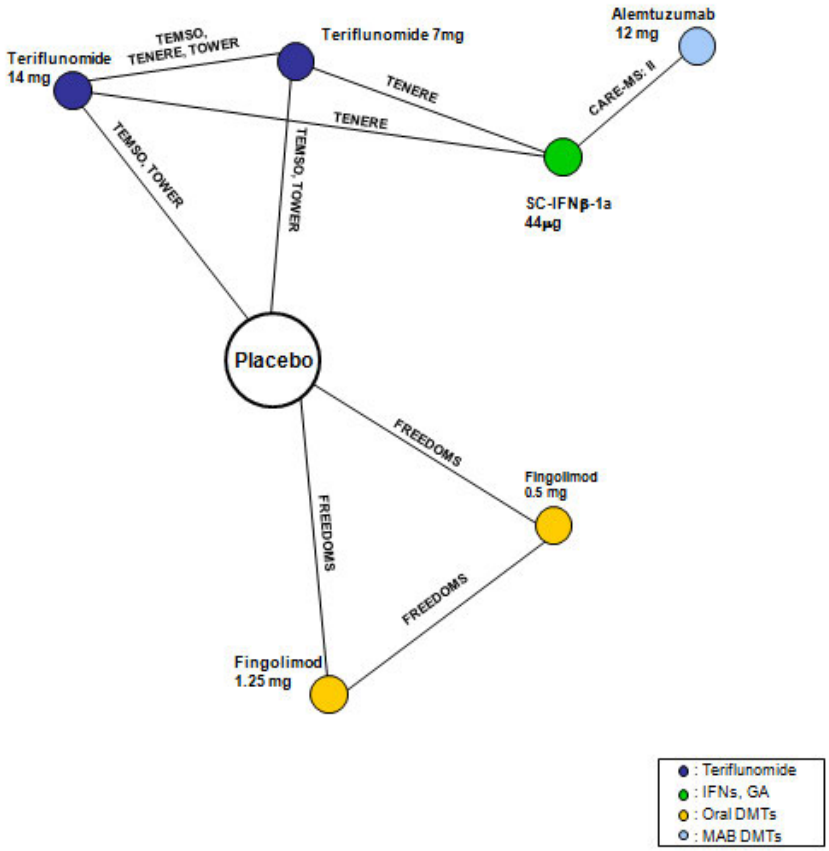


Table A.2.2.1.2: Three month SAD data inputs into 3 month SAD HR MTC

Comparison	Data Source	Subgroup	Sample size	Hazard ratio [95% CI]	Reference
Alemtuzumab 12mg versus **SC IFNβ**-1a	CARE MS II	HAD (See definition used below)*	219 vs 115	0.61 [0.37, 1.01]	Data on file
Fingolimod 0.5 mg vs placebo	FREEDOMS	HAD (See definition used below)**	57 vs 52	[redacted]	Devonshire et al, 2012
Teriflunomide 7mg vs placebo	TEMSO	Previously treated with a DMT	102 vs 90	[redacted]	Data on file
Teriflunomide 14mg vs placebo	TEMSO	Previously treated with a DMT	102 vs 90	[redacted]	Data on file
Teriflunomide 7mg vs placebo	TOWER	Previously treated with a DMT	123 vs 135	[redacted]	Data on file
Teriflunomide 14mg vs placebo	TOWER	Previously treated with a DMT	126 vs 135	[redacted]	Data on file
Teriflunomide 7 mg vs **SC IFNβ**-1a	TENERE	Full data set	109 vs 104	[redacted]	Data on file
Teriflunomide 14mg vs **SC IFNβ**-1a	TENERE	Full data set	111 vs 104	[redacted]	Data on file

* CARE MS II HAD definition: > 365 days interferon (IFN) with IFN exposure in year prior to treatment and gadolinium enhancing lesion positive (Gad+) OR T2 > 0.5 mL and 1 or more relapses in prior year

**FREEDOMS HAD definition used: Group C in Devonshire et al paper: Patients who received interferon beta during the year before study enrolment and had at least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or nine T2 lesions at baseline

A.2.2.2. A presentation and discussion of the results of the ARR RR MTC for the HA RRMS despite interferon use subgroup.

The following key points are noted in relation to the effectiveness of alemtuzumab 12mg for HA RRMS despite interferon use patients in relation to ARR RR as estimated using the associated MTC (output described in Table A.2.2.2.1 and network and inputs described in Figure A.2.2.2.1. and Table A.2.2.2.2:

- Alemtuzumab is [redacted].
- Alemtuzumab is numerically but not statistically significantly better than fingolimod 0.5mg based on the MTC results: 0.50 [0.11, 2.29].
    - The wide CI around alemtuzumab versus fingolimod 0.5mg is primarily because of the high uncertainty associated with the data that forms the links between alemtuzumab 12mg and fingolimod 0.5mg in the network (see Figure A.3.2.3.2 below) and the number of links needed to make this comparison.
    - The link from alemtuzumab to fingolimod 0.5 mg is alemtuzumab to SC IFNβ-1a 44 μg then SC IFNβ-1a 44 μg to teriflunomide 7/14mg and then teriflunomide 7/14mg to placebo and then placebo to fingolimod 0.5mg; the trial subgroup data associated with the SC IFNβ-1a 44 μg vs teriflunomide 7/14mg and teriflunomide 7/14mg to placebo adds uncertainty as it adds 2 links and in addition the SC IFNβ-1a 44 μg vs teriflunomide 7/14mg is associated with high uncertainty as can be inferred from the confidence intervals of [redacted] (see Table A.2.2.2.2. below)

Table A.2.2.2.1: Output from ARR RR MTC – HA RRMS despite interferon use

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	N/A	[redacted]
IM IFNβ-1a 30 μg	[redacted]	[redacted]
SC IFNβ-1a 44 μg	[redacted]	[redacted]
Fingolimod 0.5 mg	0.50 [0.11, 2.29]	[redacted]

Figure A.2.2.2.1: ARR RR MTC network – HA RRMS despite interferon use

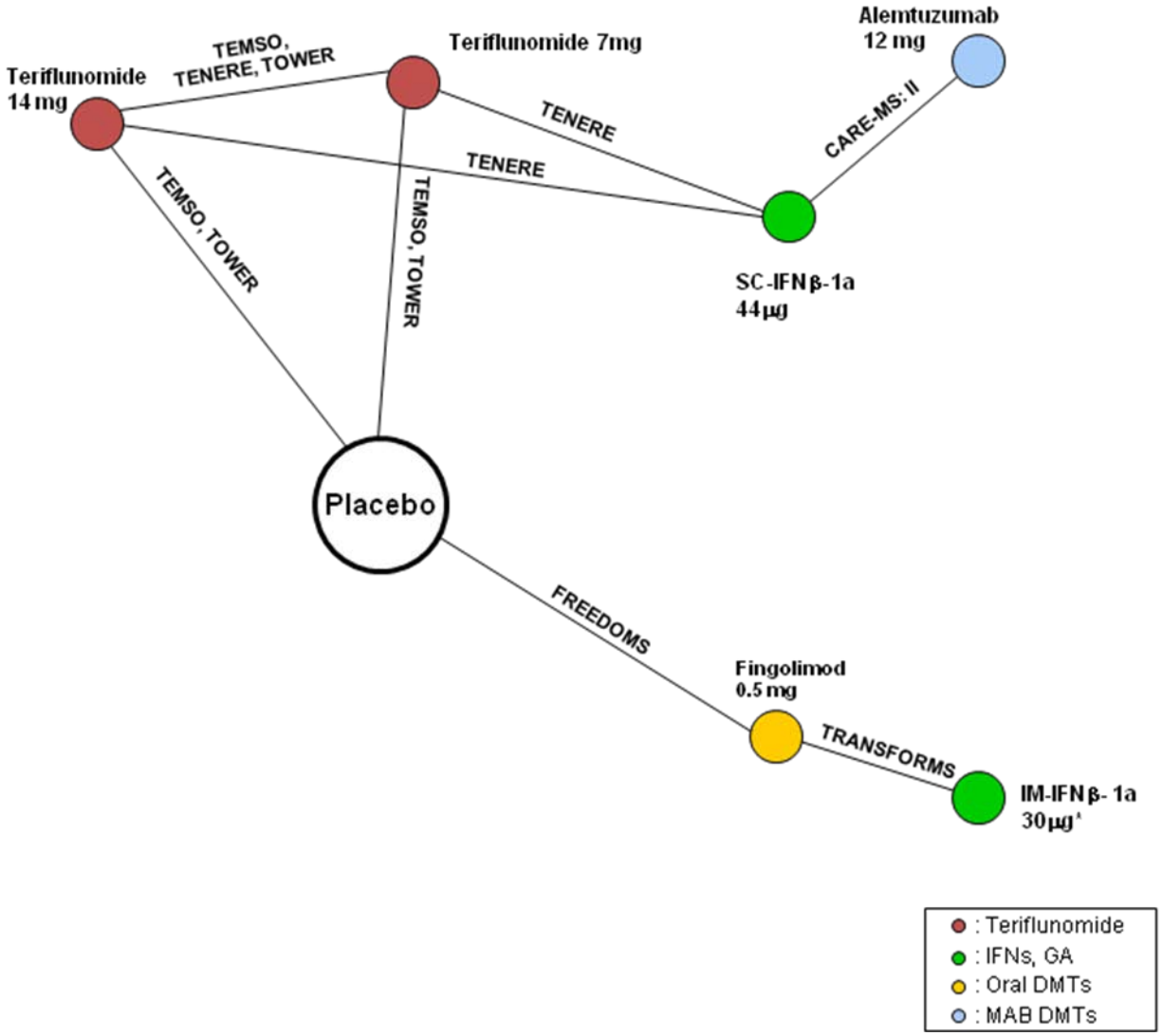


Table A.2.2.2.2: Sources and definitions of data used in ARR RR MTC

Comparison	Data Source	Subgroup	Sample size	ARR RR	Reference
Alemtuzumab 12mg versus SC **IFNβ**-1a	CARE MS II	HAD (See definition used below)*	219 vs 115	0.4 [0.28, 0.56] - HR	Data on file
Fingolimod 0.5 mg vs placebo	FREEDOMS	HAD (See definition used below)**	57 vs 52	0·38 [0·21, 0·68]	Devonshire et al, 2012
Fingolimod 0.5 mg vs Avonex	TRANSFORMS	HAD (See definition used below)***	90 vs 97	ARR RR not reported	Fingolimod EPAR [EMA, 2011]
Teriflunomide 7mg vs placebo	TEMSO	Previously treated with a DMT	[redacted]	[redacted]	Data on file
Teriflunomide 14mg vs placebo	TEMSO	Previously treated with a DMT	[redacted]	[redacted]	Data on file
Teriflunomide 7mg vs placebo	TOWER	Previously treated with a DMT	[redacted]	[redacted]	Data on file
Teriflunomide 14mg vs placebo	TOWER	Previously treated with a DMT	[redacted]	[redacted]	Data on file
Teriflunomide 7 mg vs **SC IFNβ**-1a	TENERE	Full data set	[redacted]	[redacted]	Data on file
Teriflunomide 14mg vs SC **IFNβ**-1a	TENERE	Full data set	[redacted]	[redacted]	Data on file

* CARE MS II HAD definition: > 365 days interferon (IFN) with IFN exposure in year prior to treatment and gadolinium enhancing lesion positive (Gad+) OR T2 > 0.5 mL and 1 or more relapses in prior year

**FREEDOMS HAD definition used: Group C in Devonshire et al paper: Patients who received interferon beta during the year before study enrolment and had at least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or nine T2 lesions at baseline

** *FREEDOMS HAD definition from fingolimod EPAR: Patients who had been on treatment with an approved disease-modifying MS drug for at least 6 months (sufficient duration to evaluate efficacy), were still on treatment in the year before starting study drug, and had at least 1 relapse during the last year. The relapse may or may not have occurred while on the MS disease modifying therapy and at least one Gd-enhancing lesion on baseline MRI.

A.2.2.3. An assessment of clinical heterogeneity

No data could be found describing the fingolimod baseline characteristics for the subgroup definition of HA despite interferon use used in the MTC (patients who received interferon beta during the year before study enrolment and had at least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or nine T2 lesions at baseline from the Devonshire et al paper) and hence no assessment of clinical heterogeneity was possible between the alemtuzumab 12mg and fingolimod 0.5mg subgroups in this regard.

There are differences in the data sets used in the MTC to create links between alemtuzumab 12mg and fingolimod 0.5mg (as outlined in Table A.2.2.1.2. above) and they were as follows:

- Alemtuzumab 12mg vs SC IFNβ-1a: Those with > 365 days interferon (IFN) with IFN exposure in year prior to treatment and gadolinium enhancing lesion positive (Gad+) OR T2 > 0.5 mL and 1 or more relapses in prior year

- SC IFNβ-1a vs teriflunomide 14mg / 7mg: Full TENERE data set ([redacted] had used a DMT in the previous 2 years)

- Teriflunomide 14mg / 7mg vs placebo: Previously treated with a DMT

- Placebo vs Fingolimod 0.5mg: Those who received interferon beta during the year before study enrolment and had at least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or nine T2 lesions at baseline (based on Devonshire et al)

The following points are noted in regard to the different definitions used in the MTC (the rationale for which is provided in the original submission):

- In regard to the differences between the definition used for HA despite interferon use for alemtuzumab 12mg vs SC IFNβ-1a and placebo vs fingolimod 0.5mg, it might be argued that the alemtuzumab data set with a requirement for 365 days of interferon use is closer to the definition in the marketing authorization for the use of fingolimod and a more reliable indicator of highly active disease in that it provides a greater reassurance that a full course of interferon has been given. In the SmPC for fingolimod it is stated that it has a licence for use in "adults with high disease activity despite treatment with a beta interferon. These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial magnetic resonance imaging (MRI) or at least one gadolinium-enhancing lesion."

- The use of a T2 volume of 0.5mL as a proxy for 9 or more T2 lesions was used in the fingolimod submission to NICE and was considered sufficiently robust for that purpose. Genzyme also note that:

    - In CARE-MS II, the IFNB group had a mean of 4.09 new T2 lesions in Year 2 with a corresponding increase in T2 lesion volume of 0.15 mL. The average volume of a new T2 lesion was 0.0367 mL. Since most study patients had used IFNB prior to study entry, it may be assumed (as an approximation) that their average pre-study lesion size was similar. 9 such average lesions would have a total lesion volume of 0.3301 mL, which represents 66% of 0.5 mL. To reach a total lesion volume of 0.5 mL, it would take 13.6 such lesions. These data suggest that, with regard to imaging criteria, the alemtuzumab proxy for T2 lesions is similar to, and possibly more stringent than, the FREEDOM study definition of 9 or more T2 lesions.

- The use of the full TENERE data set for the SC IFNβ-1a vs teriflunomide 14mg / 7mg link as a proxy for HA despite interferon use is hard to assess. Intuitively, the similar efficacy for three month SAD HR as shown in Table A.2.2.1.2. for SC IFNβ-1a and teriflunomide 14mg / 7mg from the full TENERE data set seems a reasonable assumption to apply to the HA despite interferon use subgroup. This is relevant since SAD HRs are the key driver of the cost effectiveness model.
- Similarly it is hard to assess the impact of using previously treated with a DMT as a proxy for HA RRMS despite interferon use for Teriflunomide 14mg / 7mg vs placebo link.
- It is noted that there is a precedent in NICE assessment of MS drugs for using data in MTC networks in which efficacy based on non-highly active RRMS is used as a proxy for highly active RRMS efficacy. In the NICE appraisal of natalizumab in RES RRMS patients effectiveness against an active comparator was based upon indirect (MTC) evidence. The indirect evidence for natalizumab accepted by NICE included people with relapsing–remitting multiple sclerosis rather than RES RRMS and did not specifically examine the clinical effectiveness of the drugs in the RES RRMS groups. NICE accepted the manufacturer of natalizumab's assumption that the treatment effect of the active comparators (beta interferon and glatiramer acetate) in RRMS was equivalent to that in the RES groups [Natalizumab final NICE guidance: Section 3.4].
- Importantly, it is worth noting as outlined in Section A.2.1. that in the highly active despite interferon use subgroups used to populate the MTC, alemtuzumab 12mg has a numerically better 3 month SAD HR against an active comparator than fingolimod 0.5mg has against placebo and so unless placebo is better than an active comparator it would be anticipated that alemtuzumab 12mg would have a central estimate 3 month SAD HR of less than 1 versus fingolimod 0.5mg. This is important from a cost effectiveness perspective since SAD HRs drive the cost effectiveness model.

A.2.2.4. A statistical assessment of heterogeneity,

For SAD3, the only instance where heterogeneity might be detected was in any difference between the two teriflunomide vs placebo studies; all other treatment comparisons were investigated in only one study each. A direct meta-analysis for the SAD3 results from the two teriflunomide studies found no sign of heterogeneity for either 7mg or 14mg of teriflunomide vs placebo ($p>0.50$, $I^2 = 0$). There was slightly more data for ARR, in that there also were two studies investigating the difference between the two doses of fingolimod. All direct meta-analyses found low ($I^2 < 50\%$) and insignificant ($p>0.20$) amounts of heterogeneity with the exception of teriflunomide (7mg) vs placebo ($p=0.03$, $I^2 = 80\%$). TEMSO found a significant effect in favour of teriflunomide (7mg), while TOWER found no difference (ARR ratio = 0.99). ARR RRs are not a driver in the cost effectiveness model whilst SAD HRs are.

A.2.2.5. An assessment of heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies

As can be seen in Figures 2.2.1.1 and 2.2.2.1, there are no instances where there is both direct and indirect evidence for a given comparison. For instance, there is only one path to connect Alemtuzumab to Teriflunomide (through TENERE), then Teriflunomide to placebo (through TOWER and TEMSO), then placebo to fingolimod (through

FREEDOMS), etc. Additional information (e.g., a study comparing SC IFNβ-1a 44 μg to placebo) would be necessary to investigate the consistency assumption for the network.

A.2.2.6. The weakness and strengths of the networks

Networks were relatively sparse, and the connection from alemtuzumab to treatments other than SC IFNβ-1a were indirect, with a two-step link to placebo (alemtuzumab studies → TENERE → TOWER/TEMSO), a three-step link to fingolimod (TOWER/TEMSO→FREEDOMS) and a four-step link to IM IFNβ-1a (FREEDOMS→TRANSFORMS). However, there was only one sign of meaningful heterogeneity; most of any random-effects variation found was in large part an artifact of the random-effects prior.

A.2.3. Additional ICER Analysis for alemtuzumab vs vs fingolimod (HA RRMS despite interferon use) – as requested in the ACD for active RRMS

Table A.2.3.1. Additional ICER Analysis carried out for alemtuzumab vs vs fingolimod (HA RRMS despite INF use) – as requested in the ACD for active RRMS

Data Request	Proposed amendment	vs. fingolimod (HA RRMS despite interferon use)
1	Sustained accumulation of disability (SAD) lasting 6 months as a primary outcome measure in the mixed treatment comparison, and incorporating the results into the economic model	Not Done (No relevant fingolimod data identified)
2	An 'all years' mixed treatment comparison that is adjusted for baseline relapse rates	Not done (no relevant baseline relapse rate data identified for fingolimod)
3	The intention-to-treat analyses developed for the CAMMS223, CARE-MS I and CARE-MS II trials adjusted for baseline Expanded Disability Status Scale (EDSS) only (unadjusted for country or region)	Done
4	EQ-5D data from the CARE-MS I and CARE-MS II trials	Done
5	An amendment to the model to allow improvements in patients' EDSS states (by using the TEMSO TOWER placebo arm natural history matrix)	Done
6	An amendment to the model incorporating the observed deaths from the trial data	Done
7	A reduction in efficacy for alemtuzumab starting at 3 or 5 years	Done
8	Additional costs of other licensed relapsing-remitting multiple sclerosis treatments after alemtuzumab treatment failure	Done
9	A time-dependent re-treatment rate for alemtuzumab	Done
10	Removing the mid-cycle correction for the costs of alemtuzumab	Done
11	Increasing the number of monitoring and neurology visits for patients treated with alemtuzumab and additional monitoring after re-starting alemtuzumab treatment	Done
12	Lower health state costs used in the Evidence Review Group's analyses [the ACD states higher but confirmation from NICE in teleconference on 3rd December 2013 confirmed this is using the lower costs]	Done
13	Costs associated with adverse effects of treatment including renal failure, renal transplantation, dialysis, and death	Done
14	Baseline characteristics from patients in the alemtuzumab trials instead of from the UK Risk Sharing Scheme	Done
15	All of the requested changes combined	Done (using efficacy data not adjusted for baseline relapses; used 3 month SAD HRs)

Table A.2.3.2. Additional ICER Analysis carried out for alemtuzumab vs fingolimod (HA RRMS despite interferon use) (list price of fingolimod used except where stated otherwise)

	Alemtuzumab		Fingolimod		Incremental		
Data Request	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Costs	QALYs	ICER
Base case	468,023	5.458	517,052	3.668948	-49,029	1.789	Dominates
Data Request 3	469,177	5.420	516,849	3.685	-47,673	1.735	Dominates
Data Request 4	468,605	5.118	517,619	2.668	-49,015	2.450	Dominates
Data Request 5	385,826	10.690	455,797	7.678	-69,971	3.012	Dominates
Data Request 6	468,023	5.447	517,052	3.669	-49,029	1.778	Dominates
Data Request 7 (at 5 years waning for both alemtuzumab and fingolimod)	495,905	4.184	520,027	3.332	-24,122	0.852	Dominates
Data Request 7 (3 years waning for both fingolimod and alemtuzumab)	498,391	4.097	521,448	3.263	-23,057	0.834	Dominates
Data Request 7 (at 5 years waning for alemtuzumab only; fingolimod assumed 100% efficacy up to 50 years)	493,796	4.239	516,724	3.684	-22,928	0.555	Dominates
Data Request 7 (at 3 years waning for alemtuzumab only; fingolimod assumed 100% efficacy up to 50 years)	497,116	4.088	517,245	3.661	-20,129	0.426	Dominates
Data Request 8	476,586	5.443	517,233	3.668	-40,647	1.776	Dominates
Data Request 9	457,307	5.437	517,093	3.666	-59,786	1.771	Dominates
Data Request 10	471,963	5.456	517,271	3.662	-45,308	1.793	Dominates
Data Request 11	472,711	5.442	517,334	3.658	-44,623	1.784	Dominates
Data Request 12	282,639	5.456	320,607	3.681	-37,968	1.775	Dominates
Data Request 13	468,501	5.445	516,773	3.674	-48,272	1.771	Dominates

	Alemtuzumab	Fingolimod	Incremental		Alemtuzumab	Fingolimod	Incremental
Data Request	Total Costs (£)	Total QALYs	Total Costs (£)	Data Request	Total Costs (£)	Total QALYs	Total Costs (£)
Data Request 14 (EDSS distribution and baseline characteristics only)	441,816	8.129	510,869	5.760	-69,052	2.369	Dominates
Combination (waning of efficacy at year 5 for alemtuzumab only; 100% efficacy for fingolimod assumed up to 50 years)	256,507	9.417	296,232	8.069	-39,724	1.347	Dominates
Combination (waning of efficacy at year 5 for alemtuzumab and fingolimod)	258,459	9.470	294,272	7.455	-35,813	2.015	Dominates
Combination (waning of efficacy at year 3 for alemtuzumab only; 100% efficacy for fingolimod assumed up to 50 years)	256,929	9.391	296,805	8.080	-39,876	1.311	Dominates
Combination (waning of efficacy at year 3 for alemtuzumab and fingolimod)	259,130	9.372	293,589	7.354	-34,460	2.018	Dominates
Combination with fingolimod assumed PAS annual price of £13000 (waning of efficacy at year 5 for alemtuzumab and fingolimod)	258,616	9.486	262,574	7.453	-3,958	2.033	Dominates
Combination with fingolimod PAS assumed annual price of £13000 (waning of efficacy at year 3 for alemtuzumab and fingolimod)	259,789	9.343	263,111	7.376	-3,321	1.967	Dominates
Combination assuming alemtuzumab vs placebo same HRs and ARRs as CARE MS II subgroup provides for alemtuzumab vs SC INF 1a with fingolimod vs placebo efficacy sourced from direct trial results of fingolimod vs placebo (FREEDOMS). Assumed PAS price of £13000 for fingolimod (waning of efficacy at 3 years assumed for both alemtuzumab and fingolimod) – using CARE MS I / II trial data for utilities	269,568	8.226	261,845	7.136	7,723	1.089	7,089
Combination assuming alemtuzumab vs placebo same HRs and ARRs as CARE MS II subgroup provides for alemtuzumab vs SC INF 1a with fingolimod vs placebo efficacy sourced from direct trial results of fingolimod vs placebo (FREEDOMS). Assumed PAS price of £13000 for fingolimod (waning of efficacy at 3 years assumed for both alemtuzumab and fingolimod) – TEMSO plus Orme decrements for utilities (plus AE disutilities as per original model)	269,319	10.134	261,792	9.697	7,528	0.437	17,232

A.3. Relevant evidence has not been considered in the Committee's decision whether alemtuzumab is clinically effective in patients with RES RRMS (this relates to the opinion expressed in Section 4.9. of the ACD that further evidence was needed by the Committee to persuade it of the clinical effectiveness of alemtuzumab in this subgroup) .

Two sets of evidence are provided to support the efficacy of alemtuzumab in the RES RRMS subgroups:

- Part A.3.1: Subgroups from the individual trials of CARE MS I and II and CAMMS 223 with meta-analysis results based on these (for 3 and 6 month SAD HRs and ARR RRs)
- Part A.3.2. : A discussion of the MTC networks in terms of the results and their interpretation. This includes a statistical assessment of heterogeneity, heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies and the weakness and strengths of the networks (this is done both for the ARR RR and 3 month SAD HR networks and for the 6 month SAD HR network which was not presented in the original submission but which is presented here as additional information)
- Part A.3.3. The additional cost effectiveness analyses requested in the ACD for active RRMS has been run for alemtuzumab versus natalizumab in the RES RRMS subgroup. This is so that if the Committee accept the clinical effectiveness of alemtuzumab in this subgroup they have available the same associated cost effectiveness analyses as they have requested for active RRMS (this data plus associated models was also sent to NICE for the ERG to critique its validity).

.3.1: Evidence based on RES RRMS subgroups from the individual trials and metaanalysis results based on these (for 3 and 6th SAD HRs and ARR RRs)

The clinical effectiveness of alemtuzumab 12mg vs SC IFNβ-1a 44µg in RES RRMS patients in relation to 6 months SAD HRs based on a meta-analysis of the relevant subgroup analyses of the 3 key studies (CARE MS I/II and CAMMS 223) are shown in Table A.3.1.1. It provides the following supportive evidence:

- Meta-analysis of 6 month SAD HRs in the RES RRMS subpopulation shows alemtuzumab 12mg to be statistically significantly better than SC IFNβ-1a 44µg: 0.50 [0.28, 0.91] (n=431).
    - These results are comparable to those in the meta-analysis of the full trial data set 0.5 [0.27, 0.92] (n=1414).
- Results are comparable between the RES RRMS subgroups in the individual trials and the overall trial results.
    - This is consistent with the assessment of alemtuzumab 12mg by the regulatory authority, the European Medicines Agency (EMA), which did not identify any difference between highly active and non-highly active subgroups in the efficacy of alemtuzumab 12mg as shown in the European Public Assessment Report for the drug.[EMA (Lemtrada EPAR), 2013]
- The clinical efficacy of natalizumab versus placebo in relation to 6 month SAD HRs in the RES RRMS subpopulation is comparable to that of alemtuzumab 12mg versus an active comparator (SC IFNβ-1a 44µg): 0.36 [0.17, 0.76] compared to 0.5 [0.28, 0.91] respectively.
    - The natalizumab subgroup analysis against placebo (n=209; 22% of full trial data set) was accepted by NICE as proof of the efficacy of natalizumab in the RES RRMS subgroup.

- Alemtuzumab 12mg has data from a larger subgroup population (n=431; 30% of full trial data set) and it is statistically significant against an active comparator.
- Natalizumab was recommended for use by NICE in both treatment naïve and experienced RES RRMS patients even though it had data only in treatment naïve RES RRMS patients. Alemtuzumab has data in both treatment naïve and experienced RES RRMS patients.

A.3.1.1: 6 month SAD HRs for alemtuzumab and natalizumab for RES RRMS subgroups compared to full trial data sets

Comparison	Data Source	Subgroup	Hazard ratio (95% CI) - RES RRMS	Hazard ratio (95% CI) - full trial data set	RES RRMS as a % of total trial data set
Alemtuzumab 12mg versus **SC IFNβ**-1a	CAMMS 223 [Genzyme (Data on file), 2013; Coles et al., 2008]	RES (see definition below)*	0.3 [0.13, 0.69] (n=125)	0.25 [0.11, 0.57] (n = 223)	56%
Alemtuzumab 12mg versus **SC IFNβ**-1a	CARE MS I [Genzyme (Data on file), 2013; Cohen, 2012]	RES (see definition below)*	0.83 [0.28, 2.42] (n=166)	0.70 [0.40, 1.23] (n=563)	29%
Alemtuzumab 12mg versus **SC IFNβ**-1a	CARE MS II [Genzyme (Data on file), 2013; Coles, 2012]	RES (see definition below)*	0.47 [0.17, 1.32] (n=143)	0.58 [0.38, 0.87] (n= 628)	23%
Alemtuzumab 12mg versus **SC IFNβ**-1a	Meta-analysis [Genzyme (Data on file), 2013]	RES (see definition below)*	0.50 [0.28, 0.91] (n=431)	0.5 [0.27, 0.92] (n=1414)	30%
Natalizumab vs placebo	AFFIRM [NICE, 2007; Polman et al., 2006]	RES (see definition below)***	0.36 [0.17, 0.76] (n=209)	0.46 [0.33, 0.64] (n=942)	22%

*RES is >= 2 episodes in prior year and Gadolinium enhancing lesion positive (Gad+)

** AFFIRM study: This subgroup is defined as those experiencing two or more relapses in the previous year, and having at least one lesion on gadolinium-enhancing MRI or a significant increase in T2 lesion load compared to a previous, recent MRI.

The clinical effectiveness of alemtuzumab 12mg vs SC IFNβ-1a 44µg in RES RRMS patients in relation to 3 month SAD HRs based on a meta-analysis of the relevant subgroup analyses of the 3 key studies (CARE MS I/II and CAMMS 223) are shown in Tables A.3.1.2. It provides the following supportive evidence:

- Meta-analysis of 3 months SAD HRs shows alemtuzumab 12mg to be [redacted]. These results are comparable to those

in the meta-analysis of the full trial data set although the results in the full data set were [redacted] (n=1414).

- These results should be considered in light of the fact that 6 month SAD is considered to be the more robust measure of sustained disability accumulation compared to 3 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 six months apart".[EMA, 2009]

- 3 month SAD HR results are comparable between the RES RRMS subgroups in the individual trials and the overall trial results.
- The clinical efficacy of natalizumab versus placebo in relation to 3 month HRs in the RES RRMS subpopulation is comparable to that of alemtuzumab 12mg versus an active comparator (SC IFNβ-1a 44µg): 0.47 [0.24, 0.93] compared to [redacted] respectively.
  - The natalizumab subgroup analysis compared against placebo (n=209; 22% of full trial data set) was accepted by NICE as proof of the efficacy of natalizumab in the RES RRMS subgroup.
  - Alemtuzumab 12mg has data from a larger subgroup population (n=431; 30% of full trial data set) and it is against an active comparator

A.3.1.2: 3 month SAD HR for alemtuzumab 12mg and natalizumab RES RRMS trial subgroups compared to the full trial data sets.

Comparison	Data Source	Subgroup	Reference	Hazard ratio (95% CI) - RES RRMS	Hazard ratio (95% CI) - full trial data set	RES RRMS as a % of total trial data set
Alemtuzumab 12mg versus **SC IFNβ**-1a	CAMMS 223	RES (see definition below)*	Data on file	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg versus **SC IFNβ**-1a	CARE MS I	RES (see definition below)*	Data on file	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg versus **SC IFNβ**-1a	CARE MS II	RES (see definition below)*	Data on file	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg versus **SC IFNβ**-1a	Meta-analysis	RES (see definition below)*	Data on file	[redacted]	[redacted]	[redacted]
Natalizumab vs placebo	AFFIRM	RES (see definition below)***	Natalizumab NICE submission	0.47 [0.24, 0.93] (n=209)	0.58 [0.43, 0.77] (n=942)	22%

*RES is >= 2 episodes in prior year and Gad+

** AFFIRM study: This subgroup is defined as those experiencing two or more relapses in the previous year and having at least one lesion on gadolinium-enhancing MRI or a significant increase in T2 lesion load compared to a previous, recent MRI.

The clinical effectiveness of alemtuzumab 12mg vs SC IFNβ-1a 44µg in RES RRMS patients in relation to annualised relapse rates relative risks (ARR RR) based on a meta-analysis of the relevant subgroup analyses of the 3 key studies (CARE MS I/II and CAMMS 223) are shown in Table A.3.1.3. It provides the following supportive evidence:

- Meta-analysis of ARR RR shows alemtuzumab 12mg to be statistically significantly better than SC IFNβ-1a 44µg: 0.37 [0.20, 0.68].
    - These results are comparable to those in the meta-analysis of the full trial data set: 0.43 [0.32, 0.58] (n=1414).
- ARR RR results are comparable between the RES RRMS subgroups in the individual trials and the overall trial results (with the exception of CAMMS 223 where the RES subgroup result was numerically better than the full data set result):
    - This is consistent with the assessment of alemtuzumab 12mg by the regulatory authority, the European Medicines Agency (EMA), which did not identify any difference between highly active and non-highly active subgroups in the efficacy of alemtuzumab 12mg as shown in the European Public Assessment Report for the drug.[EMA (Lemtrada EPAR), 2013]
- No clinical efficacy of natalizumab versus placebo in relation to ARR RRs in the RES RRMS subpopulation was found in the literature to allow comparison to that of the alemtuzumab 12mg versus an active comparator meta-analysis (SC IFNβ-1a 44µg).

Table A.3.1.3: ARR – RR alemtuzumab 12mg trial subgroup analyses compared to the full trial data sets (published natalizumab ARR RR RES RRMS data not identified)

Comparison	Data Source	Subgroup	Reference	ARR RR (95% CI) - RES RRMS	ARR RR (95% CI) - full trial data set	RES RRMS as a % of total trial data set
Alemtuzumab 12mg versus SC IFNβ-1a	CAMMS 223	RES (see definition below)*	Wingerchuk et al	0.19 [0.09,0.40]	0.31 [0.21, 0.45]	56%
Alemtuzumab 12mg versus SC IFNβ-1a	CARE MS I	RES (see definition below)*	Data on file	0.47 [0.28, 0.76]	0.46 [0.36, 0.58]	29%
Alemtuzumab 12mg versus SC IFNβ-1a	CARE MS II	RES (see definition below)*	Data on file	0.47 [0.29, 0.78]	0.5 [0.41, 0.61]	23%
Alemtuzumab 12mg versus SC IFNβ-1a	Meta-analysis	RES (see definition below)*	Data on file	0.37 [0.20, 0.68]	0.43 [0.32, 0.58]	30%

*RES is >= 2 episodes in prior year and Gad+

A.3.2: A discussion of the MTC networks for RES RRMS in terms of the results and their interpretation.

This includes the following:

- A.3.2.1. – A.3.2.3. A presentation and discussion of the results of the MTCs for 6 month and 3 month SAD HRs and ARR RRs.
- A.3.2.4. A statistical assessment of heterogeneity,
- A.3.2.5. An assessment of heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies
- A.3.2.6. The weakness and strengths of the networks

A.3.2.1. A presentation and discussion of the results of the 6 month SAD HR MTC for the RES RRMS subgroup.

The following key points are noted in relation to the effectiveness of alemtuzumab 12mg for RES RRMS patients in relation to 6 month SAD HR as estimated using the associated MTC (output described in Table A.3.2.1.1 and methodology and inputs described in Tables A.3.2.1.2-4:

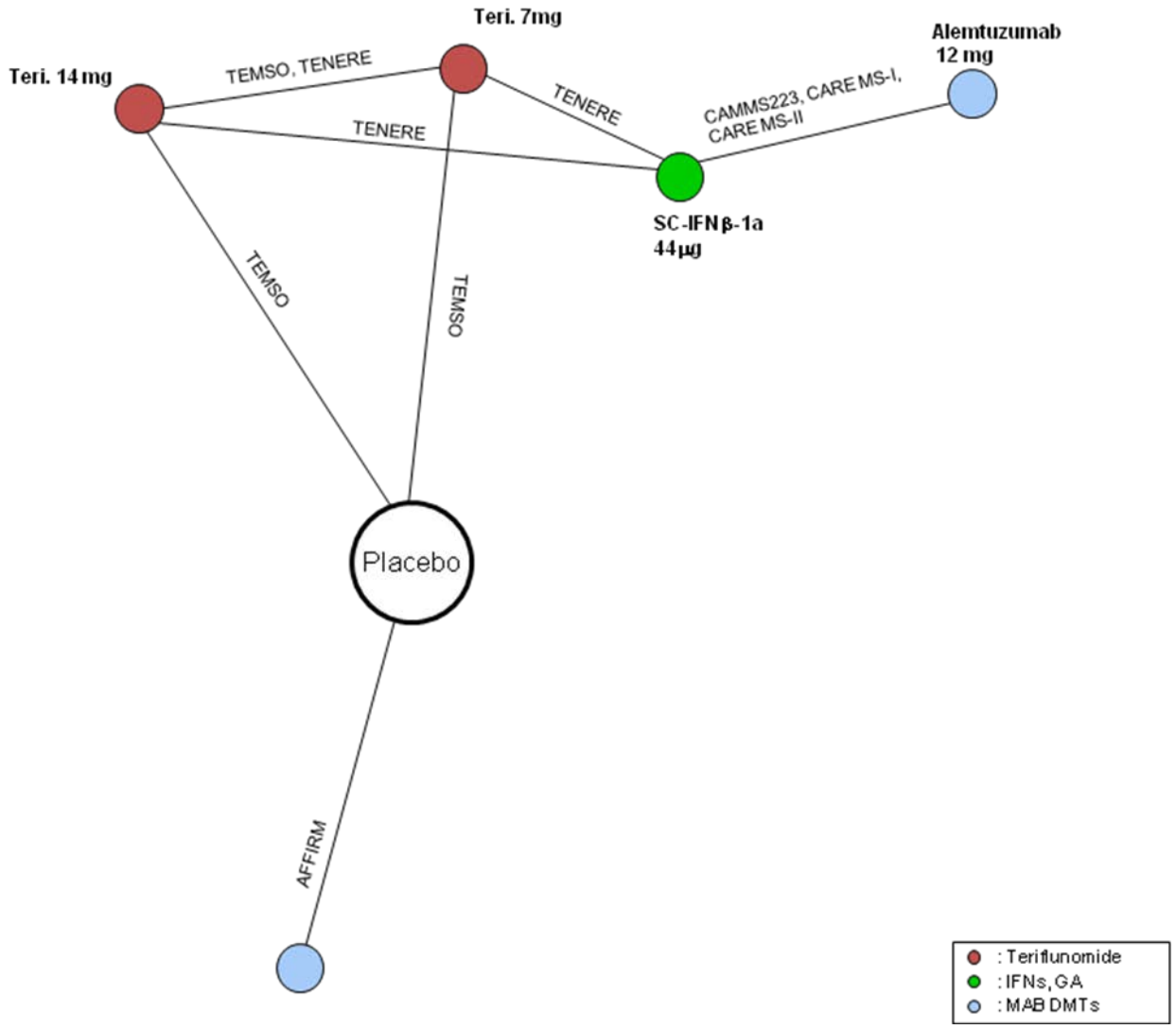
- Alemtuzumab is [redacted] [redacted].
    - This result should be seen in the context of the meta-analysis of the alemtuzumab (RES RRMS subgroup) trial data which forms the direct evidence input into this network in which alemtuzumab 12mg shows statistically significant results versus an active comparator (SC IFNβ-1a 44 μg): 0.50 [95% CI: 0.28, 0.91].
    - The wider credible intervals associated with alemtuzumab versus placebo estimations based on the MTC results in contrast to the narrower (and statistically significant) 95% CIs around alemtuzumab versus SC IFNβ-1a 44 μg based on the direct evidence is primarily because of the high uncertainty associated with the data that forms the links between alemtuzumab 12mg and placebo in the network (see Figure A.3.2.1.1 below) and the number of links involved.
        - The link from alemtuzumab to placebo is alemtuzumab to SC IFNβ-1a 44 μg then SC IFNβ-1a 44 μg to teriflunomide 14mg and then teriflunomide 14mg to placebo.
- Alemtuzumab is numerically but not statistically significantly better than natalizumab based on the MTC results for 6 monhs SAD HRs: 0.78 [95% CI: 0.06, 10.83].
    - The wide CI around alemtuzumab versus natalizumab is primarily because of the high uncertainty associated with the data that forms the links between alemtuzumab 12mg and natalizumab in the network (see Figure A.3.2.1.1 below) and the number of links involved.
        - The link from alemtuzumab to natalizumab is alemtuzumab to SC IFNβ-1a 44 μg then SC IFNβ-1a 44 μg to teriflunomide 14mg and then teriflunomide 14mg to placebo and then placebo to natalizumab; the trial subgroup data associated with the SC IFNβ-1a 44 μg vs teriflunomide 14mg [redacted] and teriflunomide 14mg to placebo [redacted] is associated with a high degree of uncertainty as described in the bullet point directly above.

- The MTC analysis has been carried out to provide parameter estimates for the HE model with cost effectiveness being driven primarily by SAD HRs. Taking the highly conservative assumption that the alemtuzumab vs SC IFNβ-1a 44µg results from the metanalysis of the CARE MS I and II and CAMMS 223 RES RRMS subgroups for 6 month SAD HRs and ARR RR are equivalent to alemtuzumab vs placebo results and populating the HE model with parameter values based on this assumption (together with using natalizumab versus placebo results from the AFFIRM RES RRMS subgroup) still provides preferential ICER of with alemtuzumab dominating natalizumab (See Table A.3.3.2. below for details). This suggests at even the most conservative assumption that SC IFNβ-1a 44µg and placebo efficacy are equivalent in RES RRMS patients that alemtuzumab remains cost effective.

Table A.3.2.1.1: Output from 6 mth SAD RES RRMS MTC

	vs. Alemtuzumab 12 mg	vs. Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg		[redacted]
SC IFNβ-1a 44 µg	[redacted]	[redacted]
Natalizumab 300mg	0.78 [0.06, 10.83]	[redacted]

Figure A.3.2.1.1. Six month SAD HR MTC network:



As outlined in the original submission, NICE guidance limited natalizumab use to:

- An option for the treatment only of rapidly evolving severe relapsing–remitting multiple sclerosis (RES). RES is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

This MTC has been carried out provide data to provide data on the effectiveness of alemtuzumab relative to natalizumab to support a cost effectiveness analysis of alemtuzumab being used in place of natalizumab in this subgroup.

As shown in Table A.3.2.1.2 below, it should be noted that only natalizumab provided data which exactly matched the definition of RES RRMS within NICE guidance. Neither alemtuzumab nor teriflunomide could do this because no data was available to provide "significant increase in T2 lesion load compared to a previous, recent MRI." TEMSO was preferred over TOWER to provide the teriflunomide versus placebo comparison within the network because TEMSO unlike TOWER reported gadolinium-enhancing (GAD) lesions on brain magnetic resonance imaging (MRI) at baseline. TENERE did not report GAD lesions at baseline but needed to be included in the network to allow an alemtuzumab versus natalizumab comparison to be carried out. The definition used for the TENERE data set in the network was two or more relapses in the prior year at baseline. No GAD data at baseline was collected in TENERE at baseline. No subgroup analysis including GAD at baseline and 2 or more relapses was found in the literature for CONFIRM and DEFINE (BG 12 versus placebo and BG 12 versus GA respectively) but a subgroup analysis of these studies using a definition of 2 or more relapses in the prior year was included in the network.

Table A.3.2.1.2: Comparison of definitions of RES by trial included in the RES subgroup MTC

Comparison	Data Source	Subgroup	Data Source
Alemtuzumab 12mg versus SC **IFNβ**-1a	CARE MS I / II and CAMMS 223	Those experiencing two or more relapses in the previous year, and having at least one lesion on gadolinium (Gd)-enhancing MRI	Data on file
Natalizumab vs. placebo	AFFIRM	Those experiencing two or more relapses in the previous year, and having at least one lesion on gadolinium (Gd)-enhancing MRI or a significant increase in T2 lesion load compared to a previous, recent MRI.	Natalizumab NICE submission
Teriflunomide 7mg vs. placebo	TEMSO	Those experiencing two or more relapses in the previous year, and having at least one lesion on gadolinium (Gd)-enhancing MRI	Data on file
Teriflunomide 14mg vs. placebo	TEMSO	Those experiencing two or more relapses in the previous year, and having at least one lesion on gadolinium (Gd)-enhancing MRI	Data on file
Teriflunomide 7 mg vs. **SC IFNβ**-1a	TENERE	Those experiencing two or more relapses in the previous year	Data on file
Teriflunomide 14mg vs. **SC IFNβ**-1a	TENERE	Those experiencing two or more relapses in the previous year	Data on file

Table A.3.2.1.3: 6 month SAD data inputs into 6 month SAD HR MTC

Comparison	Data Source	Subgroup	Sample size	Hazard ratio (95% CI)
Alemtuzumab 12mg versus SC IFNβ-1a	CAMMS 223	RES (see definition below)*	65 vs 60	0.3 [0.13, 0.69]
Alemtuzumab 12mg versus SC IFNβ-1a	CARE MS I	RES (see definition below)*	105 vs 61	0.83 [0.28, 2.42]
Alemtuzumab 12mg versus SC IFNβ-1a	CARE MS II	RES (see definition below)*	101 vs 42	0.47 [0.17, 1.32]
Natalizumab vs placebo	AFFIRM	RES (see definition below)**	148 vs 61	0.36 [0.17, 0.76]
Teriflunomide 7mg vs placebo	TEMSO	RES (see definition below)*	[redacted]	[redacted]
Teriflunomide 14mg vs placebo	TEMSO	RES (see definition below)*	[redacted]	[redacted]
Teriflunomide 7 mg vs SC IFNβ-1a	TENERE	RES (see definition below)***	[redacted]	[redacted]
Teriflunomide 14mg vs SC IFNβ-1a	TENERE	RES (see definition below)***	[redacted]	[redacted]

*Relapses in the prior year ≥2 relapses plus GAD at baseline
** AFFIRM study: This subgroup is defined as those experiencing two or more relapses in the previous year and having at least one lesion on gadolinium-enhancing MRI or a significant increase in T2 lesion load compared to a previous, recent MRI.
***Relapses in the prior year ≥2 relapses

A.3.2.2. A presentation and discussion of the results of the three month SAD HR MTC for the RES RRMS subgroup.

The following key points are noted in relation to the effectiveness of alemtuzumab 12mg for RES RRMS patients in relation to 3 month SAD HR as estimated using the associated MTC (output described in Table A.3.2.2.1 and network and inputs described in Figure A.3.2.2.1. and Table A.3.2.2.2:

- Alemtuzumab is [redacted]
    - This result should be seen in the context of the meta-analysis of the alemtuzumab (RES RRMS subgroup) trial data which forms the direct evidence input into this network in which alemtuzumab

12mg although [redacted] versus an active comparator (SC IFNβ-1a 44 μg) was associated with a narrower CI[redacted]

- The wider credible intervals associated with alemtuzumab 12mg versus placebo estimations based on the MTC results in contrast to the narrower 95% CIs around alemtuzumab versus SC IFNβ-1a 44 μg based on the direct evidence is primarily because of the high uncertainty associated with the data that forms the links between alemtuzumab 12mg and placebo in the network and the number of links involved (see Figure A.3.2.1.1 below).
  - The link from alemtuzumab to placebo is alemtuzumab to SC IFNβ-1a 44 μg then SC IFNβ-1a 44 μg to teriflunomide 7/14mg and then teriflunomide 7/14mg to placebo.

- Alemtuzumab is [redacted]
- The wide CI around alemtuzumab versus natalizumab is primarily because of the high uncertainty associated with the data that forms the links between alemtuzumab 12mg and natalizumab in the network and the number of links involved (see Figure A.3.2.1.1 below).
  - The link from alemtuzumab to natalizumab is alemtuzumab to SC IFNβ-1a 44 μg then SC IFNβ-1a 44 μg to teriflunomide 14mg and then teriflunomide 14mg to placebo and then placebo to natalizumab; the trial subgroup data associated with the SC IFNβ-1a 44 μg vs teriflunomide 14mg ([redacted] and teriflunomide 14mg to placebo ([redacted]) is associated with a high degree of uncertainty as described in the bullet point directly above.
- These 3 mth SAD results need to be considered in the context of the fact that the 6 month SAD is considered to be the more robust measure of sustained disability accumulation than the 3 month SAD , and 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 six months apart". [EMA, 2009]

Table A.3.2.2.1. Output from three month SAD MTC

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	N/A	[redacted]
SC IFNβ-1a 44 μg	[redacted]	[redacted]
Fingolimod 0.5 mg	[redacted]	[redacted]
Natalizumab 300mg	[redacted]	[redacted]

Figure A.3.2.2.2. Three month SAD HR MTC network:

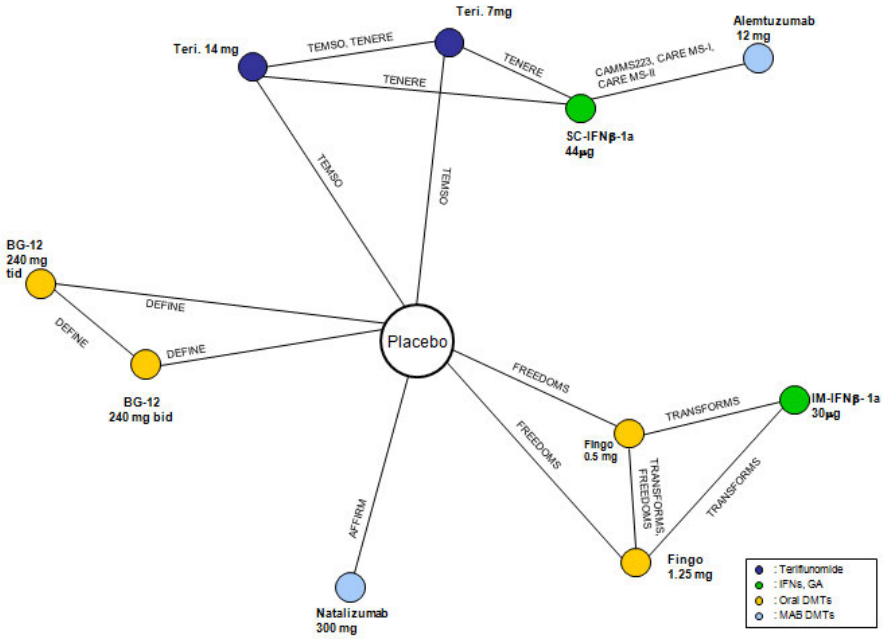


Table A.3.2.2.3: Three month SAD HRs of data input into 3 mth SAD HR MTC

Comparison	Data Source	Subgroup	Sample size	Hazard ratio [95% CI]
Alemtuzumab 12mg versus SC **IFNβ**-1a	CAMMS 223	RES (see definition below)*	[redacted]	[redacted]
Alemtuzumab 12mg versus SC **IFNβ**-1a	CARE MS I	RES (see definition below)*	[redacted]	[redacted]
Alemtuzumab 12mg versus SC **IFNβ**-1a	CARE MS II	RES (see definition below)*	[redacted]	[redacted]
Natalizumab vs placebo	AFFIRM	RES (see definition below)**	148 vs 61	0.47 [0.24, 0.93]
Fingolimod 0.5 mg vs placebo	FREEDOMS	RES (see definition below)*	77 vs 63	0.78 [0.36, 1.68]
Fingolimod 0.5 mg vs Avonex	TRANSFORMS	RES (see definition below)*	56 vs 65	0.95 [0.25, 3.53]
BG 12 BID vs placebo	DEFINE	RES (see definition below)***	121 vs 116	0.65 [0.38, 1.30]
BG 12 TID vs placebo	DEFINE	RES (see definition below)***	119 vs 116	0.70 [0.39, 1.30]
Teriflunomide 7mg vs placebo	TEMSO	RES (see definition below)*	[redacted]	[redacted]
Teriflunomide 14mg vs placebo	TEMSO	RES (see definition below)*	[redacted]	[redacted]
Teriflunomide 7 mg vs **SC IFNβ**-1a	TENERE	RES (see definition below)***	[redacted]	[redacted]
Teriflunomide 14mg vs **SC IFNβ**-1a	TENERE	RES (see definition below)***	[redacted]	[redacted]

*Relapses in the prior year ≥2 relapses plus GAD at baseline
** AFFIRM study: This subgroup is defined as those experiencing two or more relapses in the previous year and having at least one lesion on gadolinium-enhancing MRI or a significant increase in T2 lesion load compared to a previous, recent MRI.
***Relapses in the prior year ≥2 relapses

A.3.2.3. A presentation and discussion of the results of the ARR RR MTC for the RES RRMS subgroup.

The following key points are noted in relation to the effectiveness of alemtuzumab 12mg for RES RRMS patients in relation to ARR RR as estimated using the associated MTC (output described in Table A.3.2.3.1 and network and inputs described in Table A.3.2.3.2. and Figure A.3.2.3.1:

- Alemtuzumab is [redacted]
- Alemtuzumab is numerically but not statistically significantly better than natalizumab based on the MTC results: 0.69 [95% CI: 0.11, 4.53].
- The wide CI around alemtuzumab versus natalizumab is primarily because of the high uncertainty associated with the data that forms the links between alemtuzumab 12mg and natalizumab in the network and the number of links involved (see Figure A.3.2.3.1 below).
    - The link from alemtuzumab to natalizumab is alemtuzumab to SC IFNβ-1a 44 μg then SC IFNβ-1a 44 μg to teriflunomide 7/14mg and then teriflunomide 7/14mg to placebo and then placebo to natalizumab; the trial subgroup data associated with the SC IFNβ-1a 44 μg vs teriflunomide 14mg ([redacted]) and teriflunomide 14mg to placebo [redacted]) is relatively small and associated with wide confidence intervals [redacted]] and [redacted]] respectively which is most likely due to the low SAD 6 month event numbers from which these estimations are derived 6 vs 13 and 18 vs 31 respectively (see Table A.3.2.3.2. below)

Table A.3.2.3.1. Output from ARR RR MTC – RES RRMS

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	N/A	[redacted]
IM IFNβ-1a 30 μg	[redacted]	[redacted]
SC IFNβ-1a 44 μg	[redacted]	[redacted]
Fingolimod 0.5 mg	[redacted]	[redacted]
Natalizumab 300 mg	0.69 [0.11, 4.53]	[redacted]

Figure A.3.2.3.1. ARR RR MTC network:

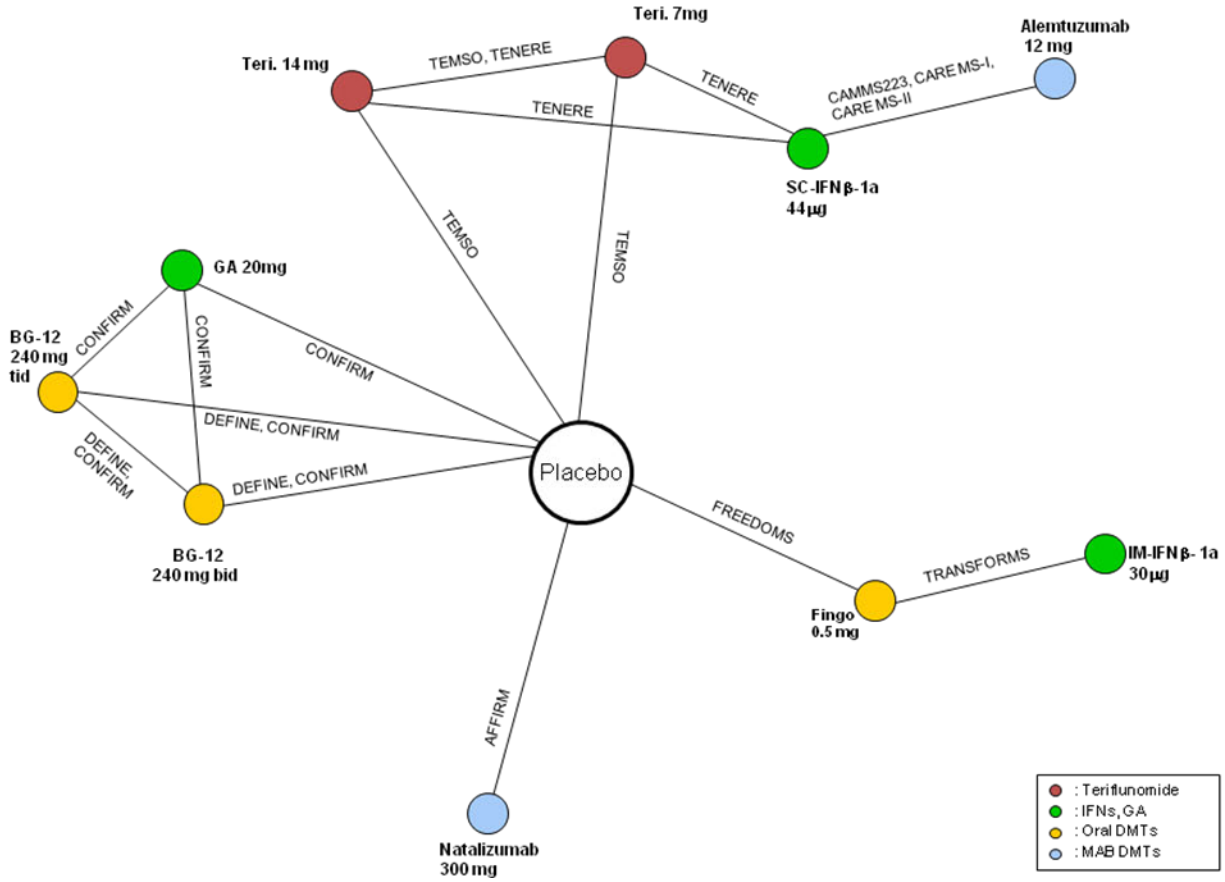


Table A.3.2.3.2: ARR RRs of data input into ARR RR MTC

Comparison	Data Source	Subgroup	Sample size	ARR (relative risk)	Reference
Alemtuzumab 12mg versus **SC IFNβ**-1a	CAMMS 223	RES (see definition below)*	65 vs 60	0.19 [0.09,0.40]	Data on file
Alemtuzumab 12mg **versus SC IFNβ**-1a	CARE MS I	RES (see definition below)*	105 vs 61	0.47 [0.28, 0.76]	Data on file
Alemtuzumab 12mg **versus SC IFNβ**-1a	CARE MS II	RES (see definition below)*	101 vs 42	0.47 [0.29, 0.78]	Data on file
Natalizumab vs placebo	AFFIRM	RES (see definition below)**	148 vs 61	0.5 absolute risk reduction	Natalizumab NICE submission
Fingolimod 0.5 mg vs placebo	FREEDOMS	RES (see definition below)*	77 vs 63	ARR RR not reported	Fingolimod EPAR
Fingolimod 0.5 mg vs Avonex	TRANSFORMS	RES (see definition below)*	56 vs 65	ARR RR not reported	Fingolimod EPAR
BG 12 bid vs placebo	DEFINE	RES (see definition below)***	121 vs 116	ARR RR not reported	Hutchinson abstract
BG 12bid vs GA	CONFIRM	RES (see definition below)***	Not reported	ARR RR not reported	Barr et al
BG 12 tid vs placebo	DEFINE	RES (see definition below)***	119 vs 116	ARR RR not reported	Hutchinson abstract
BG 12 tid vs GA	DEFINE	RES (see definition below)***	Not reported	ARR RR not reported	Barr et al
Teriflunomide 7mg vs placebo	TEMSO	RES (see definition below)*	42 vs 39	0.542 [0.328, 0.896]	Data on file
Teriflunomide 14mg vs placebo	TEMSO	RES (see definition below)*	33 vs 39	0.762 [0.48, 1.208]	Data on file
Teriflunomide 7 mg vs **SC IFNβ**-1a	TENERE	RES (see definition below)***	36 vs 35	2.044 [0.764, 5.467]	Data on file
Teriflunomide 14mg vs **SC IFNβ**-1a	TENERE	RES (see definition below)***	42 vs 35	1.491 [0.519, 4.281]	Data on file

*Relapses in the prior year ≥2 relapses plus GAD at baseline
** AFFIRM study: This subgroup is defined as those experiencing two or more relapses in the previous year and having at least one lesion on gadolinium-enhancing MRI or a significant increase in T2 lesion load compared to a previous, recent MRI.
***Relapses in the prior year ≥2 relapses

A.3.2.4. An assessment of clinical heterogeneity.

Table A.3.2.4.1. Baseline characteristics of alemtuzumab 12mg and natalizumab RES RRMS subgroups

	AFFIRM (RES RRMS)		CAMMS223 (RES RRMS)		CARE-MS II (RES RRMS)		CARE-MS I (RES RRMS)	
	Natalizumab 300mg (n=148)	Placebo (n=61)	Alemtuzumab 12 mg (n=65)	**SC IFNβ**-1a (n=60)	Alemtuzumab 12 mg (n=101)	**SC IFNβ**-1a (n=42)	Alemtuzumab 12 mg (n=105)	**SC IFNβ**-1a (n=61)
Mean Age (years)	33.7 ±8.4	36.4 ±8.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	25%	16%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	75%	84%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White (%)	95%	97%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other (%)	5%	3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease duration – yr			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	4	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	0 - 26	0 - 31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior DMT use	0%	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No of relapses in past yr – (%)			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	74%	77%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	26%	23%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EDSS score – (%)			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0	5%	7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.0 – 1.5	26%	28%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.0 -2.5	36%	34%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.0 -3.5	20%	21%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.0 -4.5	12%	10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	1%	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥5.0	0%	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of lesions on gadolinium enhanced MRI – No. of patients (%)					[redacted]	[redacted]	[redacted]	[redacted]
0	0	0			[redacted]	[redacted]	[redacted]	[redacted]
1	33%	31%			[redacted]	[redacted]	[redacted]	[redacted]
2	17%	23%	Data not collected in trial	Data not collected in trial	[redacted]	[redacted]	[redacted]	[redacted]
3	9%	11%			[redacted]	[redacted]	[redacted]	[redacted]
≥4	41%	34%			[redacted]	[redacted]	[redacted]	[redacted]
Missing data	0	0			[redacted]	[redacted]	[redacted]	[redacted]
					[redacted]	[redacted]	[redacted]	[redacted]
Mean	5.3 ±6.3	5.4 ±7.8			[redacted]	[redacted]	[redacted]	[redacted]
Range	1 to 34	1 to 39			[redacted]	[redacted]	[redacted]	[redacted]

Table A.3.2.4.1. compares baseline characteristics from the alemtuzumab RES RRMS subgroups to that in the public domain for the natalizumab subgroup. The following is noted:

- There does not appear to be clinical heterogeneity between the 4 subgroups in terms of age, sex, ethnicity, prior relapse rates or GAD lesions at baseline
- The CARE MS I and CAMMS 223 subgroups consists of patients at an earlier time from diagnosis and have a lower percentage of patients in higher EDSS states compared to the natalizumab subgroup or the CARE MS II subgroup
- CARE MS I and CAMMS 223 and the natalizumab subgroups consist of patients who had not recently received prior DMT treatment whilst the CARE MS II subgroup consisted exclusively of patients who had recently received prior treatment.
- Since NICE guidance was issued for the use of natalizumab for use in both treatment naïve and experienced patients based on the AFFIRM RES RRMS subgroup which consisted of only treatment naïve patients, it was presumably assumed by NICE that there was comparable efficacy between treatment naïve and treatment experienced RES RRMS patients for natalizumab. The mix of treatment naïve and experienced patients pooling CARE MS I and II and CAMMS 223 might be considered an appropriate data set given NICE guidance / use of natalizumab in both treatment naïve and experienced RES RRMS patients.

It is also noted that different definitions of RES RRMS are used for the subgroups (dependent upon the data available from the trials):

- Relapses in the prior year ≥2 relapses plus GAD at baseline (alemtuzumab trial subgroups) (TEMSO)

- Relapses in the prior year ≥2 relapses plus GAD at baseline or a significant increase in T2 lesion load compared to a previous, recent MRI (natalizumab subgroup).

- Relapses in the prior year ≥2 relapses (TENERE, BG 12 studies)

In considering these different definitions it is worth noting the following:

- Gadolinium-enhancement is an indication of acute inflammation, and persists for a relatively short period (weeks to few months). After enhancement resolves, a T2 lesion usually persists. Therefore, the alemtuzumab (and TEMSO) definition is more stringent as a measure of <u>current</u> disease activity than the natalizumab definition, but the clinical requirement (2 relapses in prior year) ensures <u>recent</u> disease activity under both definitions. MS severity is not inherently different in the two definitions, since a currently enhancing lesion will qualify patients under both definitions, while an increase in T2 lesion load implies a formerly enhancing lesion. Thus, both of these two RES groups have very recent MS disease activity by both clinical and MRI criteria, and the definitional difference does not imply any difference in disease severity or evolution.

- The absence of either a GAD or T2 criteria in the definition used for TENERE and BG 12 studies indicates that whilst the clinical requirement (2 relapses in prior year) ensures <u>recent</u> disease, the absence of either GAD or T2 criteria means that there is not a criteria specifically for a measure of <u>current</u> disease activity.

- It is noted that in the NICE appraisal of natalizumab in RES RRMS patients effectiveness against an active comparator was based upon indirect (MTC) evidence. The indirect evidence for natalizumab accepted by NICE included people with relapsing–remitting multiple sclerosis rather than RES RRMS and did not specifically examine the clinical effectiveness of the drugs in the RES RRMS groups. NICE accepted the manufacturer of natalizumab's assumption that the treatment effect of the active comparators (beta interferon and glatiramer acetate) in RRMS was equivalent to that in the RES groups [Natalizumab final NICE guidance: Section 3.4]. The degree of clinical heterogeneity associated with a divergence amongst input data from the definition of RES RRMS is substantially less in the alemtuzumab RES RRMS MTC than that accepted by NICE in the natalizumab RES RRMS MTC network in its appraisal by NICE.

A.3.2.4. A statistical assessment of heterogeneity

As with HAD, the RES networks were quite sparse. There were two additional treatments investigated (BG-12 and natalizumab, through DEFINE/CONFIRM and AFFIRM, respectively). For SAD3, the addition of these treatments did nothing to improve the power to detect heterogeneity, as there was no CONFIRM data, leaving only one study for information on each relative treatment effect. For ARR, power was increased slightly, as we could investigate the correspondence between the DEFINE and CONFIRM BG-12 vs placebo results. Note that unlike for HAD, there was only one teriflunomide study vs placebo (TEMSO) with RES data.

For SAD3 and SAD6, the investigation of heterogeneity was limited to the three alemtuzumab studies (CAMMS223, CARE MS-I, CARE MS-II). A direct meta-analysis for the SAD3 results from the three studies found no sign of heterogeneity for alemtuzumab vs placebo ($p>0.49$, $I2 = 0$ for both). However, there were moderately high estimates of the random-effects variation in the random-effects analysis due to the low power for the test; thus, the random-effects estimates have notably wider credible intervals than the fixed-effects, even though there was no statistical signal for heterogeneity.

There was slightly more data for ARR, in that there were the aforementioned two studies investigating BG-12 vs placebo. There was also information from two studies comparing 7mg and 14mg of teriflunomide (TEMSO, TENERE). Direct meta-analyses found low ($I2 < 50\%$) and insignificant ($p>0.20$) amounts of heterogeneity for BG-12 (240mg, tid) vs placebo,slight heterogeneity for BG-12 (240mg, bid) vs placebo ($p=0.14$, $I2=54\%$), moderate heterogeneity for the comparison between the two teriflunomide doses ($p=0.08$, $I2=68\%$), but most importantly, high heterogeneity ($p=0.006$, $I2=85\%$) in the three alemtuzumab studies vs SC IFNb-1a. As can be seen above in table 3.2.3.2, the CAMMS223 study found a much stronger relative effect for alemtuzumab (12mg) than did CARE MS-I or CARE MS-II (80% reduction in risk in CAMMS223, as opposed to 53% in CARE MS-I and CARE MS-II).

A.3.2.5. An assessment of heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies

As can be seen in Figures 3.2.3.1 and 3.2.2.2, there are no instances where there is both direct and indirect evidence for a given comparison. For instance, there is only one path to connect Alemtuzumab to Teriflunomide (through TENERE), then Teriflunomide to placebo (through TOWER and TEMSO), then placebo to fingolimod (through FREEDOMS), etc. Additional information (e.g., a study comparing SC IFNβ-1a 44 μg to placebo) would be necessary to investigate the consistency assumption for the network.

A.3.2.6. The weakness and strengths of the networks

As noted above, networks were relatively sparse, and the connection from alemtuzumab to treatments other than SC IFNβ-1a were indirect, with a two-step link to placebo (Lemtrada studies → TENERE → TOWER/TEMSO), and three-step links to fingolimod, natalizumab, and BG-12. There was not meaningful heterogeneity for SAD3 months or for SAD 6 months; as noted for HAD, it may be that the credible intervals for the fixed-effects analyses are appropriate to interpret. For ARR, there is significant heterogeneity between the three alemtuzumab trials. Although it is noted that the cost effectiveness results are sensitive to SAD 3/6 month results but not ARR RR.

A.3.3: Additional ICER Analysis for alemtuzumab vs natalizumab (RES RRMS) – as requested in ACD for active RRMS

Table A.3.3.1. Additional ICER Analysis carried out for alemtuzumab vs natalizumab (RES RRMS)

Data Request	Proposed amendment	vs Natalizumab (RES RRMS)
1	Sustained accumulation of disability (SAD) lasting 6 months as a primary outcome measure in the mixed treatment comparison, and incorporating the results into the economic model	Done
2	An 'all years' mixed treatment comparison that is adjusted for baseline relapse rates	Not done (no relevant baseline relapse rate data identified for natalizumab)
3	The intention-to-treat analyses developed for the CAMMS223, CARE-MS I and CARE-MS II trials adjusted for baseline Expanded Disability Status Scale (EDSS) only (unadjusted for country or region)	Done
4	EQ-5D data from the CARE-MS I and CARE-MS II trials	Done
5	An amendment to the model to allow improvements in patients' EDSS states (by using the TEMSO TOWER placebo arm natural history matrix)	Done
6	An amendment to the model incorporating the observed deaths from the trial data	Done
7	A reduction in efficacy for alemtuzumab starting at 3 or 5 years	Done
8	Additional costs of other licensed relapsing-remitting multiple sclerosis treatments after alemtuzumab treatment failure	Done
9	A time-dependent re-treatment rate for alemtuzumab	Done
10	Removing the mid-cycle correction for the costs of alemtuzumab	Done
11	Increasing the number of monitoring and neurology visits for patients treated with alemtuzumab and additional monitoring after re-starting alemtuzumab treatment	Done
12	Lower health state costs used in the Evidence Review Group's analyses [the ACD states higher but confirmation from NICE in teleconference on 3rd December 2013 confirmed this is using the lower costs]	Done
13	Costs associated with adverse effects of treatment including renal failure, renal transplantation, dialysis, and death	Done
14	Baseline characteristics from patients in the alemtuzumab trials instead of from the UK Risk Sharing Scheme	Done
15	All of the requested changes combined	Done (using efficacy data not adjusted for baseline relapses; used 6 months SAD HRs)

Table: A.3.3.2. Additional Analyses of cost effectiveness of alemtuzumab vs natalizumab (RES RRMS)

	Alemtuzumab		Natalizumab		Incremental		
Data Request	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Costs	QALYs	ICER
Base case	459,512	5.856	509,757	4.325	-50,245	1.531	Dominates
Data Request 1	481,384	4.829	512,961	4.065	-31,577	0.763	Dominates
Data Request 3	495,041	4.217	516,062	3.756	-21,021	0.461	Dominates
Data Request 4	458,295	5.647	509,659	3.53	-51,364	2.117	Dominates
Data Request 5	381,318	11.443	459,470	8.691	-78,151	2.752	Dominates
Data Request 6	459,512	5.844	509,757	4.325	-50,245	1.519	Dominates
Data Request 7 (at 5 years waning for alemtuzumab only; 100% efficacy assumed for fingolimod up to 50 years)	489,888	4.389	509,888	4.36	-20,000	0.028	Dominates
Data Request 7 (at 3 years waning for alemtuzumab only; 100% efficacy assumed for natalizumab up to 50 years)	492,549	4.293	509,760	4.366	-17,211	-0.073	236,172 (alemtuzumab lower costs, lower QALYs)
Data Request 7 (at 5 years waning applied to both alemtuzumab and natalizumab)	490,230	4.383	516,260	3.735	-26,030	0.648	Dominates
Data Request 7 (at 3 years waning applied to both alemtuzumab and natalizumab)	492,147	4.302	517,252	3.636	-25,105	0.667	Dominates
Data Request 8	468,199	5.865	510,191	4.337	-41,992	1.528	Dominates
Data Request 9	446,556	5.865	509,824	4.346	-63,267	1.519	Dominates
Data Request 10	462,607	5.852	509,415	4.352	-46,808	1.499	Dominates
Data Request 11	463,473	5.849	509,949	4.318	-46,476	1.531	Dominates
Data Request 12	276,472	5.836	317,657	4.348	-41,185	1.488	Dominates
Data Request 13	459,526	5.869	509,749	4.345	-50,223	1.524	Dominates
Data Request 14	422,633	8.987	498,666	6.849	-76,033	2.138	Dominates
Combination (waning of efficacy at year 5 for alemtuzumab only; 100% efficacy assumed for nataliizumab up to 50 years)	260,504	9.129	299,304	8.961	-38,799	0.168	Dominates
Combination (waning of efficacy at year 5 for alemtuzumab and natalizumab)	260,686	9.137	296,438	8.011	-35,752	1.126	Dominates
Combination (waning of efficacy at year 3 for alemtuzumab only; 100% efficacy of natalizumab assumed up to 50 years)	261,023	9.013	298,244	8.904	-37,220	0.108	Dominates
Combination (waning of efficacy at year 3 for alemtuzumab and natalizumab)	261,460	9.031	296,362	7.959	-34,902	1.072	Dominates

	Alem	Alem	Nat	Nat	Incr	Incr	
Data Analysis	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Costs	QALYs	ICER
Combination assumes alemtuzumab vs placebo same HRs and ARR RRs as meta-analysis of CARE MS I /II and CAMMS 223 estimates for alemtuzumab vs SC INF 1a with natalizumab vs placebo derived from RES RRMS subgroup of AFFIRM for natalizumab vs placebo (waning for alemtuzumab and natalizumab assumed at 3 yrs) – uses CARE MS I / II for utilities	262,617	8.537	297,548	8.051	-34,931	0.486	Dominates
Combination assumes alemtuzumab vs placebo same HRs and ARR RRs as meta-analysis of CARE MS I /II and CAMMS 223 estimates for alemtuzumab vs SC INF 1a with natalizumab vs placebo derived from RES RRMS subgroup of AFFIRM for natalizumab vs placebo (waning for alemtuzumab and natalizumab assumed at 3 yrs) – uses TEMSO plus Orme decrements for utilities (plus AE disutilities as per original model)	262,697	10.378	296,591	10.258	-33,894	0.119	Dominates

A.4. Relevant evidence has not been considered relating to the request to use the TEMSO TOWER placebo arm to derive natural history disease progression transition probabilities for the model in the additional analyses request on page 4 of the ACD.

This evidence shows that the very high regression rates seen in TEMSO/TOWER data are incompatible with evidence form real-world studies. Although some regression is observed in actual practice, it is much less, particularly at higher EDSS as shown in another large natural history dataset. In the additional analyses carried out for alemtuzumab as requested in the ACD, ICERs did not seem to be sensitive to using TEMSO / TOWER placebo arm data for all EDSS states or just for lower EDSS states (0-5) and using London Ontario data which does not allow patients to regress for higher EDSS states (6-9) when making a univariate parameter change. However, it is known from the analyses run as part of the teriflunomide assessment that the model is sensitive to this assumption (thus for the ICER of £50,743 for teriflunomide vs BSC with waning and including direct non-health care costs quoted in Section 3.51 using TEMSO / TOWER placebo arm for all EDSS states is reduced to £36,462 if TEMSO / TOWER is used just for EDSS 0-5 and London Ontario is used for EDSS 6-9). It is reasonable to assume that for certain of the combination of analyses included as part of the alemtuzumab additional analyses that have been requested in the ACD that the model may be sensitive to what Genzyme consider an inappropriate approach to modeling disease progression by using TEMSO / TOWER placebo arm data for higher EDSS states.

The following important points need to be noted:

- Over the study period, the sample size of the data used to estimate transition probabilities in EDSS states 6 or above was too small to derive accurate transition probabilities (provide number of transitions from 6. This in accordance with:
    - The inclusion criterion in TEMSO and TOWER studies related to EDSS score was 0 to 5.
    - Duration of the studies: two years for TEMSO and for TOWER a median study treatment duration of about 1.5 years.
    - There were 743 placebo patients included within the TEMSO-TOWER matrix

In addition the short time period of the period over which transitions were observed using the TEMSO-TOWER placebo arm data (2 years) makes it inappropriate to use for a life time health economic model. The London Ontario with follow up data (mean: [redacted] years) over a longer time period seems more appropriate for use in a life time model

The transition probabilities in these higher EDSS states (6 and above) derived using the TEMSO-TOWER matrix suggests a high level of regression when evidence from clinical practice suggests that patients who have reached an EDSS state of 6 (walking with support) or higher experience much more infrequent improvement.

Comparing TEMSO TOWER placebo matrix data to one recent analysis of untreated MS patients in the British Columbia MS database over the period 1980 to 2009 (Tremlett et al. Natural, innate improvements in multiple sclerosis disability. Mult Scler 2012 18: 1412-1421] leads to the following relevant points:

- 88% of the British Columbia patients had relapsing onset MS (only 12% had primary progressive MS)
- Amongst the 2472 MS suffers in the British Columbia dataset with EDSS 6 and above annual improvement occurred in 10.6% which is much lower than the regression rates for untreated patients

after one year obtained using data from the TEMSO-TOWER placebo matrix in the HE model (%, % and % for EDSS 6, 7 and 8 patients respectively).

- It would be more appropriate, if the TEMSO-TOWER placebo matrix is to be used for these higher EDSS states, to use data from the London Ontario data set (mean follow up: years) which would assume no regression amongst these patients.
- It should also be noted that the rates of regression observed in the Canadian study were substantially lower for EDSS states below 6 compared to those obtained after one year using the TEMSO-TOWER placebo matrix within the HE model (15.3% for the 3135 MS suffers with EDSS 1-3 compared to %, % and % for EDSS 1, 2 and 3 respectively using the TEMSO-TOWER matrix and 20.4% for the 1668 MS sufferers with EDSS 4-5.5 compared to % and % for EDSS 4 and 5 respectively using the TEMSO-TOWER matrix). This would call into question the validity of using the high regression rates derived using the TEMSO-TOWER matrix within the model.
- The invalidity of these high regression rates is further supported by the fact that the untreated patients reported annually as staying in the same EDSS state was 53% in the analysis of the British Columbia data set which is higher than the % of untreated patients dependent on EDSS state who stay the same after one year if the TEMSO-TOWER placebo matrix is used in the HE model.
- Patients in the British Columbia dataset reported as getting worse annually by at least one EDSS point or more was 20.5% with an additional 32.9% getting worse by 0.5 EDSS points which is not inconsistent with the % of untreated patients dependent on EDSS state who get worse by at least one EDSS state after one year in the HE model if the TEMSO-TOWER placebo matrix is used (the model does not capture EDSS changes of less than one point) and is not inconsistent with the %-% who get worse by at least one EDSS state after one year in the HE model if the London Ontario matrix is used.

A.5. Relevant evidence has not been considered to support the inclusion of direct non-health care costs sourced from Tyas et al 2007 within the cost effectiveness analysis which are excluded by using Biogen et al 2007 as requested in the additional information requested in the ACD on page 4 (although the wording "higher health state costs" is used on page 4 this should read "lower health state costs" as confirmed in a telephone call between Genzyme and NICE on 3rd December 2013).

The cost effectiveness model is sensitive to this assumption and the exclusion of direct non health care costs from the model makes the ICERs worse for alemtuzumab. The highest ICER for alemtuzumab shown in the combination of changes requested by NICE as part of the ACD is £24,472 (versus glatiramer acetate – Table 36 in additional information document sent on 090114) which excludes direct non health care costs. Including direct non healthcare costs (sourced from Tyas et al) reduces this ICER from £24,472 to £16,242. It is noted that in the FAD for teriflunomide the NICE Committee concluded, that the most plausible ICER was likely to lie between the ICERs estimated with and without non-health costs, given the uncertainty about how much of the non-health osts from the cited sources were within the NICE reference case [Teriflunomide FAD Section 4.18]. Consistency would require that a similar approach was adopted in this appraisal.

In Genzyme's opinion the exclusion of these direct non health care costs is not justified.

The following evidence supports the inclusion of direct non health care costs sourced from Tyas et al 2007 as used in Genzyme's original submission:

- Although no details of what was meant by direct non-medical costs exist in the Tyas paper the direct non-medical costs within this paper equate to those found in the Karampampa et al 2012 [1] paper which are also UK specific costs (see Table A.5.1. below) where details of what is included in this category are provided. The table shows costs from Karampampa limited to professional non-medical support with and without the inclusion of investments / modifications. Investments / modifications were defined in a separate paper (Karampampa et al 2012 [2]) as home modifications, car modifications, walking stick, wheelchairs. Professional non-medical support is split between home help (mean 37 hours a year) and professional help unspecified (mean 20 hours a year)
- The UK MS Survey carried out by the MS Society suggests that 50% of MS patients have their social care paid for entirely by the government and another 33% have their social care partly paid for by the government. Table A.5.1 also shows the direct non-medical costs from Karampampa reduced by 33% to take into account that 17% of patients will pay for social care entirely from their own pocket and 33% partially from their own pocket (MS Society report 2013). The cost gradient between higher and lower EDSS states are still comparable to those in Tyas et al (and it is this cost gradient to which the model is sensitive).
- The substantial increase in direct non-medical costs in higher EDSS states is supported by the results of the UK MS Survey which showed that 10% of patients requiring occasional assistance and 60% of those requiring constant assistance received social care (MS Society report 2013). A report from the Work Foundation also identified high costs associated with the higher dependency states of MS; high dependency home care of £1,345 per week, stay at a residential home of £758 a week and maintenance of a special needs flat of £933 per week (Work Foundation report 2011)

Table A.3.1: Comparing UK direct non-medical costs in Tyas et al to non-medical professional support and investments / modifications costs in Karampampa et al.

EDSS state	Tyas et (included in manufacturer basecase submission)	Karampampa et al (uplifted to 2013/14)	Karampampa et al - 66% (uplifted to 2013/14)
0	£5,335	£0-£53	£0-£35
1	£5,780	£0-£53	£0-£35
2	£6,735	£0-£53	£0-£35
3	£9,565	£0-£53	£0-£35
4	£6,462	£1055-£2671	£703-£1780
5	£9,489	£1055-£2671	£703-£1780
6	£9,811	£1055-£2671	£703-£1780
7	£15,761	£18241-£21558	£12160-£14371
8	£20,811	£18241-£21558	£12160-£14371
9	£12,915	£18241-£21558	£12160-£14371

A.6.. Genzyme do not believe that all evidence has been considered in requesting as part of the ACD additional analyses which applies a waning of efficacy solely to alemtuzumab at 3 years and 5 years and not to the comparators as is implied by the wording used in the additional analysis request (on page 4 of the ACD in which "a reduction in efficacy for alemtuzumab starting at 3 or 5 years" is requested without mention of applying waning to the comparators).

It would be consistent with the NICE assessment of teriflunomide to apply a waning of efficacy of 75% at years 3 to 5 and 50% beyond year 5 to both alemtuzumab and to the comparators of beta interferons and glatiramer acetate. The teriflunomide assessment was in the same population of active RRMS for which the additional analysis has been requested by NICE for alemtuzumab. In the teriflunomide ACD the additional analyses requested included waning of treatment effect but without stipulating that this should apply to just the treatment being appraised [Teriflunomide NICE ACD Section 1.2]. This was applied to both teriflunomide and the comparators of beta interferons and glatiramer acetate by the manufacturer (and this approach was accepted by the ERG / Appraisal Committee)

It is also noted in the NICE assessment of fingolimod a waning of efficacy of 50% was applied from 5 years onwards. This analysis was in the highly active RRMS despite interferon use population (NICE fingolimod guidance Section 4.13).

It is also of relevance that as outlined in Genzyme's original submission that data exists from the CAMMS 223 extension study which shows maintenance of efficacy (both ARR RR and 6 month's SAD HRs) up to 5 years against an active comparator (SC INF beta 1a). Neither teriflunomide nor fingolimod at the time of assessment had data up to 5 year's against an active comparator.

It is also noted in the NICE assessment of teriflunomide that the Committee agreed that it was important to include in the decision-making that the treatment effect could decrease over time but, given the uncertainty of how much the treatment effect would wane, the most plausible ICER was likely to lie between the estimates that included and excluded the modeled treatment waning effect [Teriflunomide FAD Section 4.19]. Consistency would require that a similar approach was taken in this assessment

The wording of this request in the ACD suggests that comparator efficacy should be assumed to be 100% for the 50 years of the model whilst waning is only applied to alemtuzumab efficacy. This is not a reasonable approach based on the precedent of other NICE assessments and also there is no rationale for assuming a divergent approach to waning assumptions between alemtuzumab and its comparators.

Applying waning to alemtuzumab but not to the comparators increases the difference between the deterministic and probabilistic ICERs. As shown in Table 1 in Genzyme's submission of the additional analyses requested by NICE (sent on 9th January 2014) the probabilistic ICER is 1-9% higher than the deterministic ICER for the analysis applying

all of the combined requested changes if waning is applied to the alemtuzumab and comparator arms but the probabilistic ICER is 53%-58% higher than the deterministic ICER if waning is applied to only the alemtuzumab arm. This increase in uncertainty in the alemtuzumab arm is an artefact of an unreasonable modelling assumption for the reasons stipulated above in Response A.6.

B. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

B.1. Genzyme do not believe that the summary of clinical effectiveness which states that alemtuzumab 12mg does not have persuasive evidence that it is clinically effective in HA RRMS despite interferon use patients is a reasonable interpretation of the evidence (Section 4.9. of the ACD).

Genzyme do not believe that it is reasonable to conclude that alemtuzumab 12mg is not clinically effective in patients with HA RRMS despite interferon use because:

- The HA RRMS despite interferon use subgroup data from CARE MS II presented in Tables A.2.1.1. and A.2.1.3. (in this document) shows that patients treated with alemtuzumab had a statistically reduced disability progression (as measured by SAD 6 months HR) and relapse rate compared to those treated with an active comparator, SC IFNβ-1a 44 μg.

- The data from CARE MS II presented in Tables A.2.1.1. and A.2.1.3.(in this document) shows that patients treated with alemtuzumab had a numerically similar reduced disability progression (as measured by SAD 6 months HR) and relapse rate compared to those treated with an active comparator, SC IFNβ-1a 44 μg. in the HA RRMS despite interferon use subgroup and the full trial data set. This is consistent with the assessment of alemtuzumab 12mg by the regulatory authority, the European Medicines Agency (EMA), which did not identify any difference between highly active and non-highly active subgroups in the efficacy of alemtuzumab 12mg as shown in the European Public Assessment Report for the drug.[EMA (Lemtrada EPAR), 2013]

- The data accepted by NICE for the clinical effectiveness of fingolimod in patients with HA RRMS despite interferon use was less compelling than that presented for alemtuzumab 12mg in that the data for fingolimod showed no significant impact on disability progression compared with an active comparator. In the case of fingolimod, the NICE Committee concluded that the available evidence showed that people with relapsing–remitting multiple sclerosis who are treated with fingolimod have lower relapse rates than people treated with an active comparator (IM IFNβ-1a 30mg) or placebo. The Committee agreed that fingolimod was shown to reduce disability progression in people with relapsing–remitting multiple sclerosis compared with placebo in the whole population of the FREEDOMS trial; however, there was no significant impact on disability progression compared with an active comparator (IM IFNβ-1a 30mg) in the TRANSFORMS trial [Fingolimod final NICE guidance: Section 4.7].

- It is also important to note that the disability progression data accepted by NICE as showing effectiveness in reducing disability progression compared to placebo was 3 month SAD HR data. Alemtuzumab 12mg shows statistical significance based on 6 month SAD HR data against an active comparator. The 6 month SAD is considered to be the more robust measure of sustained disability accumulation than the 3 month SAD, and 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 six months apart". [EMA, 2009]

- In the fingolimod appraisal by NICE it is noted that fingolimod was accepted for use in the HA RRMS despite interon use population based upon an estimated ICER vs a beta interferon, Avonex, of £17,300 [Fingolimod final NICE guidance: Section 4.16]. Using the direct evidence of alemtuzumab versus SC IFNβ-1a 44 μg efficacy from the HA RRMS despite interferon use subgroup from CARE MS II in the HE model provides a more favourable ICER for alemtuzumab versus SC IFNβ-1a 44 μg in this subgroup of £8910 (using the combination of the changed assumptions requested by NICE in the ACD) (Model 1 sent to NICE on 090114 can be used to validate this ICER value). This suggests that alemtuzumab has more compelling evidence for its cost effectiveness in the HA RRMS despite interferon use subgroup than that accepted by NICE for fingolimod in this group given that the ICER is more favourable against a beta interferon and is based on a subgroup analysis which showed a statistically significant versus this comparator for disability progression (using 6 month SAD HRs) (unlike fingolimod which as described above was not assessed to have statistically significant results for disability progression versus Avonex in this subgroup using 3 month SAD HR as an efficacy measure)

B.2. Genzyme do not believe that the summary of clinical effectiveness which states that alemtuzumab does not have persuasive evidence that it is clinically effective in RES RRMS patients is a reasonable interpretation of the evidence (as outlined in Section 4.9. of the ACD).

Genzyme do not believe that it is reasonable to conclude that alemtuzumab 12mg is not clinically effective in patients with RES RRMS because:

- The RES RRMS metanalysis of the subgroup data from CARE MS I and II and CAMMS 223 presented in Tables A.3.1.1. and A.3.1.3. above shows that patients treated with alemtuzumab had a statistically reduced disability progression (as measured by SAD 6 months HR) and relapse rate compared to those treated with an active comparator, SC IFNβ-1a 44 μg.

- The data from individual CARE MS I and II and CAMMS 223 studies and in the metanalysis of these studies presented in Tables A.3.1.1. and A.3.1.3. above shows that patients treated with alemtuzumab had a numerically similar reduced disability progression (as measured by SAD 6 months HR) and relapse rate compared to those treated with an active comparator, SC IFNβ-1a 44 μg. in the RES RRMS subgroup and the full trial data set. This is consistent with the assessment of alemtuzumab 12mg by the regulatory authority, the European Medicines Agency (EMA), which did not identify any difference between highly

active and non-highly active subgroups in the efficacy of alemtuzumab 12mg as shown in the European Public Assessment Report for the drug.[EMA (Lemtrada EPAR), 2013]

- The data accepted by NICE for the clinical effectiveness of natalizumab in patients with RES RRMS was less compelling than that presented for alemtuzumab 12mg. The data for natalizumab accepted by NICE was against placebo and effectiveness against an active comparator was based upon indirect (MTC) evidence whilst the evidence for the effectiveness for alemtuzumab against an active comparator is based upon direct metanalysis evidence The indirect evidence for natalizumab accepted by NICE included people with relapsing–remitting multiple sclerosis rather than RES RRMS and did not specifically examine the clinical effectiveness of the drugs in the RES RRMS groups. NICE accepted the manufacturer of natalizumab's assumption that the treatment effect of the active comparators (beta interferon and glatiramer acetate) in RRMS was equivalent to that in the RES groups [Natalizumab final NICE guidance: Section 3.4]. Both the direct evidence against an active comparator (SC IFNβ-1a 44 μg) and indirect evidence presented for alemtuzumab 12mg (against natalizumab) relates specifically to RES RRMS patients.

- In the natalizumab appraisal by NICE it is noted that natalizumab was accepted for use in the RES RRMS population based upon an estimated ICER vs a beta interferon of £32,000 [Natalizumab final NICE guidance: Section 4.7] using an estimation of efficacy based upon the indirect comparison outlined in the bullet point above. Using the direct evidence of alemtuzumab versus SC IFNβ-1a 44 μg efficacy from the metaanalysis of the RES RRMS subgroups from CARE MS I / II and CAMMS 223 in the HE model provides a more favourable ICER for alemtuzumab versus SC IFNβ-1a 44 μg in this subgroup of £8623 (using the combination of the changed assumptions requested by NICE in the ACD) (Model 1 sent to NICE on 090114 can be used to validate this ICER value). This suggests that alemtuzumab has more compelling evidence for its cost effectiveness in the RES RRMS subgroup than that accepted by NICE for natalizumab in this group.

C. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Genzyme are of the opinion that the provisional recommendations are not a sound and suitable basis for guidance to the NHS. Genzyme are of the opinion that in the ACD there is a lack of transparency in the explanation and conclusions which has meant that the ACD is unclear. This has prejudiced our ability to respond to the ACD fully and we consider this to be procedurally unfair. Examples of this are a lack of clarity as to why in Section 4.9. the Committee are not persuaded of the efficacy of alemtuzumab in RES RRMS and HA RRMS despite interferon use and regarding decisions underpinning the additional analyses requested in Section 1.2. (as outlined in responses A.6.. and A.5. and A.4. above).

On page 2 of the ACD it is stated that after the Committee has met again the Committee will prepare the FAD. If the Committee's recommendation after the next meeting is that alemtuzumab should be used in active RRMS excluding RES RRMS and HA RRMS despite interferon use this would be a substantial limitation on the use of the drug (as

outlined in response A.1. above) and so this should procedurally involve the production of a second ACD to allow consultation on such a substantial limitation on use of the drug. This is line with NICE's processes that only allows for the production of a FAD in such circumstances if no substantial limitation on the use of a treatment in relation to its licenced use is intended.

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