Genzyme's Response to NICE's request for additional information in the alemtuzumab Appraisal Consultation Document (ACD).

In response to the appraisal committee document (ACD) for alemtuzumab, the following analyses have been conducted to assess both the individual impact and the combined impact of all proposed amendments on the probabilistic base-case incremental cost-effectiveness ratios (ICERs). All scenarios have been run with 10,000 stochastic simulations. A fully incremental analysis, including beta interferons and glatiramer acetate as comparators, is presented incorporating all the Committee's requested amendments. The individual impact of each of the proposed amendments is given in the detailed descriptions of Data Requests 1 to 14 below (with the combination analyses described under Data Request 15).

In addition, Genzyme provides in Appendix 3, the comparable additional analyses provided for alemtuzumab in the highly active (HA) RRMS despite interferon use versus fingolimod and in rapidly evolving severe (RES) RRMS versus natalizumab. It is Genzyme's belief that in the response to the ACD we provide evidence to prove the clinical effectiveness of alemtuzumab in these subgroups (which the ACD described as not being proved in our original submission) and we assume that if the Committee accepts that we have done this that they will want to see the same additional analyses for the HARRMS despite interferon and RES RRMS as has been requested for the active RRMS. This analysis has also been provided as part of Genzyme's response to the ACD and by providing it as part of the additional analysis request (together with the associated models used) we provide an opportunity for this analysis to be validated by the ERG.

Data Request	Proposed amendment
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
2	An 'all years' mixed treatment comparison that is adjusted for baseline relapse rates
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)
4	EQ-5D data from the CARE-MS I and CARE-MS II trials
5	An amendment to the model to allow improvements in patients' EDSS states (by using the TEMSO TOWER placebo arm natural history matrix)
6	An amendment to the model incorporating the observed deaths from the trial data
7	A reduction in efficacy for alemtuzumab starting at 3 or 5 years
8	Additional costs of other licensed relapsing-remitting multiple sclerosis treatments after alemtuzumab treatment failure
9	A time-dependent re-treatment rate for alemtuzumab
10	Removing the mid-cycle correction for the costs of alemtuzumab
11	Increasing the number of monitoring and neurology visits for patients treated with alemtuzumab and additional monitoring after re-starting alemtuzumab treatment
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]
13	Costs associated with adverse effects of treatment including renal failure, renal transplantation, dialysis, and death
14	Baseline characteristics from patients in the alemtuzumab trials instead of from the UK Risk Sharing Scheme
15	All of the requested changes combined

A summary table of the results of these additional cost effectiveness analyses against glatiramer acetate are provided below (glatiramer acetate is the most cost effective comparator against which alemtuzumab is compared) (results are presented deterministically as well as probabilistically to help in confirming for the ERG the values to which the models are set to run the probabilistic analyses). A reference is provided to the which of the models sent to NICE on 090114 was used to run the results (multiple versions of the model were needed because some of the requested analyses required structural changes to be made to the base case model.

Table 1 Summary of cost effectiveness results against glatiramer acetate

Data Request	Proposed amendment	ICER vs GA deterministic	ICER vs GA probabilistic	Model (sent to NICE on 090114)
Baseline	From original submission (probabilistic Alemtuzumab vs GA total costs: £494,319 vs £484,590, total QALYs: 4.273 vs 2.887) (see Table B.7.7.9. page 337 of original submission)	£8,924	£7,017	Model 1
15	Combo with waning at 3 or 5 years (uses all years metaregression efficacy results including 6 months SAD HRs) (waning applied to alemtuzumab and comparator arm)	£11,632 or £13,498	£12,730 or £13,636	Model 7
15	Combo with waning at 3 or 5 years (uses all years metaregression efficacy results including 6 months SAD HRs) (waning only applied to alemtuzumab arm, 100% efficacy up to 50 years assumed for comparator)	£14,334 or £15,455	£22,001 or £24,472	Model 7
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	£7,582	£4,839	Model 1
2	An 'all years' mixed treatment comparison that is adjusted for baseline relapse rates (3 month SAD HR)	£11,959	£9,677	Model 1
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) (3 month SAD HR) (post 2000 MTC)	£10,388	£7820	Model 2
4	EQ-5D data from the CARE-MS I and CARE-MS II trials	£6,148	£4,779	Model 3
5	An amendment to the model to allow improvements in patients' EDSS states	£2,026	£321	Model 1
6	An amendment to the model incorporating the observed deaths from the trial data	£8,979	£7,063	No model used (see details below)
7	A reduction in efficacy for alemtuzumab starting at 3 or 5 years (assume same waning for comparators)	£22,001 or £24,548	£21,337 or £23,432	Model 1
7	A reduction in efficacy for alemtuzumab starting at 3 or 5 years (assume 100% efficacy for comparators up to 50 years)	£23,157 or £26,163	£25,875 or £30,657	Model 1
8	Additional costs of other licensed relapsing-remitting multiple sclerosis treatments after alemtuzumab treatment failure	£12,263	£10,324	Model 1 (cell D36 in "cost data" sheet)
9	A time-dependent re-treatment rate for alemtuzumab	£3,286	£1,274	Model 4
10	Removing the mid-cycle correction for the costs of alemtuzumab	£11,796	£9,431	Model 5
11	Increasing the number of monitoring and neurology visits for patients treated with alemtuzumab and additional monitoring after re-starting alemtuzumab treatment	£11,800	£9,209	Model 6
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]	£14,834	£12,802	Model 1
13	Costs associated with adverse effects of treatment including renal failure, renal transplantation, dialysis, and death	£9,082	£7,164	Model 1 (change cell H105 on "cost data" sheet)
14	Baseline characteristics from patients in the alemtuzumab trials instead of from the UK Risk Sharing Scheme	£1473	Dominates	Model 1

Data Request 1

Sustained accumulation of disability (SAD) lasting 6 months as a primary outcome measure in the mixed treatment comparison (MTC), and incorporating the results into the economic model

The base case MTC used in the cost-effectiveness analysis has the inclusion criteria of post-2000 MTCs. The 6-month SAD results versus placebo for each of the relevant comparators for the active RRMS population is given in Tables B6.7.8 of the manufacturer's original submission on page 161. Note that of the beta interferons, 6-month SAD data were not available for IFNβ-1b or SC IFNβ-1a 22µg. Results as in the original submission are run for a random effects model.

Table 2 Cost-effectiveness results using 6-month SAD in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab vs comparator
Glatiramer acetate	467,790	3.702				4,839
Alemtuzumab	474,924	5.176	7,134	1.474	4,839	
IM IFNβ-1a	478,108	3.633	3,184	-1.544	Dominated	Dominates
SC IFNβ-1a 44µg	482,486	3.178	4,379	-0.455	Dominated	Dominates

Data Request 2

An 'all years' mixed treatment comparison that is adjusted for baseline relapse rates

The results of the all years MTC adjusted for baseline annualized relapse rates (ARR) are shown in Appendix 1 (DMTs versus placebo and alemtuzumab versus other DMTs). In addition we have included a report in Appendix 2 outlining the method used to carry out this adjustment. Results as in the original submission are run for a random effects model.

The resulting probabilistic ranked ICERs and pairwise ICERs against alemtuzumab for the preferred analysis are presented in Table 3 (using the 3 month SAD HR results) and Table 4 (using the 6 month HR results). Using the all-years MTC controlling for baseline ARR, the probabilistic ICER is reduced from the base case which uses the post-2000 MTC.

Table 3 Cost-effectiveness results using all years MTC adjusted for baseline annualized relapse rates in the active RRMS population (using 3 month HRs)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	482,667	2.981				9,677
SC IFNβ-1a 44µg	488,211	2.933	5,544	-0.048	Dominated	5,108
SC IFNβ-1a 22µg	491,950	2.847	3,738	-0.087	Dominated	2,125
IM IFNβ-1a	492,737	2.882	787	0.035	22,501	1,603
Alemtuzumab	494,928	4.248	2,191	1.366	1,603	
IFNβ-1b	495,133	2.679	205	-1.570	Dominated	Dominates

Table 4 Cost-effectiveness results using all years MTC adjusted for baseline annualized relapse rates in the active RRMS population (using 6 month SAD HRs)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab vs comparator
Glatiramer acetate	472,975	3.437				4,866
Alemtuzumab	480,260	4.934	7,284	1.497	4,866	
IM IFNβ-1a	483,091	3.400	2,831	-1.533	Dominated	Dominates
SC IFNβ-1a 44µg	486,117	3.046	3,025	-0.355	Dominated	Dominates

<u>Data Request 3</u>

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)

In general, the results of the intention-to-treat (ITT) analysis adjusted for baseline EDSS (using a covariate of EDSS <2 and > or = 2), unadjusted for region, are comparable to the primary analysis. Statistical significance is identical between the analyses.

In the 3-month, 6-month SAD and ARR analyses, the differences in means between primary analysis and unadjusted for country/region analysis were ≤0.03, for the main trial populations as well as trial subgroup populations. Confidence intervals were also comparable between the different analyses; in the majority of cases the confidence intervals of the analysis adjusted for baseline EDSS, unadjusted for region, were narrower than the primary analysis.

Table 5 Comparing alemtuzumab primary analyses to analyses adjusted for baseline EDSS and unadjusted for region analyses

Comparison	6 month SAD		3 month SAD		ARR RR	
	Primary analysis	Adjusted for baseline EDSS, unadjusted for region	Primary analysis	Adjusted for baseline EDSS, unadjusted for region	Primary analysis	Adjusted for baseline EDSS, unadjusted for region
CARE MS I (active)	0.70 [0.40, 1.23]	0.71 [0.40, 1.24]	[redacted]	[redacted]	0.46 [0.36, 0.58]	0.46 [0.33, 0.64]
CARE MS II (active)	0.58 [0.38, 0.87]	0.58 [0.39, 0.87]	[redacted]	[redacted]	0.5 [0.41, 0.61]	0.51 [0.39, 0.65]
CAMMS 223 (active)	0.25 [0.11, 0.57]	0.25 [0.11, 0.56]	[redacted]	[redacted]	0.31 [0.21, 0.45]	0.34 [0.20, 0.56]

Table 6 Post 2000 MTC for alemtuzumab analyses alemtuzumab trial inputs adjusted for baseline EDSS and unadjusted for region analyses, in the active RRMS population (random effects model)

Intervention	3-month SAD HR [95% CI]		ARR RR [95% CI]	
	Alemtuzumab vs intervention	Intervention vs placebo	Alemtuzumab vs intervention	Intervention vs placebo
Alemtuzumab		[redacted]		[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]	[redacted]
IM IFNβ-1a	[redacted]	[redacted]	[redacted]	[redacted]
SC IFNβ-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]
SC IFNβ-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]

** Assume SC IFNβ-1a 22µg efficacy as per the manufacturer submission(in the absence of data)*

As shown in Table 7, using the alemtuzumab trial ITT analysis adjusted for baseline EDSS and unadjusted for region analyses has little impact on the cost-effectiveness results.

Table 7 Cost-effectiveness results using post 2000 MTC with alemtuzumab results adjusted for baseline EDSS and unadjusted for region analyses

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	484,515	2.907				7,820
SC IFNβ-1a 44µg	487,533	2.918	3,018	0.012	261,847	5,600
SC IFNβ-1a 22µg	488,096	3.039	563	0.120	4,683	5,692
IFNβ-1b	493,456	2.819	5,360	-0.220	-24,378	1,033
IM IFNβ-1a	494,921	4.238	1,466	1.419	1,033	
Alemtuzumab	497,216	2.632	2,294	-1.606	-1,429	-1,429

<u>Data Request 4</u>

EQ-5D data from the CARE-MS I and CARE-MS II trials

To address the committee's concerns regarding the disutility of adverse events, trial EQ-5D data have been included which will capture health state utility, in addition to disutilities from relapses whilst on treatment and treatment adverse events. Trial EQ-5D data will not have captured caregiver disutility so these remain in the analysis.

In the CARE MS I and II trials, EQ-5D-5L was collected at baseline and at months 6, 12, 18 and 24. Given the model parameters are extrapolated over 50 years, it is anticipated that the utility score at the longest time point (24 months) will be representative of long-term utility for each of the alemtuzumab and IFNβ-1a arms. Note that EDSS scores have been rounded down such that scores

captured in the trials for EDSS 1.0 and 1.5 have been pooled to be representative of the utility score at EDSS 1.

The utility scores at 24 months for the alemtuzumab arm are used over all time points of the model since patients may incur alemtuzumab related adverse events over their lifetime, not just when receiving treatment. The utility scores at 24 months for the IFNβ-1a arm are used only whilst patients are receiving treatment. Trial utility values are only used for EDSS states ≤6 for 24 month trial data since sample sizes in EDSS>6 are small (n=3 and 2 in the EDSS 7 in the two arms and less in EDSS states 8 and 9). From EDSS 7 to 9, utility values are sourced using decrements between EDSS states from Orme et al., as suggested by the ERG group reviewing teriflunomide STA [NICE 2013; Orme et al. 2007].

Baseline utility scores for the IFNβ-1a arm are used to represent best supportive care (i.e. for RRMS EDSS ≥ 7, SPMS and patients that withdraw from IFNβ-1a and switch to BSC). Baseline utility values are only used for EDSS states ≤5 since sample sizes in EDSS>5 are small (n=2 and 1 in the two arms for EDSS 6 and less for EDSS 7-9). From EDSS 6 to 9, utility values are sourced using decrements between EDSS states from Orme et al.

Adverse event disutilties are all set to zero. Disutilities from relapses are zero in the alemtuzumab arm since the trial utilities are assumed to capture relapses. Since alemtuzumab reduces relapse rates more than the comparator treatments this may be a conservative assumption since those relapses occurring outside of the 24 month measurement point are not captured through this approach and will be higher in the comparator arm than the alemtuzumab arm. Disutilities from relapses are zero in the IFNβ-1a arm only when patients are receiving treatment but when patients switch to best supportive care, relapse disutilities are the same as used in the manufacturer submission.

Commentary on Table 8 shown below.

- Data observed in the trial show some inconsistencies possibly due to small sample sizes, particularly in higher EDSS states as shown in Table 8 below. For example, the utility score between EDSS 5 and 6 at month 24 increases in the IFNβ-1a arm which is counterintuitive.

- There is no consistent evidence of a decreased utility between baseline and measurements at 24 months for patients in a particular EDSS states. If AEs as a result of treatment were leading to a substantial reduction in utilities it would be expected that patients in a particular EDSS states would have lower utilities on treatment than at baseline when they are not on treatment. No such consistent picture is observed:
    - For patients on alemtuzumab, as shown in Table 8, of the 7 EDSS states for which there is data at baseline and at 24 months for five of the seven EDSS states higher mean utilities were observed at 24 months than at baseline. As shown in Appendix 4, a similar pattern of improvements in mean EQ 5D from baseline occurred at 6,12 and 18 months with 6 out of 7, 5 out of 7 and 5 out of 7 EDSS states respectively showing an improvement in mean EQ 5D from baseline.

    - Similarly, for IFNβ-1a 44µg of the 7 EDSS states for which there is data at baseline and at 24 months for four of the seven EDSS states higher mean utilities were observed at 24 months than at baseline. As shown in Appendix 4, a similar pattern of

improvements in mean EQ 5D from baseline occurred at 6,12 and 18 months with 4 out of 7, 3 out of 7 and 5 out of 7 EDSS states respectively showing at improvement in mean EQ 5D from baseline.

- This trial evidence suggests that the small contribution that adverse events makes to overall differences in utility values between treatments as reflected in the model used in Genzyme's original submission is appropriate (in Table B.7.7.6. on page 334 of the original submission AEs contribute only 3% to the difference in utilities between alemtuzumab and IFNβ-1a 44µg)

Table 8 EQ-5D-5L utility scores and sample sizes from the pooled CARE MS I and II trials

EDSS		0-0.5	1-1.5	2-2.5	3-3.5	4-4.5	5-5.5	6-6.5	7-7.5	8-8.5
Alemtuzumab 12mg	Baseline EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
	Baseline n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0
	Month 24 EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24 n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
IFNβ-1a 44µg	Baseline EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
	Baseline n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0
	Month 24 EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Month 24 n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
	Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

*Small baseline sample size

In the model, the trial observation scores are combined with Orme utility values for higher EDSS states as presented in Table 9.

Table 9 Utility values used in the model, (Utility values per EDSS state derived using trial observations for EDSS ≤5 for baseline and EDSS ≤6 at 24 months and derived from decrements based Orme et al. for other EDSS states)

EDSS		0	1	2	3	4	5	6	7	8	9
Alemtuzumab 12mg (month 24 scores)	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 44µg (month 24 scores)	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care (baseline IFNβ-1a 44µg scores)	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Alemtuzumab remains cost-effective at a WTP of £30,000 per QALY when using trial EQ-5D data, as shown in Table 10. It has been assumed that the utility values observed in the trial for IFNβ-1a 44µg

would be comparable to all beta-interferons and glatiramer acetate thus the trial values for IFNβ-1a 44µg have been used for other DMTs in Table 10.

Table 10 Cost-effectiveness results using EQ-5D values from the CARE MS I and II trials, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	485,102	1.813				4,779
SC IFNβ-1a 22µg	487,572	2.074	2,469	0.261	9,447	4,070
SC IFNβ-1a 44µg	487,657	1.830	86	-0.244	Dominated	3,522
IM IFNβ-1a	493,068	1.753	5,411	-0.078	Dominated	738
Alemtuzumab	494,574	3.794	1,506	2.042	738	
IFNβ-1b	497,093	1.549	2,519	-2.245	Dominated	Dominates

It is noted that total QALYs for alemtuzumab and the comparators are lower than the base case in the manufacturer's original submission (alemtuzumab vs GA total QALYs: 4.273 vs 2.887 see Table B.7.7.9. page 337 of original submission) . This is because of the lower utilities in EDSS 5 and 6 compared to those sourced from Orme et al. Orme et al was the source of utilities used in the original submission base case. Orme sourced utilities are also lower than the utilities in the teriflunomide ERGs preferred approach (TEMSO derived EQ 5D values for EDSS 0-6 plus Orme decrements for EDSS 7-9) (see Table 11 below) and similar to utilities based on CARE MS I / II data from baseline (alemtuzumab 12mg and IFNβ-1a 44µg for EDSS 0-5 using Orme decrements to derive utilities for EDSS 6-9.

Table 11: Utility values used in Genzyme original base case and those used in teriflunomide ERG preferred analysis and those based on baseline results from CARE MS I /II.

	EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9
RRMS (based on Orme)	0.87	0.80	0.71	0.57	0.61	0.52	0.46	0.30	-0.05	-0.20
SPMS (based on Orme)	0.83	0.75	0.66	0.53	0.57	0.47	0.42	0.25	-0.09	-0.24
RRMS (based on TEMSO + Orme decrements)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SPMS (based on TEMSO + Orme decrements)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RRMS (based on CARE MS I/II + Orme decrements)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RRMS (based on CARE MS I/II + Orme decrements)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICERs have been estimated using TEMSO + Orme decrements in place of Orme in the original base case model (using Model 1 sent to NICE on 090114). This has been done given the Committee's concern about overall total QALYs being low in the original submission. It is noted that this does raise the total QALYs associated with alemtuzumab and the comparators relative to the base case in the original submission as shown in Table 12 below:.

Table 12 Cost-effectiveness results using EQ-5D values from TEMSO plus Orme decrements to derive utilities for EDSS 7-9, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	485,234	4.290				6,221
SC IFNβ-1a 22µg	487,382	4.520	2,148	0.230	9,334	5,649
SC IFNβ-1a 44µg	487,548	4.333	166	-0.187	Dominated	4,801
IM IFNβ-1a	493,428	4.265	5,879	-0.068	Dominated	681
Alemtuzumab	494,453	5.772	1,025	1.507	681	
IFNβ-1b	497,650	4.023	3,197	-1.749	Dominated	Dominates

Data Request 5

An amendment to the model to allow improvements in patients' EDSS states

The natural history matrix from the placebo arms of TEMSO and TOWER allow for regression in EDSS, i.e. allow improvement in EDSS (see page 21 of the ACD). The cost-effectiveness results using the TEMSO and TOWER placebo arm transition probability matrices for RRMS natural history are presented in Table 13.

In addition, a sensitivity analysis is presented using a natural history transition matrix that combines TEMSO and TOWER for transitions from EDSS 0 to 5, and London Ontario (active RRMS) for transitions from EDSS 6 to 8. Note that no transitions were available from EDSS 9 so the same assumptions were made as in the manufacturer submission. This combined matrix is an important consideration since it allows for regression which was the key limitation of London Ontario data, but it also removes the unlikely high regression rates for high EDSS that are likely to occur in practice but were calculated because of small sample size (as discussed in the manufacturer's response to the ACD under response A.4.)

Table 13 Probabilistic cost-effectiveness results using TEMSO and TOWER natural history transition matrix in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	401,767	6.549				321
Alemtuzumab	402,438	8.643	671	2.093	321	
SC IFNβ-1a 44µg	403,099	6.589	660	-2.054	Dominated	Dominates
SC IFNβ-1a 22µg	407,676	6.801	4,577	0.213	21,526	Dominates
IM IFNβ-1a	410,680	6.504	3,004	-0.297	Dominated	Dominates
IFNβ-1b	428,920	6.405	18,240	-0.099	Dominated	Dominates

Table 14 Cost-effectiveness results using natural history transition matrix with TEMSO and TOWER for EDSS 0-5 and London Ontario otherwise, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Alemtuzumab	447,578	6.680				
Glatiramer acetate	451,121	4.434	3,543	-2.246	Dominated	Dominates
SC IFNβ-1a 44µg	452,650	4.513	1,529	0.078	19,562	Dominates
SC IFNβ-1a 22µg	453,776	4.773	1,126	0.261	4,313	Dominates
IM IFNβ-1a	459,624	4.399	5,848	-0.374	Dominated	Dominates
IFNβ-1b	475,432	4.169	15,809	-0.230	Dominated	Dominates

<u>Data Request 6</u>

An amendment to the model incorporating the observed deaths from the trial data

There were a total of 8 deaths during the Genzyme-sponsored clinical studies, including 7 (0.5%) patients who received alemtuzumab and 1 patient who received SC IFNβ-1a.

- Three deaths were adjudged to be possibly drug related.
- The other 4 deaths were assessed as not related to study drug (i.e., fatal road accident, autopedestrian accident, aspiration pneumonia, and severe bleeding after incised wound in the alemtuzumab 12 mg/day group).
- A total of 1,485 patients with RRMS were treated with alemtuzumab with a median duration of follow up of 33 months;
- Of these 3 out of 1485 alemtuzumab related deaths 3/1485 = 0.2%
- The other 4 are at a rate over 33 months of 4/1485 = 0.27%

As conducted by the ERG in their additional analysis of alemtuzumab, to incorporate deaths observed in the trials, an adjustment was made to the total predicted QALYs. The number of QALYs are adjusted for the number of deaths in the trials i.e. reduced by 3/1485 = 0.20%. The total number of QALYs for alemtuzumab was 4.273 (as shown in the base case analysis presented in the original manufacturer's submission Table B.7.7.9. page 337), which was adjusted for the number of deaths in the trials to 4.264 with all other values in the original base case analysis left the same (see Table 13).

Table 15 Cost-effectiveness results using an adjustment for trial mortality, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	484,590	2.887				7,063
SC IFNβ-1a 22µg	487,368	2.923	2,778	0.036	77,453	5,182
SC IFNβ-1a 44µg	487,642	3.034	274	0.111	2,459	5,427
Alemtuzumab	492,860	2.872	5,218	-0.162	Dominated	1,048
IM IFNβ-1a	494,319	4.264	1,459	1.392	1,048	
IFNβ-1b	497,009	2.632	2,690	-1.632	Dominated	Dominates

Below we show the impact of reducing mortality which is to improve ICERs compared to the base case. This has been done since the rate of mortality excluding AE related events was lower in the trial at 3 years (33 months) (0.27%) than at 3 years in the alemtuzumab arm in the model (0.37%). Numbers of trial deaths are small, however, to use for such a validation and it is noted that if a reduction in the mortality rates used in the model were carried out that this would improve the ICERs reported.

Table 16 Cost-effectiveness results using a 50% reduction is MS-mortality risk, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	532,538	2.702				3,303
SC IFNβ-1a 22µg	534,123	2.900	1,585	0.198	8,024	2,553
SC IFNβ-1a 44µg	535,067	2.734	945	-0.166	Dominated	1,583
Alemtuzumab	537,298	4.143	2,230	1.409	1,583	
IM IFNβ-1a	540,857	2.652	3,559	-1.491	Dominated	Dominates
IFNβ-1b	545,169	2.432	4,313	-0.220	Dominated	Dominates

<u>Data Request 7</u>

A reduction in efficacy for alemtuzumab starting at 3 or 5 years

Results of the amendment with a reduction in alemtuzumab efficacy are presented for four scenarios:

- 50% efficacy for year 5 and onwards (applied to both alemtuzumab and comparators and to alemtuzumab only with 100% efficacy of comparator assumed up to 50 years in Table 17 and Table 19 respectively)
- 75% efficacy at 3-5 years followed by 50% efficacy for year 6 and onwards (applied to both alemtuzumab and comparators and to alemtuzumab only with 100% efficacy for comparator assumed up to 50 years in Table 18 and Table 20 respectively)

As noted in Genzyme's response B.3. to the ACD, 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 the comparators of beta interferons and glatiramer acetate in the same population of active RRMS. The wording of this request 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 does not seem a reasonable approach based on the precedent of other NICE assessments and also there does not seem to be a rationale for assuming a divergent approach for waning between alemtuzumab and its comparators.

It is also noted that in the assessment of fingolimod by NICE a waning of efficacy of 50% from 5 years onwards was applied.

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.

Given the wording of this request ICERs are presented assuming 100% efficacy up to 50 years for the comparator arms whilst applying waning only to alemtuzumab efficacy (Tables 19 and 20). However, Genzyme are strongly of the opinion that waning applied also to the comparators is more appropriate (as presented in Tables 17 and 18)

Table 17 Cost-effectiveness results using a 50% reduction in efficacy of alemtuzumab and the comparators for year 5 and onwards, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	486,964	2.790				21,337
SC IFNβ-1a 44µg	489,346	2.844	2,382	0.054	43,736	19,925
SC IFNβ-1a 22µg	489,983	2.922	636	0.078	8,196	21,083
IM IFNβ-1a	494,438	2.779	4,455	-0.143	Dominated	13,041
IFNβ-1b	498,621	2.558	4,183	-0.221	Dominated	6,898
Alemtuzumab	506,555	3.708	7,934	1.150	6,898	

Table 18 Cost-effectiveness results using a 25% reduction in efficacy in years 3, 4 and 5, with a 50% reduction in efficacy of alemtuzumab and the comparators for year 6 and onwards, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	487,069	2.772				23,432
SC IFNβ-1a 44µg	489,265	2.822	2,196	0.049	44,415	22,176
SC IFNβ-1a 22µg	490,829	2.885	1,563	0.063	24,883	21,953
IM IFNβ-1a	494,537	2.788	3,708	-0.096	Dominated	15,178
IFNβ-1b	498,625	2.553	4,088	-0.235	Dominated	8,177
Alemtuzumab	507,572	3.647	8,947	1.094	8,177	

Table 19 Cost-effectiveness results using a 50% reduction in efficacy of alemtuzumab for year 5 and onwards, in the active RRMS population (100% efficacy assumed for comparator up to 50 years)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	484,590	2.887				25,876
SC IFNβ-1a 44µg	487,368	2.923	2,778	0.036	77,453	23,536
SC IFNβ-1a 22µg	487,642	3.034	274	0.111	2,459	26,985
IM IFNβ-1a	492,860	2.872	5,218	-0.162	Dominated	15,569
IFNβ-1b	497,009	2.632	4,149	-0.24	Dominated	8,268
Alemtuzumab	505,938	3.712	8,929	1.08	8,268	

Table 20 Cost-effectiveness results using a 25% reduction in efficacy in years 3, 4 and 5, with a 50% reduction if efficacy of alemtuzumab for year 6 and onwards, in the active RRMS population (100% efficacy assumed for comparator up to 50 years)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	484,590	2.887				30,657
SC IFNβ-1a 44µg	487,368	2.923	2,778	0.036	77,453	28,318
SC IFNβ-1a 22µg	487,642	3.034	274	0.111	2,459	33,062
IM IFNβ-1a	492,860	2.872	5,218	-0.162	Dominated	19,273
IFNβ-1b	497,009	2.632	4,149	-0.240	Dominated	10,558
Alemtuzumab	507,639	3.639	10,630	1.007	10,558	

<u>Data Request 8</u>

Additional costs of other licensed relapsing-remitting multiple sclerosis treatments after alemtuzumab treatment failure

In the 1 year of CARE-MS extension studies, 1.75% (13/741) of the population received additional DMTs Fox et al 2012. A weighted average cost of additional DMTs has been calculated based in the table below. Note the cost of the beta-interferon is assumed to be equal to UK RSS price of SC IFNβ-1a 44µg. This cost has been added to the acquisition cost of alemtuzumab in the model each year from year 3 onwards. This has been added cumulatively such that year 3 has an additional cost of £134.84 (1.75% x £7,705), year 4 has an additional cost of £269.68 (3.5% x £7,705) and so on until year 50.

Glatiramer acetate	7	54%	5823
Interferon-beta	5	38%	8942
Natalizumab	1	8%	14690
	13		7705

Table 21 Cost-effectiveness results incorporating additional costs of other licensed RRMS DMTs after alemtuzumab treatment failure, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	484,590	2.887				10,324
SC IFNβ-1a 44µg	487,368	2.923	2,778	0.036	77,453	8,550
SC IFNβ-1a 22µg	487,642	3.034	274	0.111	2,459	9,092
IM IFNβ-1a	492,860	2.872	5,218	-0.162	Dominated	4,338
IFNβ-1b	497,009	2.632	4,149	-0.240	Dominated	1,187
Alemtuzumab	498,965	4.279	1,956	1.647	1,187	

Data Request 9

A time-dependent re-treatment rate for alemtuzumab

The previous model structure currently applies one rate from year 10 and onwards. The model structure has now been amended to allow the user to specify each rate from year 3 to 50, by adjusting the calculations of: acquisition costs, administration costs, monitoring costs and adverse event disutilities (note it has not been necessary to change monitoring costs as these are not dependant on re-treatment rate, and not necessary to amend adverse event costs no adverse event costs are incurred after year 10).

Two re-treatment scenarios are tested:

1. Using the re-treatment observed in CAMMS 223: [redacted] received re-treatment in years 3 to 5 [Genzyme DOF]. We assume an equal proportion received re-treatment in each year i.e. re-treatment in years 3, 4 and 5 is [redacted]).

2. Using the re-treatment observed in the CARE MS extensions: 19.2% received re-treatment in year 3 [Fox et al. 2012]. We assume that this rate of 19.2% applies to year 4 and 5 also.

The time-dependant re-treatment rate after year 5 is derived from an observational study with mean follow up of [redacted] [Tuohy, et al. Draft manuscript]. Due to the small sample size, we smooth the differences between years 6 and 8 and estimate that re-treatment reduces by half between years 5 and 6, then decreases by 10% annually after year 6. See Table 18 for the final re-treatment rates used in the model.

[redacted]

Year	Number that received dose in year	Percentage receiving re-treatment, of those that received two full initial courses
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]

Table 19 Re-treatment rates used in the model

Year	Re-treatment rates in base case scenario	Re-treatment rates in the sensitivity analysis scenario
3	[redacted]	19%
4	[redacted]	19%
5	[redacted]	19%
6	[redacted]	10%
7	[redacted]	9%
8	[redacted]	8%
9	[redacted]	7%

10	[redacted]	6%
11	[redacted]	6%

Table 22 Cost-effectiveness results incorporating a time-dependant re-treatment rate using a [redacted] rate in years 3-5 and [redacted] rate in year 6 reducing annually by 10% after year 6, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	484,590	2.887				1,274
Alemtuzumab	486,335	4.256	1,745	1.369	1,274	
SC IFNβ-1a 44µg	487,368	2.923	1,033	-1.333	Dominated	Dominates
SC IFNβ-1a 22µg	487,642	3.034	274	0.111	2,459	Dominates
IM IFNβ-1a	492,860	2.872	5,218	-0.162	Dominated	Dominates
IFNβ-1b	497,009	2.632	4,149	-0.240	Dominated	Dominates

Table 23 Cost-effectiveness results incorporating a time-dependant re-treatment rate using a 19% rate in years 3-5 and a 8.6% rate in year 6 reducing annually by 10% after year 6, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	484,590	2.887				3,701
SC IFNβ-1a 44µg	487,368	2.923	2,778	0.036	77,453	1,741
SC IFNβ-1a 22µg	487,642	3.034	274	0.111	2,459	1,676
Alemtuzumab	489,718	4.272	2,076	1.238	1,676	
IM IFNβ-1a	492,860	2.872	3,142	-1.400	Dominated	Dominates
IFNβ-1b	497,009	2.632	4,149	-0.240	Dominated	Dominates

<u>Data Request 10</u>

Removing the mid-cycle correction for the costs of alemtuzumab

It was highlighted by the ERG that due to the dosing schedule of alemtuzumab and the fact that costs are incurred within the first 5 days of each year, it is not appropriate to use mid-year estimates for costs relating to dosing of alemtuzumab. Acquisition and administration costs have been calculated using the patient cohort distribution (the Markov trace) at start of cycle, not from mid-year estimates.

Table 24 Cost-effectiveness results using the Markov trace at the start of each year rather than mid-year estimates for costs relating to alemtuzumab treatment, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	484,590	2.887				9,431
SC IFNβ-1a 44µg	487,368	2.923	2,778	0.036	77,453	7,624
SC IFNβ-1a 22µg	487,642	3.034	274	0.111	2,459	8,086
IM IFNβ-1a	492,860	2.872	5,218	-0.162	Dominated	3,425
IFNβ-1b	497,009	2.632	4,149	-0.240	Dominated	395
Alemtuzumab	497,657	4.273	648	1.641	395	

Data Request 11

Increasing the number of monitoring and neurology visits for patients treated with alemtuzumab and additional monitoring after re-starting alemtuzumab treatment

The monitoring for alemtuzumab has been increased to 4 neurology visits in first year and 2 neurology visits thereafter (from 2 neurology visits in first year and 1 neurology visit thereafter) and the number of MRIs has increased to 1 per year.

The monitoring cost in each year from year 2 and onwards is now the sum of the year 1 monitoring costs for all patients receiving re-treatment and the year 2 monitoring costs for all patients not receiving re-treatment.

Table 25 Cost-effectiveness results increasing monitoring of alemtuzumab and applying first year monitoring costs to all patients receiving re-treatment, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	484,590	2.887				9,209
SC IFNβ-1a 44µg	487,368	2.923	2,778	0.036	77,453	7,428
SC IFNβ-1a 22µg	487,642	3.034	274	0.111	2,459	7,864
IM IFNβ-1a	492,860	2.872	5,218	-0.162	Dominated	3,306
IFNβ-1b	497,009	2.632	4,149	-0.24	Dominated	337
Alemtuzumab	497,570	4.296	561	1.664	337	

Data Request 12

Higher health state costs used in the Evidence Review Group's analyses

As discussed in the teleconference with NICE on 3/12/13, health state costs used in the analysis are those from the Biogen manufacturer submission. These health state costs use only direct medical costs; no direct non-medical costs are included. The full incremental results are presented in Table 26. Removing dominated and extendedly dominated results leaves only a comparison of alemtuzumab versus glatiramer acetate, for which the probabilistic ICER is £12,802.

Table 26 Cost-effectiveness results using costs per health state from the natalizumab manufacturer submission, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	283,911	2.888				12,802
SC IFNβ-1a 44µg	287,390	2.917	3,479	0.029	119,114	10,509
SC IFNβ-1a 22µg	287,645	3.068	255	0.151	1,695	11,613
IM IFNβ-1a	292,163	2.841	4,518	-0.227	Dominated	6,612
IFNβ-1b	294,328	2.651	2,165	-0.190	Dominated	4,500
Alemtuzumab	301,619	4.271	7,290	1.620	4,500	

Data Request 13

Costs associated with adverse effects of treatment including renal failure, renal transplantation, dialysis, and death

"The Committee considered the number of deaths in the trials and the number of people with serious adverse events and concluded it was more appropriate for the manufacturer to include them fully in the modelling." [ACD]

In the base case analysis, costs associated with nephropathies were £338.96. To address the committee's concerns that costs may have been underestimated, in addition to the costs given in the base case analysis, costs associated with renal failure and subsequently transplantation or dialysis and renal associated deaths were included. Furthermore, costs were assigned to the estimated proportion of patients that died from AEs in the Phase II and III trials (see Data Request 6 for further details on trial mortality).

Costs associated with renal failure and subsequently transplantation or dialysis were calculated as follows:

- The proportion of the trial population that experienced nephropathies over the trial duration was 0.41%.

- A retrospective cohort study found that of 335 patients with chronic renal failure that had not died over the 5.5 year study period, 12% (39/335) progressed to end stage renal failure (CRF) [Drey et al, 2003; NICE, 2008]. This equates to a progression probability per year of 2.2% [1-exp(ln(1-39/335)/5.5)]. Since no progression probability for nephropathy could be sourced, this probability for CRF was used. This is a conservative assumption since the probability for ESRF in those with nephropathy would be lower than that for those in chronic renal failure

All patients with nephropathy have been assigned an annual cost of those in renal failure (again this is likely to be a conservative assumption)

- It is assumed that 50% of patients progressing to ESRF each year will receive dialysis whilst the remaining 50% will receive a transplant, based on the following statement from the National Service Framework for Renal Services: "More than 27,000 people were receiving RRT in England in 2001. Around half of these had a functioning transplant, the remainder were on dialysis." [DoH, 2004]

- The unit costs per session (Table 27) were multiplied by the frequency per year [Kidney Research UK] to gain the annual cost of dialysis per year. The cost of dialysis per year is applied to the cumulative number of patients that have progressed to ESRF and will receive dialysis. In addition, all patients receive a one-off cost of renal replacement peritoneal dialysis associated procedures (RRPDAP), which is conservative since only patients with Continuous Ambulatory Peritoneal Dialysis (CAPD) would receive this cost.

- The cost of transplantation was applied to the cohort receiving transplantation each year (not cumulative).

The unit costs used in the calculations were calculated from the most recent NHS reference costs [DoH, 2013]. Total costs for CRF, transplantation and RRPDAP were sourced from the Total HRG costs of adults, weighted by the activity where required, as shown in Table 27.

Table 27 Unit costs of renal failure, dialysis and transplantation

	Currency Code	**Activity / sessions**	**Unit cost**	**Total Cost per procedure / session**
Renal Replacement Peritoneal Dialysis Associated Procedures	LA05Z	2708	£1,049.46	£1,049.46
Kidney Transplant, [19 years and over, from Cadaver Non Heart-Beating Donor / Cadaver Heart-Beating Donor / Live Donor	LA01A	512	£16,580.03	£18,634.38
	LA02A	896	£19,803.62	
	LA03A	790	£18,639.68	
Chronic Kidney Disease with / without Interventions, all CC Scores	LA08G	419	£7,381.42	£1,822.93
	LA08H	582	£4,405.19	
	LA08J	1260	£3,072.05	
	LA08K	380	£3,725.94	
	LA08L	950	£2,842.92	
	LA08M	2276	£2,252.48	
	LA08N	3111	£1,512.96	
	LA08P	8745	£1,009.76	
Hospital/Satellite/Home Haemodialysis or Filtration	LD01A	364853	£146.91	£150.30
	LD02A	744213	£157.05	
	LD03A	12289	£159.48	
	LD04A	21719	£185.31	
	LD05A	376276	£130.84	
	LD06A	1057465	£156.56	
	LD07A	18540	£131.32	
	LD08A	56773	£172.78	
	LD09A	28859	£157.09	
	LD10A	85624	£138.71	
	LD01A	8816	£167.45	
	LD02A	14059	£174.16	

	LD03A	639	£201.15	
	LD04A	944	£201.15	
	LD05A	31670	£121.83	
	LD06A	118059	£125.90	
	LD07A	441	£172.20	
	LD08A	1016	£174.93	
	LD09A	4367	£87.07	
	LD10A	10854	£91.64	
Continuous Ambulatory Peritoneal Dialysis	LD11A	418503	£60.71	£60.71
	LD11A	30637	£60.71	
Automated Peritoneal Dialysis	LD12A	587572	£66.59	£66.48
	LD13A	50060	£65.64	
	LD12A	49205	£65.99	
	LD13A	8179	£65.99	

The estimated cost of dialysis has been calculated using:

- DH Reference cost activity data to source the split between CAPD, APD and hospital dialysis
- Information from Kidney Research UK to determine frequency of dialyses received by patients receiving CAPD, APD and hpspital dialysis sourced at http://www.kidneyresearchuk.org/health-information/treatments-management

This estimation of the annual cost of dialysis is summarized in the table below:

Table 28 Estimated annual dialysis cost

Currency Description	**% split of patients**	**Estimated patients**	**Sessions (based on DH Reference cost activity)**	**National Average Unit Cost**	**Assumption (based on information on the Kidney Research UK website)**	**Cost per year**
Hospital haemodialysis	89%	19014	2,974,382	£151.63	3x a week	£23,719
CAPD	1%	310	453,134	£61.04	4 x every day	£89,113
Automated peritoneal dialysis	9%	1935	706,344	£67.97	every day	£24,811
Estimated annual dialysis cost						£24,773

End-of-life costs from organ failure were sourced from a National Audit Office report of end of life care in England and inflated to 2013 values [NAO, 2008]. The probability of death each year was 0.08% [1-exp(ln(1-3/1208)/3)] was multiplied by the end of life costs (£18,771) to give an average cost of treatment-related death per year of £15.55.

This end of life cost was in addition added to the additional (possibly) AE related deaths observed in the alemtuzumab clinical trials of 0.2% (estimation of percentage outlined in Data Request 6 below).

The total costs applied to alemtuzumab patients in the model as result of nephropathies increased from £25.07 in year 1 to £79.92 in year 50 (see Table 29). As shown in Table 30. despite the conservative assumptions made in the analysis, alemtuzumab remained cost-effective against all comparators at a WTP of £30,000 per QALY.

Table 29 Total costs of renal failure, dialysis, kidney transplantation and death applied to the model

	Unit Cost	**Incidence year 1**	**Total Cost year 1**	**Incidence year 50**	**Total Cost year 50**
Nephropathy		0.411%		0.411%	
ESRF per year	£1,823	0.009%	£7.50	0.009%	£7.50
50% receive pre-dialysis procedure (one off cost)	£1,049	0.005%	£0.05	0.005%	£0.05
50% receive renal dialysis per year (cumulative)	£24,470	0.005%	£1.12	0.229%	£55.97
50% receive renal transplant per year (one off cost)	£18,634	0.005%	£0.85	0.005%	£0.85
Death (due to ESRF)	£18,771	0.083%	£15.55	0.083%	£15.55
Death due to (possibly) AEs in trials					
Total			**£25.07**		**£79.92**

Table 30 Cost-effectiveness results using increased costs associated with nephropathies and (possible) AE related deaths in the trials, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	484,590	2.887				7,164
SC IFNβ-1a 44µg	487,368	2.923	2,778	0.036	77,453	5,262
SC IFNβ-1a 22µg	487,642	3.034	274	0.111	2,459	5,517
IM IFNβ-1a	492,860	2.872	5,218	-0.162	Dominated	1,075
Alemtuzumab	494,339	4.248	1,479	1.376	1,075	
IFNβ-1b	497,009	2.632	2,670	-1.616	Dominated	Dominates

<u>Data Request 14</u>

Baseline characteristics from patients in the alemtuzumab trials instead of from the UK Risk Sharing Scheme

Results using the disease progression incorporating the characteristics of the placebo group from the TOWER and TEMSO trials are detailed in the response to amendment 5 above. The results using the matrix as in amendment 5 in addition to the initial EDSS distribution, age at baseline and male to female ratio from the CARE MS I and II trials are presented in Table 31.

In addition, the results changing only the initial EDSS distribution, age at baseline and male to female ratio to the CARE MS I and II trails are presented in Table 31.

Table 31 Cost-effectiveness results using the initial EDSS distribution and baseline characteristics from alemtuzumab trials and TEMSO and TOWER natural history transition matrix, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Alemtuzumab	412,091	9.795				
Glatiramer acetate	417,872	7.361	5,781	-2.434	Dominated	Dominates
SC IFNβ-1a 44µg	419,439	7.390	1,567	0.029	54,234	Dominates
SC IFNβ-1a 22µg	423,783	7.671	4,343	0.280	15,490	Dominates
IM IFNβ-1a	428,166	7.293	4,383	-0.377	Dominated	Dominates
IFNβ-1b	450,491	7.194	22,325	-0.099	Dominated	Dominates

Table 32 Cost-effectiveness results using the initial EDSS distribution and baseline characteristics from alemtuzumab trials and natural history transition matrix with TEMSO and TOWER for EDSS 0-5 and London Ontario otherwise, in the active RRMS population

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	473,815	4.831				364
SC IFNβ-1a 44µg	474,490	6.685	675	1.854	364	
SC IFNβ-1a 22µg	476,906	4.851	2,416	-1.834	Dominated	Dominates
IM IFNβ-1a	477,980	5.034	1,074	0.183	5,869	Dominates
IFNβ-1b	484,327	4.779	6,347	-0.255	Dominated	Dominates
Alemtuzumab	491,251	4.486	6,925	-0.293	Dominated	Dominates

<u>Data Request 15</u>

Combining the changes requested in data requests 0-14

The results of alemtuzumab versus the aforementioned comparators in each of these populations, using the proposed amendments are presented in Tables 33-36 (Tables 33-34 assume waning applies to alemtuzumab and its comparators whilst Tables 35-36 assumes it applies only to alemtuzumab with comparator efficacy remaining at 100% up to 50 years).

The all years MTC adjusted for baseline annualized relapse rate has been used for the active RRMS population (using 6 month SAD HRs).

As noted in Genzyme's response A.6. to the ACD and under Data Request 6 above it does not seem a reasonable approach based on the precedent of other NICE assessments and also there does not seem to be a rationale for assuming a divergent approach to waning between alemtuzumab and its comparators.

Given the wording of this request ICERs are presented assuming 100% efficacy up to 50 years for the comparator arms whilst applying waning only to alemtuzumab efficacy (Tables 35 and 36). However, Genzyme are strongly of the opinion that waning applied also to the comparators is more appropriate (as presented in Tables 33 and 34)

Table 33 Incremental cost-utility results of alemtuzumab versus beta interferons and glatiramer acetate in the active RRMS population combining all the proposed amendments and using 1st scenario from Data Request 7 (waning of efficacy at year 5 applied to alemtuzumab and the comparators)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	234,321	7.275				12,730
SC IFNβ-1a 44µg	241,140	6.859	6,820	-0.415	Dominated	7,282
Alemtuzumab	248,451	7.211	7,311	0.351	20,803	4,740
IM IFNβ-1a	257,317	9.081	8,865	1.870	4,740	

Table 34 Incremental cost-utility results of alemtuzumab versus beta interferons and glatiramer acetate in the active RRMS population combining all the proposed amendments and using 2nd scenario from Data Request 7 (waning of efficacy at year 3 for alemtuzumab and for the comparators)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	233,627	7.235				13,636
SC IFNβ-1a 44µg	241,354	6.818	7,727	-0.417	Dominated	7,566
IM IFNβ-1a	247,488	7.138	6,134	0.320	19,185	5,600
Alemtuzumab	258,072	9.028	10,584	1.890	5,600	

Table 35 Incremental cost-utility results of alemtuzumab versus beta interferons and glatiramer acetate in the active RRMS population combining all the proposed amendments and using 1st scenario from Data Request 7 (waning of efficacy at year 5 applied only to alemtuzumab, 100% efficacy for comparators assumed up to 50 years)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	231,528	7.901				22,001
SC IFNβ-1a 44µg	241,239	7.148	9,711	-0.753	Dominated	8,451
Alemtuzumab	247,722	7.833	6,483	0.685	9,461	7,899
IM IFNβ-1a	257,628	9.087	9,906	1.254	7,899	

Table 36 Incremental cost-utility results of alemtuzumab versus beta interferons and glatiramer acetate in the active RRMS population combining all the proposed amendments and using 2nd scenario from Data Request 7 (waning of efficacy at year 3 for alemtuzumab, 100% efficacy of comparators assumed up to apply up to 50 years)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	231,591	7.914				24,472
SC IFNβ-1a 44µg	240,136	7.156	8,545	-0.758	Dominated	9,773
IM IFNβ-1a	247,664	7.787	7,527	0.630	11,941	8,646
Alemtuzumab	258,148	8.999	10,484	1.213	8,646	

The cost effectiveness model is sensitive to the assumption of using the BIogen source of EDSS health state costs which excludes direct non health care costs from the model and 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 above) which excludes direct non health care costs. Including direct non healthcare costs (sourced from Tyas et al) reduces this probabilistic 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 costs from the cited sources were within the NICE reference case. Consistency would require that a similar approach was adopted in this appraisal.

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. Excluding waning of treatment effect from the combination analysis leads to a probabilistic ICER for alemtuzumab versus glatiramer acetate of £5,346.

Including direct non health care costs and excluding direct non healthcare costs in the model results in a combination cost effectiveness analysis in which alemtuzumab dominates glatiramer acetate.

Given potential concerns that total QALYs remain low in the combination approach, Tables 33 and 34 above were also run using utilities derived from the placebo arm of TEMSO for EDSS 0-6 and Orme decrement derived utilities for EDSS 7-9 (as used in the preferred ERG approach in the teriflunomide assessment – this is discussed in more detail under Request 4 above). These results are shown in Tables 37 and 38. This approach leads to higher overall total QALYs which are closer to those included in the preferred / additional analyses run in response to a request for additional information in the teriflunomide ACD (included for comparison purposes below in Table 39):

Table 37 Waning of efficacy at year 5 for alemtuzumab and all comparators using TEMSO derived utilities for EDSS 0-6 and Orme decrement derived utilities for EDSS 7-9

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Increment al QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	233,795	9.738				24,274
SC IFNβ-1a 44µg	241,509	9.358	7,714	-0.380	Dominated	11,722
IM IFNβ-1a	246,782	9.693	5,273	0.336	15,708	10,402
Alemtuzumab	257,331	10.707	10,548	1.014	10,402	

Table 38 Waning of efficacy at year 3 for alemtuzumab and all comparators using TEMSO derived utilities for EDSS 0-6 and Orme decrement derived utilities for EDSS 7-9

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	ICER alemtuzumab versus comparator
Glatiramer acetate	233,500	9.727				28,078
SC IFNβ-1a 44µg	241,409	9.317	7,908	-0.410	Dominated	13,021
IM IFNβ-1a	247,755	9.675	6,347	0.358	17,737	11,210
Alemtuzumab	258,200	10.607	10,445	0.932	11,210	

Table 39: Probabilistic results of teriflunomide versus all comparators (additional analysis requested as part of teriflunomide ACD)*

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER versus baseline (£)	ICER (£) teriflunomide versus comparator
Glatiramer acetate	[redacted]	[redacted]				13,234
Teriflunomide	[redacted]	[redacted]	2,638	0.199	13,234	
IFNβ-1a 44µg (Rebif)	[redacted]	[redacted]	7,999	-0.071	Dominated	Dominates
IFNβ-1a (Avonex)	[redacted]	[redacted]	14,202	-0.081	Dominated	Dominates
IFNβ-1a 22µg (Rebif)	[redacted]	[redacted]	14,684	-0.166	Dominated	Dominates
IFNβ-1b	[redacted]	[redacted]	15,964	-0.257	Dominated	Dominates

*Assumptions included 1) Natural history progression data from placebo arms of TOWER and TEMSO 2) Baseline characteristics and initial EDSS distribution from TOWER and TEMSO 3) ERG amended calculation for SPMS conversion probabilities 4) Direct non-medical costs not included 5) Utilities observed in TEMSO 6) using increments from Orme for high EDSS states where trial data were not available 7) Waning of treatment effect is 75% treatment effect after 2 years and 50% treatment effect after 5 years.

References

Drey et al. Population-Based Study of the Incidence and Outcomes of Diagnosed Chronic Kidney Disease. *American Journal of Kidney Diseases,* Vol 42, No 4 (October), 2003: pp 677-684

The National Service Framework for Renal Services. Part One: Dialysis and Transplantation. DH Renal Team. Jan 2004 (page 8)

Information available on Kidney Research UK website at http://www.kidneyresearchuk.org/health-information/treatments-management