Appendix 3: Additional ICER Analysis carried out for alemtuzumab vs natalizumab (RES RRMS) and vs fingolimod (HA RRMS despite interferon use)

Table Appendix .3.1. Additional ICER Analysis carried out for alemtuzumab vs natalizumab (RES RRMS) and vs fingolimod (HA RRMS despite interferon use)

Data Request	Proposed amendment	vs Natalizumab (RES RRMS)	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	Done (Model 1)	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 natalizumab)	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 (Model 2)	Done (Model 2)
4	EQ-5D data from the CARE-MS I and CARE-MS II trials	Done (Model 3)	Done (Model 3)
5	An amendment to the model to allow improvements in patients' EDSS states (by using the TEMSO TOWER placebo arm natural history matrix)	Done (Model 1)	Done (Model 1)
6	An amendment to the model incorporating the observed deaths from the trial data	Done (No model used)	Done (No model used)
7	A reduction in efficacy for alemtuzumab starting at 3 or 5 years	Done (Model 1)	Done (Model 1)
8	Additional costs of other licensed relapsing-remitting multiple sclerosis treatments after alemtuzumab treatment failure	Done (Model 1)	Done (Model 1)
9	A time-dependent re-treatment rate for alemtuzumab	Done (Model 4)	Done (Model 4)
10	Removing the mid-cycle correction for the costs of alemtuzumab	Done (Model 5)	Done (Model 5)
11	Increasing the number of monitoring and neurology visits for patients treated with alemtuzumab and additional monitoring after re-starting alemtuzumab treatment	Done (Model 6)	Done (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]	Done (Model 1)	Done (Model 1)
13	Costs associated with adverse effects of treatment including renal failure, renal transplantation, dialysis, and death	Done (Model 1)	Done (Model 1)
14	Baseline characteristics from patients in the alemtuzumab trials instead of from the UK Risk Sharing Scheme	Done (Model 1)	Done (Model 1)
15	All of the requested changes combined	Done (using efficacy data not adjusted for baseline relapses; used 6 months SAD HRs) (Model 7)	Done (using efficacy data not adjusted for baseline relapses; used 3 month SAD HRs) (Model 7)

Table: Appendix.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 Request	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Costs	QALYs	ICER
Combination assumes alemtuzumab vs placebo same HRs and ARR RRs as meta-	262,617	8.537	297,548	8.051	-34,931	0.486	Dominates

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							
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)	262,617	8.537	297,548	8.051	-34,931	0.486	Dominates

Table Appendix .3.3. Additional ICER Analysis carried out for alemtuzumab vs fingolimod (HA RRMS despite interferon use)

	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) – using TEMSO plus Orme decrements as basis of utilities (plus AE disutilities as per original model)	269,319	10.134	261,792	9.697	7,528	0.437	17,232

Table Appendix 3.4. Output from 6 mth SAD RES RRMS MTC (not included in original submission)

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